Studies on the β-C(sp^3)-H Functionalization Toward the Synthesis of β-Arylated Unnatural Amino Acid Derivatives

A thesis submitted for the partial fulfillment

of the degree of Doctor of Philosophy

By

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DEDICATED to

Beloved Parents,

Family & Friends

Declaration

I hereby declare that the work presented in this thesis entitled "Studies on the β-C(sp^3)-H Functionalization toward the Synthesis of β-Arylated Unnatural Amino Acid Derivatives" has been carried out by me under the supervision of Dr. S. Arulananda Babu at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, India. Thiswork has not been submitted in part or full for the award of any degree, diploma, or fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgements. In keeping with thegeneral practice in reporting scientific observations, acknowledgments have been madewhenever the work was described based on the findings of other investigators. Any omissionthat might have occurred due to oversight or error in judgment is regretted. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Radha Tomar

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the abovestatements by the candidate are true to the best of my knowledge.

Dr. S. Arulananda Babu

Associate Professor

Department of Chemical Sciences

Indian Institute of Science Education and Research, Mohali

Date:

Place:

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List of publications from thesis work:

(1) **Tomar, R**.; Bhattacharya, D.; Babu, S. A.* *Tetrahedron* **2019**, *75*, 2447-2465.

Title: *Assembling of Medium/Long Chain-Based β-Arylated Unnatural Amino Acid Derivatives via the Pd(II)-Catalyzed sp^3 β-C-H Arylation and a Short Route for Rolipram-Type Derivatives.*

(2) **Tomar, R**.; Bhattacharya, D.; Babu, S. A.* *Asian J. Org. Chem.* **2022**, *11*, e202100736.

Title: *Direct Lactamization of β-Arylated δ-Aminopentanoic Acid Carboxamides: En Route to 4-Aryl- 2-Piperidones, Piperidines, Antituberculosis Molecule Q203 (Telacebec) and its Analogues.*

(3) **Tomar, R**.; Kumar, A.; Dalal, A.; Bhattacharya, D.; Singh, P.; Babu, S. A.* *Asian J. Org. Chem.* **2022**, 11, e202200311. (Selected in **Very Important Paper (VIP)** Category)

Title: *Expanding the Utility of Inexpensive Pyridine-N-oxide Directing Group for the Site-Selective sp^2/sp^3 γ-C-H and sp^2 δ-C-H Functionalization of Carboxamides.*

(4) **Tomar, R**.;[†] Suwasia, S.;[†] Roychoudhury, A.; Venkataramani, S.;* Babu, S. A.* *Chem. Commun.*, **2022**, 58, 12967-12970.

Title: *Azobenzene-based Unnatural Amino Acid Scaffolds via Pd(II)-catalyzed C(sp^3)-H arylation strategy.*

List of publications as a co-author:

(5) Bhattacharya, D.; **Tomar, R.;** Babu, S. A.* *Asian J. Org. Chem.* **2020**, *9*, 829-839.

Title: *Conversion of 2,3-Dihydrobenzo[b][1,4]dioxine-2-carboxamides to 3-Oxoquinolin 2(1H)-ones via Ring-Opening and Formal 6-endo-trig Cyclization-Involved Heck Reactions.*

(6) Bisht, N.; Babu, S. A.;* **Tomar, R.** *Asian J. Org. Chem.* **2020**, *9*, 1225-1233.

Title: *Pd(II)-Catalyzed, Bidentate Directing Group-aided Alkylation of sp3 γ-C-H Bonds: Access to 3-Alkylated Thiophene/Furan and Benzothiophene/Benzofuran Motifs.*

(7) Bisht, N.; Babu, S. A.;* **Tomar, R.** *Asian J. Org. Chem.* **2022**, 11, e202200589.

Title: *Utility of 4-Amino-2,1,3-benzothiadiazole Directing Group in the Pd(II)-catalyzed Arylation of γ-C-H Bonds of Carboxamides and β-C-H Bonds of Amino Acid Carboxamides.*

(8) Babu, S. A.*; Aggarwal, Y.; Patel, P.; **Tomar, R**. *Chem. Commun*. **2022**, *58*, 2612.

Title: *Diastereoselective Palladium-Catalyzed Functionalization of Prochiral C(sp^3)-H Bonds of Aliphatic and Alicyclic Compounds.*

(9) Babu, S. A.*; Padmavathi, R.; Suwasia, S.; Dalal, A.; Bhattacharya, D.; Singh, P.; **Tomar, R**. *Stud. Nat. Prod. Chem.* **2021**, *71*, 311. (Book chapter)

Title: *Recent Developments on the Synthesis of Functionalized Carbohydrate/Sugar Derivatives Involving the Transition Metal-Catalyzed C-H Activation / C-H Functionalization.*

***Conferences/Symposia**:*

1) Participated in RAOBC, 2019 held at IISER Mohali Punjab, India. (22^{nd}-24^{th} March, 2019)

2) Participated in 1^{st} CRIKC Symposium (CCS 2019) held at IISER Mohali, Punjab, India. (2^{nd}&3^{rd} November, 2019)

3) Participated in 27^{th} CRSI-National Symposium in Chemistry held at IISER Kolkata, India. (26^{th} to 29^{th}September, 2021)

4) Oral Presentation entitled *"**Assembling of 4-Aryl-2-piperidone, 4-Arylpiperidine Scaffolds and Antituberculosis Molecule via Pd(II)-Catalyzed sp^3 β-C-H Activation/Arylation***", ispresented inonline national conference on organic chemistry at the NITT Organic Chemistry Conference '21 (NITTOCC) held at NIT Trichy, Tamil Nadu, India. (November 16^{th} to 18^{th} December, 2021) (*Best Oral Presentation Award*)

5) Participated in 29^{th} CRSI-National Symposium in Chemistry held at IISER Mohali, India. (7^{th} to 9^{th}July, 2022)

6) Participated in 2nd CRIKC Symposium (RABMC-2022) held at NIPER Mohali, Punjab, India. (19^{th} November, 2022)

Preamble

The building blocks of proteins and potential therapeutic candidates, have received significant attention in the fields of Pharmacology and Biochemistry. In this context, anenormous amount of synthetic work dealing with synthesizing unnatural amino acids has been reported. Apart from the traditional approaches, C-H activation/functionalization has emerged as the most potent tool for the synthesis of substituted unnatural amino acids. The most highlighted point of the C-H activation strategy is that the C-H bond itself acts as a transformable functional group, i.e., no need for prefunctionalization of starting material for synthesizing the targeted molecules. However, regioselectivity problems are expected to arise when this method is employed to functionalize a particular molecule with several C-H bonds. In this direction, the directing group-enabled C-H functionalization strategy has beenrecognizedas an effective method in terms of regioselectivity. In addition to academia, the pharmaceutical and agricultural sectors, as well as the field of material science and fine chemical industries, have all been modernized by the ability to produce carbon-carbon bonds in a highly selective manner. Encouraged by the effectiveness and advantages of the approach mentioned above, this thesis work aims to functionalize the natural or unnatural amino acids and peptides *via* directing group-enabled transition metal catalyzed C-H activation followed by the construction of important β-arylated lactams, amino acids, and peptides.

Chapter 1 introduces C-H activation/functionalization and a concise background about the evolution of the C-H bond activation strategy and its accessible approaches, followed by a few literature reports. These reports highlight the recent developments toward palladium-catalyzed C-H activation using the bidentate directing group to functionalizeβ-C(sp^3)-H bonds of natural or unnatural amino acids and peptides.

Chapter 2 deals with the study of Pd-catalyzed β-C-(sp^3)-H arylation of short/medium/long chain-based non-α-amino acids and synthetic transformations. Including a short route for the assembling of Rolipram-based compounds and 3-arylated GABA derivatives such as Baclofen, Phenibut, and Tolibut.

Chapter 3 represents the exploration of the synthesis of 4-aryl-2-piperidones and 4-aryl piperidine *via* the Pd(II)-catalyzed, bidentate directing group 8-aminoquinoline-aided β-C-(sp^3)-H activation/arylation methods followed by direct lacatamization methodology.

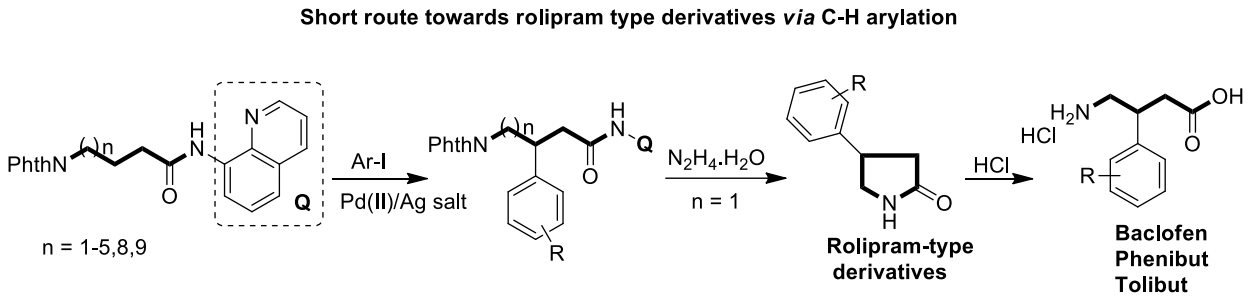
Chapter 4 focuses on the synthesis of the azobenzene-linked bioactive compounds *via* a directed C-H activation strategy. This part of the thesis deals with the generation of azobenzene-based unnatural amino acid derivatives and azobenzene-attached peptides *via* two different pathways.

Chapter 5 reveals the scope of sp^2/sp^3 γ- and δ-C-H functionalization using Pyridine-*N*-oxide as a directing group. A part of this thesis work is investigated to address the regioselective competition between β-C(sp^3)-H and γ-C(sp^2)-H bond followed by the assembling of a library of Pyridine-*N*-oxide-based carboxamide derivatives.

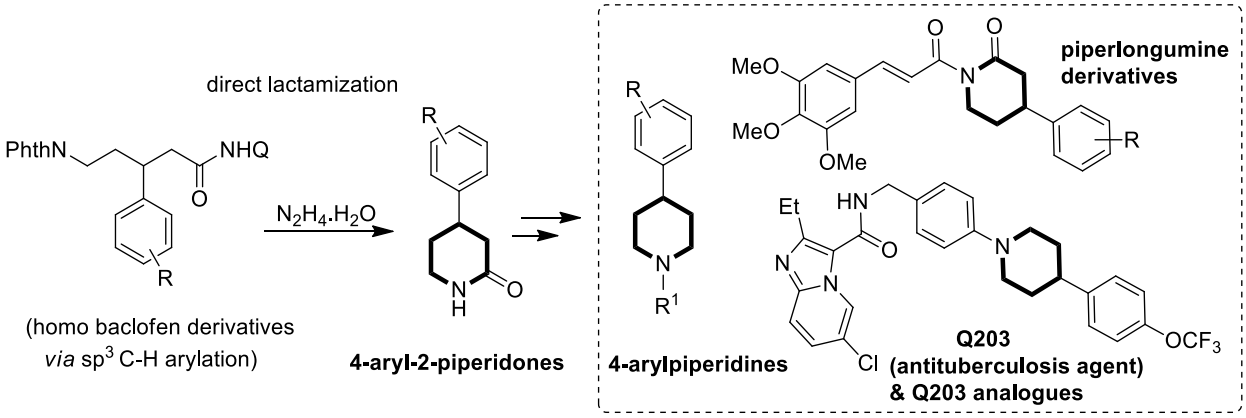
Objectives

The main objectives of the thesis work are listed below:

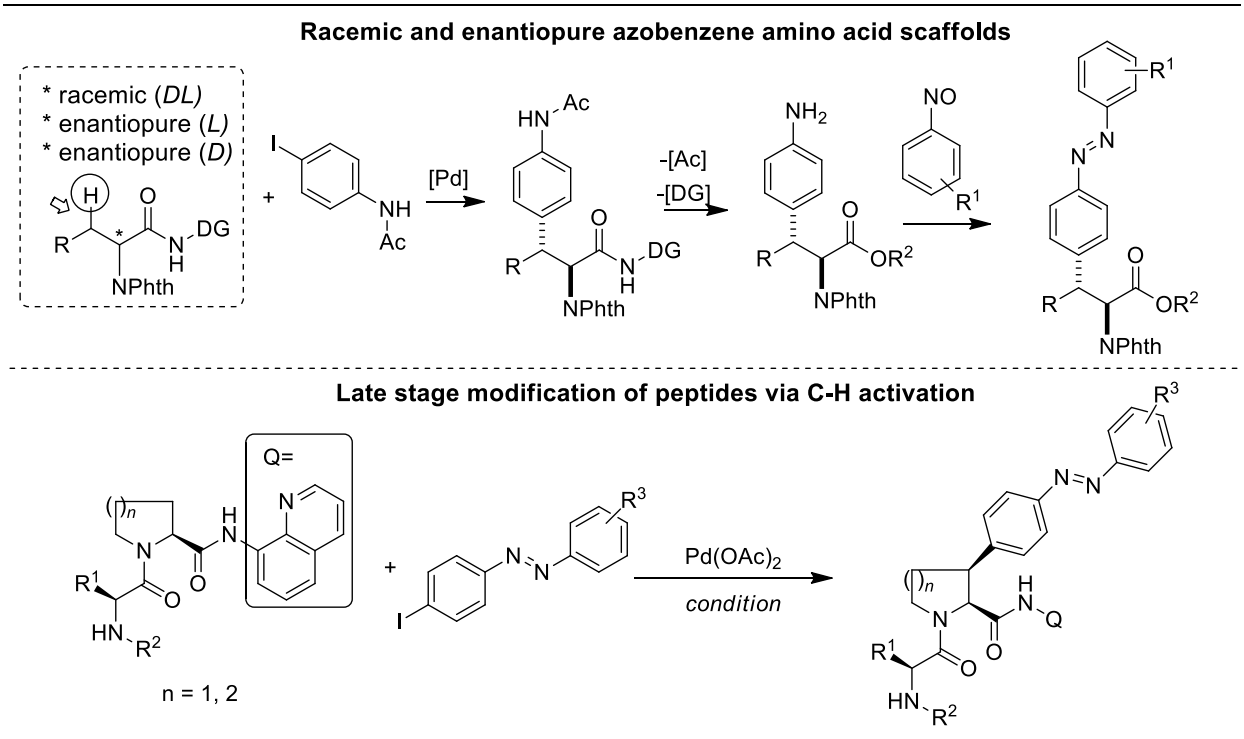
1) Short/medium chain-based unnatural amino acid derivatives containing an aryl group at the *β*-position are promising small molecules with therapeutic properties. Given the importance of these molecules, it was planned to develop a method that enables straightforward access to natural products and drug molecules bearing *β*-arylated *γ*-amino acid and *β*-arylated *γ*-lactam structural motifs. Besides we have shown a short route for assembling Rolipram and related compounds and also 3-arylated GABA derivatives suchas, Baclofen, Phenibut and Tolibut from their corresponding *β*-C-H arylated *γ*-aminobutyric acid derivatives (**Chapter 2**).



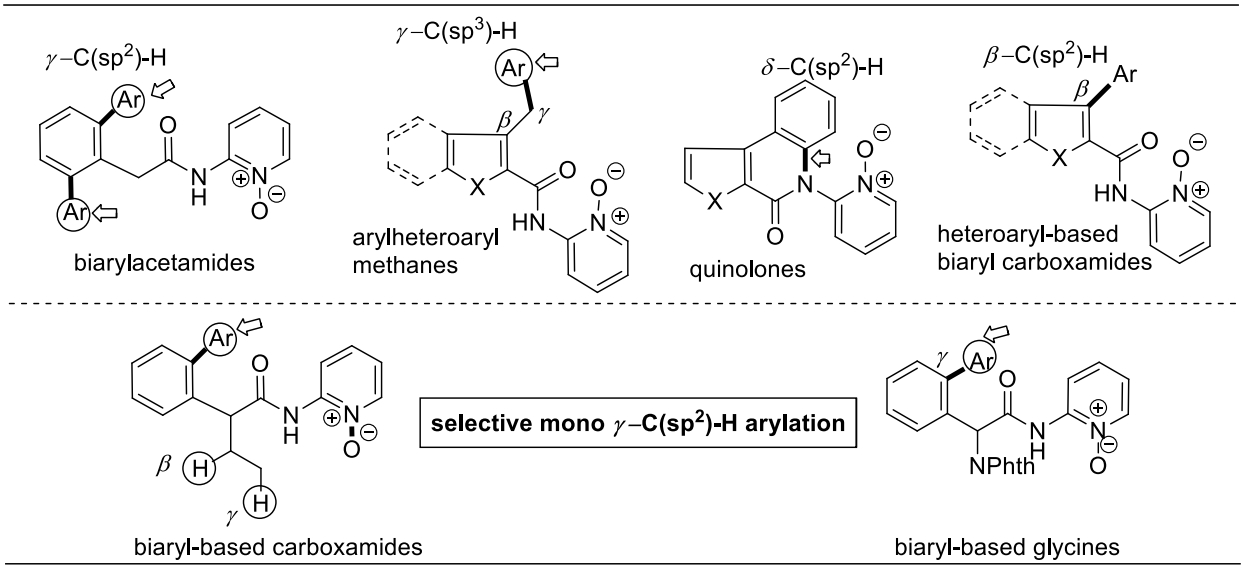
2) Specifically, piperidone and piperidine scaffolds based on heterocyclic molecules have a prominent place in medicinal chemistry and drug development research fields. Piperidone and piperidines skeletons with an aryl substituent are often found in drugs, bioactive molecules, pharmaceutical intermediates, and natural products. Encouraged by their importance, a part of the thesis work is emphasized the construction of arylated piperidone and piperidines by using Pd(II)-catalyzed C-H arylation protocol. It provides a novel approach to obtain *β*-arylated lactams and γ-arylated piperidines, as well as streamlines the synthesis of pharmaceutically significant molecules (**Chapter 3**).



3) Azobenzenes are promising motifs in chemical science due to their photoresponsive properties by which they can act as switchable molecules. Azobenzene motif-based ligands or linkers are also considered very significant as they play a key role in the studies of conformation, bioactivity, and functionalities of biological systems. Therefore, a part of the thesis work is contributed towards the enrichment of the libraries of azobenzene-linked unnatural amino acid derivatives and also for the synthesis of azobenzene-based peptides *via* the C-H activation strategy (**Chapter 4**).



4) Heteroaryl/biarylcompoundsrepresent one of the significant moietiesdue to their widespread applications in diverse fields such as pharmaceutical, industrial, agricultural, material sciences, and, various other disciplines. Motivated by the significance of functionalized heterocyclic phenyl acetyl compounds, a part of the thesis work is focused on enhancing the library of these derivatives by pyridine*N*-oxide-directed remote C-H functionalization (**Chapter 5**).



CHAPTER 1

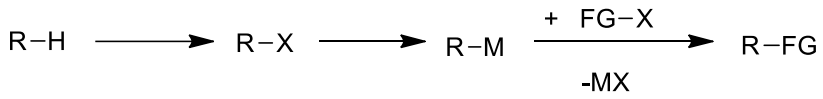
Introduction to C-H Bond Activation/Functionalization

In the last several decades, C-C bond formation is found to be the most established research area in organic chemistry and synthetic organic chemists have often been interested in finding new reactions and methodologies for the construction of C-C and C-heteroatom bonds. One of the most adaptable building blocks for peptides, proteins, chemical, and biological synthesis is amino acids. At the same time, only a limited number of amino acids (i.e., proteinogenic amino acids) are used by nature to create bioactive proteins and peptides. Nowadays, synthetic peptides and non-proteinogenic amino acids serve as important intermediates in total synthesis and also acts as potent catalysts and ligands in enantioselective reactions. The utilization of these biologics containing non-proteinogenic amino acids is witnessing a true breakthrough in the drug discovery and pharmaceutical market. Extensive research over the decades has resulted in the establishment of numerous fundamental and effective synthetic techniques, for synthesizing non-proteinogenic amino acids. Particularly, asymmetric Strecker synthesis and asymmetric alkylation of achiral glycine-based derivatives by using chiral ligands, and phase transfer catalysts are found to be valuable tactics for unnatural amino acid synthesis.[1]

Apart from this, traditional method Nobel prize-winning cross-coupling reactions were also applied for the synthesis of unnatural amino acids.[2] In organic synthesis, these traditional approaches to functionalizing inert carbon-hydrogen bonds are a powerful transformation, enabling new entries into useful structural motifs thereby improving overall synthetic efficiency.

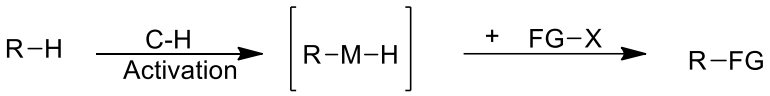
Extensive research into transition metal-catalyzed C-H activation has significantly improved our understanding to effectively cleave and functionalize inert C-H bonds. And, it has become clear that forming carbon-carbon and carbon-heteroatom bonds from unactivated C-H bonds has tremendous potential for chemical synthesis advancement.

A) Traditional Cross-Coupling



Pre-Funcationalized Starting Materials, Multiple Steps, Stoichiometric Metal Waste

B) Modern C-H activation/functionalization

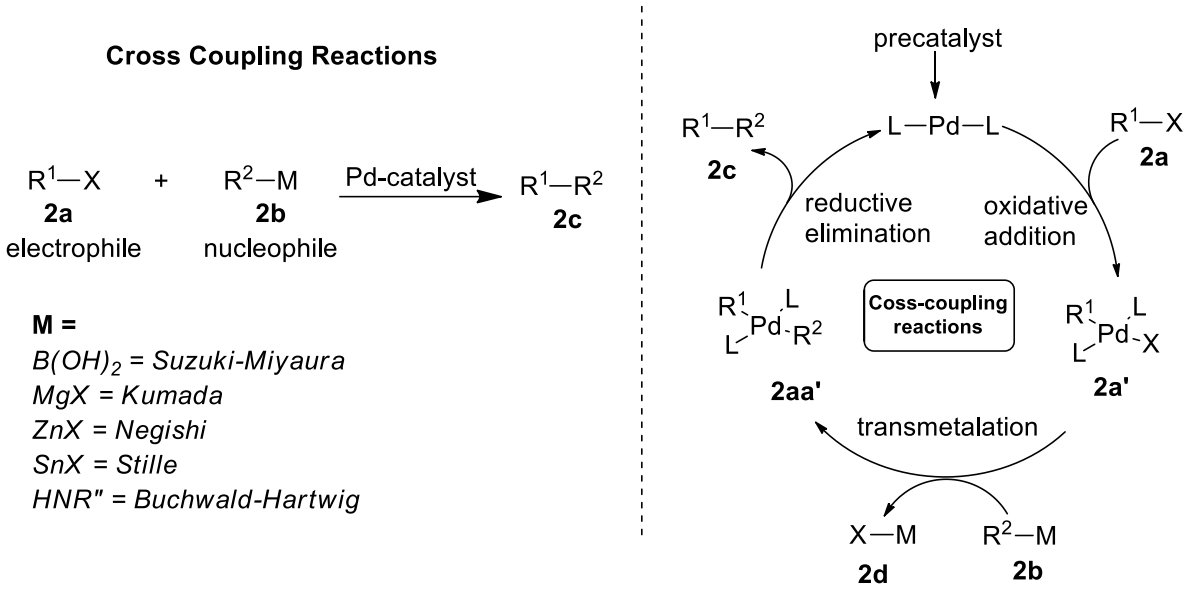


No Pre-Funcationalization of C-H bond, Single Step Coupling

Scheme 1. Traditional approach *vs* modern C-H activation.

Cross-Coupling Reaction: Cross-coupling reactions have been discovered nearly 50 years ago and are widely studied in academia and have been abundantly used in industry. In 2010, Richard F. Heck, Akira Suzuki and Ei-ichi Negishi, were awarded Nobel Prize for exceptional contribution to developing Pd-catalyzed coupling reactions. These coupling reactions are well accepted synthetic method that involves the metal-catalyzed coupling of an organometallic nucleophile with a sp^2-hybridized aryl halide electrophile.[4] A general mechanism for the Pd-catalyzed cross-coupling reactions is depicted in Scheme 2. The reactionis initiated by the oxidative addition of an electrophile **2a** with the transition metal to give an intermediate **2a'**. Further, transmetalation of metal reagent **2b** with **2a'**, resulted in the formation of an intermediate **2aa'**. In the end, the reductive elimination step involving **2aa'** afforded the desired product **2c** with a C-C bond along with the regeneration of catalyst as outlined in Scheme 2.[4]

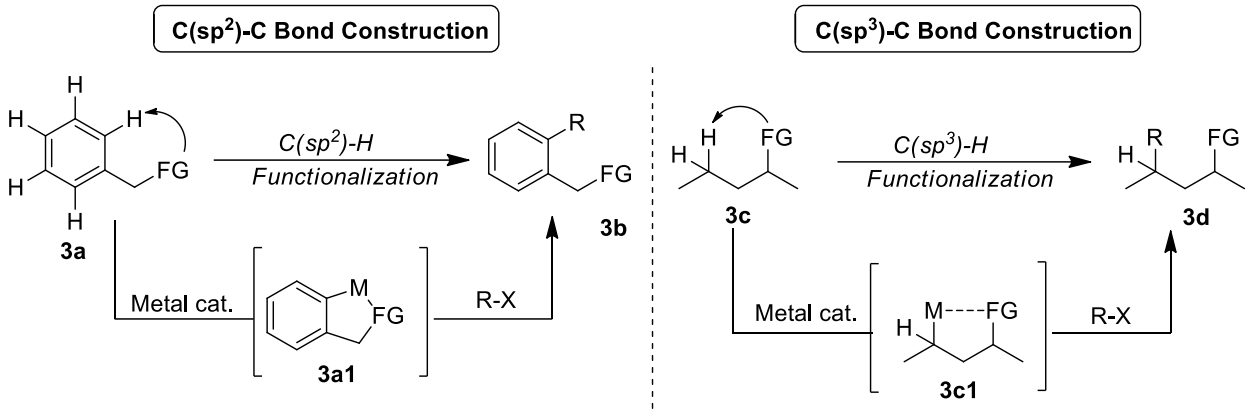
The traditional coupling reactions have led to many important discoveries, but they also have a number of limitations. Self-condensation, starting material polymerization, and the production of regioisomeric products are some of the limitations.



Scheme 2: Depiction of cross-coupling reactions and general mechanism.

But, in order to overcome the formation of other regioisomeric products, often, site-selectivity is achieved solely by the designing of the specific substrates which has disadvantages because a large number of methodologies are substrate specific. Therefore, the development of an atom-economical, step-economical and eco-friendly alternate route is always desirable.

C-H Functionalization Strategy: The discovery in the field of organometallic chemistry that a transition metal atom can insert into C-H bonds (*via* agostic interaction) to generate a metal-carbon bond gave rise to the field of transition metal-catalyzed C-H activation.[5] The divergent reactivity of the metal-carbon bond containing organometallic intermediate provides direct access to a range of substitutions in a single step. This overall procedure of C-H functionalization offers a revolutionizing way for the direct generation of the C-C species in both sp^2 as well as in sp^3 without any prefunctionalization as delineated in Scheme 3.



Scheme 3. General representation of C-C bond formation *via* transition metal catalyzed C-H activation/functionalization in both sp^2 and sp^3substrates.

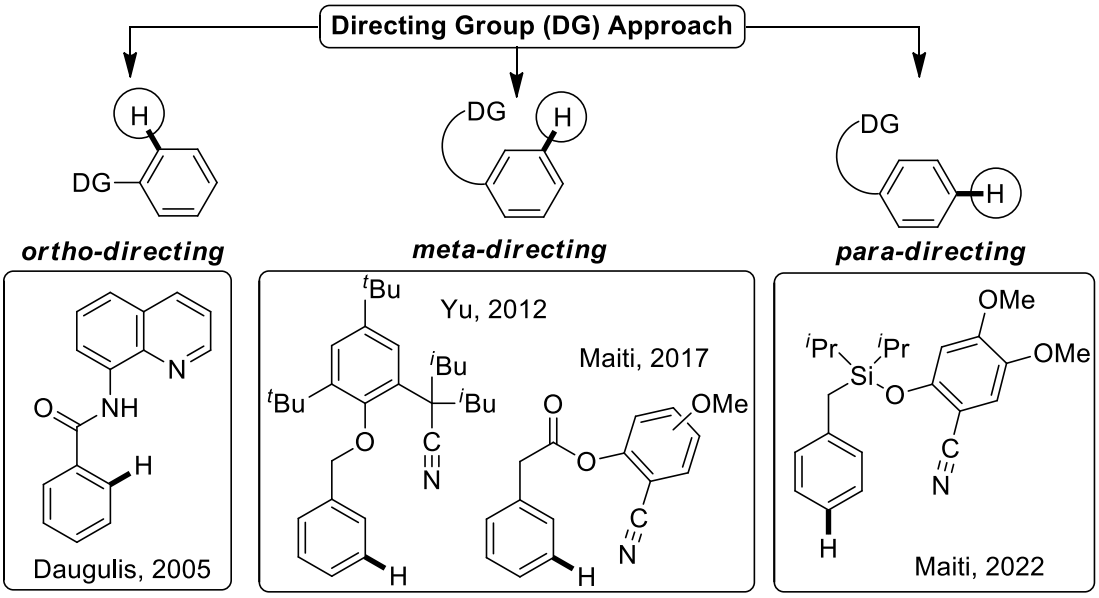
The ubiquitous nature of C-H bonds and their low reactivity poses challenges in the selective functionalization of the desired C-H bond. On the basis of regioselectivity, the existing C-H functionalization methods can be divided into three major classes:

- Direct C-H Functionalization Method
- Directed C-H Functionalization Method
- Transient Directing Group Method

Direct C-H Functionalization Method: Direct C-H functionalization is the process in which the C-H bond is activated without the involvement of any functional group or directing group. But when this approach is used to functionalize a specific molecule that contains more than one C-H bond, regioselectivity issues are likely to occur because in direct C-H activation regioselectivity is controlled by electronic and steric variables. To some extent, this technique is effective in the case of heterocyclic substrates due to the inherent reactivity of heterocyclic substrates, which include relatively active C-H bonds at the C2 position. However, in these cases, site-selective C-H bond functionalization was not achieved, thereby making the protocol inefficient and also resulting in purification problems.

Directed C-H Functionalization Method: To overcome the issue of regioselectivity the metal-catalyzed directed functionalization of inert C-H bonds is currently the most widely utilized synthetic technology, as it is more selective and efficient than the aforementioned techniques. The directed C-H functionalization strategy solves the problem of regioselectivity by employing

substrates with heteroatoms like nitrogen, oxygen, and sulphur that can co-ordinate to the metal ion. Because a molecule comprises numerous C-H bonds, the transition metal first combines with the functional group's or directing group's heteroatom, and activates the most proximal C-H bond *via* a metallacycle intermediate.

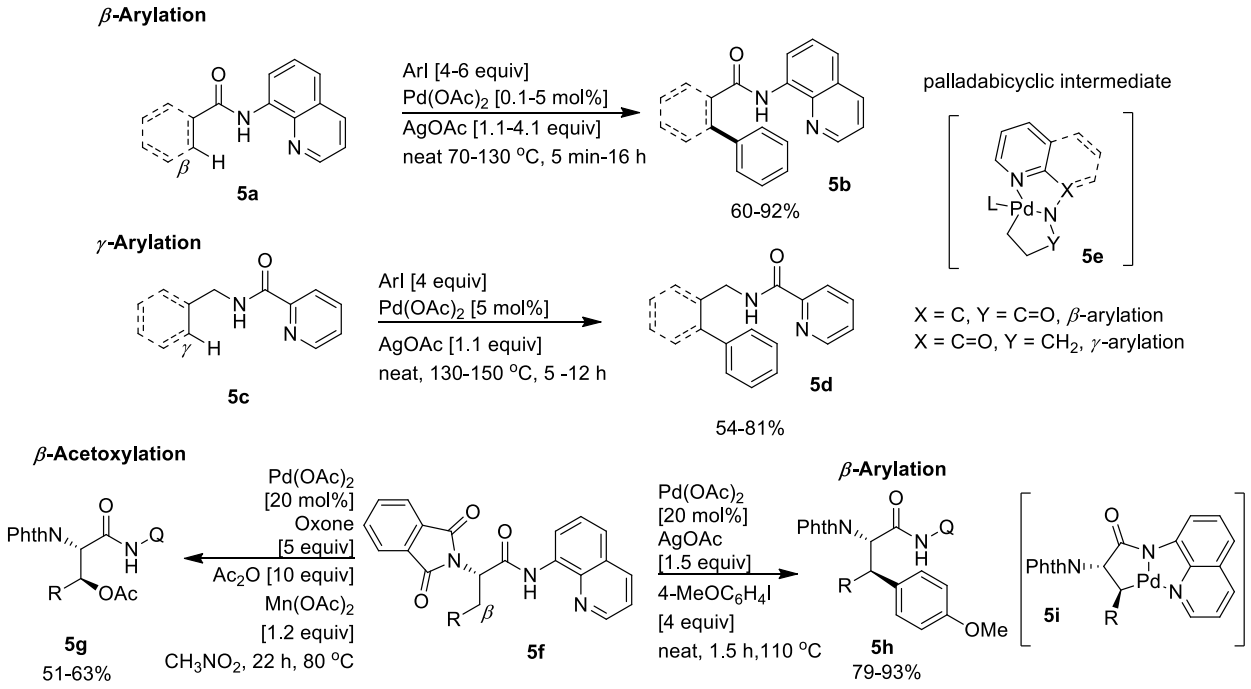


Scheme 4: Directed C-H activation/functionalization approaches for arenes.

The approach that involves the participation of directing groups (DGs) in C-H functionalization has become the most common method for accessing functionalized aromatic and aliphatic compounds *via* chelation-assisted cyclometalation or weak coordination. Initially, this methodology was restricted to only proximal C-H bond activation and allows access to *ortho*-functionalized aromatic compounds only.[6e] Next, the major challenge was to introduce new directing groups that could selectively facilitate the C-H functionalization at other sites. Recently, a significant amount of work has been done to modify or design different types of templates or directing groups that can lead to *meta* or even *para* position C-H bond functionalization in palladium-catalyzed reactions of aromatic compounds (Scheme 4).[6b-d] However directed C-H activation has certain drawbacks because it necessitates the installation of auxiliary prerequisites and the removal of the directing groups following the desired transformations, which adds extra steps to the overall strategy and lessens its step-economic character.

Transient Directing Group Method: In the past few years, the idea of transient directing groups (TDG) has made it possible to complete C-H functionalization in a single phase, by eliminating the need for further directing group installation and removal. It is considered one of the effective strategies because of the reversible *in situ* generations and removal of the DG in a transient manner. On the other hand, this method also has the potential to reduce the number of time-consuming synthetic processes andcan lead to new possibilities for research in synthetic organic chemistry.[6n]

Given the concise background about evolution of the C-H activation strategy, and accessible approaches, some of the literature papers dealing with the directing group assisted C(sp^3)-H activation/functionalization of amino acids and peptides are discussed below. As the major focus of our research is emphasized on the β-C(sp^3)-H functionalization in amino acids and peptides, the relevant literature on C(sp^3)-H functionalization with the bidentate auxiliary 8-AQ is explored in the section below.



Scheme 5: Daugulis and Corey's report on the Pd-catalyzed directing group aided C-H functionalization.

In the year 2005, Daugulis and coworkers[6e] defined the directed C-H bond functionalization, by introducing bidentate directing groups 8-Aminoquinoline & Picolinamide for carboxylic acids

and amines, respectively. The Pd(II)-catalyzed 8-Aminoquinoline directed arylation of the C-(sp^3)-H/C-(sp^2)-H bond of carboxamides with various aryl iodide, lead to the synthesis of β-arylated carboxamide (**5b**). Similarly, Picolinamides also direct the γ-C-(sp^2/sp^3)-Harylation of the aliphatic and aromatic amines, resulted into the γ-arylated amine (**5d**). The formation of a suitable five-membered palladabicyclic intermediate (**5e**) leads to a regioselective C(sp^2/sp^3)-H β- and γ-arylations (Scheme 5). Followed by this report, in the year 2006 Corey and his coworkers[8a] described the first C-C and C-O bond formation in amino acids*via* C-H functionalization approach. The α-amino functionality was protected by a phthaloyl group, while several carboxamide DGs were studied out of which only the 8-aminoquinoline (8-AQ) group, showed promising results for the C-H functionalization. Appropriately protected various amino acids were successfully acetoxylated (**5g**) and arylated (**5h**) at β-position with good diastereoselectivity (up to 99:1). In their report they have indicated that the stereochemistry of the β functionalization may be because of the sterically preferred trans palladabicyclic intermediate (**5i**) in which both R and N-Phthalimide group adapted a trans-orientation (Scheme 5).[8a]

Following the pioneering discovery of bidentate directing group many research groups developed a series of directing groups based on different heteroatoms (N, O, S). And since the breakthrough report of E. J. Corey, various methods using a diversity of directing groups for C-H functionalization of aromatic, alicyclic and aliphatic scaffolds at β and γ positions have been published using a C-terminal or N-terminal DG (Figure 1). A series of non-proteinogenic amino acids were synthesized by using different transition metals and methods which includes arylation,[8] alkylation,[9] alkenylation,[10] alkynylation,[11] acetoxylation,[8a,9d,14] silylation,[12] germylation,[13] halogenation,[15] borylation[16] and amination[17] etc. In this line our group has also introduced a new bidentate directing group ABTD (4-Amino-2,1,3-benzothiadiazole) (**DG-c**) which was found to be excellent for the C-C and C-O bond formation *via* C-H functionalization.[6a] Along with ABTD (**DG-c**), our group has intensively investigated other directing groups aided C-H functionalization of various substrates including C-(sp^2)H and C-(sp^3)H bonds. In this section, I have outlined some of our group's contributions toward the activation of a prochiral C-H bond of alicyclic and aliphatic molecules in a highly diastereoselective manner (Scheme 6).

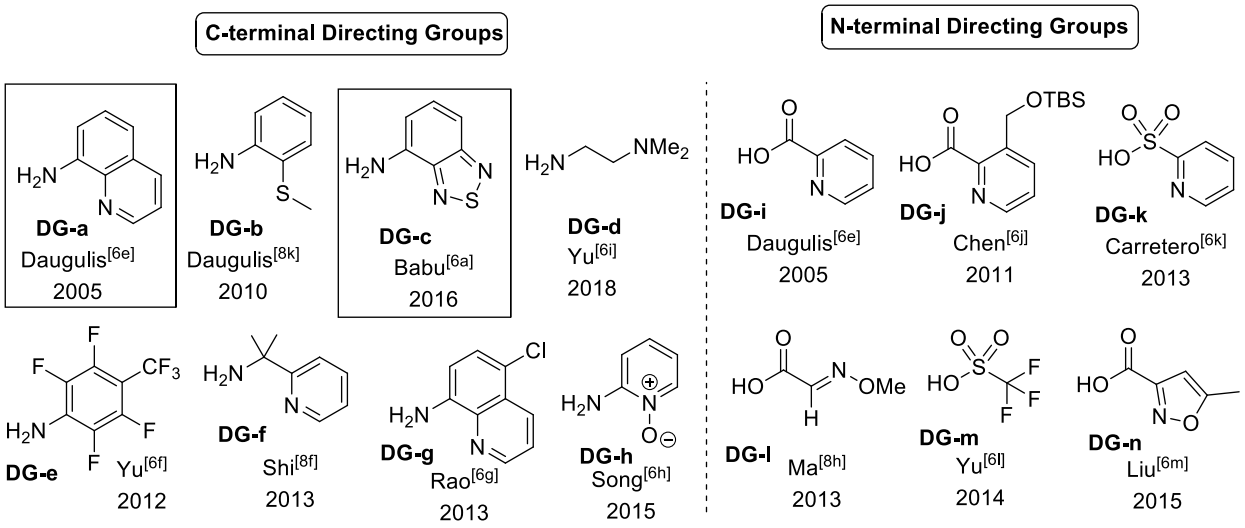
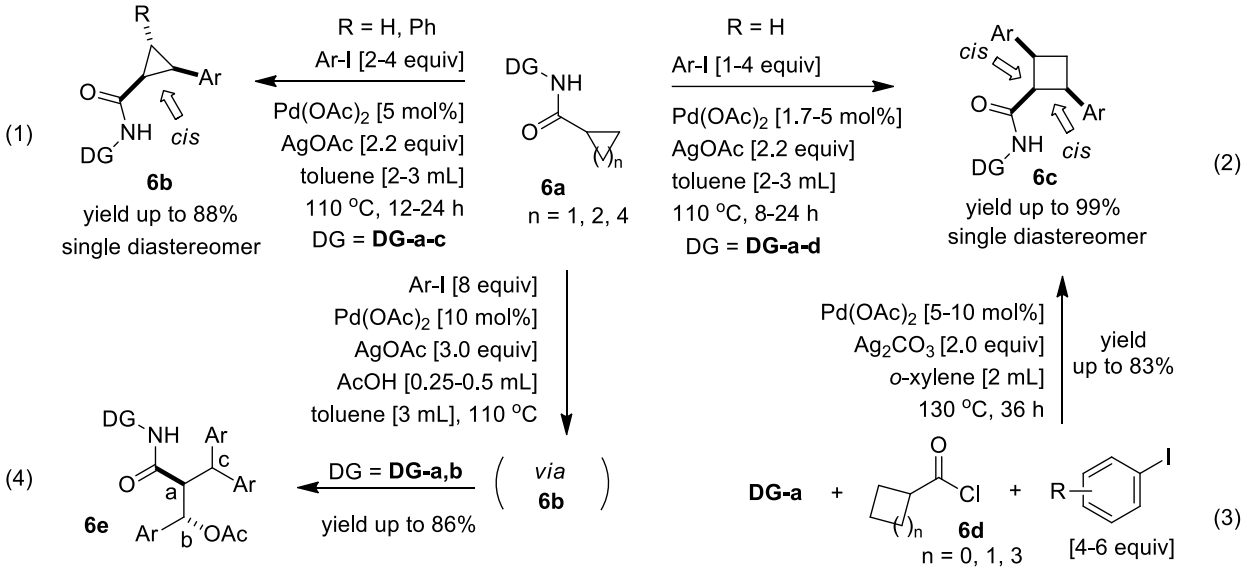


Figure 1: List of directing groups used for C-H functionalization.

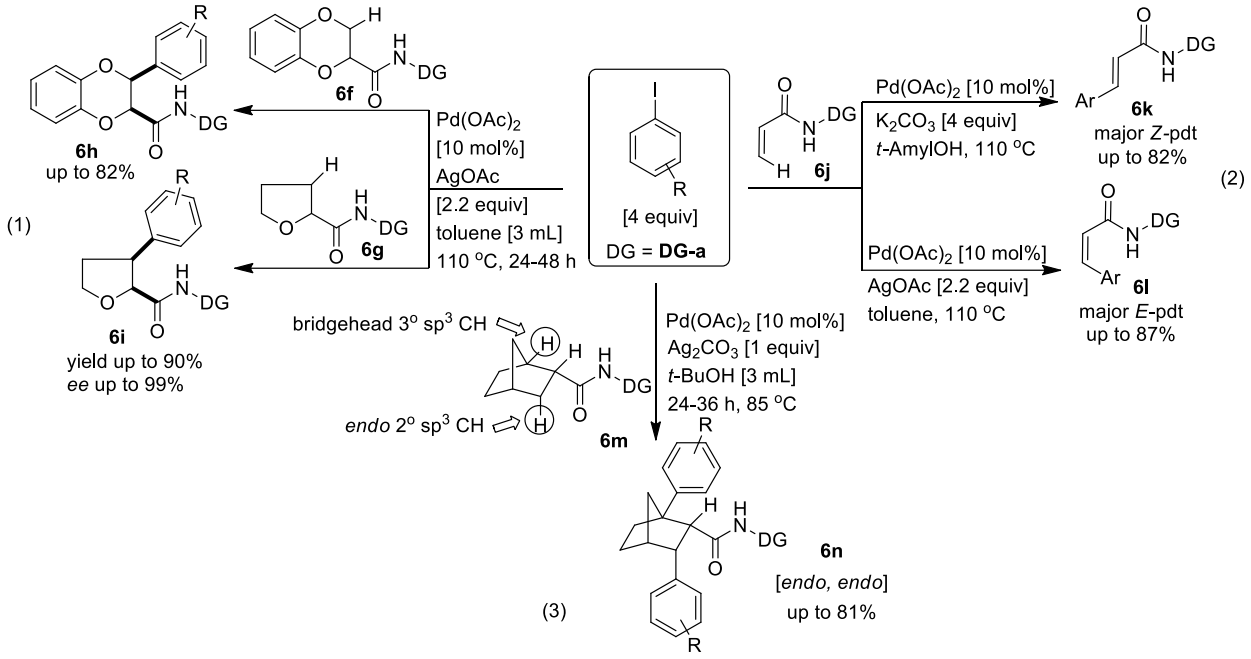
In the year 2013, our group[7a] has reported directing group (**DG-a,b**) aided C(sp^3)-H arylation of cyclopropanes in highly diastereoselective mode and constructed novel di- and trisubstituted cyclopropanecarboxamides (**6b**) with contiguous stereocenters (eq 1, Scheme 6a). Following that in same year, we have further explored this methodology for double C-H activationin cyclobutene carboxamides and directly access to the three contiguous stereocenters with all-*cis* stereochemistry (**6c**). We have screened different directing groups (**DG-a,b,d**) for having bis-arylation in cyclobutane with a high degree of stereo- and regiocontrol (eq 2, Scheme 6a).[7b] In 2016, using our directing group 4-amino-2,1,3-benzothiadiazole (ABTD) (**DG-c**), we have demonstrated the Pd/Ag catalytic system-based C-H bond functionalization of various substrates including alicyclic carboxamides (**6a**).In this report, diastereoselective arylation of alicyclic carboxamides (**6a**) were shown with remarkable diastereoselectivity and favored the formation of the only *cis*-diastereomers (**6b,c**) (eq 1,2, Scheme 6a).[6a] In the same year, we have described a multicomponent reaction in the one-pot process that involves the installation of a bidentate directing group (**DG-a,b**), followed by Pd(II)-catalyzed *β*-C-(sp^3)-H arylation in a diastereoselective manner. We have developed a set of optimal reaction conditions, which includes an appropriate alicyclic acid chloride (**6d**) and aryl iodide, directing group (**DG-a** or **DG-b**), catalyst $Pd(OAc)_2$, and additive Ag_2CO_3 in *o*-xylene resulting in *cis* arylated alicyclic carboxamides (**6b,c**) (eq 3, Scheme 6a).[7c] Subsequently, we have also described the construction of three new C-C bonds and one new C-O bond formation within a single diastereoselective

Pd(II) catalyzed C-H functionalization reaction. In this report our group have synthesized *anti*-β-acyloxy carboxamide derivatives (**6e**) *via* C-(sp^3)-H arylation of cyclopropane carboxamides followed by ring opening of arylated carboxamide (**6b**) (eq 4, Scheme 6a).[7d]



Scheme 6a: Our group reports on the Pd-catalyzed DG aided C-H functionalization in diastereoselective manner.

In the year 2015, our group[7e] reported an efficient protocol for the synthesis of analogues of neolignan (**6h**) and norlignans (**6i**) with *cis* stereochemistry and upto 99% enantiomeric excess. In this article, we have reported the direct arylation at the C3 position of 1,4-benzodioxane (**6f**) and tetrahydrofuran (racemic and enantiopure) systems (**6g**). The optimized reaction condition includes 4.0 equiv of aryl halide, 10 mol% of $Pd(OAc)_2$, 2.2 equiv of AgOAc in toluene at 110 ^oC for 24-48h (eq 1, Scheme 6b). In the year 2015, our group[7f]reported the synthesis of β-arylated Z-cinnamamide scaffolds (**6k**) through β-C(sp^2)-H activation/functionalization in stereo- and regioselective manner. In this report, selective synthesis of *Z*- and *E*-cinnamamide compounds **6k,l** was also shown by tuning the reaction conditions (eq 2, Scheme 6b). In the year 2014, we described an exceptional C-C bond formation at the most interesting bridgehead carbon of the norbornane molecule **6m** *via* tertiary C(sp^3)-H bond activation and arylation. In this article along with tertiary (*endo*), a secondary C(sp^3)-H bond (*endo*)was also functionalized in highly diastereoselective manner under the Pd/Ag catalysis and 8-aminoqinoline (**DG-a**) auxiliary assistance (eq 3, Scheme 6b).[7g]



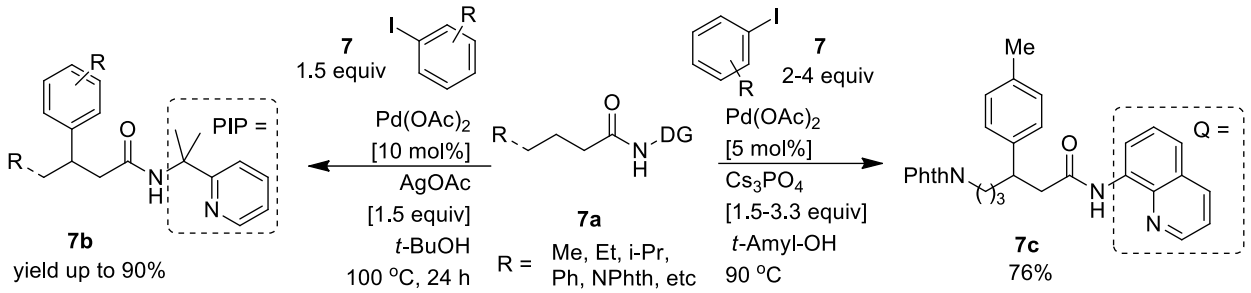
Scheme 6b: Our group reports on the Pd-catalyzed DG aided C-H functionalization in diastereoselective manner.

Therefore, it is a very interesting technique to consider the prospect of directly introducing novel functionality, such as C-C and C-X bonds, through direct and selective C-H bond transformation. In this chapter, primarily the arylation reports are presented, as the main focus of the thesis is construction of arylated α, non-α-amino acid and peptide carboxamides having 8-aminoquinoline as a directing group.

Literature reports dealing with the representative examples of C(sp^3)-H arylation of non-α-amino acid carboxamides:

In the year 2010, Daugulis's group[8k] established an efficient protocol for the silver-free, β-arylation of sp^3 and sp^2 C-H bonds with a removable bidentate directing group (8-aminoquinoline and 2-methylthioaniline). The reaction conditions could tolerate a broad range of substrate scope bearing primary and secondary C-H bonds. Whereas, in the case of amide-based substrates such as 6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide, they developed a set of optimal reaction conditions, which includes 2-4 equiv of aryl iodide, 5 mol% of $Pd(OAc)_2$, 1.5-3.3 equiv of base Cs_3PO_4 in t-Amyl-OH at 90 °C resulting into 76% yield of β-arylated ε-aminohexanoic acid derivative (**7c**).In the year 2014, Shi's group[8l] introduced a new directing

group derived from 2-(pyridine-2-yl)isopropylamine (PIP-amine), for Pd(II)-catalyzed arylation in aliphatic amides (**7a**). Broad structural versatility in both the coupling partners such as aliphatic amide (**7a**) and aryl halide (**7**) has shown while in the case of amides various functional groups such as halogens, Phth and indolyl-protected amine were well tolerated in the reaction conditions. Optimized reaction condition includes 1.5 equiv of aryl halide, 10 mol% of $Pd(OAc)_2$, 1.5-2.5 equiv of base in *t*-BuOH at 100-120 ^oC for 24 h (Scheme 7).



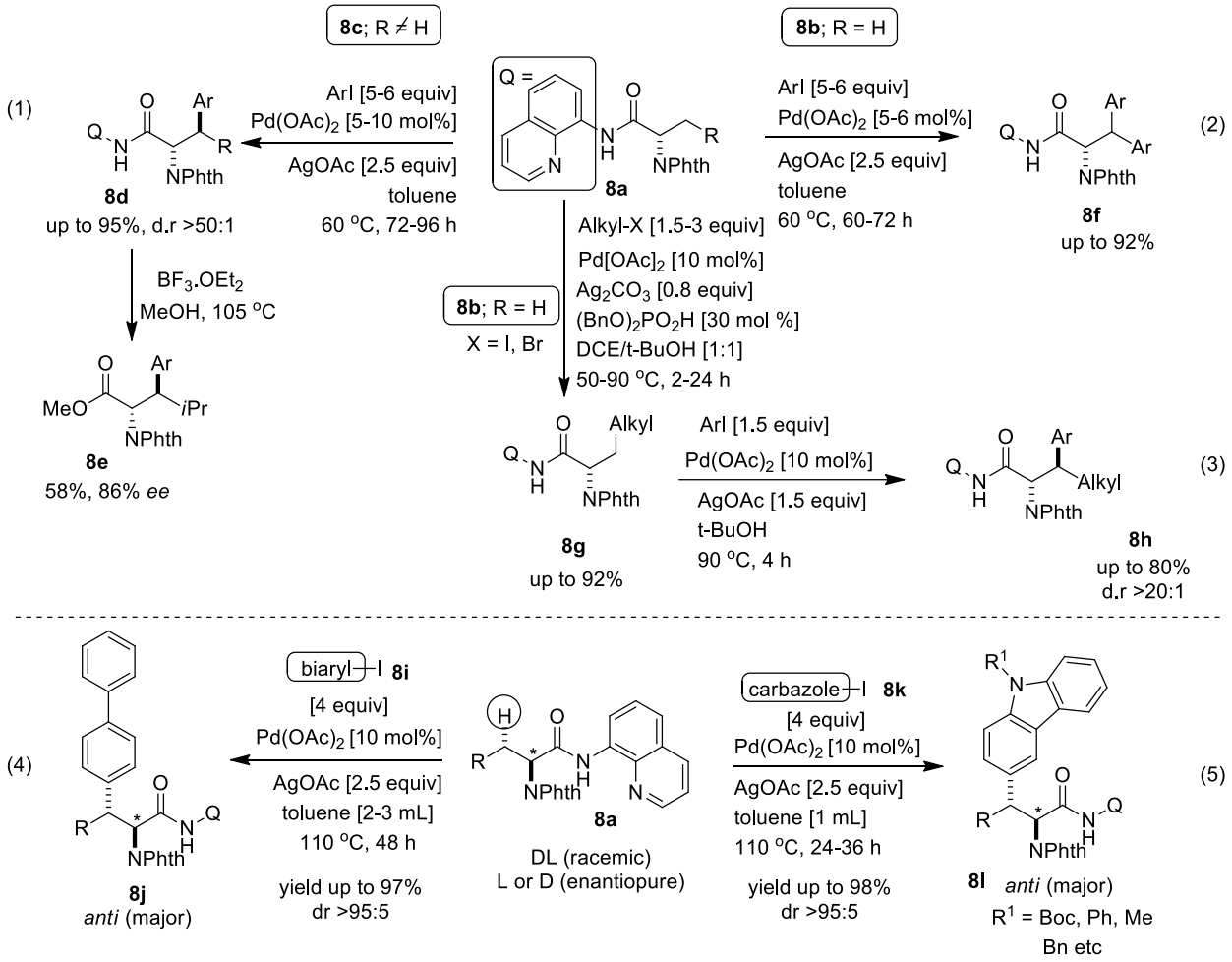
Scheme 7. Pd-catalyzed β-C(sp^3)-H arylation of non-α-amino acid carboxamides with different directing groups.

Selective literature reports dealing with the representative examples of diastereoselective C(sp^3)-H arylation of α-amino acid carboxamides:

In 2012, Daugulis and co-workers[8d] reported the diarylation of 1^oβ-C-(sp^3)-H in alanine derived amides (**8b**) and the diastereoselective monoarylation of 2^oβ-C-(sp^3)-H bonds in α-amino acids (**8c**) in the presence of 8-aminoquinoline as a directing group. The arylation of methylene groups is remarkably diastereoselective and favored the formation of the *anti*-diastereomers. For the arylation of the methylene group selected amino acid was phenylalanine, lysine and leucine (**8c**), in all the cases good diastereoselectivity was observed. Further, hydrolysis of leucine derivatives in the presence of $BF_3{\cdot}Et_2O$ in MeOH at 105^{o}C gave the ester derivatives **8e** with 58% yield and 86% enantiomeric excess (eq. 1, Scheme 8). On the other hand, arylation of alanine carboxamides **8b** occurred with aryl iodide in the presence of $Pd(OAc)_2$ (5-6 mol%) and AgOAc (2.5 equiv) in toluene at 60 ^oC for 60-72 h offered the diarylation with upto 92% yield (eq. 2, Scheme 8).

In the year 2013, Shi and coworkers[9c] are the first one to set a pathway for the alkylation of C(sp^3)-H bond in amino acids. In this report, first they developed the reaction condition for the

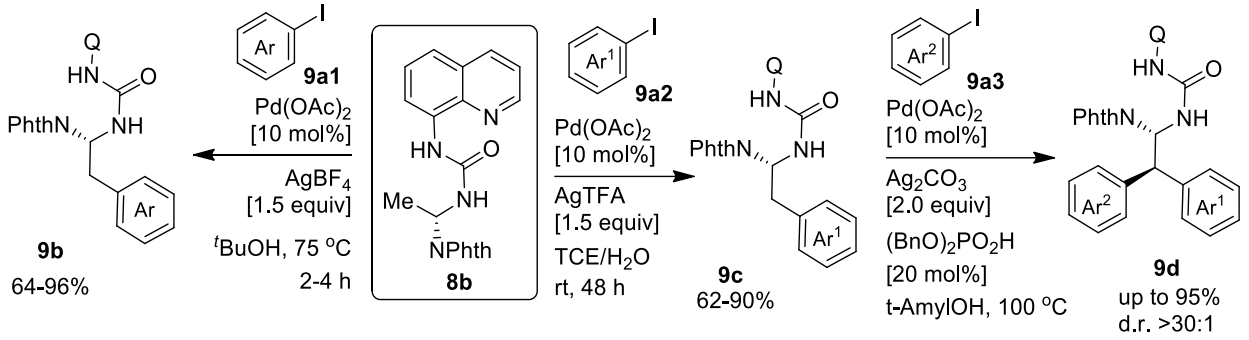
alkylation in alanine carboxamide **8b** with alkyl iodide, and the alkylation was possible with alkyl bromide as well. Following the alkylation further **8g** was treated with a number of different aryl iodides and β-branched α-amino acids (**8h**) were synthesized. In the same year, Chen's group[8j] also synthesize the β-alkylated α-amino acids (**8h**) by a series of sequential functionalizations of C(sp^3)-H bonds *via* palladium-catalyzed alkylation (eq. 3, Scheme 8).



Scheme 8: C(sp^3)-H arylation of α-amino acids carboxamides using different aryl halides as the coupling partners.

In this context of Pd-catalyzed β-C(sp^3)-H arylation of amino acids our group have also contributed for the diastereoselective construction of non-proteinogenic amino acid. These works revealed the synthesis of biaryl[8m] (**8j**) and carbazole[8n] (**8l**) containing racemic as well as enantiopure unnatural amino acid derivatives *via* bidentate directing group aided Pd-catalyzed β-C(sp^3)-H arylation. In these reports several DL-, L-, and D-amino acid derivatives were synthesized with biaryl and carbazole motifs, such as phenylalanine, leucine, norleucine,

norvaline and 2-amino octanoic acid with *anti*-stereochemistry (major isomers). Apart from α-amino acids, varieties of the short, medium and long chain-based aminoalkanoic acids were also subjected to the β-C(sp^3)-H arylation with iodo biaryl (eq. 4, Scheme 8) and iodo carbazole (eq. 5, Scheme 8) in the respective reports. To extend the practical applicability of these bioactive moieties containing amino acids, removal of the directing group and phthalimide group were also demonstrated in various arylated products (Scheme 8).



Scheme 9: Pd-catalyzed selective monoarylation onβ-methyl group of alanine.

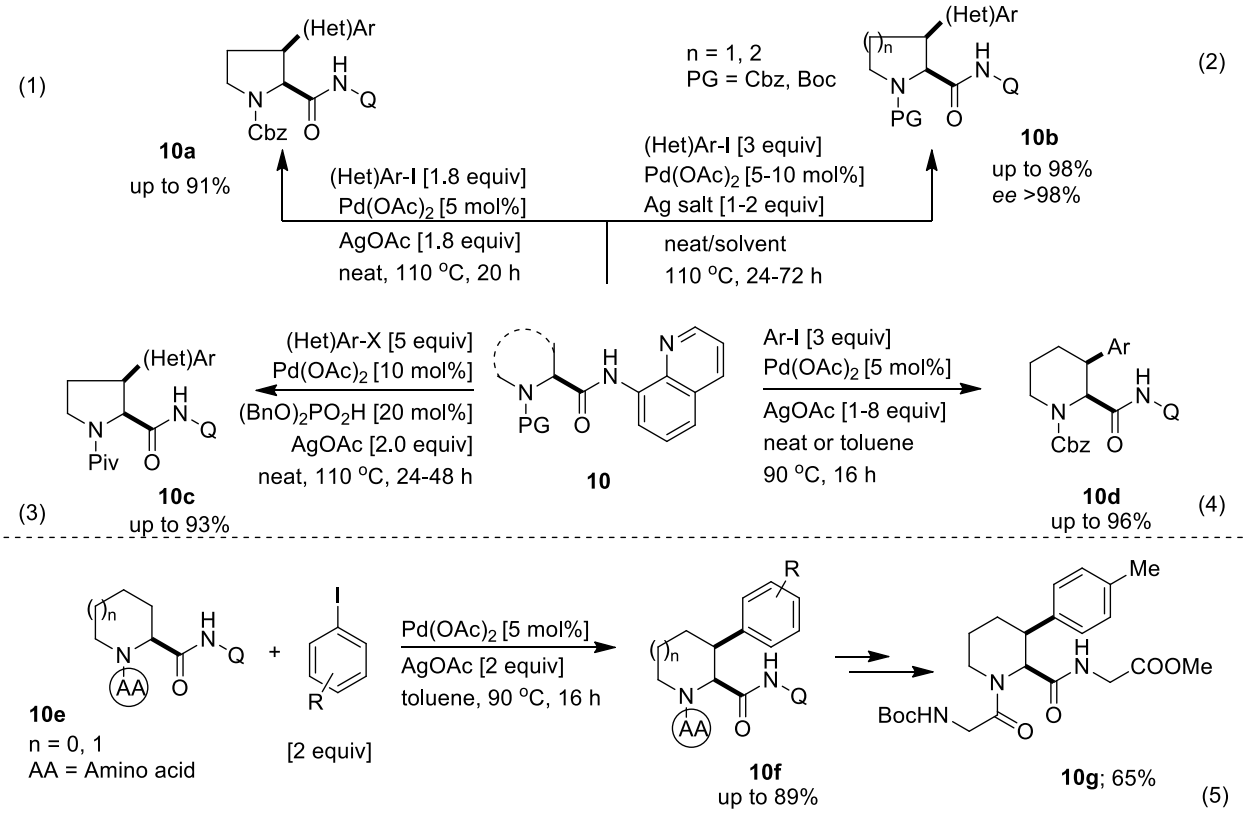
In all the aforementioned reports selectively monoarylation on alanine carboxamides (**8b**) couldn't be accomplished with the 8-aminoquinoline auxillary. Following this limitation, in 2014 Shi and co-workers[18a] developed an optimized reaction condition for selective monoarylation on methyl C-(sp^3)-H bond ofalanine carboxamide derivatives. In this protocol, $AgBF_4$ was used as a halide scavenger and the chirality of monoarylated amino acid (**9b**) was also retained upto 99%. In the same year, Chen's group[8g] also described the synthesis of mono-arylation in α-amino acids at room temperature. The arylation reaction afforded the β-arylated amino acid derivatives (**9c**), and the optimal reaction condition involved the $Pd(OAc)_2$ (10 mol%) and AgTFA (1.5 equiv) in a biphasic mixture of 1,1,2,2-tetrachloroethane (TCE)/H_2O at rt for two days. Further, with the excellent diastereoselectivity hetero-diarylation (**9d** was additionally provided by employing several aryl iodides and reaction conditions (Scheme 9).

Literature reports dealing with the representative examples of diastereoselective C(sp^3)-H arylation of cyclic amino acid carboxamides and respective peptides:

In the year 2014, Bull's team[18b] disclosed the β-C-(sp^3)-H arylation in proline-based carboxamides and directly obtained a single stereoisomer of *cis*-2,3-disubstituted pyrrolidines

(**10a**). The reaction proceeds *via* a solvent-free pathway in combination with 5 mol% of $Pd(OAc)_2$ and 1.8 equiv of AgOAc (eq 1, Scheme 10). Following this report, in the year 2016, the same group[18c] disclosed the efficient synthesis of arylated pyrrolidines, piperidines along with other saturated heterocyclic compounds withan excellent enantiomeric excess (**10b**). In this report, multiple reaction conditions were screened for all the heterocyclic substrates with different protecting groups (Cbz or Boc). In the case of Boc protected substrates (pyrrolidine/piperidines) an additive PivOH was also needed along with the optimized reaction conditions (eq 2, Scheme 10). In the year 2015, Zhang's group[18d] demonstrated the Pd-catalyzed straightforward arylation of pivalamide protecting proline carboxamides with aryl iodide and bromides. The optimal reaction conditions involve 5.0 equiv of Ar(Het)-halide,10 mol% of $Pd(OAc)_2$, 2.0 equiv of AgOAc and 20 mol% of $(BnO)_2PO_2H$. In addition to aryl halides, other coupling partners like vinyl iodide and α-bromoacetate were also screened with minimal different reaction conditions for the C(sp^3)-H alkenylation and alkylation (eq 3, Scheme 10). In the year 2016, Cao and Wu group[18e] efficiently access the C3 arylated L-Pipecolic acid (**10d**) derivatives *via* Pd-catalyzed, 8-AQ assisted β-C-(sp^3)-H arylation method. To show the generality of the reaction apart from arylation, C(sp^3)-H acyloxylation and alkoxylation were also demonstrated by the group (eq 4, Scheme 10).

In the year 2016, Kazmaier and his co-workers[8b] revealed an interesting strategy for the stereoselective late-stage modification of di and tripeptides *via* β-C-(sp^3)-H arylation having 8-AQ as a directing group. For the peptide synthesis multiple natural or unnatural amino acids like proline, pipecolic, alanine, leucine, valine, glycine, and isoleucine were included (**10e**). During the reaction chirality of all the stereogenic centers in arylated di or tripeptides (**10f**) was retained and the optimal reaction condition includes 2 equiv aryl/heteroaryl halides, 5 mol% $Pd(OAc)_2$ and 2 equiv of AgOAc in toluene at 90 ^oC for 16 h. To show the synthetic efficacy of the reaction, the directing group was removed after arylation and additional amino acid was introduced at C-terminal for the prolongation of peptide chain (**10g**) (eq 5, Scheme 10).



Scheme 10: Stereoselective C-(sp^3)-H arylation of cyclic-amino acids, dipeptide and tripeptide carboxamides using aryl halides as the coupling partners.

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CHAPTER 2

Bidentate directing group aided Pd-catalyzed *β*-C(sp^3)-H arylation of unnatural amino acids and synthesis of pyrrolidinone derivatives.

This part of the Thesis work viz. Chapter 2 has been re-used (adapted) with permission from the publication, Tomar, R.; Bhattacharya, D.; Babu, S. A. *Tetrahedron*, **2019**, *75*, 2447-2465 (https://doi.org/10.1016/j.tet.2019.03.018.). Title: Assembling of medium/long chain-based *β*-arylated unnatural amino acid derivatives *via* the Pd(II)-catalyzed sp^3 *β*-C-H arylation and a short route for rolipram-type derivatives.

Proteinogenic *α*-amino acids are indispensable small molecules of life[1] and non-proteinogenic or unnatural amino acids are those not encoded and discovered in any organism. Markedly, numerous unnatural amino acids and their derivatives have also received extensive attention in various fields. In particular, unnatural amino acids are sought after by the pharmaceutical industry for their promising biological properties.[2,3] Apart from natural and unnatural *α*-amino acid derivatives, some short/medium chain-basedaminoalkanoic acids (non-*α*-amino acids) containing an amino group at the *β*- or *γ*- or *δ*-position have also been found in organisms.[4-7] For examples; (a) *β*-alanine (**1a**) is produced by aspartate 1-decarboxylase and a precursor to coenzyme A,[4] (b) *γ*-aminobutyric acid (**1d**, GABA) is an inhibitory neurotransmitter in animals,[5] (c) *δ*-aminolevulinic acid (**1b**) is an intermediate in the tetrapyrrole biosynthesis pathway[6] and (d) 4-aminobenzoic acid (**1c**, PABA) is an intermediate in the folate biosynthesis pathway[7] (Figure 1).

Various short/medium chain-based aminoalkanoic acids (non-*α*-amino acids) possessing an aryl group at the *β*-position are noteworthy small molecules and they display valuable pharmacological properties (Figure 1).[8-13] Firstly, *γ*-aminobutyric acid (**1d**, GABA) and especially, various *β*-arylated derivatives of GABA (e.g., **2a-d**) are used as drug molecules in treating various central nervous system (CNS) disorders. Some of them are used as anticonvulsant, sedative and anxiolytic, analgesic, tranquilizing agents (e.g., baclofen (**2a**),[9] phenibut (**2b**)[10] and tolibut (**2c**)[11]). Along this line, some piracetam-based GABA derivatives are also used as drug molecules. E.g., Phenotropil (phenylpiracetam)[12] is known to exhibit antidepressant, anticonvulsant, anxiolytic effects and similarly, rolipram (**2d**)[13] is an

antidepressant agent. Next, some β-arylated δ-aminopentanoic acid derivatives (e.g., homobaclofen derivative **3**) have been found with pharmacological activity (e.g., $GABA_B$-agonistic activity).[14] Next, β-arylated ε-aminohexanoic acid derivative **4** was used as a starting material to assemble various bioactive benzazepinones.[15] Given their importance, various classical and multistep synthetic procedures have been used to construct short/medium chain-based aminoalkanoic acids (non-α-amino acids) possessing an aryl group at the β-position.[8-15]

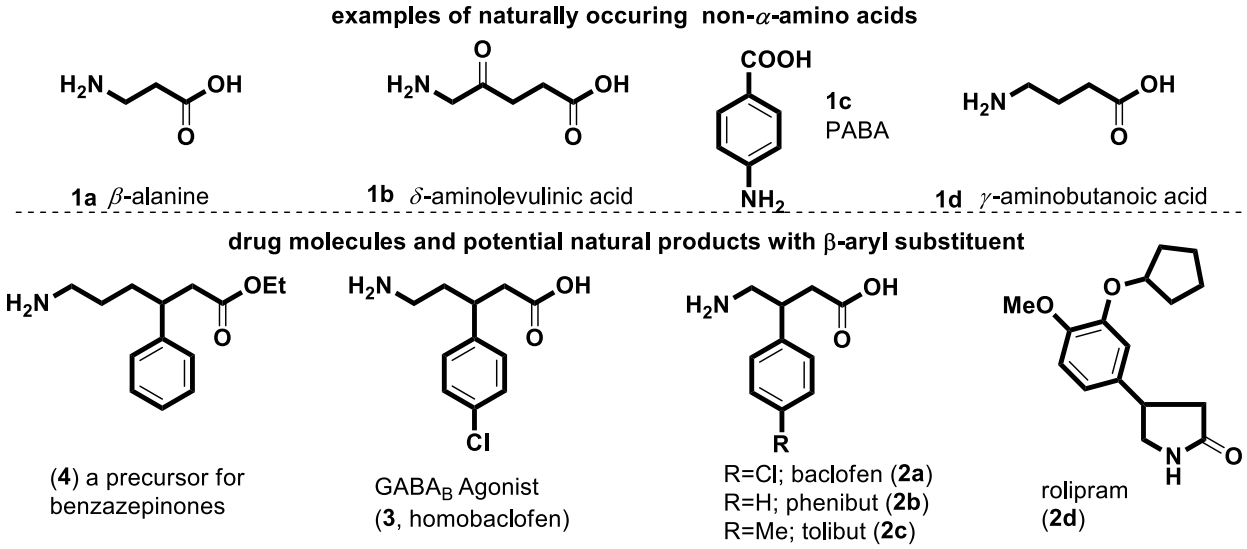
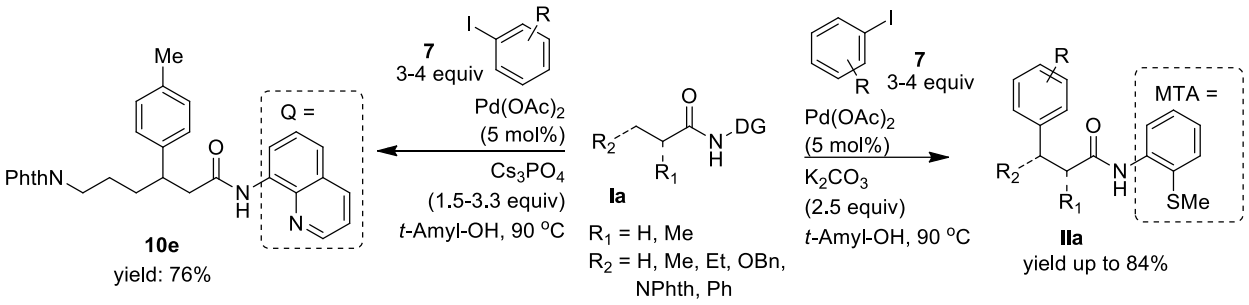


Figure 1. Examples of drug molecules and bioactive compounds with β-aryl substituent and naturally occuring non-α-amino acids.

Numerous reports are published in the context of Pd-catalyzed, auxiliary-directed, β-arylation and alkylation of sp^3 and sp^2 C-H bonds in carboxylic acid derivatives using aryl halides and other coupling partners.[16-18] Considerable attention was not paid towards the β-C(sp^3)-H arylation of medium/long chain-based aminoalkanoic acids (non-α-amino acids). Only few reports dealing with the short/medium chain-based aminoalkanoic acids (non-α-amino acids) exist till date, which includes substrates like γ-aminobutyric acid (**1d**) and ε-aminohexanoic acid (**1f**). [22,23]

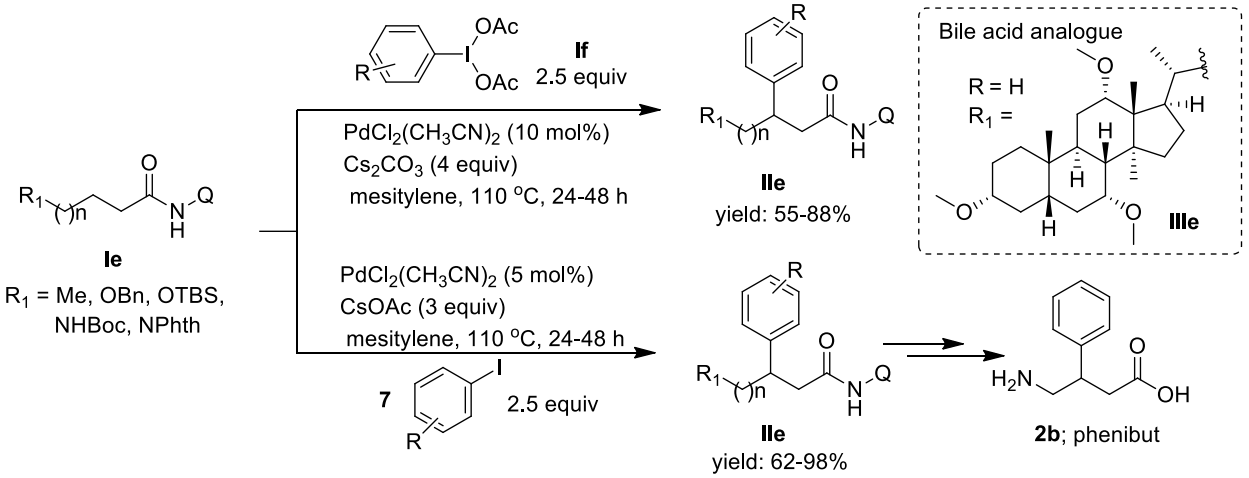
In the year 2010, Daugulis's group[19b] developed an efficient protocol for the silver free, β-arylation of sp^3 and sp^2 C-H bonds with a removable bidentate directing group (8-aminoquinoline and 2-methylthioaniline). The reaction conditions could tolerate a broad range of substrate scope bearing primary and secondary C-H bonds. The substrate ε-aminohexanoic acid (**1f**) is shown as a compatible substrate with the developed arylation condition. Whereas, in case

of amide based substrates such as 6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide, they developed a set of optimal reaction condition, which includes 2-4 equiv of aryl iodide, 5 mol% of $Pd(OAc)_2$, 1.5-3.3 equiv of base Cs_3PO_4 in t-Amyl-OH at 90 °C resulting into 76% yield of *β*-arylated *ε*-aminohexanoic acid derivative (**10e**).



Scheme 1a. Pd-catalyzed *β*-C(sp^3)-H bond activation of aliphatic carboxamides with different directing groups.

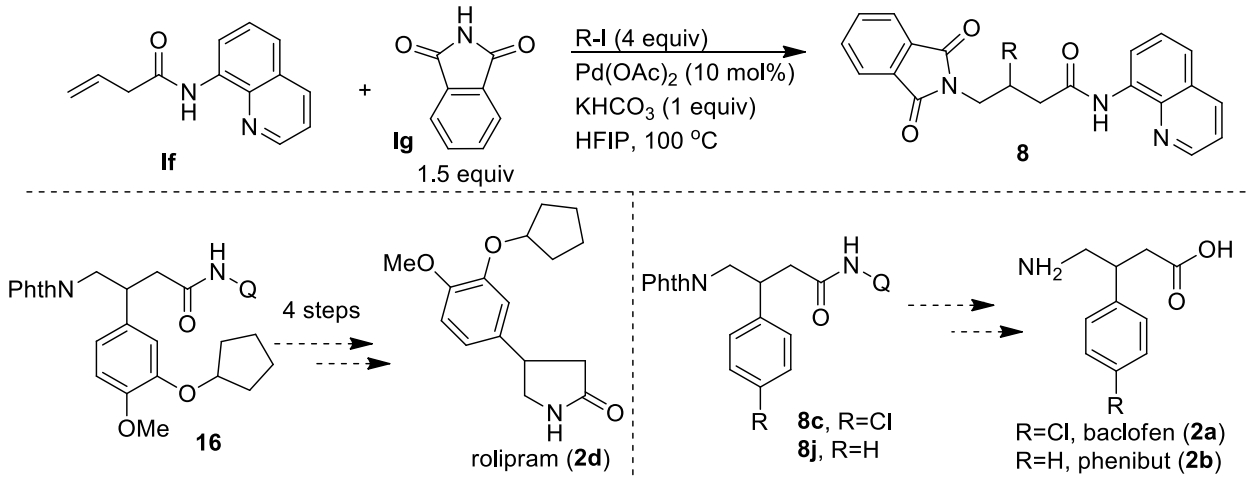
In the year 2015, Qin's team[22c] disclosed the 8-aminoquinoline directed, Pd-catalyzed *β*-C(sp^3)-H bond arylation of carboxylic acid derivatives (**Ie**). It is well known in the literature that, (diacetoxyiodo)arenes has been used as an acetoxylation reagent, herein for the first time they employed the (diacetoxyiodo)arene (**If**) as the arylating coupling partner to produce a wide variety of *β*-arylated *α*-amino or *γ*-amino acid derivatives. In the reaction condition, Cs_2CO_3 played a major role in unusual shifting of the reactivity of (diacetoxyiodo)arenes from acetoxylation to arylation.



Scheme 1b. Pd-catalyzed *β*-C(sp^3)-H bond activation of aliphatic carboxamides with different coupling partners.

Following this report, in the year 2017, the same group[22b] described a practical approach for the synthesis of *β*-arylated carboxylic acid derivatives (**IIe**), *via* Pd-catalyzed, CsOAc promoted arylation of C(sp^3)-H bond using aryl iodide (**7**) as a coupling partner. And the utility of both the methods was illustrated by the successful transformation of arylated product into bile acid analogue (**IIIe**) and phenibut **2b** (psychotropic drug) (Scheme 1b).

In 2017, Engle and co-workers[22d] revealed the regiocontrolled three-component carboamination reaction of 3-butenoic acid derivatives (**If**) *via* a Pd(II)/Pd(IV) catalytic cycle. To control the regioselectivity, bidentate 8-aminoquinoline directing group was employed and for the practical utility of the methodology, they have successfully synthesized a number of commercially available drug molecules and bioactive compounds bearing *γ*-lactams (**2d**) and *γ*-amino acids (**2a,b**) as core structure (Scheme 1c).



Scheme 1c. Pd-catalyzed intermolecular carboamination reactions and further transformations.

Theme of this work:

Given the importance of various short/medium/long chain-based aminoalkanoic acid (non-*α*-amino acid) derivatives, especially possessing an aryl group at the *β*-position with promising therapeutic properties, it will be useful to enrich the libraries of short/medium/long chain-based aminoalkanoic acid derivatives. Accordingly, in continuation of our interest on the C-H activation reactions, herein we report the sp^3*β*-C-H arylation of various aminoalkanoic acids (non-*α*-amino acids). We have paid an inclusive attention to assemble/enrich the libraries of different *β*-arylated aminoalkanoic acid (non-*α*-amino acid) and rolipram-type derivatives. While there have been a few attempts of synthesis of *β*-arylated *γ*-aminobutyric acid and *ε*-aminohexanoic acid derivatives *via* the *β*-C-H arylation, we have added some more examples to

their corresponding libraries and it was necessary to prepare different examples of β-arylated γ-aminobutyric acid derivatives to attempt a short route for assembling rolipram and related derivatives.

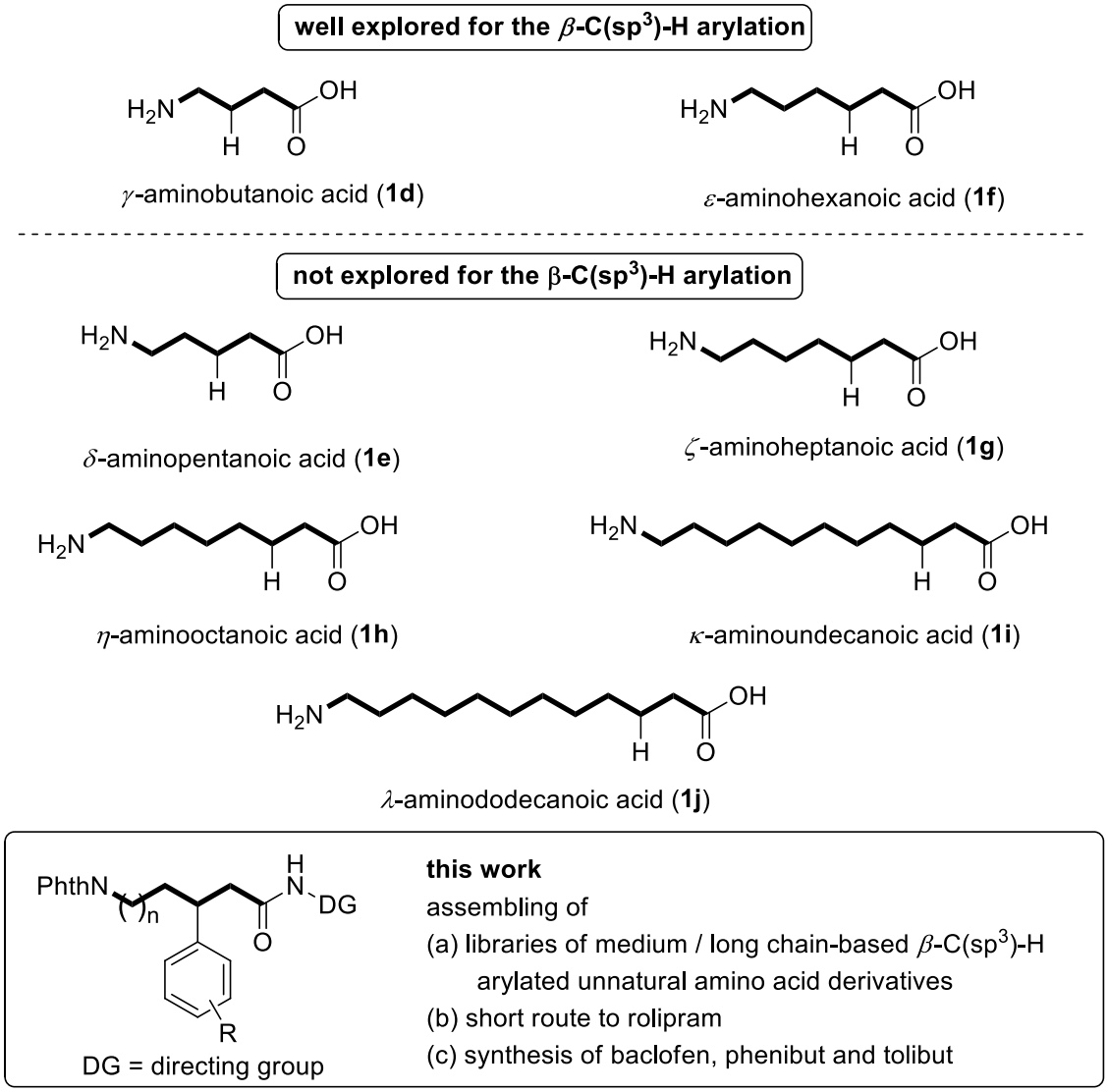
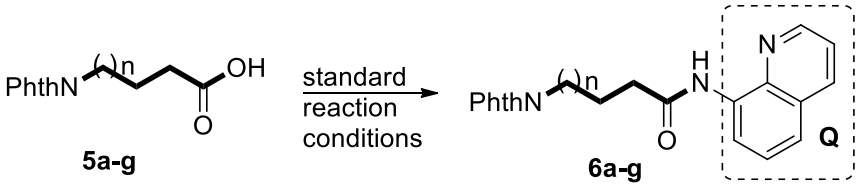


Figure 2. β-Arylated **s**hort/medium/long chain-basednon-α-amino acid derivatives.

Results and Discussion

To begin the assembling of β-C-H arylated medium/long chain-based aminoalkanoic acids (non-α-amino acids) derivatives *via* the Pd(II)-catalyzed, directing group-aided β-C-H arylation, initially we prepared the required starting materials **6a-g** possessing the directing group 8-aminoquinoline from their corresponding *N*-protected aminoalkanoic acids **5a-g** (Scheme 1d). Though a few reaction conditions of sp^3β-C-H arylation involving γ-aminobutyric acid and ε-

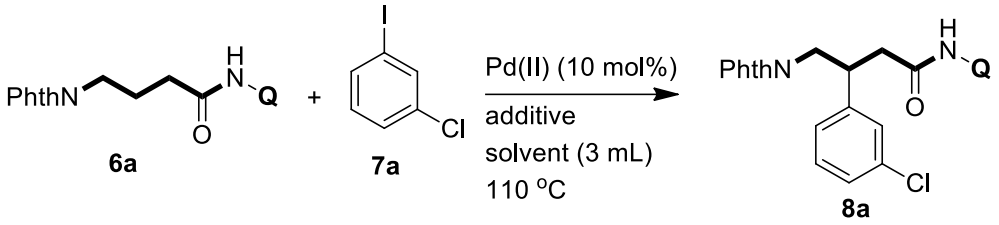
aminohexanoic acid derivatives have been already reported under different reaction conditions,[22,23] in order to get the best reaction condition in our hand, we performed some optimization reactions using different Pd catalysts, additives and solvents (Table 1). At first, we heated a mixture of substrate **6a**, ArI (**7a**) and $Pd(OAc)_2$ catalyst (10 mol%) in the absence of any additive at 110 ^oC for 24 h and this reaction did not afford the *β*-C-H arylated product **8a** (entry 1, Table 1). Next, the same reaction was carried out in the presence of only AgOAc without any Pd(II) catalyst and this reaction also did not afford the *β*-C-H arylated product **8a** (entry 2, Table 1). Typically, the bidentate directing group 8-aminoquinoline-aided *β*-C-H arylation of carboxamides have been performed using the Pd(II) catalyst and also an additive (e.g., AgOAc or Ag_2CO_3 or K_2CO_3), which will help as a halide ion scavenger and to regenerate the palladium (II) catalyst in the catalytic cycle.[18-20] Accordingly, next we heated a mixture of substrate **6a**, ArI (**7a**, 4-5 equiv), $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive in toluene at 110 ^oC for 24 h. This reaction afforded the *β*-C-H arylated *γ*-aminobutyric acid (GABA) derivative **8a** in 70-89% yields (entries 3 and 4, Table 1). The Pd(II)-catalyzed arylation of **6a** with **7a** in the presence of AgOAc in ^{t}AmylOH instead of toluene also afforded the product **8a** in 83% yield (entry 5, Table 1). Then, we performed the arylation of **6a** using different palladium catalysts, which also afforded the *β*-C-H arylated derivative **8a** in 50-88% yields (entries 6-8, Table 1). The Pd(II)-catalyzed arylation of **6a** was also performed using different additives (entries 9-14, Table 1). The reactions involving Ag_2CO_3 orNa_2CO_3 as an additive only were fruitful and the product 8a was obtained in 77 and 28% yields, respectively. We also performed the Pd(II)-catalyzed arylation of 6a using 4-bromotoluene or 4-chlorotoluene, which were not fruitful (entries 15-18, Table 1).



a; n=1, **b**; n=2, **c**; n=3, **d**; n=4, **e**; n=5, **f**; n=8, **g**; n=9

Scheme 1d. Preparation of short/medium/long chain-based non-*α*-amino acid derivatives linked with the directing group.

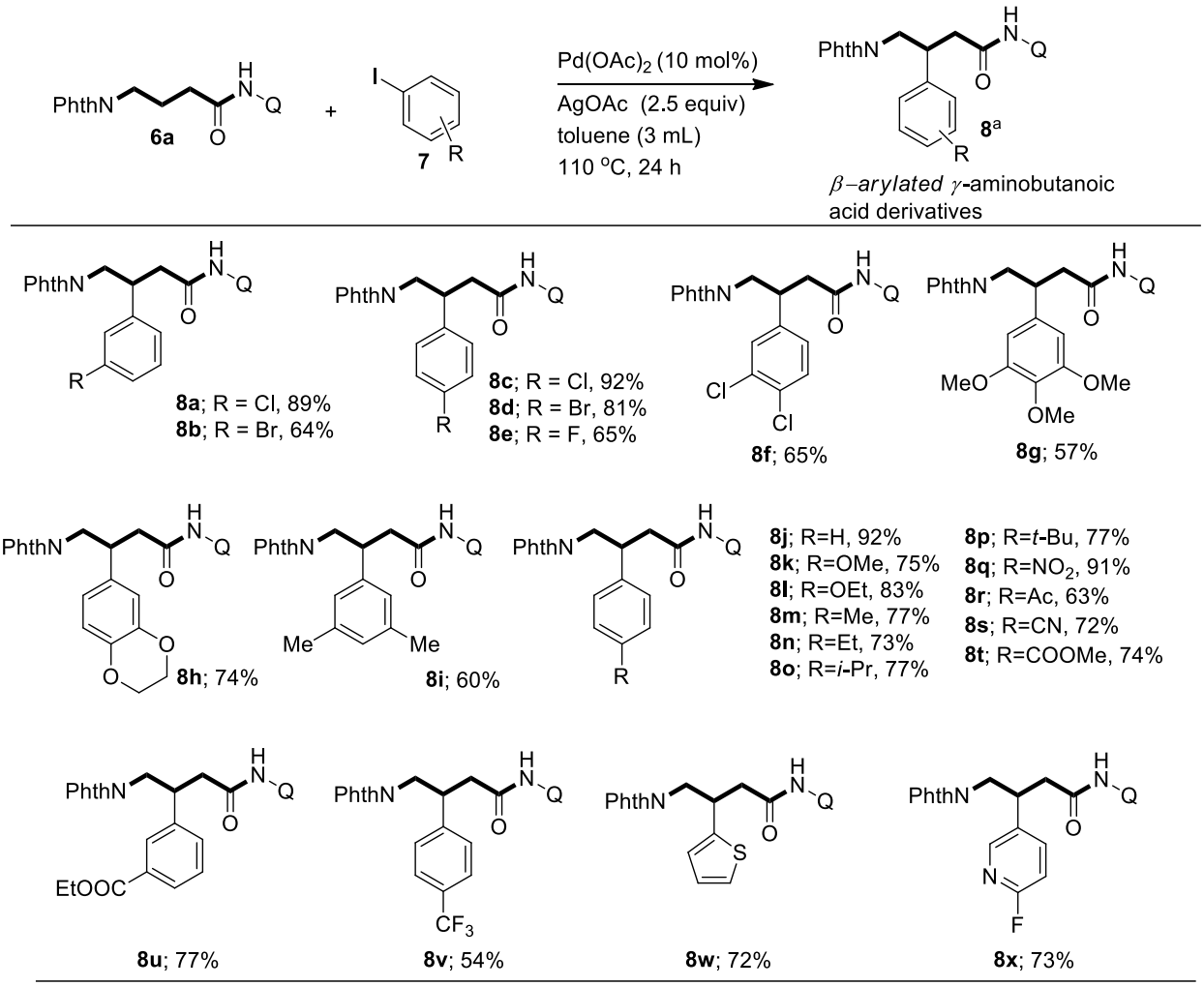
Table 1. Optimization Reactions. Pd(II)-catalyzed arylation of **6a**.



Entry[a]	6a **(mmol)**	**Pd(II) cat.**	**Additive**	8a**: Yield (%)**
1	0.15	$Pd(OAc)_2$	-	0
2	0.15	-	AgOAc	0
3[b]	0.2	$Pd(OAc)_2$	AgOAc	89
4[c]	0.2	$Pd(OAc)_2$	AgOAc	70
5[d]	0.2	$Pd(OAc)_2$	AgOAc	83
6	0.2	$PdCl_2$	AgOAc	88
7	0.2	$PdCl_2(MeCN)_2$	AgOAc	50
8	0.2	$Pd(TFA)_2$	AgOAc	85
9	0.15	$Pd(OAc)_2$	KOAc	0
10	0.15	$Pd(OAc)_2$	K_2CO_3	0
11	0.15	$Pd(OAc)_2$	Cs_2CO_3	0
12	0.2	$PdCl_2(MeCN)_2$	KOAc	0
13[b]	0.15	$Pd(OAc)_2$	Ag_2CO_3	77
14	0.15	$Pd(OAc)_2$	Na_2CO_3	28
15	0.2	$Pd(OAc)_2$	AgOAc	**8m**; (0)[e] (0)[f]
16	0.2	$PdCl_2$	AgOAc	**8m**; (0)[e] (0)[f]
17	0.2	$Pd(OAc)_2$	Ag_2CO_3	**8m**; (0)[e] (0)[f]
18[d]	0.2	$Pd(OAc)_2$	AgOAc	**8m**; (0)[e](0)[f]

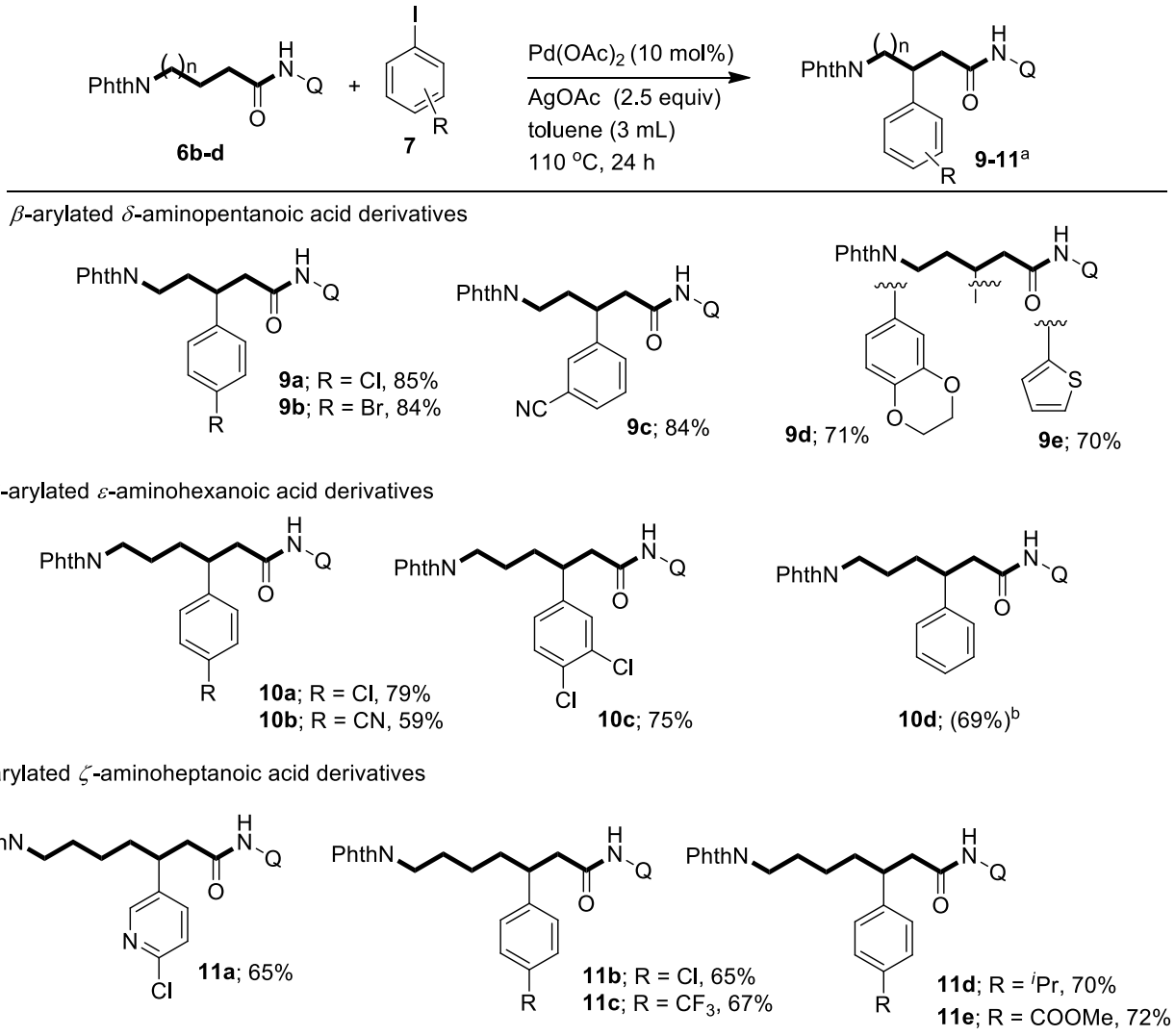
[a] Reactions were carried out using **6a** (0.15-0.2 mmol, 1 equiv), ArI (5 equiv), additive (2.5 equiv) for 24 h in toluene. Q = refers to the directing group. [b] Reaction time = 15 h. [c] 4 equiv of ArI. [d]^{t}AmylOH was instead of toluene. [e] The reaction was done using 4-bromotoluene for 24/48 h. [f] The reaction was done using 4-chlorotoluene for 24/48 h.

Having the suitable reaction conditions in hand for the Pd(II)-catalyzed *β*-C-H arylation of *γ*-aminobutyric acid (GABA) substrate 6a with 7a, we next intended to enrich the library of *β*-C-H arylated *γ*-aminobutyric acid via the Pd(II)-catalyzed *β*-C-H arylation of substrate 6a. Towards this, we performed the Pd(II)-catalyzed arylation of 6a using a variety of aryl iodides (Scheme 2). The Pd(II)-catalyzed arylation of 6a with aryl iodides containing different halogen substituents at the *meta* or *para* position afforded the corresponding *β*-C-H arylated *γ*-aminobutyric acid (GABA) derivatives 8a-f in good to high yields (64-92%, Scheme 2)**.**



Scheme 2. Enriching the library of *β*-C-H arylated *γ*-aminobutyric acid (GABA) derivatives with the Pd(II)-catalyzed arylation of **6a**.

Next, the Pd(II)-catalyzed arylation of **6a** with different di- and trisubstituted aryl iodides afforded the corresponding *β*-C-H arylated *γ*-aminobutyric acid derivatives **8g-i** in 57-74% yields (Scheme 2). The Pd(II)-catalyzed arylation of **6a** with PhI and aryl iodides containing the electron-withdrawing and donating groups (e.g., alkoxy, alkyl, NO_2, Ac, CN, ester, CF_3) at the *para or meta* position afforded the corresponding *β*-C-H arylated *γ*-aminobutyric acid derivatives **8j-v** in good to high yields (54-92%, Scheme 2). Further, the Pd(II)-catalyzed arylation of **6a** with different heteroaryl iodides also afforded the corresponding *β*-C-H arylated *γ*-aminobutyric acid derivatives **8w,x** in 72-73% yields (Scheme 2).

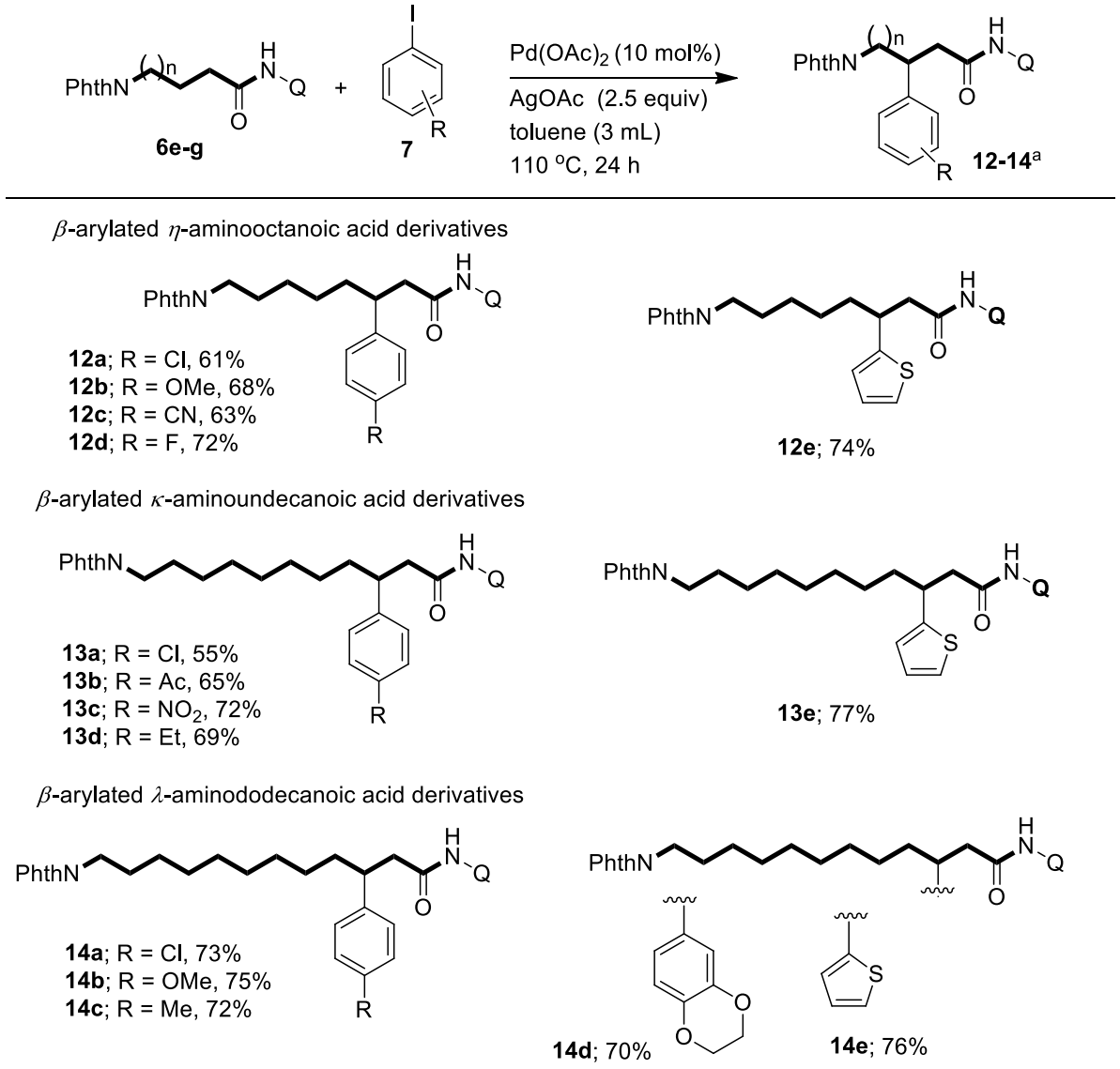


[a] Reactions are done using **6b-d** (0.15-0.2 mmol) and an appropriate aryl iodide (0.9-1 mmol). [b]**6c** (2 mmol), PhI (5 equiv) and toluene (15 mL).

Scheme 3. Enriching the library of *β*-C-H arylated medium/long chain-based amino acid derivatives *via* the Pd(II)-catalyzed *β*-C-H arylation.

After assembling various *β*-C-H arylated *γ*-aminobutyric acid (GABA) derivatives **8**, we then wished to expand the substrate scope of this work by assembling various *β*-arylated medium chain-basednon-*α*-amino acid derivatives (Schemes 3-5). In this regard, initially we performed the Pd(II)-catalyzed *β*-C-H arylation of medium chain carboxamide **6b**, which was derived from *δ*-aminopentanoic acid.The arylation of **6b** with different aryl iodides and a heteroaryl iodide afforded the corresponding *β*-C-H arylated *δ*-aminopentanoic acid (homo GABA) derivatives **9a-e** in 70-85% yields (Scheme 3). Next, we performed the Pd(II)-catalyzed *β*-C-H arylation of

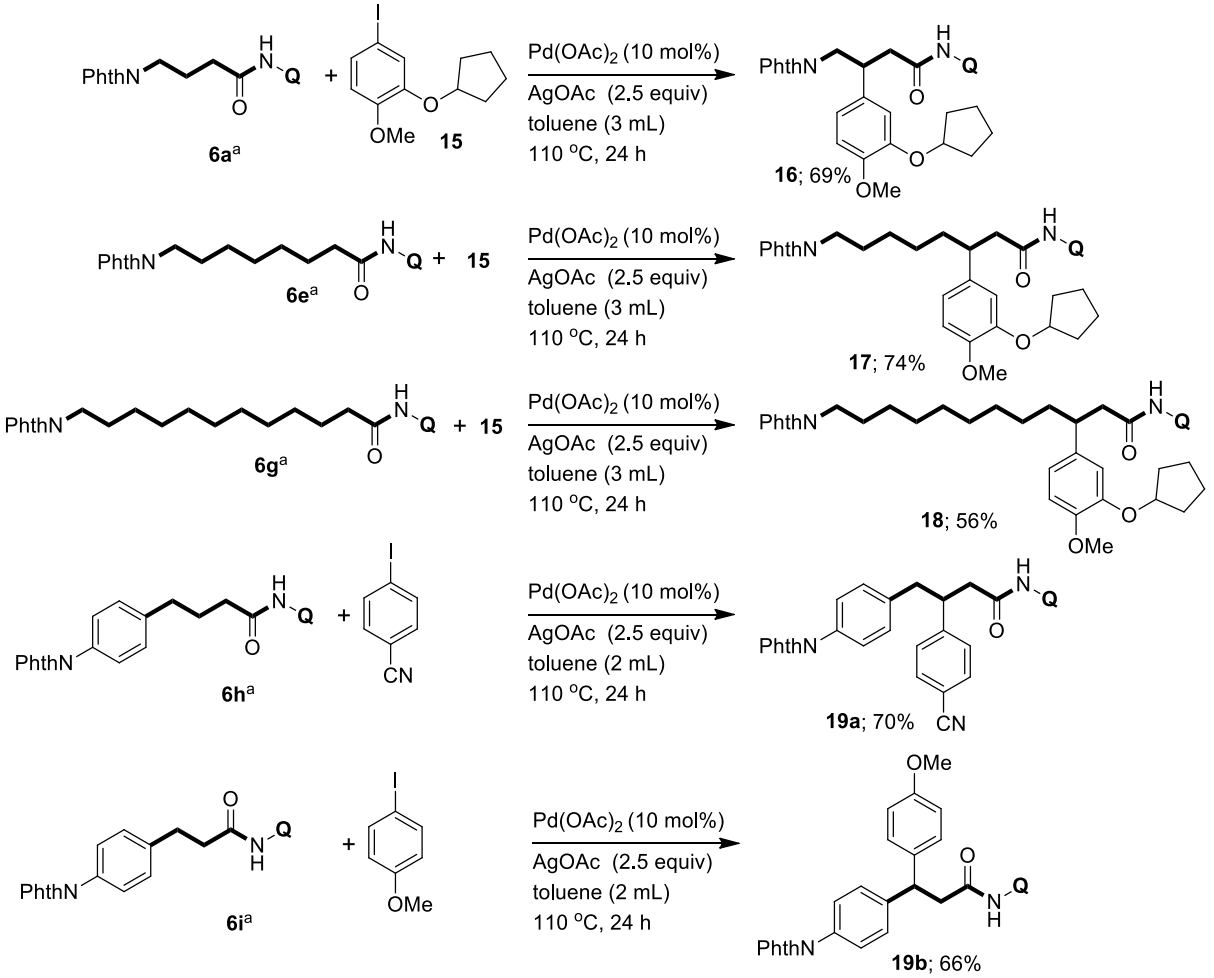
medium chain carboxamide **6c**, which was derived from ε-aminohexanoic acid.The arylation of **6c** with different aryl iodides afforded the corresponding β-C-H arylated ε-aminohexanoic acid derivatives **10a-d** in 59-79% yields (Scheme 3). Then, the Pd(II)-catalyzed β-C-H arylation of medium chain carboxamide **6d** (which was derived from ζ-aminoheptanoic acid)using a heteroaryl iodide and different aryl iodides afforded the corresponding β-C-H arylated ζ-aminoheptanoic acid derivatives **11a-e** in 65-72% yields (Scheme 3).



[a] Reactions are done using **6e-g** (0.15-0.2 mmol) and an appropriate aryl iodide (0.9-1 mmol).

Scheme 4. Enriching the library of β-C-H arylated medium/long chain-based amino acid derivatives via the Pd(II)-catalyzed β-C-H arylation.

Subsequently, we paid our attention to assemble various β-arylated long chain-based non-α-amino acid derivatives (Scheme 4). Towards this, we performed the Pd(II)-catalyzed β-C-H arylation of long chain carboxamide **6e**, which was derived from η-aminooctanoic acid.The reaction of **6e** with different aryl iodides and a heteroaryl iodide afforded the corresponding β-C-H arylated η-aminooctanoic acid derivatives **12a-e** in 61-74% yields (Scheme 4). Next, we carried out the Pd(II)-catalyzed β-C-H arylation of long chain carboxamide **6f**, which was derived from κ-aminoundecanoic acid.The reaction of **6f** with different aryl iodides and a heteroaryl iodide afforded the corresponding β-C-H arylated κ-aminoundecanoic acid derivatives **13a-e** in 55-77% yields (Scheme 4). Furthermore, the Pd(II)-catalyzed β-C-H arylation of long chain carboxamide **6g** (which was derived from λ-aminododecanoic acid) using different aryl iodides and a heteroaryl iodide afforded the corresponding β-C-H arylated λ-aminododecanoic acid derivatives **14a-e** in 70-76% yields (Scheme 4).



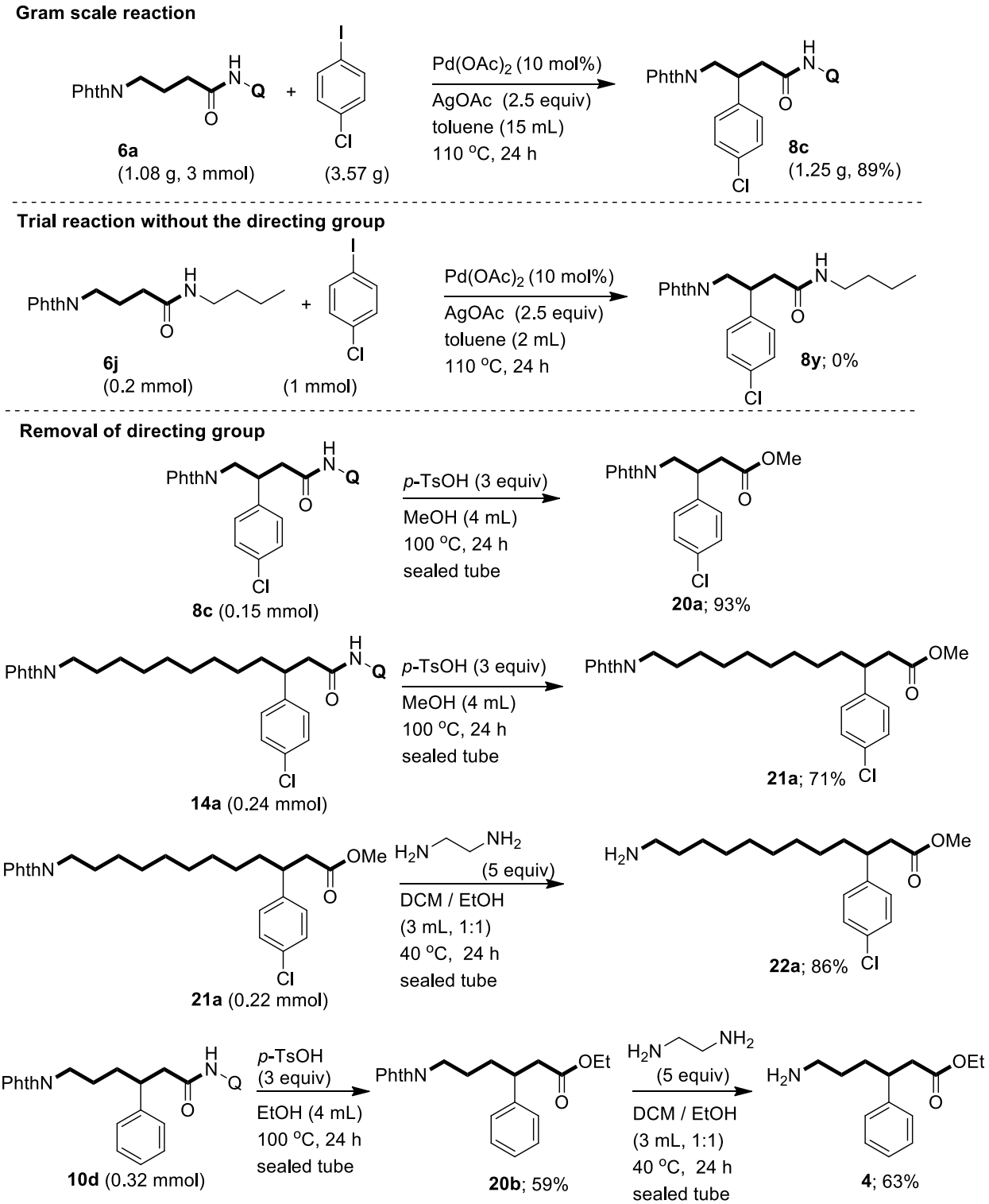
[a]Reactions are done using**6a,e,g-i** (0.15-0.2 mmol) and an appropriate aryl iodide (0.9-1 mmol).

Scheme 5. The Pd(II)-catalyzed*β*-C-H arylation of **6a,e,g-i**.

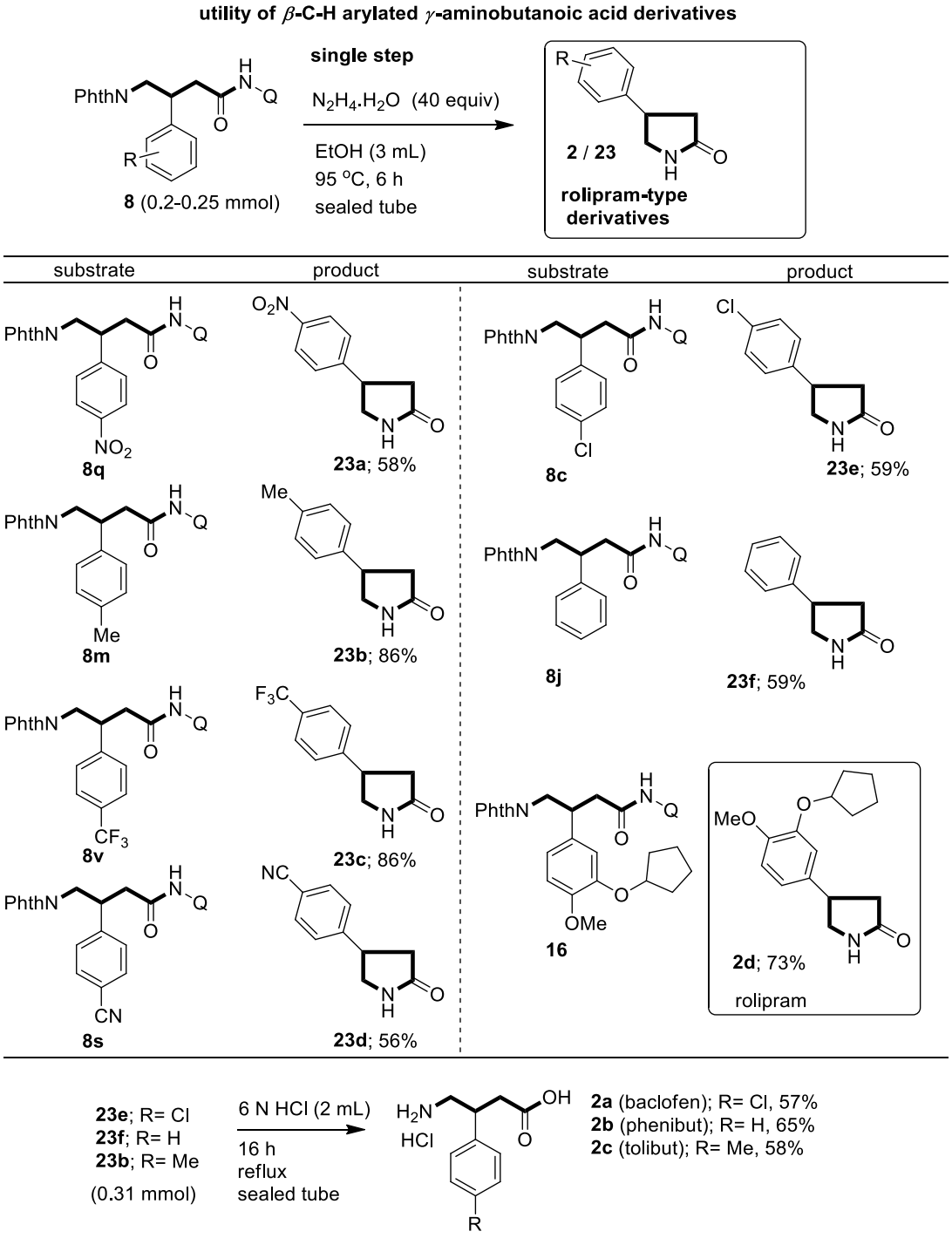
Subsequently, we were interested to expand the scope of this method and utility of the *β*-C-H arylated non-*α*-amino acid derivatives prepared in this work. In this regard, we intended to assemble rolipram (**2d**) and some 3-arylated piracetam derivatives similar to rolipram (**2d**). Towards this, it was necessary to assemble the *β*-C-H arylated *γ*-aminobutyric acid (GABA) derivative **16** (Scheme 5), which can be subjected to the lactamization to afford rolipram (**2d**). Initially, we performed the Pd(II)-catalyzed *β*-C-H arylation of **6a** with a desiredaryl iodide **15**, which successfully afforded the product **16** in 69% yield (Scheme 5). Then, we also intended to assemble some *β*-C-H arylated long chain-based amino acid derivatives similar to the product **16** by using the ArI **15**.

The Pd(II)-catalyzed *β*-C-H arylation of long chain carboxamides **6e** and **6g** with the **15** afforded the corresponding *β*-C-H arylated carboxamides **17** (74%) and **18** (56%) in moderate yields (Scheme 5). We then paid our attention towards the *β*-C-H arylation of aromatic amino acids and in this regard, we assembled the substrates **6h,i** (Scheme 5) possessing the directing group 8-aminoquinoline from their corresponding *N*-protected aromatic amino acids (**5h,i**). Then, we performed the Pd(II)-catalyzed *β*-C-H arylation of aromatic amino acid substrates **6h,i** with different aryl iodides, which afforded the corresponding *β*-C-H arylated aromatic amino acid derivatives **19a** (70%) and **19b** (66%) in moderate yields (Scheme 5).

We also tried the Pd(II)-catalyzed, *β*-C-H arylation reaction in a gram scale and towards this, we heated a mixture of substrate **6a** (1.08 g), 1-chloro-4-iodobenzene (3.57 g), $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (2.5 equiv) in toluene at 110 ^oC for 24 h. This reaction afforded the *β*-C-H arylated *γ*-aminobutyric acid derivative **8c** in 89% yield (Scheme 6). A trial reaction comprising the Pd(II)-catalyzed arylation simple amide **6j** without the directing group 8-aminoquinoline failed to afford the *β*-C-H arylated *γ*-aminobutyric acid derivative **8y** (Scheme 6). Then, we focused our attention to remove the directing group 8-aminoquinoline from the representative *β*-C-H arylated products. In this regard, we treated the *β*-C-H arylated *γ*-aminobutyric acid derivative **8c** with *p*-TsOH in MeOH at 100 ^oC for 24 h, which afforded the *γ*-aminobutyric acid ester **20a** in 93% yield (Scheme 6).



Scheme 6. Gram scale Pd(II)-catalyzed*β*-C-H arylation of **6a** and removal of directing group.



Scheme 7. Conversion of *β*-C-H arylated *γ*-aminobutyric acid derivatives **8**/**16** into rolipram-type compounds in a single step with hydrazine monohydrate in EtOH and synthesis of GABA derivatives **2a-c**.

Similarly, treatment of the *β*-C-H arylated *λ*-aminododecanoic acid derivative **14a** with *p*-TsOH in MeOH at 100 °C for 24 h afforded the *λ*-aminododecanoic acid ester **21a** in 71% yield

(Scheme 6). The removal of the phthalimide group was also achieved by treating the phthalimide protected λ-aminododecanoic acid ester **21a** with ethylene diamine in DCM/EtOH at 40 ^{o}C for 24 h and this reaction afforded the λ-aminododecanoic acid ester **22a** in 86% yield (Scheme 6). Additionally, removal of the directing group from **10d** gave the compound **20b**, which was further converted into the compound **4** (Scheme 6) and the compound **4** was used as a precursor for benzazepinones.[15]

Furthermore, we were interested to reveal the utility of representative β-C-H arylated non-α-amino acid derivatives. A literature survey revealed that the utility of some of the β-C-H arylated γ-aminobutyric acid derivatives, e.g., **8c,j** and **16** have been already reported.[22d] Accordingly, baclofen (**2a**) and phenibut (**2b**) were synthesized from **8c,j**, respectively and rolipram (**2d**) was synthesized from **16** in four steps.[22d] While we were interested in enriching the library of rolipram-type compounds and at the same time we wished to attempt the conversion of β-C-H arylated γ-aminobutyric acid derivatives **8**/**16** into rolipram-type compounds using minimum synthetic steps. With our efforts we found that the treatment of β-C-H arylated γ-aminobutyric acid derivatives **8**/**16** with hydrazine monohydrate in EtOH at 95 ^{o}C for 6 h afforded the corresponding 3-arylated pyrrolidone derivatives **2d**/**23** in a single step (Scheme 7). Accordingly, various rolipram-type compounds were obtained in 56-86% yields fromthe corresponding substrates **8q,m,v,s,c,j**. Rolipram (**2d**) was obtained in 73% yield from the corresponding β-C-H arylated γ-aminobutyric acid derivative **16** in a single step (Scheme 7). Treatment of 3-arylated pyrrolidone derivatives **23b,e,f** with 6 N HCl at reflux for 16 h in sealed tube[24h] led to the construction of the corresponding 3-arylated GABA derivatives such as, baclofen (**2a**), phenibut (**2b**) and tolibut (**2c**) in 57-65% yields (Scheme 7).

Conclusion

In conclusion, we disclose the assembling of libraries of β-arylated short/medium/long chain-based aminoalkanoic acid (non-α-amino acid) derivatives *via* the Pd(II)-catalyzed, bidentate directing group 8-aminoquinoline-aided β-C(sp^3)-H activation/arylation protocol. Given the promising therapeutic properties of short/medium chain-based aminoalkanoic acids (non-α-amino acids) containing an aryl group at the β-position, it is important to enrich the libraries of the β-arylated aminoalkanoic acids (non-α-amino acids). Accordingly, we paid an inclusive attention to study the Pd(II)-catalyzed $sp^3$$\beta$-C-H arylation of various short/medium/long chain-

basednon-α-amino acids. Though there have been a few attempts on the Pd-catalyzed, bidentate directing group-aided $sp^3\beta$-C-H arylation involving γ-aminobutyric acid (**1d**) and ε-aminohexanoic acid (**1f**), we have also enriched the library of β-arylated γ-aminobutyric acid and ε-aminohexanoic acid derivatives with further examples. We have described a gram scale Pd(II)-catalyzed reaction and also removal of the directing group after the β-C-H arylation. We have shown a short route for assembling rolipram (**2d**) and related compounds and also 3-arylated GABA derivatives such as, baclofen (**2a**), phenibut (**2b**) and tolibut (**2c**) from their corresponding β-C-H arylated γ-aminobutyric acid derivatives **8**/**16**.

Experimental Section

3.1. General information. The ^{1}H and ^{13}C{H} NMR spectra of all compounds have been recorded in 400 and ~101 MHz spectrometers by using TMS as an internal standard, respectively. The HRMS analysis data of samples reported here were obtained from QTOF mass analyzer by ESI method. The IR spectra of samples reported here were recorded as neat or thin films. Column chromatography purification of crude reaction mixtures/samples was carried out on silica gel (100-200 mesh). Thin layer chromatography (TLC) analyses were carried out on alumina or silica gel plates. The components of TLC analysis were visualized by observation under iodine vapor. Reactions were performed in dry solvents (prepared using standard drying methods) under a nitrogen atm wherever required. Isolated yields of all the β-C-H arylated products are reported and yields were not optimized. The compounds **2a**,[22d,24h] **2b**,[22d,24h] **2c**,[24h] **2d**,[22d,24i] **4**,[15] **5a**,[24a] **5b**,[24b] **5c**,[24c] **5e**,[24d] **5f**,[24e] **5i**,[24f] **6a**,[24g] **6c**,[19b] **8c**,[22d] **8j**,[22d] **8k**,[22d] **8w**,[22d] **8x**,[22d] **10d**,[22b] **16**,[22d] **23b**,[24h] **23c**,[24i] **23e**,[24h] and **23f**[24h] are known compounds and their characterization data are reported in the literature and we have also included their corresponding NMR spectra in the supplementary data section. The preparation of **15** was carried out using the literature method from 2-methoxyphenol (via acetylation, iodination followed by deacetylation and alkylation) and the NMR of **15** was compared with the literature.[24j] The synthesis of compounds **2a-c** from the corresponding starting compounds **23b,e,f** was carried out using the procedure reported in the literature.[24h]

3.2. General procedure for the phthalimide protection of amino acids (1): A dry RB flask containing a mixture of amino acid (1 mmol), phthalic anhydride (1 mmol) and triethylamine (20

mol% mmol) in toluene (5 mL) was heated for 12 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in dichloromethane (5 mL), washed with 10% hydrochloric acid solution (7-10 mL), followed by water. The combined organic layers were dried over anhydrous Na_2SO_4 and then, the solvent was evaporated under reduced pressureto afford the phthalimide protected amino acid (**1**).

3.3. General procedure for the synthesis of carboxamides (6): A dry RB flask containing the corresponding carboxylic acid **5** (1-5 mmol) and $SOCl_2$ (9 equiv) was stirred for 24 h at rt under a nitrogen atmosphere. Then, the reaction mixture was concentrated under reduced pressure to remove the volatiles and the resultant crude reaction mixture was diluted with anhydrous DCM (2-10 mL). The DCM solution of corresponding acid chloride was slowly added to another RB flask containing the 8-aminoquinoline (0.9 equiv), Et_3N (1.2 equiv) and DCM (5-12 mL) under a nitrogen atmosphere. The resulting crude mixture was stirred at rt for 24 h. After this period, the reaction mixture was diluted with DCM (2-10 mL, if needed) and washed with water and saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, and then, the solvent was evaporated under reduced pressureto afford a crude mixture, which was purified by column chromatography on silica gel to afford the corresponding carboxamide (**6**).

3.4. General procedure for the Pd(II)-catalyzed, 8-aminoquinoline-aided *β*-C-H arylation of short/medium/long chain-based unnatural amino acid carboxamides (6): A mixture ofan appropriate unnatural amino acid carboxamide **6** (0.15-0.2 mmol, 1 equiv), an appropriate aryl iodide (5 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.5 equiv) in anhydrous toluene (2-3 mL) was heated at 110 ^oC for 15-24 h under a nitrogen atm or in a sealed tube. After the reaction period, the reaction mixture was concentrated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography on neutral alumina or silica gel (eluent = EtOAc:hexane) to give the corresponding arylated amino acid (see the respective Schemes/Tables for the specific entries).

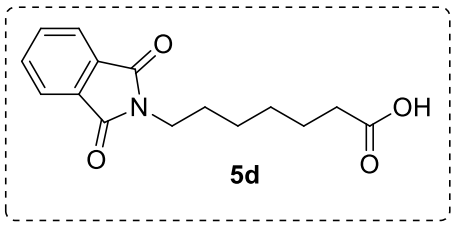
3.5. Procedure for theremoval of the directing group 8-aminoquinoline and preparation of the carboxylate derivatives 20a,b and 21a: Arylated carboxamide **8c**/**14a/10d** (0.15-0.25 mmol, 1 equiv), *p*-$TsOH.H_2O$ (3 equiv) and methanol/ethanol (3-4 mL) were added to screw-cap

seal tube. The vial containing the mixture was sealed and submerged into a silicon oil bath pre-heated to 100 ºC. After 24 h, the dark brown solution was cooled to rt. After the reaction period, the solvent was evaporated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography to afford the corresponding carboxylate derivatives **20a,b**/**21a**.

3.6. Procedure for deprotection of phthalimide group from substrate 21a/20b:[211]A RB flaskcontainingsubstrate **21a/20b** (0.19-0.22 mmol) in DCM (1-1.5 mL), EtOH (1-1.5 mL) and ethylenediamine (5 equiv) was heated to 40 °C for 24 h with vigorous stirring. Then, the solvents were removed under reduced pressure. $CuCl_2$ (2.5 equiv.) and deionized water (10 mL) were added into the resulting mixture. The aqueous solution was extracted with EtOAc (3 × 10 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding products.

3.7. General procedure preparation of the pyrrolidonederivatives (2d/23): *β*-C-H Arylated *γ*-aminobutyric acid derivatives **8**/**16** (0.2-0.25 mmol, 1 equiv), $N_2H_4.H_2O$ (40 equiv) and ethanol (3 mL) were added to screw-cap seal tube. Then, the resulting mixture was sealed and the tube was submerged into a silicon oil bath pre-heated to 95 ºC. After 6 h, the solution was cooled to rt. After the reaction period, the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water and then the organic layers were collected and dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatography to afford the corresponding pyrrolidone derivatives (**2d**/**23**).

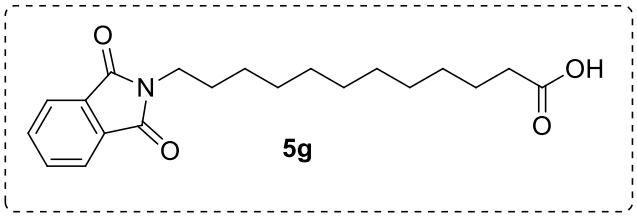
7-(1,3-Dioxoisoindolin-2-yl)heptanoic acid (5d)*:*The compound **5d** was obtained by following the general procedure as a colourless solid (210 mg, 76%); mp: 116-118 ºC; IR (DCM): 2930, 1718, 1395, 1360, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.73 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 3.69 (2H, t, J = 7.2 Hz), 2.36 (2H, t, J = 7.4 Hz), 1.72-1.63 (4H,



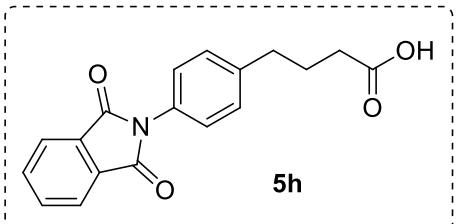
5d

m), 1.40-1.38 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 179.9, 168.5, 133.9, 132.1, 123.2, 37.9, 33.9, 28.6, 28.4, 26.5, 24.5; HRMS (ESI) calcd for $C_{15}H_{16}NO_4$ $[M-H]^+$ 274.1079 found, 274.1087. The carboxylic acid proton could not be detected in the ^{1}H NMR.

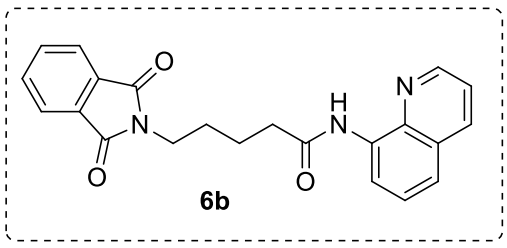
12-(1,3-Dioxoisoindolin-2-yl)dodecanoic acid (5g): The compound **5g** was obtained by following the general procedure as a colourless solid (564 mg, 80%); mp: 90-92 ^{o}C; IR (DCM): 3055, 2987, 1713, 1265, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.72 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 3.68 (2H, t, J = 7.4 Hz), 2.35 (2H, t, J = 7.6 Hz), 1.71-1.59 (4H, m), 1.33-1.26 (14H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 180.1, 168.5, 133.9, 132.2, 123.2, 38.1, 34.1, 29.4, 29.4, 29.4, 29.2, 29.2, 29.0, 28.6, 26.8, 24.7; HRMS (ESI) calcd for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$ 368.1838 found 368.1820. The carboxylic acid proton could not be detected in the ^{1}H NMR.



4-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)butanoic acid (5h): The compound **5h** was obtained by following the general procedure as a colourless solid (537 mg, 87%); mp: 138-140 ^{o}C; IR (DCM): 3041, 1703, 1234, 1112, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.98 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.40-7.34 (4H, m), 2.78 (2H, t, J = 7.9 Hz), 2.45 (2H, t, J = 7.4 Hz), 2.03 (2H, quint, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 179.4, 167.4, 141.4, 134.4, 131.8, 129.6, 129.2, 126.6, 123.8, 34.7, 33.3, 26.1; HRMS (ESI) calcd for $C_{18}H_{15}NNaO_4$ $[M+Na]^+$ 332.0899 found, 332.0887. The carboxylic acid proton could not be detected in the ^{1}H NMR.

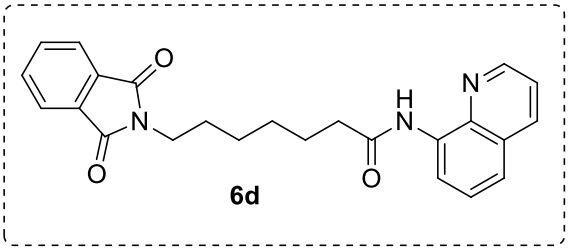


5-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (6b): The compound **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (228 mg, 61%); R_f (40% EtOAc/hexane) = 0.5; mp: 110-112 ^{o}C; IR (DCM): 3055, 2986, 1711, 1265,

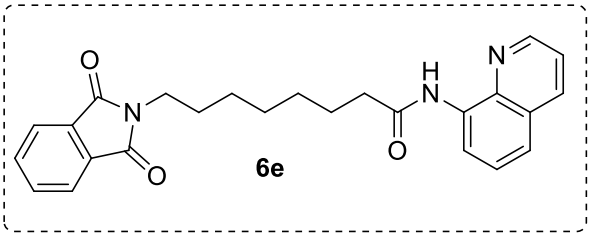


743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.78 (1H, br. s), 8.75-8.72 (2H, m), 8.10 (1H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.79 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.65 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.50-7.43 (2H, m), 7.40 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 3.74 (2H, t, J = 6.4 Hz), 2.61 (2H, t, J = 7.1Hz), 1.87-1.83 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C171.1, 168.4, 148.1, 138.2, 136.3, 134.4, 133.9, 132.0, 127.9, 127.4, 123.2, 121.6, 121.4, 116.4, 37.5, 37.4, 28.2, 22.8; HRMS (ESI) calcd for $C_{22}H_{20}N_3O_3$ $[M+H]^+$ 374.1505 found 374.1519.

7-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (6d): The compound **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (1.2 g, 64%); R_f (40% EtOAc/hexane) = 0.4; mp: 124-126 ^oC; IR (DCM): 2936, 1710, 1525, 1396, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.81 (1H, br. s), 8.82 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.79 (1H, dd, J_1 = 7.3, J_2 = 1.4 Hz), 8.17 (1H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.85 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.72 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.57-7.50 (2H, m), 7.47 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 3.71 (2H, t, J = 7.3 Hz), 2.58 (2H, t, J = 7.6 Hz), 1.88-1.80 (2H, m) 1.73 (2H, quint, J = 7.4 Hz),) 1.53-1.40 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.7, 168.4, 148.1, 138.3, 136.3, 134.5, 133.8, 132.1, 127.9, 127.4, 123.1, 121.6, 121.3, 116.4, 38.0, 37.9, 28.8, 28.5, 26.7, 25.5; HRMS (ESI) calcd for $C_{24}H_{24}N_3O_3$ $[M+H]^+$ 402.1818, found 402.1834.

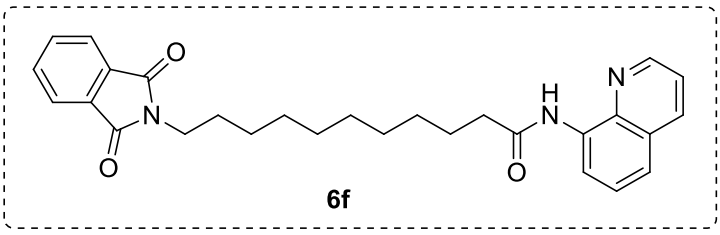


8-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (6e): The compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a grey color solid (329 mg, 66%); R_f (40% EtOAc/hexane) = 0.4; mp: 86-88 ^oC; IR (DCM): 3353, 3055, 1721, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.78 (1H, br. s), 8.76-8.74 (2H, m), 8.10 (1H, dd, J_1 = 8.3, J_2 = 1.6Hz), 7.77 (2H, dd, J_1 = 5.4, J_2 = 2.0 Hz), 7.64 (2H, dd, J_1 = 5.6, J_2 = 3.0 Hz), 7.50-7.38 (3H, m), 3.64 (2H, t, J = 7.4 Hz), 2.53 (2H, t, J = 7.6 Hz), 1.82-1.75 (2H, m) 1.69-1.62 (2H, m) 1.38 (6H, br. s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.8, 168.4, 148.0, 138.2, 136.4, 134.5, 133.8,



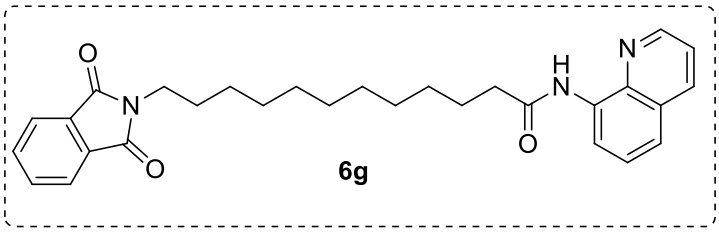
132.1, 127.9, 127.4, 123.1, 121.6, 121.3, 116.4, 38.1, 37.9, 29.1, 28.9, 28.5, 26.7, 25.5; HRMS (ESI) calcd for $C_{25}H_{26}N_3O_3$ $[M+H]^+$ 416.1974 found 416.1989.

11-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)undecanamide (6f): The compound **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (419 mg, 59%); R_f (40% EtOAc/hexane) = 0.6; mp: 70-72 ^oC; IR (DCM): 3055, 2928, 1709, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.72-8.68 (2H, m), 8.03 (1H, dd, J_1 = 6.7, J_2 = 1.7 Hz), 7.71 (2H, dd, J_1 = 5.3, J_2 = 2.4 Hz), 7.57 (2H, dd, J_1 = 5.2, J_2 = 2.9 Hz), 7.44-7.31 (3H, m), 3.58 (2H, t, J = 6.7 Hz), 2.47 (2H, t, J = 6.6 Hz), 1.75-1.71 (2H, m) 1.58 (2H, br. s), 1.33-1.20 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.8, 168.3, 148.0, 138.2, 136.2, 134.5, 133.7, 132.0, 127.8, 127.3, 123.0, 121.5, 121.3, 116.3, 38.1, 37.9, 29.4, 29.3, 29.3, 29.2, 29.1, 28.5, 26.8, 25.6; HRMS (ESI) calcd for $C_{28}H_{32}N_3O_3$ $[M+H]^+$ 458.2444 found 458.2426.



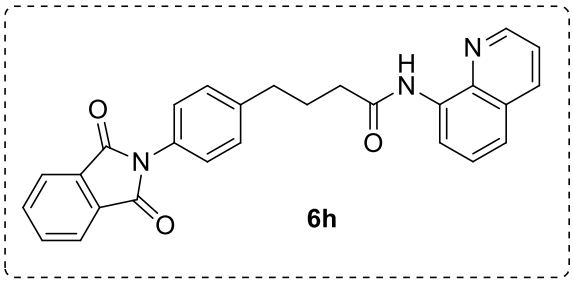
6f

12-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)dodecanamide (6g): The compound **6g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (262 mg, 55%); R_f (40% EtOAc/hexane) = 0.6; mp: 48-50 ^oC; IR (DCM): 3055, 2987, 1709, 1265, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, br. s), 8.76-8.75 (2H, m), 8.09 (1H, d, J = 8.2 Hz), 7.79 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.64 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.50-7.42 (2H, m), 7.40 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 3.63 (2H, t, J = 7.3 Hz), 2.53 (2H, t, J = 7.6 Hz), 1.82-1.77 (2H, m), 1.65-1.62 (2H, m), 1.42-1.35 (2H, m), 1.28-1.23 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.9, 168.4, 148.1, 138.3, 136.3, 134.5, 133.8, 132.1, 127.9, 127.4, 123.1, 121.5, 121.3, 116.4, 38.2, 38.0, 29.5, 29.4, 29.3, 29.3, 29.1, 28.6, 26.8, 25.7; HRMS (ESI) calcd for $C_{29}H_{34}N_3O_3$ $[M+H]^+$ 472.2600 found 472.2584.

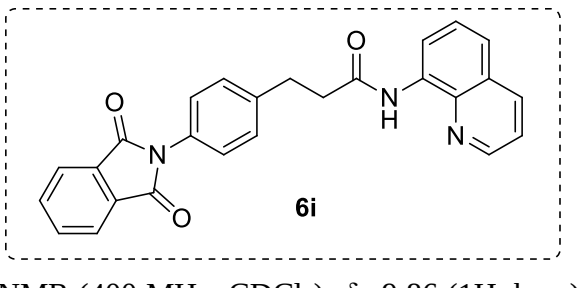


6g

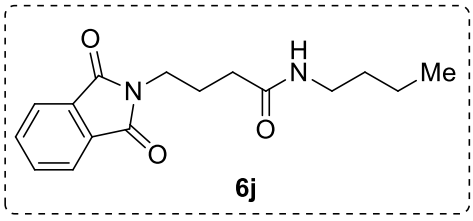
4-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-*N*-(quinolin-8-yl)butanamide (6h): The compound **6h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (611 mg, 88%); R_f (40% EtOAc/hexane) = 0.5; mp: 162-164 ^oC; IR (DCM): 2923, 1716, 1524, 1381, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (1H, br. s), 8.84-8.81 (2H, m), 8.18 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.97 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.80 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.59-7.55 (1H, m), 7.52 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.48 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.43-7.38 (4H, m), 2.85 (2H, t, J = 7.8 Hz), 2.65 (2H, t, J = 7.4 Hz), 2.22 (2H, quint, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.3, 167.4, 148.2, 141.7, 138.3, 136.4, 134.5, 134.4, 131.8, 129.6, 129.3, 127.9, 127.4, 126.6, 123.7, 121.6, 121.5, 116.5, 37.2, 34.9, 26.9; HRMS (ESI) calcd for $C_{27}H_{22}N_3O_3$ $[M+H]^+$ 436.1661 found 436.1646.



3-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-*N*-(quinolin-8-yl)propanamide (6i): The compound **6i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (258 mg, 76%); R_f (40% EtOAc/hexane) = 0.5; mp: 182-184 ^oC; IR (DCM): 2927, 1718, 1523, 1382, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.86 (1H, br. s), 8.81 (2H, d, J = 5.0 Hz), 8.17 (1H, d, J = 8.2 Hz), 7.96 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.79 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.59-7.51 (2H, m), 7.48-7.39 (5H, m), 2.23 (2H, t, J = 8.1Hz), 2.95 (2H, t, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 167.3, 148.1, 141.0, 138.2, 136.5, 134.4, 131.8, 129.8, 129.2, 128.0, 127.4, 126.7, 123.7, 121.6, 121.6, 116.7, 39.4, 31.1; HRMS (ESI) calcd for $C_{26}H_{20}N_3O_3$ $[M+H]^+$ 422.1505 found 422.1484.

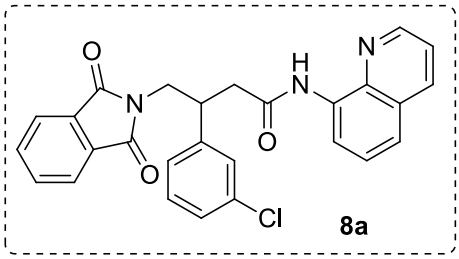


***N*-Butyl-4-(1,3-dioxoisoindolin-2-yl)butanamide (6j):** The compound **6j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (355 mg, 62%); R_f (40% EtOAc/hexane) = 0.6; mp: 108-110 ^oC; IR (DCM): 3305, 2935, 1713, 1399, 720 cm^{-1}; ^1H NMR



(400 MHz, $CDCl_3$): δ_H 7.86 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.74 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 6.04 (1H, br. s), 3.76 (2H, t, J = 6.4 Hz), 3.27-3.22 (2H, m), 2.21 (2H, t, J = 7.0 Hz), 2.08-2.01 (2H, m), 1.54-1.47 (2H, m), 1.42-1.34 (2H, m), 0.93 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.9, 168.7, 134.1, 132.0, 123.3, 39.4, 37.2, 33.9, 31.6, 25.1, 20.1, 13.8; HRMS (ESI) calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ 289.1552 found 289.1540.

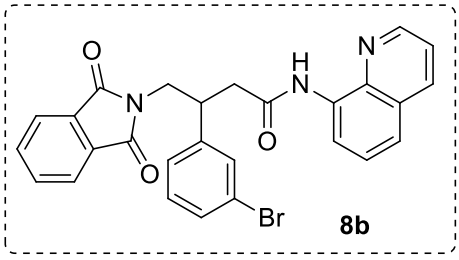
3-(3-Chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8a): The



8a

compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (84 mg, 89%); R_f (40% EtOAc/hexane) = 0.6; mp: 170-172 ^{o}C; IR (DCM): 3055, 2986, 1713, 1265, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.82 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.46 (1H, dd, J_1 = 7.6, J_2 = 1.1 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.67 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.57 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.48-7.42 (3H, m), 7.36 (1H, t, J = 8.0 Hz), 7.32 (1H, dt, J_1 = 7.5, J_2 = 1.5 Hz), 7.25 (1H, t, J = 7.8 Hz), 7.20 (1H, dt, J_1 = 8.0, J_2 = 1.6 Hz), 4.05-3.95 (3H, m), 3.04-2.93 (2H, m), ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.7, 168.3, 148.1, 143.0, 138.1, 136.2, 134.6, 134.1, 133.8, 131.7, 130.1, 128.0, 127.7, 127.5, 127.2, 126.1, 123.2, 121.6, 121.4, 116.2, 43.1, 41.8, 40.7; HRMS (ESI) calcd for $C_{27}H_{21}ClN_3O_3$ $[M+H]^+$ 470.1271 found 470.1252.

3-(3-Bromophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamidebutanamide

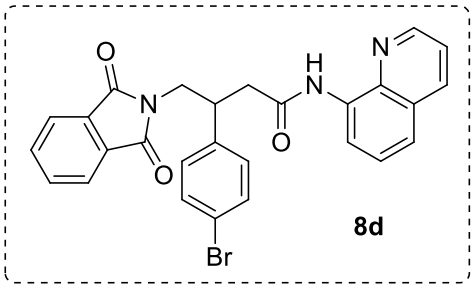


8b

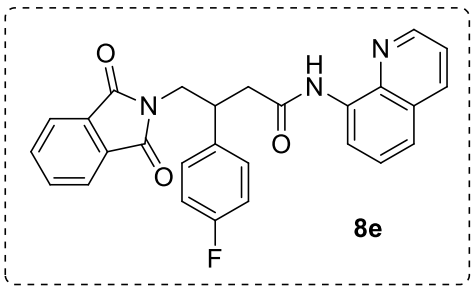
(8b): The compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (87 mg, 64%); R_f (40% EtOAc/hexane) = 0.6; mp: 146-148 ^{o}C; IR (DCM): 3055, 2987, 1712, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.82 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.45 (1H, dd, J_1 = 7.6, J_2 = 1.0 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 7.67 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.59-7.56 (3H, m), 7.46 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.43 (1H, dd, J_1 = 8.4, J_2 = 1.3 Hz), 7.38- 7.34 (3H, m), 7.18 (1H, t, J = 7.8 Hz), 4.07-3.93 (3H, m), 3.03-2.92 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.7, 168.3, 148.2, 143.2, 138.1, 136.2, 134.0, 133.8, 131.7, 130.8, 130.5, 130.4, 127.7, 127.2, 126.6, 123.2,

122.8, 121.6, 121.4, 116.2, 43.1, 41.8, 40.6; HRMS (ESI) calcd for $C_{27}H_{21}BrN_3O_3$ $[M+H]^+$ 514.0766 found 514.0745.

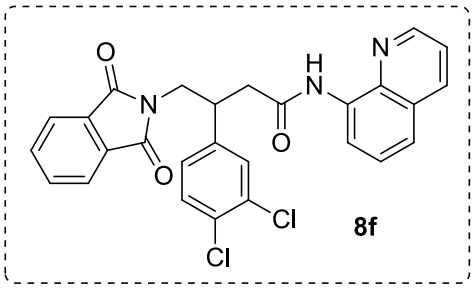
3-(4-Bromophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8d): The compound **8d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (84 mg, 81%); R_f (40% EtOAc/hexane) = 0.6; mp: 174-176 °C; IR (DCM): 3055, 2987, 1710, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.80 (1H, dd, J_1 = 4.3, J_2 = 1.6 Hz), 8.49 (1H, dd, J_1 = 7.6, J_2 = 1.2 Hz), 8.13 (1H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.68 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.58 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.47-7.42 (4H, m), 7.38 (1H, t, J = 8.1 Hz), 7.30 (2H, d, J = 8.5 Hz), 4.03-3.96 (3H, m), 3.03-2.91 (2H, m), ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.0, 168.2, 147.6, 139.8, 137.3, 137.3, 133.9, 133.7, 131.9, 131.7, 129.6, 127.9, 127.6, 123.2, 121.6, 121.5, 121.1, 117.3, 43.0, 41.9, 40.5; HRMS (ESI) calcd for $C_{27}H_{21}BrN_3O_3$ $[M+H]^+$ 514.0766 found 514.0778.



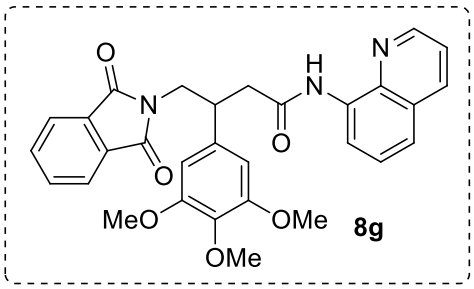
4-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(quinolin-8-yl)butanamide (8e): The compound **8e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (59 mg, 65%); R_f (40% EtOAc/hexane) = 0.6; mp: 200-202 °C; IR (DCM): 3055, 2987, 1424, 1265, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.81 (1H, d, J = 3.9 Hz), 8.50 (1H, d, J = 7.4 Hz), 8.10 (1H, d, J = 8.2 Hz), 7.69 (2H, dd, J_1 = 4.6, J_2 = 3.2 Hz), 7.59 (2H, dd, J_1 = 5.6, J_2 = 3.0 Hz), 7.48-7.37 (5H, m), 7.00 (2H, t, J = 8.3 Hz), 4.04-3.96 (3H, m), 3.02-2.91 (2H, m), ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.9, 168.3, 162.0 (d, J = 243.7 Hz), 148.1, 138.2, 136.4 (d, J = 3.0 Hz), 136.2, 134.1, 133.8, 131.8, 129.3 (d, J = 8.0 Hz), 127.8, 127.2, 123.2, 121.6, 121.4, 116.3, 115.6 (d, J = 21.1 Hz), 43.2, 42.2, 40.3; HRMS (ESI) calcd for $C_{27}H_{21}FN_3O_3$ $[M+H]^+$ 454.1567, found 454.1547.



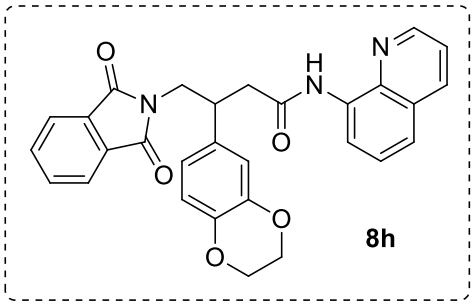
3-(3,4-Dichlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide(8f): The compound **8f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (65 mg, 65%); R_f (40% EtOAc/hexane) = 0.6; mp: 186-188 ^oC; IR (DCM): 3055, 2985, 1711, 1265, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.70 (1H, br. s), 8.81 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.47 (1H, dd, J_1 = 7.5, J_2 = 1.0 Hz), 8.14 (1H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.70 (2H, dd, J_1 = 5.4, J_2 = 3.1Hz), 7.60 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.53 (1H, d, J = 2.0 Hz), 7.48-7.44 (2H, m), 7.41-7.36 (2H, m), 7.28–7.26 (1H, m), 4.03-3.95 (3H, m), 3.03-2.90 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.4, 168.2, 148.2, 141.1, 138.1, 136.2, 134.0, 133.9, 132.8, 131.7, 131.3, 130.7, 129.8, 127.8, 127.3, 127.2, 123.3, 121.6, 121.5, 116.3, 42.8, 41.8, 40.3; HRMS (ESI) calcd for $C_{27}H_{20}Cl_2N_3O_3$ $[M+H]^+$ 504.0882 found 504.0901.



4-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)butanamide (8g): The compound **8g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (60 mg, 57%); R_f (40% EtOAc/hexane) = 0.4; mp: 168-170 ^oC; IR (DCM): 3345, 3055, 1709, 1264, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, br. s), 8.79 (1H, d, J = 3.5 Hz), 8.49 (1H, d, J = 7.4 Hz), 8.13 (1H, d, J = 8.2 Hz), 7.67 (2H, dd, J_1 = 5.2, J_2 = 3.2 Hz), 7.58 (2H, dd, J_1 = 5.2, J_2 = 3.3 Hz), 7.47-7.43 (2H, m), 7.38 (1H, t, J = 8.0 Hz), 6.61 (2H, s), 4.04-3.97 (3H, m), 3.84 (6H, s), 3.72 (3H, s), 2.95 (2H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.2, 168.3, 153.3, 148.1, 138.1, 137.0, 136.3, 136.2, 134.1, 133.8, 131.8, 127.7, 127.2, 123.1, 121.6, 121.4, 116.2, 104.6, 60.7, 56.1, 43.1, 42.6, 41.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_6$ $[M+H]^+$ 526.1978 found 526.1965.

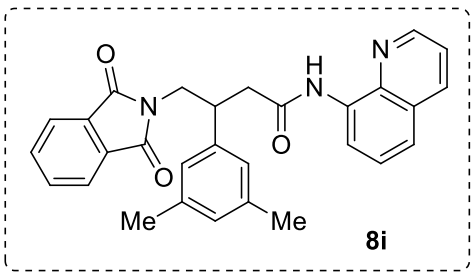


3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8h): The compound **8h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (55 mg, 74%); R_f (40% EtOAc/hexane) = 0.3; mp: 190-192 ^oC; IR (DCM): 3347, 2929, 1711, 1286, 724 cm^{-1}; ^1H

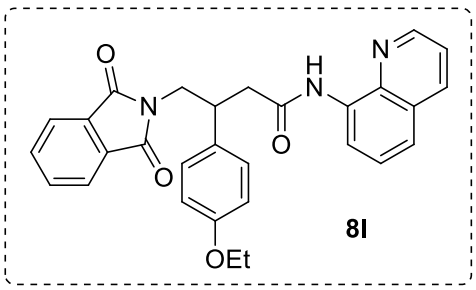


NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, br. s), 8.79 (1H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.46 (1H, dd, J_1 = 7.6, J_2 = 1.2 Hz), 8.10 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 7.64 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.54 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.43 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.39 (1H, dd, J_1 = 8.3, J_2 = 1.3 Hz), 7.33 (1H, t, J = 8.0 Hz), 6.93 (1H, d, J = 2.0 Hz), 6.70 (1H, dd, J_1 = 8.3, J_2 = 2.1 Hz), 6.80 (1H, d, J = 8.2 Hz), 4.19 (4H, s), 4.03-3.89 (3H, m), 2.97-2.88 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.3, 168.3, 148.1, 143.6, 142.6, 138.1, 136.2, 134.2, 134.1, 133.7, 131.8, 127.7, 127.2, 123.1, 121.5, 121.3, 120.7, 117.5, 116.5, 116.2, 64.3, 43.4, 42.2, 40.2; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_5$ $[M+H]^+$ 494.1716 found 494.1696.

3-(3,5-Dimethylphenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8i): The compound **8i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (37 mg, 60%); R_f (40% EtOAc/hexane) = 0.6; mp: 104-106 ^{o}C; IR (DCM): 3055, 2986, 1714, 1265, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.70 (1H, br. s), 8.81 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.43 (1H, dd, J_1 = 7.6, J_2 = 1.2 Hz), 8.12 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.64 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.54 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.46 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.41 (1H, dd, J_1 = 8.2, J_2 = 1.2 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.05 (2H, s), 6.86 (1H, s), 4.05-3.89 (3H, m), 2.97 (2H, d, J = 6.8 Hz), 2.29 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.4, 148.0, 140.8, 138.3, 138.2, 136.2, 134.2, 133.7, 131.9, 128.9, 127.7, 127.2, 125.5, 123.0, 121.5, 121.2, 116.1, 43.6, 42.1, 40.7, 21.3; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_3$ $[M+H]^+$ 464.1974 found 464.1996.

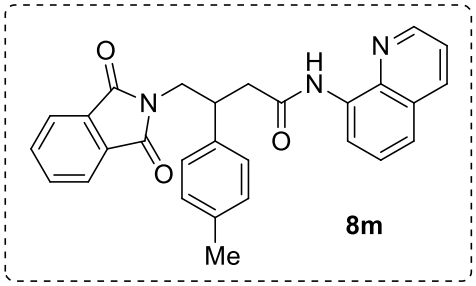


4-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethoxyphenyl)-*N*-(quinolin-8-yl)butanamide (8l): The compound **8l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (60 mg, 83%); R_f (40% EtOAc/hexane) = 0.4; mp: 129-131 ^{o}C; IR (DCM): 3348, 2980, 1712, 1245, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.69



(1H, br. s), 8.78 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.48 (1H, dd, J_1 = 7.5, J_2 = 1.0 Hz), 8.10 (1H, dd, J_1 = 8.4, J_2 = 1.5 Hz), 7.65 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.54 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.44-7.35 (3H, m), 7.32 (2H, d, J = 8.5 Hz), 6.82 (2H, d, J = 8.6 Hz), 4.04-3.92 (5H, m), 3.00-2.91 (2H, m), 1.36 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.3, 168.3, 158.0, 148.1, 138.1, 136.2, 134.2, 133.7, 132.6, 131.8, 128.7, 127.7, 127.2, 123.1, 121.5, 121.3, 116.2, 114.7, 63.3, 43.4, 42.4, 40.1, 14.8; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_4$ $[M+H]^+$ 480.1923 found 480.1902.

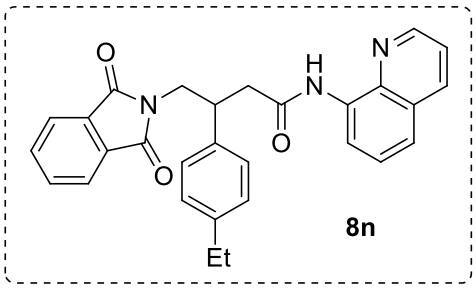
4-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(*p*-tolyl)butanamide (8m): The compound



8m

8m was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (70 mg, 77%); R_f (40% EtOAc/hexane) = 0.7; mp: 158-160 ^{o}C; IR (DCM): 3055, 2986, 1708, 1265, 743cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.80 (1H, dd, J_1 = 4.3, J_2 = 1.4 Hz), 8.47 (1H, dd, J_1 = 7.5, J_2 = 0.7 Hz), 8.12 (1H, dd, J_1 = 8.2, J_2 = 0.9 Hz), 7.65 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.55 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.45 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.41-7.32 (2H, m), 7.32 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 7.8 Hz), 4.05-3.95 (3H, m), 2.99-2.96 (2H, m), 2.29 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.3, 168.4, 148.1, 138.1, 137.8, 136.8, 136.2, 134.2, 133.7, 131.8, 129.5, 127.7, 127.6, 127.2, 123.1, 121.5, 121.3, 116.2, 43.4, 42.2, 40.5, 21.1; HRMS (ESI) calcd for $C_{28}H_{24}N_3O_3$ $[M+H]^+$ 450.1818 found 450.1833.

4-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethylphenyl)-*N*-(quinolin-8-yl)butanamide (8n): The

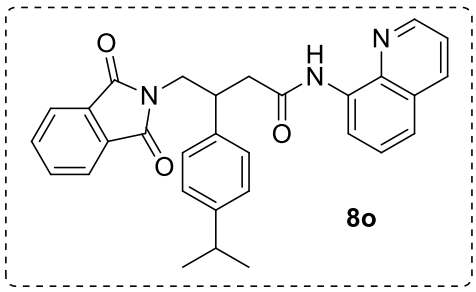


8n

compound **8n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (68 mg, 73%); R_f (40% EtOAc/hexane) = 0.75; mp: 138-140 ^{o}C; IR (DCM): 3348, 2965, 1713, 1326, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.81 (1H, br. s), 8.80 (1H, dd, J_1 = 4.2, J_2 = 1.4 Hz), 8.47 (1H, d, J = 7.4 Hz), 8.15 (1H, d, J = 8.0 Hz), 7.64 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.53 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.46 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.42-7.38 (1H, m), 7.34 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 7.9 Hz), 4.08-3.95 (3H, m), 3.00 (2H, d, J = 5.7 Hz), 2.58

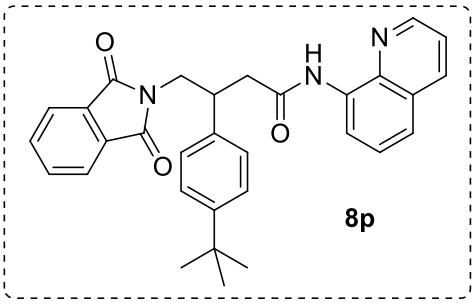
(2H, q, J = 7.6 Hz), 1.16 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.4, 148.0, 143.1, 138.1, 136.3, 134.2, 133.7, 131.9, 128.2, 127.7, 127.7, 127.3, 123.0, 121.5, 121.3, 116.3, 43.4, 42.2, 40.5, 28.4, 15.4; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_3$ $[M+H]^+$ 464.1974 found 464.1994.

4-(1,3-Dioxoisoindolin-2-yl)-3-(4-isopropylphenyl)-*N*-(quinolin-8-yl)butanamide (8o): The



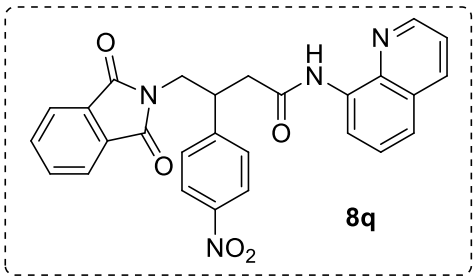
compound **8o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane =40:60) as a brown color solid (55 mg, 77%); R_f (40% EtOAc/hexane) = 0.6; mp: 90-92 ^{o}C; IR (DCM): 3054, 2961, 1713, 1265, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.70 (1H, br. s), 8.81-8.80 (1H, m), 8.43 (1H, dd, J_1 = 7.6, J_2 = 1.0 Hz), 8.11 (1H, d, J = 8.2 Hz), 7.62 (2H, dd, J_1 = 5.1, J_2 = 3.6 Hz), 7.53-7.51 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.3 Hz), 7.41-7.31 (4H, m), 7.18 (2H, d, J = 8.1 Hz), 4.09-3.93 (3H, m), 3.01-2.97 (2H, m), 2.88-2.81 (1H, m), 1.19 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.4, 148.0, 147.7, 138.3, 138.1, 136.2, 134.2, 133.6, 131.9, 127.7, 127.6, 127.2, 126.8, 123.0, 121.5, 121.2, 116.1, 43.4, 42.2, 40.4, 33.7, 23.9; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_3$ $[M+H]^+$ 478.2131 found 478.2109.

3-(4-(*Tert*-butyl)phenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8p): The



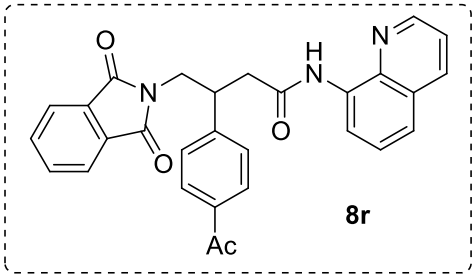
compound **8p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (57 mg, 77%); R_f (40% EtOAc/hexane) = 0.6; mp: 120-122 ^{o}C; IR (DCM): 3054, 2963, 1714, 1265, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.70 (1H, br. s), 8.80 (1H, dd, J_1 = 4.2, J_2 = 1.9 Hz), 8.42 (1H, dd, J_1 = 7.6, J_2 = 0.9 Hz), 8.09 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.61 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.51 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.43 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.40-7.29 (6H, m), 4.09-3.93 (3H, m), 3.01-2.95 (2H, m), 1.26 (9H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.4, 150.0, 148.1, 138.1, 137.9, 136.2, 134.2, 133.7, 131.8, 127.7, 127.3, 127.2, 125.7, 123.0, 121.5, 121.2, 116.1, 43.4, 42.2, 40.3, 34.4, 31.3; HRMS (ESI) calcd for $C_{31}H_{30}N_3O_3$ $[M+H]^+$ 492.2287 found 492.2267.

4-(1,3-Dioxoisoindolin-2-yl)-3-(4-nitrophenyl)-*N*-(quinolin-8-yl)butanamide (8q): The compound **8q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (88 mg, 91%); R_f (40% EtOAc/hexane) = 0.3; mp: 148-150 ^oC; IR (DCM): 3343, 3057, 1714, 1348, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.73 (1H, br. s), 8.79 (1H, dd, J_1 = 4.2, J_2 = 1.4 Hz), 8.51-8.49 (1H, m), 8.18-8.14 (3H, m), 7.72 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.63 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.59 (2H, d, J = 8.7 Hz), 7.48-7.45 (2H, m), 7.42-7.38 (1H, m), 4.20-4.10 (1H, m), 4.09-4.01 (2H, m), 3.09 (1H, dd, J_1 = 15.4, J_2 = 6.2 Hz), 3.00 (1H, dd, J_1 = 15.3, J_2 = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.2, 168.1, 148.4, 148.2, 147.2, 138.1, 136.3, 134.1, 133.9, 131.6, 128.9, 127.8, 127.2, 124.0, 123.3, 121.7, 116.4, 42.6, 41.6, 40.9; HRMS (ESI) calcd for $C_{27}H_{21}N_4O_5$ $[M+H]^+$ 481.1512 found 481.1534.



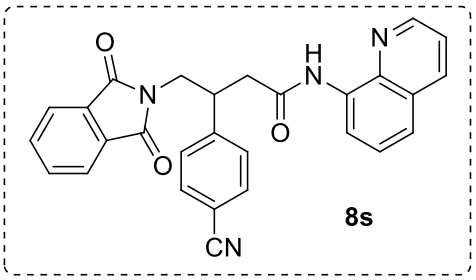
8q

3-(4-Acetylphenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8r): The compound **8r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (60 mg, 63%); R_f (40% EtOAc/hexane) = 0.3; mp: 178-180 ^oC; IR (DCM): 3343, 1715, 1527, 1267, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.79 (1H, dd, J_1 = 4.2, J_2 = 1.4 Hz), 8.48 (1H, dd, J_1 = 7.7, J_2 = 0.8 Hz), 8.13 (1H, dd, J_1 = 8.3, J_2 = 1.4 Hz), 7.90 (2H, d, J = 8.2 Hz), 7.69 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.59 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.52 (2H, d, J = 8.2 Hz), 7.47-7.43 (2H, m), 7.38 (1H, t, J = 8.0 Hz), 4.13-4.0 (3H, m), 3.09-2.96 (2H, m), 2.55 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.7, 168.7, 168.2, 148.1, 146.4, 138.1, 136.2, 136.1, 134.0, 133.9, 131.7, 128.9, 128.1, 127.7, 127.2, 123.2, 121.6, 121.5, 116.3, 42.8, 41.7, 40.9, 26.6; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_4$ $[M+H]^+$ 478.1767 found 478.1789.



8r

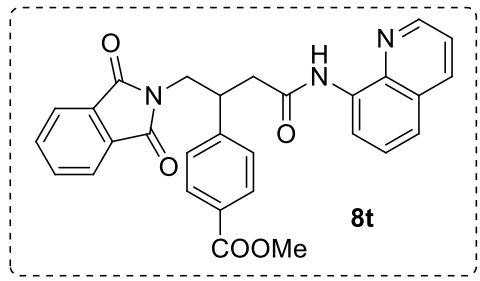
3-(4-Cyanophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (8s): The compound **8s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (50 mg, 72%); R_f (40% EtOAc/hexane) = 0.4; mp: 156-158 ^oC; IR (DCM): 3344, 3057, 2229, 1526, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H



8s

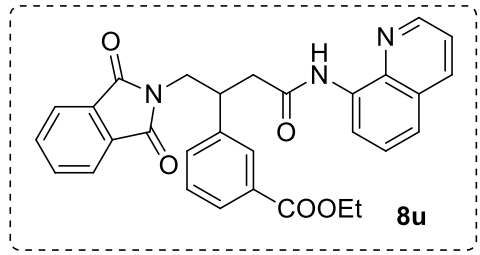
9.72 (1H, br. s), 8.79 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.48 (1H, dd, J_1 = 7.5, J_2 = 1.3 Hz), 8.14 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.70 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.63-7.59 (4H, m), 7.53 (2H, d, J = 8.3 Hz), 7.48-7.44 (2H, m), 7.39 (1H, t, J = 8.1 Hz), 4.12-3.97 (3H, m), 3.06 (1H, dd, J_1 = 15.4, J_2 = 6.2 Hz), 2.97 (1H, dd, J_1 = 15.4, J_2 = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.3, 168.2, 148.2, 146.3, 138.1, 136.3, 134.0, 133.9, 132.6, 131.6, 128.8, 127.8, 127.2, 123.3, 121.7, 121.6, 118.7, 116.4, 111.2, 42.6, 41.5, 41.1; HRMS (ESI) calcd for $C_{28}H_{21}N_4O_3$ $[M+H]^+$ 461.1614 found 461.1595.

Methyl 4-(1-(1,3-dioxoisoindolin-2-yl)-4-oxo-4-(quinolin-8-ylamino)butan-2-yl)benzoate (8t): The compound **8t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (55 mg, 74%); R_f (40% EtOAc/hexane) = 0.3; mp: 194-196 ^{o}C; IR (DCM):3056, 2922, 1716, 1269, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.80 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.48 (1H, dd, J_1 = 7.6, J_2 = 1.2 Hz), 8.13 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.98 (2H, d, J= 8.3 Hz), 7.68 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.58 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.50 (2H, d, J = 8.3 Hz), 7.47-7.42 (2H, m), 7.37 (1H, t, J = 8.1 Hz), 4.13-3.98 (3H, m), 3.88 (3H, s), 3.08-2.96 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.7, 168.2, 166.9, 148.1, 146.1, 138.1, 136.2, 134.0, 133.9, 131.7, 130.1, 129.2, 127.9, 127.7, 127.2, 123.2, 121.6, 121.5, 116.3, 52.1, 42.9, 41.8, 40.9; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_5$ $[M+H]^+$ 494.1716 found 494.1696.



8t

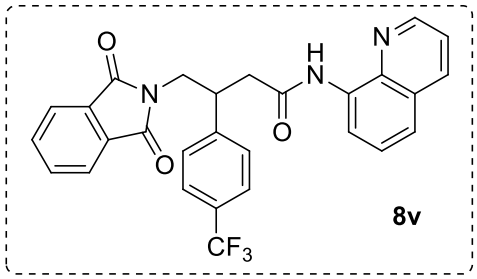
Ethyl 3-(1-(1,3-dioxoisoindolin-2-yl)-4-oxo-4-(quinolin-8-ylamino)butan-2-yl)benzoate (8u): The compound **8u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (59 mg, 77%); R_f (40% EtOAc/hexane) = 0.3; mp: 142-144 ^{o}C; IR (DCM):3054, 2986, 1713, 1266, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.80-8.79 (1H, m), 8.45 (1H, d, J = 7.5 Hz), 8.12-8.10 (2H, m), 7.92 (2H, d, J= 7.6 Hz), 7.67-7.62 (3H, m), 7.56 (2H, dd, J_1 = 5.6, J_2 = 3.0 Hz), 7.46-7.33 (4H, m),



8u

4.37 (2H, q, J = 7.1 Hz), 4.10-3.97 (3H, m), 3.08-2.97 (2H, m), 1.39 (3H, t, J= 7.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.9, 168.3, 166.4, 148.1, 141.3, 138.1, 136.2, 134.1, 133.8, 132.6, 131.8, 131.0, 128.8, 128.6, 127.7, 127.2, 123.1, 121.6, 121.4, 116.2, 61.0, 43.1, 41.8, 40.8, 14.4; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_5$ $[M+H]^+$ 508.1872 found 508.1847.

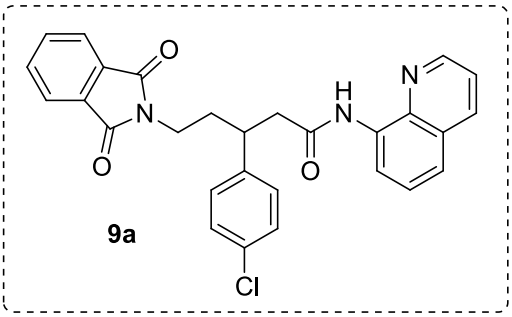
4-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(4-(trifluoromethyl)phenyl)butanamide



8v

(8v): The compound **8v** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (41 mg, 54%); R_f (40% EtOAc/hexane) = 0.6; mp: 168-170 ^{o}C; IR (DCM): 3351, 2935, 1711, 1326, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.79 (1H, dd, J_1 = 4.1, J_2 = 1.4 Hz), 8.48 (1H, d, J = 7.5 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.3 Hz), 7.69 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.60-7.54 (6H, m), 7.47-7.43 (2H, m), 7.38 (1H, t, J = 8.0 Hz), 4.14-3.97 (3H, m), 3.08-2.95 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.6, 168.2, 148.1, 145.0, 138.1, 136.3, 134.0, 133.9, 131.7, 129.5 (q, J_{C-F}= 32.4Hz), 128.2, 127.8, 127.2, 125.8 (q, J_{C-F} = 3.7Hz), 124.1 (q, J_{C-F} = 271Hz), 123.2, 121.6, 121.5, 116.3, 42.9, 41.8, 40.8; HRMS (ESI) calcd for $C_{28}H_{21}F_3N_3O_3$ $[M+H]^+$ 504.1535 found 504.1521.

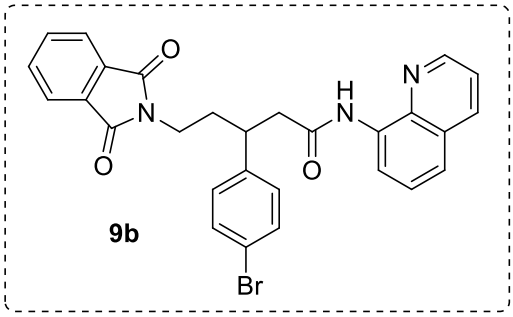
3-(4-Chlorophenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (9a): The compound **9a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color solid (83 mg, 85%); R_f (40% EtOAc/hexane) = 0.6; mp: 91-93 ^{o}C; IR (DCM): 3055, 1704, 1422, 1265, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, br. s), 8.74 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.67 (1H, dd, J_1 = 6.2, J_2 = 2.7 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.67 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.51-7.46 (2H, m), 7.43 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.20 (2H, d, J = 8.4 Hz), 3.70-3.62 (2H, m), 3.44-3.37 (1H, m), 2.91-2.77 (2H, m), 2.28-2.15 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.2, 168.2, 148.1, 141.2, 138.1, 136.3, 134.1, 133.8, 132.4, 131.9, 128.9, 128.8, 127.8, 127.3, 123.0, 121.6,



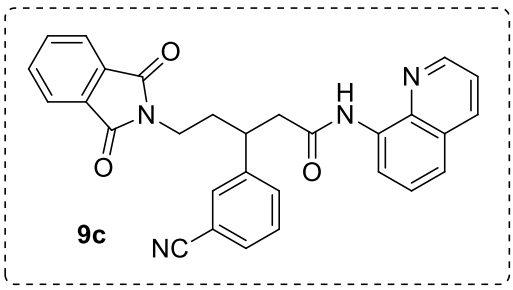
9a

121.6, 116.5, 45.8, 40.0, 36.4, 33.7; HRMS (ESI) calcd for $C_{28}H_{23}ClN_3O_3$ $[M+H]^+$ 484.1428 found 484.1444.

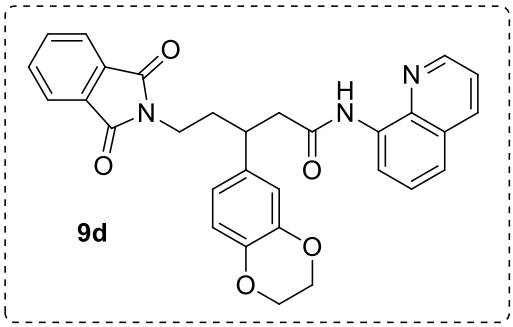
3-(4-Bromophenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (9b): The compound **9b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid (67 mg, 84%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2929, 17014, 1530, 1326, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, br. s) 8.75 (1H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.67 (1H, dd, J_1 = 6.2, J_2 = 2.7 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 7.76 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.67 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.52-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 3.66 (2H, t, J = 7.4 Hz), 3.43-3.36 (1H, m), 2.87 (1H, dd, J_1 = 14.7, J_2 = 6.7 Hz), 2.79 (1H, dd, J_1 = 14.7, J_2 = 8.0 Hz), 2.31-2.15 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.2, 168.2, 148.1, 141.8, 138.2, 136.3, 134.1, 133.9, 132.0, 131.8, 129.3, 127.8, 127.3, 123.0, 121.6, 120.5, 116.5, 45.8, 40.2, 36.4, 33.6; HRMS (ESI) calcd for $C_{28}H_{23}BrN_3O_3$ $[M+H]^+$ 528.0923, found 528.0906.



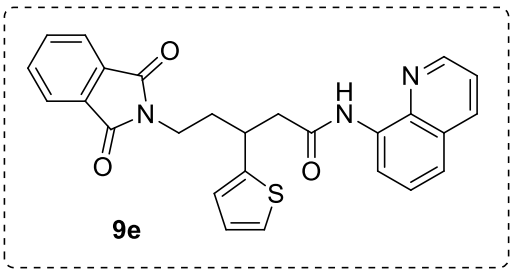
3-(3-Cyanophenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (9c): The compound **9c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown color solid (60 mg, 84%); R_f (40% EtOAc/hexane) = 0.3; mp: 132-134 ^oC; IR (DCM): 3055, 2987, 1710, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.65 (1H, br. s), 8.76 (1H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.66-8.61 (1H, m), 8.14 (1H, dd, J_1 = 8.3, J_2 = 1.7 Hz), 7.78 (2H, dd, J_1 = 5.6, J_2 = 3.1 Hz), 7.69 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.65 (1H, s), 7.61-7.58 (1H, m), 7.49-7.48 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.33-7.32 (2H, m), 3.68 (2H, t, J = 7.0 Hz), 3.51-3.44 (1H, m), 2.95 (1H, dd, J_1 = 14.9, J_2 = 6.4 Hz), 2.82 (1H, dd, J_1 = 14.9, J_2 = 8.3 Hz), 2.30-2.17 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.7, 168.2, 148.2, 144.4, 138.1, 136.4, 133.9, 132.5, 131.9, 131.1, 130.4, 129.4, 127.8, 127.3, 123.1, 121.7, 121.7, 118.7, 116.5, 112.6, 45.2, 40.1, 36.2, 33.7, 29.7; HRMS (ESI) calcd for $C_{29}H_{23}N_4O_3$ $[M+H]^+$ 475.1770 found 475.1790.



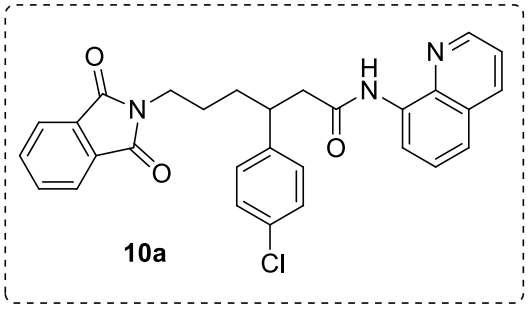
3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (9d): The compound **9d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (54 mg, 71%); R_f (40% EtOAc/hexane) = 0.3; mp: 142-144 ^oC; IR (DCM): 3055, 2986, 1709, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.65 (1H, br. s), 8.76 (1H, dd, J_1 = 4.4, J_2 = 1.6 Hz), 8.70 (1H, dd, J_1 = 7.2, J_2 = 2.0 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.77 (2H, dd, J_1 = 5.6, J_2 = 3.2 Hz), 7.67 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.52-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.0 Hz), 6.83-6.81 (2H, m), 6.73 (1H, d, J = 8.0 Hz), 4.16-4.12 (4H, m), 3.67 (2H, t, J = 7.2 Hz), 3.33-3.28 (1H, m), 2.87-2.77 (2H, m), 2.24-2.12 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 168.2, 148.0, 143.4, 142.2, 138.2, 136.3, 136.0, 134.3, 133.7, 132.1, 127.8, 127.4, 123.0, 121.5, 121.4, 120.5, 117.4, 116.5, 116.1, 64.2, 64.2, 46.1, 40.1, 36.6, 33.8; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_5$ $[M+H]^+$ 508.1872 found 508.1846.



5-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)pentanamide (9e): The compound **9e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid(48 mg, 70%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2929, 1707, 1526, 1264, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, br. s), 8.76 (1H, dd, J_1 = 4.2, J_2 = 1.6Hz), 8.72 (1H, dd, J_1 = 6.8, J_2 = 2.2 Hz), 8.14 (1H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.80 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.68 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.53-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.11 (1H, d, J = 5.1 Hz), 7.03 (1H, d, J = 3.4 Hz), 6.86 (1H, dd, J_1 = 5.0, J_2 = 3.5 Hz), 3.82-3.69 (3H, m), 2.99-2.88 (2H, m), 2.31-2.17 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.1, 168.3, 148.1, 146.5, 138.2, 136.3, 134.3, 133.8, 132.1, 127.8, 127.3, 126.7, 125.0, 123.7, 123.1, 121.6, 121.5, 116.5, 46.5, 36.3, 35.9, 35.4; HRMS (ESI) calcd for $C_{26}H_{22}N_3O_3S$ $[M+H]^+$ 456.1382 found 456.1399.

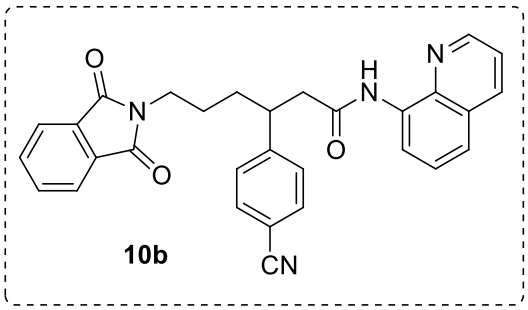


3-(4-Chlorophenyl)-6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (10a): The compound **10a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(59 mg, 79%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 3054, 2939, 1711, 1527, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1H, br. s), 8.75 (1H, dd, J_1 = 2.9, J_2 = 1.7 Hz), 8.66 (1H, dd, J_1 = 5.7, J_2 = 3.3 Hz), 8.14-8.11 (1H, m), 7.80-7.78 (2H, m), 7.69-7.67 (2H, m), 7.48-7.42 (3H, m), 7.25-7.20 (4H, m), 3.67-3.63 (2H, m), 3.37-3.29 (1H, m), 2.89-2.77 (2H, m), 1.91-1.83 (1H, m), 1.78-1.61 (2H, m), 1.57-1.50 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.6, 168.3, 148.1, 142.0, 138.2, 136.3, 134.2, 133.9, 132.3, 132.0, 128.9, 128.9, 127.8, 127.3, 123.2, 121.6, 121.5, 116.4, 45.4, 41.7, 37.8, 33.3, 26.5; HRMS (ESI) calcd for $C_{29}H_{25}ClN_3O_3$ $[M+H]^+$ 498.1584, found 498.1567.



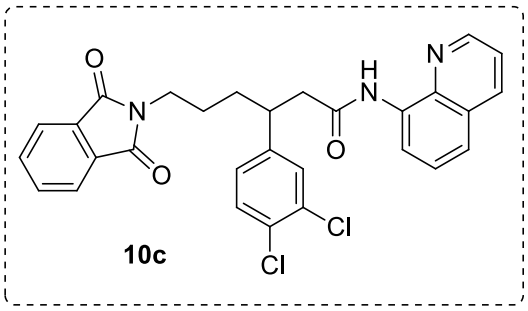
10a

3-(4-Cyanophenyl)-6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (10b): The compound **10b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid(43 mg, 59%); R_f (40% EtOAc/hexane) = 0.4; IR (DCM): 3056, 2938, 1701, 1327, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1H, br. s), 8.77 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.65-8.63 (1H, m), 8.16 (1H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.82 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.71 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.51-7.46 (3H, m), 7.42 (2H, d, J = 8.2 Hz), 3.73-3.64 (2H, m), 3.48-3.41 (1H, m), 2.93 (1H, dd, J_1 = 14.9, J_2 = 6.3 Hz), 2.83 (1H, dd, J_1 = 14.9, J_2 = 8.4 Hz), 1.95-1.87 (1H, m), 1.83-1.67 (2H, m), 1.59-1.50 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.1, 168.3, 149.3, 148.1, 138.1, 136.4, 134.0, 134.0, 132.5, 132.0, 128.5, 127.9, 127.3, 123.2, 121.7, 118.9, 116.5, 110.5, 44.8, 42.2, 37.6, 33.0, 26.5; HRMS (ESI) calcd for $C_{30}H_{25}N_4O_3$ $[M+H]^+$ 489.1927, found 489.1940.



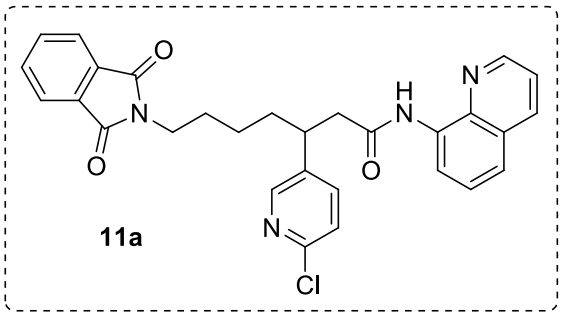
10b

3-(3,4-Dichlorophenyl)-6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (10c): The compound **10c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color solid (60 mg, 75%); R_f (40% EtOAc/hexane) = 0.7;



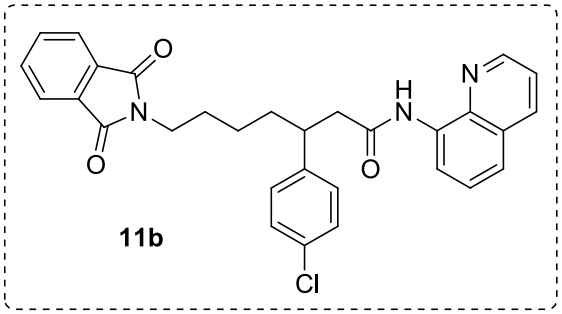
mp: 110-112 ^{o}C; IR (DCM): 3346, 2937, 1771, 1394, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1H, br. s), 8.78 (1H, d, J = 3.2 Hz), 8.65 (1H, t, J = 4.5 Hz), 8.15 (1H, d, J = 7.7 Hz), 7.81 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.70 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.49 (2H, d, J = 4.6 Hz), 7.46 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.39 (1H, d, J = 1.4 Hz), 7.32 (1H, d, J = 8.2 Hz), 7.13 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.36–3.29 (1H, m), 2.87 (1H, dd, J_1 = 14.8, J_2 = 6.4 Hz), 2.80 (1H, dd, J_1 = 14.8, J_2 = 8.3 Hz), 1.92-1.82 (1H, m), 1.78-1.65 (2H, m), 1.60-1.52 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.2, 168.3, 148.1, 143.9, 138.2, 136.3, 134.1, 133.9, 132.7, 132.0, 130.6, 130.6, 129.4, 127.9, 127.3, 127.2, 123.2, 121.6, 121.6, 116.5, 45.1, 41.6, 37.7, 33.2, 26.5; HRMS (ESI) calcd for $C_{29}H_{24}Cl_2N_3O_3$ $[M+H]^+$ 532.1195 found 532.1177.

3-(6-Chloropyridin-3-yl)-7-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (11a):



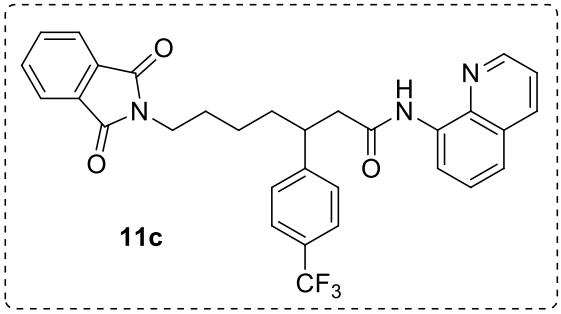
The compound **11a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (50 mg, 65%); R_f (40% EtOAc/hexane) = 0.4; mp: 92-94 ^{o}C; IR (DCM): 2936, 1708, 1524, 1396, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, br. s), 8.78 (1H, d, J = 3.8 Hz), 8.67 (1H, t, J = 4.4 Hz), 8.33 (1H, s), 8.15 (1H, d, J = 8.2 Hz), 7.82 (2H, dd, J_1 = 5.0, J_2 = 3.2 Hz), 7.70 (2H, dd, J_1 = 5.2, J_2 = 3.3 Hz), 7.59 (1H, dd, J_1 = 8.2, J_2 = 1.9 Hz), 7.53-7.49 (2H, m), 7.45 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.23 (1H, d, J = 8.2 Hz), 3.64 (2H, t, J = 7.2 Hz), 3.37-3.32 (1H, m), 2.92 (1H, dd, J_1 = 15.0, J_2 = 6.6 Hz), 2.80 (1H, dd, J_1 = 14.9, J_2 = 8.2 Hz), 1.92-1.83 (1H, m), 1.81-1.70 (2H, m), 1.68-1.61 (1H, m), 1.36-1.29 (1H, m), 1.25-1.21 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.1, 168.3, 149.6, 149.2, 148.2, 138.2, 138.2, 138.0, 136.4, 134.0, 133.9, 132.0, 127.9, 127.3, 124.2, 123.2, 121.7, 121.7, 116.5, 44.8, 39.2, 37.5, 35.2, 28.2, 24.4; HRMS (ESI) calcd for $C_{29}H_{26}ClN_4O_3$ $[M+H]^+$ 513.1693, found 513.1667.

3-(4-Chlorophenyl)-7-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (11b): The compound **11b** was obtained after purification by column chromatography on silica gel



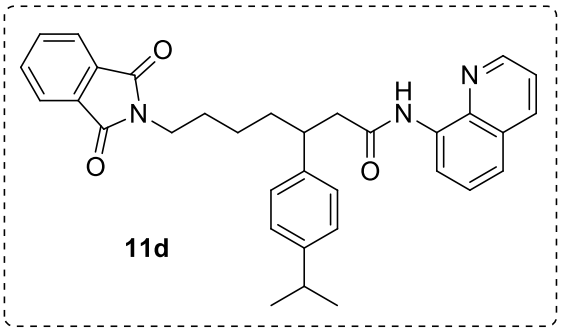
(EtOAc:hexane = 40:60) as a green color viscous liquid(50 mg, 65%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2938, 1712, 1526, 1326, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1H, br. s), 8.77 (1H, d, J = 4.1 Hz), 8.70 (1H, dd, J_1 = 6.6, J_2 = 1.4 Hz), 8.14 (1H, dd, J_1 = 8.2, J_2 = 0.2 Hz), 7.82 (2H, dd, J_1 = 5.0, J_2 = 3.3 Hz), 7.70 (2H, dd, J_1 = 5.9, J_2 = 3.2 Hz), 7.53-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.21 (4H, s), 3.62 (2H, t, J = 7.2 Hz), 3.33-3.26 (1H, m), 2.89-2.77 (2H, m), 1.88-1.81 (1H, m), 1.75-1.68 (2H, m), 1.66-1.59 (1H, m), 1.32-1.20 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 168.4, 148.1, 142.3, 138.2, 136.3, 134.3, 133.9, 132.1, 132.1, 128.9, 128.7, 127.9, 127.3, 123.1, 121.6, 121.5, 116.5, 45.5, 41.8, 37.7, 35.5, 28.3, 24.5; HRMS (ESI) calcd for $C_{30}H_{27}ClN_3O_3$ $[M+H]^+$ 512.1741, found 512.1765.

7-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(4-(trifluoromethyl)phenyl)heptanamide



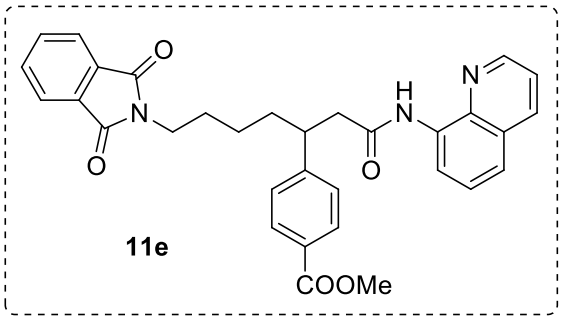
(11c): The compound **11c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(55 mg, 67%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2936, 1710, 1524, 1326, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.66 (1H, br. s), 8.76 (1H, d, J = 2.8 Hz), 8.70 (1H, dd, J_1 = 6.4, J_2 = 2.2 Hz), 8.14 (1H, d, J = 7.1 Hz), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.70 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.51-7.48 (4H, m), 7.45 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.40 (2H, d, J = 8.0 Hz), 3.63 (2H, t, J = 6.9 Hz), 3.41-3.38 (1H, m), 2.93-2.81 (2H, m), 1.93-1.84 (1H, m), 1.82-1.75 (2H, m), 1.67-1.58 (1H, m), 1.31-1.30 (1H, m), 1.25-1.20 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.6, 168.4, 148.1, 138.2, 136.3, 134.2, 133.9, 132.0, 128.7 (q, J_{C-F} = 32.2Hz), 127.9, 127.9, 127.3, 125.5 (q, J_{C-F} = 3.6Hz), 124.2 (q, J_{C-F} = 271Hz), 123.1, 122.8, 121.6, 121.6, 116.5, 45.2, 42.2, 37.6, 35.4, 28.2, 24.5; HRMS (ESI) calcd for $C_{31}H_{27}F_3N_3O_3$ $[M+H]^+$ 546.2005, found 546.2027.

7-(1,3-Dioxoisoindolin-2-yl)-3-(4-isopropylphenyl)-*N*-(quinolin-8-yl)heptanamide (11d): The compound **11d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid(55 mg, 70%); R_f (40% EtOAc/hexane) =



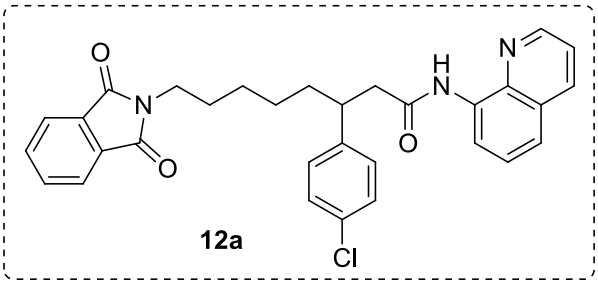
0.7; IR (DCM): 2933, 1711, 1525, 1326, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, br. s), 8.77 (1H, d, J = 4.0 Hz), 8.74 (1H, d, J = 7.2Hz), 8.14 (1H, d, J = 8.2 Hz), 7.81 (2H, dd, J_1 = 5.0, J_2 = 3.2 Hz), 7.69 (2H, dd, J_1 = 5.1, J_2 = 3.2 Hz), 7.53-7.47 (2H, m), 7.43 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.20 (2H, d, J = 7.8 Hz), 7.12 (2H, d, J = 7.8 Hz), 3.62 (2H, t, J = 7.2 Hz), 3.32-3.25 (1H, m), 2.85-2.78 (3H, m), 1.89-1.82 (1H, m), 1.78-1.70 (2H, m), 1.65-1.56 (1H, m), 1.35-1.31 (1H, m), 1.26-1.24 (1H, m), 1.17 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 168.4, 148.0, 146.8, 141.2, 138.3, 136.3, 134.4, 133.8, 132.1, 127.9, 127.4, 127.3, 126.6, 123.1, 121.5, 121.3, 116.4, 45.7, 42.0, 37.8, 35.7, 33.6, 28.4, 24.7, 24.0, 23.9; HRMS (ESI) calcd for $C_{33}H_{34}N_3O_3$ $[M+H]^+$ 520.2600, found 520.2623.

Methyl 4-(7-(1,3-dioxoisoindolin-2-yl)-1-oxo-1-(quinolin-8-ylamino)heptan-3-yl)benzoate



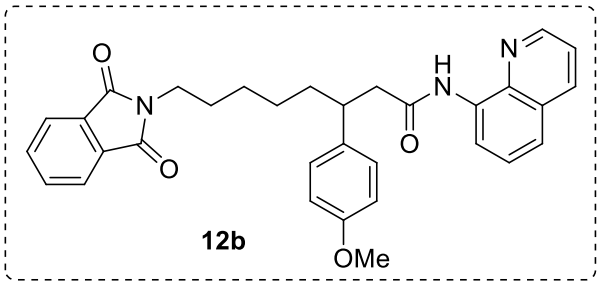
(11e): The compound **11e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(58 mg, 72%); R_f (40% EtOAc/hexane) = 0.3; IR (DCM): 2939, 1712, 1525, 1282, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.67 (1H, br. s), 8.76 (1H, d, J = 3.8 Hz), 8.69 (1H, dd, J_1 = 6.9, J_2 = 2.0 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.93 (2H, d, J = 8.0 Hz), 7.81 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.69 (2H, dd, J_1 = 5.3, J_2 = 3.2 Hz), 7.52-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.36 (2H, d, J = 8.0 Hz), 3.88 (3H, s), 3.62 (2H, t, J = 7.2 Hz), 3.43-3.36 (1H, m), 2.93-2.81 (2H, m), 1.92-1.85 (1H, m), 1.82-1.74 (2H, m), 1.66-1.59 (1H, m), 1.34-1.29 (1H, m), 1.24-1.17 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 168.3, 166.9, 149.4, 148.1, 138.2, 136.3, 134.2, 133.8, 132.0, 130.0, 128.4, 127.8, 127.6, 127.3, 123.1, 121.6, 121.5, 116.5, 51.9, 45.2, 42.4, 37.6, 35.4, 28.3, 24.5; HRMS (ESI) calcd for $C_{32}H_{30}N_3O_5$ $[M+H]^+$ 536.2185, found 536.2204.

3-(4-Chlorophenyl)-8-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (12a): The compound **12a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid (64 mg, 61%); R_f (40% EtOAc/hexane)



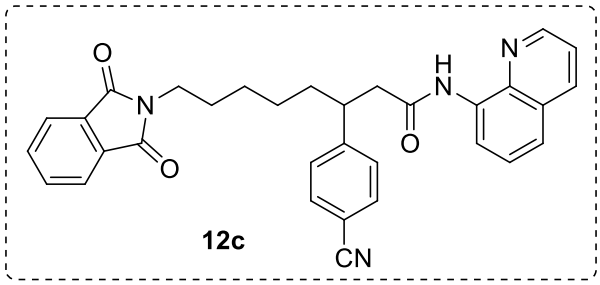
= 0.5; IR (DCM): 3351, 2933, 1709, 1531, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1H, br. s), 8.75 (1H, dd, J_1 = 4.1, J_2 = 1.2 Hz), 8.70 (1H, dd, J_1 = 6.8, J_2 = 2.0 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.0 Hz), 7.81 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.68 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.51–7.46 (2H, m), 7.43 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.25-7.20 (4H, m), 3.62 (2H, t, J = 7.2 Hz), 3.31-3.24 (1H, m), 2.87-2.75 (2H, m), 1.83-1.76 (1H, m), 1.71-1.58 (3H, m), 1.38-1.18 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 168.4, 148.1, 142.6, 138.1, 136.4, 134.2, 133.8, 132.1, 132.0, 128.9, 128.7, 127.9, 127.3, 123.1, 121.6, 121.5, 116.5, 45.7, 42.0, 37.9, 36.0, 28.4, 27.0, 26.8; HRMS (ESI) calculated for $C_{31}H_{29}ClN_3O_3$ $[M+H]^+$ 526.1897 found 526.1876.

8-(1,3-Dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)octanamide (12b): The



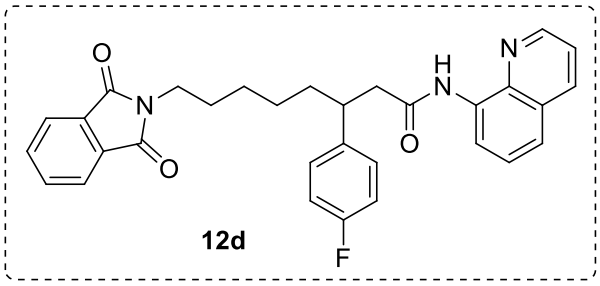
compound **12b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid(53 mg, 68%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2930, 1708, 1523, 1246, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.66 (1H, br. s), 8.77 (1H, d, J = 4.1 Hz), 8.72 (1H, d, J = 7.0 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.83 (2H, dd, J_1 = 5.1, J_2 = 3.1 Hz), 7.70 (2H, dd, J_1 = 5.2, J_2 = 3.2 Hz), 7.53-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.20 (2H, d, J = 8.4 Hz), 6.82 (2H, d, J = 8.4 Hz), 3.75 (3H, s), 3.63 (2H, t, J = 7.3 Hz), 3.28-3.21 (1H, m), 2.86-2.76 (2H, m), 1.82-1.76 (1H, m), 1.63-1.58 (3H, m), 1.40-1.32 (3H, m), 1.24-1.18 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 168.4, 158.1, 148.0, 138.3, 136.2, 136.1, 134.4, 133.8, 132.2, 128.4, 127.9, 127.4, 123.1, 121.5, 121.3, 116.4, 114.0, 55.2, 46.1, 41.8, 38.0, 36.2, 28.5, 27.0, 26.9; HRMS (ESI) calculated for $C_{32}H_{32}N_3O_4$ $[M+H]^+$ 522.2393 found 522.2418.

3-(4-Cyanophenyl)-8-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (12c): The compound **12c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color solid (49 mg, 63%); R_f (40% EtOAc/hexane) = 0.4; mp: 48-50 ^{o}C; IR (DCM): 2934, 2227, 1710, 1524, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H



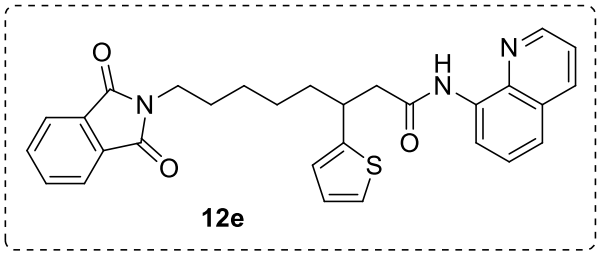
9.64 (1H, br. s), 8.77 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.67 (1H, dd, J_1 = 5.3, J_2 = 3.7 Hz), 8.15 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.83 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.53-7.48 (2H, m), 7.46 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.40 (2H, d, J = 8.2 Hz), 3.63 (2H, t, J = 7.2 Hz), 3.40-3.36 (1H, m), 2.90 (1H, dd, J_1 = 14.8, J_2 = 6.4 Hz), 2.80 (1H, dd, J_1 = 14.8, J_2 = 8.3 Hz), 1.86-1.79 (1H, m), 1.76-1.69 (1H, m), 1.66-1.59 (2H, m), 1.39-1.29 (3H, m), 1.22-1.13 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.4, 149.9, 148.1, 138.2, 136.4, 134.1, 133.9, 132.4, 132.1, 128.4, 127.9, 127.3, 123.2, 121.7, 119.0, 116.5, 110.3, 45.1, 42.6, 37.8, 35.7, 28.3, 26.9, 26.7; HRMS (ESI) calculated for $C_{32}H_{29}N_4O_3$ $[M+H]^+$ 517.2240 found 517.2217.

8-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(quinolin-8-yl)octanamide (12d): The



compound **12d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless viscous liquid (50 mg, 72%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2934, 1713, 1525, 1222, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1H, br. s), 8.77 (1H, d, J = 3.8 Hz), 8.71 (1H, d, J = 6.6Hz), 8.14 (1H, d, J = 8.2 Hz), 7.83 (2H, dd, J_1 = 5.2, J_2 = 3.3 Hz), 7.71 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.53-7.47 (2H, m), 7.45 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 7.26-7.23 (2H, m), 6.97 (2H, t, J = 8.6 Hz), 3.63 (2H, t, J = 7.2 Hz), 3.30-3.27 (1H, m), 2.88-2.75 (2H, m), 1.83-1.77 (1H, m), 1.66-1.59 (3H, m), 1.44-1.30 (3H, m) 1.22-1.16 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.0, 168.4, 161.4 (d, J_{C-F} = 242.6Hz), 148.0, 139.7 (d, J_{C-F} = 2.9Hz), 138.2, 136.3, 134.3, 133.8, 132.1, 128.9 (d, J_{C-F} = 7.9Hz), 127.9, 127.3, 123.1, 121.6, 121.4, 116.4, 115.3 (d, J_{C-F} = 21.0Hz), 41.2, 37.1, 33.2, 31.4, 23.7, 22.2, 22.0; HRMS (ESI) calcd for $C_{31}H_{29}FN_3O_3$ $[M+H]^+$ 510.2193 found 510.2219.

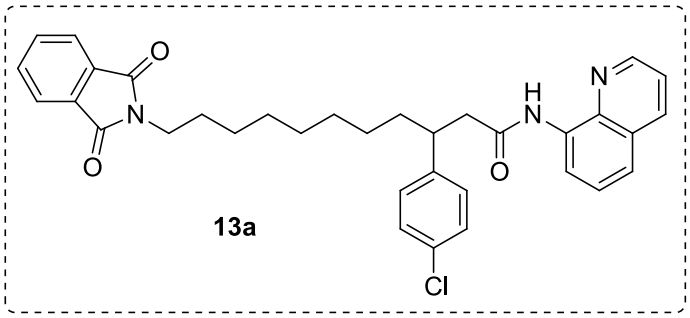
8-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)octanamideoctanamide (12e): The compound **12e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid (55 mg, 74%); R_f (40%



12e

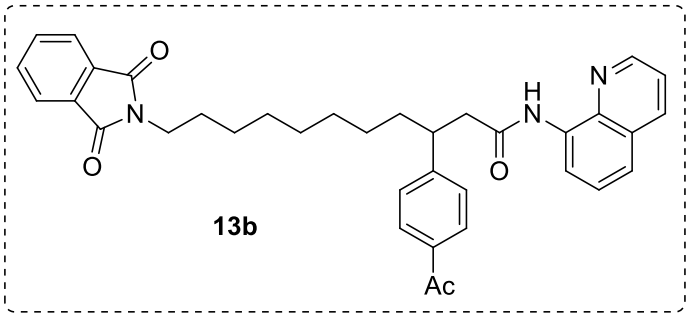
EtOAc/hexane) = 0.5; IR (DCM): 2935, 1712, 1525, 1325, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.74 (1H, br. s), 8.79 (1H, d, J = 4.0 Hz), 8.75 (1H, d, J = 7.0 Hz), 8.15 (1H, d, J = 8.2 Hz), 7.83 (2H, dd, J_1 = 5.1, J_2 = 3.3 Hz), 7.70 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.55-7.48 (2H, m), 7.45 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.13 (1H, d, J = 4.9 Hz), 6.91-6.88 (2H, m), 3.68-3.63 (3H, m), 2.88 (2H, d, J = 7.2 Hz), 1.87-1.81 (1H, m), 1.76-1.61 (3H, m), 1.44-1.31 (4H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 168.4, 148.1, 148.1, 138.3, 136.3, 134.4, 133.8, 132.1, 127.9, 127.4, 126.6, 124.3, 123.2, 123.1, 121.6, 121.5, 116.5, 46.7, 38.0, 37.2, 28.5, 26.9, 26.8; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_3S$ $[M+H]^+$ 498.1851, found 498.1830.

3-(4-Chlorophenyl)-11-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)undecanamide (13a): The compound **13a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a pale yellow color semisolid (47 mg, 55%); R_f (40% EtOAc/hexane) = 0.6; IR (DCM): 3351, 2933, 1709, 1531, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1H, br. s), 8.77 (1H, d, J = 3.1 Hz), 8.71 (1H, dd, J_1 = 6.9, J_2 = 1.2 Hz), 8.14 (1H, dd, J_1 = 8.2, J_2 = 0.6 Hz), 7.84 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.70 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.53-7.47 (2H, m), 7.45 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.27-7.22 (4H, m), 3.66 (2H, t, J = 7.3 Hz), 3.32-3.24 (1H, m), 2.89-2.76 (2H, m), 1.82-1.75 (1H, m), 1.70-1.58 (3H, m), 1.27-1.13 (10H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.0, 168.5, 148.1, 142.8, 138.2, 136.3, 134.3, 133.8, 132.2, 132.0, 128.9, 128.7, 127.9, 127.4, 123.1, 121.6, 121.5, 116.4, 45.7, 42.1, 38.0, 36.2, 29.4, 29.3, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{34}H_{35}ClN_3O_3$ $[M+H]^+$ 568.2367 found 568.2390.



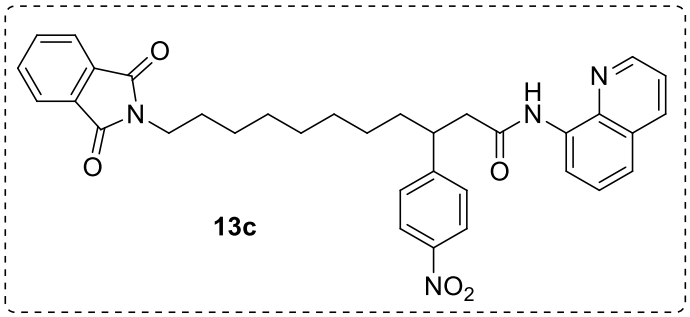
13a

3-(4-Acetylphenyl)-11-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)undecanamide (13b): The compound **13b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a pale yellow color viscous liquid(56 mg, 65%); R_f (40% EtOAc/hexane) = 0.3; IR (DCM): 2929, 1710, 1528, 1267, 720 cm^{-1}; ^1H NMR (400 MHz,



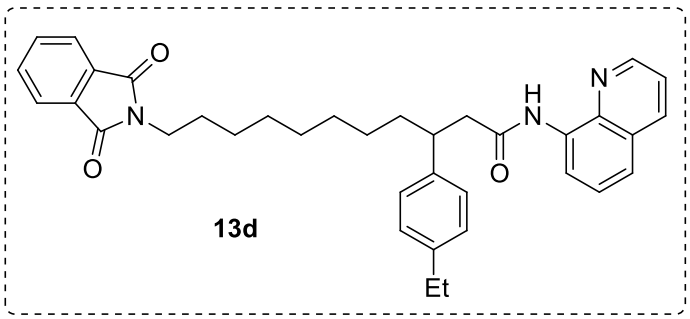
$CDCl_3$) δ_H 9.68 (1H, br. s), 8.74–8.69 (2H, m), 8.12 (1H, dd, J_1 = 8.2, J_2 = 1.2 Hz), 7.89 (2H, d, J = 7.9 Hz), 7.83-7.82 (2H, m), 7.70-7.68 (2H, m), 7.51-7.38 (5H, m), 3.64 (2H, t, J = 7.3 Hz), 3.42-3.35 (1H, m), 2.94-2.81 (2H, m), 2.54, (3H, s), 1.84-1.59 (4H, m), 1.26-1.12 (10H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.9, 169.9, 168.5, 150.2, 148.1, 138.2, 136.3, 135.5, 134.2, 133.9, 132.2, 128.7, 127.8, 127.3, 123.1, 121.6, 121.5, 116.4, 45.3, 42.6, 38.0, 36.0, 29.4, 29.3, 29.0, 28.5, 27.3, 26.8, 26.8; HRMS (ESI) calcd for $C_{36}H_{38}N_3O_4$ $[M+H]^+$ 576.2862 found 576.2882.

11-(1,3-Dioxoisoindolin-2-yl)-3-(4-nitrophenyl)-*N*-(quinolin-8-yl)undecanamide (13c): The



compound **13c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(63 mg, 72%); R_f (40% EtOAc/hexane) = 0.4; IR (DCM): 2927, 1711, 1523, 1395, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.66 (1H, br. s), 8.76 (1H, d, J = 3.3 Hz), 8.62 (1H, dd, J_1 = 5.6, J_2 = 3.1 Hz), 8.17-8.15 (3H, m), 7.85 (2H, dd, J_1 = 5.2, J_2 = 3.2 Hz), 7.72 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.53-7.44 (5H, m), 3.66 (2H, t, J = 7.3 Hz), 3.49-3.42 (1H, m), 2.95 (1H, dd, J_1 = 14.8, J_2 = 6.2 Hz), 2.84 (1H, dd, J_1 = 14.8, J_2 = 8.5 Hz), 1.84-1.68 (4H, m), 1.24-1.13 (10H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 168.5, 152.4, 148.1, 146.7, 138.2, 136.4, 134.1, 133.8, 132.1, 128.5, 127.9, 127.3, 123.9, 123.1, 121.7, 116.5, 45.1, 42.5, 38.0, 36.0, 29.3, 29.2, 29.0, 28.5, 27.3, 26.7; HRMS (ESI) calcd for $C_{34}H_{35}N_4O_5$ $[M+H]^+$ 579.2607 found 579.2584.

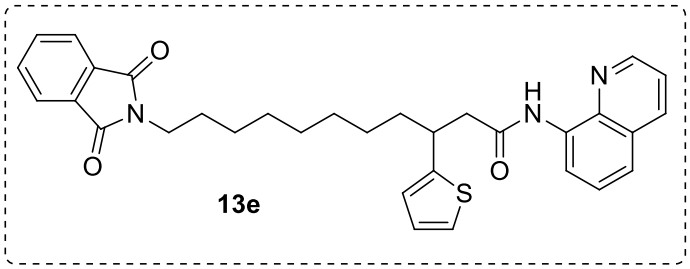
11-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethylphenyl)-*N*-(quinolin-8-yl)undecanamide (13d): The



compound **13d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color liquid (58 mg, 69%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM):

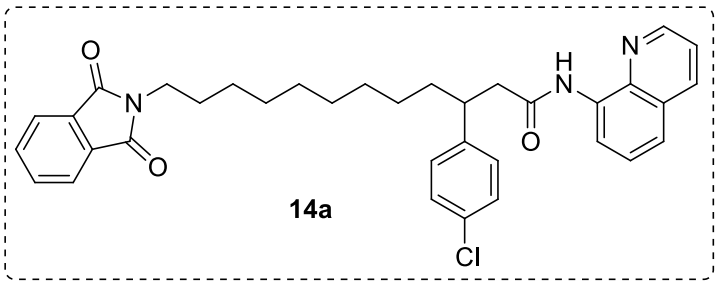
2927, 1710, 1523, 1395, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, br. s), 8.78-8.74 (2H, m), 8.15 (1H, d, J = 8.2 Hz), 7.85 (2H, dd, J_1 = 5.3, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.54-7.43 (3H, m), 7.21 (2H, d, J = 7.8 Hz), 7.13 (2H, d, J = 7.8 Hz), 3.66 (2H, t, J = 7.3 Hz), 3.29-3.25 (1H, m), 2.84 (2H, d, J = 7.4 Hz), 2.60 (2H, q, J = 7.6 Hz), 1.81-1.58 (4H, m), 1.32-1.17 (13H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.6, 168.4, 148.0, 142.1, 141.6, 138.2, 136.3, 134.5, 133.8, 132.2, 128.0, 127.9, 127.9, 127.4, 123.1, 121.5, 121.3, 116.4, 45.9, 42.2, 38.0, 36.2, 29.5, 29.3, 29.1, 28.6, 28.4, 27.4, 26.8, 15.4; HRMS (ESI) calcd for $C_{36}H_{40}N_3O_3$ $[M+H]^+$ 562.3070 found 562.3087.

11-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)undecanamide (13e): The compound **13e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color viscous liquid(62 mg, 77%); R_f (40% EtOAc/hexane) = 0.3; IR (DCM): 2928, 1712, 1525, 1325, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, br. s), 8.80-8.76 (2H, m), 8.15 (1H, d, J = 8.2 Hz),), 7.85 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.71 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.55-7.48 (2H, m), 7.45 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.14 (1H, d, J = 4.8 Hz), 6.92-6.89 (2H, m) 3.70-3.63 (3H, m), 2.89 (2H, d, J = 7.3 Hz), 1.86-1.80 (1H, m), 1.74-1.63 (3H, m), 1.31-1.28 (10H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 168.5, 148.3, 148.1, 138.3, 136.3, 134.4, 133.8, 132.2, 127.9, 127.4, 126.6, 124.2, 123.1, 123.1, 121.6, 121.4, 116.5, 46.7, 38.0, 38.0, 37.3, 29.3, 29.3, 29.1, 28.6, 27.2, 26.8; HRMS (ESI) calcd for $C_{32}H_{34}N_3O_3S$ $[M+H]^+$ 540.2321 found 540.2296.



13e

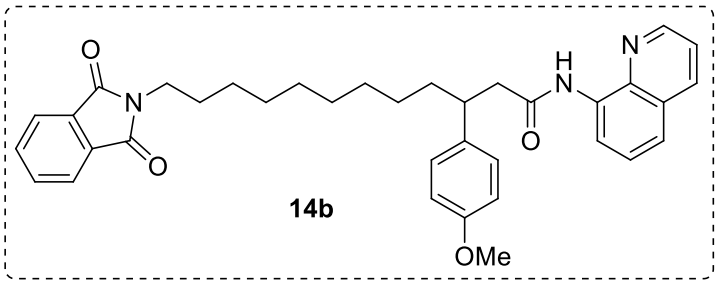
3-(4-Chlorophenyl)-12-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)dodecanamide (14a): The compound **14a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a pale yellow color viscous liquid(64 mg, 73%); R_f (40% EtOAc/hexane) = 0.6; IR (DCM): 3352, 2928, 1698, 1530, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.65 (1H, br. s),



14a

8.75 (1H, dd, J_1 = 4.2, J_2 = 1.7 Hz), 8.71 (1H, dd, J_1 = 7.0, J_2 = 2.1Hz), 8.13 (1H, dd, J_1 = 8.3, J_2 = 1.7Hz), 7.83 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.69 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.52-7.45 (2H, m), 7.43 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.27-7.21 (4H, m), 3.66 (2H, t, J = 7.4 Hz), 3.32-3.24 (1H, m), 2.89-2.75 (2H, m), 1.80-1.73 (1H, m), 1.70-1.61 (3H, m), 1.31-1.12 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 168.5, 148.1, 142.9, 138.2, 136.3, 134.3, 133.8, 132.1, 132.0, 129.0, 128.7, 127.8, 127.3, 123.1, 121.6, 121.5, 116.4, 45.7, 42.1, 38.0, 36.2, 29.5, 29.4, 29.4, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{35}H_{37}ClN_3O_3$ $[M+H]^+$ 582.2523 found 582.2496.

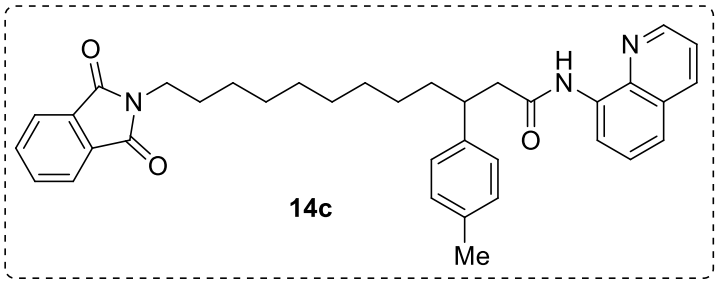
12-(1,3-Dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)dodecanamide (14b):



14b

The compound **14b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a pale green color viscous liquid(65 mg, 75%); R_f (40% EtOAc/hexane) = 0.5; IR (DCM): 2928, 1731, 1527, 1247, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.67 (1H, br. s), 8.77-8.73 (2H, m), 8.15 (1H, d, J = 7.8 Hz), 7.84 (2H, dd, J_1 = 5.2, J_2 = 3.1 Hz), 7.71 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.53-7.47 (2H, m), 7.44 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.22 (2H, d, J = 8.4 Hz), 6.84 (2H, d, J = 8.5 Hz), 3.75 (3H, s), 3.67 (2H, t, J = 7.3 Hz), 3.26-3.23 (1H, m), 2.88-2.77 (2H, m), 1.80-1.74 (1H, m), 1.66-1.61 (3H, m), 1.31-1.20 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.6, 168.5, 158.0, 147.9, 138.1, 136.5, 136.4, 134.3, 133.8, 132.2, 128.4, 127.9, 127.4, 123.1, 121.5, 121.4, 116.7, 113.9, 55.1, 46.1, 41.9, 38.1, 36.4, 29.7, 29.5, 29.4, 29.1, 28.6, 27.4, 26.8; HRMS (ESI) calcd for $C_{36}H_{40}N_3O_4$ $[M+H]^+$ 578.3019 found 578.3033.

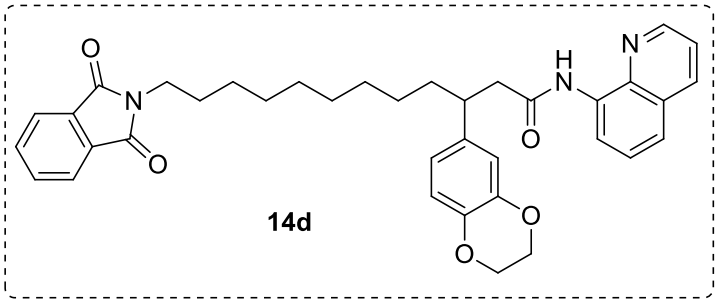
12-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(*p*-tolyl)dodecanamide (14c): The compound **14c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless viscous liquid(61 mg, 72%); R_f (40% EtOAc/hexane) = 0.5;



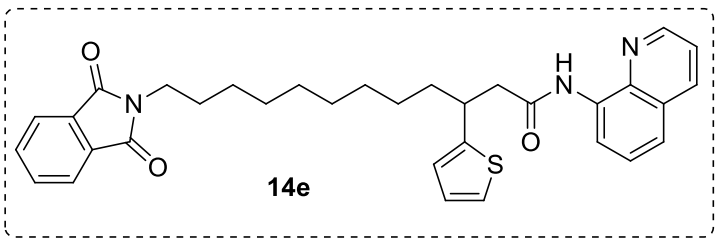
14c

IR (DCM): 2926, 1711, 1524, 1395, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.69 (1H, br. s), 8.78-8.74 (2H, m), 8.14 (1H, d, J = 8.2 Hz), 7.84 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.70 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.53-7.46 (2H, m), 7.44 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 7.19 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 7.9 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.28-3.23 (1H, m), 2.87-2.79 (2H, m), 2.29 (3H, s), 1.82-1.75 (1H, m), 1.71-1.61 (3H, m), 1.32-1.20 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 168.4, 148.0, 141.3, 138.3, 136.3, 135.7, 134.5, 133.8, 132.2, 129.2, 127.8, 127.4, 127.4, 123.1, 121.5, 121.3, 116.4, 46.0, 42.2, 38.1, 36.3, 29.5, 29.4, 29.4, 29.1, 28.6, 27.4 26.8, 21.0; HRMS (ESI) calcd for $C_{36}H_{40}N_3O_3$ $[M+H]^+$ 562.3070 found 562.3097.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-12-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)dodecanamide (14d): The compound **14d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a pale yellow color liquid (64 mg, 70%); R_f (40% EtOAc/hexane) = 0.3; IR (DCM): 2928, 1708, 1526, 1286, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.68 (1H, br. s), 8.79-8.74 (2H, m), 8.15 (1H, d, J = 8.2 Hz), 7.85 (2H, dd, J_1 = 5.0, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 4.8, J_2 = 3.0 Hz), 7.54-7.49 (2H, m), 7.45 (1H, dd, J_1 = 8.3, J_2 = 4.3 Hz), 6.80-6.78 (3H, m), 4.20 (4H, s), 3.67 (2H, t, J = 7.2 Hz), 3.20-3.16 (1H, m), 2.80 (2H, d, J = 7.2 Hz), 1.75-1.72 (1H, m), 1.67-1.64 (3H, m), 1.31-1.21 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 168.5, 148.0, 143.4, 141.9, 138.3, 137.8, 136.3, 134.5, 133.8, 132.2, 127.9, 127.4, 123.1, 121.5, 121.3, 120.6, 117.2, 116.4, 116.0, 64.3, 64.3, 46.0, 42.0, 38.1, 36.3, 29.5, 29.4, 29.1, 29.1, 28.6, 27.4, 26.8; HRMS (ESI) calcd for $C_{37}H_{40}N_3O_5$ $[M+H]^+$ 606.2968 found 606.2943.

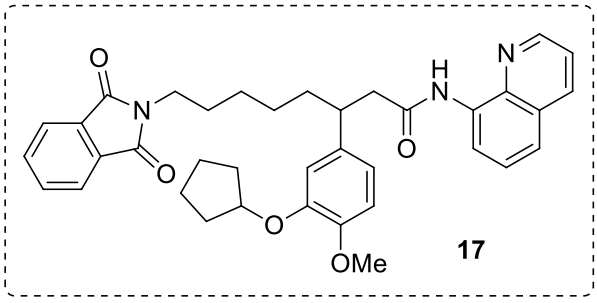


12-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)dodecanamide (14e): The compound **14e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(60 mg, 76%); R_f

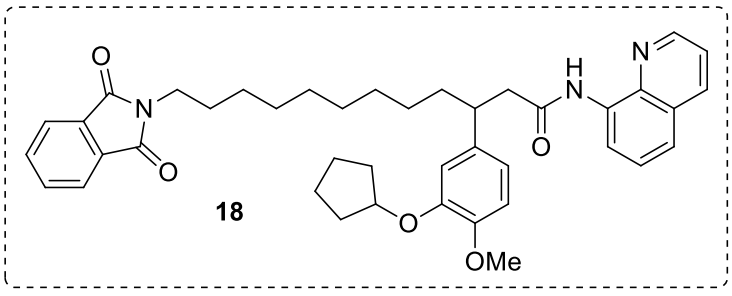


(40% EtOAc/hexane) = 0.5; IR (DCM): 2927, 1711, 1527, 1393, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, br. s), 8.79-8.76 (2H, m), 8.15 (1H, d, J = 8.3 Hz), 7.85 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.71 (2H, dd, J_1 = 5.3, J_2 = 3.2 Hz), 7.55-7.49 (2H, m), 7.45 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.15-7.14 (1H, m), 6.93-6.89 (2H, m), 3.68-3.65 (3H, m), 2.89 (2H, d, J = 7.2 Hz), 1.85-1.81 (1H, m), 1.75-1.62 (3H, m), 1.31-1.23 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 168.5, 148.4, 148.1, 138.3, 136.3, 134.4, 133.8, 132.2, 127.9, 127.4, 126.6, 124.2, 123.2, 123.1, 121.6, 121.5, 116.5, 46.7, 38.1, 38.0, 37.3, 29.7, 29.7, 29.4, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{33}H_{36}N_3O_3S[M+H]^+$ 554.2477 found 554.2497.

3-(3-(Cyclopentyloxy)-4-methoxyphenyl)-8-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (17): The compound **17** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(67 mg, 74%); R_f (40% EtOAc/hexane) = 0.2; IR (DCM): 3353, 2936, 1711, 1260, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.62 (1H, br. s), 8.75-8.72 (2H, m), 8.14 (1H, d, J = 8.2 Hz), 7.83 (2H, dd, J_1 = 5.3, J_2 = 3.2 Hz), 7.71-7.69 (2H, m), 7.52-7.42 (3H, m), 6.81-6.76 (3H, m), 4.72 (1H, br. s), 3.76 (3H, s), 3.63 (2H, t, J = 7.2 Hz), 3.23-3.16 (1H, m), 2.85-2.74 (2H, m), 1.88-1.54 (11H, m), 1.35-1.27 (5H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 168.4, 148.6, 148.0, 147.6, 138.2, 136.5, 136.3, 134.4, 133.8, 132.2, 127.9, 127.4, 123.1, 121.5, 121.3, 119.4, 116.5, 114.6, 112.2, 80.2, 56.0, 46.3, 42.4, 38.0, 36.2, 32.8, 28.5, 271, 26.9, 24.1, 24.0; HRMS (ESI) calcd for $C_{37}H_{40}N_3O_5$ $[M+H]^+$ 606.2968 found 606.2938.

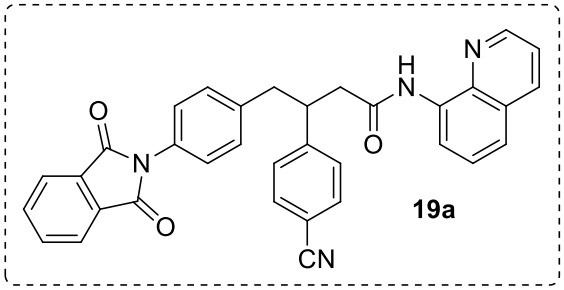


3-(3-(Cyclopentyloxy)-4-methoxyphenyl)-12-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)dodecanamide (18): The compound **18** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a yellow color viscous liquid(56 mg, 56%); R_f (40% EtOAc/hexane) = 0.2; IR (DCM): 3354, 2929, 1693, 1259, 724 cm^{-1}; ^1H NMR (400 MHz,



$CDCl_3$) δ_H 9.64 (1H, br. s), 8.75-8.74 (2H, m), 8.14 (1H, d, J = 8.2Hz), 7.84 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.70 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.52-7.46 (2H, m), 7.43 (1H, dd, J_1 = 8.3, J_2 = 4.2 Hz), 6.82-6.77 (3H, m), 4.75-4.71 (1H, m), 3.77 (3H, s), 3.66 (2H, t, J = 7.3 Hz), 3.23-3.16 (1H, m), 2.86-2.75 (2H, m), 1.89-1.85 (2H, m), 1.83-1.74 (5H, m), 1.70-1.63 (3H, m), 1.60-1.50 (2H, m), 1.31-1.21 (12H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.7, 168.5, 148.5, 147.9, 147.5, 138.1, 136.7, 136.4, 134.4, 133.8, 132.2, 127.9, 127.4, 123.1, 121.5, 121.3, 119.4, 116.5, 114.6, 112.1, 80.2, 56.0, 46.4, 42.4, 38.1, 36.3, 32.8, 32.7, 29.5, 29.4, 29.2, 28.6, 27.4, 26.8, 24.1, 24.0; HRMS (ESI) calcd for $C_{41}H_{48}N_3O_5$ $[M+H]^+$ 662.3594 found 662.3562.

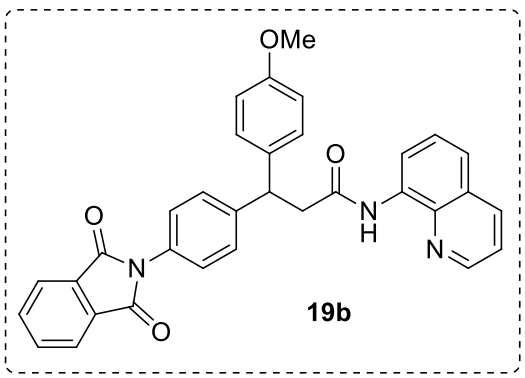
3-(4-Cyanophenyl)-4-(4-(1,3-dioxoisoindolin-2-yl)phenyl)-*N*-(quinolin-8-yl)butanamide



19a

(19a): The compound **19a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (52 mg, 70%); R_f (40% EtOAc/hexane) = 0.4; mp: 140-142 ^{o}C; IR (DCM): 2968, 1701, 1485, 1382, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.79 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.68 (1H, dd, J_1 = 5.5, J_2 = 3.4 Hz), 8.16 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.95 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.79 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.54-7.49 (2H, m), 7.47 (1H, dd, J_1 = 8.2, J_2 = 4.2 Hz), 7.39 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 3.83-3.76 (1H, m), 3.18 (1H, dd, J_1 = 13.6, J_2 = 6.7 Hz), 3.08-3.01 (2H, m), 2.92 (1H, dd, J_1 = 15.2, J_2 = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.0, 167.3, 148.9, 148.2, 138.7, 138.2, 136.4, 134.4, 134.1, 132.4, 131.7, 130.1, 129.8, 128.6, 127.9, 127.3, 126.4, 123.7, 121.7, 121.7, 118.9, 116.5, 110.6, 44.0, 43.3, 41.9; MS *m/z* (ASAP) 537 $(M+H)^+$.

3-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)propanamide

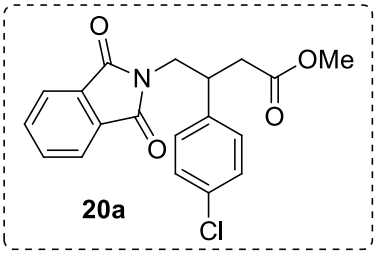


19b

(19b): The compound **19b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a green color solid (52 mg, 66%); R_f (40% EtOAc/hexane) = 0.4; mp: 70-72 ^{o}C; IR (DCM): 2923, 1717, 1523, 1382, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.81 (1H, br. s), 8.80-

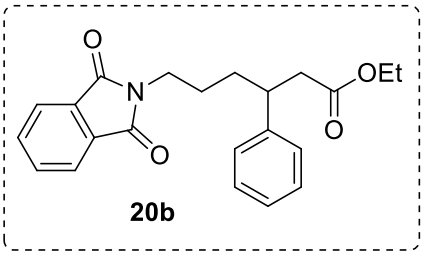
8.78 (1H, m), 8.73 (1H, dd, J_1 = 6.6, J_2 = 1.5 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.95 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.78 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.54-7.43 (5H, m), 7.39 (2H, d, J = 8.3 Hz), 7.30 (2H, d, J = 8.6 Hz), 6.85 (2H, d, J = 8.5 Hz), 4.84 (1H, t, J = 7.6 Hz), 3.76 (3H, s), 3.33 (2H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.4, 167.3, 158.3, 148.1, 144.2, 138.3, 136.3, 135.3, 134.4, 134.3, 131.7, 129.9, 128.9, 128.4, 127.9, 127.4, 126.5, 123.7, 121.6, 121.5, 116.6, 114.1, 55.2, 46.0, 44.5. MS *m/z* (ASAP) 528 $(M+H)^+$.

Methyl 3-(4-chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoate (20a): The compound **20a**



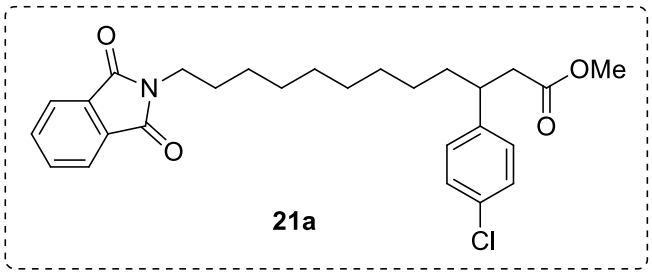
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (50 mg, 93%); R_f (40% EtOAc:hexane) 0.7; mp: 104-106 ^{o}C; IR (DCM): 2949, 1714, 1397, 1171, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, J = 4.0 Hz), 7.72 (2H, d, J = 4.0 Hz), 7.28-7.22 (4H, m), 3.94-3.84 (2H, m), 3.75 (1H, quint, J = 7.6 Hz), 3.52 (3H, m), 2.79-2.67 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.7, 168.1, 138.8, 134.1, 133.1, 131.7, 129.1, 128.8, 123.4, 51.7, 42.9, 40.2, 38.3; HRMS (ESI) calcd for $C_{19}H_{16}ClNNaO_4$ $[M+Na]^+$ 380.0666 found 380.0650.

Ethyl 6-(1,3-dioxoisoindolin-2-yl)-3-phenylhexanoate (20b): The compound **20b** was obtained



after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colourless liquid (69 mg, 59%); R_f(30% EtOAc/hexane) = 0.6; IR (DCM): 2920, 1711, 1396, 1031, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83-7.81 (2H, m), 7.71-7.70 (2H, m), 7.29-7.26 (2H, m), 7.20-7.17 (3H, m), 4.01 (2H, q, J = 7.1 Hz), 3.64 (2H, t, J = 7.2 Hz), 3.16-3.09 (1H, m), 2.66-2.54 (2H, m), 1.78-1.56 (3H, m), 1.52-1.43 (1H, m), 1.12 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.1, 168.3, 143.3, 133.9, 132.1, 128.5, 127.5, 126.6, 123.2, 60.3, 41.9, 41.8, 37.8, 33.3, 26.5, 14.1; HRMS (ESI) calcd for $C_{22}H_{23}NNaO_4$ $[M+Na]^+$ 388.1525 found 388.1514.

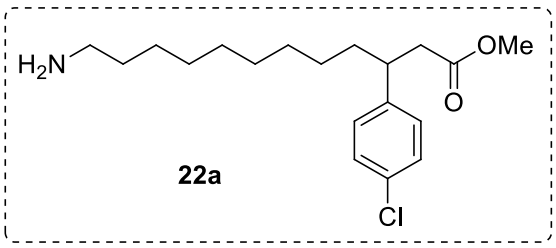
Methyl 3-(4-chlorophenyl)-12-(1,3-dioxoisoindolin-2-yl)dodecanoate (21a): The compound **21a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colourless liquid (80 mg, 71%); R_f (30% EtOAc/hexane) = 0.6; IR (DCM): 2928, 2855, 1713, 1397, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz),



21a

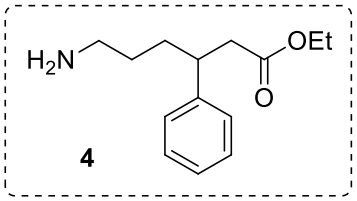
7.72 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.4 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.59 (3H, s), 3.10-3.03 (1H, m), 2.65-2.50 (2H, m), 1.70-1.54 (4H, m), 1.30-1.29 (4H, m), 1.20-1.08 (8H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.6, 168.4, 142.6, 133.8, 132.2, 132.0, 128.8, 128.5, 123.1, 51.5, 41.6, 41.5, 38.0, 36.1, 29.4, 29.3, 29.3, 29.1, 28.6, 27.2, 26.8; HRMS (ESI) calcd for $C_{27}H_{32}ClNaNO_4$ $[M+Na]^+$ 492.1918 found 492.1924.

Methyl 12-amino-3-(4-chlorophenyl)dodecanoate (22a): The compound **22a** was obtained by following the above procedure as a pale green color liquid (73 mg, 86%); IR (DCM): 2928, 2855, 1735, 1261, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.27 (2H, d, J = 7.8 Hz), 7.12 (2H, d, J = 7.5 Hz), 3.59 (3H, s), 3.07 (1H, br. s), 2.65-2.51 (2H, m), 1.61-1.09 (18H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.6, 142.6, 132.0, 128.8, 128.6, 51.5, 41.6, 41.5, 36.1, 30.2, 29.4, 27.2; HRMS (ESI) calcd for $C_{19}H_{31}ClNO_2$ $[M+H]^+$ 340.2043 found 340.2054.



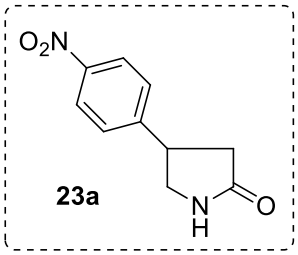
22a

Ethyl 6-amino-3-phenylhexanoate (4): The compound **4** was obtained by following the above procedure as a brown color liquid (28 mg, 63%, the purity of this sample around 85-90%); IR (DCM): 2928, 1730, 1643, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32-7.27 (2H, m), 7.19-7.17 (3H, m), 4.01 (2H, q, J = 6.8 Hz), 3.10-3.08 (1H, m), 2.67-2.54 (2H, m), 1.79-1.42 (4H, m), 1.30-1.27 (2H, m), 1.13 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.3, 143.2, 128.6, 127.5, 126.7, 60.4, 41.7, 29.7, 14.1; HRMS (ESI) calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651 found 236.1656. The NH protons could not be clearly identified in the proton NMR.



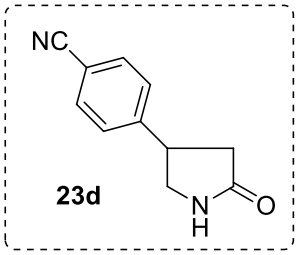
4

4-(4-Nitrophenyl)pyrrolidin-2-one (23a): The compound **23a** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 90:10) as a brown color solid (24 mg,



58%); R_f (90% EtOAc:MeOH) 0.2; mp: 166-168 ^oC; IR (DCM): 3256, 1690, 1513, 1254, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (2H, d, J = 8.7 Hz), 7.45 (2H, d, J = 8.6 Hz), 6.96 (1H, br. s), 3.91-3.81 (2H, m), 3.47 (1H, dd, J_1 = 9.1, J_2 = 6.2 Hz), 2.83 (1H, dd, J_1 = 17.0, J_2 = 8.8 Hz), 2.51 (1H, dd, J_1 = 17.1, J_2 = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 177.1, 149.8, 147.1, 127.7, 124.2, 49.0, 39.9, 37.8; HRMS (ESI) calcd for $C_{10}H_{11}N_2O_3$ $[M+H]^+$ 207.0770 found 207.0761.

4-(5-Oxopyrrolidin-3-yl)benzonitrile(23d): The compound **23d** was obtained after purification



by column chromatography on silica gel (EtOAc:MeOH = 90:10) as a brown color solid (21 mg, 56%); R_f (90% EtOAc:MeOH) 0.3; mp: 166-168 ^oC; IR (DCM): 3270, 2905, 1686, 1255, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, J = 8.3 Hz), 7.39 (2H, d, J = 8.2 Hz), 6.90 (1H, br. s), 3.88-3.75 (2H, m), 3.43 (1H, dd, J_1 = 9.4, J_2 = 6.6 Hz), 2.80 (1H, dd, J_1 = 17.0, J_2 = 8.9 Hz), 2.48 (1H, dd, J_1 = 17.0, J_2 = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 177.1, 147.7, 132.8, 127.7, 118.6, 111.2, 49.0, 40.1, 37.6; HRMS (ESI) calcd for $C_{11}H_{11}N_2O[M+H]^+$ 187.0871 found 187.0866.

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24. For articles dealing with the synthesis and characterization data of some of the compounds discussed in this paper, see: (a) Guénin, E.; Monteil, M.; Bouchemal, N.; Prangé, T.; Lecouvey, *Eur. J. Org. Chem.* **2007**, 3380; (b) Zav'yalov, S. I.; Dorofeeva, O. V.; Rumyantseva, E. E.; Kulikova, L. B.; Ezhova, G. I.; Kravchenko, N. E.; Zavozin, A. G. *Pharm. Chem. J.* **2002**, *36*, 440; (c) Ventre, S.; Petronijevic, F. R.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654; (d) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1986**, *34*, 2078; (e) Wada, M.; Nakai, H.; Sato, Y. *Tetrahedron* **1983**, *39*, 2691; (f) Kumar, V.; Yarravarapu, N.; Lapinsky, D. J.; Perley, D.; Felts, B.; Tomlinson, M. J.; Vaughan, R. A.; Henry, L. K.; Lever, J. R.; Newman, A. H. *J. Med. Chem.* **2015**, *58*, 5609; (g) Gurak, Jr., J. A.; Yang, K. S.; Liu, Z.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 5805; (h) Biswas, K.; Gholap, R.; Srinivas, P.; Kanyal, S.; Sarma, K. D. *RSC Adv.* **2014**, *4*, 2538 and references therein; (i) Lang, Q.; Gu, G.; Cheng, Y.; Yin, Q.; Zhang, X. *ACS Catal.* **2018**, *8*, 4824; (j) Muraoka, N.; Mineno, M.; Itami, K.; Yoshida, J.-i. *J. Org. Chem.* **2005**, *70*, 6933.

CHAPTER 3

Assembling of 4-aryl 2-piperidones, piperidines, antituberculosis molecule (Telacebec) and its analogues *via* Pd(II)-catalyzed sp^3 *β*-C-H activation/arylation.

This part of the Thesis work viz. Chapter 3 has been re-used (adapted) with permission from the publication, Tomar, R.; Bhattacharya, D.; Babu, S. A. *Asian J. Org. Chem.* **2022**, *11*, e202100736 (https://doi.org/10.1002/ajoc.202100736.). Title; Direct lactamization of *β*-arylated *δ*-aminopentanoic acid carboxamides: En route to 4-aryl- 2-piperidones, piperidines, antituberculosis molecule Q203 (Telacebec) and its analogues.

Nitrogen-based heterocyclic compounds have occupied a distinguished position in organic and medicinal chemistry research areas.[1] 2-Piperidone and piperidine motifs are present in various natural products (alkaloids), biologically active molecules and pharmaceuticals.[2-9] Notably, piperidones and piperidines are promising motifs in various medicinal chemistry research programs.[2-9] 2-Piperidone (*δ*-valerolactam) is a member of the lactam family and in general, there has been substantial interest in the synthesis, biomimetic synthesis and biological activities of various lactams.[2,6-9]

Despite the available significant amount of literature methods for the synthesis of 2-piperidones, piperidines and given their strong participation in medicinal chemistry programs, still there is an interest in developing new synthetic protocols. Of particular interest, 4-aryl-2-piperidone and 4-arylpiperidine motifs are prevalent in pharmaceuticals and medicinally active building blocks.[2-9] Various 4-aryl-2-piperidone and 4-arylpiperidine scaffolds were found to exhibit a wide range of biological activities (Figure 1). In particular, the compound Q203 (Telacebec, **1j**) is an orally-available antibiotic drug in phase II clinical trials for the treatment of tuberculosis (TB). The compound Q203 was found to target the *Mycobacterium tuberculosis* cellular energy production via the selective inhibition of the cytochrome bc1 complex of *Mycobacterium tuberculosis*.[8] The compound Q203 (Telacebec) is possessing a 4-arylpiperidine motif and an imidazopyridine unit.

The typical methods employed for the synthesis of 4-aryl-2-piperidones include: (a) the transition metal-catalyzed conjugate addition of aryl nucleophiles to *α,β*-unsaturated *δ*-

valerolactam (**2a**), and (b) the cross-coupling reaction method involving boronic acid derivatives (Scheme 1a).[2,6-9] Similarly, typical methods used for the synthesis of 4-arylpiperidine include: (a) the condensation of a 4-piperidone (**2e**) with an aryl organometallic reagent, and (b) the cross-coupling reaction involving 3,4-unsaturated piperidine or saturated piperidine reagents (**2d**, Scheme 1a).[3-5,8]

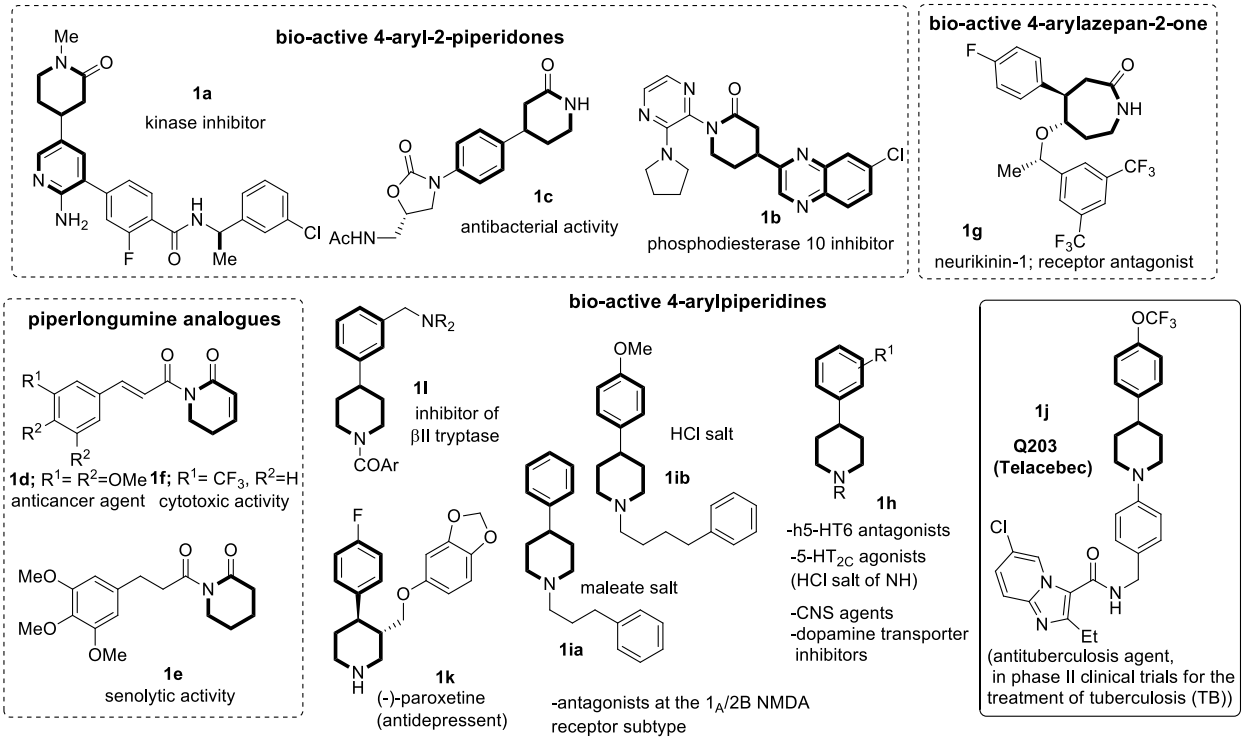
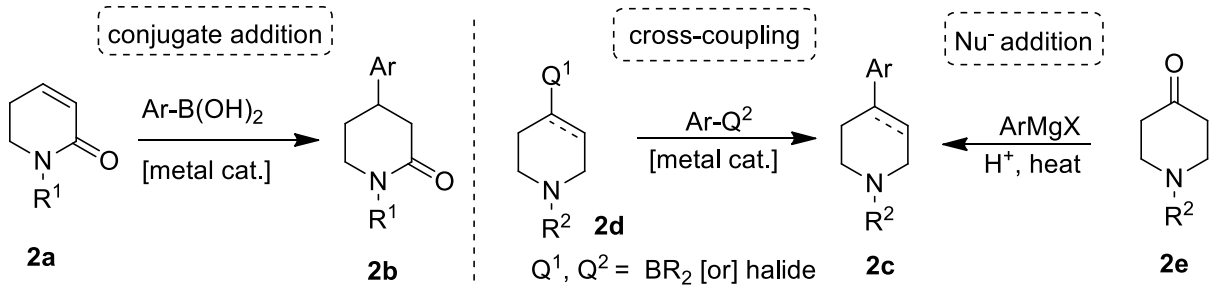


Figure 1. Examples of bioactive 4-aryl lactams and piperidines.

The existing traditional methods used for the construction of 4-aryl-2-piperidone and 4-arylpiperidine scaffolds are efficient. At the same time, it may be noted that the traditional methods employed thus far include the usage of organometallic reagents for the introduction of aryl groups at the C(4) position in 2-piperidone and piperidine motifs.[2-9]



Scheme 1a. Traditional routes toward the synthesis of 4-aryl-2-piperidones and 4-arylpiperidines.

The transition metal-catalyzed C-H activation and functionalization method is a phenomenal synthetic transformation in organic synthesis.[10-17] In particular, the Pd(II)-catalyzed, 8-aminoquinoline- or picolinamide- types bidentate directing groups directed sp^2 and sp^3 C-H functionalization of carboxamides derived from carboxylic acids and amines are valuable synthetic transformations.[10-17] Accordingly, the arylation, alkylation, acetoxylation, amination/amidation and halogenation of the sp^2 and sp^3 C-H bonds of aromatic, aliphatic/alicyclic compounds have been well documented.[10-17] The synthesis of unnatural amino acids via the C(sp^3)-H functionalization of *α*-amino acid derivatives and non-*α*-amino acids (short/medium/long chain-based aminoalkanoic acid derivatives) have also been well documented.[11,12,15]

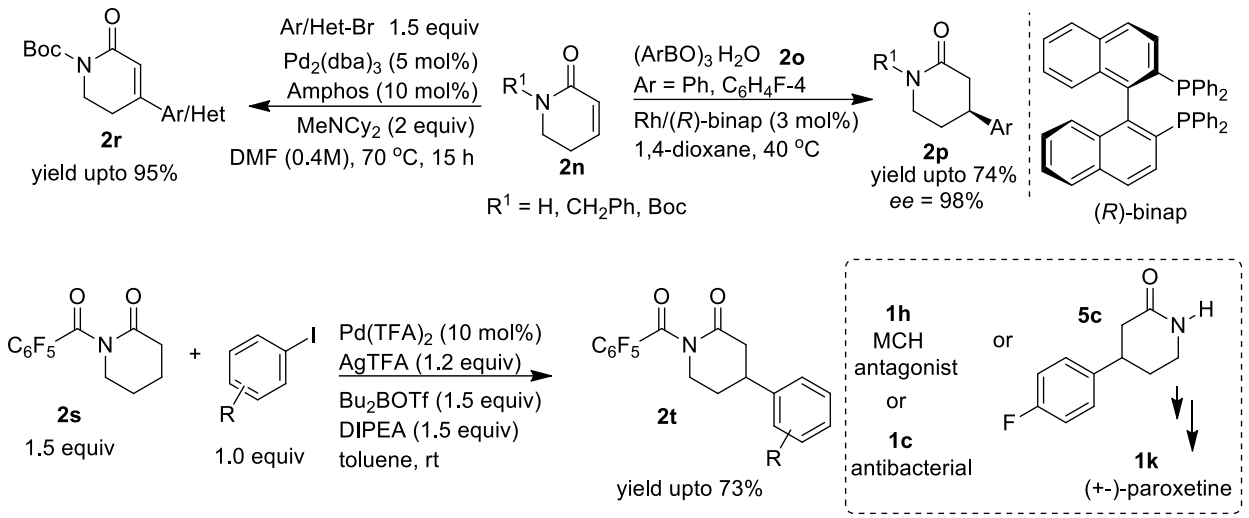
While the existing numerous standard procedures for assembling 4-aryl 2-piperidone and 4-aryl piperidine scaffolds are effective, nevertheless, novel approaches to synthesize these moieties have generated considerable attention for the researchers. In this regard, some of the representative examples related to functionalization of lactams and direct lactamization methods are presented in the section below.

Literature reports dealing with the representative examples of direct arylation of lactams for the synthesis of 4-aryl 2-piperidone.

In 2001, Hayashi and co-workers[9a] demonstrated the first example of asymmetric synthesis by 1,4-addition of aryl boron reagents to synthesize 4-aryl-2-piperidones (**2p**) under rhodium catalysis. Motivated by the fact that no example related to asymmetric synthesis of 4-aryl-2-piperidonesby 1,4-addition reported so far, they subjected 5,6-dihydro-2(1*H*)-pyridinone substrate (**2n**) in the presence of a chiral bisphosphine-rhodium based catalyst, with 4-fluorophenylboroxine (with 1 equiv of water) (**2o**) and upto 74% yield of arylated 2-piperidones (**2p**) with high enantioselectivity was obtained (Scheme 1b).

In 2016, Polivkova's group[9l] established a method for Pd mediated arylation of valerolactams (**2n**) that is widely applicable and this protocol was proven to be successful with a broad range of aryl, and heteroaryl bromides. For this reaction optimal reaction condition includes 1.5 equiv of aryl or hetetoaryl halide, 5 mol% of $Pd_2(dba)_3$, 10 mol% of electron rich Amphos ligand, 2 equiv

of base $MeNCy_2$ in DMF at 70 °C for 15 h. This approach was also demonstrated on *α, β*-unsaturated caprolactam, but with considerable tuning in the reaction condition (Scheme 1b).



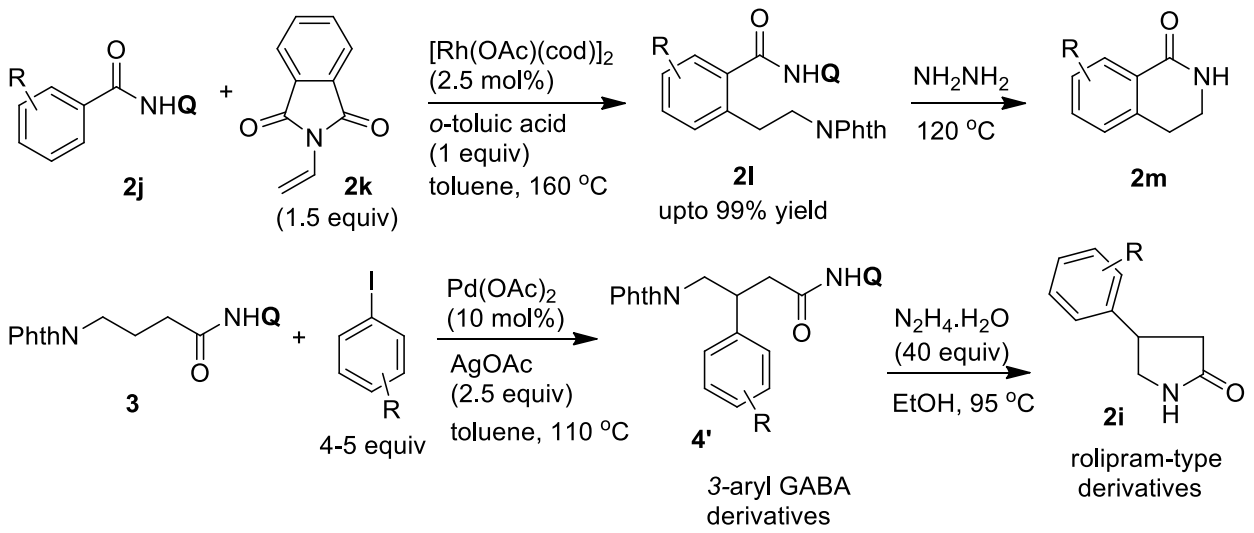
Scheme 1b. Direct arylation of lactam for the synthesis of *β*-arylated lactams.

Since the pioneering work of the Daugulis group, arylation of amides has been possible by utilising a directing-group technique. Unfortunately, this technique does not apply to lactams, due to the lack of chelation help necessitates a different mode of arylation in lactams. Following that, in the year 2018, Dong and co-workers[9c] demonstrated the Pd catalyzed redox cascade strategy for the direct C-H arylation of lactams (**2s**) with simple and readily available aryl iodides. The proposed mechanism states that the soft enolization of lactams occurs first, followed by Pd-catalyzed desaturation, aryl-halide bond activation, and the conjugate addition of aryl group at the last step allows for this transition. To demonstrate the practical utility of the methodology, they have successfully synthesized a number of commercially available drug molecules (**1c** and **1h**) and shown a formal synthesis of paroxetine (**1k**) a bioactive compound (Scheme 1b).

Literature reports dealing with the representative examples of direct lactamization methodology to construct arylated lactams.

In 2018, Chatani and co-workers[17] described the rhodium catalyzed, 8-aminoquinoline aided sp^2 C-H activation of carboxamides (**2j**) followed by one pot lactamization of alkylated carboxamides (**2l)** for the synthesis of dihydroisoquinolinones (**2m**). For alkylation of aromatic amide N-vinylphthalimide (**2k**) was used as an alkylating agent, and a 2-aminoethyl moiety was inserted at the ortho-position of aromatic amide. Further, dihydroisoquinolinones (**2m**) were

successfully synthesized by treating the alkylating carboxamides with hydrazine in one pot manner (Scheme 1c).



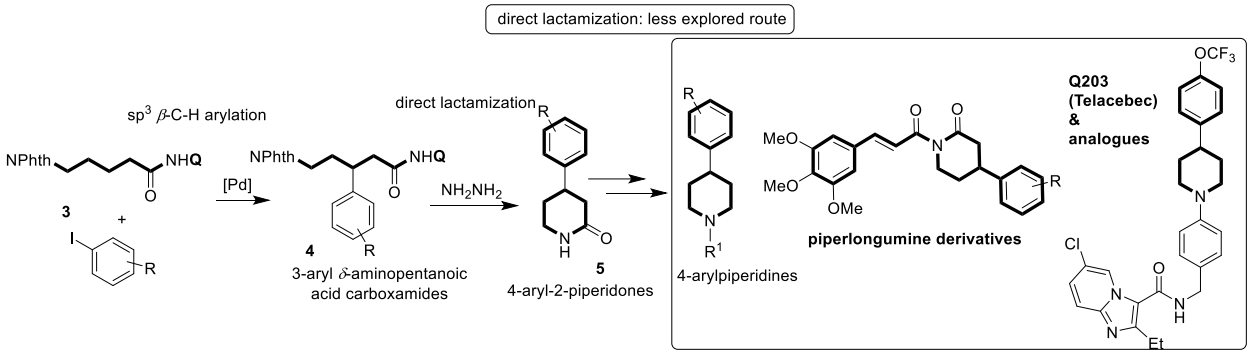
Scheme 1c. Direct lactamization methods for the synthesis of *β*-arylated lactams.

In the year 2019, our group[15d] reported the 8-aminoquinoline aided *β*-C(sp^3)-H bond arylation followed by assembling of rolipram and other pyrrolidone scaffolds (**2i**) and also constructed 3-arylated GABA derivatives such as, phenibut, baclofen, and tolibut from their corresponding *β*-C-H arylated *γ*-aminobutyric acid derivatives (**4'**) (Scheme 1c).

Taking an impetus from the earlier works[15d,17] and in considering an alternative disconnection for obtaining 4-aryl-2-piperidones (and 4-arylpiperidines), we envisioned utilizing the sp^3*β*-C-H arylation as a key step and the hydrazine-mediated synthesis of various 4-aryl-2-piperidones (**5**) via a one-pot direct lactamization of *β*-C-H arylated *δ*-aminopentanoic acid carboxamides (**4**) containing both 8-aminoquinoline and phthalimide protecting groups (Scheme 2). It is relevant to mention here that *δ*-aminopentanoic acid derivatives[18] are important synthetic building blocks in the synthesis of medicinally active molecules.

The required 3-aryl *δ*-aminopentanoic acid carboxamides for the current investigation can be assembled via the Pd(II)-catalyzed, 8-aminoquinoline-aided sp^3*β*-C-H arylation[11,15] of phthalimide-protected *δ*-aminopentanoic acid carboxamides (**3**).The assembled 3-aryl *δ*-aminopentanoic acid carboxamides (**4**) can be subjected to the direct lactamization reaction to afford various 4-aryl-2-piperidones (**5**) and then, 4-aryl-2-piperidones can be converted into various *N*-functionalized 4-aryl-2-piperidones and 4-arylpiperidine motifs (Scheme 2). Accordingly, herein we report a practical method for assembling a library of 4-aryl-2-

piperidones from *β*-C-H arylated carboxamides of *δ*-aminopentanoic acid by using Pd(II)-catalyzed sp^3*β*-C-H arylation as the key step. We also envisioned the synthesis of 4-arylazepan-2-ones and conversion of 4-aryl-2-piperidones into various *N*-functionalized 4-aryl-2-piperidones, 4-arylpiperidines and assembling of antituberculosis molecule Q203 (Telacebec) and its analogues from the corresponding 4-aryl-2-piperidone.

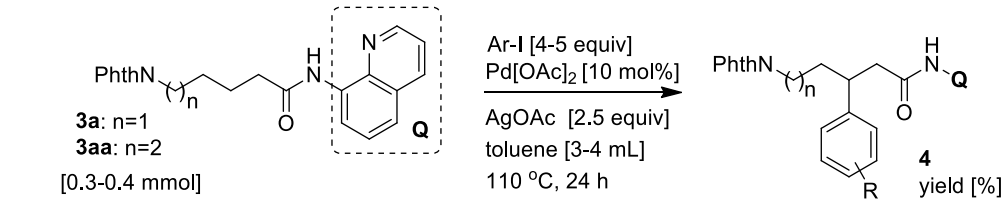


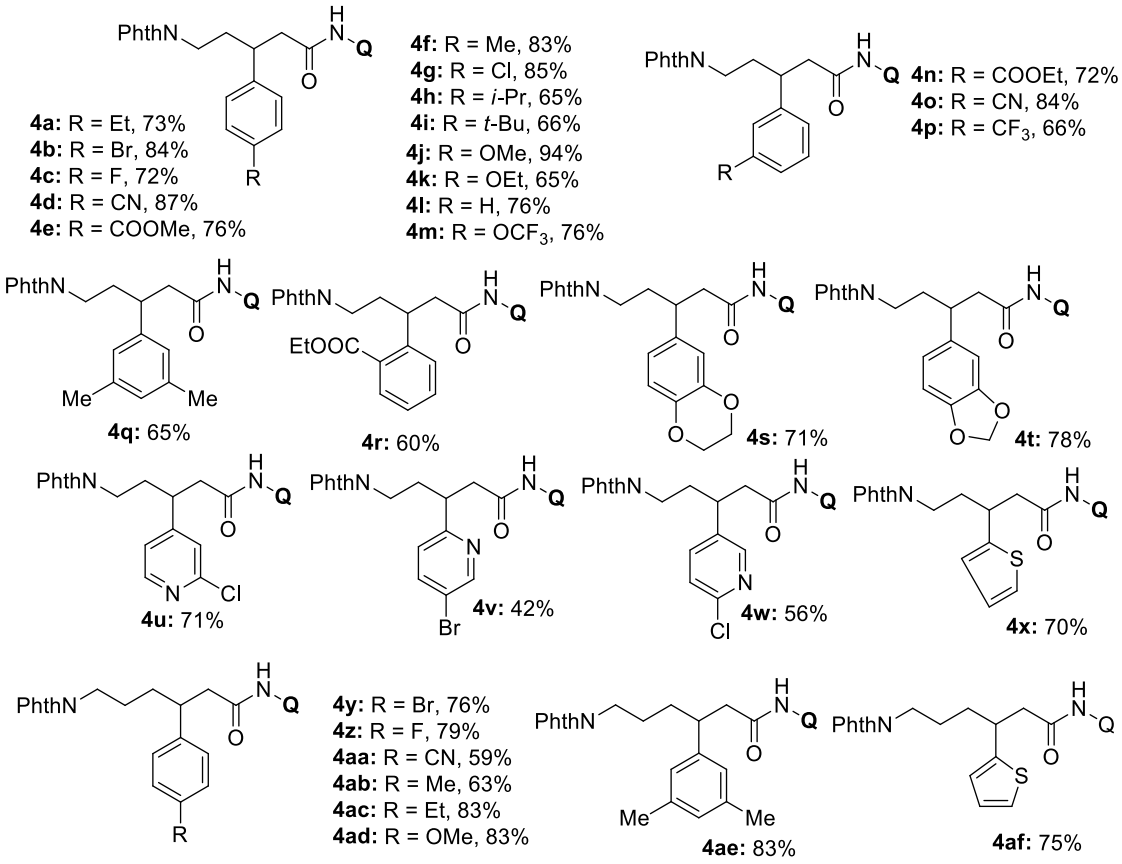
Scheme 2. Direct lactamization method and synthesis of 4-aryl-2-piperidones, 4-arylpiperidines, antituberculosis molecule Q203 and its analogues.

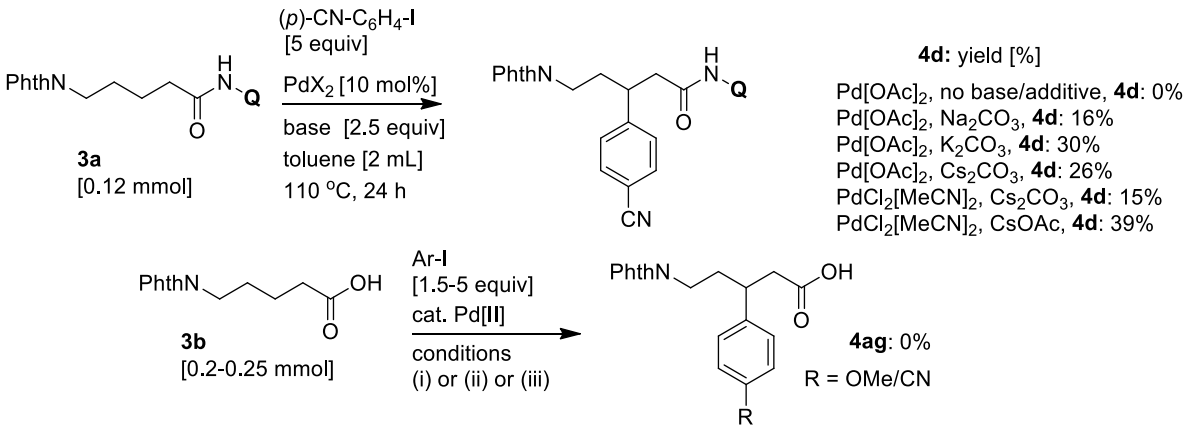
Results and Disscusion

To begin the assembling of 4-aryl-2-piperidones *via* the direct lactamization of carboxamides of 3-aryl *δ*-aminopentanoic acid, initially, we attempted the preparation of the required 3-arylated *δ*-aminopentanoic acid carboxamides *via* the Pd(II)-catalyzed, 8-aminoquinoline-aided sp^3 *β*-C-H activation and arylation method.[13a,15] At first, the carboxamide **3a** possessing the directing group 8-aminoquinoline was prepared from *N*-phthaloyl *δ*-aminopentanoic acid. We then heated a mixture of *N*-phthaloyl *δ*-aminopentanoic acid carboxamide **3a** possessing the directing group 8-aminoquinolinewith various aryl iodides in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive in toluene at 110 ^oC for 24 h (under the standard sp^3 *β*-C-H arylation reaction conditions).[11,13a,15]

The *β*-C-H arylated *δ*-aminopentanoic acid carboxamides **4a-m** and **4n-p** containing a substituent at the *meta or para* position in the aryl rings were obtained in 65-94% yields (Scheme 3). In particular, the arylation of **3a** with 4-(trifluoromethoxy)iodobenzene gave the *β*-C-H arylated *δ*-aminopentanoic acid carboxamide **4m** in 76% yield (in the later stage, we used the compound **4m** as a valuable intermediate for obtaining the precursor of Q203). The *β*-C-H arylated *δ*-aminopentanoic acid carboxamides **4q-t** were obtained in 60-78% yields from their







(i) $Pd[OAc]_2$ [6 mol%], NMe_4Cl [1.25 equiv], KOAc [1.5 equiv], AcOH [1.5 equiv],120 °C, 36 h, sealed tube. (ii) $Pd[OAc]_2$ [10 mol%], Ag_2CO_3 [2 equiv], K_2HPO_4 [1 equiv], NaOAc [2 equiv], *t*-BuOH [2 mL], 130 °C, 14 h. (iii) $Pd[OAc]_2$ [5 mol%], Ag_2CO_3 [1 equiv], Ac-Gly-OH [30 mol%], K_2CO_3 [50 mol%], HFIP [2 mL], 100 °C, 14 h.

Scheme 3. Synthesis of 3-arylated *δ*-aminopentanoic acid and *ε*-aminohexanoic acidcarboxamides *via* the Pd(II)-catalyzed *β*-C-H arylation.

corresponding aryl iodides (5-iodo-*m*-xylene, ethyl 2-iodobenzoate, 6-iodo-1,4-benzodioxane, and 5-iodo-1,3-benzodioxole).

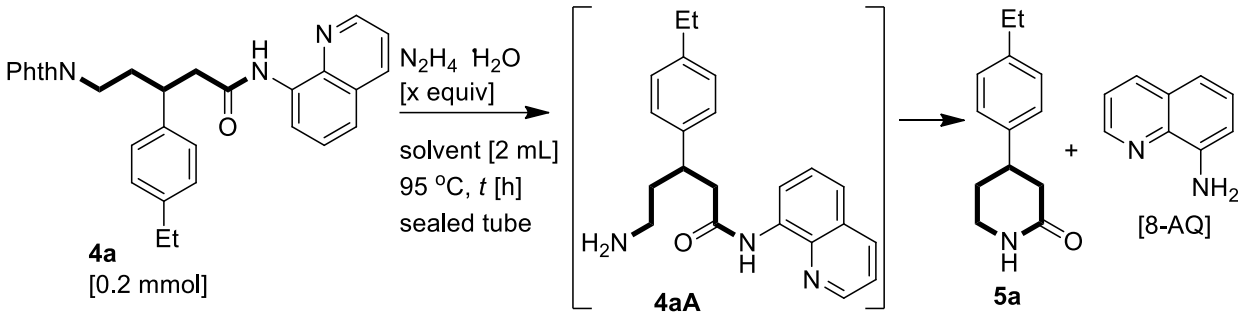
The *β*-C-H arylated *δ*-aminopentanoic acid carboxamides **4u-x** were obtained in 42-71% yields by using the corresponding heteroaryl iodides. Subsequently, we also assembled various 3-aryl *ε*-aminohexanoic acid carboxamides **4y,z** and **4aa-af** in 59-83% yields. The 3-aryl *ε*-aminohexanoic acid carboxamides **4y,z** and **4aa-af** were assembled to attempt the preparation of 4-arylazepan-2-ones (3-aryl *ε*-caprolactams). In general, the bidentate directing group-directed C-H arylation reactions require the employment of a halide ion scavenger and thus, reactions were carried out by using silver salts such as AgOAc, Ag_2CO_3 or alkali metal-based salts/bases such as Na_2CO_3, K_2CO_3,Cs_2CO_3, CsOAc, Cs_2PO_4 etc.[1116,19]

These salt additives function as the I^- (iodide anion) scavenger to regenerate the Pd(II) catalyst in the proposed Pd^{II}-Pd^{IV} catalytic cycle.[11,13a] Often the silver salts are used in the sp^3 *β*-C-H arylation reactions and the C-H arylated products are obtained in good yields.[11-16,19]In a typical case comprising of arylation of **3a** with 4-iodobenzonitrile, we used different salt additives and the product **4d** was obtained in poor yields (15-39%) when compared to the reaction in which we used AgOAc as the additive (87%). The reaction in the absence of AgOAc or any additive did not afford the C-H arylated product **4d**. Furthermore, we also tried the direct arylation of *N*-phthaloyl*δ*-aminopentanoic acid **3b** with an aryl iodide and the expected *β*-C-H arylated product **4ag** was not obtained (Scheme 3).

After assembling the required 3-aryl *δ*-aminopentanoic acid carboxamides (**4a-x**), we then subjected them to the one-pot direct lactamization reaction condition. We heated a mixture of 3-aryl *δ*-aminopentanoic acid carboxamide **4a** with hydrazine hydrate (5-40 equiv) in EtOH at 95 ^oC for 6-15 h. These trial reactions were successful and yielded the 4-aryl-2-piperidone (3-aryl *δ*-valerolactam) derivative **5a** in 50-86% yields (entries 1-3, Table 1). Heating the compound **4a** with hydrazine hydrate in water as the solvent medium did not give the product **5a** (entry 5, Table 1). Notably, heating the compound **4a** with hydrazine hydrate (40 equiv) in neat condition also afforded the product **5a** in 84% yield (entry 4, Table 1). The product **5a** is formed from **4a***via* the standard phthalimide deprotection of **4a** generating the carboxamide **4aA**, which then

undergoes intramolecular transamidation to afford **5a**. In these reactions, we have recovered the 8-aminoquinoline in good amounts (Table 1).

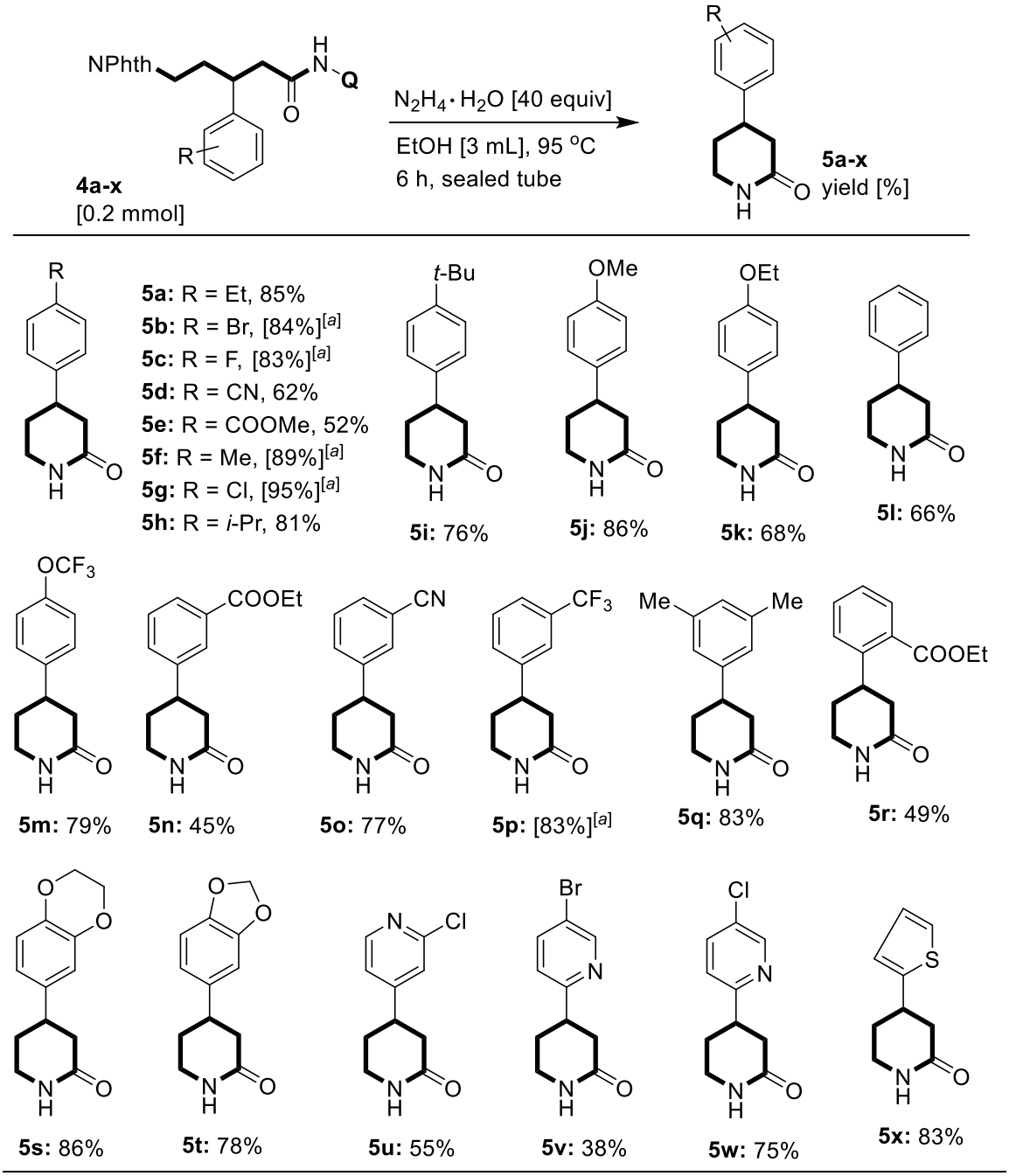
Table 1. Optimization of the direct lactamization of *β*-aryl *δ*-aminopentanoic acid carboxamide **4a** into 4-aryl-2-piperidone **5a**.



entry	$N_2H_4 \cdot H_2O$ [x equiv]	solvent	*t* [h]	**5a**: yield [%]
1[a]	5	EtOH	15	50
2[a]	10	EtOH	15	62
3[a]	40	EtOH	6	86
4[a]	40	neat	6	84
5	40	H_2O	6	[-][b]

[a] In entries 1-4, 69-88% of 8-AQ was recovered. [b] 94% of **4a** was recovered.

Having obtained the expected 4-aryl-2-piperidone **5a** in the first attempt, we then subjected various *β*-C-H arylated *δ*-aminopentanoic acid carboxamides **4b-m** and **4n-p** to the hydrazine-mediated direct lactamization in EtOH at 95 °C. The corresponding 4-aryl-2-piperidones **5b-m** and **5n-p** containing a substituent at the *meta* or *para* position in the aryl rings were obtained in 45-95% yields (Scheme 4). Of particular interest, the 4-aryl-2-piperidone **5m** containing a trifluoromethoxy substituent in the aryl ring was obtained in 79% yield (Scheme 4). The corresponding 4-aryl-2-piperidones **5q,r** containing two *meta* substituents and an *ortho* substituent in the aryl rings and 1,4-benzodioxane and 1,3-benzodioxole group containing 2-piperidones **5s,t** were obtained in 49-86% yields. Furthermore, various heteroaryl rings containing 2-piperidones **5u-x** were also obtained in 38-83% yields (Scheme 4).

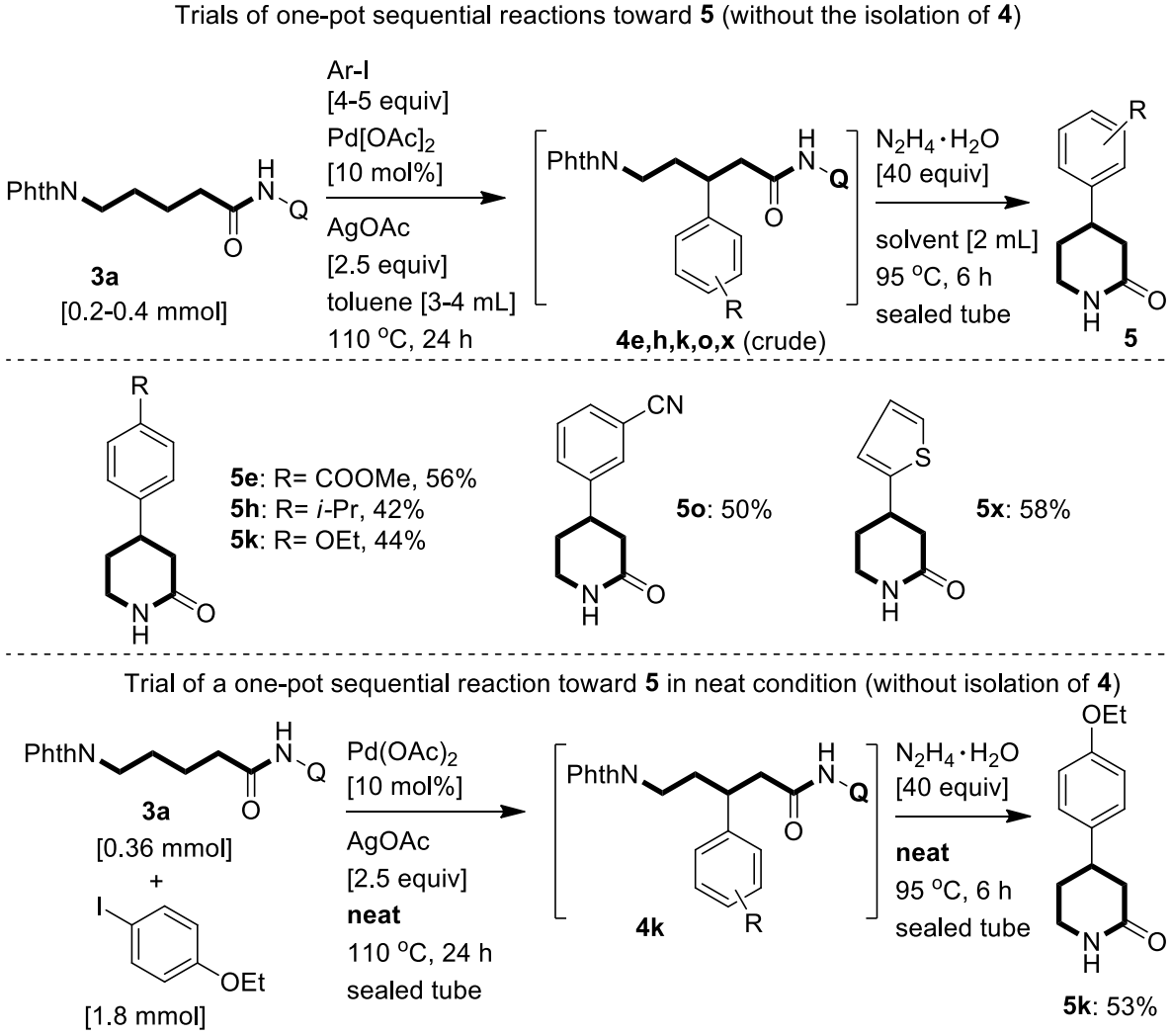


[*a*] During column purification, 8-AQ [77-88%] was recovered along with the corresponding lactam products.

Scheme 4. Substrate scope and generality. Synthesis of 4-aryl-2-piperidones **5a-x** from the lactamization of *β*-C-H arylated *δ*-aminopentanoic acid carboxamide **4a-x**.

The lactamization of *β*-C-H arylated *δ*-aminopentanoic acid carboxamides **4a-x** into 4-aryl-2-piperidones **5a-x** were carried out by using the pure substrates **4a-x**, which were isolated by the column purification method. We were interested to reduce the column chromatography

purification step and use the crude material of the β-C-H arylated carboxamides **4**, which were obtained from the corresponding Pd(II)-catalyzed β-C-H arylation of **3a**. In this regard, we performed a few trial runs of one-pot sequential processes. At first, the Pd(II)-catalyzed, sp^3 β-C-H arylation of carboxamide **3a** was carried out with a few aryl iodides to afford the respective crude reaction mixtures of 3-aryl δ-aminopentanoic acid carboxamides **4e,h,k,o,x** (Scheme 5a). After evaporating toluene, the corresponding crude reaction mixtures were then subjected to the hydrazine-mediated direct lactamization in EtOH at 95 ^oC (Scheme 5a). And the corresponding 4-aryl-2-piperidones **5e,h,k,o,x** were obtained in 42-58% (isolated yield).



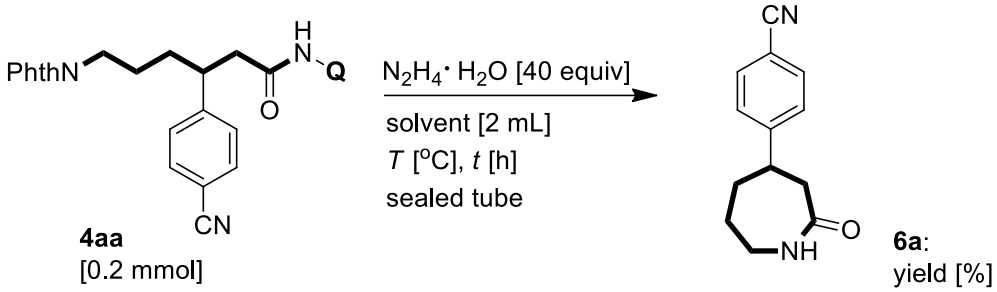
Scheme 5a. One-pot arylation and lactamization of β-C-H arylated δ-aminopentanoic acid carboxamide **3a** into 4-aryl-2-piperidones **5** (without the isolation of **4**).

Furthermore, a one-pot process comprising of the Pd(II)-catalyzed, sp^3 β-C-H arylation of carboxamide **3a** generating **4k** and subsequent lactamization of **4k** was performed in neat condition (without using a solvent in any of the steps). This process also afforded the 4-aryl-2-piperidone **5k**in 53% (isolated yield). Except for product **5e,** decreased yields were observed for the other products **5h,k,o,x**. Given that the crude material used for the lactamization would contain unused ArI, palladium catalyst and silver salt additive (which have been used in the C-H arylation step), these might have interfered in the lactamization step and thus a trend of decreased yield was observed for **5h,k,o,x**. We next attempted the lactamization of 3-aryl ε-aminohexanoic acid carboxamides **4y,z** and **4aa-af** to obtain the corresponding 4-arylazepan-2-one (4-aryl ε-caprolactam) derivatives. Heating a mixture of substrate **4aa** with hydrazine hydrate in neat condition at 150 ^{o}C or in EtOH at 95 ^{o}C for 6-24 h did not yield the expected 4-arylazepan-2-one derivative **6a** (entries 1-4, Table 2). Heating the carboxamide **4aa** in EtOH at a higher temperature (150 ^{o}C) for 6 h yielded the product **6a** in 19% yield (entry 5, Table 2). Heating the carboxamide **4aa** in EtOH at a higher temperature (150 ^{o}C) for 24 h yielded the product **6a** in 35% yield (entry 6, Table 2). Attempts including heating the substrate **4aa** under microwave heating or prolonging the reaction period or using different alcohols as the solvent did not improve the yield of the product **6a** (entries 7-12, Table 2). We then performed the lactamization of other 3-aryl ε-aminohexanoic acid carboxamide substrates. Accordingly, the 4-arylazepan-2-one (4-aryl ε-caprolactam) derivatives **6b-e** were obtained in 31-37% yields from their corresponding carboxamides of 3-aryl ε-aminohexanoic acid **4z**, **4ab, 4ae, 4af** (Scheme 5b).

Given the observed low yield of the 4-arylazepan-2-ones (4-aryl caprolactams) **6** in the direct lactamization of the corresponding 3-aryl ε-aminohexanoic acid carboxamides containing both 8-aminoquinoline and phthalimide protecting group, we decided to remove the 8-aminoquinoline and then try the lactamization reaction. Accordingly, we heated the 3-aryl ε-aminohexanoic acid carboxamide **4ab** in MeOH in the presence of PTSA·H_2O to afford the corresponding methyl ester derivative **7a** in 81% (Scheme 5b). Then, the methyl ester derivative **7a** was treated with hydrazine hydrate in EtOH at 150 ^{o}C for 24 h. Again, this reaction yielded the 4-arylazepan-2-one derivative **6c** in only 23% yield. The lactamization trial involving the methyl ester derivative **7a** indicated that the transamidation step perhaps is not a facile reaction in the overall process of direct lactamization of the substrates **4z**, **4aa**, **4ab**, **4ae** and **4af** (carboxamides of ε-aminohexanoic acid) containing both the 8-aminoquinoline and phthalimide protecting groups. It

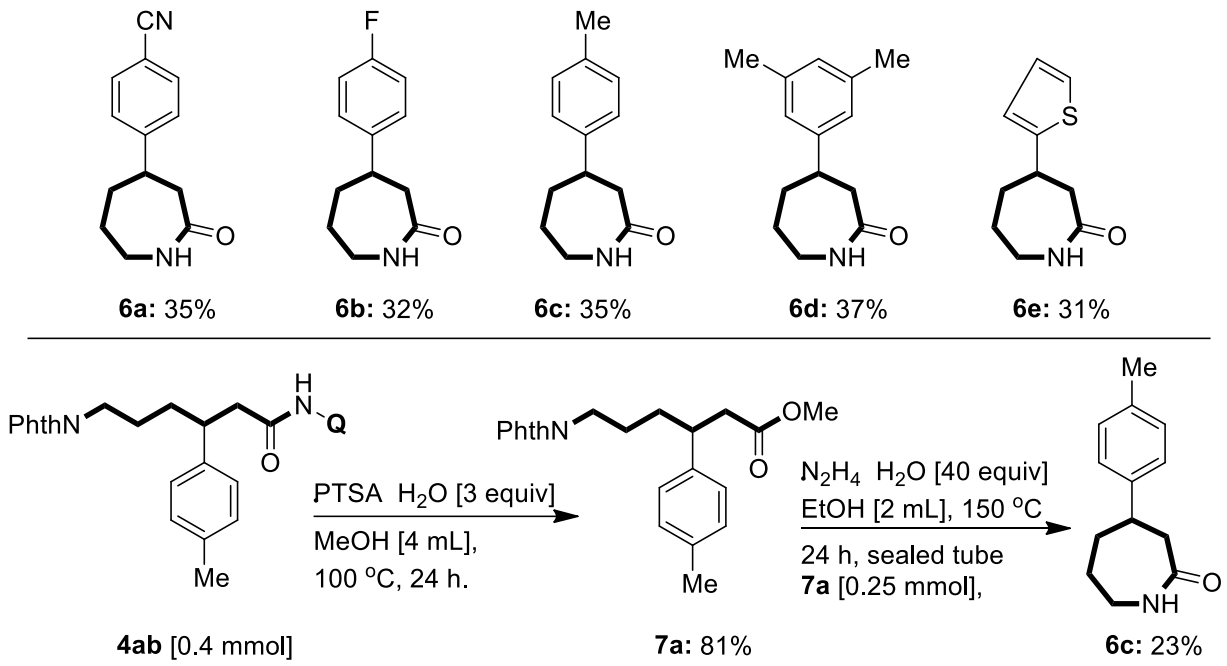
may be further correlated with the general trend that the formation of a 7-membered ring is not a facile process when compared to the process involving the formation of the 6- or 5-membered rings. Accordingly, the observed low yield of the products **6a-e** in the attempted direct lactamization may be correlated to the relative easiness with which the medium rings are generally formed.

Table 2. Direct lactamization of *β*-C-H arylated *ε*-aminohexanoic acid carboxamides **4aa**, into 4-arylazepan-2-one derivatives **6a.**



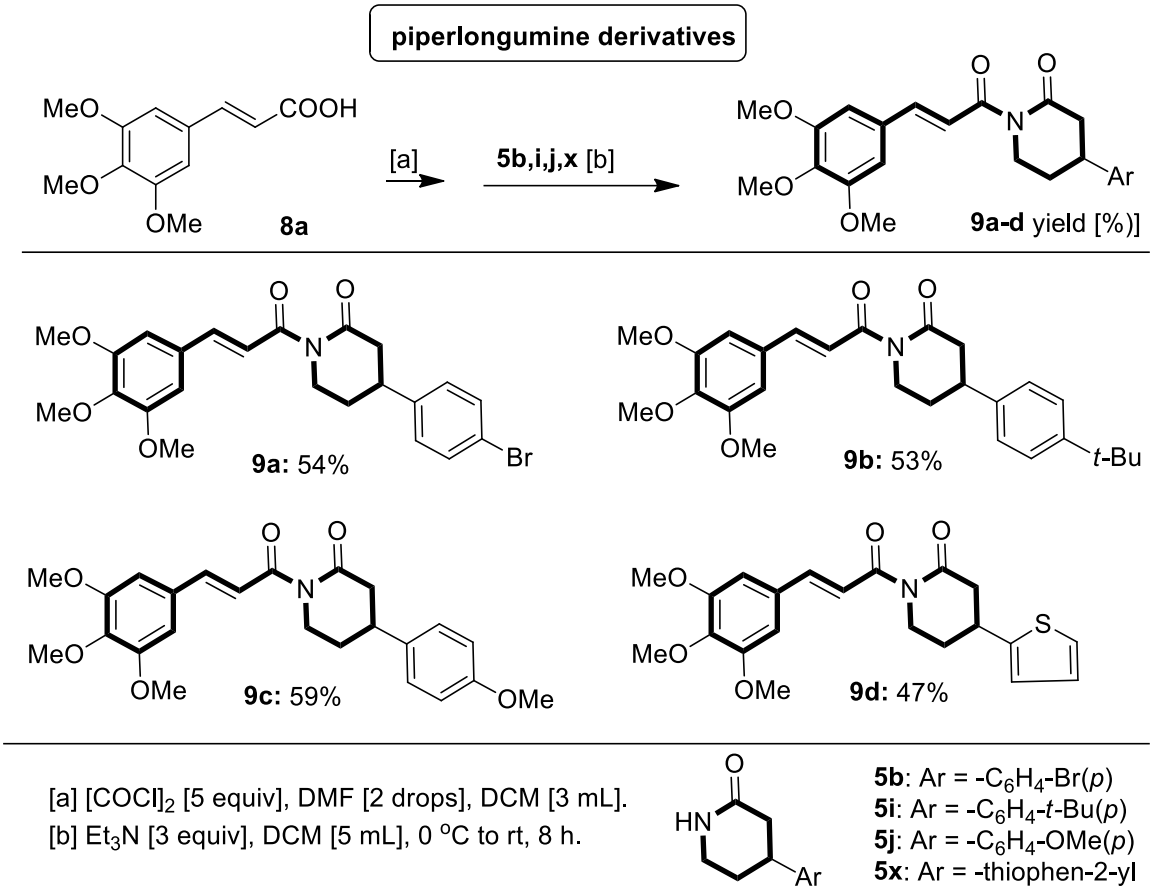
entry	solvent	*T* [°C]	*t* [h]	**6a**: yield [%]
1	neat	150	24	-
2[a]	neat	150	24	-
3	EtOH	95	6	-
4	EtOH	95	24	-
5	EtOH	150	6	19
6	**EtOH**	**150**	**24**	**35**
7	EtOH	150	48	16
8	EtOH	180	24	19
9	MeOH	150	24	19
10	*i*-PrOH	150	24	22
11	*t*-PrOH	150	24	20
12	EtOH	150	1 [MW heating]	35

[a] 200 equiv of $N_2H_4 \cdot H_2O$ was used.



Scheme 5b. Synthesis of 4-arylazepan-2-one derivatives **6a-e** derivatives from the *β*-C-H arylated *ε*-aminohexanoic acid carboxamides **4z**, **4aa**, **4ab**, **4ae** and **4af**.

We then focused our attention to show the utility of this work comprised of the synthesis of 4-aryl-2-piperidones. Accordingly, we planned to synthesize various *N*-functionalized 4-aryl-2-piperidones, 4-arylpiperidines, which would be structurally closer to already reported biologically active 4-aryl-2-piperidone, 4-arylpiperidine scaffolds (Figure 1). In this regard, initially, we wished to prepare some piperlongumine analogues. We treated representative 4-aryl-2-piperidones **5b,i,j,x** with 3,4,5-trimethoxycinnamoyl chloride. These reactions yielded the *N*-(3,4,5-trimethoxycinnamoyl)piperidin-2-ones **9a-d** (piperlongumine analogues, Scheme 6).

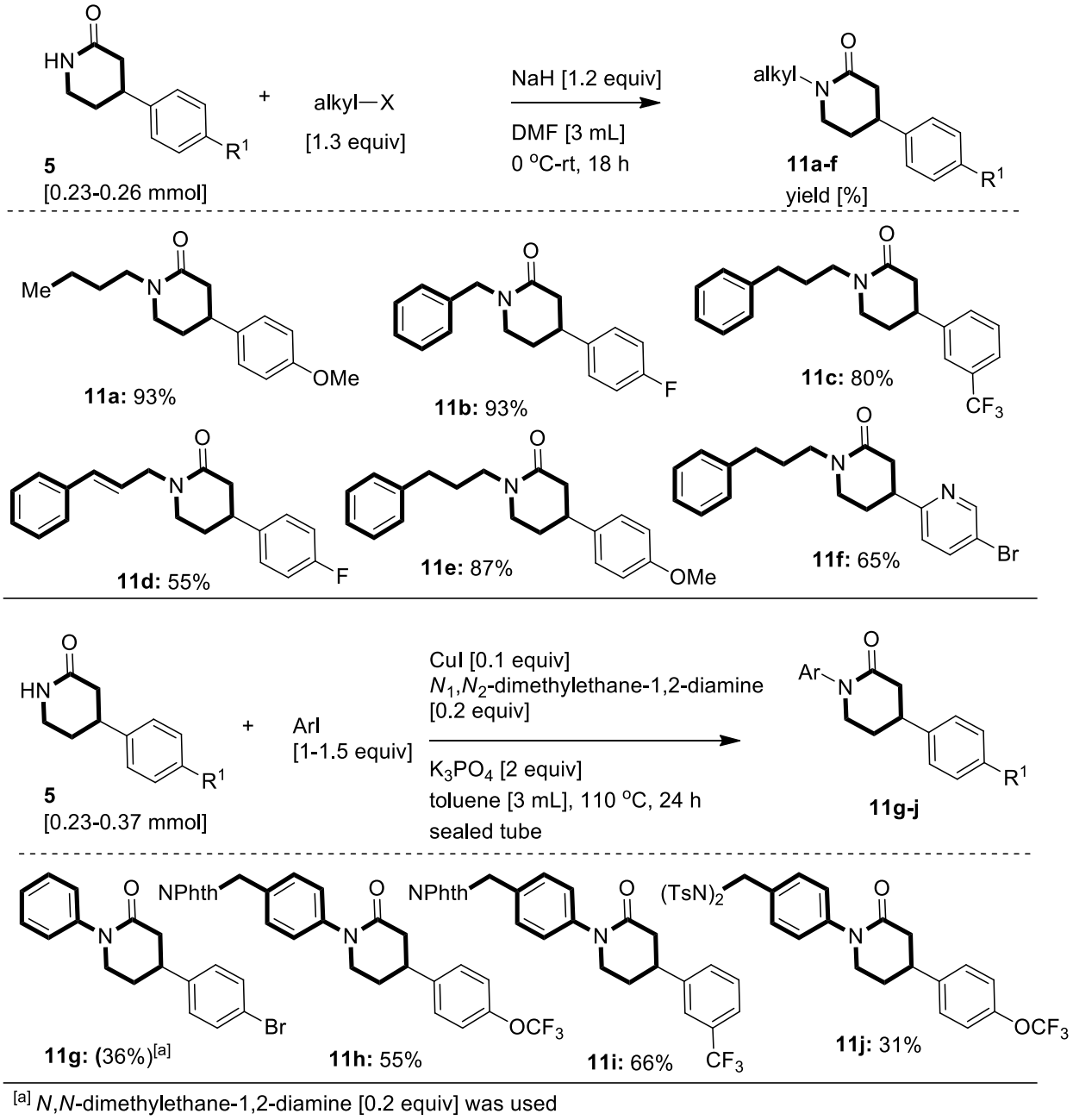


Scheme 6. Assembling *N*-(3,4,5-trimethoxycinnamoyl)piperidin-2-ones **9a-d** (piperlongumine analogues).

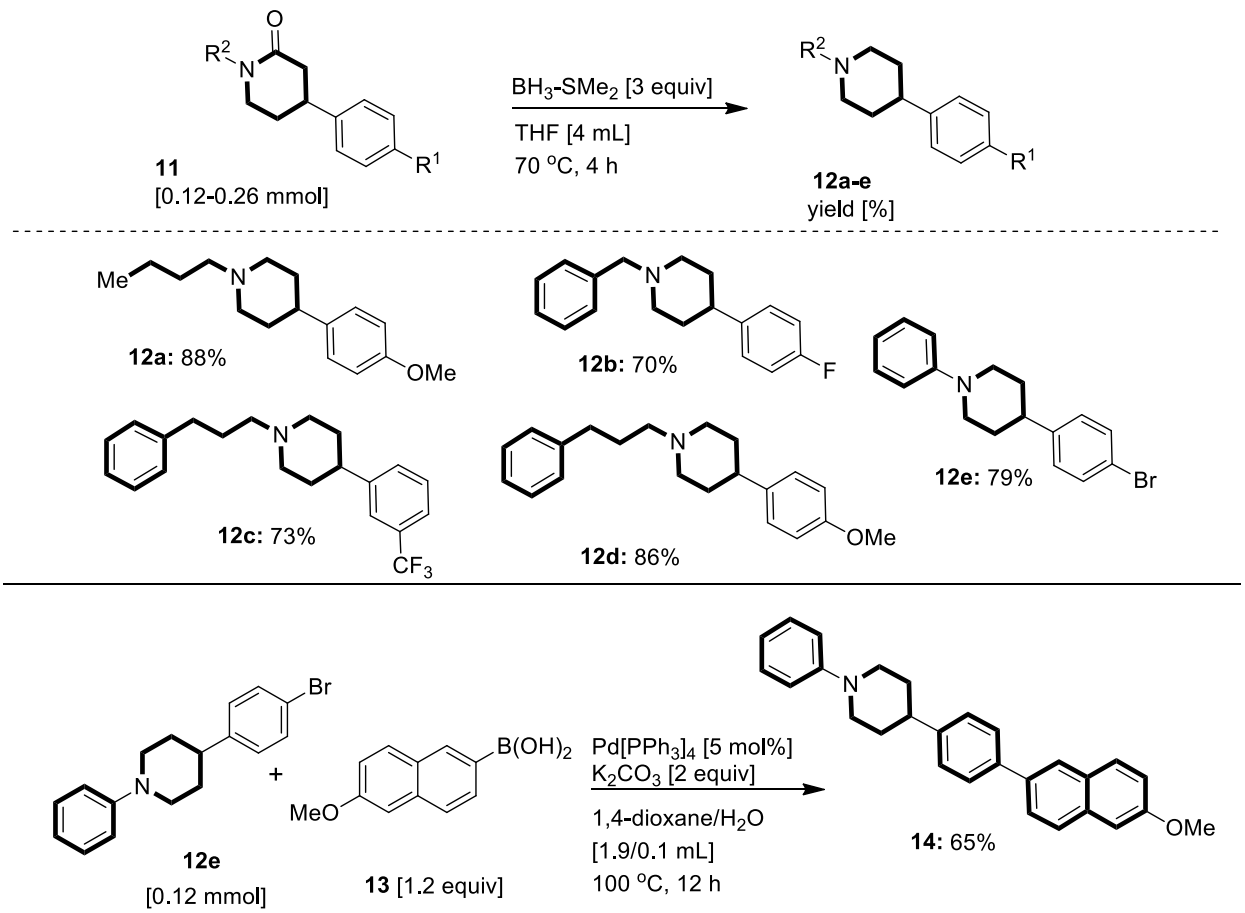
We next subjected representative 4-aryl-2-piperidones **5j,c,p,v** to the standard *N*-alkylation reaction conditions. Accordingly, the *N*-alkyl-4-aryl-2-piperidones **11a-c,e,f** and *N*-cinnamyl-4-aryl-2-piperidone **11d** were obtained in 55-93% yields (Scheme 7). Representative 4-aryl-2-piperidones **5b,m,p** were subjected to the standard Cu-catalyzed *N*-arylation method. Accordingly, the *N*-aryl-4-aryl-2-piperidones **11g-j** were obtained in 31-66% yields (Scheme 7).

Furthermore, we intended to convert the *N*-alkylated and *N*-arylated 4-arylpiperidones **11** into *N*-alkylated and *N*-arylated 4-arylpiperidines, those would be structurally closer to medicinally important motifs reported in the literature (Figure 1). Representative *N*-alkylated and *N*-arylated 4-aryl-2-piperidones **11** were subjected to the standard amide reduction conditions in the presence of $BH_3 \cdot SMe_2$ in THF at 70 °C. Accordingly, the *N*-alky-4-arylpiperidine scaffolds **12a-d** and *N*-aryl-4-arylpiperidine scaffold **12e** were obtained in 70-88% yields (Scheme 8).

Furthermore, we treated the *N*-arylated 4-arylpiperidine **12e** to the Suzuki coupling reaction to afford the *N*-phenyl-4-biarylpiperidine derivative **14** in 65% yield (Scheme 8).



Scheme 7. Assembling examples of *N*-alkylated and *N*-arylated 4-aryl-2-piperidones.

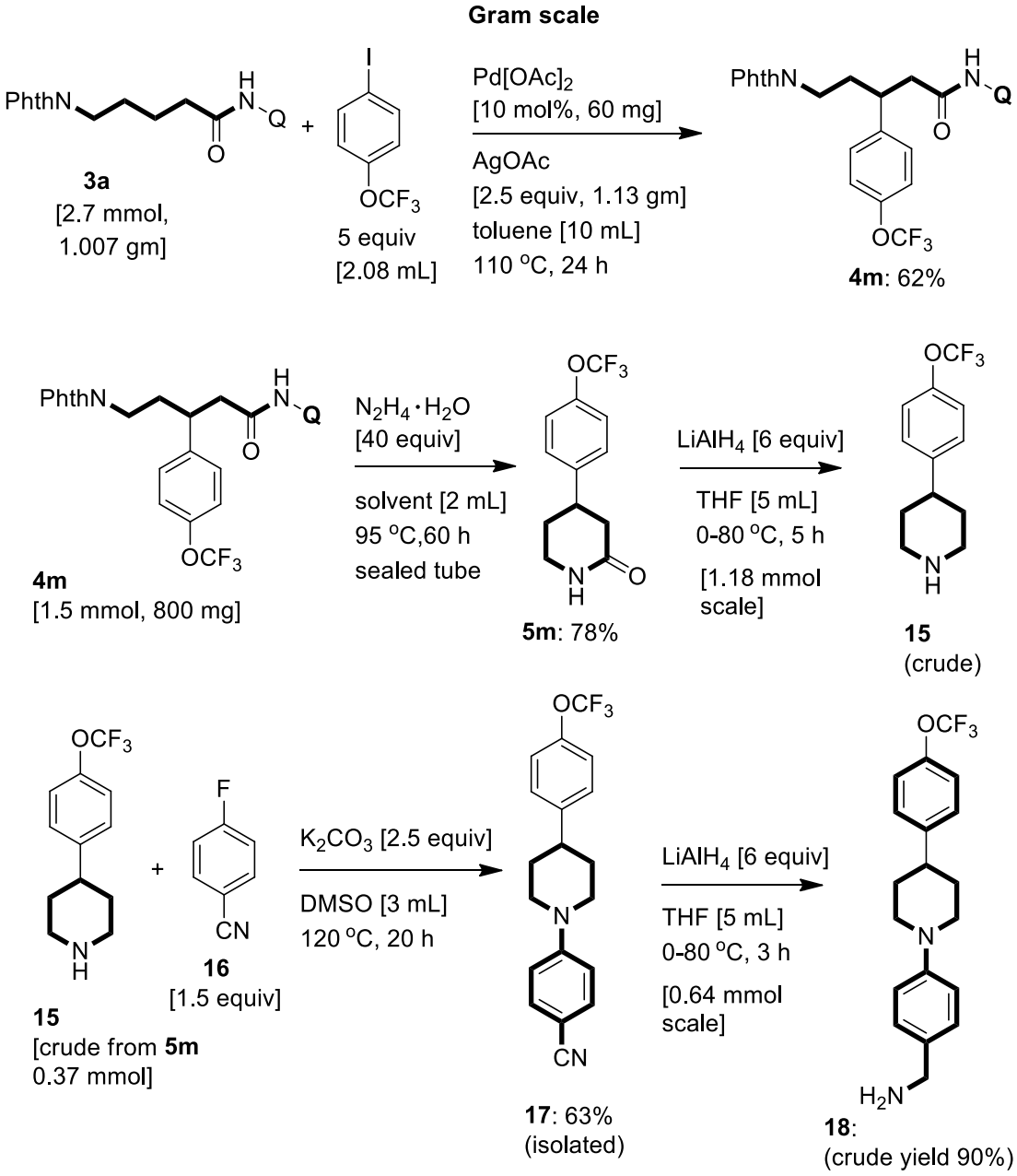


Scheme 8. Assembling examples of *N*-alkylated and *N*-arylated 4-arylpiperidines.

We wished to further extend the synthetic utility of this work comprised of the Pd(II)-catalyzed, 8-aminoquinoline-aided sp^3 *β*-C-H arylation and direct lactamization of 3-aryl *δ*-aminopentanoic acid carboxamides. Accordingly, we targeted synthesizing the compound Q203 (Telacebec, **1j**) and its analogues. The compound Q203 is an antibiotic drug molecule in phase II clinical trials for the treatment of tuberculosis (TB).[8] The compound Q203 (Telacebec) is an amide derivative derived from an *N*-aryl-4-arylpiperidine motif (**18**) and an imidazopyridine motif (**20b**) (Schemes 9 and 10).

At first, we performed a gram scale arylation of **3a** with 4-(trifluoromethoxy)iodobenzene, which yielded the *β*-C-H arylated *δ*-aminopentanoic acid carboxamide **4m** in 62% yield (Scheme 9). We then subjected the carboxamide **4m** to the hydrazine-mediated direct lactamization in EtOH at 95 °C and obtained the 4-aryl-2-piperidone **5m** containing a trifluoromethoxy substituent in the aryl ring in 78% yield. The 4-aryl-2-piperidone **5m** was then subjected to the amide reduction

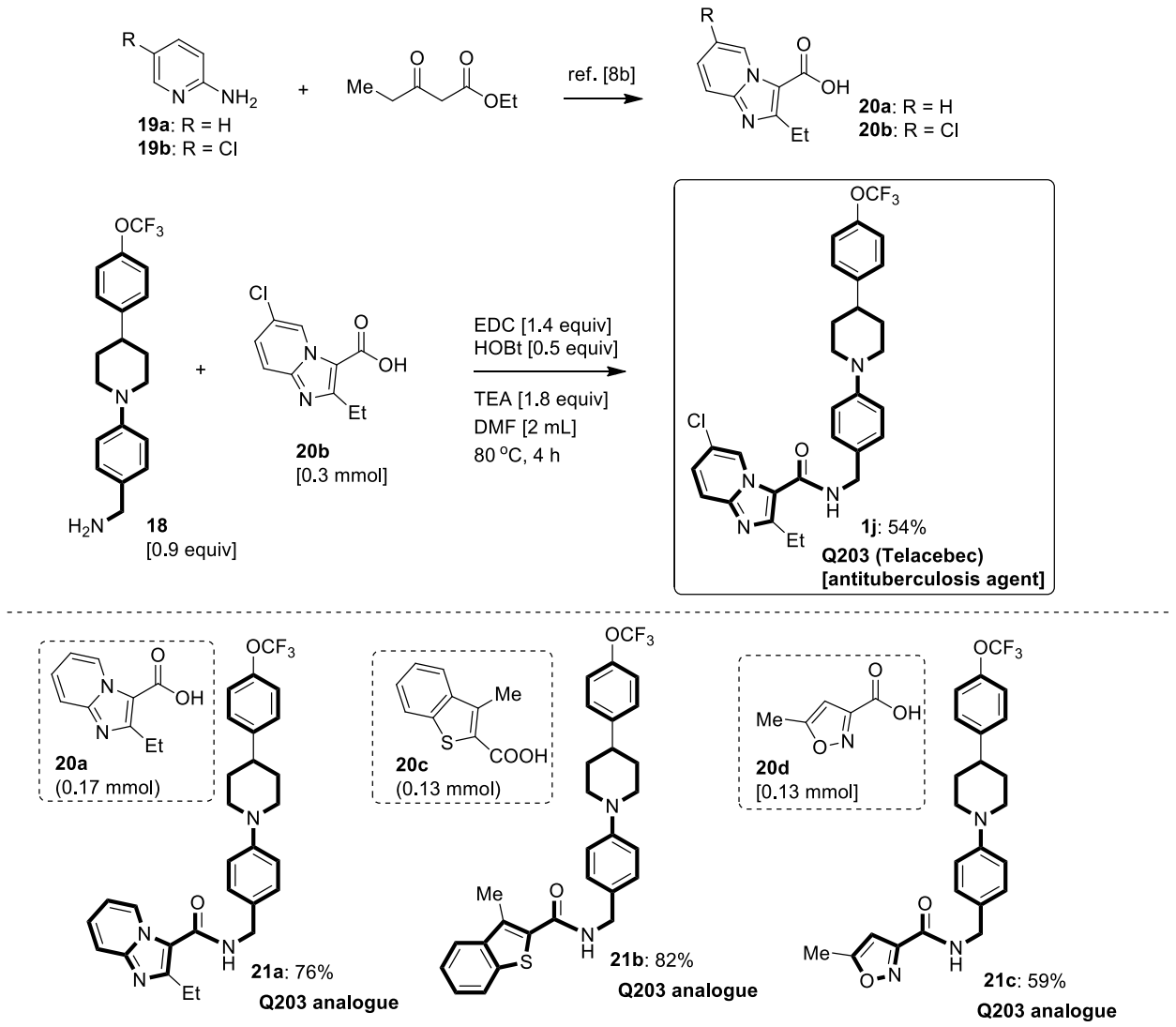
conditions in the presence of $LiAlH_4$ in THF at 80 °C and we obtained the 4-arylpiperidine scaffold **15**.



Scheme 9. Assembling the piperidine fragment **18** for the synthesis of the molecule Q203 (Telacebec).

We then treated the 4-arylpiperidine motif **15** with 4-fluorobenzonitrile in the presence of K_2CO_3 in DMSO at 120 °C, which yielded the *N*-aryl-4-arylpiperidine scaffold **17** in 63% yield. The $LiAlH_4$-mediated reduction of the nitrile group of the *N*-aryl-4-arylpiperidine scaffold **17** yielded

the required Q203 precursor **18**.[8d] In parallel, we also assembled the imidazo[1,2-*a*]pyridine-3-carboxylic acid fragments **20a,b** (Scheme 10). The EDC/HOBt-mediated amide coupling of both the Q203 precursors **18** and **20b** yielded the compound Q203 (Telacebec, **1j**)[8b,c] in 54% yield (Scheme 10). We then prepared another Q203 analogue **21a** from the Q203 precursor **18** and the carboxylic acid **20a**.[8b,c] Finally, we prepared two new Q203 analogues **21b** and **21c** *via* the EDC/HOBt-mediated amide coupling of the Q203 precursor **18** and heterocyclic carboxylic acids **20c,d** (Scheme 10).



Scheme 10. Synthesis of the molecule Q203 (Telacebec, **1j**) and Q203 analogues **21a-c** from the Q203 precursor **18** and **20a-c**.

Conclusion

In summary, we have reported the synthesis of various 4-aryl-2-piperidones, 4-arylpiperidine scaffolds and antituberculosis molecule Q203 (Telacebec) and its analogues involving the sp^3 *β*-C-H arylation method as a key step. At first, we have assembled various *β*-C-H arylated *N*-phthaloyl *δ*-aminopentanoic acid carboxamide *via* the Pd(II)-catalyzed, 8-aminoquinoline-aided, sp^3 *β*-C-H activation and arylation method. We then performed the direct lactamization of the *β*-C-H arylated *δ*-aminopentanoic acid carboxamides by using hydrazine hydrate, which afforded the corresponding 4-aryl-2-piperidones. It may be noted that the *β*-C-H arylated *N*-phthaloyl *δ*-aminopentanoic acid carboxamides containing both 8-aminoquinoline and phthaloyl protecting groups directly underwent the hydrazine-mediated lactamization to afford 4-aryl-2-piperidones. Representative 4-aryl-2-piperidones were converted into the corresponding *N*-functionalized 4-aryl-2-piperidones. Next, representative 4-aryl-2-piperidones were converted into 4-arylpiperidines. Furthermore, we have shown the synthesis of antituberculosis molecule Q203 (Telacebec) and Q203 analogues (**21a-c**) from the corresponding *β*-C-H arylated *N*-phthaloyl *δ*-aminopentanoic acid carboxamide (**4m**) and 4-aryl-2-piperidone (**5m**). 4-Aryl-2-piperidones and 4-arylpiperidine motifs are ubiquitous in pharmaceuticals and widely used in various medicinal chemistry research programs. In general, 4-aryl-2-piperidones, 4-arylpiperidine scaffolds have been assembled *via* the traditional cross-coupling methods involving organometallic reagents. Thus, this work is an example of the organometallic reagent-free synthesis of 4-aryl-2-piperidones and 4-arylpiperidine scaffolds (when compared to the traditional cross-coupling methods used for assembling these scaffolds).[2-9] While lactamization (cyclization) is a metal-free process, the introduction of the 4-aryl group requires a palladium complex for the sp^3 C-H functionalization. Overall, this work comprising of the sp^3 C-H activation/arylation and direct lactamization generating 4-aryl-2-piperidones and their conversion into 4-arylpiperidines will be a contribution towards enriching the library of 4-aryl-2-piperidones and 4-arylpiperidines.

Experimental Section

General. IR spectra of compounds were recorded as neat or thin films or KBr pellets. ^1H and ^{13}C NMR spectra of all compounds were recorded in 400 (or 500) and 101 (or 126) MHz spectrometers, respectively, using TMS as an internal standard. The HRMS analysis data were

obtained from QTOF mass analyzer using the electrospray ionization (ESI) method. Column chromatography purification was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after workup were dried using anhydrous Na_2SO_4. Thin-layer chromatography (TLC) analysis was performed on alumina and silica plates, and components were visualized by observation under irradiation with a UV lamp or iodine vapour. Isolated yields of all of the products are reported and yields were not optimized. The compounds **4b**,[15d] **4g**,[15d] **4o**,[15d] **4s**,[15d] **4x**,[15d] **4aa**,[15d] **4ab**,[13a] **5g**,[9b] **5b**,[9c] **5c**,[9c] **5l**,[9c] **6b**,[20f] **6c**,[20f] **6d**,[20f] **7a**,[20a] **11b**,[20c] **12a**,[4a] **12b**,[20b] **16**,[8d] **17**,[8d] **18**,[8d] **1j**,[8b,c] and **21a**[8b,c,20d] in this work are known compounds and their characterization data were reported in the literature.

General procedure for the Pd(II)-catalyzed, 8-aminoquinoline-aided *β*-C-H arylation of unnatural amino acid carboxamides (4): A mixture of an appropriate unnatural amino acid carboxamide (0.3-0.4 mmol, 1 equiv), an appropriate aryl iodide (5 equiv),$Pd(OAc)_2$ (10 mol%) and AgOAc (2.5 equiv) in anhydrous toluene(3-4 mL) was heated at 110 ^oC for 24 h under a nitrogen atm. After the reaction period, the reaction mixture wasconcentrated under reduced pressure to afford a crude reactionmixture, which was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to give the corresponding*β*-C-Harylated amino acid carboxamide **4**.

General procedure for the preparation of the 4-aryl-2-piperidone scaffolds (5): An appropriate *β*-C-H arylated *δ*-aminopentanoic acid carboxamide (0.17-0.20 mmol, 1 equiv), $N_2H_4{\cdot}H_2O$ (40 equiv) and ethanol (3 mL) were added to screw-cap seal tube. Then, the reaction mixture containing the tube was sealed and the tube was submerged into a silicon oil bath preheated to 95 ^oC. After 6 h, the solution was cooled to rt and then, the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water (2 times) and then, the combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatographyto furnish the corresponding 4-aryl-2-piperidone scaffold (**5**).

General procedure for the preparation of the 4-arylazepan-2-one derivatives (6): An appropriate *β*-C-H arylated *ε*-aminohexanoic acid carboxamide (0.17-0.20 mmol, 1 equiv), $N_2H_4{\cdot}H_2O$ (40 equiv) and ethanol (3 mL) were added to the screw-cap seal tube. Then, the

reaction mixture containing the tube was sealed and the tube was submerged into a silicon oil bath preheated to 150 ^{o}C. After 24 h, the solution was cooled to rt and then, the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water (2 times) and then the combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture, and purification of the resulting reaction mixture by column chromatography on silica gel gave the corresponding 4-arylazepan-2-one derivative (**6**).

General procedure for the synthesis of piperlongumine derivatives (9): To the solution of 3,4,5-trimethoxy cinnamic acid (0.1-0.15 mmol) in DCM (3 mL) and DMF (1 drop), oxalyl chloride (5 equiv) was slowly added at 0 ^{o}C. Then, the resultant mixture was stirred for 5 h at rt under a nitrogen atmosphere. After removing the volatiles under reduced pressure, the resultant crude reaction mixture was diluted with anhydrous DCM (5 mL). Corresponding 4-aryl-2-piperidinone (1.2 equiv) and Et_3N (3 equiv) were slowly added to the DCM solution of acid chloride under a nitrogen atmosphere. The resulting crude mixture was stirred at rt overnight. After this period, the reaction mixture was diluted with DCM (2-10 mL) and washed with water and saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4, and then, the solvent was evaporated under reduced pressure to afford a crude mixture, which was purified by column chromatography on silica gel to afford the corresponding piperlongumine derivative (**9**).

General procedure for the synthesis of *N*-alkylated 4-aryl 2-piperidones (11a-f): To the solution of appropriate 4-aryl-2-piperidone (1 equiv) in DMF (4 mL) was added NaH (1.2 equiv) at 0 °C and after 45 min. an appropriate alkyl bromide/iodide was added. The mixture was stirred at rt for 18 h under a nitrogen atmosphere, and then, the reaction was quenched with water. The reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water (2 times) and then, the combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatographyto afford the corresponding *N*-alkylated piperidones derivative (**11a-f**).

General procedure for the synthesis of *N*-arylated 4-aryl 2-piperidone (11g-j): A mixture of an appropriate 4-aryl-2-piperidone (0.2 mmol), CuI (0.1 equiv), K_3PO_4 (2 equiv) and toluene (3

mL) was added into a sealed tube. The tube was purged with nitrogen three times. Then N_1, N_2-dimethylethane-1,2-diamine (0.2 equiv) was added followed by an appropriate aryl iodide (1.5 equiv). The tube was again purged with nitrogen, and then the mixture was heated to 110 °C. After 24 h, the mixture was cooled to rt, and diluted with EtOAc. The mixture was filtered through a celite plug and the filtrate was concentrated to afford a crude mixture, which was purified by column chromatography on silica gel to afford the *N*-arylated 4-aryl 2-piperidone **11g-j**.

General procedure for the synthesis of *N*-alkylated and *N*-arylated 4-arylpiperidines (12): To the solution of an appropriate *N*-substituted 4-aryl-2-piperidone (0.12 mmol, 1 equiv) in THF (4 mL) was added borane dimethylsulfide complex (3 equiv). The mixture was heated at 70 °C for 4 h, then the reaction mixture was cooled to rt, and then MeOH (5 mL) was added slowly. The mixture was concentrated under the reduced pressure to afford a crude mixture, which was purified by column chromatography on silica gel to afford the corresponding piperidine (**12**).

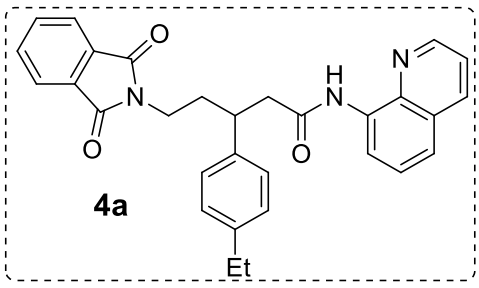
Procedure[20e] **for the synthesis of compound 14:** A mixture of 4-(4-bromophenyl)-1-phenylpiperidine **12e** (0.07 mmol), (6-methoxynaphthalen-2-yl)boronic acid (1.2 equiv), K_2CO_3 (2 equiv), [$Pd(PPh_3)_4$] (5 mol%) and 1,4-dioxane (1.8 mL) were added to a screw-cap seal tube. Nitrogen was purged (3 times) before the addition of water (0.2 mL) to the sealed tube. The tube was submerged into a silicon oil bath preheated to 100 ^oC and the reaction was continued overnight. After cooling to rt, the product was extracted with dichloromethane. The organic layers were collected, dried over anhydrous Na_2SO_4, and the solvent was evaporated. The crude mixture was subjected to column chromatography to afford the compound 4-(4-(6-methoxynaphthalen-2-l)phenyl)-1-phenylpiperidine**14**.

Procedure for the preparation of the Q203 precursor 18 from 5m: A solution of the *N*-aryl-4-aryl-2-piperidone **5m** (1.18 mmol) in anhydrous THF (5 mL) was added to a suspension of LAH (6 equiv) in THF at 0 °C. The reaction mixture was stirred for 10 min and then the reaction mixture was refluxed for 5 h. The reaction was quenched with aq. NaOH (2 M, 0.5 mL) and water (1 mL) and then, the mixture was filtered through a celite plug, the residue was washed with brine solution and extracted using DCM. The organic layers were separated and concentrated to afford the crude compound **15**. Then, the crude compound **15** was used as such in the next step. A mixture of the crude compound 4-arylpiperidine **15** (0.37 mmol) and

anhydrous K_2CO_3 (2.5 equiv) in DMSO (3 mL) was added 4-fluorobenzonitrile (4.5 equiv). The reaction was stirred at 120 °C for 20 h. After the reaction was finished, the solution was washed with water, extracted using EtOAc, concentrated and purification through column chromatography afforded the compound **17**. A solution of the *N*-aryl-4-arylpiperidine **17**(0.64 mmol) in anhydrous THF (5 mL) was added LAH (6 equiv) at 0 °C. The reaction mixture was stirred for a few min and then was refluxed at 80 °C for 3 h. The reaction was quenched with aq. NaOH (2 M, 1 mL) and water (2 mL) and then, the mixture was filtered through a celite plug and the residue was washed with brine solution and extracted by using DCM. The organic layers were separated and concentrated to afford the Q203 precursor **18**[8b-d] as a crude compound, which was used in the next step.

Procedure for the preparation of the compounds 21a-c and 1j: To a solution of an appropriate carboxylic acid (1 equiv) in DMF (2 mL), EDCI (1.4 equiv), HOBt (0.5 equiv), Et_3N (1.8 equiv), and piperidine derivative (Q203 precursor) **18** (0.9 equiv) were added and the reaction mixture was heated to 80 °C for 4 h. The mixture was cooled to rt and diluted with ethyl acetate, washed with water and brine solution, the organic layers were separated and dried with Na_2SO_4 and concentrated. The crude mixture was purified by column chromatography to afford the Q203 compound **1j**[8b-d] andQ203 analogues **21a**,[8b-d] **21b** and **21c**.

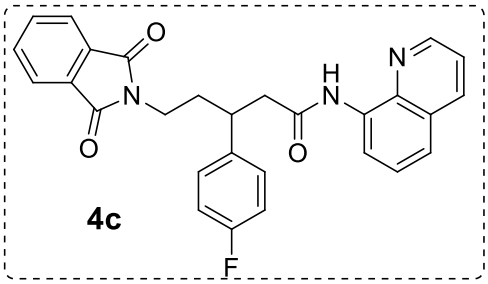
5-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethylphenyl)-*N*-(quinolin-8-yl)pentanamide (4a)*:* The



compound **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale green coloured solid (104 mg, 73%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.4;mp: 78-80 ^oC; IR (DCM): 2962, 1703, 1522, 1386, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.71 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.65 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.52-7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 3.72-3.64 (m, 2H), 3.44-3.36 (m, 1H), 2.90-2.80 (m, 2H), 2.47 (q, *J*= 7.6 Hz, 2H), 2.34-2.24 (m, 1H), 2.22-2.14 (m, 1H), 1.09 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.3, 148.0, 142.4, 139.9, 138.2, 136.3, 134.3, 133.7,

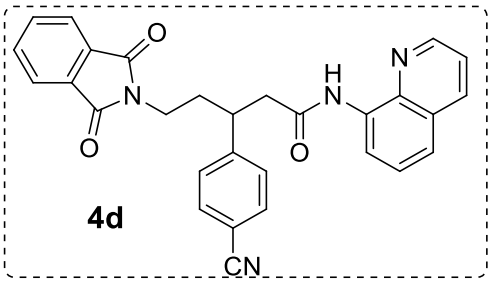
132.1, 128.1, 127.8, 127.4, 127.3, 123.0, 121.5, 121.4, 116.4, 46.2, 40.3, 36.7, 33.6, 28.3, 15.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_3$ $[M+H]^+$478.2131 found 478.2115.

5-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(quinolin-8-yl)pentanamide (4c):The



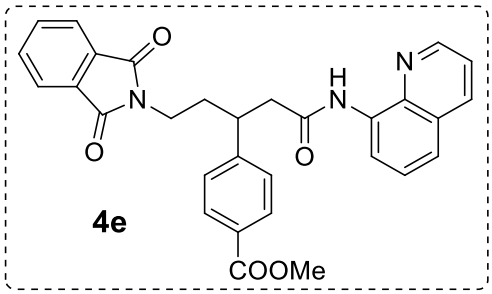
compound **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid (135 mg, 72%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 154-156 ^oC; IR (DCM): 2933, 1706, 1522, 1390, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$):δ_H 9.62 (br. s, 1H), 8.73 (dd, *J* = 4.2, 1.3 Hz, 1H), 8.67 (dd, *J* = 6.7, 2.1 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.76 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.50-7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32-7.28 (m, 2H), 6.91 (t, *J* = 8.7 Hz, 2H), 3.70-3.60 (m, 2H), 3.44-3.38 (m, 1H), 2.88 (dd, *J* = 14.7, 6.7 Hz, 1H), 2.80 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.25-2.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz):δ_C169.3, 168.2, 161.6 (d, J_{C-F} = 243.4 Hz), 148.0, 138.4 (d, J_{C-F} = 2.8 Hz), 138.2, 136.3, 134.2, 133.8, 132.0, 129.0 (d, J_{C-F} = 8.0 Hz), 127.8, 127.3, 123.0, 121.6, 121.5, 116.5, 115.5, (d, J_{C-F} = 21.4 Hz), 46.0, 39.9, 36.5, 33.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -116.33; HRMS (ESI) calcd for $C_{28}H_{23}FN_3O_3$ $[M+H]^+$468.1723 found 468.1743.

3-(4-Cyanophenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4d):The



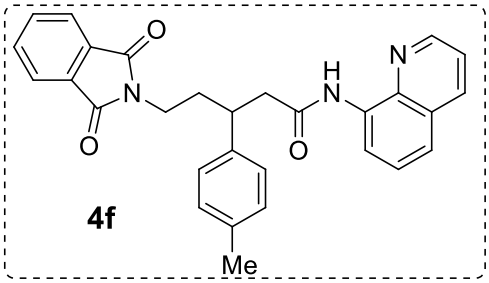
compound **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown coloured solid (124 mg, 87%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.2;mp: 162-164 ^oC; IR (DCM): 2934, 1703, 1524, 1388, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.62 (br. s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67-8.62 (m, 1H), 8.16 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.77 (dd, *J* = 5.7, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.53-7.44 (m, 7H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.54-3.47 (m, 1H), 2.94 (dd,*J* = 14.8, 6.4 Hz, 1H), 2.82 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.37-2.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.7, 168.2, 148.5, 148.1, 138.1, 136.4, 134.0, 133.9, 132.4, 131.8, 128.5, 127.9, 127.3, 123.1, 121.8, 121.7, 118.7, 116.5, 110.4, 45.3, 40.7, 36.3, 33.4; HRMS (ESI) calcd for $C_{29}H_{23}N_4O_3$ $[M+H]^+$475.1770 found 475.1750.

Methyl 4-(5-(1,3-dioxoisoindolin-2-yl)-1-oxo-1-(quinolin-8-ylamino)pentan-3-yl)benzoate



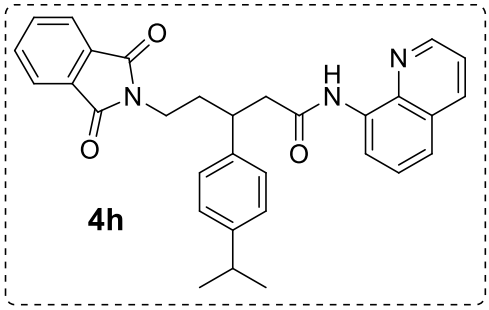
(4e)*:*The compound **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid (155 mg, 76%, 0.4 mmol scale);R_f(30% EtOAc/hexane) 0.2; mp: 160-162 ^oC; IR (DCM): 2939, 1705, 1525, 1275, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H9.65 (br. s, 1H), 8.74 (dd, *J* = 4.2,1.6 Hz, 1H), 8.67 (dd, *J* = 6.0, 3.0 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.75 (dd, *J* = 5.5,3.1 Hz, 2H), 7.65 (dd, *J* = 5.4,3.1 Hz, 2H), 7.50-7.48 (m, 2H), 7.45-7.40 (m, 3H), 3.85 (s, 3H), 3.72-3.64 (m, 2H), 3.54-3.47 (m, 1H), 2.95 (dd, *J* = 14.8, 6.9 Hz, 1H), 2.85 (dd, *J* = 14.8, 7.9 Hz, 1H), 2.36-2.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.1, 168.2, 166.7, 148.2, 148.1, 138.1, 136.3, 134.1, 133.7, 131.9, 130.0, 128.5, 127.8, 127.6, 127.3, 123.0, 121.6, 121.6, 116.5, 51.9, 45.4, 40.6, 36.4, 33.6; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_5$ $[M+H]^+$508.1872 found 508.1896.

5-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(*p*-tolyl)pentanamide (4f)*:*The compound **4f**



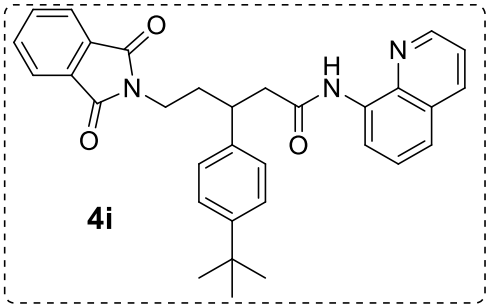
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) colouSrless solid (109 mg, 78%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 150-152 ^oC; IR (DCM): 2933, 1703, 1523, 1387, 721 cm^{-1};^1H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.75 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.71 (dd, *J* = 6.9, 1.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.76 (dd, *J*= 5.4, 3.1 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.53-7.47 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 3.72-3.61 (m, 2H), 3.43-3.35 (m, 1H), 2.90-2.80 (m, 2H), 2.32-2.13 (m, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.7, 168.2, 148.0, 139.6, 138.2, 136.3, 136.2, 134.3, 133.7, 132.1, 129.4, 127.8, 127.3, 123.0, 121.5, 121.4, 116.5, 46.1, 40.3, 36.6, 33.7, 21.0; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_3$ $[M+H]^+$464.1974 found 464.1955.

5-(1,3-Dioxoisoindolin-2-yl)-3-(4-isopropylphenyl)-*N*-(quinolin-8-yl)pentanamide (4h): The compound **4h** was obtained after purification by column chromatography on silica gel

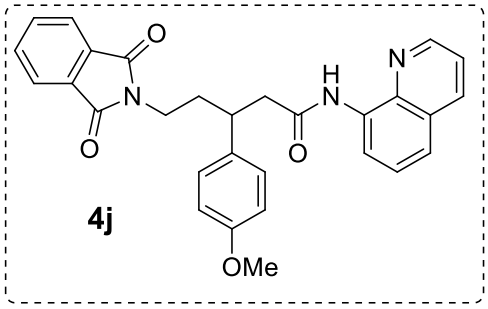


(EtOAc:hexane = 60:40) as a colourless solid (95 mg, 65%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 142-144 ^oC; IR (DCM): 2957, 1706, 1524, 1389, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.65 (br. s, 1H), 8.75 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.71 (dd, *J* = 7.1, 1.6 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.64 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.53-7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 3.69 (t, *J* = 7.4 Hz, 2H), 3.44-3.37 (m, 1H), 2.90-2.80 (m, 2H), 2.73 (m, 1H), 2.35-2.25 (m, 1H), 2.22-2.15 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.3, 148.0, 147.0, 140.1, 138.2, 136.3, 134.3, 133.7, 132.1, 127.8, 127.4, 127.3, 126.6, 122.9, 121.5, 121.4, 116.4, 46.2, 40.3, 36.8, 33.6, 33.5, 23.9, 23.9; HRMS (ESI) calcd for $C_{31}H_{30}N_3O_3$ $[M+H]^+$492.2287 found 492.2271.

3-(4-(Tert-Butyl)phenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4i)*:*The compound **4i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (134 mg, 66%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 178-180 ^oC; IR (DCM): 2956, 1707, 1525, 1391, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$):δ_H 9.64 (br. s, 1H), 8.74-8.70 (m, 2H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.62 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.50-7.46 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 3.69 (t, *J* = 7.1 Hz, 2H), 3.43-3.38 (m, 1H), 2.88-2.80 (m, 2H),2.34-2.27 (m, 1H), 2.22-2.15 (m, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.2, 149.3, 148.0, 139.7, 138.2, 136.2, 134.4, 133.6, 132.1, 127.8, 127.3, 127.0, 125.4, 122.9, 121.5, 121.4, 116.4, 46.1, 40.2, 36.8, 34.2, 33.5, 31.3; HRMS (ESI) calcd for $C_{32}H_{32}N_3O_3$ $[M+H]^+$506.2444 found 506.2462.

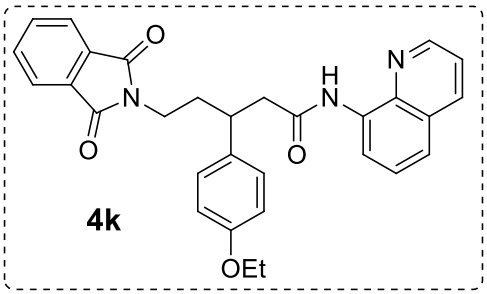


5-(1,3-Dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)pentanamide (4j)*:*The compound **4j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid(136 mg, 94%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 125-127 ^oC; IR (DCM): 2940, 1702, 1520, 1387, 722 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$):δ_H 9.63 (br. s, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 6.9, 2.0 Hz,



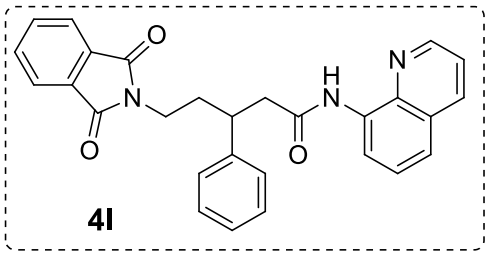
1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52-7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.26 (d, *J* = 8.6, 2H), 6.77-6.74 (m, 2H), 3.72-3.60 (m, 2H), 3.67 (s, 3H), 3.41-3.34 (m, 1H), 2.89-2.78 (m, 2H), 2.27-2.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.7, 168.3, 158.2, 148.0, 138.2, 136.3, 134.7, 134.3, 133.7, 132.1, 128.4, 127.8, 127.3, 123.0, 121.5, 121.4, 116.4, 114.0, 55.1, 46.3, 39.9, 36.6, 33.9; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_4$ $[M+H]^+$480.1923 found 480.1906.

5-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethoxyphenyl)-*N*-(quinolin-8-yl)pentanamide (4k):The



compound **4k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale green coloured solid (97 mg, 65%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.3;mp: 64-66 ^{o}C; IR (DCM): 2933, 1703, 1520, 1243, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.63 (br. s, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.69 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52-7.45 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.26-7.23 (m, 2H), 6.77-6.73 (m, 2H), 3.90-3.84 (m, 2H), 3.72-3.60 (m, 2H), 3.40-3.33 (m, 1H), 2.89-2.78 (m, 2H), 2.29-2.12 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.2, 157.7, 148.0, 138.2, 136.2, 134.5, 134.3, 133.6, 132.1, 128.4, 127.8, 127.3, 123.0, 121.5, 121.4, 116.5, 114.6, 63.2, 46.3, 40.0, 36.6, 33.9, 14.8; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_4$ $[M+H]^+$494.2080 found 494.2059.

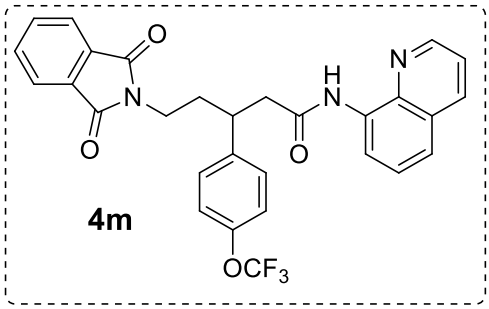
5-(1,3-Dioxoisoindolin-2-yl)-3-phenyl-*N*-(quinolin-8-yl)pentanamide (4l):The compound **4l**



was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid (103 mg, 76%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 140-142 ^{o}C; IR (DCM): 3350, 1702, 1523, 1386, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.74 (d, *J* = 4.0 Hz, 1H), 8.70 (d, *J* = 6.8 Hz, 1H), 8.13 (d,

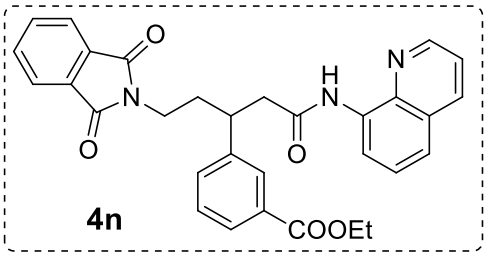
J = 8.2 Hz, 1H), 7.76-7.73 (m, 2H), 7.67-7.65 (m, 2H), 7.52-7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 3.73-3.59 (m, 2H), 3.47-3.40 (m, 1H), 2.93-2.83 (m, 2H), 2.31-2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.6, 168.3, 148.0, 142.7, 138.2, 136.3, 134.3, 133.7, 132.1, 128.7, 127.8, 127.5, 127.3, 126.7, 123.0, 121.6, 121.5, 116.5, 45.9, 40.6, 36.6, 33.8; HRMS (ESI) calcd for $C_{28}H_{24}N_3O_3$ $[M+H]^+$450.1818 found 450.1796.

5-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(4-(trifluoromethoxy)phenyl)pentanamide



(4m): The compound **4m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a green coloured viscous liquid (810 mg, 76%, 0.2 mmol scale);R_f(30% EtOAc/hexane) 0.3; IR (DCM): 2927, 1771, 1525, 1397, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.64 (br. s, 1H), 8.75 (dd, *J* = 4.2,1.5 Hz, 1H), 8.68 (dd, *J* = 6.2, 2.7 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.77 (dd, *J* = 5.5,3.1 Hz, 2H), 7.68 (dd, *J* = 5.4,3.1 Hz, 2H), 7.53-7.48 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 3.72-3.65 (m, 2H), 3.50-3.42 (m, 1H), 2.90 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.81 (dd, *J* = 14.8, 7.9 Hz, 1H), 2.33-2.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.9, 167.9, 147.8, 147.6, 147.6, 141.4, 137.8, 136.0, 133.9, 133.5, 131.6, 128.7, 127.5, 127.0, 122.7, 121.3, 120.8, 120.1 (q, $J_{C\text{-}F}$ = 255.5 Hz), 116.2, 45.5, 39.7, 36.2, 33.5; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.90; HRMS (ESI) calcd for $C_{29}H_{23}F_3N_3O_4$ $[M+H]^+$534.1641 found 534.1636.

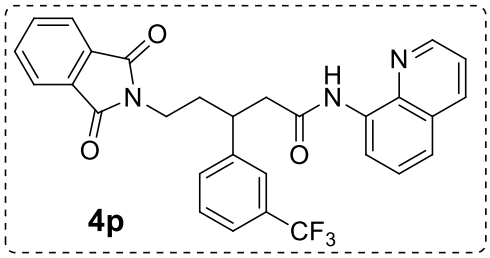
Ethyl 3-(5-(1,3-dioxoisoindolin-2-yl)-1-oxo-1-(quinolin-8-ylamino)pentan-3-yl)benzoate



(4n): The compound **4n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid (151 mg, 72%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.2; mp: 62-64 ^{o}C; IR (DCM): 3347, 1705, 1525, 1270, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.73 (dd, *J*= 4.2,1.7 Hz, 1H), 8.67 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.02 (t, *J* = 1.6 Hz, 1H), 7.78-7.74 (m, 3H), 7.66 (dd, *J* = 5.5,3.0 Hz, 2H), 7.56 (d,*J* = 7.8 Hz, 1H), 7.49-7.48 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32

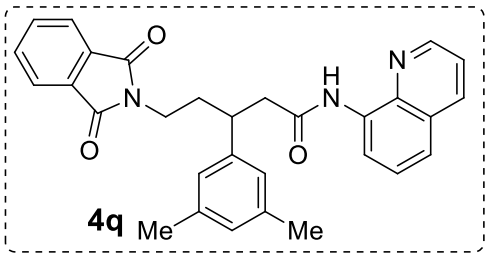
(t, *J* = 7.7 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.74-3.61 (m, 2H), 3.54-3.46 (m, 1H), 2.98-2.85 (m, 2H), 2.33-2.21 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.3, 168.2, 166.5, 148.1, 143.2, 138.2, 136.3, 134.2, 133.8, 132.6, 132.0, 130.8, 128.7, 128.2, 128.0, 127.8, 127.3, 123.0, 121.6, 121.5, 116.5, 61.0, 45.6, 40.4, 36.4, 33.8, 14.4; HRMS (ESI) calcd for $C_{31}H_{28}N_3O_5$ $[M+H]^+$522.2029 found 522.2052.

5-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(3-(trifluoromethyl)phenyl)pentanamide



(4p)*:*The compound **4p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (136 mg, 66%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 114-116 ^{o}C; IR (DCM): 2938, 2357, 1704, 1388, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.65 (br. s, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 6.2, 2.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.59 (br. s, 1H), 7.55-7.48 (m, 3H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.35-7.28 (m, 2H), 3.70 (t, *J* = 7.0 Hz, 2H), 3.55-3.48 (m, 1H), 2.93 (dd, *J* = 14.8, 7.0 Hz, 1H), 2.84 (dd, *J* = 14.8, 7.7 Hz, 1H), 2.36-2.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.0, 168.2, 148.1, 143.9, 138.2, 136.3, 134.1, 133.8, 131.3, 131.2, 130.8 (q, $J_{C\text{-}F}$ = 31.9Hz), 129.1, 127.8, 127.3, 124.0 (q, $J_{C\text{-}F}$ = 270.0Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.9Hz), 123.5 (q, $J_{C\text{-}F}$= 4.0Hz), 123.1, 121.6, 121.6, 116.5, 45.7, 40.5, 36.4, 33.5;^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -62.56; HRMS (ESI) calcd for $C_{29}H_{23}F_3N_3O_3$ $[M+H]^+$ 518.1692 found 518.1710.

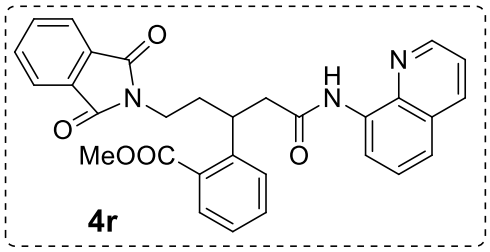
3-(3,5-Dimethylphenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4q)*:*The



compound **4q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (93 mg, 65%, 0.3 mmol scale);R_f(30% EtOAc/hexane) 0.4; mp: 154-156 ^{o}C; IR (DCM): 2929, 1706, 1525, 1390, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.64 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.53-7.46 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.91 (s, 2H), 6.57 (s, 1H), 3.74-3.68 (m, 2H), 3.37-3.31 (m, 1H), 2.84 (d, *J* = 7.4 Hz, 2H), 2.36-2.27 (m, 1H), 2.19-2.13 (m, 6H), 2.18 (s, 6H);

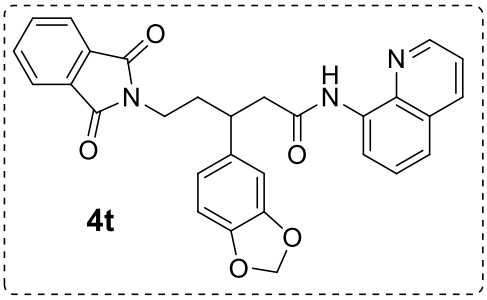
^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.9, 168.2, 148.0, 142.6, 138.2, 137.9, 136.2, 134.3, 133.5, 132.0, 128.1, 127.8, 127.3, 125.3, 122.7, 121.5, 121.4, 116.4, 46.1, 40.7, 36.8, 33.4, 21.3; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_3$ $[M+H]^+$478.2131 found 478.2114.

Methyl 2-(5-(1,3-dioxoisoindolin-2-yl)-1-oxo-1-(quinolin-8-ylamino)pentan-3-yl)benzoate



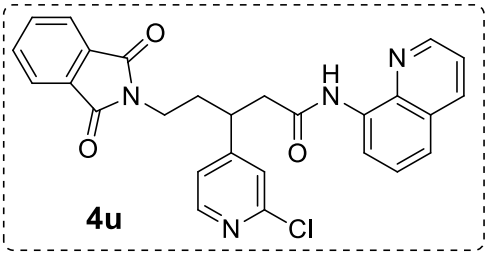
(4r): The compound **4r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (92 mg, 60%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 120-125 ^{o}C; IR (DCM): 2944, 1707, 1525, 1389, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.91 (br. s, 1H), 8.77-8.73 (m, 2H), 8.18 (d, *J* = 8.1Hz, 1H), 7.77-7.73 (m, 3H), 7.65-7.63 (m, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.54-7.44 (m, 4H), 7.18 (t, *J* = 7.5Hz, 1H), 4.37-4.30 (m, 1H), 3.91 (s, 3H), 3.76-3.69 (m, 1H), 3.65-3.58 (m, 1H), 3.03 (dd, *J* = 14.4,6.3Hz, 1H), 2.87 (dd, *J* = 14.4, 8.1Hz, 1H), 2.38-2.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.3, 168.2, 148.0, 143.8, 138.3, 136.2, 134.5, 133.7, 132.1, 132.1, 130.7, 130.6, 127.8, 127.4, 126.9, 126.3, 122.9, 121.5, 121.3, 116.6, 52.2, 45.7, 36.4, 36.0, 33.0; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_5$ $[M+H]^+$ 508.1872 found 508.1855.

3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide



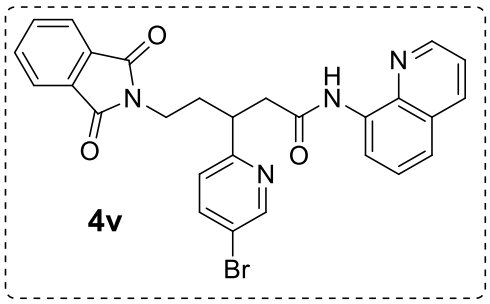
(4t): The compound **4t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured solid (41 mg, 69%, 0.12 mmol scale);R_f(30% EtOAc/hexane) 0.2; mp: 140-142 ^{o}C; IR (DCM): 2928, 1770, 1525, 1325, 720 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.64 (br. s, 1H), 8.76 (dd, *J* = 4.2,1.6 Hz, 1H), 8.70 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.78 (dd, *J* = 5.4,3.1 Hz, 2H), 7.68 (dd, *J* = 5.4,3.0 Hz, 2H), 7.53-7.46 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.82-6.79 (m, 2H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.80 (dd, *J* = 11.4 Hz, 2H), 3.70-3.66 (m, 2H), 3.38-3.31 (m, 1H), 2.88-2.76 (m, 2H), 2.25-2.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.5, 168.1, 147.9, 147.7, 146.1, 138.1, 136.4, 136.2, 134.2, 133.6, 132.0, 127.7, 127.2, 122.9, 121.4, 121.4, 120.7, 116.4, 108.3, 107.5, 100.7, 46.1, 40.4, 36.5, 33.8; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_5$ $[M+H]^+$494.1716 found 494.1722.

3-(2-Chloropyridin-4-yl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4u):



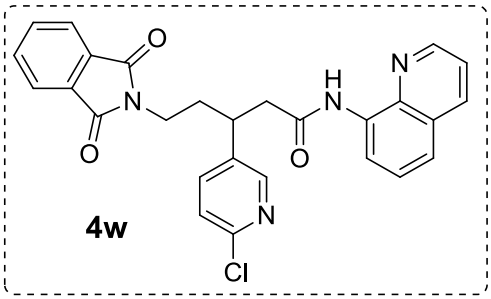
The compound **4u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (103 mg, 71%, 0.3 mmol scale); R_f(30% EtOAc/hexane) 0.2; mp: 182-184 ^oC; IR (DCM): 3342, 1707, 1529, 1392, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.64 (t, *J* = 4.5 Hz, 1H), 8.20 (d, *J* = 5.1 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.51 (d, *J* = 4.5 Hz, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 (s, 1H), 7.21 (dd, *J* = 5.2, 1.3 Hz, 1H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.47-3.40 (m, 1H), 2.94 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.83 (dd, *J*= 15.0, 8.1 Hz, 1H), 2.33-2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.3, 168.2, 155.6, 151.9, 149.9, 148.1, 138.0, 136.6, 134.1, 133.8, 131.7, 127.9, 127.4, 123.4, 123.2, 121.9, 121.9, 121.7, 116.8, 44.4, 39.6, 36.1, 33.2; HRMS (ESI) calcd for $C_{27}H_{22}ClN_4O_3$ $[M+H]^+$485.1380 found 485.1361.

3-(5-Bromopyridin-2-yl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4v):



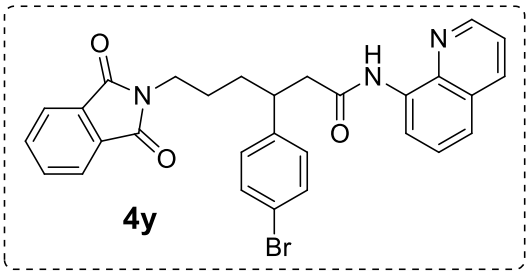
The compound **4v** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 40:60) as a brown coloured viscous liquid; (110 mg,42%, 0.5 mmol scale);R_f(50% EtOAc:Hexanes) 0.6;IR (DCM): 2926, 1709, 1525, 1396, 1264 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (br. s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.62 (dd, *J* = 5.1, 4.0 Hz, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H),7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.62 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.47-7.46 (m, 2H),7.44 (dd, *J* = 8.3, 4.2 Hz, 1H),7.24 (d, *J* = 8.2 Hz, 1H), 3.70-3.66 (m, 2H), 3.53-3.48 (m, 1H), 3.13 (dd, *J* = 14.6, 9.2 Hz, 1H),2.92 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.43-2.37 (m, 1H), 2.19-2.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.6, 168.1, 160.3, 150.5, 148.0, 138.8, 138.0, 136.1, 134.1, 133.8, 131.8, 127.7, 127.1, 125.5, 123.0, 121.4, 121.4, 118.5, 116.2, 43.3, 41.1, 35.9, 33.2; HRMS (ESI) calcd for $C_{27}H_{22}BrN_4O_3$ $[M+H]^+$529.0875 found 529.0869.

3-(6-Chloropyridin-3-yl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (4w):



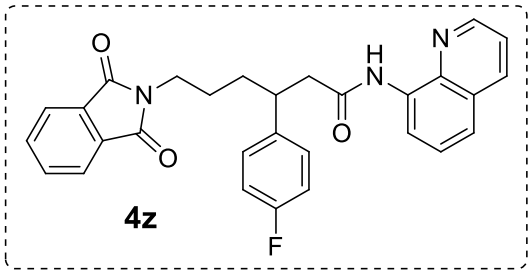
The compound **4w** was obtained after purification by column chromatography on silica (EtOAc:Hexanes = 40:60) as a brown coloured viscous liquid; (136 mg, 56%, 0.5 mmol scale);R_f(50% EtOAc:Hexanes) 0.6;IR (DCM): 2924, 1710, 1525, 1396, 1264 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (br. s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.64-8.62 (m, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71-7.66 (m, 3H), 7.49 (d, *J* = 4.4 Hz, 2H),7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 3.70-3.65 (m, 2H), 3.47-3.44 (m, 1H), 2.96 (dd, *J* = 15.0, 6.3 Hz, 1H), 2.81 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.26-2.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.4, 168.1, 149.8, 149.1, 148.0, 138.0, 137.9, 137.1, 136.2, 133.9, 133.8, 131.7, 127.7, 127.1, 124.1, 123.1, 121.6, 121.5, 116.4, 44.9, 37.1, 36.0, 33.4; HRMS (ESI) calcd for $C_{27}H_{22}ClN_4O_3$ $[M+H]^+$485.1380 found 485.1394.

3-(4-Bromophenyl)-6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (4y)*:*The



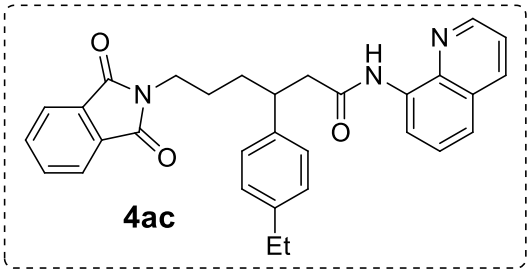
compound **4y** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colourless solid (166 mg, 76%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 142-144 ^{o}C; IR (DCM): 2936, 1705, 1523, 1394, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ_H 9.64 (br. s, 1H), 8.77 (d, *J* = 4.1 Hz, 1H), 8.66 (dd, *J* = 5.4, 3.9 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.51-7.48 (m, 2H), 7.45 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.70-3.62 (m, 2H), 3.36-3.28 (m, 1H), 2.90-2.78 (m, 2H), 1.92-1.83 (m, 1H), 1.78-1.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.6, 168.3, 148.1, 142.5, 138.2, 136.3, 134.2, 133.9, 132.0, 131.8, 129.3, 127.8, 127.3, 123.2, 121.6, 121.5, 120.4, 116.4, 45.3, 41.7, 37.7, 33.3, 26.5; HRMS (ESI) calcd for $C_{29}H_{25}BrN_3O_3$ $[M+H]^+$542.1079 found 542.1097.

6-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(quinolin-8-yl)hexanamide (4z): The compound **4z** was obtained after purification by column chromatography on silica gel



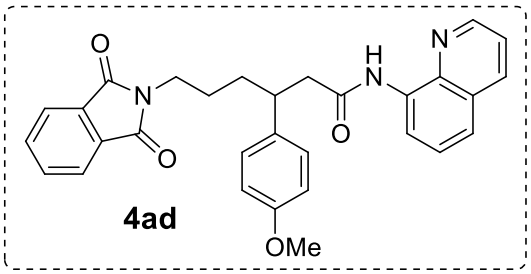
(EtOAc:hexane = 60:40) as a pale yellow coloured solid (152 mg, 79%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 62-64ºC; IR (DCM): 3348, 1708, 1523, 1395, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.65 (br. s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J*= 5.7, 3.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.81 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.52-7.49 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.27-7.23 (m, 2H), 6.98-6.94 (m, 2H), 3.70-3.63 (m, 2H), 3.38-3.31 (m, 1H), 2.90-2.78 (m, 2H),1.93-1.85 (m, 1H), 1.79-1.64 (m, 2H), 1.59-1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.8, 168.4, 161.6 (d, J_{C-F} = 242.9 Hz), 148.1, 139.1 (d, J_{C-F} = 3.1 Hz), 138.2, 136.3, 134.2, 133.9, 132.1, 128.9 (d, J_{C-F} = 7.9 Hz), 127.9, 127.3, 123.2, 121.6, 121.5, 116.4, 115.5 (d, J_{C-F} = 21.1Hz), 45.7, 41.6, 37.8, 33.5, 26.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -116.46; HRMS (ESI) calcd for $C_{29}H_{25}FN_3O_3$ $[M+H]^+$482.1880 found 482.1870.

6-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethylphenyl)-*N*-(quinolin-8-yl)hexanamide (4ac): The



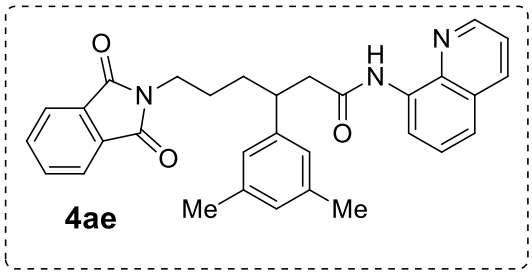
compound **4ac** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown coloured solid (163 mg, 83%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 140-142 ºC; IR (DCM): 2933, 1707, 1521, 1394, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.68 (br. s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (dd, *J* = 6.6, 2.3 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.51-7.42 (m, 3H), 7.21 (d, *J* = 8.1Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 3.66 (t, *J*= 7.3 Hz, 2H), 3.36-3.28 (m, 1H), 2.85 (d, *J*= 7.4 Hz, 2H), 2.57 (q, *J*= 7.6 Hz, 2H), 1.93-1.84 (m, 1H), 1.82-1.51 (m, 3H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C170.2, 168.4, 148.0, 142.4, 140.7, 138.2, 136.3, 134.4, 133.8, 132.1, 128.1, 127.8, 127.4, 127.4, 123.1, 121.5, 121.3, 116.4, 45.7, 41.9, 37.9, 33.4, 28.4, 26.6, 15.4; HRMS (ESI) calcd for $C_{31}H_{30}N_3O_3$ $[M+H]^+$492.2287 found 492.2266.

6-(1,3-Dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)hexanamide (4ad): The compound **4ad** was obtained after purification by column chromatography on silica gel

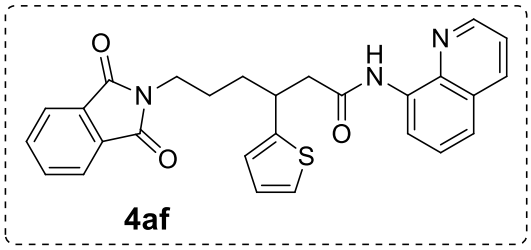


(EtOAc:hexane = 60:40) as a colourless solid (163 mg, 83%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 145-147 ^oC; IR (DCM): 2938, 1708, 1520, 1246, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.66 (br. s, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.69 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.14 (dd, *J*= 8.3, 1.4 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.52-7.43 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 3.71-3.62 (m, 2H), 3.33-3.26 (m, 1H), 2.88-2.78 (m, 2H), 1.91-1.83 (m, 1H),1.79-1.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C170.1, 168.4, 158.2, 148.0, 138.2, 136.3, 135.4, 134.4, 133.8, 132.1, 128.4, 127.8, 127.3, 123.1, 121.5, 121.4, 116.4, 114.1, 55.1, 45.9, 41.5, 37.9, 33.5, 26.6; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_4$ $[M+H]^+$494.2080 found 494.2102.

3-(3,5-Dimethylphenyl)-6-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (4ae): The compound **4ae** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a yellow coloured solid (164 mg, 83%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 60-62^{o}C; IR (DCM): 2938, 1712, 1524, 1395, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.67 (br. s, 1H), 8.78 (dd,*J* = 4.2, 1.7 Hz, 1H), 8.70 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.52-7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.3 Hz, 1H), 6.89 (s, 2H), 6.78 (s, 1H), 3.66 (t, *J* = 7.2 Hz, 2H), 3.29-3.22 (m, 1H), 2.89-2.80 (m, 2H), 2.25 (s, 6H), 1.91-1.83 (m, 1H), 1.80-1.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C170.2, 168.4, 148.0, 143.4, 138.3, 138.0, 136.2, 134.4, 133.8, 132.1, 128.3, 127.8, 127.3, 125.3, 123.1, 121.5, 121.3, 116.4, 45.7, 42.2, 37.9, 33.4, 26.7, 21.4; HRMS (ESI) calcd for $C_{31}H_{30}N_3O_3$ $[M+H]^+$ 492.2287 found 492.2272.

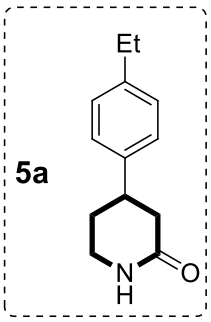


6-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)hexanamide (4af): The compound **4af** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a pale yellow coloured viscous liquid (142 mg, 76%, 0.4 mmol scale); R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2932, 1709, 1524, 1396, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ_H 9.73 (br. s, 1H), 8.78 (dd, *J* = 4.2, 1.1 Hz, 1H), 8.71 (dd, *J* = 6.1, 2.8 Hz, 1H),

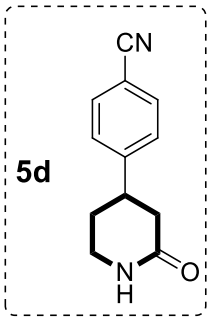


8.15 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.53-7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.13 (d, *J* = 5.0 Hz, 1H), 6.94 (d, *J* = 3.3 Hz, 1H), 6.90-6.87 (m, 1H), 3.74-3.67 (m, 3H), 2.90 (d, *J*= 7.2 Hz, 2H), 1.98-1.89 (m, 1H), 1.82-1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.5, 168.3, 148.1, 147.3, 138.2, 136.3, 134.3, 133.8, 132.0, 127.8, 127.3, 126.8, 124.6, 123.5, 123.1, 121.6, 121.5, 116.5, 46.4, 37.7, 37.6, 34.5, 26.5; HRMS (ESI) calcd for $C_{27}H_{24}N_3O_3S$ $[M+H]^+$470.1538 found 470.1560.

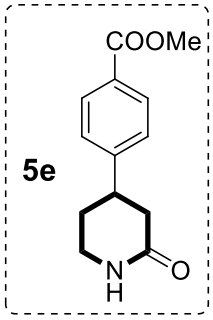
4-(4-Ethylphenyl)piperidin-2-one (5a): The compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid(35 mg, 86%, 0.2 mmol scale); R_f(100% EtOAc) 0.2; mp: 154-156 ^{o}C; IR (DCM): 2961, 2357, 1658, 1265, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.21 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.40 (br. s, 1H), 3.44-341 (m, 2H), 3.14-3.06 (m, 1H), 2.73-2.63 (m, 3H), 2.51 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.11-2.08 (m, 1H), 1.99-1.89 (m, 1H), 1.26 (t, *J* =7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.5, 142.8, 140.8, 128.3, 126.5, 41.4, 38.8, 38.0, 29.6, 28.4, 15.6; HRMS (ESI) calcd for $C_{13}H_{18}NO[M+H]^+$ 204.1388 found 204.1379.



4-(2-Oxopiperidin-4-yl)benzonitrile (5d) : The compound **5d** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid(25 mg, 62%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 222-224 ^{o}C; IR (DCM): 2926, 2357, 1656, 1332, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.66 (d, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 6.84 (br. s, 1H), 3.45-3.43 (m, 2H), 3.22-3.16 (m, 1H), 2.70 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.47 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.13-2.10 (m, 1H), 2.01-1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C171.3, 148.8, 132.7, 127.5, 118.7, 110.9, 41.2, 38.6, 38.2, 29.1; HRMS (ESI) calcd for $C_{12}H_{13}N_2O[M+H]^+$ 201.1028 found 201.1018.

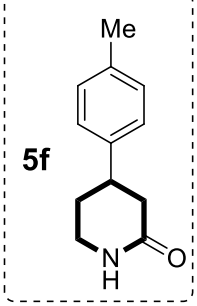


Methyl 4-(2-oxopiperidin-4-yl)benzoate (5e) : The compound **5e** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (24 mg, 52%, 0.2 mmol scale); R_f(100% EtOAc) 0.2; mp: 164-166 ^{o}C; IR (DCM): 2948, 2357, 1657,

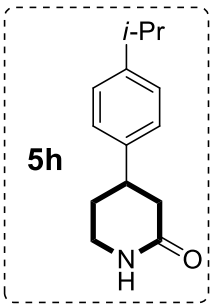


1271, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02 (dt, *J* = 8.6, 1.9 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.93 (br. s, 1H), 3.92 (s, 3H), 3.45-3.41 (m, 2H), 3.22-3.14 (m, 1H), 2.73-2.67 (m, 1H), 2.50 (dd, *J* = 17.6, 10.9 Hz, 1H), 2.13-2.10 (m, 1H), 2.01-1.93 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C171.8, 166.8, 148.7, 130.2, 128.9, 126.7, 52.2, 41.3, 38.5, 38.4, 29.2; HRMS (ESI) calcd for $C_{13}H_{16}NO_3[M+H]^+$ 234.1130 found 234.1121.

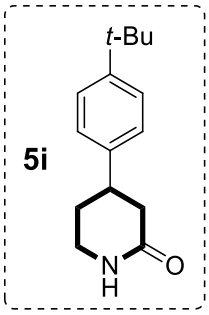
4-(*p*-Tolyl)piperidin-2-one (5f): The compound **5f** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a colourless solid (34 mg, 90%, 0.2 mmol scale); R_f (100% EtOAc) 0.2; mp: 180-182^{o}C; IR (DCM): 2938, 2357, 1657, 1331, 812 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.18 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.40 (br. s, 1H), 3.44-3.41 (m, 2H), 3.13-3.05 (m, 1H), 2.72-2.66 (m, 1H), 2.50 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.36 (s, 3H), 2.10-2.07 (m, 1H), 1.98-1.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.5, 140.6, 136.5, 129.5, 126.5, 41.4, 38.8, 38.0, 29.7, 21.0; HRMS (ESI) calcd for $C_{12}H_{16}NO[M+H]^+$ 190.1232 found 190.1236.



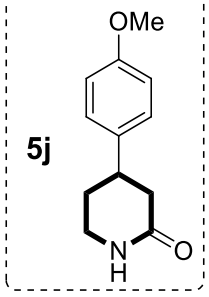
4-(4-Isopropylphenyl)piperidin-2-one (5h): The compound **5h** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (30 mg, 81%, 0.17 mmol scale); R_f(100% EtOAc) 0.2; mp: 180-182 ^{o}C; IR (DCM): 2957, 2357, 1659, 1266, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.23 (d, *J* = 7.4 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.92 (br. s, 1H), 3.43-3.42 (m, 2H),3.12-3.06 (m, 1H), 2.95-2.88 (m, 1H), 2.70 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.51 (dd, *J* = 17.6, 11.1 Hz, 1H), 2.11-2.08 (m, 1H), 1.98-1.88 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.5, 147.5, 140.9, 126.8, 126.5, 41.4, 38.7, 38.0, 33.7, 29.7, 24.0; HRMS (ESI) calcd for $C_{14}H_{20}NO[M+H]^+$ 218.1545 found 218.1541.



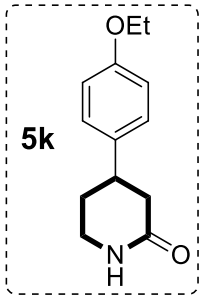
4-(4-(Tert-butyl)phenyl)piperidin-2-one (5i): The compound **5i** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a colourless solid (33 mg, 75%, 0.19 mmol scale); R_f(100% EtOAc) 0.2; mp: 202-204 ^oC; IR (DCM): 2956, 2357, 1659, 1265, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.39 (dt, J = 8.4, 2.4 Hz, 2H), 7.18 (dt, J = 8.4, 2.4 Hz, 2H), 6.65 (br. s, 1H), 3.45-3.41 (m, 2H), 3.14-3.07 (m, 1H), 2.73-2.67 (m, 1H), 2.52 (dd, J = 17.6, 11.0 Hz, 1H), 2.13-2.09 (m, 1H), 1.99-1.87 (m, 1H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.6, 149.7, 140.6, 126.2, 125.7, 41.4, 38.7, 37.9, 34.5, 31.4, 29.6;HRMS (ESI) calcd for $C_{15}H_{22}NO[M+H]^+$ 232.1701 found 232.1695.



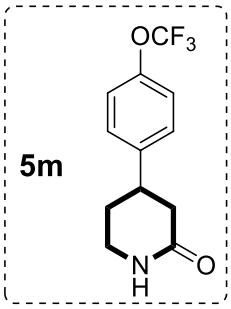
4-(4-Methoxyphenyl)piperidin-2-one (5j): The compound **5j** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a yellow coloured solid(24 mg, 58%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 158-160 ^oC; IR (DCM): 2951, 2357, 1656, 1246, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.16 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 6.73 (br. s, 1H), 3.82 (s, 3H), 3.42-3.40 (m, 2H), 3.10-3.05 (m, 1H), 2.68 (dd, J = 17.6, 5.1 Hz, 1H), 2.47 (dd, J = 17.6, 11.0 Hz, 1H), 2.09-2.06 (m, 1H), 1.99-1.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.3, 158.4, 135.7, 127.5, 114.1, 55.3, 41.4, 39.0, 37.6, 29.8; HRMS (ESI) calcd for $C_{12}H_{16}NO_2[M+H]^+$ 206.1181 found 206.1173.



4-(4-Ethoxyphenyl)piperidin-2-one (5k): The compound **5k** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a colourless solid (30 mg, 68%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 176-178^oC; IR (DCM): 2928, 2357, 1655, 1247, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.15 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.02 (br. s, 1H), 4.04 (q, J = 7.0 Hz, 2H), 3.44-3.41 (m, 2H), 3.11-3.04 (m, 1H), 2.72-2.66 (m, 1H), 2.48 (dd, J = 17.6, 10.9 Hz, 1H), 2.12-2.06 (m, 1H), 1.97-1.88 (m, 1H), 1.43 (t, J =7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.4, 157.8, 135.5, 127.5, 114.7, 63.5, 41.4, 38.9, 37.6, 29.8, 14.9;HRMS (ESI) calcd for $C_{13}H_{18}NO_2[M+H]^+$ 220.1338 found 220.1333.

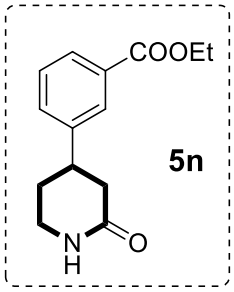


4-(4-(Trifluoromethoxy)phenyl)piperidin-2-one (5m): The compound **5m** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (295 mg, 79%, 1.44 mmol scale);R_f(100% EtOAc) 0.1; mp: 110-112 ^oC; IR



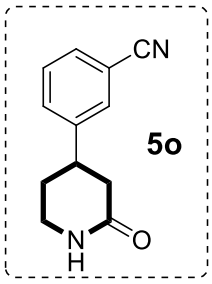
(DCM): 3189, 1674, 1509, 1264, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.26 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.40 (br. s, 1H), 3.46-3.42 (m, 2H), 3.19-3.11 (m, 1H), 2.73-7.67 (m, 1H), 2.49 (dd, J = 17.6, 11.0 Hz, 1H), 2.13-2.09 (m, 1H), 1.99-1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.0, 147.9 (d, $J_{C\text{-}F}$ = 2 Hz), 142.2, 127.8, 121.2, 120.4 (q, $J_{C\text{-}F}$ = 255.5 Hz), 41.1, 38.6, 37.7, 29.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.91; HRMS (ESI) calcd for $C_{12}H_{13}F_3NO_2$ $[M+H]^+$ 260.0898 found 260.0894.

Ethyl 3-(2-oxopiperidin-4-yl)benzoate (5n): The compound **5n** was obtained after purification



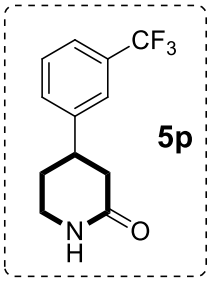
by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a colourless solid (22 mg, 45%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 158-160 ^oC; IR (DCM): 2940, 2357, 1660, 1276, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.96-7.92 (m, 2H), 7.45-7.41 (m, 2H), 7.16 (br. s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.45-3.42 (m, 2H), 3.20-3.12 (m, 1H), 2.72-2.66 (m, 1H), 2.50 (dd, J = 17.6, 11.3 Hz, 1H), 2.12-2.08 (m, 1H), 2.02-1.92 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.1, 166.5, 143.9, 131.0, 131.0, 128.9, 128.1, 127.7, 61.1, 41.3, 38.7, 38.3, 29.4, 14.4; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$ 248.1287 found 248.1280.

3-(2-Oxopiperidin-4-yl)benzonitrile (5o): The compound **5o** was obtained after purification by



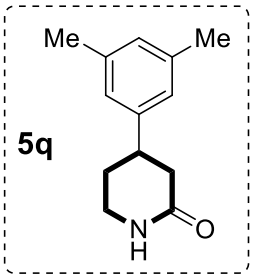
column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown colouredsolid (31 mg, 77%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 184-186 ^oC;IR (DCM): 2919, 2357, 1655, 1333, 796 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ_H7.59-7.56 (m, 1H), 7.53 (s, 1H), 7.50-7.46 (m, 2H), 6.66 (br. s, 1H), 3.46-3.43 (m, 2H), 3.21-3.13 (m, 1H), 2.73-2.67 (m, 1H), 2.47 (dd, J = 17.5, 11.1 Hz, 1H), 2.13-2.07 (m, 1H), 2.01-1.91 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C171.3, 144.9, 131.2, 130.7, 130.3, 129.7, 118.7, 112.9, 41.1, 38.4, 38.1, 29.2; HRMS (ESI) calcd for $C_{12}H_{13}N_2O[M+H]^+$ 201.1028 found 201.1022.

4-(3-Ttrifluoromethyl)phenyl)piperidin-2-one (5p): The compound **5p** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as brown coloured solid(38 mg, 82%, 0.19 mmol scale); R_f(100% EtOAc) 0.1; mp: 138-140 ^oC; IR (DCM): 2929, 2357, 1663, 1327, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.55 (d, J = 7.7Hz, 1H), 7.51-7.48



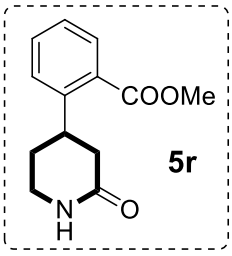
(m, 2H), 7.45-7.43 (m, 1H), 6.66-6.45 (m, 1H), 3.48-3.44 (m, 2H), 3.24-3.16 (m, 1H), 2.76-2.70 (m, 1H), 2.51 (dd, J = 17.5, 11.2 Hz, 1H), 2.16-2.12 (m, 1H), 2.04-1.93 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C171.8, 144.5, 131.1 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.0, 129.3, 124.1 (q, $J_{C\text{-}F}$ = 270.8 Hz), 123.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 41.2, 38.6, 38.4, 29.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -62.60; HRMS (ESI) calcd for $C_{12}H_{13}F_3NO[M+H]^+$ 244.0949 found 244.0941.

4-(3,5-Dimethylphenyl)piperidin-2-one (5q): The compound **5q** was obtained after purification



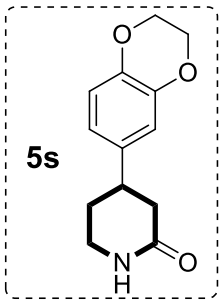
by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (32 mg, 83%, 0.19 mmol scale); R_f(100% EtOAc) 0.2; mp: 178-180^{o}C; IR (DCM): 2918, 2357, 1653, 1336, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.10 (br. s, 1H), 6.92 (s, 1H), 6.86 (s, 2H), 3.43-3.41 (m, 2H), 3.07-3.01 (m, 1H), 2.67 (dd, J = 17.6, 5.1 Hz, 1H), 2.50 (dd, J = 17.6, 11.4 Hz, 1H), 2.34 (s, 6H), 2.09-2.05 (m, 1H), 1.98-1.88 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.6, 143.7, 138.3, 128.5, 124.4, 41.4, 38.8, 38.3, 29.6, 21.4; HRMS (ESI) calcd for $C_{13}H_{18}NO[M+H]^+$ 204.1388 found 204.1381.

Methyl 2-(2-oxopiperidin-4-yl)benzoate (5r): The compound **5r** was obtained after purification



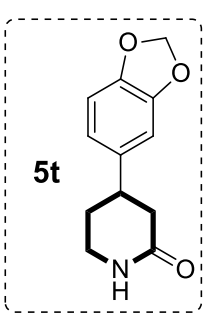
by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (23 mg, 49%, 0.2 mmol scale); R_f(100% EtOAc) 0.1; mp: 138-140 ^{o}C; IR (DCM): 2948, 2356, 1655, 1257, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.86 (d, J = 7.8 Hz, 1H),7.53 (t, J = 7.6 Hz, 1H), 7.37(d, J = 7.9 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.93 (br. s, 1H), 4.04-3.99 (m, 1H), 3.91 (s, 3H), 3.49-3.39 (m, 2H), 2.74 (dd, J = 17.5, 5.1 Hz, 1H), 2.46 (dd, J = 17.5, 11.1 Hz, 1H), 2.09-2.06 (m, 1H), 2.00-1.90 (m, 1H);^{13}C NMR ($CDCl_3$, 75 MHz):δ_C172.2, 168.0, 144.7, 132.3, 130.6, 129.6, 126.5, 126.3, 52.1, 41.5, 38.6, 34.2, 29.6; HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1130 found 234.1137.

4-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)piperidin-2-one (5s): The compound **5s** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a yellow coloured solid(40 mg, 86%, 0.2 mmol scale);R_f(100% EtOAc) 0.1; mp: 160-162 ^{o}C; IR (DCM): 2938, 2357, 1496, 1246, 735 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.85 (d, J = 8.2Hz, 1H), 6.74-

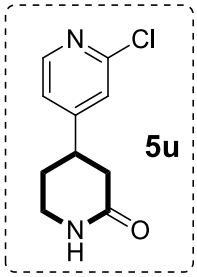


6.69 (m, 2H), 6.18 (br. s, 1H), 4.27 (s, 4H), 3.43-3.41 (m, 2H), 3.04-2.99 (m, 1H), 2.67 (dd,*J* = 17.6, 4.1 Hz, 1H), 2.45 (dd, *J* = 17.5, 11.2 Hz, 1H), 2.08-2.05 (m, 1H), 1.94-1.84 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.4, 143.6, 142.3, 137.0, 119.4, 117.4, 115.3, 64.4, 64.3, 41.3, 38.9, 37.7, 29.7; HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1130 found 234.1136.

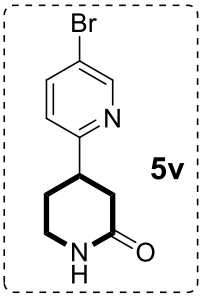
4-(Benzo[*d*][1,3]dioxol-5-yl)piperidin-2-one (5t): The compound **5t** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a colourless solid (125 mg, 78%, 0.73 mmol scale);R_f(100% EtOAc) 0.1; mp: 202-204 ^{o}C; IR (DCM): 2923, 1663, 1490, 1245, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H6.79 (d, 1H, *J* = 8.0Hz), 6.72-6.67 (m, 3H), 5.96 (s, 2H), 3.43-3.39 (m, 2H), 3.08-3.00 (m, 1H), 2.69-2.62 (m, 1H), 2.43 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.07-2.04 (m, 1H), 1.93-1.85 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C172.2, 147.8, 146.2, 137.5, 119.4, 108.3, 106.9, 100.9, 41.1, 39.0, 38.1, 29.6; HRMS (ESI) calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$ 220.0974 found 220.0973.



4-(2-Chloropyridin-4-yl)piperidin-2-one (5u): The compound **5u** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (22 mg, 55%, 0.19 mmol scale); R_f(100% EtOAc) 0.1; mp: 154-156 ^{o}C; IR (DCM): 2937, 2357, 1654, 1337, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H8.37 (d, *J* =5.1 Hz, 1H), 7.21 (s, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 6.81 (br. s, 1H), 3.45-3.44 (m, 2H), 3.16-3.10 (m, 1H), 2.70 (dd, *J* = 17.5, 5.1 Hz, 1H), 2.46 (dd,*J* = 17.4, 11.0 Hz, 1H), 2.14-2.11 (m, 1H), 2.00-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C170.7, 155.5, 152.2, 150.2, 122.5, 120.8, 41.0, 37.7, 37.5, 28.5; HRMS (ESI) calcd for $C_{10}H_{12}ClN_2O[M+H]^+$ 211.0638 found 211.0628.

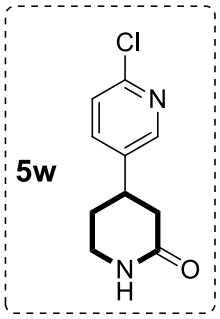


4-(5-Bromopyridin-2-yl)piperidin-2-one (5v): The compound **5v** was obtained after purification by column chromatography on silica gel(EtOAc:MeOH = 90:10) as a brown coloured solid; (24 mg, 38%, 0.25 mmol scale); R_f(EtOAc:MeOH= 95:5) 0.6;mp: 204-206 ^{o}C; IR (DCM): 2924, 1668, 1465, 1344, 1094 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ_H8.62 (d, *J* = 2.1 Hz, 1H), 7.78 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.84 (s, 1H), 3.43-

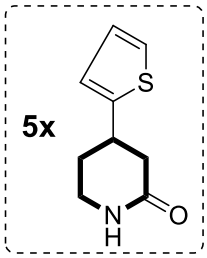


3.39 (m, 2H), 3.25-3.20 (m, 1H), 2.73-2.66 (m, 2H), 2.14-1.99 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.8, 160.7, 150.6, 139.2, 122.7, 118.7, 41.0, 39.7, 36.6, 28.2; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{10}H_{12}BrN_2O$: 255.0133 found 255.0136.

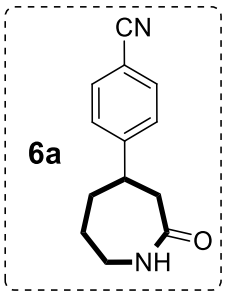
4-(6-Chloropyridin-3-yl)piperidin-2-one (5w)*:* The compound **5w** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 90:10) as a brown coloured solid; (40 mg,75%, 0.25 mmol scale); R_f (EtOAc:MeOH = 95:5) 0.6; mp: 208-210 ^{o}C; IR (DCM): 2922, 1655, 1463, 1336, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.31 (d, *J* = 2.5 Hz, 1H), 7.53 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.46 (s, 1H), 3.47-3.44 (m, 2H), 3.20-3.13 (m, 1H), 2.74-2.68 (m, 1H), 2.46 (dd, *J* = 17.5, 11.2 Hz, 1H), 2.14-2.10 (m, 1H), 2.01-1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 170.7, 150.1, 148.3, 137.6, 136.8, 124.4, 41.2, 38.2, 35.5, 29.1; HRMS (ESI) calcd for $C_{10}H_{12}ClN_2O[M+H]^+$ 211.0638 found 211.0644.



4-(Thiophen-2-yl)piperidin-2-one (5x): The compound **5x** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (30 mg, 83%, 0.2 mmol scale); R_f (100% EtOAc) 0.1; mp: 126-128 ^{o}C; IR (DCM): 2922, 2357, 1656, 1332, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.21-7.15 (m, 2H), 6.97 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.87 (d, *J* = 3.4 Hz, 1H), 3.44-3.37 (m, 3H), 2.84-2.78 (m, 1H), 2.55 (dd, *J* = 17.5, 10.4 Hz, 1H), 2.24-2.20 (m, 1H), 1.98-1.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 171.6, 147.2, 126.7, 123.4, 122.9, 40.8, 39.0, 33.7, 30.5; HRMS (ESI) calcd for $C_9H_{12}NOS[M+H]^+$ 182.0640 found 182.0632.

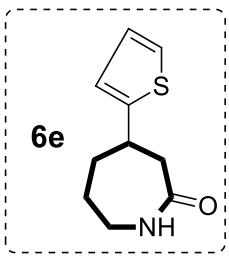


4-(2-Oxoazepan-4-yl)benzonitrile (6a): The compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (15 mg, 35%, 0.2 mmol scale); R_f(100% EtOAc) 0.1;mp: 168-170^{o}C; IR (DCM): 2926, 2226, 1660, 1524, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.62 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.51 (br. s, 1H), 3.38-3.31 (m, 2H), 2.97-2.94 (m, 2H), 2.59-2.56 (m, 1H), 2.14-2.10 (m, 1H), 2.02-1.95 (m, 1H), 1.79-1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 101

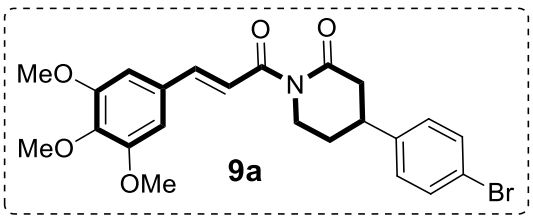


MHz):δ_C176.3, 152.0, 132.6, 127.3, 118.8, 110.5, 43.0, 42.5, 40.8, 38.9, 29.5; HRMS (ESI) calcd for $C_{13}H_{15}N_2O[M+H]^+$ 215.1184 found 215.1179.

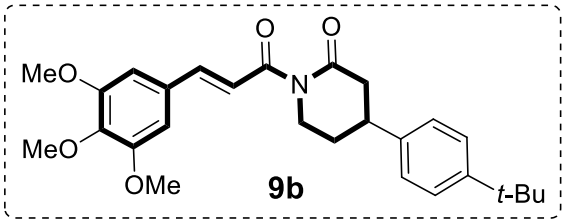
4-(Thiophen-2-yl)azepan-2-one (6e): The compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 85:15) as a brown coloured solid (14 mg, 31%, 0.23 mmol scale); R_f (100% EtOAc) 0.1; mp: 110-112ºC; IR (DCM): 2926, 1661, 1435, 1342, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (d, J = 5.0 Hz, 1H), 6.94 (t, J = 3.6 Hz, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.55 (br. s, 1H), 3.37-3.25 (m, 3H), 2.92 (dd, J = 13.6, 11.1 Hz, 1H), 2.78 (dd, J = 13.8, 1.1 Hz, 1H), 2.33-2.29 (m, 1H), 1.99-1.84 (m, 2H), 1.74-1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C176.3, 149.8, 126.6, 122.9, 122.8, 44.7, 42.5, 39.6, 35.8, 29.1; HRMS (ESI) calcd for $C_{10}H_{14}NOS[M+H]^+$ 196.0796 found 196.0790.



(*E*)-4-(4-Bromophenyl)-1-(3-(3,4,5-trimethoxyphenyl)acryloyl)piperidin-2-one (9a): The compound **9a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown coloured solid (38 mg, 54%, 0.15 mmol scale); R_f (30% EtOAc/hexane) 0.6; mp: 176-178ºC; IR (DCM): 2940, 1580, 1504, 1275, 1124 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H7.67 (d, J = 15.5 Hz, 1H), 7.50-7.47 (m, 2H), 7.38 (d, J = 15.5 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.80 (s, 2H), 4.11 (dt, J = 13.6, 4.5 Hz, 1H), 3.89 (s, 6H), 3.88 (m, 3H),3.70-3.64 (m, 1H), 3.20-3.14 (m, 1H), 2.93-2.88 (m,1H), 2.70 (dd, J = 17.1, 11.1 Hz, 1H), 2.29-2.23 (m, 1H), 2.01-1.93 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz):δ_C172.6, 169.5, 153.4, 144.0, 141.9, 140.1, 132.0, 130.6, 128.2, 121.0, 120.9, 105.5, 61.0, 56.2, 44.0, 42.1, 38.1, 30.0; HRMS (ESI) calcd for $C_{23}H_{24}BrNNaO_5$ $[M+Na]^+$ 496.0736 found 496.0714.

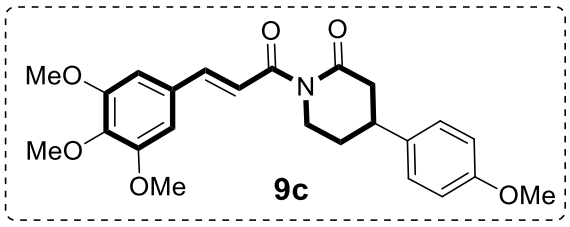


(*E*)-4-(4-(Tert-butyl)phenyl)-1-(3-(3,4,5-trimethoxyphenyl)acryloyl)piperidin-2-one (9b): The compound **9b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (24 mg, 53%, 0.1 mmol scale); R_f(30% EtOAc/hexane)

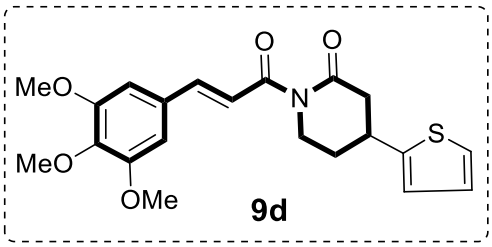


0.6; mp: 148-150°C; IR (DCM): 2953, 1682, 1504, 1272, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.69 (d, *J* = 15.5 Hz, 1H),7.43-7.39 (m, 3H),7.19 (d, *J* = 8.3 Hz, 2H), 6.83 (s, 2H), 4.11 (dt, *J* = 13.6, 4.6 Hz, 1H), 3.91 (s, 6H), 3.90 (s, 3H), 3.73-3.66 (m, 1H), 3.24-3.16 (m, 1H), 2.97-2.91 (m, 1H), 2.78 (dd, *J* = 17.2, 11.0 Hz, 1H), 2.31-2.26 (m, 1H), 2.07-1.96 (m, 1H), 1.34 (s, 9H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C173.3, 169.7, 153.4, 150.1, 143.7, 140.0, 139.8, 130.6, 126.2, 125.8, 121.2, 105.5, 61.0, 56.2, 44.2, 42.2, 38.0, 34.5, 31.4, 30.2; HRMS (ESI) calcd for $C_{27}H_{33}NNaO_5$ $[M+Na]^+$ 474.2256 found 474.2269.

(*E*)-4-(4-Methoxyphenyl)-1-(3-(3,4,5-trimethoxyphenyl)acryloyl)piperidin-2-one (9c): The compound **9c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (25 mg, 59%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 160-162°C; IR (DCM): 2924, 1694, 1514, 1274, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.68 (d, *J* = 15.5 Hz, 1H), 7.40 (d, *J* = 15.5 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.82 (s, 2H), 4.10 (dt, *J* = 13.5, 4.6 Hz, 1H), 3.91 (s, 6H), 3.89 (s, 3H), 3.82 (s, 3H), 3.73-3.64 (m, 1H), 3.21-3.13 (m, 1H), 2.95-2.89 (m, 1H), 2.73 (dd, *J* = 17.2, 11.1 Hz, 1H), 2.29-2.24 (m, 1H), 2.03-1.92 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C173.2, 169.7, 158.6, 153.4, 143.7, 140.0, 135.0, 130.6, 127.4, 121.1, 114.3, 105.4, 61.0, 61.0, 56.2, 55.3, 44.2, 42.5, 37.8, 30.4; HRMS (ESI) calcd for $C_{24}H_{27}NNaO_6$ $[M+Na]^+$ 448.1736 found 448.1744.

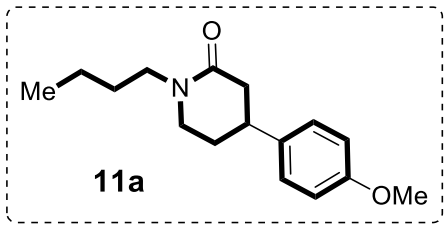


(*E*)-4-(Thiophen-2-yl)-1-(3-(3,4,5-trimethoxyphenyl)acryloyl)piperidin-2-one (9d): The compound **9d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown coloured viscous liquid (19 mg, 47%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.6;IR (DCM): 2932, 1673, 1504, 1274, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.68 (d, *J* = 15.5 Hz, 1H), 7.38 (d, *J* = 15.5 Hz, 1H), 7.24 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.99 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.90 (d, *J* = 3.4 Hz, 1H), 6.82 (s, 2H), 4.08 (dt, *J* = 13.6, 4.8 Hz, 1H), 3.91 (s, 6H), 3.90 (s, 3H), 3.75-3.68 (m, 1H), 3.56-3.48 (m, 1H), 3.09-3.03 (m, 1H), 2.83 (dd,*J* = 17.2, 10.4 Hz, 1H), 2.43-2.38 (m, 1H), 2.10-2.00 (m, 1H);^{13}C NMR ($CDCl_3$, 101



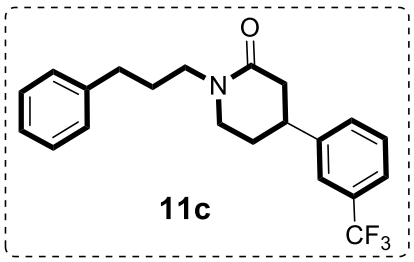
MHz):δ_C172.3, 169.6, 153.4, 146.5, 143.9, 140.0, 130.6, 127.0, 123.9, 123.3, 121.0, 105.4, 61.0, 56.2, 43.8, 42.7, 34.1, 31.2; HRMS (ESI) calcd for $C_{21}H_{23}NNaO_5S$ $[M+Na]^+$ 424.1195 found 424.1203.

1-Butyl-4-(4-methoxyphenyl)piperidin-2-one (11a): The compound **11a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless liquid (56 mg, 93%, 0.23 mmol scale); R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2930, 1641, 1512, 1250, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.15-7.11 (m,2H), 6.90-6.86 (m,2H), 3.81 (s, 3H), 3.45-3.29 (m, 4H), 3.08-3.01 (m, 1H), 2.73-2.67 (m, 1H), 2.47 (dd, J = 17.4, 10.9 Hz, 1H), 2.13-2.07 (m, 1H), 1.97-1.87 (m, 1H), 1.61-1.52 (m, 2H), 1.40-1.30 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.0, 158.3, 135.7, 127.4, 114.0, 55.2, 46.9, 46.8, 39.6, 37.8, 30.5, 29.1, 20.2, 13.9; HRMS (ESI) calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1807 found 262.1810.



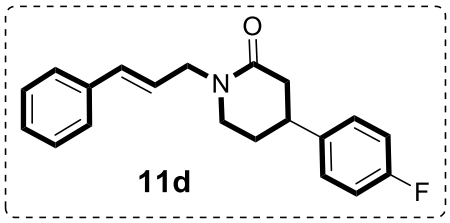
11a

1-(3-Phenylpropyl)-4-(3-(trifluoromethyl)phenyl)piperidin-2-one (11c) : The compound **11c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless liquid (63 mg, 80%, 0.22 mmol scale); R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2928, 1642, 1329, 1123, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.53 (d, J = 7.8 Hz, 1H), 7.49-7.45 (m, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 3.60-3.52 (m, 1H), 3.49-3.42 (m, 1H), 3.39-3.29 (m, 2H), 3.13-3.05 (m, 1H), 2.77-2.67 (m, 3H), 2.47 (dd, J = 17.4, 11.1 Hz, 1H), 2.13-2.07 (m, 1H), 2.00-1.85 (m, 3H);^{13}C NMR ($CDCl_3$, 101MHz):δ_C168.4, 144.3, 141.5, 131.0 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.9, 129.2, 128.3, 128.2, 125.9, 124.0 (q, $J_{C\text{-}F}$ = 270.7 Hz), 123.7 (q, $J_{C\text{-}F}$ = 3.9 Hz), 123.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 46.7, 46.7, 39.2, 38.5, 33.2, 29.9, 28.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -62.58;HRMS (ESI) calcd for $C_{21}H_{23}F_3NO$ $[M+H]^+$ 362.1732 found 362.1735.



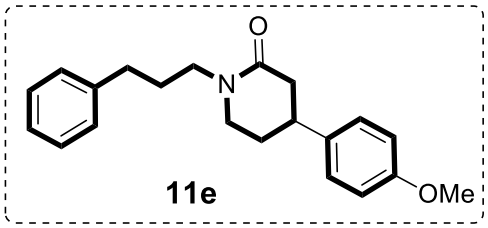
11c

1-Cinnamyl-4-(4-fluorophenyl)piperidin-2-one (11d): The compound **11d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless solid (44 mg, 55%, 0.26 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 102-104^{o}C; IR (DCM): 2925, 1639, 1509, 1224, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.41-7.39 (m, 2H),7.36-7.32



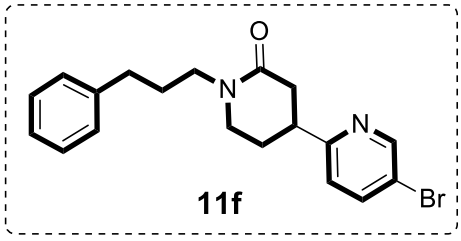
(m, 2H), 7.29-7.25 (m, 1H), 7.20-7.17 (m, 2H), 7.06-7.02 (m, 2H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.32-4.27 (m, 1H), 4.15 (dd, *J* = 14.6, 6.8 Hz, 1H), 3.46-3.36 (m, 2H), 3.16-3.08 (m, 1H), 2.81-2.74 (m,1H), 2.53 (dd, *J* = 17.4, 11.1 Hz, 1H), 2.16-2.10 (m, 1H), 2.01-1.91 (m,1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.9, 161.7 (d, J_{C-F} = 243.5 Hz), 139.1 (d, J_{C-F} = 3.0 Hz), 136.5, 133.3, 128.6, 128.0 (d, J_{C-F}= 7.7 Hz), 127.8, 126.4, 124.1, 115.6 (d, J_{C-F}= 21.7 Hz), 48.8, 46.3, 39.6, 38.0, 30.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -116.06;HRMS (ESI) calcd for $C_{20}H_{21}FNO$ $[M+H]^+$ 310.1607 found 310.1604.

4-(4-Methoxyphenyl)-1-(3-phenylpropyl)piperidin-2-one (11e) : The compound **11e** was



obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a green coloured liquid (70 mg, 87%, 0.25 mmol scale); R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2930, 1641, 1512, 1250, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.33-7.28 (m, 2H), 7.24-7.20 (m, 3H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.57-3.42 (m, 2H), 3.39-3.26 (m, 2H), 3.04-2.96 (m, 1H), 2.73-2.66 (m, 3H), 2.46 (dd, *J* = 17.4, 10.8 Hz, 1H), 2.08-2.05 (m, 1H), 1.98-1.84 (m, 3H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.1, 158.2, 141.6, 135.5, 128.3, 128.2, 127.3, 125.8, 113.9, 55.2, 46.7, 46.6, 39.5, 37.6, 33.2, 30.3, 28.3;HRMS (ESI) calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$ 324.1964 found 324.1967.

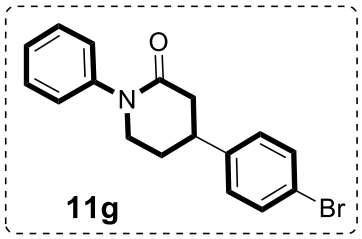
4-(5-Bromopyridin-2-yl)-1-(3-phenylpropyl)piperidin-2-one (11f) : The compound **11f** was



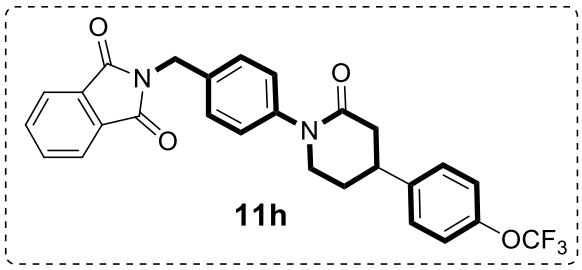
obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 50:50) as a brown coloured viscous liquid; (61 mg, 65%, 0.25 mmol scale);R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2928, 1635, 1463, 1264, 1007 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ_H8.61 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.31-7.27 (m, 2H), 7.21-7.19 (m, 3H), 7.06 (d, *J* = 8.3 Hz, 1H), 3.56-3.49 (m, 1H), 3.45-3.27 (m, 3H), 3.18-3.14 (m, 1H), 2.71-2.64 (m, 4H), 2.15-2.11 (m, 1H), 2.06-1.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 168.6, 160.6, 150.4, 141.5, 139.1,

128.3, 128.2, 125.8, 122.5, 118.6, 46.6, 46.4, 39.9, 37.4, 33.1, 28.8, 28.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{22}BrN_2O$ 373.0916 found 373.0928.

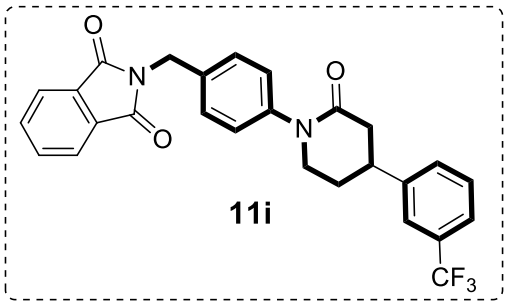
4-(4-Bromophenyl)-1-phenylpiperidin-2-one (11g): The compound **11g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown coloured solid (19 mg, 36%, 0.16 mmol scale); R_f(30% EtOAc/hexane) 0.5; mp: 125-127 ^{o}C; IR (DCM): 2926, 1651, 1491, 1009, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.52 (dt, *J* = 8.4, 2.6 Hz, 2H), 7.46-7.42 (m, 2H), 7.33-7.28 (m, 3H), 7.18 (dt, *J* = 8.4, 2.6 Hz, 2H), 3.84-3.78 (m, 1H), 3.70-3.65 (m, 1H), 3.31-3.24 (m, 1H), 2.93-2.87 (m, 1H), 2.69 (dd, *J* = 17.5, 10.7 Hz, 1H), 2.29-2.23 (m, 1H), 2.19-2.09 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C169.0, 142.8, 142.2, 131.9, 129.3, 128.3, 127.0, 126.2, 120.6, 50.4, 39.7, 38.2, 30.4; HRMS (ESI) calcd for $C_{17}H_{17}BrNO$ [M+H]$^+$ 330.0494 found 330.0487.



2-(4-(2-Oxo-4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)isoindoline-1,3-dione (11h) : The compound**11h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a yellow coloured solid (101 mg, 55%, 0.37 mmol scale); R_f(50% EtOAc/hexane) 0.4; mp: 220-222^{o}C; IR (DCM): 2926, 1716, 1650, 1255, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.31-7.22 (m, 6H), 4.86 (s, 2H), 3.82-3.75 (m, 1H), 3.66-3.61 (m, 1H), 3.33-3.26 (m, 1H), 2.92-2.86 (m,1H), 2.67 (dd, *J* = 17.5, 11.0 Hz, 1H), 2.62-2.23 (m, 1H), 2.18-2.07 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.9, 167.9, 147.9 (d, J_{C-F} = 1.7 Hz), 142.3, 141.9, 134.9, 134.0, 132.0, 129.7, 127.8, 126.3, 123.3, 121.3, 120.4 (q, J_{C-F} = 255.7 Hz), 50.3, 41.0, 39.8, 38.1, 30.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.88;HRMS (ESI) calcd for $C_{27}H_{22}F_3N_2O_4$[M+H]$^+$ 495.1532 found 495.1539.

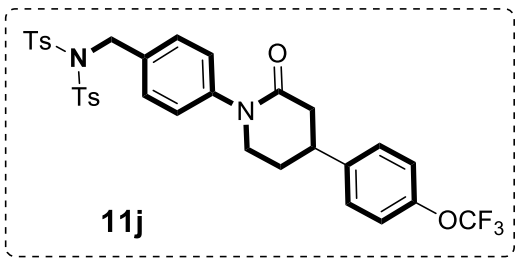


2-(4-(2-Oxo-4-(3-(trifluoromethyl)phenyl)piperidin-1-yl)benzyl)isoindoline-1,3-dione (11i) : The compound**11i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless solid (66 mg, 66%, 0.21 mmol scale); R_f(50% EtOAc/hexane) 0.4; mp: 204-206 ^{o}C; IR (DCM): 2928, 1715, 1653, 1327, 716 cm^{-1}; ^{1}H NMR

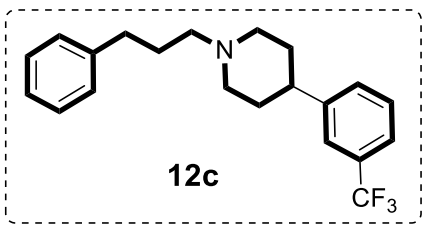


(400 MHz, $CDCl_3$) δ_H7.87 (dd, J = 5.4, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 7.57-7.46 (m, 6H), 7.25 (d, J = 8.4 Hz, 2H), 4.87 (s, 2H), 3.84-3.77 (m, 1H), 3.68-3.63 (m, 1H), 3.39-3.31 (m, 1H), 2.95-2.89 (m,1H), 2.71 (dd, J = 17.5, 11.0 Hz, 1H), 2.31-2.25 (m, 1H), 2.23-2.13 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz):δ_C168.8, 168.0, 144.2, 142.4, 135.1, 134.1, 132.1, 131.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.0, 129.8, 129.4, 126.4, 124.1 (q, $J_{C\text{-}F}$ = 271.0 Hz), 123.9 (q, $J_{C\text{-}F}$ = 3.9 Hz), 123.4(q, $J_{C\text{-}F}$ = 3.7 Hz), 123.4, 50.4, 41.1, 39.7, 38.7, 30.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -62.60;HRMS (ESI) calcd for $C_{27}H_{22}F_3N_2O_3$ $[M+H]^+$ 479.1583 found 479.1579.

4-Methyl-*N*-(4-(2-oxo-4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)-*N*-tosylbenzenesulfonamide (11j) : The compound **11j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a brown coloured solid (56 mg, 31%, 0.27 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 195-197^{o}C; IR (DCM):2926, 1655, 1261, 1165, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.69 (d, J = 8.2 Hz, 4H), 7.47 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H),7.28-7.25 (m, 6H), 7.19 (d, J = 8.2 Hz, 2H), 4.91 (s, 2H), 3.82 (td, J = 11.6, 4.2 Hz, 1H), 3.69-3.64 (m, 1H), 3.38-3.30 (m, 1H), 2.96-2.90 (m, 1H), 2.71 (dd, J = 17.4, 11.0 Hz, 1H), 2.44 (s, 6H), 2.33-2.28 (m, 1H), 2.23-2.13 (m, 1H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C168.8, 148.0, 144.7, 142.7, 141.9, 136.9, 133.6, 130.1, 129.5, 128.1, 127.8, 126.1, 121.3, 120.4 (q, $J_{C\text{-}F}$ = 256.0 Hz), 51.6, 50.5, 39.9, 38.2, 30.5, 21.6, 21.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.87;HRMS (ESI) calcd for $C_{33}H_{31}F_3N_2NaO_6S_2$ $[M+H]^+$ 695.1473 found 695.1467.

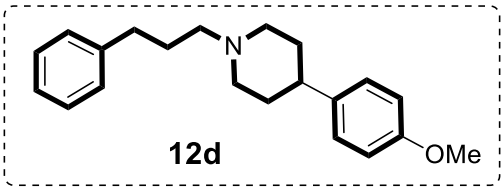


1-(3-Phenylpropyl)-4-(3-(trifluoromethyl)phenyl)piperidine (12c): The compound **12c**was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:90) as acolorless liquid (31 mg, 73%, 0.123 mmol scale); R_f(10% EtOAc/hexane) 0.7; IR (DCM): 2926, 1712, 1329, 1123, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.53-7.43 (m, 3H), 7.38-7.23 (m, 6H), 3.23-

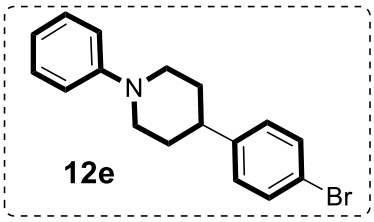


3.18 (m, 2H), 3.10-3.02 (m, 1H), 2.90-2.80 (m, 2H), 2.74-2.52 (m, 5H), 2.32-2.12 (m, 2H), 1.74-1.63 (m, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -62.52; HRMS (ESI) calcd for $C_{21}H_{25}F_3N$ $[M+H]^+$ 348.1939found 348.1935. The proton/carbon NMR revealed that this compound seems to exist as conformers. Due to fluorine coupling the carbon NMR signals could not be precisely assigned. The NMR chart is provided.

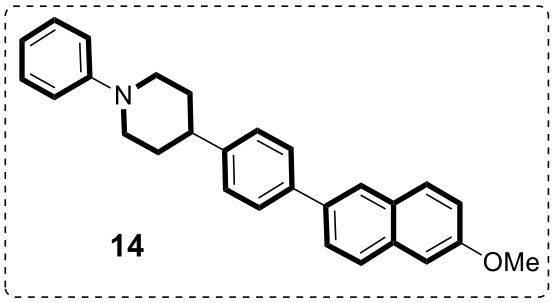
4-(4-Methoxyphenyl)-1-(3-phenylpropyl)piperidine (12d) : The compound **12d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:90) as a colourless solid (37 mg, 86%, 0.14 mmol scale);R_f(10% EtOAc/hexane) 0.7; mp: 112-114 ^{o}C; IR (DCM): 2928, 1512, 1245, 1179, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.38-7.32 (m, 2H),7.30-7.20 (m, 4H), 7.00-6.98 (m, 1H), 6.89-6.86 (m, 2H), 3.83 (s, 3H), 3.20-3.16 (m, 2H), 3.08-3.00 (m, 1H), 2.91-2.79 (m, 2H), 2.72-2.65 (m, 2H), 2.63-2.52 (m, 3H), 2.31-2.11 (m, 2H), 1.70-1.62 (m, 3H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C158.2, 158.1, 140.9, 140.8, 137.0, 136.4, 128.5, 128.5, 128.4, 128.3, 127.7, 127.4, 126.2, 126.1, 113.9, 113.9, 68.0, 59.2, 57.4, 55.2, 53.4, 41.0, 39.5, 33.5, 33.3, 28.9, 27.3, 24.7, 24.4; HRMS (ESI) calcd for $C_{21}H_{28}NO$ $[M+H]^+$ 310.2171 found 310.2169.The proton/carbon NMR revealed that this compound seems to exist as conformers.



4-(4-Bromophenyl)-1-phenylpiperidine (12e): The compound **12e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:90) as a colourlesssolid (30 mg, 79%, 0.12 mmol scale); R_f(10% EtOAc/hexane) 0.7; mp: 120-122 ^{o}C; IR (DCM): 2937, 1488, 1264, 1008, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.47 (d, J = 8.2 Hz, 2H), 7.33-7.28 (m, 2H), 7.16 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 3.84 (d, J = 12.3 Hz, 2H), 2.84 (td, J = 12.1, 2.6 Hz, 2H), 2.69-2.61 (m, 1H), 1.98-1.84 (m, 4H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C151.7, 145.1, 131.6, 129.2, 128.7, 119.9, 119.7, 116.7, 50.5, 42.0, 33.2; HRMS (ESI) calcd for $C_{17}H_{19}BrN$ $[M+H]^+$ 316.0701 found 316.0691.

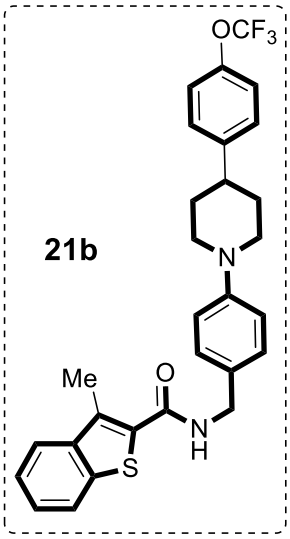


4-(4-(6-Methoxynaphthalen-2-yl)phenyl)-1-phenylpiperidine (14): The compound**14** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:90) as a pale green colorsolid (18 mg, 65%, 0.07 mmol scale); R_f(10% EtOAc/hexane) 0.7; mp: 120-



122°C; IR (DCM): 2924, 2360, 1725, 1261, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.99 (d, *J* = 1.4 Hz, 1H), 7.84-7.80 (m, 2H), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.34-7.30 (m, 2H), 7.21-7.19 (m, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.90 (t, *J* = 7.2 Hz, 1H), 3.97 (s, 3H), 3.87 (d, *J* = 12.3 Hz, 2H), 2.92-2.86 (m, 2H), 2.79-2.71 (m, 1H), 2.09-1.95 (m, 4H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C157.7, 151.8, 145.0, 139.2, 136.1, 133.7, 129.7, 129.2, 129.1, 127.3, 127.3, 127.2, 126.0, 125.4, 119.6, 119.1, 116.7, 105.5, 55.3, 50.6, 42.2, 33.3;HRMS (ESI) calcd for $C_{28}H_{28}NO$ $[M+H]^+$ 394.2171 found 394.2174.

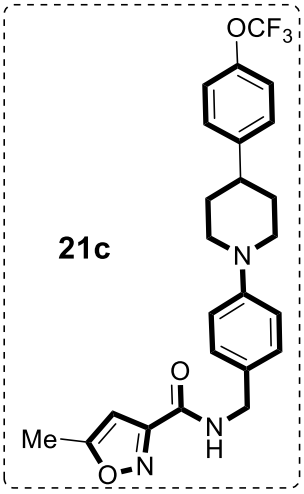
3-Methyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)benzo[*b*]thiophene-2-



carboxamide(21b) : The compound **21b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colourlesssolid (56 mg, 82%, 0.13 mmol scale); R_f(20% EtOAc/hexane) 0.3;mp: 183-185°C; IR (DCM): 2918, 1509, 1264, 1150, 731 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ_H7.82 (dd, *J* = 5.9, 3.5 Hz, 2H),7.46 (dd, *J* = 6.1, 3.2 Hz, 2H), 7.33-7.28 (m, 4H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.20 (s, 1H), 4.60 (d, *J* = 5.5 Hz, 2H), 3.84 (d, *J* = 12.4 Hz, 2H), 2.89-2.82 (m, 2H), 2.75-2.66 (m, 4H), 1.99-1.84 (m, 4H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C163.4, 151.2, 147.6, 144.7, 140.6, 138.4, 136.3, 130.1, 129.0, 128.6, 128.1, 126.5, 124.7, 123.3, 122.6, 121.1, 120.5 (q, $J_{C\text{-}F}$ = 258.8 Hz), 116.8, 50.4, 43.8, 41.9, 33.2, 13.1; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.88; HRMS (ESI) calcd for $C_{29}H_{28}F_3N_2O_2S[M+H]^+$ 525.1823 found 525.1807.

5-Methyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)isoxazole-3-

carboxamide (21c) : The compound **21c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown coloured solid (35 mg, 59%, 0.13 mmol scale); R_f(30% EtOAc/hexane) 0.3;mp: 150-152 °C; IR (DCM): 2928, 1662, 1513, 1277, 1154 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ_H7.30-7.25 (m, 4H),7.18 (d, *J* = 8.3 Hz, 2H), 7.04



(s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 1H), 4.55 (d, *J* = 5.8 Hz, 2H), 3.83 (d, *J* = 12.4 Hz, 2H), 2.88-2.81 (m, 2H), 2.73-2.66 (m, 1H), 2.50 (s, 3H), 1.98-1.83 (m, 4H);^{13}C NMR ($CDCl_3$, 101 MHz):δ_C171.2, 158.9, 158.8, 151.3, 147.6, 144.7, 129.1, 128.1, 128.1, 121.1, 120.5 (q, $J_{C\text{-}F}$ = 255.2 Hz), 116.8, 101.5, 50.4, 43.1, 41.9, 33.2, 12.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ_F -57.89; HRMS (ESI) calcd for $C_{24}H_{25}F_3N_3O_3[M+H]^+$ 460.1848 found 460.1855.

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CHAPTER 4

Application of Pd(II)-catalyzed, directing group (DG)-assisted C-H arylation strategy for the synthesis of azobenzene-based unnatural amino acid scaffolds and peptides.

This part of the Thesis work viz. Chapter 4 has been re-used (adapted) with permission from the publication, Tomar, R.; Suwasia, S.; Roychoudhury, A.; Venkataramani, S.; Babu, S. A. *Chem. Commun.*, **2022**, 58, 12967-12970. Title: Azobenzene-based unnatural amino acid scaffolds *via* Pd(II)-catalyzed C(sp^3)-H arylation strategy.

The transition metal-catalyzed sp^3 C-H bond functionalization reactions have received paramount attention in recent years.[1-3] Especially, the Pd(II)-catalyzed, directing group-aided site-selective C-H functionalization has emerged as a valuable method.[2,3] This method has also enabled the diastereoselective functionalization of prochiral C(sp^3)-H bonds present in the aliphatic compounds.[2,3] Unnatural amino acid derivatives are versatile building blocks for assembling bioactive molecules/pharmaceuticals and are used as molecular probes for studying the functions of biomolecules (e.g. peptides). Accordingly, the construction of unnatural amino acid derivatives and functionalized peptides is a renowned research area.[4]

Azobenzene derivatives are an imperative class of photo-responsive compounds, which have found applications in chemical, materials, biological sciences and medicinal chemistry[5] and are used as tools for studying the functions of biological molecules. For carrying out such studies, azobenzene motifs were incorporated in amino acids or peptides (e.g. at the *N*- or *C*-terminus or side chain sites).[5,6] Subsequently, they have been used to study the functions of proteins.[6a,b,e] E.g. Azophenylalanines (azoPhe **1**, Figure 1) were assembled from Mills coupling between 4-aminophenylalanine with nitrosobenzenes.[6a,b] Gluazo[6f] (**2**) and an azobenzene-based glycine polymer[6g] were synthesized using the Stille and Sonogashira-Hagihara coupling reactions, respectively. Examples of azobenzene-based unnatural amino acids such as azophenylalanines and some azotyrosines have been synthesized by using modified phenylalanine and tyrosine as substrates. Some azobenzene-based glycine derivatives were prepared *via* the alkylation of ethyl isocyanoacetate or dialkyl aminomalonate with azobenzene-based alkyl bromides.[6h,i]

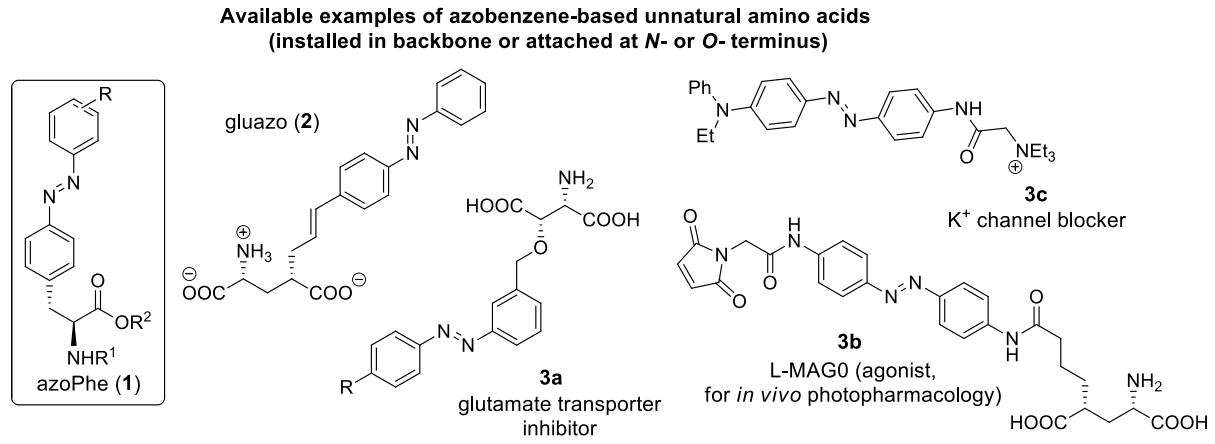
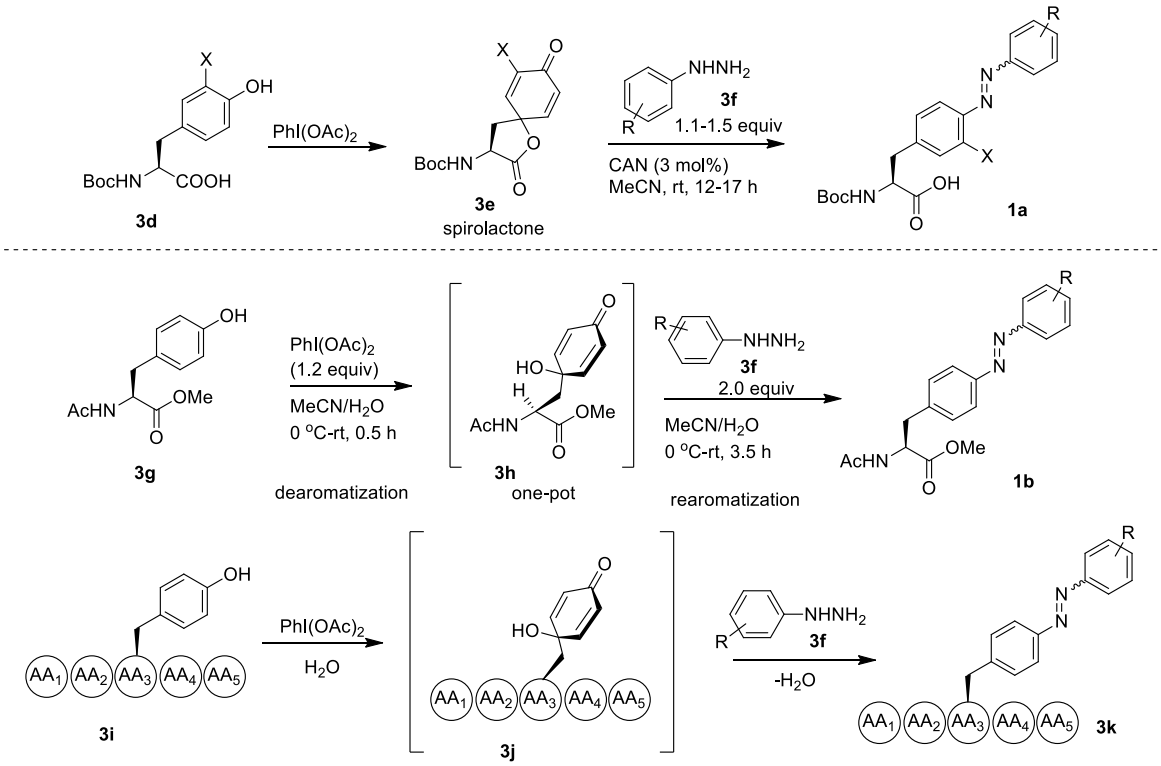


Figure 1. Azobenzene-based amino acid scaffolds.

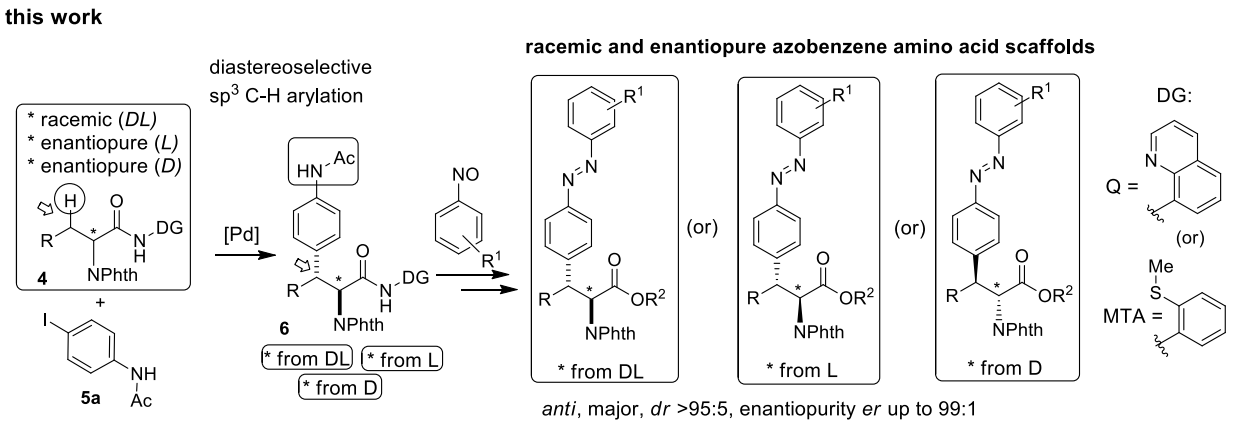
On the other hand, in the year 2015, Qin's group[6e] disclosed an alternate route for the synthesis of azophenylalanines (**1a**) *via* a two-step process including dearomatization and then rearomatization. This group reported the synthesis of quinonoidal spirolactone (**3e**) which was derived from tyrosine amino acid (**3d**) in the presence of an oxidant i.e., phenyl iodo diacetate (PIDA). Further, spirolactone was treated with phenylhydrazine (**3f**) in the presence of a catalytic amount of ceric ammonium nitrate (CAN) and substituted azophenylalanines (**1a**) were synthesized (Scheme 1a).



Scheme 1a. Synthesis ofAzobenzene-based amino acid scaffolds and peptides.

Following the same strategy in 2021, Fang's group has also synthesized the azobenzene-based amino acid (**1b**) along with late-stage modification of specific tyrosine-containing peptides (**3i**) and without CAN an azobenzene has been installed in amino acids (**1b**) and peptides (**3k**) in one pot manner (Scheme 1a).

In this line, we envisioned utilizing the Pd(II)-catalyzed, directing group (DG)-assisted diastereoselective C-H arylation strategy[2,3] for constructing azobenzene-based unnatural amino acid derivatives. Our strategy involves the initial installation of acetanilide units in amino acids *via* the Pd(II)-catalyzed *β*-C(sp^3)-H arylation tactic[2,3] by using an iodoacetanilide as an arylating agent. Then, the transformation of the acetanilide unit into an azobenzene motif in the amino acid backbone would afford an azobenzene-based unnatural amino acid scaffold (Scheme 1b).

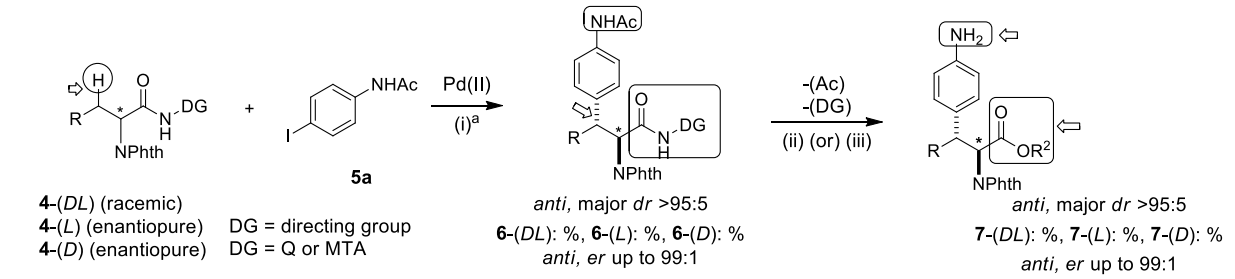


Scheme 1b. Theme of our work.

Results and Discussion

Towards this, we prepared directing group 8-aminoquinoline (8-AQ) or 2-(methylthio)aniline (MTA) containing various racemic and enantiopure *N*-phthaloyl carboxamides **4**-(DL), **4**-(L) and **4**-(D) from their corresponding racemic (DL) and enantiopure (L) and (D) α-amino acids. We then subjected amino acid carboxamides **4**-(DL) to the Pd(II)-catalyzed DG-aided diastereoselective *β*-C-H arylation reaction conditions[2,3] using 4-iodoacetanilide (**5a**). For example, a mixture of leucine derivative **4a**-(DL) containing 8-aminoquinoline DG, 4-iodoacetanilide (**5a**, 5 equiv), $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (2.5 equiv, iodide ion scavenging additive) was heated in toluene at 110 ^oC for 24 h. This reaction afforded the *β*-C-H arylated leucine derivative **6a**-(DL) possessing acetanilide unit in 81% yield (*anti* isomer).

Similarly, the Pd(II)-catalyzed arylation of phenylalanine derivative **4c**-(DL) containing 2-(methylthio)aniline DG with **5a** afforded the *β*-C-H arylated racemic phenylalanine derivative **6c**-(DL) (73% yield, *anti* isomer). Along these lines, the *β*-C-H arylated racemic norleucine derivative **6b**-(DL), norvaline derivative **6f**-(DL), 2-aminocaprylic acid derivative **6i**-(DL) and bis *β*-C-H arylated alanine derivative **6e**-(DL) were synthesized (Scheme 2).



(*DL*) (racemic)

6a-(*DL*): 81 (R = *i*-Pr)
6b-(*DL*): 74 (R = *n*-Pr)
6c-(*DL*): 73 (R = Ph, DG = MTA) **(X-ray)**
6f-(*DL*): 73 (R = Et)
6i-(*DL*): 90 (R = -$(CH_2)_4$Me)

7a-(*DL*): 54 (R = *i*-Pr, R^2 = Et)[c]
7b1-(*DL*): 43 (R = *n*-Pr, R^2 = Et)[c]
7b2-(*DL*): 52 (R = *n*-Pr, R^2 = Me)[b]
7c-(*DL*): 69 (R = Ph, R^2 = Et)[c]
7f-(*DL*): 18 (R = Et, R^2 = Me)[b]
7i-(*DL*): 29 (R = -$(CH_2)_4$Me, R^2 = Me)[b]

6e-(*DL*): 78

7e-(*DL*): 43[d]

(*L*) (enantiopure)

6a-(*L*): 68 (*er* 98:2) (R = *i*-Pr)
6b-(*L*): 61 (*er* 96:4) (R = *n*-Pr)
6c-(*L*): 85 (*er* 96:4) (R = Ph, DG = MTA)

7a-(*L*): 53 (R = *i*-Pr, R^2 = Et)[c]
7b1-(*L*): 45 (R = *n*-Pr, R^2 = Et)[c] (*er* 98:2)
7c-(*L*): 69 (R = Ph, R^2 = Et)[c]

6e-(*L*): 50 (*er* 96:4)

7e-(*L*): 47[d]

(*D*) (enantiopure)

6a-(*D*): 62 (*er* 95:5) (R = *i*-Pr)
6b-(*D*): 67 (*er* 98:2) (R = *n*-Pr)
6c-(*D*): 88 (*er* 98:2) (R = Ph, DG = MTA)

7a-(*D*): 54 (R = *i*-Pr, R^2 = Et)[c]
7b1-(*D*): 45 (R = *n*-Pr, R^2 = Et)[c] (*er* 95:5)
7c-(*D*): 57 (R = Ph, R^2 = Et)[c]

6e-(*D*): 78 (*er* 99:1)

7e-(*D*): 58[d]

[a] Conditions (i): **4** (1 equiv), **5a/5b** (5 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.5 equiv), toluene (3 mL), 110 °C, 24 h. [b] Conditions (ii): **6** (1 equiv), PTSA (6 equiv), MeOH or EtOH (2-4 mL), 100 °C, 24 h. [c] Conditions (iii): **6** (1 equiv), BF_3-OEt_2 (20 equiv), EtOH (2-3 mL), 130 °C, 60-72 h. [d] Conditions (iii): **6** (1 equiv), BF_3-OEt_2 (30 equiv), EtOH (2 mL), 130 °C, 60 h.

Scheme 2. Synthesis of *α*-amino acid derivatives containing acetanilide unit *via* C(sp^3)-H arylation and *α*-amino acid derivatives containing aniline unit.

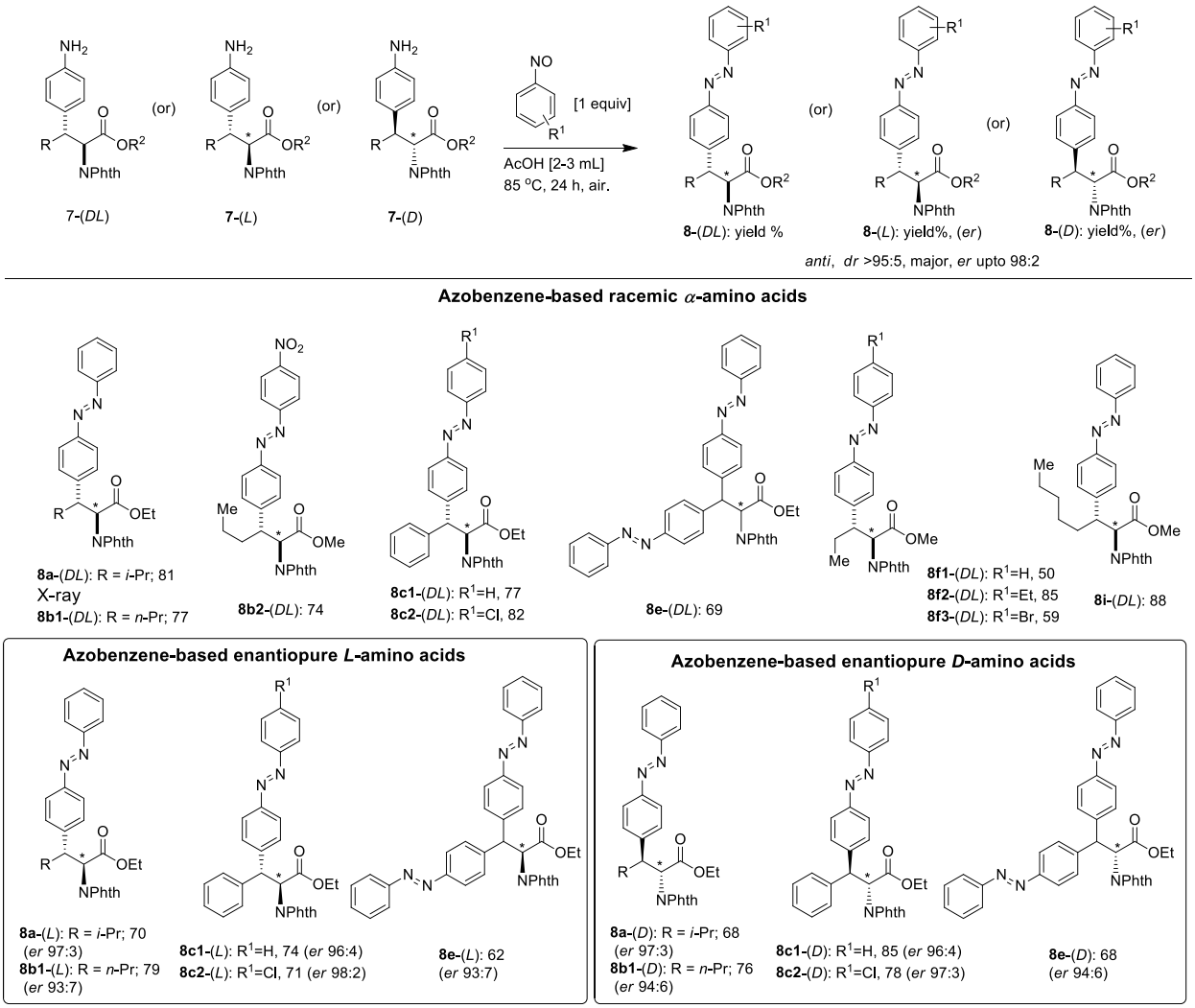
Next, we attempted the deacetylation of acetanilide moiety to obtain the *α*-amino acid derivatives **7**-(DL) possessing the aniline moiety by using the PTSA or $BF_3{\cdot}OEt_2$-mediated amide hydrolysis in MeOH or EtOH (Scheme 2). For example, the leucine carboxamide **6a**-(DL) containing acetanilide unit and 8-AQ DG was treated with $BF_3{\cdot}OEt_2$ in EtOH. This reaction condition has

deprotected the acetyl group in the acetanilide moiety and also converted the 8-AQ DG-linked carboxamide unit into an ester group. Accordingly, the *N*-phthaloyl leucine carboxylate derivative **7a**-(DL) possessing an aniline unit was obtained in 54% yield (*anti* isomer). Along these lines, various *N*-phthaloyl amino acid ester derivatives **7b1**-(DL), **7b2**-(DL) **7c,f-i**-(DL) (*anti* isomers) and **7e**-(DL) possessing aniline unit were obtained from their corresponding substrates **6**-(DL).

Next, we performed the diastereoselective Pd(II)-catalyzed *β*-C-H arylation of various enantiopure **4**-(L) or **4**-(D) amino acid carboxamides with 4-iodoacetanilide **5a** (Scheme 2). Accordingly, the enantiopure *β*-C-H arylated leucine derivatives **6a**-(L), **6a**-(D), norleucine derivatives **6b**-(L), **6b**-(D), and phenylalanine derivatives **6c**-(L), **6c**-(D) possessing the acetanilide unit were obtained (*anti* isomers, *er* up to 98:2). Additionally, the enantiopure bis *β*-C-H arylated alanine derivatives **6e**-(L) and **6e**-(D) containing two acetanilide units were synthesized. Then, the enantiopure *α*-amino acid carboxamide **6a**-(L) / **6a**-(D), **6b**-(L) / **6b**-(D), **6c**-(L) / **6c**-(D) (*anti* isomers) and **6e**-(L) / **6e**-(D) possessing the acetanilide unit and corresponding DGs were subjected to the amide hydrolysis conditions (Scheme 2). Accordingly, the enantiopure leucine carboxylate derivatives **7a**-(L), **7a**-(D), norleucine carboxylate derivatives **7b1**-(L), **7b1**-(D), and phenylalanine carboxylate derivatives **7c**-(L), **7c**-(D) (*anti* isomers) possessing aniline unit were obtained from their corresponding substrates. Then, the enantiopure alanine carboxylate derivatives **7e**-(L) and **7e**-(D) possessing two aniline units were obtained from their corresponding substrates.

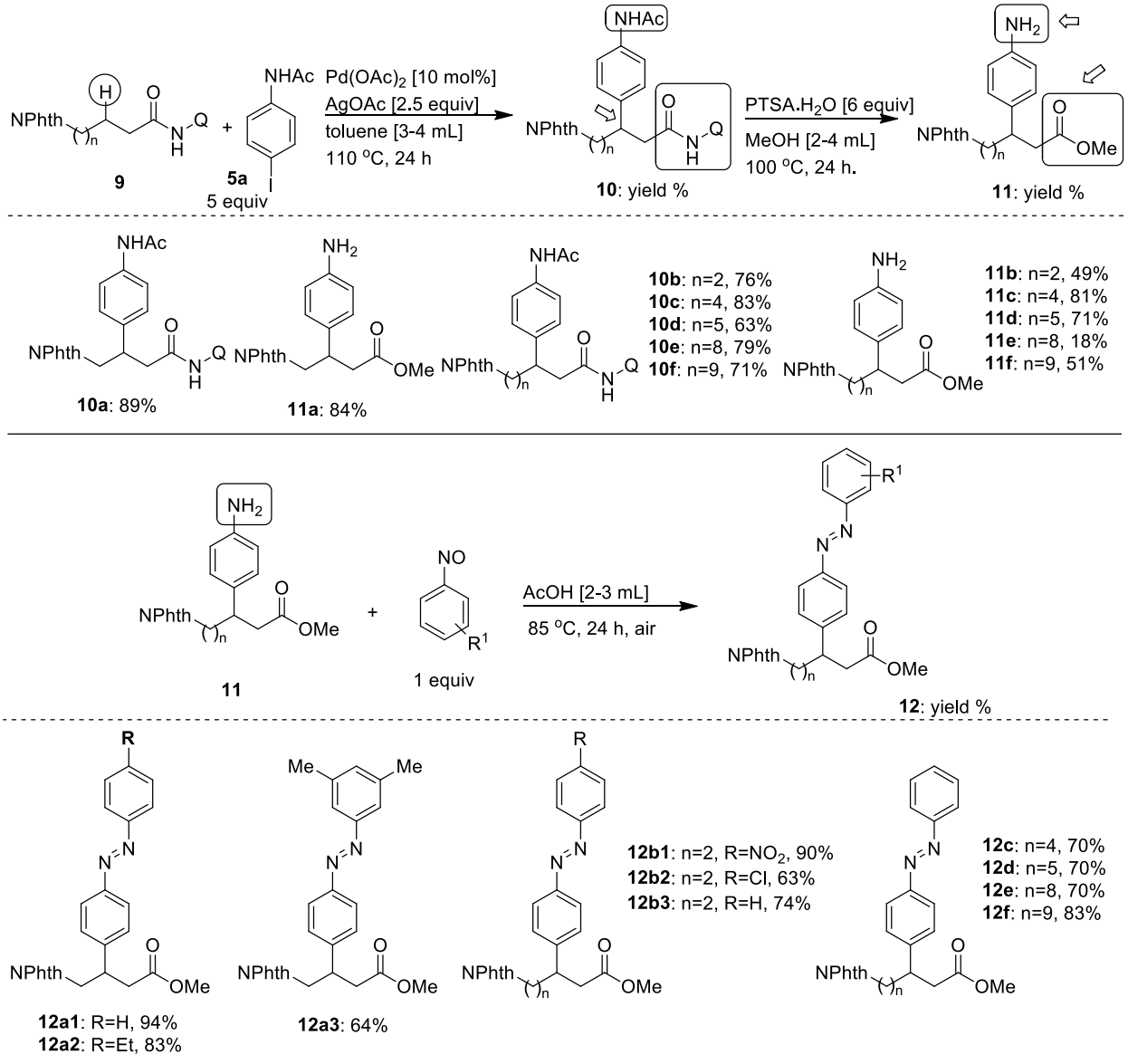
We then attempted to convert the aniline unit present in compounds **7**-(DL), **7**-(L) and **7**-(D) into azobenzene unit and obtain azobenzene-based unnatural amino acid scaffolds **8**-(DL), **8**-(L) and **8**-(D) (Scheme 3). Treatment of the leucine carboxylate derivative **7a**-(DL) having the aniline unit with nitrosobenzene in AcOH at 85 ^{o}C successfully yielded the corresponding azobenzene-based leucine derivatives **8a**-(DL) (*anti* isomers). Next, the azobenzene-based norleucine derivatives **8b1**-(DL), and **8b2**-(DL) (*anti* isomers) were obtained from their corresponding substrates **7b1**-(DL) and **7b2**-(DL). Then, the azobenzene-based phenylalanine derivatives **8c1**-(DL) and **8c2**-(DL) (*anti* isomers) were obtained from **7c**-(DL) and respective nitrosobenzenes. Subsequently, the azobenzene-based norvaline derivatives **8f1**-(DL), **8f2**-(DL) and **8f3**-(DL) (*anti* isomers) were obtained from their respective substrates **7f**-(DL) and nitrosobenzenes. Furthermore, the azobenzene-based 2-aminocaprylic acid derivative **8i**-(DL) (*anti* isomer) and

bis azobenzene-based alanine derivative **8e**-(DL) were obtained from their respective substrates **7i**-(DL) and **7e**-(DL). Subsequently, we treated the enantiopure leucine carboxylate derivatives **7a**-(L), and**7a**-(D), containing the aniline unit with nitrosobenzene in AcOH at 85 ^{o}C. These attempts yielded their respective enantiopure azobenzene-based leucine derivatives **8a**-(L), and **8a**-(D) (*anti* isomers, Scheme 3). Next, the enantiopure azobenzene-based norleucine derivatives **8b1**-(L), and **8b1**-(D) (*anti* isomers) were obtained from their respective substrates **7b1**-(L), **7b1**-(D) and nitrosobenzene. Then, the enantiopure azobenzene-based phenylalanine derivatives **8c1**-(L), **8c1**-(D), **8c2**-(L) and **8c2**-(D) (*anti* isomers) were obtained from their respective substrates **7c**-(L) and **7c**-(D) and nitrosobenzenes. Next, the enantiopure bis azobenzene-based alanine derivatives **8e**-(L) and **8e**-(D) were obtained from their respective substrates **7e**-(L) and **7e**-(D) and nitrosobenzenes.



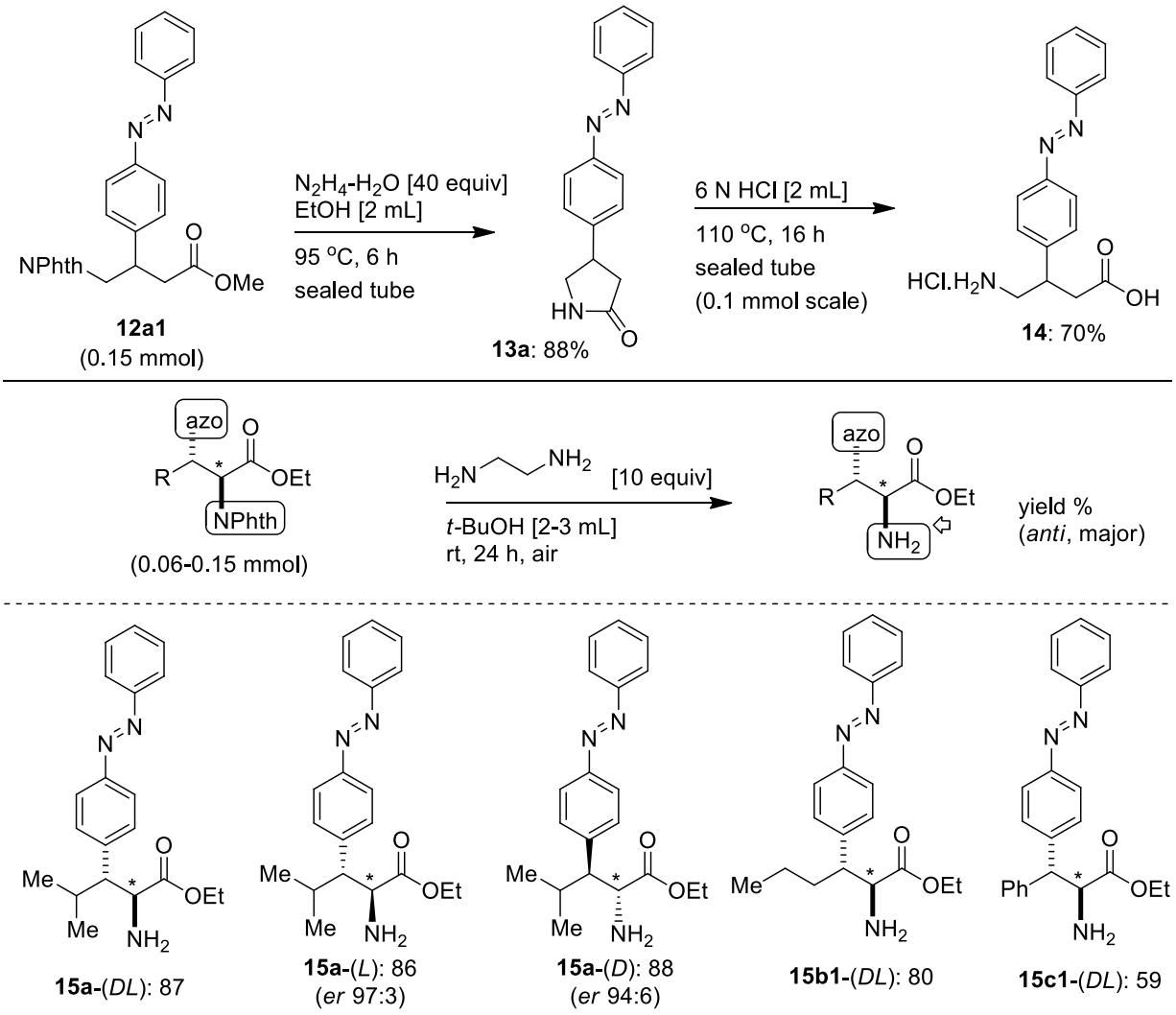
Scheme 3. Synthesis of azobenzene-based α-amino acid motifs.

Successively, we also prepared a wide range of azobenzene-based non-α-amino acid methyl esters **12** *via* the β-C-H arylated non-α-amino acid derivatives **10** containing acetanilide unit (Scheme 4). We then subjected the *N*-phthaloyl azobenzene-based GABA ester **12a1** to a hydrazine-mediated direct lactamization process, which gave the azobenzene moiety installed 2-pyrrolidone **13a** (Scheme 5).



Scheme 4. Synthesis of azobenzene-based non-α-amino acid motifs.

Next, we performed the ethylenediamine-mediated phthalimide group deprotection in the azobenzene-based leucine esters **8a**-(DL), **8a**-(L), **8a**-(D). These reactions afforded the corresponding azobenzene-based, free amino group containing leucine esters **15a**-(DL), **15a**-(L), **15a**-(D) (Scheme 5). Similarly, the azobenzene-based free amino group-containing compounds **15b1**-(DL), and **15c1**-(DL) were obtained from their corresponding substrates (Scheme 5).



Scheme 5. Synthetic transformations towards azobenzene-based amino acid derivatives.

We then performed photo-switching studies of representative azobenzene-based leucine esters (Figure 2). The *trans* azobenzenes **15a**-(L) and **15a**-(D) were irradiated at 365 nm to convert them into their corresponding *cis* azobenzenes. Subsequently, the conversion of *cis* isomers into *trans* compounds was observed at 470 nm. In about 20-30 min the *cis* isomers were converted into their corresponding *trans* azobenzenes **15a**-(L) and **15a**-(D). The *anti* stereochemistry of

compounds **6**-(DL), **6**-(L) and **6**-(D) (major isomers) obtained from the C-H arylation reaction and all the corresponding subsequent compounds prepared using them were assigned based on the X-ray structures of representative compounds **6c**-(DL) and **8a**-(DL) (Figure 3).

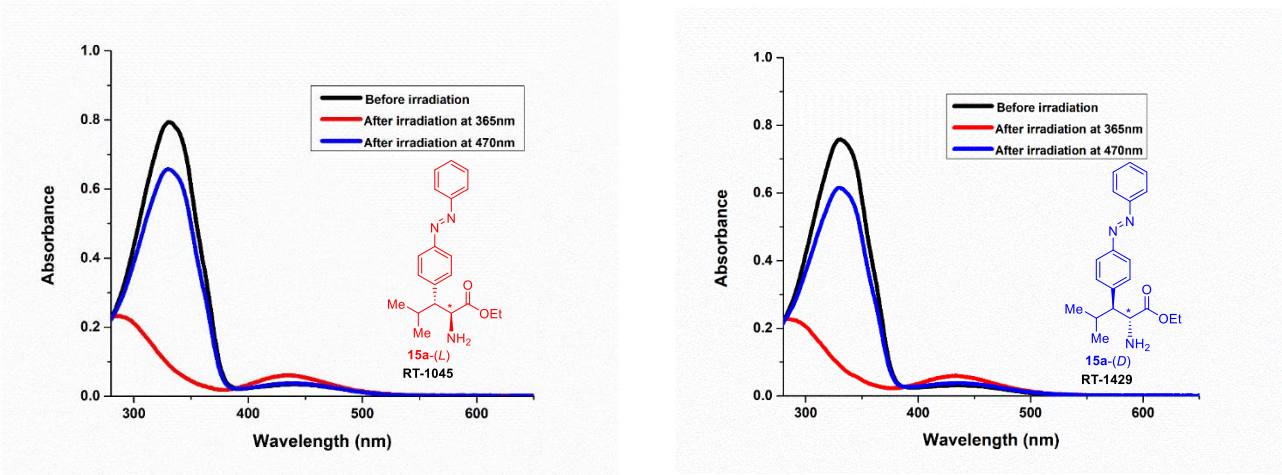
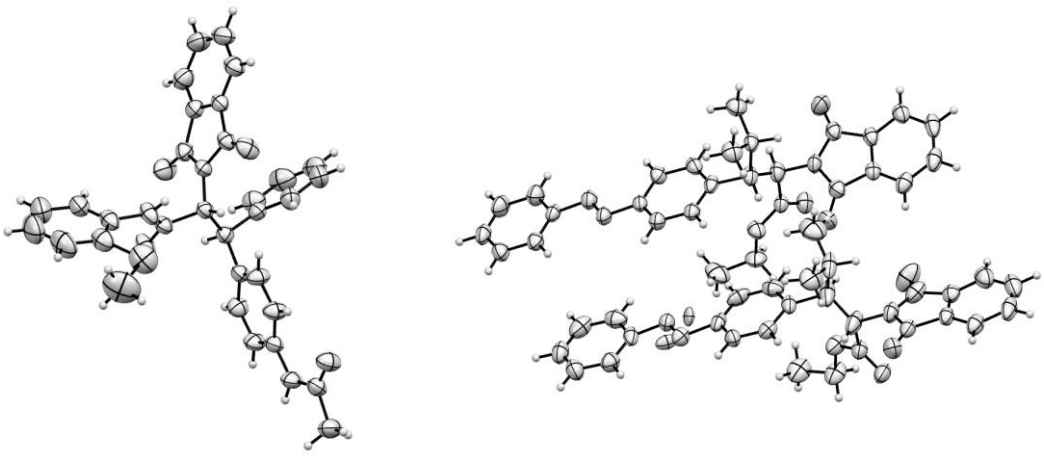


Figure 2. Photo-switching studies of representative azobenzene-based leucine esters.

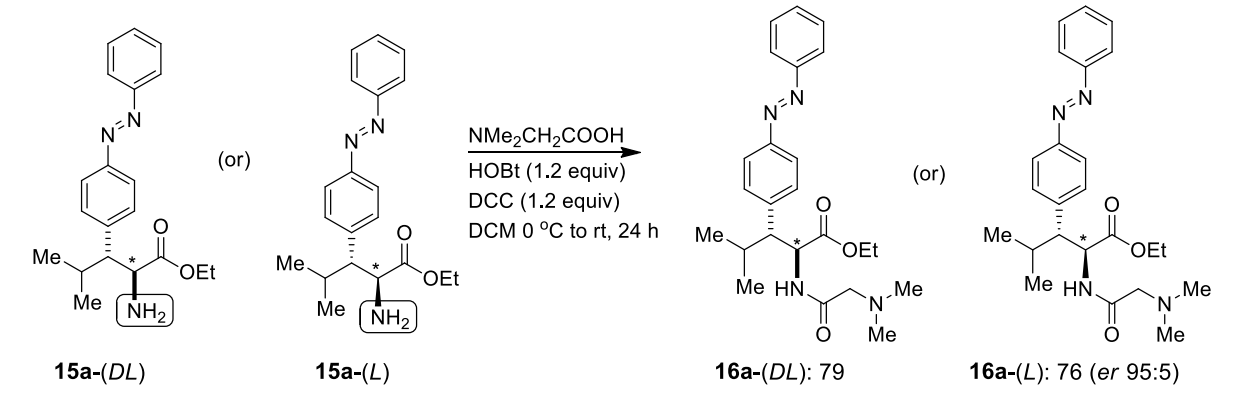


6c-(DL) **8a**-(DL) (The unit cell contains two molecules)

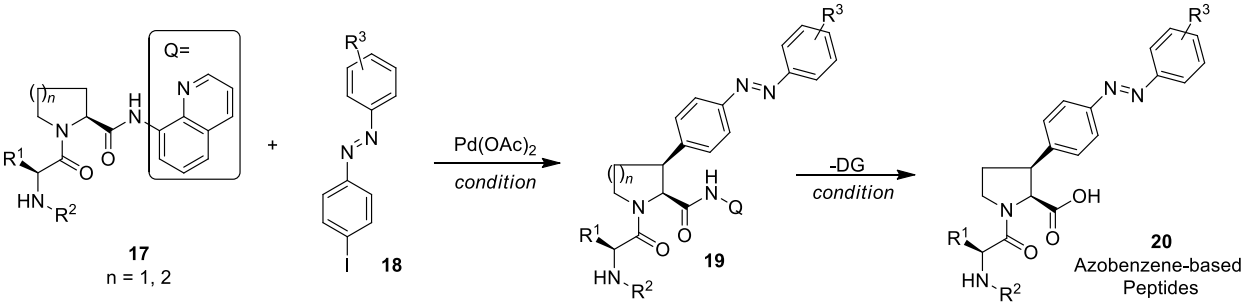
Figure 3. X-ray (ORTEP diagrams) structures of compounds **6c**-(DL) and **8a**-(DL) (Description of crystallographic data is given in experimental section.)

We have also prepared azobenzene-based dipeptide compounds **16a**-(DL) and **16a**-(L) from the corresponding compounds **15a**-(DL) and **15a**-(L) using the standard peptide synthesis conditions (Scheme 6). In this direction following the synthesis of azobenzene-based dipeptides *via* Pd(II)-

catalyzed diastereoselective β-C(sp^3)-H arylation, we next attempted the synthesis of azobenzene-based peptides *via* Pd(II)-catalyzed directing group-aided stereoselective β-C-H arylation of short peptides. With the increased interest in peptides as possible medicines, targeted ligands, and molecular probes, the demand for direct functionalization of these structurally complicated molecules has grown.[7] Therefore, this chapter also emphasizes the direct installation of azobenzene on peptides *via* late-stage modification of dipeptides through stereoselective Pd-catalyzed C-(sp^3)-H arylation with the help of a removable directing group.



Scheme 6. Synthesis of azobenzene-based dipeptide derivatives.

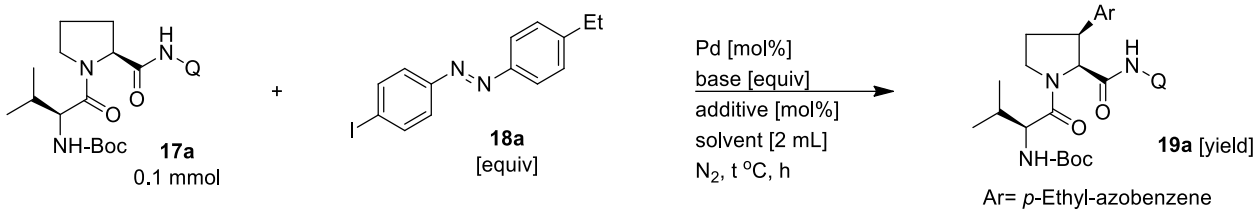


Scheme 7: Generalised scheme for the late-stage modification of peptides and removal of directing group.

We commenced our investigation with the literature reported Pd(II)/Pd(IV) catalytic system-based bidentate directing group-aided, arylation conditions for the stereoselective C-H bond functionalization in short peptides with iodo azobenzene as a coupling partner (Scheme 7). We first assembled the Valine-Proline based dipeptide carboxamide (**17a**) by linking the directing group 8-aminoquinoline following the standard reaction procedure for the peptide synthesis. Table 1 shows the direct installation of azobenzeneon the C3 position of dipeptide with an aryl

iodide (iodo azobenzene) under stereoselective Pd catalysis. Further, we carried out a wide range of optimization reactions to determine the best reaction condition and solvent (Table 1).

Table 1. Optimization reaction conditions for Pd(II)-catalyzed stereoselective *β*-C-H arylation of dipeptide.



S. No.	Iodo	Catalyst (10 mol%)	Base (equiv.)	Additive (20 mol%)	Solvent	t °C/hr	Yield (%)
1.	2 equiv	$Pd(OAc)_2$	AgOAc (2.0)	_	toluene	110 °C/48 h	39%
2.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	_	toluene	110 °C/60 h	43%
3.	5 equiv	$Pd(OAc)_2$	Ag_2CO_3 (2.5)	_	toluene	110 °C/60 h	28%
4.	5 equiv	$Pd(OAc)_2$	K_2CO_3 (2.5)	_	toluene	110 °C/60 h	traces
5.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	toluene	110 °C/60 h	63%
6.	5 equiv	$Pd(OAc)_2$	Ag_2CO_3 (2.5)	$(BnO)_2PO_2H$	*t*-AmylOH	110 °C/60 h	34%
7.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	DCE	110 °C/60 h	68%
8.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	*p*-xylene	130 °C/60 h	68%
9.	5 equiv	$Pd(OAc)_2$	K_2CO_3 (2.5)	$(BnO)_2PO_2H$	*p*-xylene	130 °C/60 h	traces
10.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	PivOH	*p*-xylene	130 °C/60 h	traces
11.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	_	*p*-xylene	130 °C/24 h	49%
12.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	toluene	130 °C/24 h	74%
13.	3 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	toluene	130 °C/60 h	49%
14.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	DCE	120 °C/36 h	57%
15.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	dioxane	110 °C/48 h	traces
16.	5 equiv	$Pd(OAc)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	CH_3CN	110 °C/60 h	60%
17.	5 equiv	$PdCl_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	toluene	130 °C/24 h	71%
18.	5 equiv	$Pd(TFA)_2$	AgOAc (2.5)	$(BnO)_2PO_2H$	toluene	130 °C/48 h	57%

As shown in Table 1, at first we performed a reaction for the stereoselective *β*-C(sp^3)-H arylation of the Val-Pro-based dipeptide (**17a**) with 2 equiv of (*E*)-1-(4-ethylphenyl)-2-(4-

iodophenyl)diazene (**18a**)in the presence of 10 mol% $Pd(OAc)_2$ and 2 equiv of AgOAc in toluene at 110 ^oC for a period of 48 h. This reaction afforded the *p*-ethyl-azobenzene installed dipeptide **19a** in 39% yield with *syn* stereochemistry (entry 1, Table 1). The observed stereochemistry and the formation of *syn* isomers as a major product were in resemblance to literature reports dealing with the C3 arylation of proline-based dipeptides.[7]

Next, heating a mixture of dipeptide with the same reaction condition with a higher equiv of (*E*)-1-(4-ethylphenyl)-2-(4-iodophenyl)diazene (**18a**) (5 equiv) yielded the arylated product **19a** in 43% yield (entry 2, Table 1) in addition to a change in halide scavenger (Ag_2CO_3, K_2CO_3) also did not afford a satisfactory yield (entries 3 and 4, Table 1). So following the obtained result we then added an additional additive $(BnO)_2PO_2H$ to the reaction mixture along with $Pd(OAc)_2$ (10 mol%), AgOAc (2.5 equiv) in toluene, and heated the mixture at 110 ^oC for a period of 60 h which afforded the azobenzene comprising dipeptide **19a** in 63% yield (entry 5, Table 1). Further, we heated a mixture of aryl iodide (**18a**), dipeptide carboxamide **17a**, $Pd(OAc)_2$ (10 mol%), bases (e.g., AgOAc or Ag_2CO_3 or K_2CO_3) and an additive $(BnO)_2PO_2H$ (20 mol%) in different solvents such as *t*-AmylOH or DCE or *p*-xylene at 110-130 ^oC for 60 h. These reactions gave the arylated dipeptide carboxamide **19a** in 0-68% yields (entries 6-9, Table 1). Next, heating a mixture of **17a** with **18a** in the presence of $Pd(OAc)_2$, AgOAc and another additive PivOH in *p*-xylene did not afford the desired arylated product **19a** (entry 10, Table 1). While in the absence of any additive heating a reaction mixture at 130 ^oC for 24 h yielded the arylated product **19a** with 49% yield (entry 11, Table 1). Following the obtained results, we have screened different solvents including toluene, DCE, dioxane and CH_3CN (entries 12-16, Table 1) and also screened different Pd catalysts (e.g., $PdCl_2$ or $Pd(TFA)_2$) (entries 17-18, Table 1) these reactions gave the arylated dipeptide carboxamide **19a** in 0-74% yields. The reaction involving Val-Pro-based dipeptide (**17a**), (*E*)-1-(4-ethylphenyl)-2-(4-iodophenyl)diazene (**18a**) (5 equiv), $Pd(OAc)_2$ (10 mol%) AgOAc (2.5 equiv) and $(BnO)_2PO_2H$ (20 mol%) in toluene yielded the arylated product **19a** in a maximum of 74% yield and this condition is found to be the best possible reaction condition for obtaining the stereoselectiveβ-C(sp^3)-H arylated dipeptide carboxamide **19a** (entry 12, Table 1).

After obtaining the best optimized reaction currently we are working in the direction of assembling of various dipeptides using different amino acid for Pd(II)-catalyzed 8-aminoquinoline-assisted installation of azobenzene in a stereoselective manner. Further we will

be working towards the elongation of peptide chain. In order to make this approach truly appropriate for the synthesis of natural products or further peptide coupling we are also interested to demonstrate the removal of the AQ-directing group from the peptide **19a** without decomposing the peptide.

Conclusion

In conclusion, this part of the thesis deals with the scope and efficiency of the Pd(II)-catalyzed diastereoselective and stereoselective C(sp^3)-H arylation methods for the construction of fascinating azobenzene-based unnatural amino acid motifs and azobenzene containing dipeptide carboxamide. Herein we disclosed a new route for the synthesis of racemic and enantiopure azobenzene-based unnatural amino acid motifs. At first, the acetanilide unit was installed in amino acids *via* Pd(II)-catalyzed diastereoselective arylation of prochiral C(sp^3)-H bond of amino acid carboxamides. Then, the acetanilide unit was successfully converted into azobenzene motif in the corresponding amino acid backbones.Along this line we have also explored the late stage modification tactic of pepitdes *via* Pd(II)-catalyzed stereoselective arylation at C3 position of proline-based dipeptide and synthesized azobenzene moiety containing dipeptides.

Experimental Section

General. IR spectra of samples were recorded as neat or thin films. ^{1}H and $^{13}C\{H\}$ NMR spectra of all compounds were recorded in 400 (or 500) and ~101 (or 126) MHz spectrometers by using TMS as an internal standard, respectively. Column chromatographic purification of the crude reaction mixtures was performed by using silica gel (100-200 mesh). Thin layer chromatography (TLC) analyses were carried out on alumina and silica gel 60 F_{254} pre-coated plates, and components were visualized by observation under iodine vapour or by irradiation under a UV lamp. The HRMS analysis data were obtained from the QTOF mass analyzer using the electrospray ionization (ESI) technique. Reactions were carried out by using anhydrous solvents under a nitrogen atm wherever required. Organic layers obtained after the workup procedure were dried using anhydrous Na_2SO_4. For obtaining the specific rotations of enantiopure samples, the solutions were prepared in $CHCl_3$ and polarimeter analysis data were recorded at 589 nm wavelength using 100 mm cell length, concentration (*c*) taken as g per 100 mL. All the HPLC analysis patterns were determined using isolated compounds. Isolated yields of all the compounds are reported and yields of all the reactions were not optimized. Sometimes there is

variation in yields and enantiomeric ratio for the corresponding racemic/enantiopure pairs, this is perhaps based on the collection of pure fractions from the column chromatography based on the TLC and also may be due to inadvertent handling/processing errors of samples. For recording the NMRs of some azobenzene-based samples which were having minor *cis* isomers the samples were heated to completely convert the traces of *cis* isomers to *trans* isomers beforethe recording of NMR.

The *β*-C(sp^3)-H arylation of racemic substrates **4**-(*DL*) and enantiopure compounds **4**-(*L*) and **4**-(*D*) afforded the corresponding products **6**-(*DL*) and enantiopure products **6**-(*L*) and **6**-(*D*) with *anti* stereochemistry as the major diastereomers. In all these reactions, the column chromatography purification yielded the corresponding products with *anti* stereochemistry as the major compound. We did not obtain the corresponding *syn* isomers in characterizable amounts in any of the reactions. The *anti* stereochemistry of representative major diastereomers **6c**-(*DL*) and **8a**-(*DL*) was assignedbased on the X-ray structure analysis. Based on the X-ray structure analysis of these compounds, the *anti* stereochemistry of all similar compounds **6**-(*DL*), **7**-(*DL*), **8**-(*DL*), and enantiopure products **6**-(*L*), **7**-(*L*), **8**-(*L*) and **6**-(*D*), **7**-(*D*), **8**-(*D*) were assigned. In analogy, the *anti* stereochemistry of all similar compounds **15**-(*DL*) and enantiopure products **15**-(*L*) and **15**-(*D*) were assigned. We obtained the HPLC analysis patterns of the racemic products **6**-(*DL*) (*anti* isomers) and enantiopure products **6**-(*L*) and **6**-(*D*) (*anti* isomers). Accordingly, the enantiopurity of the major products **6**-(*L*) and **6**-(*D*) (*anti* isomers) was determined from the HPLC analysis. We obtained the HPLC analysis patterns of the racemic products **7b1**-(*DL*) (*anti* isomers) and enantiopure products **7b1**-(*L*) and **7b1**-(*D*) (*anti* isomers). In some cases, a clear HPLC pattern for the racemic compounds **7a,c**-(*DL*) (*anti* isomers) and **7e**-(*DL*) could not be obtained under different conditions which have been tried. The corresponding enantiopure products **7a,c**-(*L*) (*anti* isomers), **7e**-(*L*) and **7a,c**-(*D*) (*anti* isomers), **7e**-(*D*) were assumed to be enantiopure as they were obtained from their corresponding enantiopure compounds **6a,c,e**-(*L*) and **6a,c,e**-(*D*). We obtained the HPLC analysis patterns of the racemic products **8a,b1,c1,c2**-(*DL*) (*anti* isomers), **8e**-(*DL*) and enantiopure products **8a,b1,c1,c2**-(*L*) (*anti* isomers), **8e**-(*L*) and **8a,b1,c1,c2**-(*D*) (*anti* isomers), **8e**-(*D*). Accordingly, the enantiopurity of these products was determined from the HPLC analysis. We obtained the HPLC analysis patterns of the racemic products **15a**-(*DL*) (*anti* isomers) and enantiopure products **15a**-(*L*) (*anti* isomers) and **15a**-(*D*) (*anti* isomers). Accordingly, the enantiopurity of these products was determined from the HPLC

analysis. The starting materials racemic **4**-(*DL*) and enantiopure **4**-(*L*) and **4**-(*D*) required for the *β*-C(sp^3)-H arylation are known in the literature (Chen et al. *Acc. Chem. Res.*, 2016, 49, 635, Shi et al. *Chem. Commun.*, 2020, 56, 13950) and accordingly, we prepared them by using the standard procedures (Babu et al. *Org. Biomol. Chem.*, 2022, 20, 4391, Babu et al. *Eur. J. Org. Chem.*, 2021, 3641).

General procedure for the Pd(II)-catalyzed, directing group-aided sp^3 C-H arylation of amino acid carboxamides with 4-iodoacetanilide, preparation of α-amino acid derivatives containing acetanilide unit: A mixture of an appropriate amino acid carboxamide (0.15-0.9 mmol, 1 equiv), 4-iodoacetanilide (4-6 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.5 equiv) and anhydrous toluene (3-4 mL) were added to screw-cap seal tube and nitrogen was purged to the tube and then, it was heated at 110 ºC for 24 h. After the reaction period, the reaction mixture wascooled to rt and concentrated under reduced pressure to afford a crude reactionmixture, which was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to give the corresponding sp^3C-H arylated unnatural amino acid carboxamide.

General procedure for the removal of the directing group along with deacetylation of amino acid derivative containing acetanilide unit by *p*-TsOH.H_2O for the preparation of the carboxylate derivatives containing aniline unit: Amino acid derivative containing acetanilide unit (0.11-0.75 mmol, 1 equiv), *p*-TsOH.H_2O (6 equiv) and methanol/ethanol (2-4 mL) were added to a screw-cap seal tube. The vial containing the mixture was sealed and heated at 100 ºC. After 24 h, the dark brown solution was cooled to rt. After the reaction period, the solvent was evaporated under reduced pressure to afford a crude reaction mixture (or) the crude reaction mixture was diluted with EtOAc (8-10 mL) and washed with water, concentrated and the crude mixture which was purified by column chromatography to afford the corresponding Phth-protected amino acid carboxylate derivative containing aniline unit.

General procedure for the removal of the directing group along with deacetylation of amino acid derivative containing acetanilide unit by BF_3.Et_2O for the preparation of the carboxylate derivatives containing aniline unit: To a solution of amino acid derivative containing acetanilide unit (0.14-0.31 mmol, 1 equiv) in dry ethanol (2-3 mL), in a screw-cap seal tube BF_3.Et_2O (20-30 equiv) was added dropwise. After 5 min the tube was purged with nitrogen and then, the resulting mixture was stirred at 130 °C for 60-72 h. After the reaction period, the solution was cooled to rt and neutralized with NEt_3 and the solvent was evaporated

under reduced pressure. The reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water and then, the combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatography to furnish the corresponding Phth-protected amino acid carboxylate derivative containing an aniline unit.

General procedure for the synthesis of azobenzene-based unnatural amino acid derivatives from their corresponding carboxylate derivative containing aniline unit: A mixture of an appropriate Phth-protected amino acid carboxylate derivative containing aniline unit (0.06-0.17 mmol) and corresponding nitrosobenzene (1.0-2.0 equiv) was stirred in AcOH (2-3 mL) at 85 ^oC for 24 h in air. The progress of the reaction was monitored by using TLC. After completion, the solution was cooled to rt and concentrated under reduced pressure. Then, the reaction mixture was diluted with EtOAc (7-10 mL), and the organic layers were washed with sat. $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction mixture and subjected to column chromatography to obtain the azoarene-based Phth-protected unnatural amino acid derivative.

General procedure for the phthalimide deprotection and synthesis of azobenzene-based free amino ester derivatives: To an appropriate Phth-protected amino acid derivative (0.05–0.156 mmol, 1 equiv) in *t*-BuOH (1-2 mL), ethylenediamine (10 equiv) was added. The reaction mixture was stirred at rt for 24 h and then, the solvent was removed under reduced pressure. The resultant reaction mixture was diluted with EtOAc (5-7 mL) and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude reaction mixture was purified by column chromatography to afford the corresponding azobenzene-based Phth-deprotected amino acid carboxylate derivative.

A typical procedure for the construction of azobenzene-based pyrrolidone derivative:

A solution ofazobenzene-based *N*-phthaloyl GABA ester derivative (0.13-0.15 mmol, 1 equiv), N_2H_4-H_2O (40 equiv) and ethanol (2 mL) were added to a screw-cap seal tube. The tube was sealed and submerged into an oil bath preheated to 95 ^oC. After 6 h, the solution was cooled to rt and then, the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water. Then, the combined organic layers were dried over anhydrous Na_2SO_4. Next, the solvent was evaporated to afford a crude reaction

mixture, which was purified by column chromatography to furnish the corresponding azobenzene-based pyrrolidone derivative ((*E*)-4-(4-(phenyldiazenyl)phenyl)pyrrolidin-2-one).

Typical procedure for the synthesis of (*E*)-4-amino-3-(4-(phenyldiazenyl)phenyl)butanoic acid: A solution of (*E*)-4-(4-(phenyldiazenyl)phenyl)pyrrolidin-2-one (0.15 mmol) in 6 M HCl (2 mL) was refluxed for 16 h. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and after that, it was triturated with isopropanol to obtain (*E*)-4-amino-3-(4-(phenyldiazenyl)phenyl)butanoic acid.

Procedure for the synthesis of azobenzene-based dipeptide derivatives *via* amide formation reaction: A solution of corresponding azobenzene-based N-Phth-deprotected amino acid carboxylate derivative (0.05-0.08 mmol) in dry DCM was cooled to 0 ^{o}C in an ice bath. After 5 minutes *N*,*N*-dimethylglycine (1 equiv) and HOBt (1.2 equiv) were added, and then DCC (1.2 equiv) was added to the reaction mixture. The reaction mixture was stirred at 0 ^{o}C for 30 minutes and after that ice bath was removed and the reaction mixture was stirred at rt for 24 h under a nitrogen atmosphere. Then, the mixture was diluted with DCM (2-8 mL) and washed with water and saturated aqueous $NaHCO_3$ solution, the organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatography to obtain the corresponding azobenzene-based dipeptide derivative.

General procedure for the Pd(II)-catalyzed, stereoselective sp^3 C-H arylation of dipeptide carboxamide with iodoazobenzene:A mixture of Val-Pro-based dipeptide carboxamide(0.1mmol, 1 equiv), (*E*)-1-(4-ethylphenyl)-2-(4-iodophenyl)diazene(5 equiv),$Pd(OAc)_2$ (10 mol%), AgOAc (2.5 equiv), $(BnO)_2PO_2H$ (20 mol%) and toluene (2 mL) were added to screw-cap sealed tube and after purging nitrogen the tube was heated at 130 ^{o}C for 24 h. After the reaction period, the solvent was evaporated to afford a crude reaction mixture, which was purified by column chromatography on silica gelto obtain the corresponding azobenzene installed dipeptide carboxamide.

Brief crystal data of compound **6c**-(*DL*)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) iiserm-rt869

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

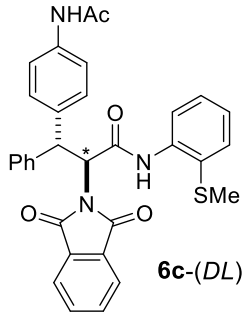
No syntax errors found. CIF dictionary Interpreting this report

Datablock: iiserm-rt869

```
Bond precision:   C-C = 0.0033 A          Wavelength=0.71073

Cell:             a=20.4643(6)     b=8.6783(2)         c=15.5406(5)
                  alpha=90         beta=91.069(3)      gamma=90
Temperature:      293 K
```

	Calculated	Reported
Volume	2759.46(14)	2759.45(14)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C32 H27 N3 O4 S	C32 H27 N3 O4 S
Sum formula	C32 H27 N3 O4 S	C32 H27 N3 O4 S
Mr	549.63	549.62
Dx,g cm-3	1.323	1.323
Z	4	4
Mu (mm-1)	0.160	0.160
F000	1152.0	1152.0
F000'	1152.98	
h,k,lmax	25,10,19	25,10,19
Nref	5649	5639
Tmin,Tmax	0.997,0.998	0.795,1.000
Tmin'	0.997	



6c-(*DL*)

```
Correction method= # Reported T Limits: Tmin=0.795 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.998           Theta(max)= 26.372

R(reflections)= 0.0505( 3418)                    wR2(reflections)=
                                                 0.1368( 5639)
S = 1.079                 Npar= 363
```

Brief crystal data of compound **8a**-(*DL*)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) iiserm-928

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

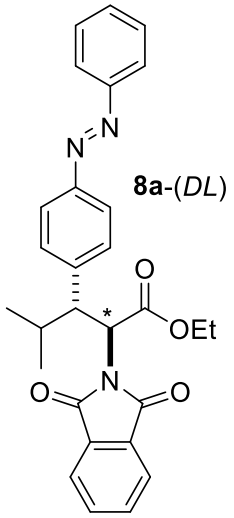
No syntax errors found. CIF dictionary Interpreting this report

Datablock: iiserm-928

Bond precision: C-C = 0.0050 A Wavelength=0.71073

Cell: a=13.6279(11) b=14.2193(12) c=14.7408(11)
alpha=69.902(7) beta=75.360(7) gamma=67.226(8)
Temperature: 160 K

	Calculated	Reported
Volume	2449.6(4)	2449.6(4)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C28 H27 N3 O4	2(C28 H27 N3 O4)
Sum formula	C28 H27 N3 O4	C56 H54 N6 O8
Mr	469.53	939.05
Dx,g cm-3	1.273	1.273
Z	4	2
Mu (mm-1)	0.086	0.086
F000	992.0	992.0
F000'	992.44	
h,k,lmax	17,17,18	17,17,18
Nref	10017	9969
Tmin,Tmax	0.997,0.998	0.577,1.000
Tmin'	0.997	



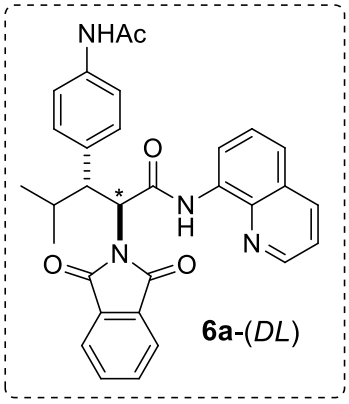
8a-(*DL*)

Correction method= # Reported T Limits: Tmin=0.577 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.995 Theta(max)= 26.372

R(reflections)= 0.0804(5099) wR2(reflections)= 0.2531(9969)

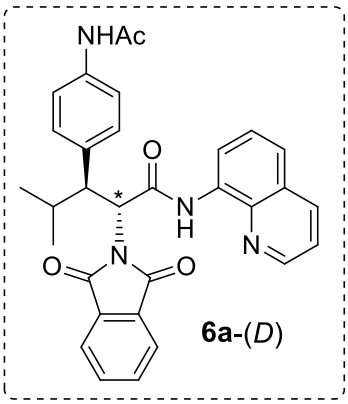
S = 1.066 Npar= 657



(2*S,3*R**)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methyl-*N*-(quinolin-8-yl)pentanamide (6a-(*DL*)):** The compound **6a**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (338 mg, 81%, 0.8 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 192-194 ^oC; IR (DCM): 3334, 1714, 1526, 1382, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.20 (1H, br. s), 8.77 (1H, d, J = 3.1Hz), 8.53 (1H, d, J = 7.4Hz), 8.06 (1H, d, J = 8.3 Hz), 7.93 (2H, dd, J_1 = 5.3, J_2 = 3.1Hz), 7.77 (2H, dd, J_1 = 5.4, J_2 = 3.0Hz), 7.51 (2H, d, J = 8.3Hz), 7.43-7.34 (6H, m), 5.63 (1H, d, J = 12.4Hz), 4.26 (1H, dd, J_1 = 12.5, J_2 = 3.1Hz), 2.16 (3H, s), 2.02-1.95 (1H, m), 0.83 (3H, d, J = 6.8Hz), 0.79 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, ~101 MHz, $CDCl_3$): δ_C 168.7, 168.5, 166.4, 148.3, 138.5, 137.6, 135.9, 134.4, 134.0, 131.7, 130.5, 130.5, 127.7, 127.0, 123.8, 122.0, 121.6, 119.5, 116.8, 58.1, 47.9, 29.0, 24.6, 21.5, 16.3; HRMS (ESI) calcd for $C_{31}H_{28}N_4NaO_4$ $[M+Na]^+$ 543.2008 found 543.1984.

The HPLC of compound **6a**-(*DL*) was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 45:55, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.40 min, t_L= 14.00 min.

(2*R*,3*S*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methyl-*N*-(quinolin-8 yl)pentanamide (6a-(*D*)): The compound **6a**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (259 mg, 62%, 0.8 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 192-194 ^oC; IR (DCM): 2965, 1715, 1526, 1264, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.20 (1H, br. s), 8.77 (1H, dd, J_1 = 4.2, J_2 = 1.6Hz), 8.53 (1H, dd, J_1 = 7.5, J_2 = 1.2Hz), 8.06 (1H, dd, J_1 = 8.3, J_2 = 1.4Hz), 7.93 (2H, dd, J_1 = 5.4, J_2 = 3.0Hz), 7.77 (2H, dd, J_1 = 5.5, J_2 = 3.0Hz), 7.52 (2H, d, J = 8.5Hz), 7.44-7.34 (6H, m), 5.63 (1H, d, J = 12.4Hz), 4.26 (1H, dd, J_1 = 12.4, J_2 = 3.3Hz), 2.16 (3H, s), 2.03-1.95 (1H, m), 0.83 (3H, d, J = 6.8Hz), 0.79 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 168.5, 166.4, 148.3, 138.5, 137.6, 135.9, 134.4,

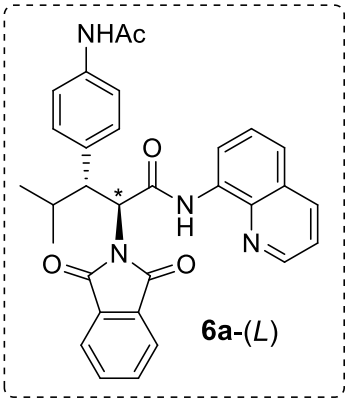


134.0, 131.7, 130.4, 130.4, 127.7, 126.9, 123.8, 122.0, 121.6, 119.5, 116.8, 58.0, 47.9, 29.0, 24.6, 21.5, 16.3; HRMS (ESI) calcd for $C_{31}H_{29}N_4O_4$ $[M+H]^+$ 521.2189 found 521.2205.

$[\alpha]^{25}_D$= 23.6 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 95:5) of compound **6a**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 45:55, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.49 min, t_L= 14.14 min.

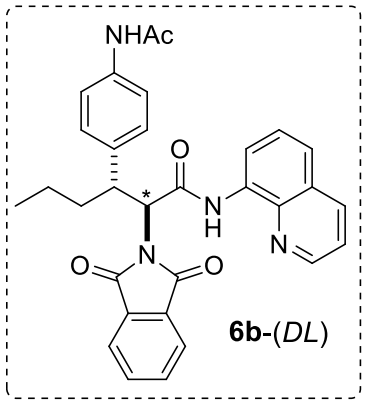
(2*S*,3*R*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methyl-*N*-(quinolin-8-yl)pentanamide (6a-(*L*)): The compound **6a**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (71 mg, 68%, 0.2 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 192-194 °C; IR (DCM): 3297, 1714, 1525, 1383, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.21 (1H, br. s), 8.77 (1H, d, *J* = 4.2Hz), 8.53 (1H, d, *J* = 7.5Hz), 8.06 (1H, d, *J* = 8.2 Hz), 7.94-7.92 (2H, m), 7.78-7.76 (2H, m), 7.55-7.50 (3H, m), 7.42-7.33 (5H, m), 5.63 (1H, d, *J* = 12.4Hz), 4.26 (1H, dd, J_1 = 12.4, J_2 = 2.8Hz), 2.16 (3H, s), 2.02-1.95 (1H, m), 0.82 (3H, d, *J* = 6.8Hz), 0.78 (3H, d, *J* = 6.7Hz); ^{13}C NMR (~101 MHz, ~101 MHz, $CDCl_3$): δ_C 168.6, 168.5, 166.4, 148.3, 138.5, 137.5, 135.9, 134.4, 134.1, 131.8, 131.8, 130.5, 127.7, 127.0, 123.8, 122.0, 121.6, 119.5, 116.8, 58.0, 47.9, 29.0, 24.6, 21.5, 16.3; HRMS (ESI) calcd for $C_{31}H_{29}N_4O_4$ $[M+H]^+$ 521.2189 found 521.2213.



$[\alpha]^{25}_D$= -22.4 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 98:2) of compound **6a**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 45:55, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.47 min, t_L= 13.99 min.

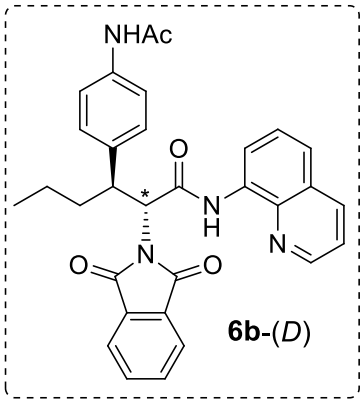
(2*S,3*R**)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (6b-(*DL*)):**The compound **6b**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colorless solid (77 mg, 74%, 0.2 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 226-228 °C; IR (DCM): 2926, 1715, 1530, 1383, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.16 (1H, br. s), 8.77 (1H, d, *J* = 3.9Hz), 8.53 (1H, d, *J* = 7.5Hz), 8.06 (1H, d, *J* = 8.2 Hz), 7.92 (2H, dd, J_1= 4.9, J_2= 3.4 Hz), 7.83 (1H, br. s), 7.76 (2H, dd, J_1= 5.1, J_2=



3.5 Hz), 7.42 (2H, d, *J* = 8.2Hz), 7.42-7.34 (5H, m), 5.30 (1H, d, *J* = 11.7Hz), 4.22-4.15 (1H, m), 2.11 (3H, s), 1.60-1.54 (2H, m), 1.13-1.03 (2H, m), 0.77 (3H, t, *J* = 7.3Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 168.4, 166.2, 148.3, 138.5, 137.4, 136.0, 135.8, 134.4, 133.9, 131.7, 129.1, 127.7, 127.0, 123.8, 122.0, 121.6, 120.1, 116.8, 61.3, 43.3, 35.2, 24.5, 19.8, 13.9; HRMS (ESI) calcd for $C_{31}H_{29}N_4O_4$ $[M+H]^+$ 521.2189 found 521.2205.

The HPLC of compound **6b**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50 flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.99 min, t_L= 19.29 min.

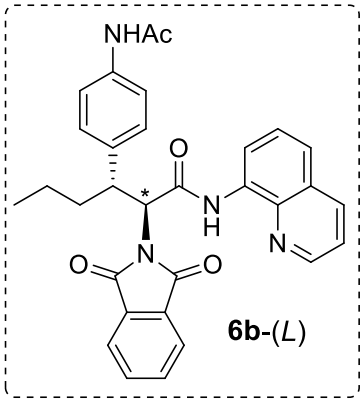
(2*R*,3*S*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (6b-(*D*)): The compound **6b**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colorless solid (180 mg, 67%, 0.52 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 220-222 ^{o}C; IR (DCM): 2959, 1713, 1520, 1381, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.14 (1H, br. s), 8.76 (1H, d, *J* = 4.0Hz), 8.53 (1H, d, *J* = 7.4Hz), 8.06 (1H, d, *J* = 8.2 Hz), 7.93 (2H, dd, J_1= 5.0, J_2= 3.3 Hz), 7.77 (2H, dd, J_1= 5.3, J_2= 3.2 Hz), 7.73 (1H, br. s), 7.46-7.34 (7H, m), 5.29 (1H, d, *J* = 11.7Hz), 4.22-4.15 (1H, m), 2.12 (3H, s), 1.61-1.55 (2H, m), 1.13-1.03 (2H, m), 0.77 (3H, t, *J* = 7.3Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 168.3, 166.1, 148.3, 138.5, 137.3, 136.0, 135.8, 134.4, 133.9, 131.7, 129.1, 127.7, 127.0, 123.8, 122.0, 121.6, 120.1, 116.8, 61.3, 43.3, 35.2, 24.5, 19.8, 13.8; HRMS (ESI) calcd for $C_{31}H_{29}N_4O_4$ $[M+H]^+$ 521.2189 found 521.2184.



$[\alpha]^{25}_D$= -5.2 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 98:2) of compound **6b**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 13.12 min, t_L= 18.94 min.

(2*S*,3*R*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (6b-(*L*)): The compound **6b**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colorless solid (164 mg, 61%, 0.52 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 227-229 ^{o}C; IR (DCM): 2947, 1713, 1525, 1381, 717 cm^{-1}; ^{1}H NMR

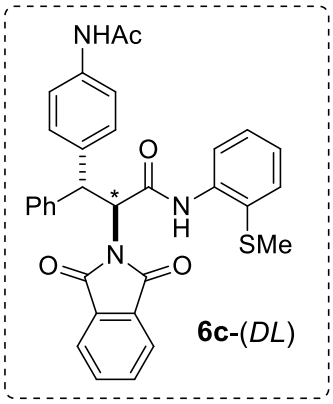


(400 MHz, $CDCl_3$): δ_H 10.16 (1H, br. s), 8.76 (1H, d, J = 3.9Hz), 8.52 (1H, d, J = 7.5Hz), 8.06 (1H, d, J = 8.2 Hz), 7.92 (2H, dd, J_1= 5.2, J_2= 3.3 Hz), 7.85 (1H, br. s), 7.76 (2H, dd, J_1= 5.2, J_2= 3.2 Hz), 7.46-7.34 (7H, m), 5.29 (1H, d, J = 11.7Hz), 4.22-4.15 (1H, m), 2.11 (3H, s), 1.60-1.55 (2H, m), 1.11-1.03 (2H, m), 0.77 (3H, t, J = 7.3Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 168.3, 166.2, 148.3, 138.5, 137.4, 136.0, 135.8, 134.4, 133.9, 131.7, 129.0, 127.7, 127.0, 123.8, 122.0, 121.6, 120.1, 116.8, 61.3, 43.3, 35.2, 24.5, 19.8, 13.9; HRMS (ESI) calcd for $C_{31}H_{29}N_4O_4$ $[M+H]^+$ 521.2189 found 521.2186.

$[\alpha]^{25}_D$= 10.4 (c = 0.05 g/100 mL, $CHCl_3$).

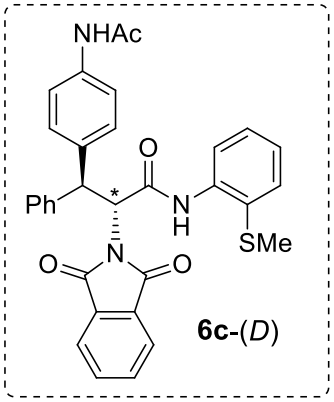
The enantiomeric ratio (*er* = 96:4) of compound **6b**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 13.05 min, t_L= 19.18 min.

(2*S,3*R**)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(methylthio)phenyl)-3-phenylpropanamide (6c-(*DL*)):** The compound **6c**-(*DL*)was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a colorless solid (60 mg, 73%, 0.15 mmol scale); R_f(60% EtOAc/hexane) 0.3; mp: 150-152 ^{o}C; IR (DCM): 2924, 1714, 1515, 1384, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.91 (1H, s), 9.47 (1H, s), 7.79-7.78 (4H, m), 7.53-7.47 (4H, m), 7.28-7.22 (3H, m), 7.19-7.08 (5H, m), 7.00 (1H, t, J = 7.2Hz), 5.80 (1H, d, J = 11.9Hz), 5.32 (1H, d, J = 11.8Hz), 2.28 (3H, s), 2.02 (3H, s); ^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 168.6, 167.6, 166.4, 141.6, 138.3, 136.5, 135.4, 135.2, 133.7, 131.2, 128.8, 128.6, 128.3, 127.6, 127.1, 127.0, 126.1, 125.9, 123.6, 119.7, 56.7, 49.5, 24.4, 15.8; HRMS (ESI) calcd for $C_{32}H_{28}N_3O_4S$ $[M+H]^+$ 550.1801 found 550.1778.



The HPLC of compound **6c**-(*DL*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D =23.28 min, t_L= 28.49 min.

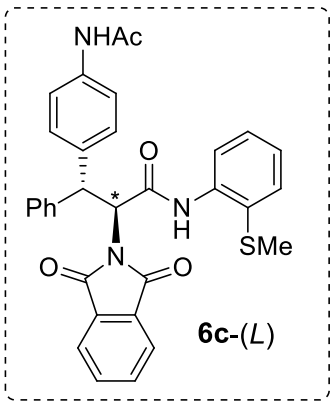
(2*R*,3*S*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(methylthio)phenyl)-3-phenylpropanamide (6c-(*D*))*:* The compound **6c**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a colorless solid (238 mg, 88%, 0.58 mmol scale); R_f(60% EtOAc/hexane) 0.3; mp: 150-152 ^oC; IR (DCM): 2922, 1713, 1514, 1382, 717 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.92 (1H, br. s), 9.46 (1H, br. s), 7.81-7.75 (4H, m), 7.53-7.47 (4H, m), 7.27-7.22 (3H, m), 7.18-7.08 (5H, m), 6.99 (1H, t, J = 7.2Hz), 5.80 (1H, d, J = 11.9Hz), 5.32 (1H, d, J = 11.9Hz), 2.27 (3H, s), 2.01 (3H, s); ^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 168.7, 167.6, 166.4, 141.6, 138.3, 136.5, 135.4, 135.2, 133.7, 131.2, 128.8, 128.6, 128.3, 127.6, 127.1, 127.0, 126.1, 125.9, 123.6, 119.7, 56.7, 49.5, 24.4, 15.7; HRMS (ESI) calcd for $C_{32}H_{27}N_3NaO_4S$ $[M+Na]^+$ 572.1620 found 572.1628.



$[\alpha]^{25}_D$= 40.0 (c = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 98:2) of compound **6c**-(*D*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 22.89 min, t_L= 29.61 min.

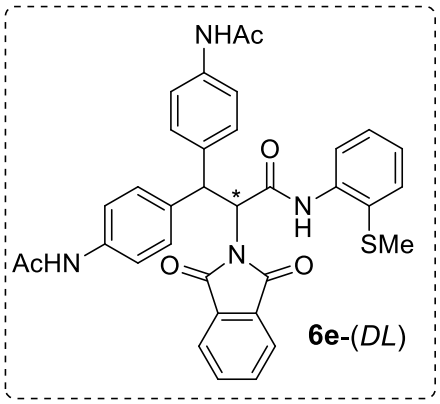
(2*S*,3*R*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(methylthio)phenyl)-3-phenylpropanamide (6c-(*L*))*:* The compound **6c**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a colorless solid (233 mg, 85%, 0.5 mmol scale); R_f(60% EtOAc/hexane) 0.3; mp: 150-152 ^oC; IR (DCM): 2923, 1713, 1514, 1382, 717 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 9.91 (1H, br. s), 9.46 (1H, br. s), 7.81-7.76 (4H, m), 7.53-7.47 (4H, m), 7.27-7.22 (3H, m), 7.18-7.08 (5H, m), 6.99 (1H, t, J = 7.2Hz), 5.79 (1H, d, J = 11.9Hz), 5.32 (1H, d, J = 11.9Hz), 2.27 (3H, s), 2.01 (3H, s); ^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 168.6, 167.6, 166.4, 141.6, 138.3, 136.5, 135.4, 135.2, 133.6, 131.2, 128.8, 128.6, 128.3, 127.6, 127.1, 126.9, 126.1, 125.9, 123.6, 119.7, 56.7, 49.5, 24.4, 15.8; HRMS (ESI) calcd for $C_{32}H_{27}N_3NaO_4S$ $[M+Na]^+$ 572.1620 found 572.1615.



$[\alpha]^{25}_D$= -48.0 (c = 0.05 g/100 mL, $CHCl_3$).

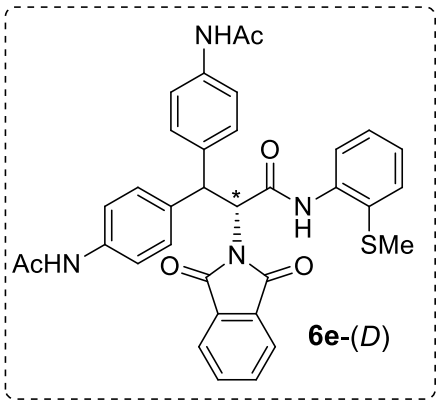
The enantiomeric ratio (*er* = 96:4) of compound **6c**-(*L*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 24.36 min, t_L= 28.36 min.

N,N'*-((2-(1,3-Dioxoisoindolin-2-yl)-3-((2-(methylthio)phenyl)amino)-3-oxopropane-1,1-diyl)bis(4,1-phenylene))diacetamide (6e-(*DL*)*: The compound **6e**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 95:05) as a colorless solid (96 mg, 78%, 0.2 mmol scale); R_f(100% EtOAc) 0.2; mp: 172-174 ^oC; IR (DCM): 2924, 1714, 1512, 1371, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ_H 9.89 (1H, br. s), 9.74 (1H, br. s), 9.42 (1H, br. s), 7.83-7.78 (4H, m), 7.51-7.44 (4H, m), 7.32-7.26 (3H, m), 7.18-7.07 (5H, m), 5.74 (1H, d, *J* = 12.0Hz), 5.26 (1H, d, *J* = 11.9Hz), 2.27 (3H, s), 2.01 (3H, s), 1.92 (3H, s); ^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 168.7, 168.6, 167.6, 166.4, 138.3, 138.2, 136.6, 136.1, 135.4, 135.2, 133.5, 131.2, 128.6, 128.5, 127.7, 126.9, 125.9, 123.7, 119.7, 119.2, 57.0, 48.9, 24.4, 24.3, 15.8; HRMS (ESI) calcd for $C_{34}H_{31}N_4O_5S$ $[M+H]^+$ 607.2015 found 607.2040.



The HPLC of compound **6e**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 46.38 min, t_L= 64.69 min.

(*R*)-*N,N'*-((2-(1,3-Dioxoisoindolin-2-yl)-3-((2-(methylthio)phenyl)amino)-3-oxopropane-1,1-diyl)bis(4,1-phenylene))diacetamide (6e-(*D*)): The compound **6e**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 95:05) as a colorless solid (350 mg, 78%, 0.9 mmol scale); R_f(100% EtOAc) 0.2; mp: 172-174 ^oC; IR (DCM): 2919, 1713, 1508, 1383, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ_H 9.89 (1H, br. s), 9.74 (1H, br. s), 9.42 (1H, br. s), 7.83-7.78 (4H, m), 7.51-7.44 (4H, m), 7.32-7.26 (3H, m), 7.18-7.07 (5H, m), 5.73 (1H, d, *J* = 12.0 Hz), 5.25 (1H, d, *J* = 11.9 Hz), 2.27 (3H, s), 2.01 (3H, s), 1.92 (3H, s); ^{13}C NMR (~126 MHz, DMSO-d_6): δ_C 168.7, 168.6, 167.6, 166.3, 138.3, 138.2, 136.6,

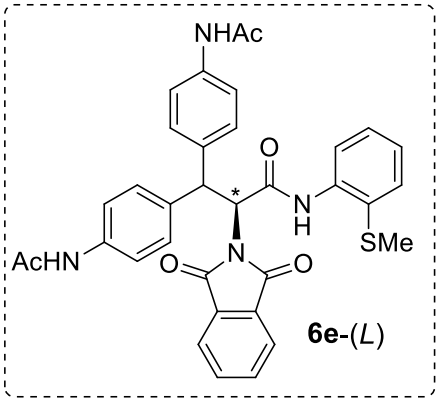


136.1, 135.5, 135.2, 133.3, 131.2, 128.6, 128.5, 127.9, 126.9, 126.0, 125.9, 123.7, 119.7, 119.3, 57.0, 48.9, 24.4, 24.3, 15.9; HRMS (ESI) calcd for $C_{34}H_{30}N_4NaO_5S$ $[M+Na]^+$ 629.1835 found 629.1812.

$[\alpha]^{25}_D$= 53.2 (*c* = 0.04 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 99:1) of compound **6e**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 46.59 min, t_L= 67.38 min.

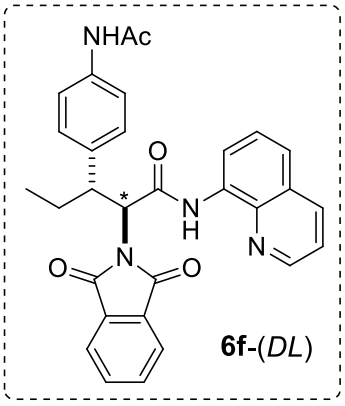
(*S*)-*N*,*N'*-((2-(1,3-Dioxoisoindolin-2-yl)-3-((2-(methylthio)phenyl)amino)-3-oxopropane-1,1-diyl)bis(4,1-phenylene))diacetamide (6e-(*L*)): The compound **6e**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:MeOH = 95:05) as a colorless solid (215 mg, 50%, 0.7 mmol scale); R_f(100% EtOAc) 0.2; mp: 172-174 ^oC; IR (DCM): 2923, 1710, 1511, 1267, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ_H 9.89 (1H, br. s), 9.74 (1H, br. s), 9.42 (1H, br. s), 7.83-7.77 (4H, m), 7.51-7.44 (4H, m), 7.32-7.26 (3H, m), 7.18-7.07 (5H, m), 5.73 (1H, d, *J* = 11.9 Hz), 5.25 (1H, d, *J* = 11.9 Hz), 2.27 (3H, s), 2.01 (3H, s), 1.92 (3H, s); ^{13}C NMR (~126 MHz, DMSO-d_6): δ_C 168.6, 168.6, 167.6, 166.3, 138.3, 138.2, 136.6, 136.1, 135.5, 135.2, 133.3, 131.2, 128.6, 128.5, 127.9, 126.9, 126.0, 125.9, 123.7, 119.7, 119.2, 57.0, 48.9, 24.4, 24.3, 15.9; HRMS (ESI) calcd for $C_{34}H_{30}N_4NaO_5S$ $[M+Na]^+$ 629.1835 found 629.1808.



$[\alpha]^{25}_D$= -53.0 (*c* = 0.04 g/100 mL, $CHCl_3$).

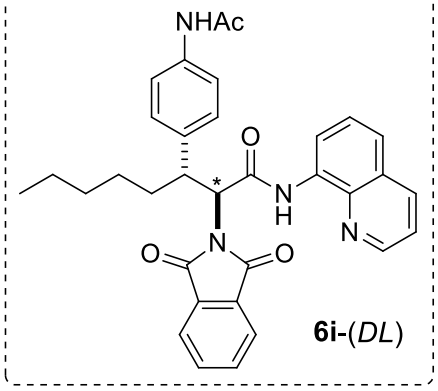
The enantiomeric ratio (*er* = 96:4) of compound **6e**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 48.61 min, t_L= 64.87 min.

(2*S,3*R**)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (6f-(*DL*)):** The compound **6f**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a colorless solid (74 mg, 73%, 0.2 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 203-205 ^oC; IR (DCM): 3301, 1713, 1525, 1381, 718 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ_H 10.20 (1H, br. s), 8.76 (1H, d, *J* = 4.1Hz), 8.53 (1H, d, *J* = 7.5Hz), 8.05 (1H, d, *J* = 8.2 Hz), 7.97 (1H, br. s), 7.91 (2H, dd, J_1 = 4.9, J_2= 3.3 Hz), 7.75

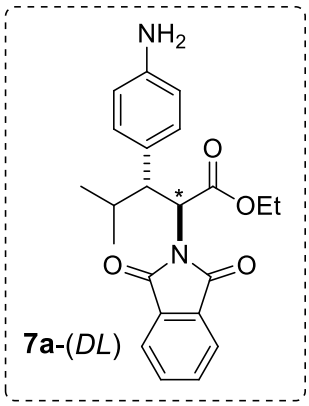


(2H, dd, J_1= 5.1, J_2= 3.4 Hz), 7.47 (2H, d, J = 8.2Hz), 7.42-7.33 (5H, m), 5.32 (1H, d, J = 11.7Hz), 4.07 (1H, td, J_1= 11.4, J_2= 3.1 Hz), 2.11 (3H, s), 1.77-1.69 (1H, m), 1.60-1.49 (1H, m), 0.69 (3H, t, J = 7.2Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 168.4, 166.2, 148.3, 138.5, 137.5, 136.0, 135.3, 134.4, 133.9, 131.7, 129.1, 127.7, 127.0, 123.8, 122.0, 121.6, 120.1, 116.8, 61.1, 45.1, 26.2, 24.6, 11.2; HRMS (ESI) calcd for $C_{30}H_{27}N_4O_4$ $[M+H]^+$ 507.2032 found 507.2008.

(2*S,3*R**)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (6i-(*DL*)):** The compound **6i**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a grey colored solid (395 mg, 90%, 0.8 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 178-180 ^{o}C; IR (DCM): 2928, 1714, 1525, 1322, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.16 (1H, br. s),8.77 (1H, dd, J_1= 4.2, J_2= 1.0 Hz), 8.52 (1H, d, J = 7.4 Hz), 8.06 (1H, d, J = 8.2 Hz), 7.92 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.77-7.75 (3H, m), 7.46 (2H, d, J = 8.3 Hz), 7.42-7.34 (5H, m), 5.29 (1H, d, J = 11.6Hz), 4.17 (1H, td, J_1= 10.8, J_2= 4.6 Hz),2.11 (3H, s), 1.64-1.55 (2H, m), 1.18-1.01 (6H, m), 0.75 (3H, t, J = 6.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 168.4, 166.2, 148.3, 138.5, 137.3, 136.0, 135.8, 134.4, 133.9, 131.7, 129.1, 127.7, 127.0, 123.8, 122.0, 121.6, 120.1, 116.8, 61.4, 43.5, 33.1, 31.6, 26.3, 24.5, 22.5, 14.0; HRMS (ESI) calcd for $C_{33}H_{33}N_4O_4$ $[M+H]^+$ 549.2502 found 549.2487.

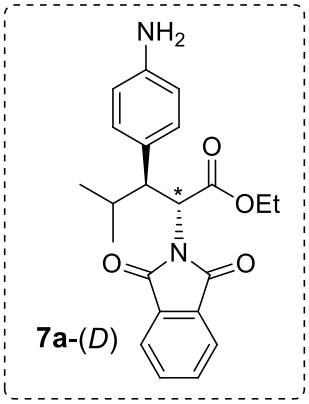


(2*S,3*R**)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoate (7a-(*DL*)):** The compound **7a**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (41 mg, 54%, 0.2 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 88-90 ^{o}C; IR (DCM): 2963, 1712, 1516, 1383, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.78 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.10 (2H, d, J = 8.4Hz), 6.68 (2H, d, J = 8.4Hz), 5.32 (1H, d, J = 11.7Hz), 3.98-3.93 (2H, m), 3.82 (1H, dd, J_1= 11.8, J_2= 3.9 Hz), 3.64-3.62 (2H, m), 1.89-



1.81 (1H, m), 0.97 (3H, t, J = 7.1 Hz), 0.77 (3H, d, J = 6.8 Hz), 0.76 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 167.9, 145.0, 134.3, 131.8, 130.6, 127.8, 123.6, 114.7, 61.3, 54.9, 48.2, 28.6, 21.5, 16.9, 13.8; HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$ 403.1634 found 403.1625.

(2*R*,3*S*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoate (7a-(*D*)):

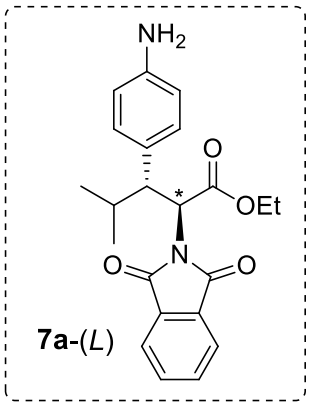


The compound **7a**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (32 mg, 54%, 0.154 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 88-90 ^{o}C; IR (DCM): 2961, 1712, 1516, 1383, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.78 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.10 (2H, d, J = 8.4Hz), 6.68 (2H, d, J = 8.4Hz), 5.32 (1H, d, J = 11.7Hz), 3.98-3.93 (2H, m), 3.82 (1H, dd, J_1= 11.7, J_2= 3.8 Hz), 3.63-3.61 (2H, m), 1.89-1.81 (1H, m), 0.97 (3H, t, J = 7.1Hz), 0.77 (3H, d, J = 6.8Hz), 0.76 (3H, d, J = 6.89Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 167.9, 145.0, 134.3, 131.8, 130.6, 127.8, 123.6, 114.7, 61.2, 54.9, 48.2, 28.6, 21.5, 16.9, 13.8; HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$ 403.1634 found 403.1616.

$[\alpha]^{25}_D$= -39.2 (c = 0.05 g/100 mL, $CHCl_3$).

The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and indirectly ascertained from the product obtained in the next step.

(2*S*,3*R*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoate (7a-(*L*)):



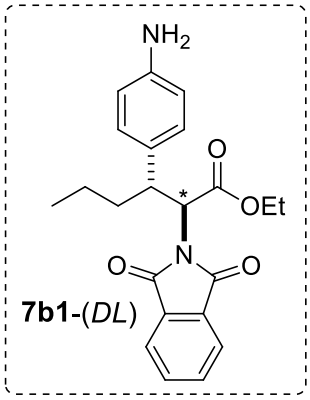
The compound **7a**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (40 mg, 53%, 0.2 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 88-90 ^{o}C; IR (DCM): 2964, 1713, 1517, 1384, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.78 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.10 (2H, d, J = 8.4Hz), 6.68 (2H, d, J = 8.4Hz), 5.33 (1H, d, J = 11.7Hz), 3.98-3.93 (2H, m), 3.82 (1H, dd, J_1= 11.7, J_2= 3.8 Hz), 3.63-3.62 (2H, m), 1.89-1.81 (1H, m), 0.97 (3H, t, J

= 7.1Hz), 0.77 (3H, d, *J* = 6.80Hz), 0.76 (3H, d, *J* = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 167.9, 145.0, 134.3, 131.8, 130.6, 127.8, 123.6, 114.7, 61.3, 54.9, 48.2, 28.6, 21.5, 16.9, 13.8; HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$ 403.1634 found 403.1650.

$[\alpha]^{25}_D$= 36.4 (*c* = 0.05 g/100 mL, $CHCl_3$).

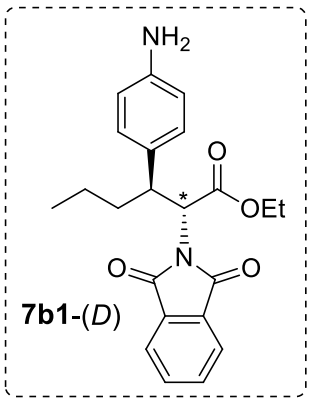
The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and indirectly ascertained from the product obtained in the next step.

(2*S,3*R**)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)hexanoate (7b1-(*DL*))*:*** The compound **7b1**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (33 mg, 43%, 0.2 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 72-74 °C; IR (DCM): 2958, 1712, 1384, 1180, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.78 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.12 (2H, d, *J* = 8.4Hz), 6.67 (2H, d, *J* = 8.4Hz), 5.01 (1H, d, *J* = 10.2Hz), 4.05-3.97 (2H, m), 3.77-3.64 (3H, m), 1.53-1.41 (2H, m), 1.08-1.01 (2H, m), 1.04 (3H, t, *J* = 7.1Hz), 0.74 (3H, t, *J* = 7.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.8, 145.0, 134.3, 131.7, 131.4, 129.4, 123.6, 115.2, 61.3, 57.7, 43.4, 34.3, 20.0, 13.9, 13.8; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_4$ $[M+H]^+$ 381.1814 found 381.1829.



The HPLC of compound **7b1**-(*DL*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 32.14 min, t_L= 35.93 min.

(2*R*,3*S*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)hexanoate (7b1-(*D*))*:* The compound **7b1**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (38 mg, 45%, 0.22 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 80-82 °C; IR (DCM): 2925, 1714, 1385, 1181, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.78 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.13 (2H, d, *J* = 8.4Hz), 6.67 (2H, d, *J* = 8.4Hz), 5.01 (1H, d, *J* = 10.2Hz), 4.05-3.97 (2H, m), 3.77-3.64 (3H, m), 1.51-1.43 (2H, m), 1.08-1.01 (2H, m), 1.04 (3H, t, *J* = 7.2Hz),

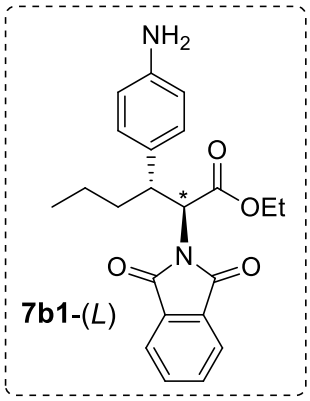


0.75 (3H, t, J = 7.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.7, 144.9, 134.2, 131.7, 131.4, 129.3, 123.6, 115.2, 61.3, 57.6, 43.4, 34.3, 19.9, 13.8, 13.8; HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$ 403.1634 found 403.1647.

$[\alpha]^{25}_D$= 84.8 (c = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 95:5) of compound **7b1**-(*D*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 32.63 min, t_L= 36.37 min.

(2*S*,3*R*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)hexanoate (7b1-(*L*)): The

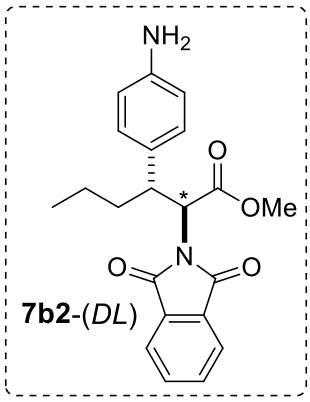


compound **7b1**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (48 mg, 45%, 0.28 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 75-77 °C; IR (DCM): 2959, 1712, 1384, 1180, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.78 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.13 (2H, d, J = 8.4Hz), 6.67 (2H, d, J = 8.3Hz), 5.02 (1H, d, J = 10.2Hz), 4.05-3.97 (2H, m), 3.77-3.66 (3H, m), 1.52-1.44 (2H, m), 1.08-1.02 (2H, m), 1.04 (3H, t, J = 7.2Hz), 0.75 (3H, t, J = 7.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.7, 144.9, 134.2, 131.7, 131.4, 129.3, 123.6, 115.2, 61.3, 57.6, 43.4, 34.3, 19.9, 13.8, 13.8; HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$ 403.1634 found 403.1647.

$[\alpha]^{25}_D$= -89.2 (c = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 98:2) of compound **7b1**-(*L*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 32.74 min, t_L= 36.44 min.

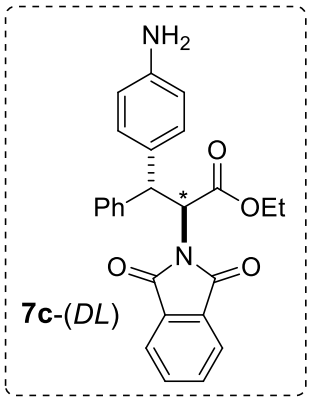
(2*S,3*R**)-Methyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)hexanoate (7b2-(*DL*)):** The



compound **7b2**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (51 mg, 52%, 0.26 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 74-76 °C; IR (DCM): 2955, 1712, 1516, 1384, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.79 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.13 (2H, d, J = 8.2Hz), 6.68 (2H, d, J = 8.2Hz), 5.03 (1H, d, J = 10.1Hz), 3.76-3.56 (3H, m), 3.55 (3H, s),

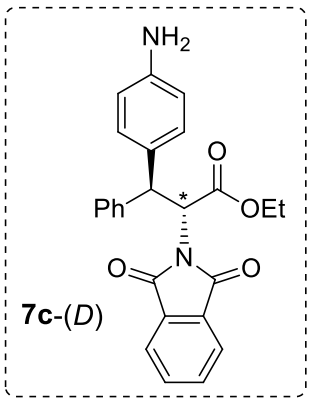
1.52-1.39 (2H, m), 1.09-0.98 (2H, m), 0.75 (3H, t, J = 7.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 169.0, 167.7, 145.0, 134.3, 131.7, 131.4, 129.3, 123.7, 115.3, 57.3, 52.3, 43.3, 34.2, 20.0, 13.8; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_4$ $[M+H]^+$ 367.1658 found 367.1643.

(2*S,3*R**)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (7c-(*DL*)):** The compound **7c**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (40 mg, 69%, 0.14 mmol scale); R_f(50% EtOAc/hexane) 0.4; mp: 188-190 ^{o}C; IR (DCM): 2928, 1712, 1384, 1263, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (2H, dd, J_1= 5.3, J_2= 3.1 Hz),7.64 (2H, dd, J_1= 5.3, J_2= 3.1 Hz),7.30 (2H, d, J = 8.4Hz), 7.25 (2H, t, J = 7.2Hz), 7.10 (2H, t, J = 7.6Hz), 6.99 (1H, t, J = 7.4Hz), 6.66 (2H, d, J = 8.2Hz), 5.67 (1H, d, J = 12.0Hz), 5.21 (1H, d, J = 12.0Hz), 4.09-4.03 (2H, m), 1.05 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 167.4, 145.2, 141.1, 134.0, 131.5, 131.3, 128.7, 128.4, 127.8, 126.6, 123.4, 115.4, 61.6, 55.5, 49.7, 13.9; HRMS (ESI) calcd for $C_{25}H_{22}N_2NaO_4$ $[M+Na]^+$ 437.1477 found 437.1487. (In the proton NMR spectrum the NH_2 signal appeared as a broad signal (3.88-3.77) and precise chemical shift value could not be ascertained).



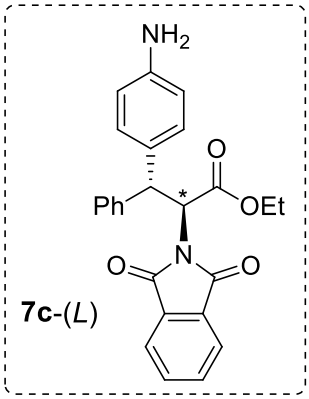
(2*R*,3*S*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (7c-(*D*)): The compound **7c**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (59 mg, 57%, 0.25 mmol scale); R_f(50% EtOAc/hexane) 0.4; mp: 188-190 ^{o}C; IR (DCM): 2928, 1712, 1516, 1384, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (2H, dd, J_1= 5.6, J_2= 3.0 Hz),7.64 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.30-7.24 (4H, m), 7.10 (2H, t, J = 7.8Hz), 6.99 (1H, tt, J_1= 7.4, J_2= 1.2 Hz), 6.66 (2H, td, J_1= 8.4, J_2= 2.7 Hz), 5.66 (1H, d, J = 12.0Hz), 5.21 (1H, d, J = 12.0Hz), 4.10-4.02 (2H, m), 3.61 (2H, br. s), 1.06 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 167.4, 145.2, 141.1, 134.0, 131.6, 131.4, 128.7, 128.4, 127.8, 126.6, 123.4, 115.4, 61.6, 55.5, 49.7, 13.9; HRMS (ESI) calcd for $C_{25}H_{22}N_2NaO_4$ $[M+Na]^+$ 437.1477 found 437.1491.

$[\alpha]^{25}_D$= 115.2 (c = 0.02 g/100 mL, $CHCl_3$).



The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and indirectly ascertained from the product obtained in the next step.

(2*S*,3*R*)-Ethyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (7c-(*L*)):

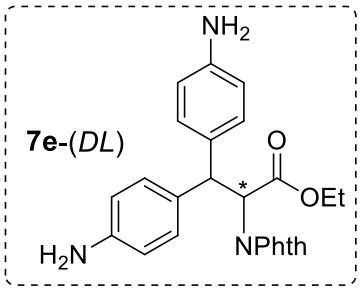


The compound **7c**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (40 mg, 69%, 0.14 mmol scale); R_f(50% EtOAc/hexane) 0.4; mp: 188-190 ^oC; IR (DCM): 2926, 1713, 1516, 1385, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (2H, dd, J_1= 5.6, J_2= 3.1 Hz), 7.65 (2H, dd, J_1= 5.5, J_2= 3.0 Hz), 7.30-7.24 (4H, m), 7.10 (2H, t, J = 7.8Hz), 6.99 (1H, tt, J_1= 7.4, J_2= 1.2 Hz), 6.66 (2H, td, J_1= 8.4, J_2= 2.7 Hz), 5.66 (1H, d, J = 12.0Hz), 5.21 (1H, d, J = 12.0Hz), 4.10-4.02 (2H, m), 3.60 (2H, br. s), 1.05 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 167.4, 145.2, 141.1, 134.0, 131.6, 131.3, 128.7, 128.4, 127.8, 126.6, 123.4, 115.4, 61.6, 55.5, 49.7, 13.9; HRMS (ESI) calcd for $C_{25}H_{22}N_2NaO_4$ $[M+Na]^+$ 437.1477 found 437.1480.

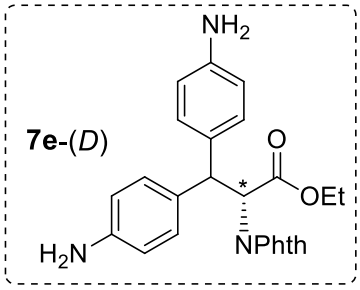
$[\alpha]^{25}_D$= -103.1 (c = 0.02 g/100 mL, $CHCl_3$).

The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and indirectly ascertained from the product obtained in the next step.

Ethyl 3,3-bis(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (7e-(*DL*)): The compound **7e**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a brown colored solid (37 mg, 43%, 0.2 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 90-92 ^oC; IR (DCM): 3376, 1710, 1513, 1384, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.64 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.23 (2H, d, J = 8.4Hz), 7.00 (2H, d, J = 8.4Hz), 6.63 (2H, d, J = 8.3Hz), 6.41 (2H, d, J = 8.4Hz), 5.56 (1H, d, J = 12.0Hz), 5.07 (1H, d, J = 12.0Hz), 4.06-3.98 (2H, m), 3.52-3.48 (4H, br. s), 1.02 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.5, 144.9, 144.7, 134.0, 132.3, 131.4, 131.2, 128.6, 128.6, 123.4, 115.4, 115.3, 61.5, 55.7, 48.9, 13.9; HRMS (ESI) calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$ 430.1767 found 430.1784.



(*R*)-Ethyl 3,3-bis(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (7e-(*D*))*:* The

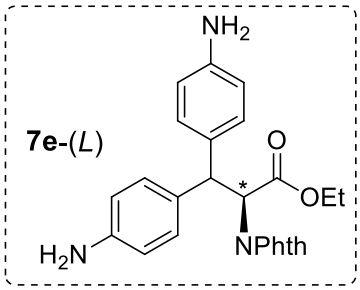


compound **7e**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a brown colored solid (57 mg, 58%, 0.23 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 90-92 ^{o}C; IR (DCM): 3372, 1711, 1513, 1382, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.66 (2H, dd, J_1= 5.6, J_2= 3.1 Hz),7.25 (2H, d, J = 8.4Hz), 7.02 (2H, d, J = 8.4Hz), 6.65 (2H, d, J = 8.4Hz), 6.43 (2H, d, J = 8.4Hz), 5.59 (1H, d, J = 12.0Hz), 5.09 (1H, d, J = 12.0Hz), 4.07-4.01 (2H, m), 3.52-3.51 (4H, br. s), 1.04 (3H, t, J = 7.1Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ_C 168.6, 167.5, 144.9, 144.7, 134.0, 132.3, 131.5, 131.2, 128.6, 128.6, 123.4, 115.4, 115.3, 61.5, 55.7, 48.9, 13.8; HRMS (ESI) calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$ 430.1767 found 430.1750.

$[\alpha]^{25}_D$= 77.2 (c = 0.05 g/100 mL, $CHCl_3$).

The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and indirectly ascertained from the product obtained in the next step.

(*S*)-Ethyl 3,3-bis(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (7e-(*L*))*:* The

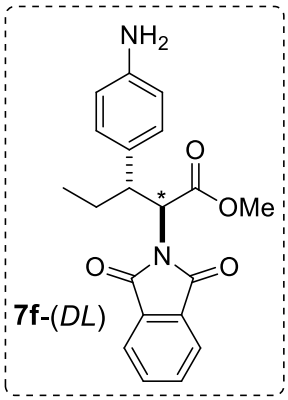


compound **7e**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30) as a brown colored solid (30 mg, 47%, 0.15 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 90-92 ^{o}C; IR (DCM): 3370, 1711, 1513, 1385, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.66 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.25 (2H, d, J = 8.4Hz), 7.02 (2H, d, J = 8.4Hz), 6.65 (2H, d, J = 8.4Hz), 6.43 (2H, d, J = 8.5Hz), 5.59 (1H, d, J = 12.0Hz), 5.09 (1H, d, J = 12.0Hz), 4.07-4.01 (2H, m), 3.52-3.50 (4H, br. s), 1.04 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.5, 145.0, 144.8, 134.0, 132.3, 131.4, 131.2, 128.6, 128.6, 123.4, 115.4, 115.3, 61.5, 55.7, 48.9, 13.8; HRMS (ESI) calcd for $C_{25}H_{23}N_3NaO_4$ $[M+Na]^+$ 452.1586 found 452.1582.

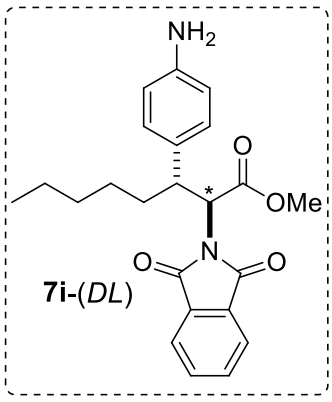
$[\alpha]^{25}_D$= -76.4 (c = 0.05 g/100 mL, $CHCl_3$).

The HPLC analysis profile for this compound could not be clearly ascertained for this compound and used as such in the next step and was indirectly ascertained from the product obtained in the next step.

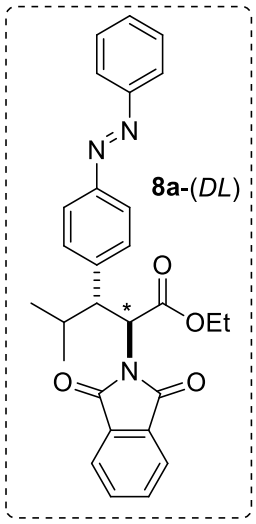
(2*S,3*R**)-Methyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)pentanoate (7f-(*DL*)):**The compound **7f**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored solid (49 mg, 18%, 0.75 mmol scale); R_f(30% EtOAc/hexane) 0.4; mp: 55-57 ^oC; IR (DCM): 2930, 1714, 1522, 1384, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, dd, J_1= 5.4, J_2= 3.1 Hz),7.78 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.13 (2H, d, J = 8.4Hz), 6.68 (2H, d, J = 8.4Hz), 5.05 (1H, d, J = 10.1Hz), 3.65-3.56 (1H, m), 3.56 (3H, s), 1.64-1.54 (1H, m), 1.51-1.43 (1H, m), 0.66 (3H, t, J = 7.3Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 169.0, 167.7, 145.0, 134.3, 131.7, 131.1, 129.4, 123.7, 115.3, 57.2, 52.3, 45.4, 25.1, 11.5; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4$ $[M+H]^+$ 353.1501 found 353.1497. (In the proton NMR spectrum the NH_2 signal could not be precisely ascertained).



(2*S,3*R**)-Methyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)octanoate (7i-(*DL*)):** The compound **7i**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a brown colored viscous liquid (23 mg, 29%, 0.28 mmol scale); R_f(30% EtOAc/hexane) 0.4; IR (DCM): 2929, 1713, 1517, 1384, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H7.92-7.90 (2H, m),7.79-7.77 (2H, m), 7.12 (2H, d, J = 7.9 Hz), 6.67 (2H, d, J = 7.8 Hz), 5.02 (1H, d, J = 10.0Hz), 3.75-3.55 (3H, m), 3.55 (3H, s), 1.52-1.46 (2H, m), 1.14-1.02 (6H, m), 0.75 (3H, t, J = 6.2Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 169.0, 167.7, 145.0, 134.3, 131.7, 131.4, 129.3, 123.7, 115.3, 57.4, 52.3, 43.7, 32.0, 31.6, 26.5, 22.5, 14.0; HRMS (ESI) calcd for $C_{23}H_{26}N_2NaO_4$ $[M+Na]^+$ 417.1790 found 417.1805. (In the proton NMR spectrum the NH_2 signal appeared as a broad signal (3.75-3.55) and precise chemical shift value could not be ascertained).

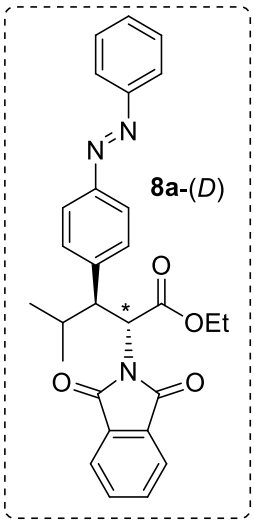


(2*S,3*R**)-Ethyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-4-methyl-3-(4-(phenyldiazenyl)phenyl)pentanoate (8a-(*DL*))*:*** The compound **8a**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (65 mg, 81%, 0.17 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 130-132 ºC; IR (DCM): 2964, 1715, 1384, 1258, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.91 (6H, m), 7.81 (2H, dd, J_1= 5.5, J_2= 3.1 Hz),7.57-7.48 (5H, m), 5.46 (1H, d, J = 11.7Hz), 4.03-3.94 (3H, m), 2.00-1.92 (1H, m), 0.95 (3H, t, J = 7.1Hz), 0.83 (3H, d, J = 6.8Hz), 0.82 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 167.9, 152.7, 151.5, 141.8, 134.4, 131.7, 130.9, 130.4, 129.1, 123.8, 122.8, 122.3, 61.6, 54.4, 49.1, 28.8, 21.6, 16.8, 13.7; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2091.



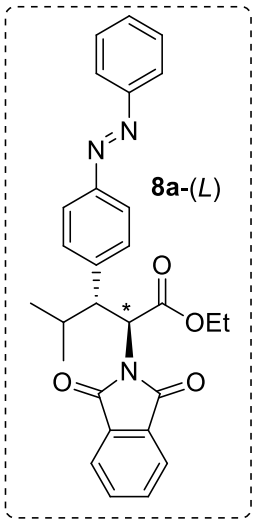
The HPLC of compound **8a**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.87 min, t_L= 13.66 min.

(2*R*,3*S*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-4-methyl-3-(4-((*E*)-phenyldiazenyl)phenyl)pentanoate (8a-(*D*))*:* The compound **8a**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (32 mg, 68%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 130-132 ºC; IR (DCM): 2960, 1710, 1381, 1260, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.91 (6H, m), 7.81 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.57-7.48 (5H, m), 5.46 (1H, d, J = 11.7Hz), 4.03-3.94 (3H, m), 2.00-1.92 (1H, m), 0.95 (3H, t, J = 7.1Hz), 0.83 (3H, d, J = 6.8Hz), 0.82 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 167.8, 152.8, 151.5, 141.8, 134.4, 131.7, 130.9, 130.4, 129.1, 123.8, 122.8, 122.3, 61.6, 54.5, 49.1, 28.8, 21.6, 16.8, 13.7; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2073.



$[\alpha]^{25}_D$= 64.4 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 97:3) of compound **8a**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.78 min, t_L= 13.76 min.

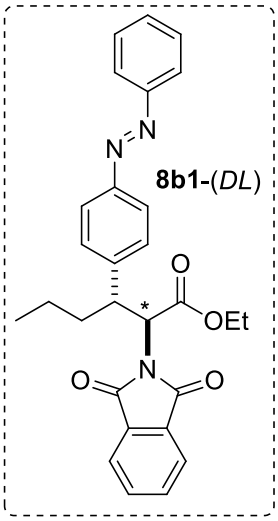


(2*S*,3*R*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-4-methyl-3-(4-((*E*)-phenyldiazenyl)phenyl)pentanoate (8a-(*L*))*:* The compound **8a**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (26 mg, 70%, 0.08 mmol scale); R_f(30% EtOAc/hexane) 0.6; mp: 130-132 ^{o}C; IR (DCM): 2963, 1715, 1383, 1259, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.95-7.92 (6H, m), 7.81 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.57-7.48 (5H, m), 5.46 (1H, d, J = 11.7Hz), 4.03-3.94 (3H, m), 2.00-1.92 (1H, m), 0.95 (3H, t, J = 7.1Hz), 0.83 (3H, d, J = 6.8Hz), 0.82 (3H, d, J = 6.8Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 167.8, 152.8, 151.5, 141.8, 134.4, 131.7, 130.9, 130.4, 129.1, 123.7, 122.8, 122.3, 61.6, 54.5, 49.1, 28.8, 21.6, 16.8, 13.7; HRMS (ESI) calcd for $C_{28}H_{27}N_3NaO_4$ $[M+Na]^+$ 490.1899 found 492.1910.

$[\alpha]^{25}_D$= -66.8 (*c* = 0.05 g/100 mL, $CHCl_3$).

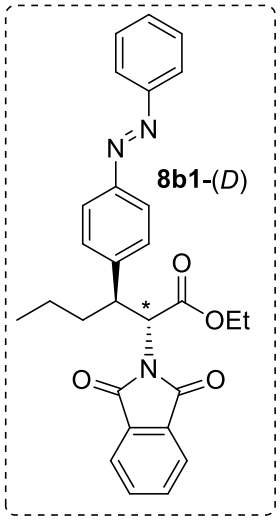
The enantiomeric ratio (*er* = 97:3) of compound **8a**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 10.99 min, t_L = 13.52 min.

(2*S,3*R**)-Ethyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)hexanoate (8b1-(*DL*))*:*** The compound **8b1**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (35 mg, 77%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 108-110 ^{o}C; IR (DCM): 2930, 1715, 1384, 1253, 716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.92 (6H, m), 7.81 (2H, dd, J_1= 5.4, J_2= 3.0 Hz),7.56-7.47 (5H, m), 5.16 (1H, d, J = 10.3Hz), 4.07-3.99 (2H, m), 3.93 (1H, td, J_1= 10.9, J_2= 4.3 Hz), 1.66-1.52 (2H, m), 1.10-1.02 (2H, m), 1.03 (3H, t, J = 7.2 Hz), 0.77 (3H, t, J = 7.4Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.3, 167.8, 152.7, 151.6, 145.4, 134.4, 131.7, 130.9, 129.3, 129.1, 123.8, 123.0, 122.8, 61.6, 57.0, 44.3, 34.5, 19.9, 13.8, 13.8; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2097.



The HPLC of compound **8b1**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5 flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.97 min, t_L= 21.02 min.

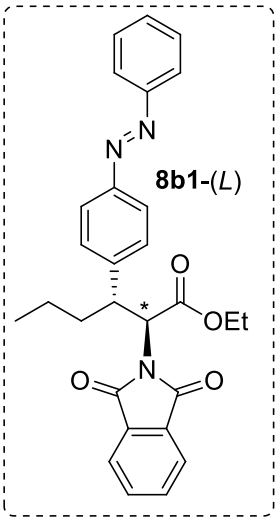
(2*R*,3*S*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3-(4-((*E*)-phenyldiazenyl)phenyl)hexanoate (8b1-(*D*))*:* The compound **8b1**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (25 mg, 76%, 0.07 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 112-114 °C; IR (DCM): 2927, 1716, 1384, 1251, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.92 (6H, m), 7.81 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.57-7.47 (5H, m), 5.16 (1H, d, J = 10.3 Hz), 4.07-3.99 (2H, m), 3.93 (1H, td, J_1 = 10.9, J_2 = 4.3 Hz), 1.64-1.51 (2H, m), 1.10-1.01 (2H, m), 1.03 (3H, t, J = 7.1 Hz), 0.77 (3H, t, J = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.3, 167.8, 152.7, 151.6, 145.4, 134.4, 131.7, 130.9, 129.3, 129.1, 123.8, 123.0, 122.8, 61.6, 57.0, 44.3, 34.5, 19.9, 13.8, 13.8; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2092.



$[\alpha]^{25}_D$= 66.4 (*c* = 0.05 g/100 mL, $CHCl_3$).

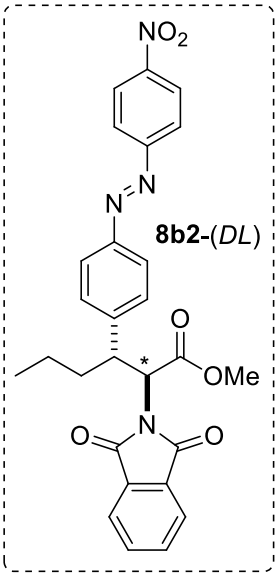
The enantiomeric ratio (*er* = 94:6) of compound **8b1**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.65 min, t_L= 20.87 min.

(2*S*,3*R*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3-(4-((*E*)-phenyldiazenyl)phenyl)hexanoate (8b1-(*L*)): The compound **8b1**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (26 mg, 79%, 0.07 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 107-109 °C; IR (DCM): 2929, 1715, 1384, 1251, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.92 (6H, m), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz),7.57-7.47 (5H, m), 5.16 (1H, d, J = 10.3Hz), 4.07-3.99 (2H, m), 3.93 (1H, td, J_1 = 10.9, J_2 = 4.3 Hz), 1.64-1.51 (2H, m), 1.03 (3H, t, J = 7.1 Hz), 1.11-1.01 (2H, m), 0.77 (3H, t, J = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.3, 167.7, 152.7, 151.6, 145.4, 134.4, 131.7, 130.9, 129.3, 129.1, 123.8, 123.0, 122.8, 61.6, 57.0, 44.3, 34.5, 19.9, 13.8, 13.8; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2090.

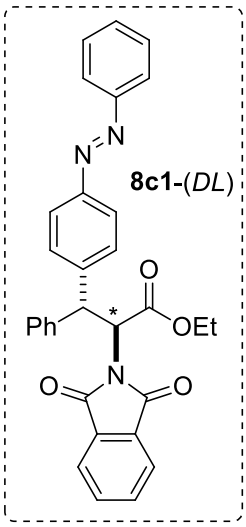


$[\alpha]^{25}_{D}$= -67.2 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 93:7) of compound **8b1**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.71 min, t_L= 20.39 min.

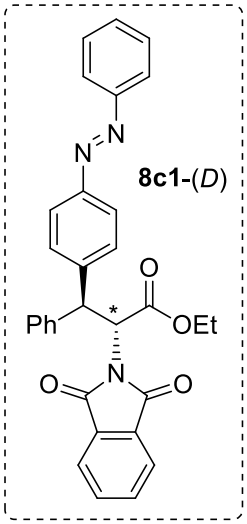


(2*S,3*R**)-Methyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-((4-nitrophenyl)diazenyl)phenyl)hexanoate (8b2-(*DL*))*:*** The compound **8b2**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (37 mg, 74%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 164-166 ^oC; IR (DCM): 2956, 1715, 1385, 1343, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.41 (2H, d, *J* = 8.9 Hz), 8.04 (2H, d, *J* = 8.9 Hz), 8.00-7.94 (4H, m), 7.82 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz),7.57 (2H, d, *J* = 8.4 Hz), 5.17 (1H, d, *J* = 10.2 Hz), 3.93 (1H, td, J_1= 10.8, J_2= 4.3 Hz), 3.58 (3H, s), 1.66-1.51 (2H, m), 1.11-1.01 (2H, m), 0.78 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.6, 167.7, 155.9, 151.3, 148.6, 147.1, 134.5, 131.6, 129.4, 124.8, 123.9, 123.6, 123.4, 56.5, 52.6, 44.5, 34.3, 19.9, 13.8; HRMS (ESI) calcd for $C_{27}H_{25}N_4O_6$ $[M+H]^+$ 501.1774 found 501.1779.



(2*S,3*R**)-Ethyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-3-(4-(phenyldiazenyl)phenyl)propanoate (8c1-(*DL*))*:*** The compound **8c1**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (27 mg, 77%, 0.07 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 172-174 ^oC; IR (DCM): 2926, 1715, 1385, 1118, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (4H, m),7.77 (2H, dd, J_1= 4.9, J_2= 3.4 Hz),7.69-7.66 (4H, m), 7.55-7.45 (3H, m), 7.32-7.28 (2H, m), 7.14 (2H, t, *J* = 7.6 Hz), 7.04 (1H, t, *J* = 7.3Hz), 5.82 (1H, d, *J* = 11.9 Hz), 5.38 (1H, d, *J* = 11.9 Hz), 4.09 (2H, q, *J* = 6.9 Hz), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.1, 167.3, 152.7, 151.5, 144.9, 139.9, 134.1, 131.3, 130.9, 129.1, 128.7, 128.5, 128.0, 127.1, 123.5, 123.3, 122.8, 61.9, 54.9, 50.6, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}N_3NaO_4$ $[M+Na]^+$ 526.1743 found 526.1758.

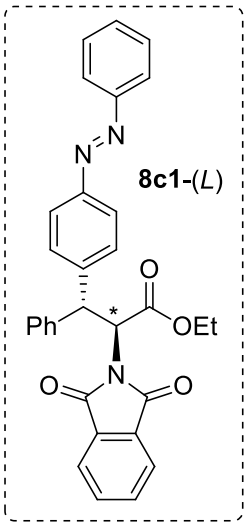
The HPLC of compound **8c1**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.53 min, t_L= 18.15 min.



(2*R*,3*S*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-3-(4-((*E*)-phenyldiazenyl)phenyl)propanoate (8c1-(*D*))*:* The compound **8c1**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (34 mg, 85%, 0.08 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 172-174 ^oC; IR (DCM): 2924, 1714, 1384, 1118, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (4H, m),7.77 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz),7.69-7.66 (4H, m), 7.55-7.46 (3H, m), 7.30 (2H, d, J = 7.4 Hz), 7.14 (2H, t, J = 7.8 Hz), 7.04 (1H, t, J = 7.4 Hz), 5.81 (1H, d, J = 11.9 Hz), 5.37 (1H, d, J = 11.9 Hz), 4.12-4.06 (2H, m), 1.05 (3H, t, J = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.1, 167.3, 152.7, 151.5, 144.9, 139.9, 134.1, 131.3, 130.9, 129.1, 128.7, 128.5, 128.0, 127.1, 123.5, 123.3, 122.8, 61.9, 54.9, 50.6, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}N_3NaO_4$ $[M+Na]^+$ 526.1743 found 526.1751.

$[\alpha]^{25}_D$= 159.3 (c = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 96:4) of compound **8c1**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.69 min, t_L= 18.58 min.

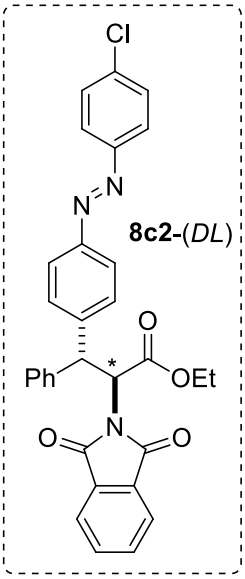


(2*S*,3*R*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-3-(4-((*E*)-phenyldiazenyl)phenyl)propanoate (8c1-(*L*))*:* The compound **8c1**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (26 mg, 74%, 0.07 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 172-174 ^oC; IR (DCM): 2925, 1715, 1386, 1118, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (4H, m),7.77 (2H, dd, J_1 = 5.1, J_2 = 3.4 Hz), 7.69-7.67 (4H, m), 7.55-7.45 (3H, m), 7.32-7.28 (2H, m), 7.14 (2H, t, J = 7.6 Hz), 7.04 (1H, t, J = 7.4 Hz), 5.82 (1H, d, J = 12.0 Hz), 5.37 (1H, d, J = 11.9 Hz), 4.09 (2H, q, J = 7.0 Hz), 1.05 (3H, t, J = 7.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C

168.1, 167.3, 152.7, 151.5, 144.9, 139.9, 134.1, 131.3, 130.9, 129.1, 128.7, 128.5, 128.0, 127.1, 123.5, 123.3, 122.8, 61.9, 54.9, 50.6, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}N_3NaO_4$ $[M+Na]^+$ 526.1743 found 526.1737.

$[\alpha]^{25}_D$= -183.3 (*c* = 0.05 g/100 mL, $CHCl_3$).

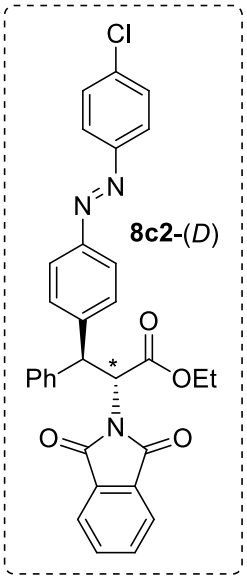
The enantiomeric ratio (*er* = 96:4) of compound **8c1**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.78 min, t_L= 18.32 min.



(2*S,3*R**)-Ethyl (*E*)-3-(4-((4-chlorophenyl)diazenyl)phenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (8c2-(*DL*))*:*** The compound **8c2**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a yellow colored solid (44 mg, 82%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 172-174 ^oC; IR (DCM): 2921, 1710, 1380, 1264, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, dt, J_1 = 8.5, J_2 = 1.6 Hz),7.87 (2H, dt, J_1 = 8.7, J_2 = 2.7 Hz),7.77 (2H, dd, J_1= 5.5, J_2= 3.1 Hz), 7.70-7.65 (4H, m), 7.49 (2H, dt, J_1 = 8.7, J_2 = 2.7 Hz), 7.31-7.28 (2H, m), 7.14 (2H, t, *J* = 7.8 Hz), 7.06-7.01 (1H, m), 5.81 (1H, d, *J* = 11.9 Hz), 5.37 (1H, d, *J* = 12.0 Hz), 4.13-4.04 (2H, m), 1.05 (3H, t, *J* = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 167.3, 151.2, 151.0, 145.2, 139.8, 136.8, 134.1, 131.3, 129.3, 128.6, 128.5, 127.9, 127.1, 124.0, 123.4, 123.3, 61.9, 54.8, 50.5, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}ClN_3O_4$ $[M+H]^+$ 538.1534 found 538.1539.

The HPLC of compound **8c2**-(*DL*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 330 nm, t_D = 16.36 min, t_L= 17.95 min.

(2*R*,3*S*)-Ethyl 3-(4-((*E*)-(4-chlorophenyl)diazenyl)phenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (8c2-(*D*))*:* The compound **8c2**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a yellow colored solid (42 mg, 78%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 171-173 ^oC; IR (DCM): 2920, 1710, 1385, 1266, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, d, *J* = 8.4Hz),7.87 (2H, dt, J_1= 8.7, J_2= 2.7 Hz),7.77 (2H, dd, J_1= 5.5, J_2= 3.0 Hz),7.69-7.66 (4H, m), 7.49 (2H, dt, J_1= 8.7, J_2= 2.6

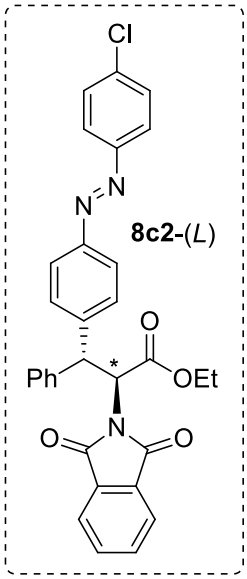


Hz), 7.30 (2H, d, *J* = 7.9 Hz), 7.14 (2H, t, *J* = 7.8 Hz), 7.03 (1H, t, *J* = 7.4 Hz), 5.81 (1H, d, *J* = 11.9 Hz), 5.37 (1H, d, *J* = 11.9 Hz), 4.12-4.05 (2H, m), 1.05 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.1, 167.3, 151.2, 151.0, 145.2, 139.8, 136.8, 134.1, 131.3, 129.3, 128.6, 128.5, 127.9, 127.1, 124.1, 123.4, 123.3, 61.9, 54.8, 50.6, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}ClN_3O_4$ $[M+H]^+$ 538.1534 found 538.1537.

$[\alpha]^{25}_D$= 151.2 (*c* = 0.02 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 97:3) of compound **8c2**-(*D*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 330 nm, t_D = 16.07 min, t_L= 17.68 min.

(2*S*,3*R*)-Ethyl 3-(4-((*E*)-(4-chlorophenyl)diazenyl)phenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (8c2-(*L*)):

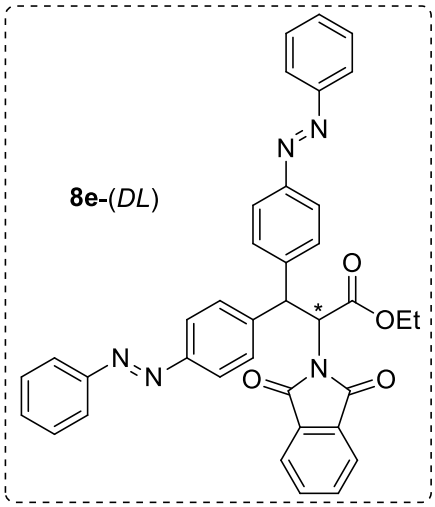


The compound **8c2**-(*L*)was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a yellow colored solid (38 mg, 71%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 172-174 ^oC; IR (DCM): 2920, 1720, 1388, 1268, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, d, *J* = 8.4 Hz),7.87 (2H, d, *J* = 8.6 Hz),7.77 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz),7.69-7.66 (4H, m), 7.49 (2H, d, *J* = 8.6 Hz), 7.30 (2H, d, *J* = 7.5 Hz), 7.14 (2H, t, *J* = 7.7 Hz), 7.03 (1H, t, *J* = 7.4 Hz), 5.81 (1H, d, *J* = 11.9 Hz), 5.37 (1H, d, *J* = 11.9 Hz), 4.13-4.06 (2H, m), 1.05 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 167.3, 151.2, 151.0, 145.2, 139.8, 136.8, 134.1, 131.3, 129.3, 128.6, 128.5, 127.9, 127.1, 124.0, 123.4, 123.3, 61.9, 54.8, 50.5, 13.8; HRMS (ESI) calcd for $C_{31}H_{25}ClN_3O_4$ $[M+H]^+$ 538.1534 found 538.1538.

$[\alpha]^{25}_D$= -158.2 (*c* = 0.02 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 98:2) of compound **8c2**-(*L*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 330 nm, t_D = 15.39 min, t_L= 16.93 min.

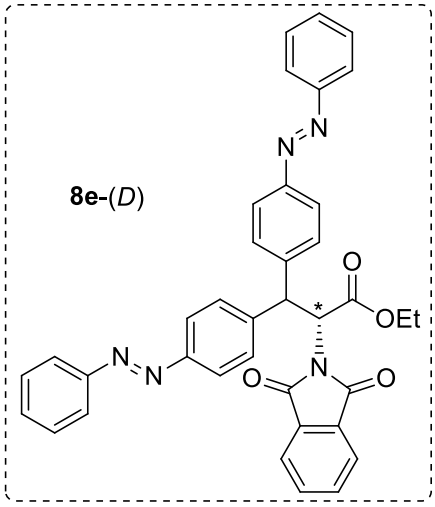
Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3,3-bis(4-((*E*)-phenyldiazenyl)phenyl)propanoate (8e-(*DL*)): The compound **8e**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (29 mg, 69%, 0.07 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 190-192 °C; IR (DCM): 2925, 1715, 1384, 1264, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.92 (4H, m), 7.83-7.78 (4H, m),7.22 (4H, t, J = 8.0 Hz), 7.67 (2H, dd, J_1 = 5.3, J_2 = 3.1 Hz), 7.55-7.44 (8H, m), 5.88 (1H, d, J = 12.0 Hz), 5.50 (1H, d, J = 12.0 Hz), 4.11 (2H, q, J = 7.1 Hz), 1.06 (3H, t, J = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 167.4, 152.7, 152.5, 151.6, 151.4, 144.3, 143.1, 134.3, 131.3, 131.0, 131.0, 129.1, 129.1, 128.8, 128.5, 123.6, 123.4, 123.3, 122.9, 122.8, 62.0, 54.8, 50.4, 13.9; HRMS (ESI) calcd for $C_{37}H_{30}N_5O_4$ $[M+H]^+$ 608.2298 found 608.2271.



The HPLC of compound **8e**-(*DL*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.28 min, t_L= 8.21 min.

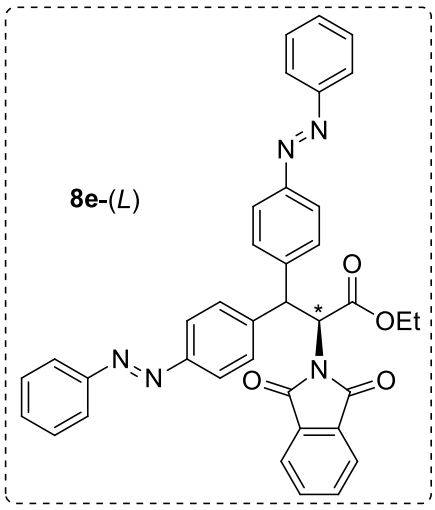
(*R*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3,3-bis(4-((*E*)-phenyldiazenyl)phenyl)propanoate (8e-(*D*)): The compound **8e**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (33 mg, 68%, 0.08 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 190-192 °C; IR (DCM): 2925, 1714, 1384, 1263, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.97-7.92 (4H, m),7.83-7.78 (4H, m),7.74-7.66 (6H, m), 7.55-7.44 (8H, m), 5.88 (1H, d, J = 11.9 Hz), 5.50 (1H, d, J = 12.0 Hz), 4.11 (2H, q, J = 7.0 Hz), 1.06 (3H, t, J = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 167.4, 152.7, 152.5, 151.6, 151.5, 144.3, 143.1, 134.3, 131.3, 131.0, 131.0, 129.1, 129.1, 128.8, 128.5, 123.6, 123.4, 123.3, 122.9, 122.8, 62.0, 54.8, 50.4, 13.9; HRMS (ESI) calcd for $C_{37}H_{30}N_5O_4$ $[M+H]^+$ 608.2298 found 608.2319.

$[\alpha]^{25}_D$= 166.1 (c = 0.05 g/100 mL, $CHCl_3$).



The enantiomeric ratio (*er* = 94:6) of compound **8e**-(*D*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.20 min, t_L= 8.14 min.

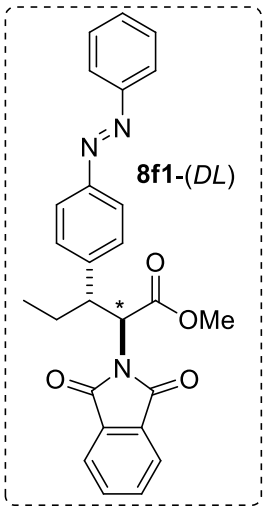
(*S*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-3,3-bis(4-((*E*)-phenyldiazenyl)phenyl)propanoate (8e-(*L*))*:* The compound **8e**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (34 mg, 62%, 0.09 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 190-192 °C; IR (DCM): 2925, 1716, 1385, 1263, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.90 (4H, m),7.83-7.76 (4H, m),7.74-7.65 (6H, m), 7.56-7.42 (8H, m), 5.87 (1H, d, *J* = 12.0Hz), 5.49 (1H, d, *J* = 12.0 Hz), 4.13-4.07 (2H, m), 1.06 (3H, t, *J* = 7.1Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 167.4, 152.7, 152.5, 151.6, 151.5, 144.3, 143.1, 134.3, 131.3, 131.0, 131.0, 129.1, 129.1, 128.8, 128.5, 123.6, 123.4, 123.3, 122.9, 122.8, 62.0, 54.8, 50.4, 13.9; HRMS (ESI) calcd for $C_{37}H_{30}N_5O_4$ $[M+H]^+$ 608.2298 found 608.2305.



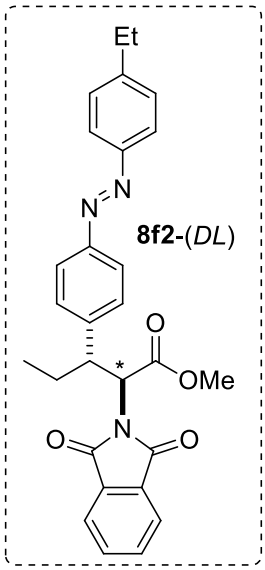
$[\alpha]^{25}_D$= -176.9 (*c* = 0.05 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 93:7) of compound **8e**-(*L*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.30 min, t_L= 8.16 min.

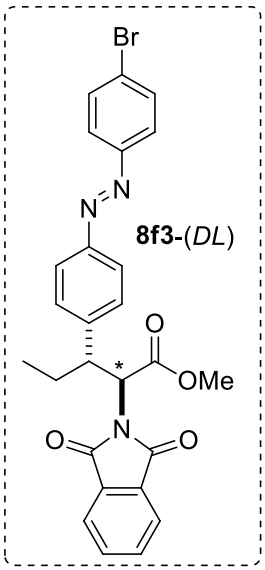
(2*S,3*R**)-Methyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)pentanoate (8f1-(*DL*))*:*** The compound **8f1**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (13 mg, 50%, 0.06 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 154-156 °C; IR (DCM): 2966, 1715, 1384, 1259, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.96-7.93 (6H, m), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz),7.57-7.48 (5H, m), 5.19 (1H, d, *J* = 10.2Hz), 3.81 (1H, td, J_1 = 11.2, J_2 = 3.9 Hz), 3.58 (3H, s), 1.71-1.55 (2H, m), 0.69 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 167.7, 152.8, 151.6, 144.9, 134.4, 131.6, 130.9, 129.3, 129.1, 123.8, 123.0, 122.8, 56.6, 52.5, 46.2, 25.3, 11.4; HRMS (ESI) calcd for



$C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1767 found 442.1782.

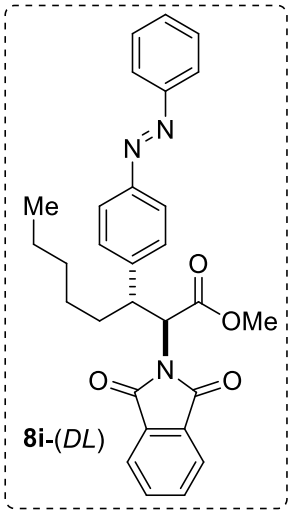


(2*S,3*R**)-Methyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-((4-ethylphenyl)diazenyl)phenyl)pentanoate (8f2-(*DL*))*:*** The compound **8f2**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (36 mg, 85%, 0.09 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 150-152 ^oC; IR (DCM): 2966, 1714, 1383, 1258, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.95-7.91 (4H, m), 7.87 (2H, d, J = 8.3Hz), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.3Hz), 5.20 (1H, d, J = 10.3 Hz), 3.84-3.78 (1H, m), 3.58 (3H, s), 2.76 (2H, q, J = 7.6 Hz), 1.73-1.53 (2H, m), 1.31 (3H, t, J = 7.6 Hz), 0.69 (3H, t, J = 7.3 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 167.7, 151.7, 151.0, 147.7, 144.6, 134.4, 131.7, 129.2, 128.6, 123.8, 122.9, 56.7, 52.5, 46.2, 28.9, 25.3, 15.4, 11.4; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2092.



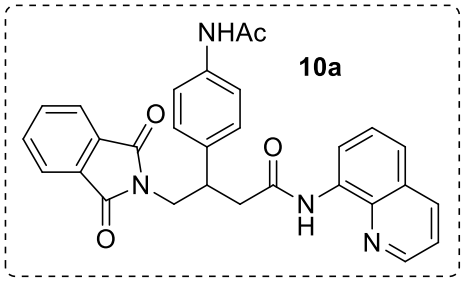
(2*S,3*R**)-Methyl (*E*)-3-(4-((4-bromophenyl)diazenyl)phenyl)-2-(1,3-dioxoisoindolin-2-yl)pentanoate (8f3-(*DL*))*:*** The compound **8f3**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (34 mg, 59%, 0.11 mmol scale); R_f(30% EtOAc/hexane) 0.7; mp: 160-162 ^oC; IR (DCM): 2956, 1714, 1384, 1064, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.95-7.92 (4H, m), 7.83-7.80 (4H, m), 7.67 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.4 Hz), 5.19 (1H, d, J = 10.3 Hz), 3.84-3.78 (1H, m), 3.57 (3H, s), 1.71-1.54 (2H, m), 0.68 (3H, t, J = 7.3 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 167.7, 151.4, 151.4, 145.4, 134.4, 132.3, 131.6, 129.3, 125.2, 124.3, 123.8, 123.1, 56.5, 52.5, 46.2, 25.3, 11.4; HRMS (ESI) calcd for $C_{26}H_{23}BrN_3O_4$ $[M+H]^+$ 520.0872 found 520.0896.

(2*S,3*R**)-Methyl (*E*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)octanoate (8i-(*DL*))*:*** The compound **8i**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored viscous liquid (30 mg, 88%, 0.07 mmol



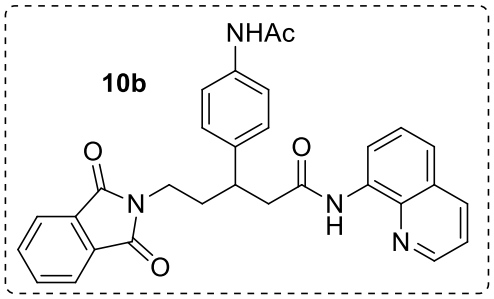
scale); R_f(30% EtOAc/hexane) 0.7; IR (DCM): 2923, 1713, 1385, 1189, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H7.96-7.92 (6H, m), 7.81 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz),7.57-7.47 (5H, m), 5.17 (1H, d, J = 10.2 Hz), 3.90 (1H, td, J_1 = 10.6, J_2 = 4.6 Hz),3.57 (3H, s), 1.64-1.53 (2H, m), 1.20-1.00 (6H, m), 0.75 (3H, t, J = 6.8 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 167.7, 152.8, 151.6, 145.3, 134.4, 131.6, 130.9, 129.2, 129.1, 123.8, 123.0, 122.8, 56.8, 52.5, 44.6, 32.1, 31.5, 26.4, 22.4, 13.9; HRMS (ESI) calcd for $C_{29}H_{29}N_3NaO_4$ $[M+Na]^+$ 506.2056 found 506.2050.

3-(4-Acetamidophenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (10a)*:*



The compound **10a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown colored solid (88 mg, 89%, 0.2 mmol scale); R_f(100% EtOAc) 0.4; mp: 150-152 ^oC; IR (DCM): 2926, 1713, 1525, 1393, 720 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 10.04 (1H, br. s), 9.83 (1H, br. s), 8.92-8.91 (1H, m), 8.42-8.35 (2H, m), 7.74 (4H, s), 7.62-7.58 (2H, m), 7.47-7.42 (3H, m), 7.24 (2H, d, J = 8.1 Hz), 3.83 (2H, d, J = 7.5 Hz), 3.75-3.71 (1H, m), 3.05 (2H, d, J = 7.0 Hz), 1.97 (3H, s); ^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 170.2, 168.6, 168.2, 149.2, 138.4, 138.4, 137.0, 136.0, 134.8, 134.7, 131.8, 128.5, 128.2, 127.3, 123.4, 122.5, 122.2, 119.3, 116.9, 43.5, 41.1, 24.4; HRMS (ESI) calcd for $C_{29}H_{25}N_4O_4$ $[M+H]^+$ 493.1876 found 493.1854.

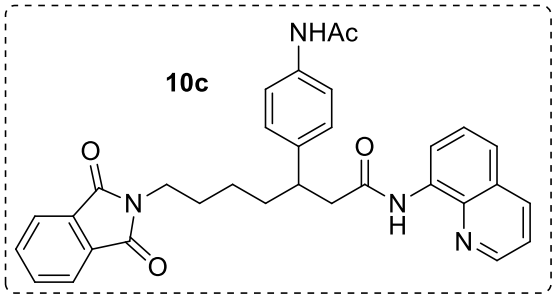
3-(4-Acetamidophenyl)-5-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (10b)*:*



The compound **10b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a faint yellow colored solid (192 mg, 76%, 0.5 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 202-204 ^oC; IR (DCM): 2360, 1708, 1524, 1397, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (1H, br. s), 8.75 (1H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.67 (1H, dd, J_1 = 6.3, J_2 = 2.6 Hz), 8.12 (1H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.77 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.66 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.50-7.45 (2H, m),

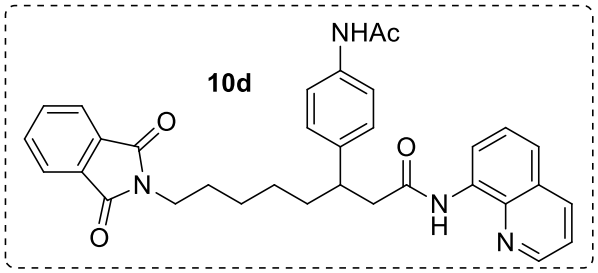
7.44-7.39 (3H, m), 7.31-7.28 (2H, m), 7.22 (1H, s), 3.71-3.57 (2H, m), 3.43-3.35 (1H, m), 2.92-2.79 (2H, m), 2.26-2.12 (2H, m), 2.12 (3H, s); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 169.7, 168.5, 168.3, 148.1, 138.3, 138.2, 136.9, 136.2, 134.1, 133.8, 132.0, 128.0, 127.8, 127.2, 123.1, 121.6, 120.1, 116.4, 45.8, 40.0, 36.5, 34.1, 24.5; HRMS (ESI) calcd for $C_{30}H_{27}N_4O_4$ $[M+H]^+$ 507.2032 found 507.2057.

3-(4-Acetamidophenyl)-7-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (10c):



The compound **10c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as brown colored solid (222 mg, 83%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 185-187 ^{o}C; IR (DCM): 2930, 1708, 1520, 1264, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1H, br. s), 8.77 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.70 (1H, dd, J_1 = 6.4, J_2 = 2.6 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.6 Hz), 7.81 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.69 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.49-7.40 (6H, m), 7.22 (2H, d, J = 8.4 Hz), 3.61 (2H, t, J = 7.3 Hz), 3.31-3.23 (1H, m), 2.88-2.77 (2H, m), 2.13 (3H, s), 1.88-1.57 (4H, m), 1.31-1.22 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 170.2, 168.4, 168.3, 148.1, 139.7, 138.2, 136.4, 136.3, 134.3, 133.8, 132.1, 128.0, 127.9, 127.3, 123.2, 121.6, 121.5, 120.0, 116.4, 45.7, 41.9, 37.8, 35.7, 28.4, 24.7, 24.5; HRMS (ESI) calcd for $C_{32}H_{31}N_4O_4$ $[M+H]^+$ 535.2345, found 535.2368.

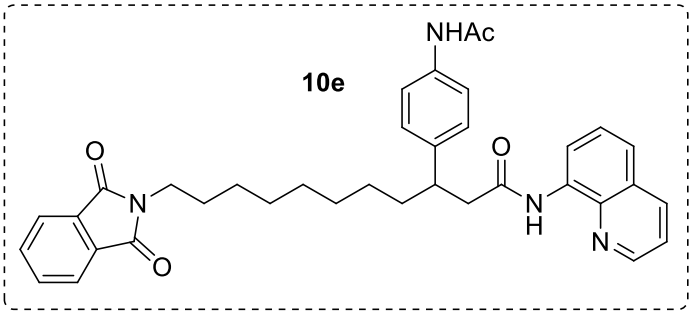
3-(4-Acetamidophenyl)-8-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)octanamide (10d):The



compound **10d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a light yellow colored solid (172 mg, 63%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 76-78 ^{o}C; IR (DCM): 2931, 1708, 1524, 1396, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H9.69 (1H, br. s), 8.78 (1H, dd, J_1 = 4.2, J_2 = 1.6 Hz), 8.71 (1H, dd, J_1 = 6.7, J_2 = 2.2 Hz), 8.14 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.83 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.52-7.41 (5H, m), 7.24 (2H, d, J = 8.4 Hz), 7.19 (1H, s), 3.62 (2H, t, J = 7.2 Hz), 3.30-3.23 (1H, m), 2.87-2.76 (2H, m), 2.15 (3H, s), 1.82-1.57 (4H, m), 1.35-1.19 (4H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 168.5, 168.5, 148.1, 139.8, 138.2, 136.5,

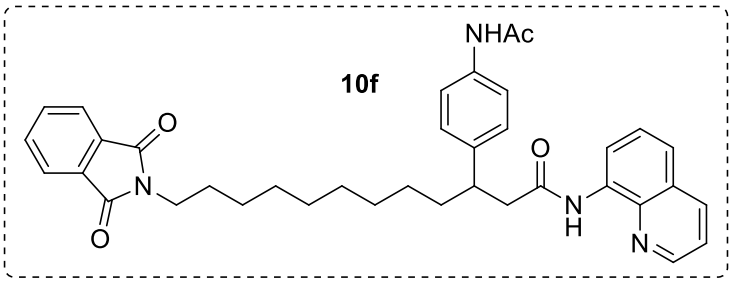
136.3, 134.3, 133.9, 132.1, 128.0, 127.8, 127.3, 123.1, 121.6, 121.5, 120.1, 116.4, 45.7, 42.0, 37.9, 36.1, 28.5, 27.0, 26.8, 24.5; HRMS (ESI) calculated for $C_{33}H_{33}N_4O_4$ $[M+H]^+$ 549.2502 found 549.2479.

3-(4-Acetamidophenyl)-11-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)undecanamide (10e):



The compound **10e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (234 mg, 79%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 50-52 ^oC; IR (DCM): 2928, 1707, 1520, 1395, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.78 (1H, dd, J_1 = 4.2, J_2 = 1.4 Hz), 8.71 (1H, dd, J_1 = 6.8, J_2 = 2.2 Hz), 8.13 (1H, dd, J_1 = 8.2, J_2 = 1.4 Hz), 7.84 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.51-7.48 (3H, m), 7.46-7.42 (3H, m), 7.23 (2H, d, J = 8.3 Hz), 3.64 (2H, t, J = 7.4 Hz), 3.30-3.22 (1H, m), 2.88-2.77 (2H, m), 2.14 (3H, s), 1.80-1.73 (1H, m), 1.69-1.58 (3H, m), 1.31-1.11 (10H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 168.5, 168.4, 148.1, 140.1, 138.2, 136.3, 136.3, 134.3, 133.9, 132.1, 128.0, 127.9, 127.3, 123.2, 121.6, 121.5, 120.1, 116.4, 45.8, 42.1, 38.1, 36.2, 29.3, 29.2, 29.0, 28.6, 27.2, 26.8, 24.5; HRMS (ESI) calcd for $C_{36}H_{39}N_4O_4$ $[M+H]^+$ 591.2971 found 591.2950.

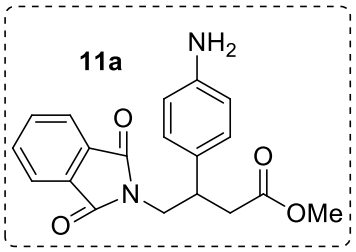
3-(4-Acetamidophenyl)-12-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)dodecanamide (10f):



The compound **10f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a brown colored solid (214 mg, 71%, 0.5 mmol scale); R_f(50% EtOAc/hexane) 0.3; mp: 98-100 ^oC; IR (DCM): 2927, 1707, 1521, 1395, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H9.70 (1H, br. s), 8.78 (1H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.72 (1H, dd, J_1 = 6.8, J_2 = 2.0 Hz), 8.14 (1H, dd, J_1 = 8.3, J_2 = 1.5 Hz), 7.85 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.72 (2H, d, J_1 = 5.4, J_2 = 3.0 Hz), 7.53-7.42 (5H, m), 7.36 (1H, m), 7.24 (2H, d, J = 8.4 Hz), 3.66 (2H, t, J = 7.4 Hz), 3.31-3.23 (1H, m), 2.88-2.77 (2H, m), 2.16 (3H, s), 1.81-1.73 (1H, m), 1.68-1.60 (3H, m), 1.27-1.19 (12H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 168.4, 168.4, 148.0, 139.9, 138.1, 136.3,

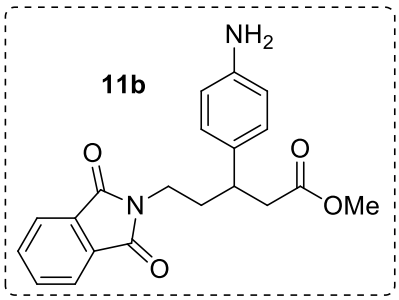
136.2, 134.2, 133.8, 132.0, 127.9, 127.7, 127.2, 123.0, 121.5, 121.3, 119.9, 116.3, 45.7, 42.0, 38.0, 36.1, 29.2, 29.2, 28.9, 28.5, 27.1, 26.7, 24.3; HRMS (ESI) calcd for $C_{37}H_{41}N_4O_4$ $[M+H]^+$ 605.3128, found 605.3127.

Methyl 3-(4-aminophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoate (11a): The compound **11a**

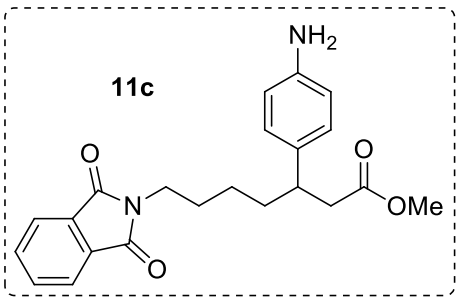


was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colored solid (31 mg, 84%, 0.11 mmol scale); R_f(30% EtOAc:hexane) 0.6; mp: 100-102 ^oC; IR (DCM): 3374, 1704, 1395, 1169, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.82 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.5, J_2 = 3.1Hz), 7.07 (2H, d, J = 8.4 Hz), 6.61 (2H, d, J = 8.4 Hz), 3.91-3.81 (2H, m), 3.70-3.62 (3H, m), 3.50 (3H, s), 2.72-2.64 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 168.2, 145.4, 133.9, 131.9, 130.2, 128.5, 123.3, 115.3, 51.6, 43.3, 39.9, 38.6; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1345 found 339.1328.

Methyl 3-(4-aminophenyl)-5-(1,3-dioxoisoindolin-2-yl)pentanoate (11b): The compound **11b**



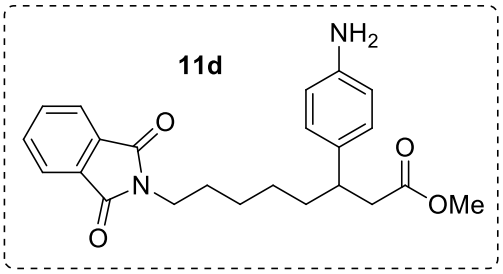
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colour viscous (53 mg, 50%, 0.31 mmol scale); R_f (30% EtOAc:hexane) 0.6; IR (DCM): 2949, 1699, 1516, 1396, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.81-7.79 (2H, m), 7.70-7.68 (2H, m), 7.03 (2H, d, J = 7.7Hz), 6.61 (2H, d, J = 7.7Hz), 3.64-3.51 (2H, m), 3.56 (3H, s), 3.41-3.21 (2H, m), 3.12-3.05 (1H, m), 2.64-2.53 (2H, m), 2.10-1.95 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 168.3, 145.0, 133.8, 132.3, 132.1, 128.2, 123.1, 115.4, 51.5, 42.2, 39.3, 36.5, 34.0; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4$ $[M+H]^+$ 353.1501 found 353.1497. (In the proton NMR spectrum the NH_2 signal appeared as a broad signal (3.41-3.21) and precise chemical shift value could not be ascertained).



Methyl 3-(4-aminophenyl)-7-(1,3-dioxoisoindolin-2-yl)heptanoate (11c)*:* The compound **11c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colour viscous (96 mg, 81%, 0.31 mmol scale); R_f(30% EtOAc/hexane) 0.6; IR (DCM): 2940, 1704, 1396, 1266, 718 cm^{-1}; ^1H NMR

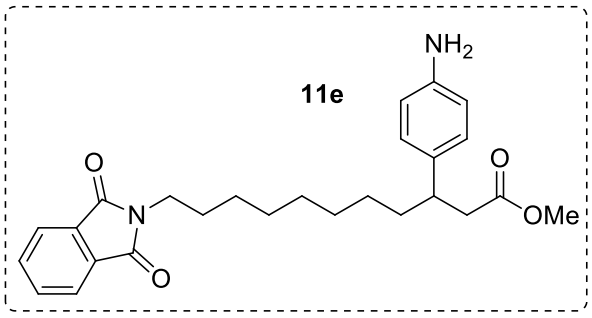
(400 MHz, $CDCl_3$): δ_H 7.83 (2H, dd, J_1 = 5.4, J_2 = 3.2 Hz), 7.71 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 6.95 (2H, d, J = 8.1 Hz), 6.60 (2H, d, J = 8.2 Hz), 3.62-3.58 (2H, m), 3.58 (3H, s), 3.01-2.94 (1H, m), 2.61-2.48 (2H, m), 1.70-1.53 (4H, m), 1.25-1.17 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 173.0, 168.4, 144.8, 133.9, 133.6, 132.1, 128.2, 123.2, 115.3, 51.5, 41.9, 41.2, 37.8, 35.6, 28.4, 24.6; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_4$ $[M+H]^+$ 381.1814 found 381.1805. (In the proton NMR spectrum the NH_2 signal could not be clearly ascertained).

Methyl 3-(4-aminophenyl)-8-(1,3-dioxoisoindolin-2-yl)octanoate (11d)*:* The compound **11d**



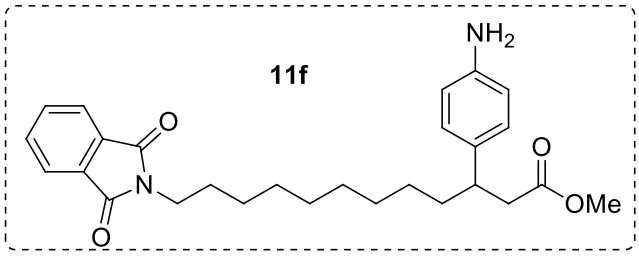
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colour viscous (95 mg, 71%, 0.34 mmol scale); R_f(30% EtOAc/hexane) 0.6; IR (DCM): 2932, 1703, 1395, 1159, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2H, dd, J_1 = 5.1, J_2 = 3.3 Hz), 7.71 (2H, dd, J_1 = 5.2, J_2 = 3.5 Hz), 6.95 (2H, d, J = 8.1 Hz), 6.62 (2H, d, J = 8.0 Hz), 3.64-3.58 (4H, m), 3.58 (3H, s), 3.00-2.92 (1H, m), 2.59-2.47 (2H, m), 1.64-1.50 (4H, m), 1.36-1.14 (4H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 173.1, 168.5, 144.7, 133.9, 132.1, 128.2, 123.2, 115.3, 51.5, 42.0, 41.3, 38.0, 36.0, 28.5, 26.9, 26.8; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_4$ $[M+H]^+$ 395.1971 found 395.1956.

Methyl 3-(4-aminophenyl)-11-(1,3-dioxoisoindolin-2-yl)undecanoate (11e)*:* The compound



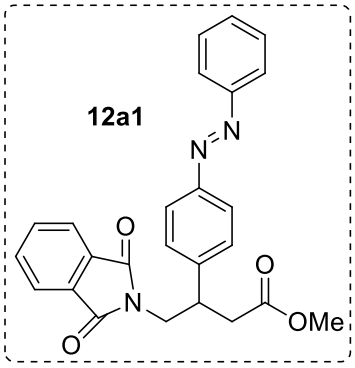
11e was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colour viscous (29 mg, 18%, 0.37 mmol scale); R_f(30% EtOAc/hexane) 0.6; IR (DCM): 2932, 1703, 1395, 1159, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2H, dd, J_1 = 4.4, J_2 = 3.6 Hz), 7.72 (2H, dd, J_1 = 4.4, J_2 = 3.6 Hz), 6.96 (2H, d, J = 7.8 Hz), 6.64 (2H, d, J = 7.8 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.59 (3H, s), 3.00-2.93 (1H, m), 2.61-2.48 (2H, m), 1.68-1.51 (4H, m), 1.33-1.10 (10H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 173.2, 168.5, 144.6, 134.2, 133.9, 132.2, 128.2, 123.2, 115.3, 51.5, 42.0, 41.4, 38.1, 36.2, 29.4, 29.3, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_4$ $[M+H]^+$ 437.2440 found 437.2420. (In the proton NMR spectrum the NH_2 signal could not be clearly ascertained).

Methyl 3-(4-aminophenyl)-12-(1,3-dioxoisoindolin-2-yl)dodecanoate (11f)*:* The compound

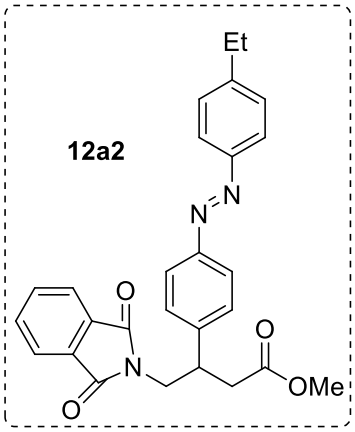


11f was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown colour viscous (60 mg, 51%, 0.26 mmol scale); R_f(30% EtOAc/hexane) 0.6; IR (DCM): 2926, 2360, 1705, 1395, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2H, dd, J_1 = 5.0, J_2 = 3.3 Hz), 7.72 (2H, dd, J_1 = 5.1, J_2 = 3.4 Hz), 6.96 (2H, d, J = 8.0 Hz), 6.63 (2H, d, J = 8.0 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.58 (3H, s), 3.00-2.93 (1H, m), 2.61-2.48 (2H, m), 1.69-1.62 (2H, m), 1.59-1.51 (2H, m), 1.29-1.14 (12H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 173.2, 168.5, 144.6, 134.2, 133.9, 132.2, 128.2, 123.2, 115.3, 51.4, 42.0, 41.4, 38.1, 36.2, 29.4, 29.4, 29.4, 29.1, 28.6, 27.3, 26.9; HRMS (ESI) calcd for $C_{27}H_{35}N_2O_4$ $[M+H]^+$ 451.2597 found 451.2585. (In the proton NMR spectrum the NH_2 signal could not be clearly ascertained).

(*E*)-Methyl 4-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)butanoate (12a1): The

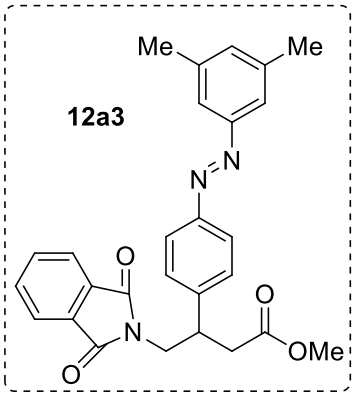


compound **12a1** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (50 mg, 93%, 0.125 mmol scale); R_f(30% EtOAc:hexane) 0.7; mp: 144-146 ^oC; IR (DCM): 2941, 1706, 1394, 1172, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.92-7.82 (6H, m), 7.72 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.55-7.45 (5H, m), 4.03-3.84 (3H, m), 3.54 (3H, s), 2.82-2.80 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 168.1, 152.6, 151.8, 143.6, 134.1, 131.8, 131.0, 129.1, 128.5, 123.4, 123.2, 122.8, 51.8, 42.9, 40.6, 38.3; HRMS (ESI) calcd for $C_{25}H_{22}N_3O_4$ $[M+H]^+$ 428.1610 found 428.1630.



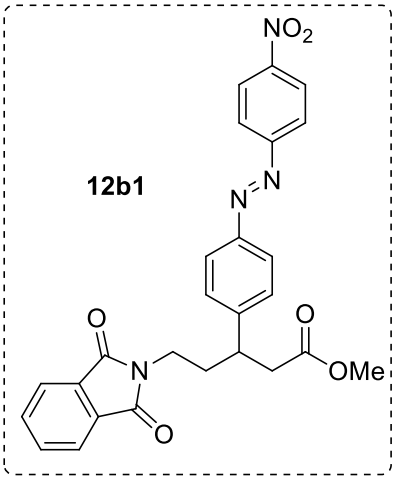
(*E*)-Methyl 4-(1,3-dioxoisoindolin-2-yl)-3-(4-((4-ethylphenyl)diazenyl)phenyl)butanoate (12a2): The compound **12a2** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (38 mg, 83%, 0.1 mmol scale); R_f (30% EtOAc:hexane) 0.7; mp: 125-127 ^oC; IR (DCM): 2966, 1709, 1394, 1170, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.85-7.82 (6H, m), 7.72 (2H, dd, J_1 = 5.5, J_2

= 3.1 Hz), 7.45-7.43 (2H, m), 7.35 (2H, d, *J* = 8.5 Hz), 4.03-3.86 (3H, m), 3.53 (3H, s), 2.81-2.79 (2H, m), 2.75 (2H, q, *J* = 7.6 Hz),1.30 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 168.1, 151.9, 150.9, 147.8, 143.2, 134.1, 131.8, 128.6, 128.5, 123.4, 123.0, 122.9, 51.7, 42.9, 40.6, 38.3, 28.9, 15.4; HRMS (ESI) calcd for $C_{27}H_{26}N_3O_4$ $[M+H]^+$ 456.1923 found 456.1942.



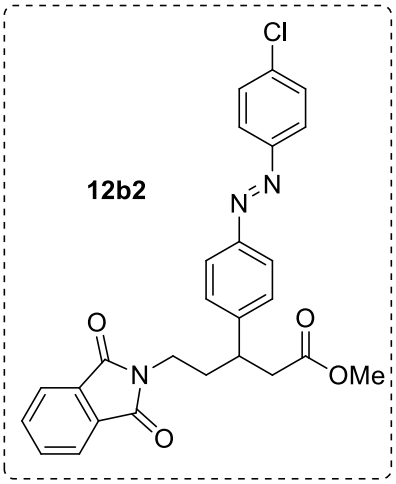
(*E*)-methyl 3-(4-((3,5-dimethylphenyl)diazenyl)phenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoate (12a3): The compound **12a3** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (29 mg, 64%, 0.1 mmol scale); R_f(30% EtOAc:hexane) 0.7; mp: 128-130 ^{o}C; IR (DCM): 2923, 1713, 1395, 1264, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85-7.82 (4H, m), 7.72 (2H, dd, J_1 = 4.7, J_2 = 3.6 Hz), 7.52 (2H, s), 7.45 (2H, d, *J* = 8.0 Hz), 7.13 (1H, s), 4.03-3.84 (3H, m), 3.53 (3H, s), 2.81 (2H, d, *J* = 7.2 Hz), 2.43 (6H, s); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 168.1, 152.8, 151.9, 143.3, 138.8, 134.1, 132.7, 131.8, 128.5, 123.4, 123.1, 120.6, 51.8, 42.9, 40.6, 38.3, 21.3; HRMS (ESI) calcd for $C_{27}H_{26}N_3O_4$ $[M+H]^+$ 456.1923 found 456.1934.

(*E*)-Methyl 5-(1,3-dioxoisoindolin-2-yl)-3-(4-((4-nitrophenyl)diazenyl)phenyl)pentanoate

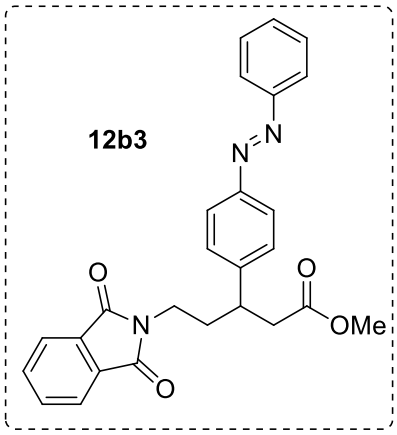


(12b1): The compound **12b1** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (44 mg, 90%, 0.1 mmol scale); R_f (30% EtOAc:hexane) 0.7; mp: 146-148 ^{o}C; IR (DCM): 2944, 2360, 1708, 1343, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H8.42-8.39 (2H, m), 8.02-7.99 (2H, m), 7.87 (2H, d, *J* = 8.4 Hz), 7.79 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.65 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.44 (2H, d, *J* = 8.4 Hz), 3.68-3.63 (2H, m), 3.60 (3H, s), 3.36-3.29 (1H, m), 2.75 (1H, dd, J_1 = 15.6, J_2 = 6.8 Hz), 2.66 (1H, dd, J_1 = 15.6, J_2 = 8.2 Hz), 2.28-2.18 (1H, m), 2.16-2.08 (1H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 168.2, 155.8, 151.3, 148.6, 147.6, 133.9, 132.0, 128.5, 124.8, 123.8, 123.3, 123.1, 51.7, 41.7, 40.1, 36.3, 33.9; HRMS (ESI) calcd for $C_{26}H_{23}N_4O_6$ $[M+H]^+$ 487.1618 found 487.1635.

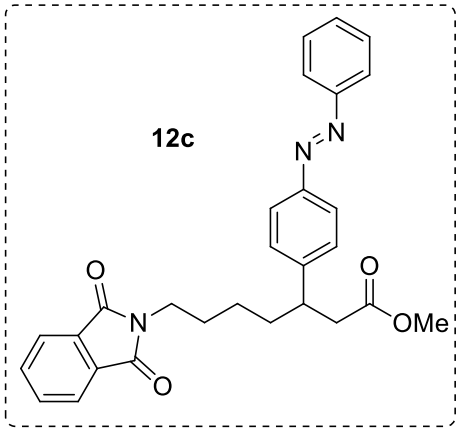
(*E*)-Methyl 3-(4-((4-chlorophenyl)diazenyl)phenyl)-5-(1,3-dioxoisoindolin-2-yl)pentanoate (12b2): The compound **12b2** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored solid (30 mg, 63%, 0.1 mmol scale); R_f(30% EtOAc:hexane) 0.7; mp: 108-110 ^oC; IR (DCM): 2925, 1705, 1395, 1085, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.85-7.83 (2H, m), 7.81-7.76 (4H, m), 7.64 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.51-7.49 (2H, m), 7.40 (2H, d, J = 8.4 Hz), 3.69-3.61 (2H, m), 3.59 (3H, s), 3.34-3.27 (1H, m), 2.73 (1H, dd, J_1 = 15.5, J_2 = 6.9 Hz), 2.65 (1H, dd, J_1 = 15.5, J_2 = 8.1 Hz), 2.27-2.18 (1H, m), 2.14-2.06 (1H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 168.2, 151.3, 151.0, 146.2, 136.8, 133.8, 132.0, 129.3, 128.2, 124.0, 123.2, 123.1, 51.7, 41.6, 40.1, 36.3, 33.7; HRMS (ESI) calcd for $C_{26}H_{23}ClN_3O_4$ $[M+H]^+$ 476.1377 found 476.1355.



(*E*)-Methyl 5-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)pentanoate (12b3): The compound **12b3** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow colored solid (23 mg, 74%, 0.07 mmol scale); R_f(30% EtOAc:hexane) 0.7; mp: 110-112 ^oC; IR (DCM): 2950, 2359, 1709, 1396, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H7.89 (2H, d, J = 7.8 Hz), 7.81-7.75 (4H, m), 7.64 (2H, dd, J_1 = 5.2, J_2 = 3.6Hz), 7.56-7.47 (3H, m), 7.39 (2H, d, J = 8.0 Hz), 3.66 (2H, t, J = 7.1 Hz), 3.59 (3H, s), 3.34-3.27 (1H, m), 2.76-2.62 (2H, m), 2.28-2.19 (1H, m), 2.14-2.06 (1H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 168.3, 152.7, 151.5, 145.8, 133.8, 132.0, 130.9, 129.1, 128.2, 123.2, 123.1, 122.8, 51.7, 41.7, 40.1, 36.4, 33.7; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1767 found 442.1771.

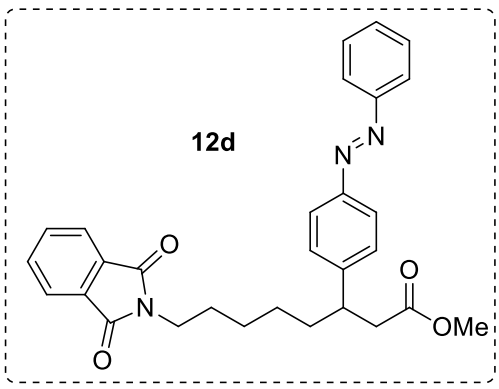


(*E*)-Methyl 7-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)heptanoate (12c): The compound **12c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored viscous liquid (33 mg, 70%, 0.1 mmol scale); R_f(30% EtOAc:hexane) 0.7; IR (DCM): 2941, 1708, 1395, 1157, 719 cm^{-1}; ^1H NMR (400 MHz,

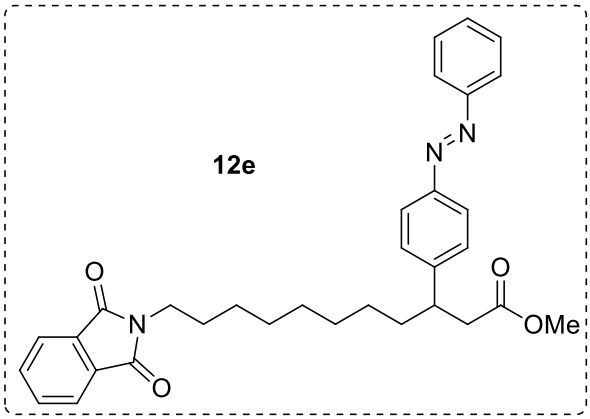


$CDCl_3$) δ_H7.93-7.90 (2H, m), 7.84-7.80 (4H, m), 7.68 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.56-7.47 (3H, m), 7.32 (2H, d, J = 8.4 Hz), 3.63 (2H, d, J = 7.2 Hz), 3.60 (3H, s), 3.24-3.17 (1H, m), 2.72-2.61 (2H, m), 1.82-1.58 (4H, m), 1.31-1.20 (2H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 168.4, 152.7, 151.4, 147.1, 133.9, 132.1, 130.9, 129.1, 128.2, 123.2, 123.1, 122.8, 51.6, 41.8, 41.4, 37.6, 35.4, 28.2, 24.4; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2080 found 470.2097.

(*E*)-Methyl 8-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)octanoate (12d): The compound **12d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored viscous liquid (34 mg, 70%, 0.1 mmol scale); R_f (30% EtOAc:hexane) 0.7; IR (DCM): 2932, 1734, 1395, 1156, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93-7.90 (2H, m), 7.87-7.82 (4H, m), 7.71 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.55-7.46 (3H, m), 7.34 (2H, d, J = 8.4 Hz), 3.65 (2H, t, J = 7.2 Hz), 3.60 (3H, s), 3.23-3.15 (1H, m), 2.72-2.59 (2H, m), 1.75-1.59 (4H, m), 1.39-1.16 (4H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.6, 168.4, 152.7, 151.4, 147.4, 133.9, 132.1, 130.8, 129.1, 128.2, 123.2, 123.1, 122.8, 51.6, 42.0, 41.4, 37.9, 35.9, 28.4, 26.9, 26.8; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_4$ $[M+H]^+$ 484.2236 found 484.2250.

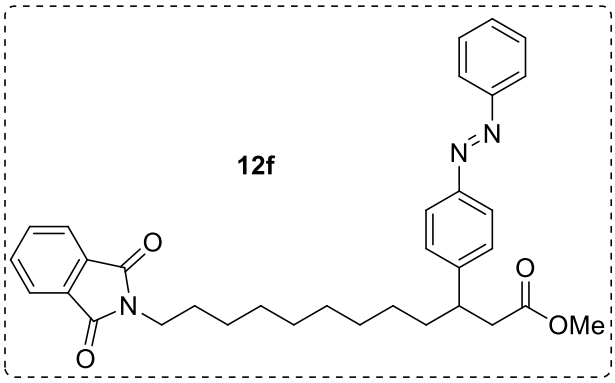


(*E*)-Methyl 11-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)undecanoate (12e): The compound **12e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored viscous liquid (22 mg, 70%, 0.06 mmol scale); R_f(30% EtOAc:hexane) 0.7; IR (DCM): 2927, 1708, 1395, 1155, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.92-7.86 (4H, m), 7.85 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz),7.71 (2H, dd, J_1 =



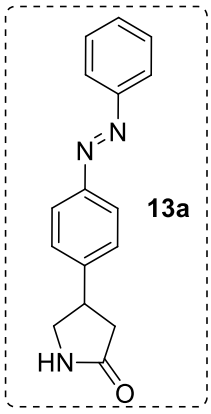
5.4, J_2 = 3.0 Hz), 7.55-7.46 (3H, m), 7.35 (2H, d, J = 8.3 Hz), 3.67 (2H, t, J = 7.3 Hz), 3.61 (3H, s), 3.23-3.15 (1H, m), 2.73-2.60 (2H, m), 1.67-1.62 (4H, m), 1.30-1.15 (10H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 168.5, 152.7, 151.4, 147.6, 133.9, 132.2, 130.8, 129.1, 128.2, 123.2, 123.0, 122.8, 51.6, 42.1, 41.5, 38.0, 36.1, 29.4, 29.3, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{32}H_{36}N_3O_4$ $[M+H]^+$ 526.2706 found 526.2681.

(*E*)-methyl 12-(1,3-dioxoisoindolin-2-yl)-3-(4-(phenyldiazenyl)phenyl)dodecanoate (12f):



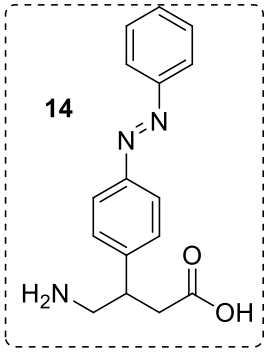
The compound **12f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as an orange colored viscous liquid (45 mg, 83%, 0.1 mmol scale); R_f(30% EtOAc:hexane) 0.7; IR (DCM): 2927, 2360, 1708, 1394, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.93-7.83 (6H, m), 7.71 (2H, dd, J_1 = 5.5, J_2 = 2.8Hz), 7.55-7.46 (3H, m), 7.35 (2H, d, J = 7.6 Hz), 3.68 (2H, t, J = 7.2 Hz), 3.61 (3H, s), 3.23-3.16 (1H, m), 2.73-2.60 (2H, m), 1.68-1.63 (4H, m), 1.31-1.15 (12H, m); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 168.5, 152.7, 151.4, 147.7, 133.9, 132.2, 130.8, 129.1, 128.2, 123.2, 123.0, 122.8, 51.6, 42.1, 41.5, 38.1, 36.2, 29.5, 29.4, 29.4, 29.1, 28.6, 27.3, 26.8; HRMS (ESI) calcd for $C_{33}H_{38}N_3O_4$ $[M+H]^+$ 540.2862 found 540.2876.

(*E*)-4-(4-(Phenyldiazenyl)phenyl)pyrrolidin-2-one (13a): The compound **13a** was obtained



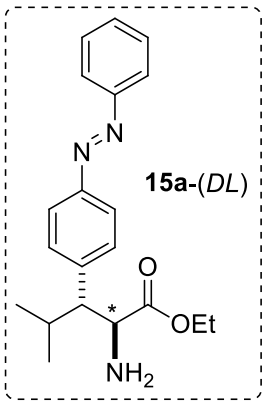
after purification by column chromatography on silica gel (EtOAc:MeOH = 90:10) as an orange colored solid (35 mg, 88%, 0.15 mmol scale); R_f(90% EtOAc:MeOH) 0.2; mp: 156-158 ^{o}C; IR (DCM): 3091, 1702, 1682, 1264, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.95-7.93 (4H, m), 7.57-7.49 (3H, m), 7.43 (2H, d, J = 7.4Hz), 6.46 (1H, br. s), 3.89-3.77 (2H, m), 3.50 (1H, t, J = 7.4Hz), 2.82 (1H, dd, J_1 = 17.1, J_2 = 8.6Hz), 2.61-2.55 (1H, dd, J_1 = 17.0, J_2 = 8.2Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 177.4, 152.6, 151.8, 145.2, 131.1, 129.1, 127.6, 123.4, 122.9, 49.3, 40.2, 37.9; HRMS (ESI) calcd for $C_{16}H_{16}N_3O[M+H]^+$ 266.1293 found 266.1288.

(*E*)-4-Amino-3-(4-(phenyldiazenyl)phenyl)butanoic acid (14): The compound **14**was obtained by following the above procedure as a brown colored solid (20 mg, 70%, 0.1 mmol scale); mp:



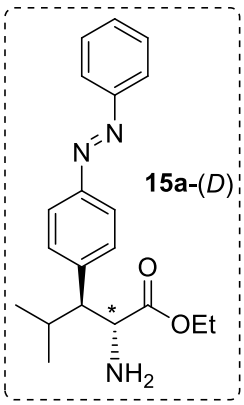
236-238 °C; IR (DCM): 2942, 2356, 1717, 1511, 765 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ_H7.98-7.93 (4H, m), 7.59-7.51 (5H, m), 3.60-3.52 (1H, m), 3.43 (1H, dd, J_1= 12.7, J_2= 5.3 Hz), 3.33-3.27 (1H, m), 2.91 (1H, dd, J_1= 16.6, J_2= 6.6 Hz), 2.78 (1H, dd, J_1= 16.5, J_2= 7.5 Hz); ^{13}C NMR (~101 MHz, CD_3OD): δ_C 173.1, 152.5, 152.2, 142.7, 131.1, 128.9, 128.6, 123.2, 122.4, 43.5, 40.2, 37.9; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_2$ $[M+H]^+$ 284.1399 found 284.1387. (In the proton NMR spectrum the NH_2 and COOH signals could not be clearly ascertained).

(2*S,3*R**)-Ethyl (*E*)-2-amino-4-methyl-3-(4-(phenyldiazenyl)phenyl)pentanoate (15a-(*DL*)):**



The compound **15a**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20) as an orange colored viscous liquid (35 mg, 87%, 0.12 mmol scale); R_f(60% EtOAc/hexane) 0.3; IR (DCM): 2959, 1730, 1180, 1020, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.93 (2H, d, J = 7.4 Hz), 7.86 (2H, d, J = 8.3Hz), 7.56-7.47 (3H, m),7.32 (2H, d, J = 8.3 Hz), 4.11-4.03 (2H, m), 3.89 (1H, d, J = 6.7 Hz), 2.79 (1H, t, J = 7.5 Hz), 2.51-2.42 (1H, m), 1.82 (2H, br. s), 1.15 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.7 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 175.0, 152.7, 151.6, 143.2, 130.9, 130.1, 129.1, 122.8, 122.4, 60.8, 57.3, 56.6, 28.3, 21.5, 19.9, 14.1; HRMS (ESI) calcd for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2025 found 340.2016.

The enantiomeric ratio compound **15a**-(*DL*) was determined by HPLC using the Daicel Chiralcel IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 310 nm, t_L = 14.32 min, t_D= 16.47 min.



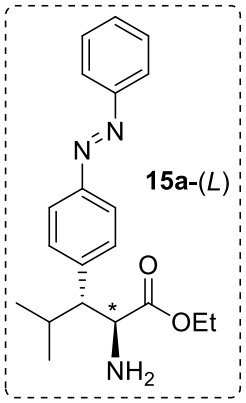
Ethyl (2*R*,3*S*)-2-amino-4-methyl-3-(4-((*E*)-phenyldiazenyl)phenyl)pentanoate (15a-(*D*)):The compound **15a**-(*D*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20) as an orange colored viscous liquid (15 mg, 88%, 0.05 mmol scale); R_f(60% EtOAc/hexane) 0.3; IR (DCM): 2958, 1710, 1180, 1030, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (2H, m), 7.88-7.85 (2H, m), 7.56-7.47 (3H, m),7.32 (2H, d, J = 8.4Hz), 4.14-4.04 (2H, m), 3.92 (1H, d, J = 6.6Hz), 2.80 (1H, t, J = 7.9Hz), 2.50-2.42 (1H,

m), 2.27 (2H, br. s), 1.15 (3H, t, *J* = 7.2Hz), 1.07 (3H, d, *J* = 6.6Hz), 0.82 (3H, d, *J* = 6.7Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 174.6, 152.7, 151.6, 143.0, 130.9, 130.1, 129.1, 122.7, 122.4, 60.8, 57.2, 56.4, 28.3, 21.4, 19.9, 14.0; HRMS (ESI) calcd for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2025 found 340.2029.

$[\alpha]^{25}_D$= 43.1 (*c* = 0.02 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 94:6) of compound **15a**-(*D*) was determined by HPLC using the Daicel Chiralcel IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 310 nm, t_L = 14.11 min, t_D= 15.99 min.

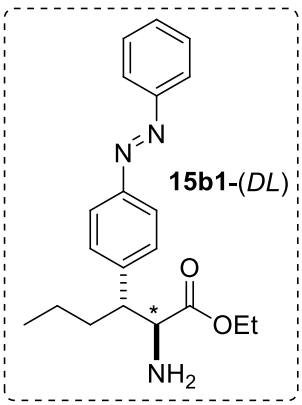
(2*S*,3*R*)-Ethyl 2-amino-4-methyl-3-(4-((*E*)-phenyldiazenyl)phenyl)pentanoate (15a-(*L*)):The



compound **15a**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20) as an orange colored viscous liquid (32 mg, 86%, 0.11 mmol scale); R_f(60% EtOAc/hexane) 0.3; IR (DCM): 2960, 1731, 1185, 1015, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (2H, m), 7.87-7.85 (2H, m), 7.56-7.47 (3H, m),7.34-7.31 (2H, m), 4.11-4.04 (2H, m), 3.89 (1H, d, *J* = 6.8Hz), 2.79 (1H, t, *J* = 7.8Hz), 2.51-2.42 (1H, m), 1.61 (2H, br. s), 1.15 (3H, t, *J* = 7.2Hz), 1.06 (3H, d, *J* = 6.7Hz), 0.82 (3H, d, *J* = 6.7Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 174.9, 152.7, 151.6, 143.2, 130.9, 130.1, 129.1, 122.8, 122.5, 60.8, 57.3, 56.5, 28.3, 21.5, 19.9, 14.1; HRMS (ESI) calcd for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2025 found 340.2027.

$[\alpha]^{25}_D$= -46.1 (*c* = 0.02 g/100 mL, $CHCl_3$).

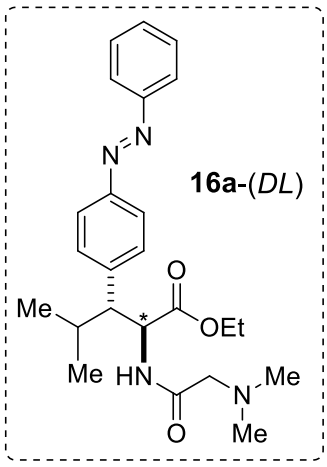
The enantiomeric ratio (*er* = 97:3) of compound **15a**-(*L*) was determined by HPLC using the Daicel Chiralcel IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 310 nm, t_L = 13.97 min, t_D= 17.29 min.



(2*S,3*R**)-Ethyl (*E*)-2-amino-3-(4-(phenyldiazenyl)phenyl)hexanoate (15b1-(*DL*)):** The compound **15b1-(*DL*)** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as an orange colored viscous liquid (16 mg, 80%, 0.06 mmol scale); R_f(30% EtOAc/hexane) 0.3; IR (DCM): 2927, 1731, 1681, 1181, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.93 (2H, d, *J* = 7.7 Hz), 7.89 (2H, d, *J* = 7.7 Hz), 7.56-7.47 (3H, m), 7.40 (2H, d, *J* = 7.8 Hz), 4.06 (2H, q, *J* = 7.1 Hz), 3.64 (1H, d,

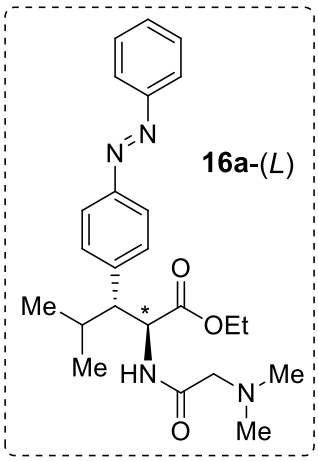
J= 6.4 Hz), 3.07-3.01 (1H, m), 2.12 (2H, br. s), 1.88-1.81 (2H, m), 1.24-1.17 (2H, m), 1.13 (3H, t, *J* = 7.1Hz), 0.90 (3H, t, *J* = 7.2Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 174.6, 152.7, 151.7, 144.7, 130.9, 129.3, 129.1, 122.8, 122.8, 60.8, 59.9, 49.8, 32.5, 20.5, 14.1, 14.0; HRMS (ESI) calcd for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2025 found 340.2018.

(2*S,3*R**)-Ethyl (*E*)-2-amino-3-phenyl-3-(4-(phenyldiazenyl)phenyl)propanoate (15c1-(*DL*)):** The compound **15c1**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as an orange colored viscous liquid (22 mg, 59%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.3; IR (DCM): 2922, 1725, 1580, 1211, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (2H, d, *J* = 7.4Hz), 7.86 (2H, d, *J* = 7.6Hz), 7.56-7.47 (5H, m),7.37-7.28 (5H, m), 4.35 (1H, d, *J* = 8.6Hz), 4.29 (1H, d, *J* = 8.6Hz), 4.03 (2H, q, *J* = 7.1Hz), 1.67 (2H, br. s), 1.06 (3H, t, *J* = 7.2Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ_C 174.3, 152.7, 151.4, 144.7, 140.0, 130.9, 129.1, 129.0, 128.9, 128.8, 127.3, 123.0, 122.8, 61.0, 58.7, 56.4, 13.9; HRMS (ESI) calcd for $C_{23}H_{24}N_3O_2$ $[M+H]^+$ 374.1869 found 374.1865.



Ethyl (*2S*,3R)-2-(2-(dimethylamino)acetamido)-4-methyl-3-(3-((*E*)-phenyldiazenyl)phenyl)pentanoate 16a-(*DL*):** The compound **16a**-(*DL*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20) as an orange color viscous liquid (27 mg, 79%, 0.08 mmol scale); R_f(100% EtOAc) 0.5; IR (DCM): 2957, 1734, 1680, 1504, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (2H, m), 7.87 (2H, dt, J_1= 8.4, J_2= 2.1 Hz), 7.60 (1H, d, *J* = 9.1Hz), 7.56-7.47 (3H, m),7.29-7.27 (2H, m), 5.18 (1H, dd, J_1= 9.2, J_2= 7.1 Hz), 4.12-4.04 (2H, m), 3.06 (1H, d, *J* = 16.3 Hz), 2.96 (1H, d, *J* = 16.3 Hz), 2.87 (1H, t, *J* = 7.9 Hz), 2.36-2.25 (1H, m), 2.29 (6H, s), 1.15 (3H, d, *J* = 6.6 Hz),1.13 (3H, t, *J* = 7.2 Hz), 0.83 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ_C 171.1, 170.3, 152.7, 151.8, 142.0, 130.9, 130.0, 129.1, 122.8, 122.5, 63.0, 61.1, 56.0, 53.4, 46.0, 29.0, 21.4, 20.1, 13.9; HRMS (ESI) calcd for $C_{24}H_{33}N_4O_3$ $[M+H]^+$ 425.2553 found 425.2569.

The HPLC of compound **16a**-(*DL*) was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.20 min, t_L= 15.00 min.

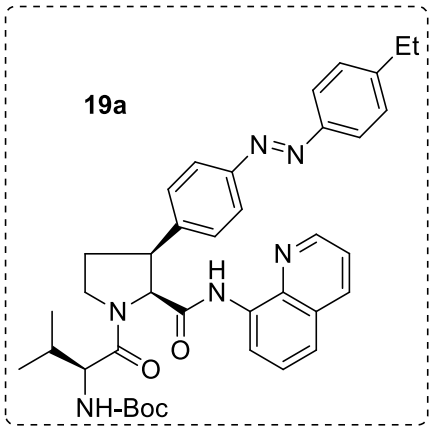


Ethyl (*2S,3R*)-2-(2-(dimethylamino)acetamido)-4-methyl-3-(3-((*E*)-phenyldiazenyl)phenyl)pentanoate 16a-(*L*): The compound **16a**-(*L*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20) as an orange color viscous liquid (16 mg, 76%, 0.05 mmol scale); R_f(100% EtOAc) 0.5; IR (DCM): 2931, 1737, 1680, 1512, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.94-7.91 (2H, m), 7.87 (2H, dt, J_1= 8.4, J_2= 2.2 Hz), 7.60 (1H, d, J = 9.2 Hz), 7.57-7.48 (3H, m),7.28 (2H, dt, J_1 = 8.4, J_2 = 2.1 Hz), 5.18 (1H, dd, J_1 = 9.2, J_2 = 7.1 Hz), 4.14-4.02 (2H, m), 3.06 (1H, d, J = 16.3 Hz), 2.96 (1H, d, J = 16.3 Hz), 2.87 (1H, t, J = 7.8 Hz), 2.37-2.22 (1H, m), 2.29 (6H, s), 1.15 (3H, d, J = 6.6 Hz),1.14 (3H, t, J = 7.2 Hz), 0.83 (3H, d, J = 6.7 Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ_C 171.1, 170.3, 152.7, 151.8, 142.0, 131.0, 130.1, 129.1, 122.8, 122.5, 63.1, 61.2, 56.0, 53.4, 46.0, 29.0, 21.4, 20.1, 13.9; HRMS (ESI) calcd for $C_{24}H_{32}N_4NaO_3$ $[M+Na]^+$ 447.2372 found 447.2377.

$[\alpha]^{25}_D$= 52.0 (*c* = 0.02 g/100 mL, $CHCl_3$).

The enantiomeric ratio (*er* = 95:5) of compound **16a**-(*L*) wasdetermined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 12.46 min, t_L= 15.20 min.

tert*-Butyl ((S)-1-((2*S*,3*S*)-3-(4-((*E*)-(4-ethylphenyl)diazenyl)phenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (19a)*: The compound



19a was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40) as a yellow color solid (48 mg, 74%, 0.1 mmol scale); R_f(30% EtOAc/hexane) 0.3; mp: 82-84 °C; IR (DCM): 2965, 1699, 1529, 1166, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.48 (1H, br. s), 8.52 (1H, dd, J_1 = 4.2, J_2 = 1.5 Hz), 8.39 (1H, dd, J_1 = 6.5, J_2 = 2.5 Hz), 7.89 (1H, dd, J_1 = 8.3, J_2 = 1.4 Hz), 7.62 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.35-7.29

(4H, m),7.23-7.16 (3H, m),5.16 (1H, d, J = 9.4Hz), 5.00 (1H, d, J = 8.3Hz), 4.32 (1H, dd, J_1 = 9.4, J_2 = 6.7 Hz), 4.10 (1H, t, J = 9.3 Hz), 3.95-3.89 (1H, m), 3.76-3.69 (1H, m), 2.91-2.80 (1H, m), 2.64 (2H, q, J = 7.6 Hz), 2.34-2.28 (1H, m), 2.10-2.06 (1H, m), 1.40 (9H, s), 1.20 (3H, t, J = 7.6 Hz), 1.04 (3H, d, J = 6.7Hz), 0.88 (3H, d, J = 6.7Hz); $^{13}C\{^1H\}$ NMR (~76 MHz, $CDCl_3$): δ_C 171.8, 167.7, 155.9, 151.8, 150.8, 147.9, 147.7, 139.2, 138.2, 135.9, 133.7, 128.6, 128.4, 127.6, 126.9, 122.8, 122.7, 121.6, 121.3, 116.4, 79.5, 65.6, 56.5, 46.8, 31.4, 28.8, 28.8, 28.4, 19.6, 17.6, 15.3; HRMS (ESI) calcd for $C_{38}H_{45}N_6O_4$ $[M+H]^+$ 649.3502 found 649.3510.

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CHAPTER 5

Pyridine *N*-oxide directed remote functionalization of phenylacetamides, phenylglycine and heterocyclic amides *via* Pd-catalyzed regioselective γ-C(sp^2/sp^3)-H and δ-C-(sp^2)-H functionalization.

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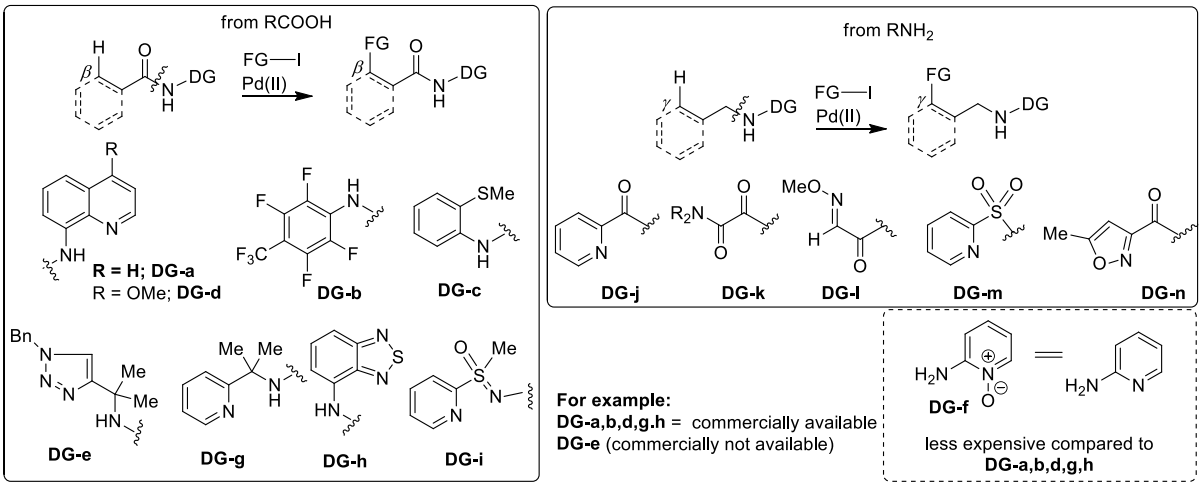
The transition metal-catalyzed C-H activation/functionalization has emerged as a remarkable transformation for incorporating functional groups in small organic molecules.[1,2] Especially, the Pd(II)-catalyzed directing group-aided and chelation-assisted C-H activation/functionalization tactic is emerging as a reliable method for functionalizing organic molecules with a high level of site-selectivity.[1,2] For example, the site-selective C-H activation/functionalization of carboxylic acid and amine substrates have been accomplished using Daugulis's bidentate directing groups such as 8-aminoquinoline and picolinamide, respectively.[2,3a,b] Subsequently, other bidentate directing groups (DGs, Scheme 1) were identified for performing the C-H functionalization of carboxamides.[2-5] For example, the bidentate directing group 8- aminoquinoline provides chelation assistance for the site-selective functionalization through the *N*,*N*-coordination.[3a,b] Other DGs such as **DG-c** or **DG-f** provide the chelation assistance for the site-selective functionalization through the *N*,*S*-coordination[3b,c] and *N*,*O*-coordination,[5] respectively. With regard to site-selectivity, in most of the Pd(II)-catalyzed bidentate directing group-aided C-H functionalization of carboxylic acid derivatives, the transformation takes place at the β-C-H bonds.[2] Markedly, the Pd(II)-catalyzed functionalization of the remote sp^2/sp^3 γ- and δ-C-H bonds of carboxamides have been studied mostly by using the 8-aminoquinoline-type DGs which operate *via* the *N*,*N*-coordination.[6-8] Consequently, the Pd(II)-catalyzed functionalization of the remote sp^2/$sp^3$$\gamma$- and δ-C-H bonds of carboxamides assisted by the DGs other than 8-aminoquinoline-type DG is seldom explored.[1s,2,9] Furthermore, the Pd(II)-catalyzed bidentate directing group-aided site-selective C-H functionalization (e.g., arylation or alkylation) of

substrates containing competitive $sp^2/sp^3\gamma$- and δ-C-H bonds is not a fully established research topic.[2]



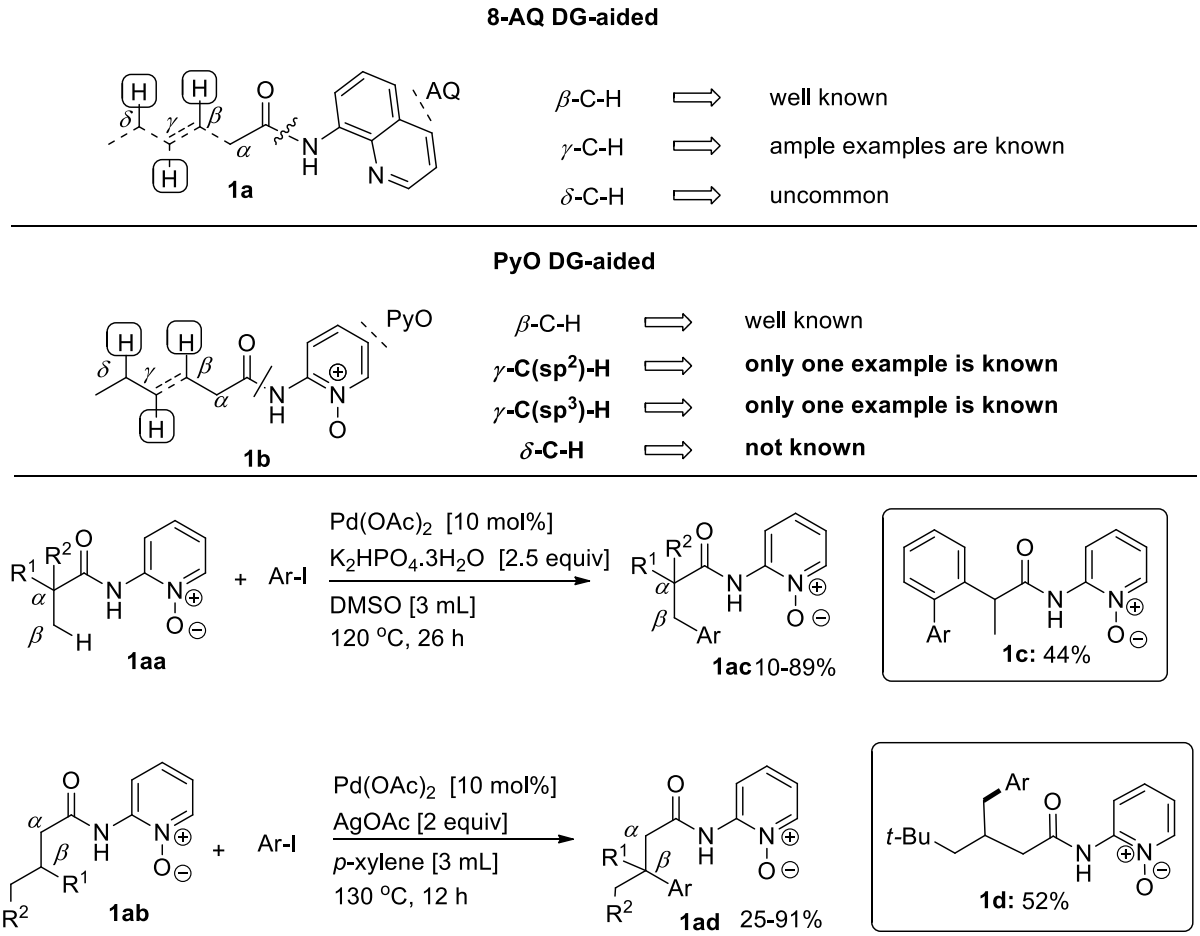
Scheme 1. Examples of bidentate directing groups were explored for the site-selective C-H functionalization.

We chose to expand the scope of pyridine-*N*-oxide (**DG-f**) for the functionalization of the remote $sp^2/sp^3\gamma$- and δ-C-H bonds of carboxamides. The pyridine-*N*-oxide bidentate directing group which provides the chelation assistance for the C-H functionalization through the *N,O*-coordination has been well utilized for functionalizing the β-C(sp^2)-H bonds[10] and is rarely used for functionalizing the β-C(sp^3)-H bonds.[11]

In 2015, Song's gruop[5a] reported a method for the Pd catalyzed β-C(sp^3)-H aylation of aliphatic amides in the presence of $K_2HPO_4.3H_2O$ by employing pyridine-*N*-oxide (**DG-f**) as a directing group. There exists only a single example of pyridine-*N*-oxide (**DG-f**)-aided remote γ-C(sp^2)-H arylation of a propionamide affording **1c** in 44% yield (Scheme 2). In the same year Lu and Zeng's group[5b] also reported pyridine-*N*-oxide (**DG-f**)-aided arylation of β-C(sp^3)-H bonds of aliphatic amides. Optimized reaction condition includes 1.5 equiv of aryl halide, 10 mol% of $Pd(OAc)_2$, 2.0 equiv of AgOAc in *p*-xylene at 130 ^oC for 12 h (Scheme 2). Similarly, they have also reported only a single example of pyridine-*N*-oxide (**DG-f**)-aided remote γ-C(sp^3)-H arylation of an aliphatic carboxamide affording **1d** in 52% yield (Scheme 2).

Given these two isolated examples, we felt it is important to expand the utility of the pyridine-*N*-oxide directing group for the γ-C(sp^2)-H, γ-C(sp^3)-H and δ-C(sp^2)-H functionalization. Pyridine-

N-oxide (PyO) DG can be easily attached to carboxylic acid and its precursor 2-aminopyridine is an easily available and inexpensive chemical compared to most of the other bidentate directing groups (**DG-a,b,d,g,h**).[2]



Scheme 2. Expanding the scope of pyridine-*N*-oxide DG-aided site-selective γ-C(sp^2)-H, γ-C(sp^3)-H and δ-C(sp^2)-H functionalization.

On the other hand, the heteroaromatic *N*-oxides and in particular, pyridine-*N*-oxide (2-aminopyridyl) unit have found significant application in the medicinal chemistry research area (Figure 1).[12,13] For example, pyridine-*N*-oxide-based compound (**IX**) was found to exhibit anti-HIV activity[13a] and arimoclomol (**XI**) is a drug molecule used for Niemann-Pick type C. Pyridine-*N*-oxide-based compound (**X**) was found to be a potent P1 *N*-benzylamide thrombin inhibitor.[13b] Various 2-aminopyridine-based compounds (**XII)** derived from arylacetic acids have been found to be potent SHIP2 inhibitors.[13c] Furthermore, independently biaryl-based small organic molecules,[14] arylacetamide and arylacetic acid derivatives[15] are significant

classes of compounds in organic synthesis and pharmaceuticals (Figure 1). There have been continuous efforts in establishing newer methods for synthesizing these types of medicinally relevant small organic molecules including pyridine-*N*-oxide unit containing molecules.

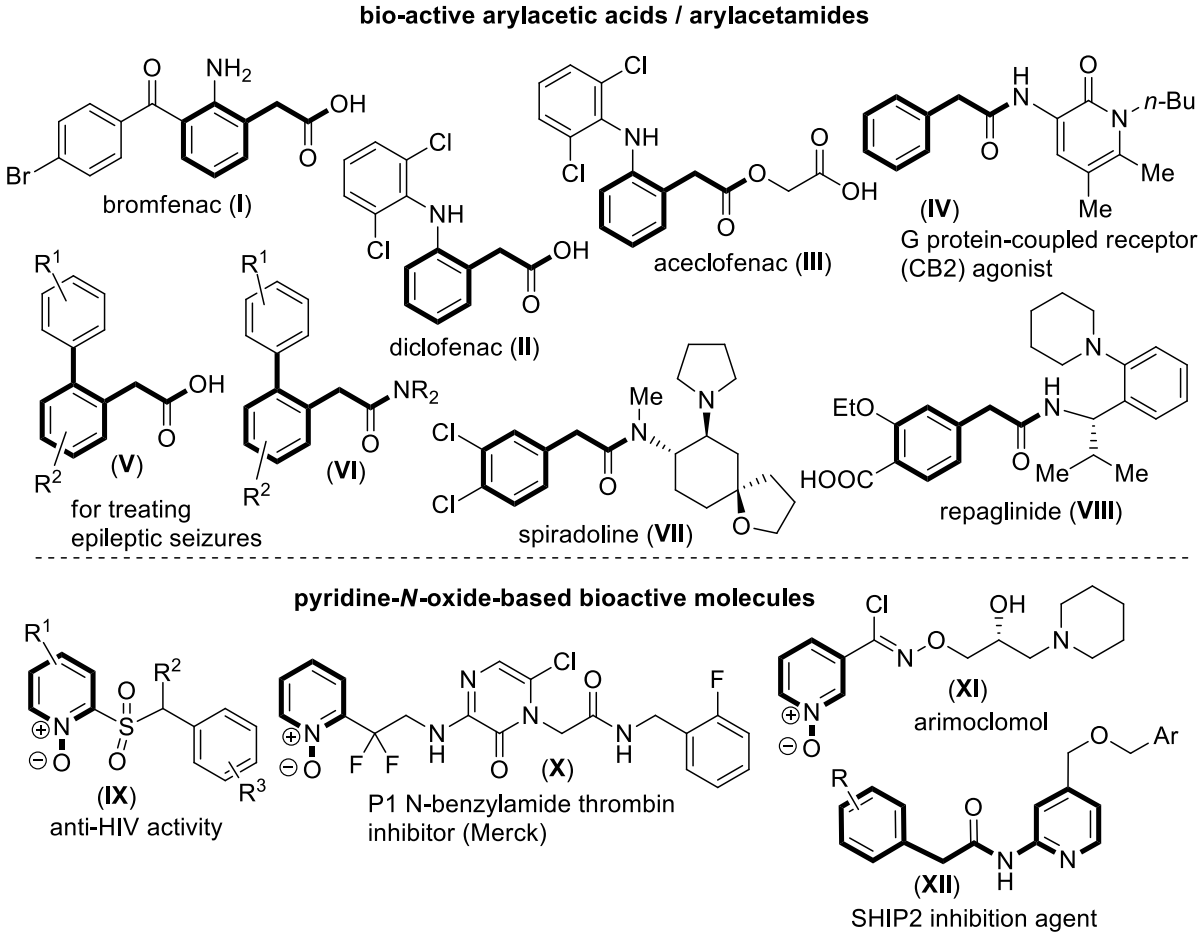


Figure 1. Examples of bio-active arylacetic acid and arylacetamide derivatives and pyridine-*N*-oxide-based compounds.

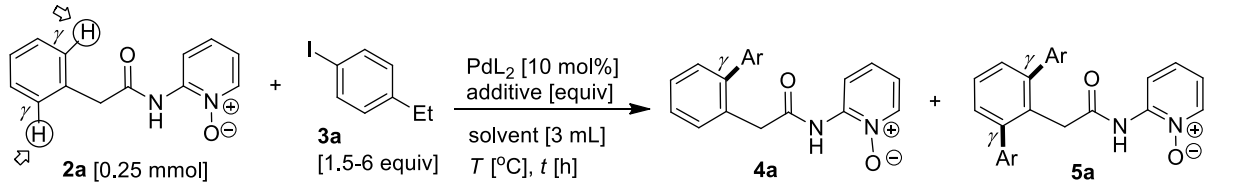
Consequently, exploring the scope of pyridine-*N*-oxide as the DG for the C-H functionalization of arylacetamides and related carboxamides not only will expand the scope of the sp^2/sp^3-γ- and δ- C-H functionalization and it will also enable to assemble a library of new pyridine-*N*-oxide-based biaryl-based carboxamides. In continuation of our lab's research interest in C-H bond functionalization, we herein report our efforts toward expanding the utility of the pyridine-*N*-oxide directing group for the site-selective γ-C(sp^2)-H, γ-C(sp^3)-H and δ-C(sp^2)-H functionalization and synthesis of a wide range of pyridine-*N*-oxide-based biaryl-based carboxamides. Furthermore, we have compared the performance of pyridine-*N*-oxide **DG-f** with

the commonly used 8-aminoquinoline **DG-a** and picolinamide **DG-j** (Scheme 1). The scope of pyridine-*N*-oxide DG was examined for accomplishing the site-selective and mono selective arylation in substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds. These investigations have enabled to assemble a library of new pyridine-*N*-oxide-based biarylacetamides, heteroaryl-based biaryl carboxamides, tricyclic quinolones, arylheteroarylmethanes, biaryl-based aliphatic carboxamides and mono (*ortho*) arylated phenylglycine derivatives.

Results and Disscusion

To begin our study of expanding the utility of pyridine-*N*-oxide directing group in the Pd(II)-catalyzed site-selective sp^2*γ*-C-H arylation, we performed the optimization of reaction conditions comprising the arylation of arylacetamide substrate **2a** with **3a** (Table 1). At first, we assembled pyridine-*N*-oxide DG linked arylacetamide substrate **2a** from arylacetic acid and 2-aminopyridine-*N*-oxide. Then, substrate **2a** was subjected to the *ortho γ*-C-H arylation reaction in the presence of various Pd(II) catalysts, silver salt additives and solvents. Generally, an additive e.g., a silver salt (AgOAc, or Ag_2CO_3) or alkali metal-based salt/base (K_2CO_3 or KOAc) is required for accomplishing the Pd(II)-catalyzed C-H arylation.[3-11] The additive helps in regenerating the Pd(II)-catalyst and acts as a halide ion scavenger in the proposed Pd^{II}-Pd^{IV} catalytic cycle.[3-11] Earlier, we reported[7b] that 8-aminoquinoline (**DG-a**)-directed arylation of arylacetamide afforded the corresponding bis (*ortho*) *γ*-C-H arylated product as the predominant product and the corresponding mono (*ortho*) *γ*-C-H arylated product was not obtained in characterizable amounts. We hoped to find out independent conditions to selectively obtain the mono as well as bis (*ortho*) *γ*-C-H arylated products **4a** and **5a** by using the pyridine-*N*-oxide DG. The arylation of pyridine-*N*-oxide DG installed arylacetamide **2a** was attempted using 1.5 equiv of 4-ethyliodobenzene (**3a**) in the presence of the $Pd(OAc)_2$ catalyst (10-15 mol%) and $NaHCO_3$ as an additive in toluene at 110 ^oC for 16 h. These trials afforded the mono (*ortho*) *γ*-C-H arylated product **4a** in 18-20% yields (entries 1 and 2, Table 1). Though the product **4a** was obtained in a low yield, these reactions selectively afforded the mono (*ortho*) *γ*-C-H arylated product **4a** and the corresponding bis (*ortho*) *γ*-C-H arylated product **5a** was not obtained in characterizable amounts. Heating a mixture of **2a** with **3a** (1.5 equiv) in the presence of $PdCl_2$ (10 mol%) and $NaHCO_3$ in toluene afforded the product **4a** in 24% yield and traces of the product **5a** (entry 3, Table 1).

Table 1. Optimization of reaction conditions. Pd(II)-catalyzed pyridine-*N*-oxide DG-aided γ-C(sp^2)-H arylation of arylacetamide **2a**.

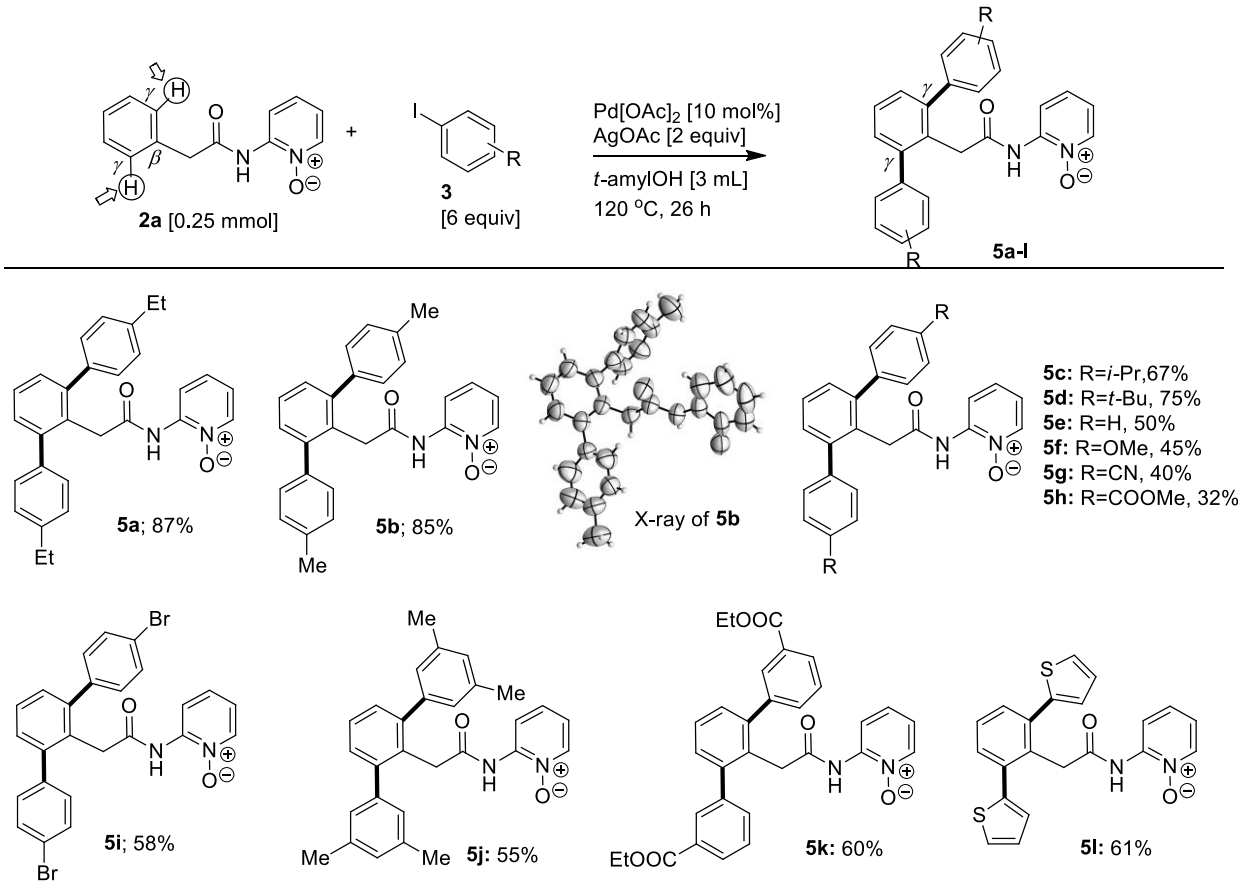


entry	PdL_2[10 mol%]	3a[equiv]	additives[equiv]	solvent	T [oC] / t [h]	4a: yield [%]	5a: yield[%]
1	$Pd[OAc]_2$	1.5	$NaHCO_3$ [4]	toluene	110 / 16	18	0
2[a]	$Pd[OAc]_2$	1.5	$NaHCO_3$ [5]	toluene	110 / 16	20	0
3	$PdCl_2$	1.5	$NaHCO_3$ [4]	toluene	110 / 16	24	<5
4	$Pd[OAc]_2$	2	$NaHCO_3$ [2] N-Boc-proline [30mol%]	t-amylOH/H_2O	110 / 10	24	<5
5	$Pd[OAc]_2$	2	$NaHCO_3$ [2] $[BnO]_2PO_2H$ [30 mol%]	t-amylOH/H_2O	110 / 10	22	8
6	$Pd[OAc]_2$	2	AgOAc [2] $[BnO]_2PO_2H$ [30 mol%]	t-amylOH	120 / 10	36	43
7	$Pd[OAc]_2$	2	AgOAc [2] $[BnO]_2PO_2H$ [30mol%]	p-xylene	130 / 10	36	23
8	$Pd[OAc]_2$	3	AgOAc [2]	p-xylene	130 / 15	18	41
9[b]	$Pd[OAc]_2$	3	Ag_2CO_3 [1]	t-amylOH	120 / 18	38	25
10[a,b]	$Pd[OAc]_2$	3	Ag_2CO_3 [1]	t-amylOH	120 / 15	44	46
11	$Pd[OAc]_2$	3	K_2CO_3 [2]	toluene	110 / 26	44	42
12[b]	$Pd[OAc]_2$	3	Ag_2CO_3 [1]	t-amylOH	120 / 24	55	35
13	$Pd[OAc]_2$	5	AgOAc [2]	p-xylene	130 / 26	8	68
14	$Pd[OAc]_2$	6	AgOAc [2]	p-xylene	130 / 26	20	73
15	$Pd[OAc]_2$	6	AgOAc [2]	toluene	110 / 26	40	53
16	$Pd[TFA]_2$	6	AgOAc [2]	p-xylene	120 / 26	26	72
17	$Pd[PhCN]_2Cl_2$	6	AgOAc [2]	p-xylene	120 / 26	7	67
18	$Pd[MeCN]_2Cl_2$	6	AgOAc [2]	t-amylOH	120 / 26	8	71
19	$Pd[OAc]_2$	6	K_2CO_3 [2]	t-amylOH	120 / 26	10	70

20	$PdCl_2$ [10]	6	AgOAc [2]	p-xylene	120 / 26	0	67
21	$Pd[OAc]_2$	6	AgOAc [2]	t-amylOH	120 / 26	0	87

[a] After a few hours additional 5 mol% catalyst was added. [b] Reaction was done using a 5 mol% catalyst.

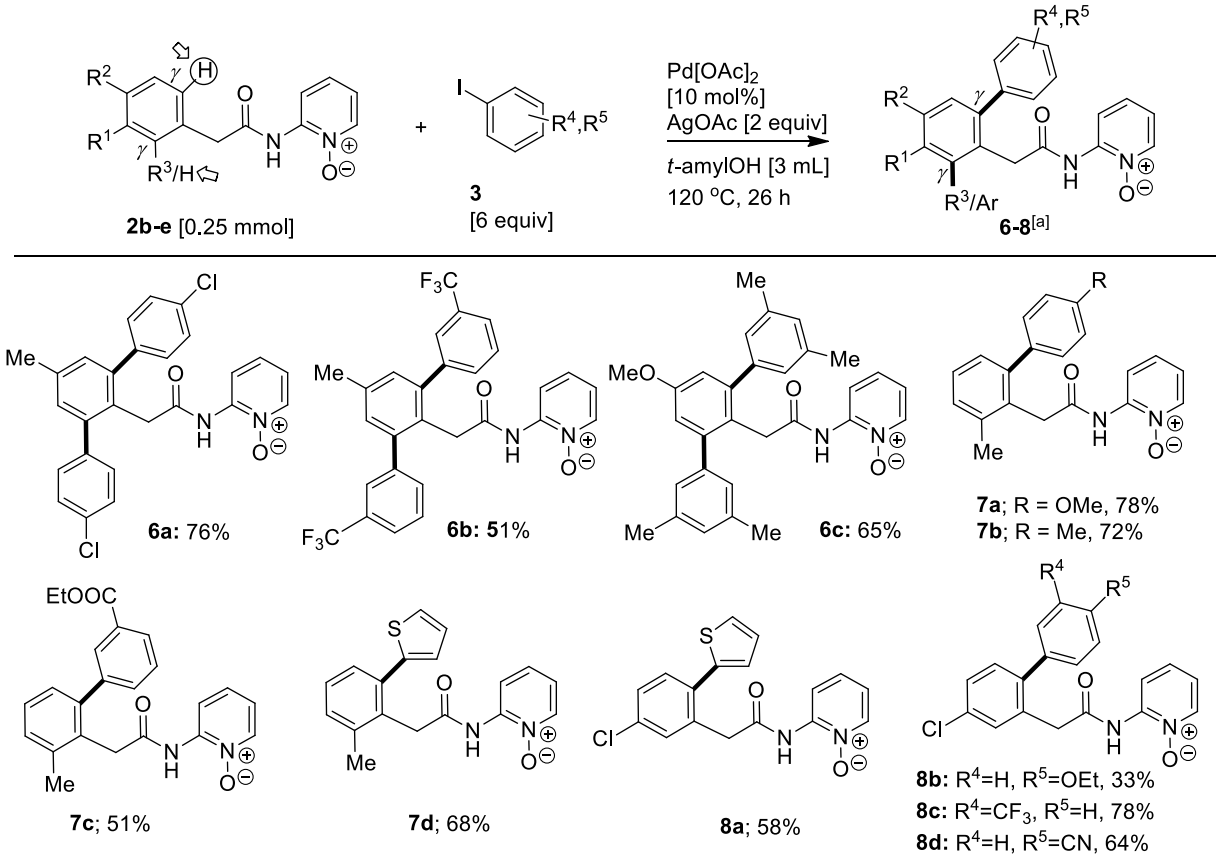
The Pd(II)-catalyzed arylation of **2a** with **3a** (2 equiv) was performed in the presence of $NaHCO_3$ and additional additives such as *N*-Boc-proline or $(BnO)_2POH$ in *t*-AmylOH/H_2O mixture. These reactions afforded the product **4a** in 22-24% yield and traces of the product **5a** (entries 4 and 5, Table 1). The Pd(II)-catalyzed arylation of **2a** with **3a** (2 equiv) in only *t*-AmylOH or *p*-xylene in the presence of AgOAc and $(BnO)_2POH$ afforded the product **4a** in 36% yield and also the bis C-H arylated product **5a** in 23-43% yields (entries 6 and 7, Table 1). The reactions of entries 4-7 indicated that along with mono (*ortho*) arylated product **4a**, the bis (*ortho*) C-H arylated product **5a** is formed in considerable amounts when using 2 equiv of **3a**.



Scheme 3. Substrate scope investigation. Pd(II)-catalyzed pyridine-*N*-oxide DG-aided γ-C(sp^2)-H arylation of **2a**.

We then aimed to find out the best condition for obtaining the bis (*ortho*) *γ*-C-H arylated product **5a** alone in good yield. Accordingly, we performed the Pd(II)-catalyzed arylation of **2a** with **3a** (3 or 5 equiv) by using AgOAc or Ag_2CO_3 or K_2CO_3 in *t*-amylOH or *p*-xylene or toluene. These trials gave both the products **4a** (8-55% yields) and **5a** (25-68% yields, entries 8-13, Table 1). The trials involving Pd(II)-catalyzed arylation of **2a** with **3a** (6 equiv) in the presence AgOAc or K_2CO_3 in *p*-xylene or *t*-amylOH or toluene were found to afford both the products **4a** (7-40% yields) and **5a** (53-73% yields, entries 14-19, Table 1). These reactions indicated that the yield of **5a** has notably increased when using 6 equiv of **3a**. With additional two trials, we found suitable conditions affording the bis (*ortho*) *γ*-C-H arylated product **5a** alone in good yield. Heating a mixture of **2a** with **3a** (6 equiv) in the presence of $PdCl_2$ (10 mol%) and AgOAc in *p*-xylene at 120 ^oC for 26 h was found to afford the bis (*ortho*) *γ*-C-H arylated product **5a** in 67% yield and only traces of **4a** (entry 20, Table 1). Similarly, heating a mixture of **2a** with **3a** (6 equiv) in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in *t*-amylOH at 120 ^oC for 26 h was found to afford the bis (*ortho*) *γ*-C-H arylated product **5a** in a maximum of 87% yield and only traces of **4a** (entry 21, Table 1). It may be noted that the condition used in entries 10-12 gave the mono (*ortho*) *γ*-C-H arylated product **4a** in a maximum of 44 and 55% yields.

Having performed the optimization reactions, we then moved on to expand the utility of pyridine-*N*-oxide directing group for the site-selective *γ*-C(sp^2)-H, *γ*-C(sp^3)-H arylation, *δ*-C(sp^2)-H amidation and synthesis of various pyridine-*N*-oxide-based carboxamide derivatives. In this regard, at first, we investigated the substrate scope and generality of the *γ*-C(sp^2)-H arylation of arylacetamides. The pyridine-*N*-oxide DG-aided arylation of **2a** was performed using various aryl iodides containing different electron-donating and electron-withdrawing substituents at the *p*-position and PhI in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in *t*-amylOH at 120 ^oC. These reactions afforded the corresponding bis (*ortho*) *γ*-C-H arylated arylacetamide derivatives **5a-i** in 32-87% yields (Scheme 3). Additionally, the Pd(II)-catalyzed arylation of **2a** with an aryl iodide containing a substituent at the *m*-position or a disubstituted aryl iodide or a heteroaryliodide afforded the corresponding bis (*ortho*) *γ*-C-H arylated arylacetamide derivatives **5j-l** in 55-61% yields (Scheme 3).

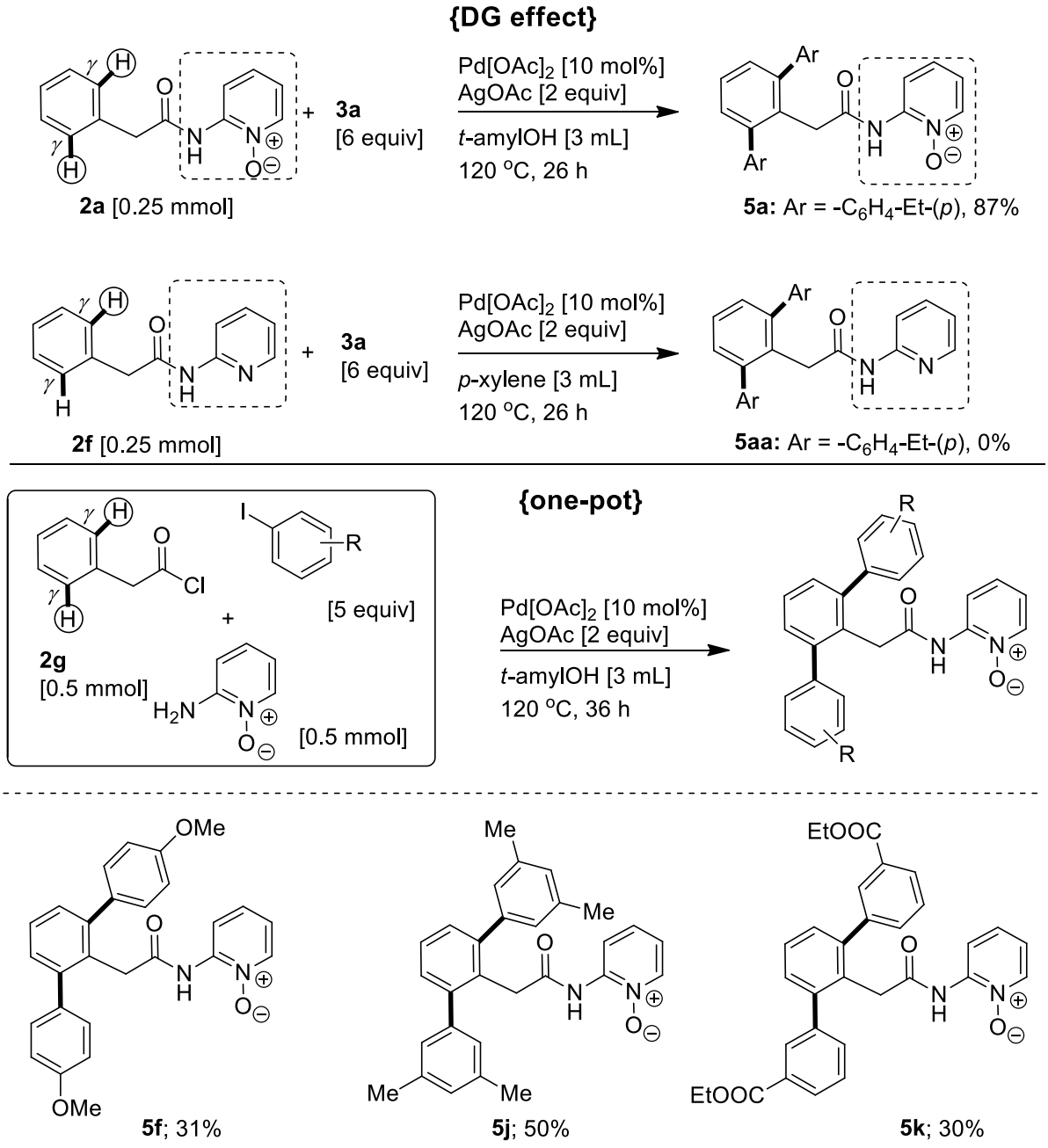


[a] Products **6a,b** were obtained from substrate **2b**. Product **6c** was obtained from substrate **2c**. Products **7a-d** were obtained from substrate **2d**. Products **8a-d** was obtained from substrate **2e**.

Scheme 4. Substrate scope investigation. Pd(II)-catalyzed pyridine-*N*-oxide DG-aided γ-C(sp^2)-H arylation of arylacetamides **2b-e**.

Subsequently, we assembled various pyridine-*N*-oxide-based arylacetamides (**2b-e**) containing different substituents at the *o/m/p* positions. We performed the arylation of arylacetamides **2b,c** containing a substituent at the *p*-position (e.g., Me, OMe) with aryl iodides containing a substituent at the *m/p*-positions or a disubstituted aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in *t*-amylOH at 120 °C. These reactions afforded the corresponding bis (*ortho*) γ-C-H arylated arylacetamide derivatives **6a-c** in 51-76% yields (Scheme 4). Next, we performed the Pd(II)-catalyzed arylation of arylacetamides **2d,e** containing a substituent at the *o-/m*-positions (e.g., Me, Cl) with aryl iodides containing a substituent at the *m/p*-positions or a heteroaryliodide. These reactions afforded the corresponding mono (*ortho*) γ-C-H arylated arylacetamide derivatives **7a-d** and **8a-d** in 33-78% yields (Scheme 4). Due to steric hindrance by the substituent at the *m*-position in arylacetamide **2e**, the arylation of **2e** gave only the mono

(*ortho*) *γ*-C-H arylated products **8a-d**. This observation is a commonly reported trend in substrates including benzamides/arylacetamides containing a substituent at the *m*-position.[2,3]

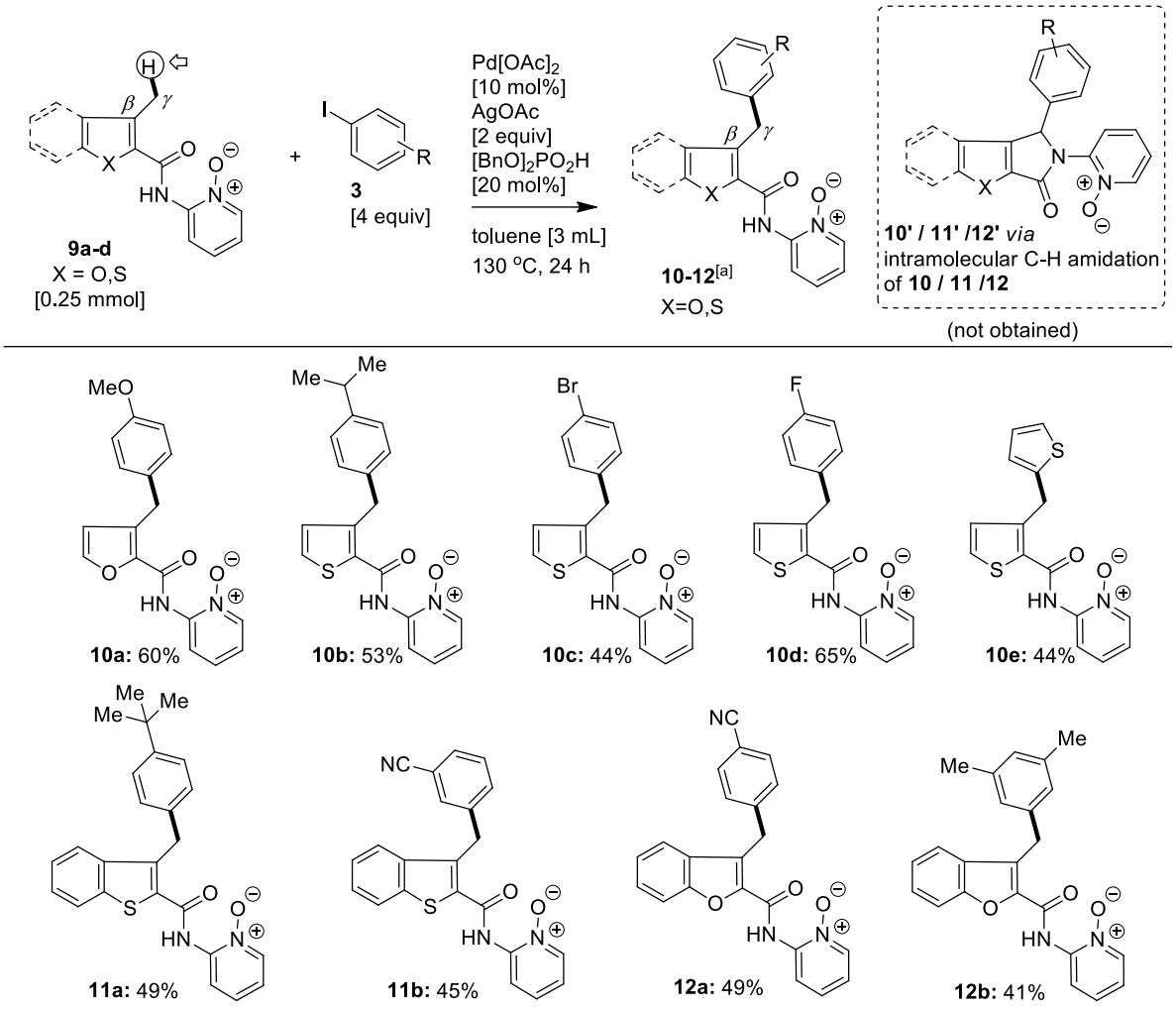


Scheme 5. Scope of the pyridine-*N*-oxide ligand in *γ*-C(sp^2)-H arylation of arylacetamide.

To understand the role of the pyridine-*N*-oxide DG[5] in the Pd(II)-catalyzed (*ortho*) *γ*-C-H arylation of **2a**, we assembled the simple pyridine-DG linked arylacetamide substrate **2f** from arylacetic acid and 2-aminopyridine. We then attempted the arylation of arylacetamide **2f** with

3a in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in *p*-xylene at 120 ^oC under similar conditions employed to obtain the product **5a** from **2a** and **3a**. In contrast to the pyridine-*N*-oxide DG-aided arylation of **2a** which afforded the product **5a** in 87% yield, the arylation of **2f** with **3a** did not yield the expected product **5aa** (Scheme 5). This indicated that the Pd(II)-catalyzed (*ortho*) γ-C-H arylation of **2a** is assisted by the bidentate directing group 2-aminopyridine-*N*-oxide through the *N,O*-coordination.[5] This is similar to the functioning of the bidentate directing group 8-aminoquinoline, which assists the site-selective C-H functionalization through the *N,N*-coordination.[3a,b] To further understand the scope and limitation of the bidentate directing group 2-aminopyridine-*N*-oxide, we attempted the Pd(II)-catalyzed one-pot arylation reaction comprising of *in situ* linking of 2-aminopyridine-*N*-oxide with phenylacetyl chloride. Accordingly, we heated a mixture phenylacetyl chloride, 2-aminopyridine-*N*-oxide, an appropriate aryl iodide in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (2 equiv) in *t*-amylOH at 120 ^oC. Under this one-pot method, we could obtain the corresponding products **5f**, **5j** and **5k** in low to satisfactory yields (30-50%, Scheme 5).

Having examined the γ-C(sp^2)-H arylation of arylacetamides, with an emphasis to expand the scope of the pyridine-*N*-oxide directing group, we wished to examine the site-selective γ-C(sp^3)-H arylation (Scheme 6). Towards this, we assembled pyridine-*N*-oxide directing group installed 3-methylfuran-2-carboxamide (**9a**), 3-methylthiophene-2-carboxamide (**9b**), 3-methylbenzothiophene-2-carboxamide (**9c**) and 3-methylbenzofuran-2-carboxamide (**9d**). Initially, we performed the pyridine-*N*-oxide DG-aided arylation of γ-C(sp^3)-H bond of the methyl group of substrates **9a,b** with various aryl iodides (4 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%), AgOAc (as an iodide ion scavenger) and $(BnO)_2PO_2H$ (20 mol%, as an additional additive/promoter). These reactions gave the corresponding γ-C(sp^3)-H arylated furan- or thiophene-2-carboxamide (arylheteroarylmethane) scaffolds **10a-e** in 44-65% yields. Similarly, we subjected **9c** and **9d** to the Pd(II)-catalyzed methyl γ-C(sp^3)-H arylation reaction with various aryl iodides. The corresponding γ-C(sp^3)-H arylated 3-methylbenzothiophene-2-carboxamide and 3-methylbenzofuran-2-carboxamide (arylheteroarylmethane) motifs **11a,b** and **12a,b** were obtained in 41-49% yields (Scheme 6).

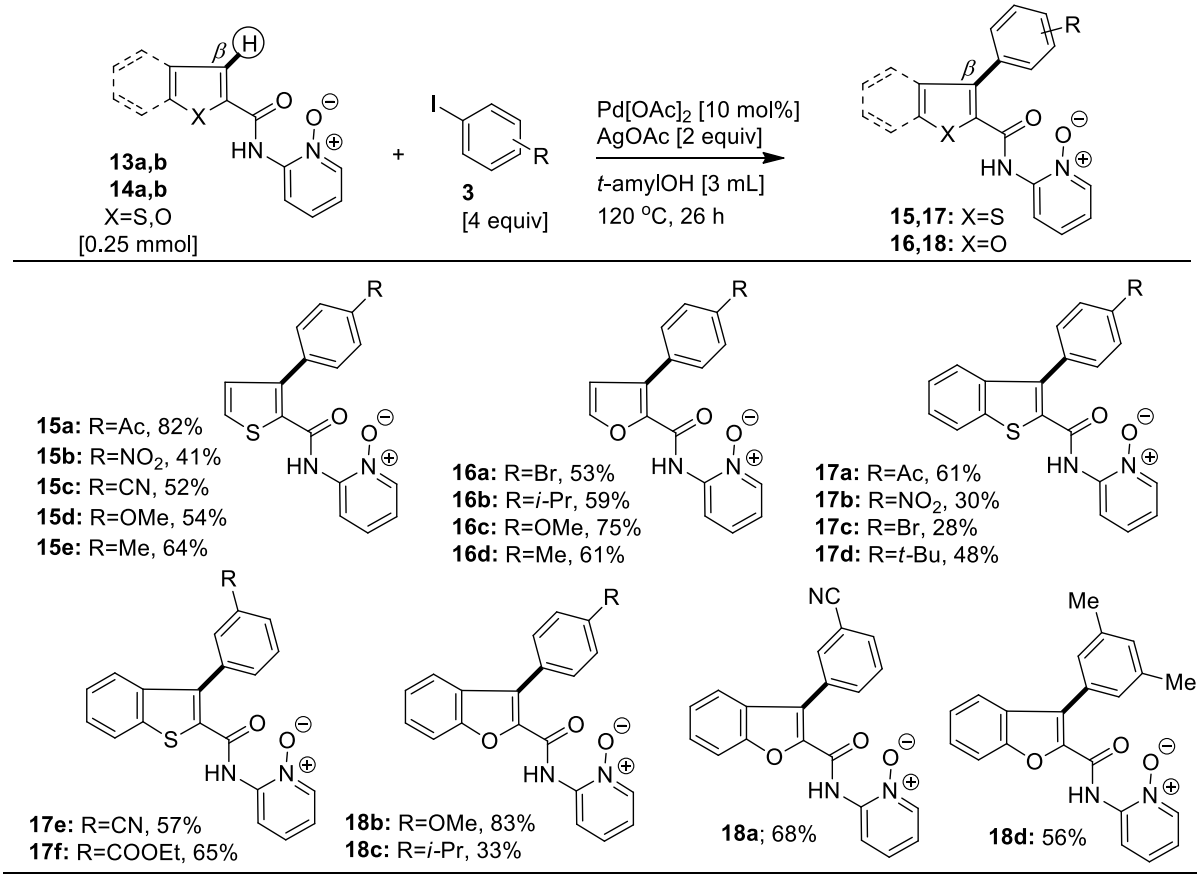


[a] Products **10a** and **10b-e** were obtained from substrates **9a** and **9b**, respectively. Products **11a,b** and **12a,b** were obtained from **9c** and **9d**, respectively.

Scheme 6. γ-C(sp^3)-H Arylation of 3-methylheteroaryl-2-carboxamides and synthesis of arylheteroarylmethanes.

It may be noted that earlier we reported the Pd(II)-catalyzed γ-C(sp^3)-H arylation of 3-methylthiophene-2-carboxamide or 3-methylfuran-2-carboxamide or 3-methylbenzothiophene-2-carboxamide using the 8-aminoquinoline DG.[6b] In our previous work[6b] the treatment of 8-aminoquinoline DG linked 3-methylbenzothiophene-2-carboxamide with 4-tolyliodide (4 equiv) in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in toluene for 4 h gave the expected γ-C(sp^3)-H arylated (arylheteroarylmethane) product. However, the same reaction when performed under a prolonged reaction period of 24 h gave a mixture of products. The observed products were the γ-C(sp^3)-H arylated product (40% yield), successively C-H amidated pyrrolidone-ring annulated product (20% yield) and traces of a ketone by-product. In the current work involving

the pyridine-*N*-oxide DG-aided arylation of methyl γ-C(sp^3)-H bond of 3-methylheteroaryl-2-carboxamides seem to be gentle and even under a prolonged reaction time we did not obtain the corresponding successively C-H amidated pyrrolidone-ring annulated products **10′/11′/12′** in characterizable amounts from their corresponding γ-C(sp^3)-H arylated products **10**/**11**/**12** (Scheme 6).



[a] Products **15a-e** and **16a-d** were obtained from **13a** and **13b**, respectively. Products **17a-f** and **18a-d** were obtained from **14a** and **14b**, respectively.

Scheme 7. β-C(sp^2)-H Arylation of heteroaryl-2-carboxamides and synthesis of heteroaryl-based biaryl carboxamides.

Having investigated the γ-C(sp^2)-H arylation of arylacetamides and methyl γ-C(sp^3)-H bond of 3-methylheteroaryl-2-carboxamides using the pyridine-*N*-oxide DG, we then wished to attempt the δ-C(sp^2)-H functionalization in carboxamides. Taking an impetus from our earlier work,[8b] involving the Pd(II)-catalyzed, 8-aminoquinoline DG-aided aided δ-C(sp^2)-H amidation (C-N bond formation) of heteroaryl-based biaryl carboxamides, we intended to investigate the scope of

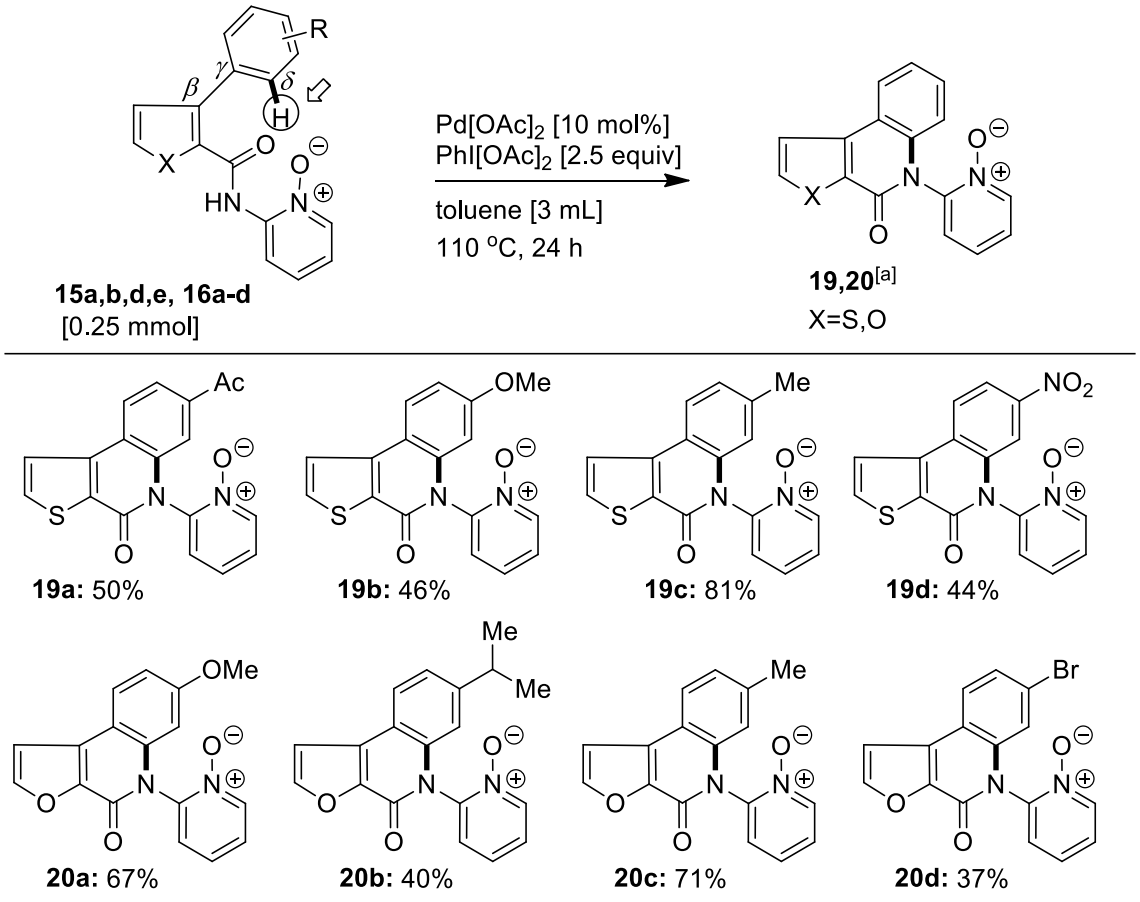
the pyridine-*N*-oxide DG in the *δ*-C(sp^2)-H amidation (C-N bond formation) of heteroaryl-based biaryl carboxamides (Scheme 8).

Towards attempting the pyridine-*N*-oxide DG-aided *δ*-C(sp^2)-H amidation (C-N bond formation) of heteroaryl-based biaryl carboxamides, we started to assemble the required heteroaryl-based biaryl carboxamides **15**/**16** (Scheme 7). The required heteroaryl-based biaryl carboxamides **15**/**16** can be prepared *via* thepyridine-*N*-oxide DG-aided *β*-C(sp^2)-H arylation of heteroaryl-2-carboxamides including thiophene- and furan-2-carboxamides (**13a,b**, Scheme 7). Furthermore, we also noticed that the *β*-C(sp^2)-H arylation of heteroaryl-2-carboxamides **13a,b** and **14a,b** the preparation of heteroaryl-based biaryl carboxamides **15-18** have not been explored using the pyridine-*N*-oxide DG.[10]

At first, the required pyridine-*N*-oxide DG linked thiophene- / furan-2-carboxamides (**13a,b**) and benzothiophene- / benzofuran-2-carboxamides (**14a,b**) were prepared from their corresponding carboxylic acids and 2-aminopyridine-*N*-oxide. Then, the thiophene- / furan-2-carboxamide substrates **13a,b** were subjected to the pyridine-*N*-oxide DG-aided *β*-C(sp^2)-H arylation withvarious aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in *t*-amylOH at 120 ^oC. These reactions afforded the thiophene/furan-based biaryl carboxamides **15a-e** and **16a-d** in 41-82% yields (Scheme 7). Similarly, the Pd(II)-catalyzed *β*-C(sp^2)-H arylation of benzothiophene- / benzofuran-2-carboxamide substrates **14a,b** with various aryl iodides afforded the corresponding benzothiophene/benzofuran-based biaryl carboxamides **17a-f** and **18a-d** in 28-83% yields. We noticed that the performance of the *N*-oxide DG in the *β*-C(sp^2)-H arylation of heteroaryl-2-carboxamides (which afforded the products **15-18** in low to good yields) is comparable to the earlier reported process involving the 8-aminoquinoline DG-aided *β*-C(sp^2)-H arylation of heteroaryl-2-carboxamides.[3v]

Having assembled the required examples of heteroaryl-based biaryl carboxamides **15**/**16** with suitably positioned *δ*-C(sp^2)-H bond with respect to the pyridine-*N*-oxide DG, we then subjected the substrates **15**/**16** to the Pd(II)-catalyzed *δ*-C(sp^2)-H amidation reaction conditions[8b] (Scheme 8). These reactions are expected to afford the corresponding phenanthridin-6(5*H*)-ones (tricyclic quinolones) *via* the pyridine-*N*-oxide DG-aided intramolecular *δ*-C(sp^2)-H amidation (via C-N bond formation). Treatment of thiophene/furan-based biaryl carboxamides **15a,b,d,e** and **16a-d** with $PhI(OAc)_2$ in the presence of $Pd(OAc)_2$ (10 mol%) in toluene at 110 ^oC successfully

afforded the expected thieno[2,3-*c*]quinolin-4(5*H*)-one and furano[2,3-*c*]quinolin-4(5*H*)-one motifs **19a-d** and **20a-d** in 37-81% yields (Scheme 8). It was noted that the performance of the pyridine-*N*-oxide DG in the *δ*-C(sp^2)-H amidation of substrates **15**/**16** is comparable to the earlier reported process involving the 8-aminoquinoline DG.[8b] Nevertheless, functionalized thiophenes/furans and benzothiophenes/benzofurans are an important class of compounds in organic synthesis, materials, and medicinal chemistry.[16] Herein, we have shown the assembling of various arylheteroarylmethanes, heteroaryl-based biaryl carboxamides and quinolone motifs possessing the pyridine-*N*-oxide unit.



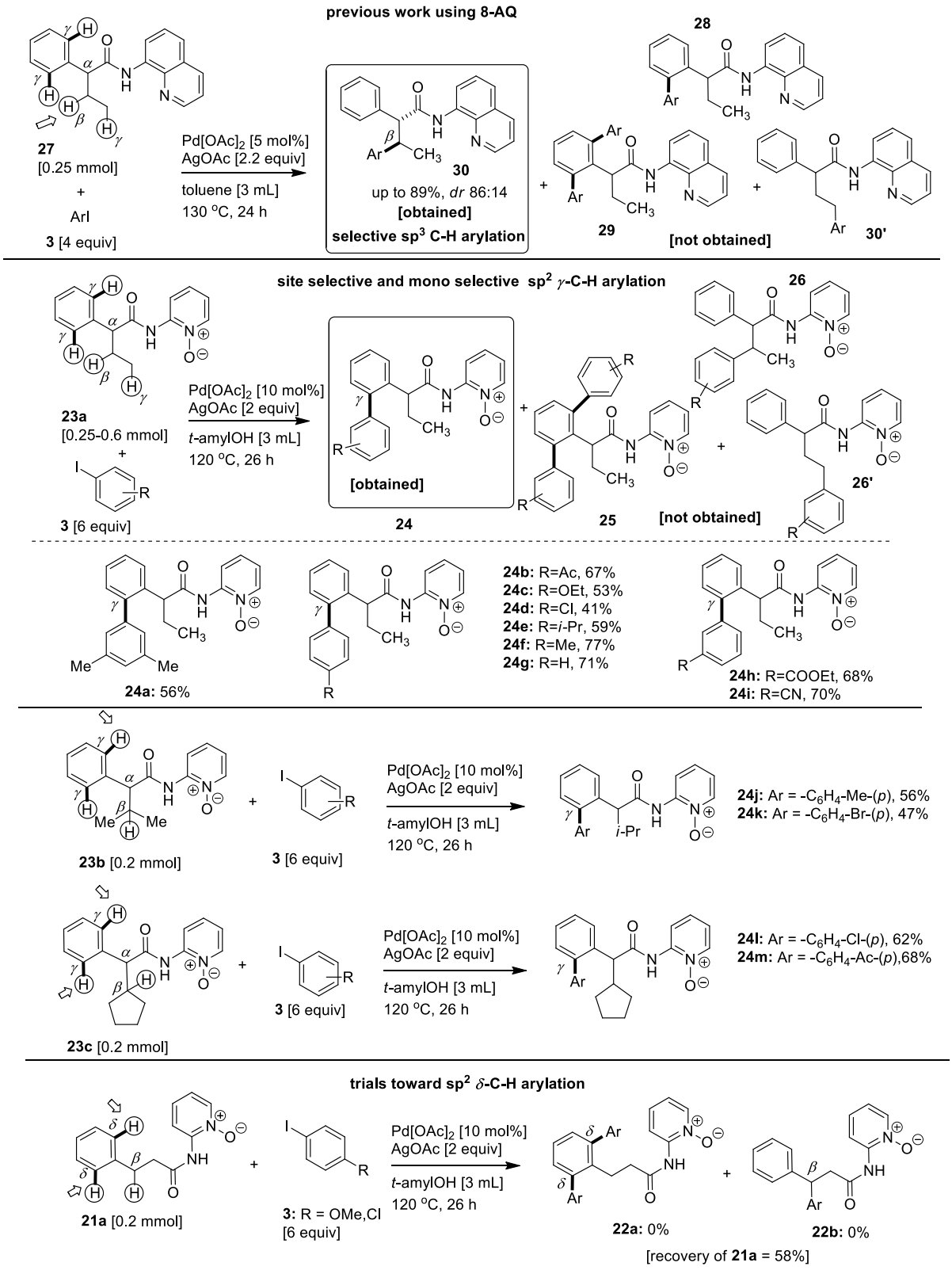
[a] Products **19a-d** and **20a-d** were obtained from their corresponding substrates **15a,b,d,e** and **16a-d**.

Scheme 8. Pd(II)-catalyzed pyridine-*N*-oxide DG-aided *δ*-C(sp^2)-H amidation of biaryl carboxamides towards tricyclic quinolones.

Next, we focused our attention to expand the utility of pyridine-*N*-oxide DG for accomplishing site-selective arylation in substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds. Earlier, Niu/Song revealed[5a] a single example of *ortho*-*γ*-C(sp^2)-H arylation in 2-

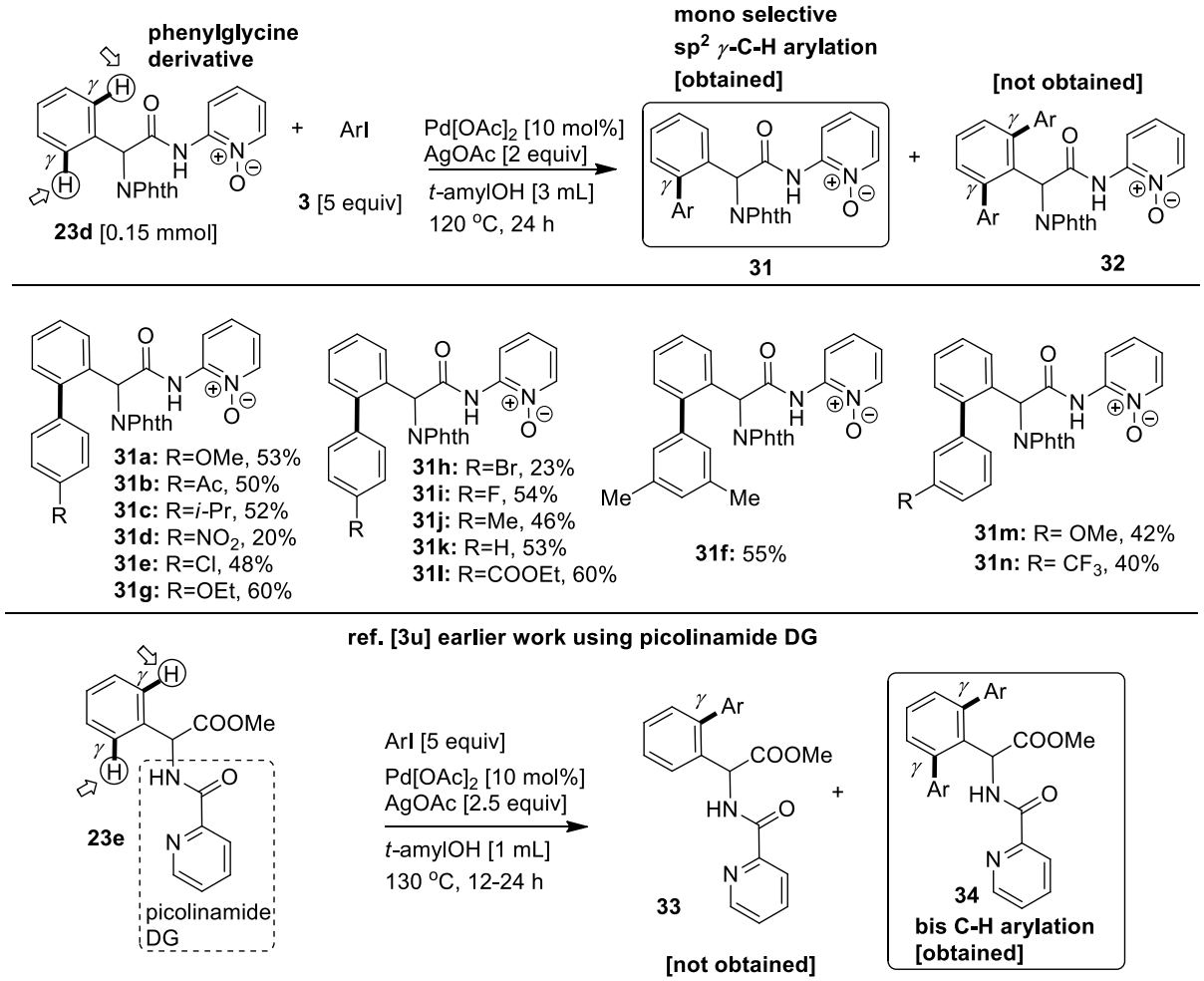
phenylpropionamide containing a competitive methyl β-C(sp^3)-H bond, which afforded the product **1c** in 44% yield (Scheme 2). Inspired by this observation, we assembled pyridine-*N*-oxide DG linked 2-phenylbutyramide **23a** and subjected it to the Pd(II)-catalyzed arylation conditions. The substrate 2-phenylbutyramide **23a** contains competitive γ-C(sp^2)-H, β-C(sp^3)-H and γ-C(sp^3)-H bonds and the expected arylation products are **24**, **25**, **26** and **26′**, respectively. We attempted the arylation of **23a** withvarious aryl iodides in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (as an additive) in *t*-amylOH at 120 ^oC. All the attempted reactions selectively afforded the corresponding mono (*ortho*) γ-C(sp^2)-H arylated products **24a-i** in 41-77% yields *via* the pyridine-*N*-oxide DG-aided selective *ortho*γ-C(sp^2)-H functionalization. Other expected products including the bis (*ortho*) γ-C(sp^2)-H arylated compound **25** or β-C(sp^3)-H and γ-C(sp^3)-H arylated compounds **26** and **26′** were not obtained in characterizable amounts (Scheme 9).

At this juncture, the performance of pyridine-*N*-oxide DG was found to differ from the bidentate directing group 8-aminoquinoline. Earlier, we reported[3t] that the Pd(II)-catalyzed, 8-aminoquinoline-aided arylation of 2-butyramide gave the β-C(sp^3)-H arylated 2-phenylbutyramide **30** possessing *anti* stereochemistry as the major product. And the corresponding other possible products including γ-C(sp^2)-H arylated compounds **28**, **29** and γ-C(sp^3)-H arylated compound **30′** were not obtained in characterizable amounts. In contrast to this observation, the Pd(II)-catalyzed pyridine-*N*-oxide DG-aided arylation of 2-phenylbutyramide **23a** has led to the selective mono (*ortho*) γ-C(sp^2)-H arylation of the phenyl ring in 2-phenylbutyramide affording the products **24a-i**. This observation indicated that the pyridine-*N*-oxide DG-aided arylation reaction seems to be gentle and made the site-selective C-H functionalization possible. Though the pyridine-*N*-oxide DG-aided functionalization of β-C(sp^3)-H bond in substrate **23a** might proceed *via* the generally proposed (favorable) 5-membered palladacycle intermediate. Presumably, the pyridine-*N*-oxide DG prefers functionalizing the *ortho* C(sp^2)-H bond *via* the proposed 6-membered palladacycle intermediate involving substrate **23a**.[5,10] Thus, this contrasting behavior of pyridine-*N*-oxide DG compared to 8-aminoquinoline DG further strengthens the available options for establishing efficient site-selective C-H functionalization reactions.



Scheme 9. Scope of pyridine-*N*-oxide DG for accomplishing site-selective and mono selective arylation in substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds.

We have also found a limitation of pyridine-*N*-oxide DG and all our attempts to establish the selective δ-C(sp^2)-H arylation using 3-phenylbutyramide substrate **21a** containing the pyridine-*N*-oxide DG failed at this stage (Scheme 9). The substrate **21a** contains competitive methylene β-C(sp^3)-H and δ-C(sp^2)-H bonds and the Pd(II)-catalyzed arylation of **21a** did not yield any of the expected methylene β-C(sp^3)-H or *ortho*δ-C(sp^2)-H arylated products **22a** or **22b**. The expected *ortho*δ-C(sp^2)-H functionalization in **21a** requires the generation of a less favored 7-membered palladacycle intermediate. It seems that in substrate **21a**, the arylation of both δ-C(sp^2)-H bond as well as the methylene β-C(sp^3)-H bond are not assisted by the pyridine-*N*-oxide DG.

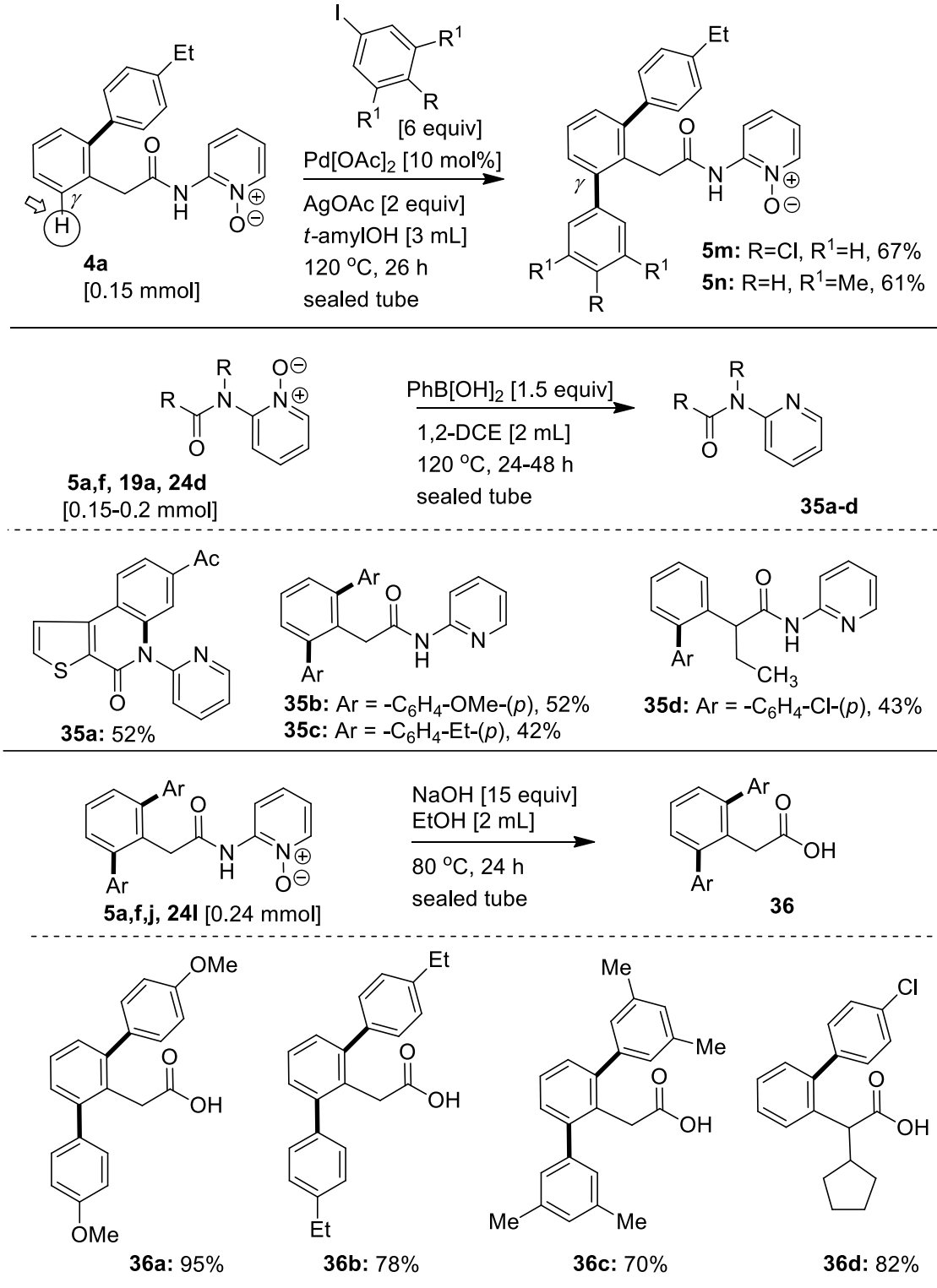


Scheme 10. Scope of pyridine-*N*-oxide DG for accomplishing site-selective mono (*ortho*) arylation of phenylglycine.

Having done the selective mono arylation of γ-C(sp^2)-H bond of 2-phenylbutyramide **23a** linked withpyridine-*N*-oxide DG, we then prepared additional substrates **23b** and **23c** containing competitive C(sp^3)-H and C(sp^2)-H bonds. We performed the arylation of carboxamides **23b** or

23c possessing the pyridine-*N*-oxide DG with various aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in *t*-amylOH at 120 °C. These reactions were also found to afford the corresponding mono (*ortho*) *γ*-C(sp^2)-H arylated products **24j,k** and **24l,m** in 47-68% yields *via* the pyridine-*N*-oxide DG-aided selective mono (*ortho*) *γ*-C(sp^2)-H functionalization of substrates **23b,c** (Scheme 9).

Along this line, we intended to check whether the mono arylation of phenylglycine can be accomplished. It may be noted that earlier, Jiang reported[3u] that the arylation of picolinamide DG-linked phenylglycine afforded the bis (*ortho*) *γ*-C(sp^2)-H arylated phenylglycine as a major compound and occasionally, the mono (*ortho*) *γ*-C(sp^2)-H arylated phenylglycine was obtained as a minor compound. Keeping this observation in mind, we assembled the pyridine-*N*-oxide DG linked phenylglycine substrate **23d** and then we subjected it to the Pd(II)-catalyzed arylation conditions (Scheme 10). The arylation of phenylglycine derivative **23d** possessing pyridine-*N*-oxide DG was attempted with various aryl iodides in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc in *t*-amylOH at 120 °C. Notably, all these reactions were found to afford the corresponding mono (*ortho*) *γ*-C(sp^2)-H arylated products **31a-n** in 20-60% yields *via* the pyridine-*N*-oxide DG-aided selective mono (*ortho*) *γ*-C(sp^2)-H functionalization of substrate **23d**. Again, when compared to the picolinamide-aided DG-aided arylation of phenylglycine, the performance of the pyridine-*N*-oxide DG seems to be reasonably selective and provided the required mono (*ortho*) *γ*-C(sp^2)-H arylated products **31a-n** of substrate **23d**. Furthermore, we wished to perform a second *γ*-C(sp^2)-H arylation in the mono (*ortho*) *γ*-C(sp^2)-H arylated products, e.g. **4a**, **24** and **31**. At first, we attempted the second *γ*-C(sp^2)-H arylation in a few mono (*ortho*) *γ*-C(sp^2)-H arylated products including **24c,k,l** and **31j** using selected aryl iodides under the reaction conditions used to obtain these compounds. We did not obtain the expected second *γ*-C(sp^2)-H arylated products from **24c,k,l** and some trials resulted in inseparable mixtures of compounds and starting materials. Similarly, the treatment of **31j** with aryl iodides did not yield the expected second *γ*-C(sp^2)-H arylated products. Then, we attempted the Pd(II)-catalyzed second *γ*-C(sp^2)-H arylation in the mono (*ortho*) *γ*-C(sp^2)-H arylated product **4a** with different aryl iodides. Fortunately, we succeeded in introducing a second aryl group at the second *γ*-C(sp^2)-H bond of **4a**. Accordingly, we obtained the bis *γ*-C(sp^2)-H arylated products **5m,n** containing two different aryl groups *via* the second *γ*-C(sp^2)-H arylation of **4a** with the corresponding aryl iodides (Scheme 11).



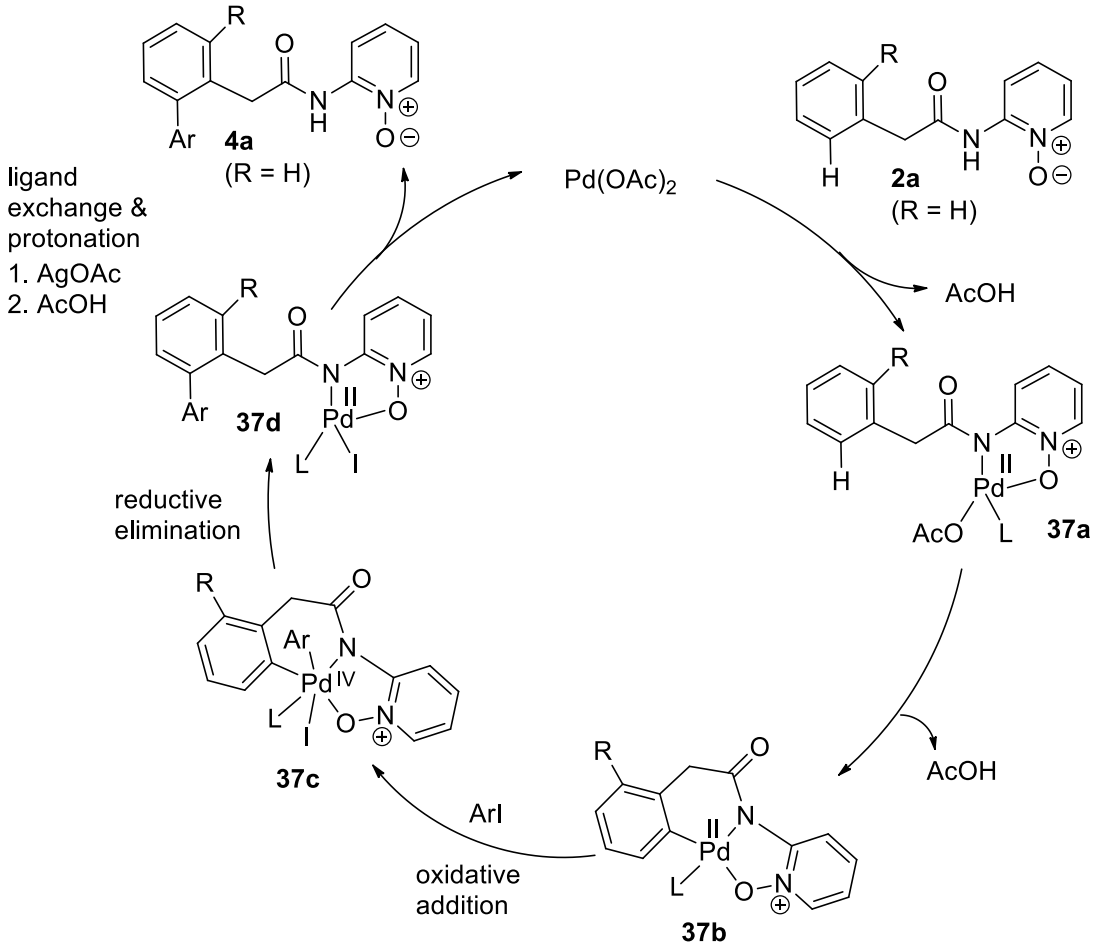
Scheme 11. Synthetic utility, removal of the pyridine-*N*-oxide DG and preparation of biaryl acetic acid derivatives.

Finally, we intended to show the synthetic utility of this protocol and the removal of the pyridine-*N*-oxide DG. In this regard, initially, we attempted the deoxygenation of the pyridine-*N*-oxide unit using the thieno[2,3-*c*]quinolin-4(5*H*)-one **19a** (which was prepared *via* the *β*-C(sp^2)-H arylation and *δ*-C(sp^2)-H amidation process). Heating a mixture of **19a** with $PhB(OH)_2$ in 1,2-DCE for 120 ^oC afforded the *N*-pyridyl thieno[2,3-*c*]quinolin-4(5*H*)-one **35a** in 52% yield (Scheme 11). Similarly, heating a mixture of pyridine-*N*-oxide DG containing biarylacetamide compound **5a**/**5f** or biaryl-based butyramide **24d** with $PhB(OH)_2$ in 1,2-DCE for 120 ^oC afforded the corresponding 2-aminopyridyl-based biarylacetamides **35b,c** andbiaryl-based butyramide **35d** in 42-52% yields (Scheme 11). Furthermore, we attempted the removal of the pyridine-*N*-oxide DG *via* the NaOH-mediated amide hydrolysis of biarylacetamide **5f**. This reaction gave the terphenyl-based acetic acid derivative **36a** in a 95% yield. Similarly, other terphenyl-based acetic acid derivatives **36b-d** were obtained in 70-82% yields *via* the NaOH-mediated hydrolysis of their corresponding amides **5a,j** and **24l** (Scheme 11).

The structures of all the compounds obtained were ascertained by NMR spectra and HRMS data. Furthermore, we have confirmed the structure of a representative bis *γ*-C(sp^2)-H arylated product by single-crystal X-ray structure analysis of compound **5b**[17](Scheme 3). In general, the bidentate directing group-assisted C-H functionalization process is proposed to proceed via a Pd(II)/Pd(IV) redox cycle mechanism.[2,3,5-10]

Along this line, Zeng/Lu[5b] and Niu/Song[5a] have independently proposed the plausible mechanism for the pyridine-*N*-oxide (*N*,*O*-bidentate) directing group-assisted Pd(II)-catalyzed arylation of *β*-C(sp^2)-H bonds of carboxamides. In concurrence with the proposed mechanism[2,3,5-10] for the bidentate directing group-assisted C–H functionalization process, a plausible mechanism for the pyridine-*N*-oxide (*N*,*O*-bidentate) directing group-assisted Pd(II)-catalyzed *ortho* arylation of *γ*-C(sp^2)-H bonds of arylacetamide system **2a** is proposed in Scheme 12. The coordination of the pyridine-*N*-oxide directing group in substrate **2a**to the Pd(II) metal center is followed by concerted metalation deprotonation (CMP), generating the six-membered Pd(II) species **37b**. Oxidative addition of Pd(II) species **37b** with an aryl iodide then forms the Pd(IV) species **37c**, which then undergoes reductive elimination to generate the new C–C bond in intermediate **37d**. Halide abstraction by a halide ion scavenger (AgOAc) followed by

proteolysis of intermediate **37d** yields the γ-C(sp^2)-H arylated product **4a** and regenerates the active Pd(II) species in the catalytic cycle.



Scheme 12. Plausible mechanism in concurrence with the mechanism proposed in the literature.[2,3,5-10]

Conclusion

In summary, we have reported the utility of the pyridine-*N*-oxide directing group for the Pd(II)-catalyzed site-selective γ-C(sp^2)-H, γ-C(sp^3)-H and δ-C(sp^2)-H functionalization and synthesis of a wide range of pyridine-*N*-oxide-based carboxamides. The Pd(II)-catalyzed pyridine-*N*-oxide DG-aided mono and bis (*ortho*) γ-C(sp^2)-H arylation of aryl acetamides afforded biaryl acetamides. The Pd(II)-catalyzed pyridine-*N*-oxide DG-aided γ-C(sp^3)-H arylation of 3-methylheteroaryl-2-carboxamides afforded arylheteroarylmethane motifs. We have shown the preparation of heteroaryl-based biaryl carboxamides *via* the Pd(II)-catalyzed pyridine-*N*-oxide

DG-aided β-C(sp^2)-H arylation. Then, they were subjected to the Pd(II)-catalyzed pyridine-*N*-oxide DG-aided δ-C(sp^2)-H amidation to afford the corresponding phenanthridin-6(5*H*)-ones (tricyclic quinolones). We examined the scope of pyridine-*N*-oxide DG for accomplishing site-selective arylation in substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds. We also compared the performance of the pyridine-*N*-oxide DG with the 8-aminoquinoline DG. In contrast to the 8-aminoquinoline DG, the pyridine-*N*-oxide DG-aided arylation of 2-phenylbutyramide has led to the mono (*ortho*) γ-C(sp^2)-H arylation of the phenyl ring in 2-phenylbutyramide and related carboxamides. Similarly, the pyridine-*N*-oxide DG-aided arylation of phenylglycine afforded mono (*ortho*) arylated phenylglycine derivative. These observations indicated that the Pd(II)-catalyzed pyridine-*N*-oxide DG-aided arylation reaction seems to be gentle and enabled the required selective mono (*ortho*) γ-C(sp^2)-H arylation of substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds. While various bidentate directing groups (DGa-i, Scheme 1) have been introduced by many research groups,[1s,2] generally, 8-aminoquinoline has been employed for performing the site-selective C-H functionalization of carboxylic acid substrates.[2] While most of the introduced bidentate directing groups are efficient. As such the substrate scope elaboration and finding of suitable directing groups for accomplishing single or multiple (site-selective) C-H functionalization are still in emerging mode.[1,2] The efficiency of the available directing groups for accomplishing site-selective C-H arylation in substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds are not fully addressed. In this work, we have shown some examples of selective mono (*ortho*) γ-C(sp^2)-H arylation of substrates containing competitive C(sp^3)-H and C(sp^2)-H bonds by using pyridine-*N*-oxide DG. To date, there exist only rare reports dealing with the functionalization of the sp^2/sp^3 γ- and δ-C-H bonds of carboxamides assisted by bidentate directing groups providing the *N,O*-coordination. Additionally, pyridine-*N*-oxide DG (its precursor 2-aminopyridine) is an easily available and inexpensive chemical. While this work aimed to reveal the scope of the sp^2/sp^3 γ- and δ-C-H functionalization using pyridine-*N*-oxide. It also enabled the assembly of a library of pyridine-*N*-oxide-based carboxamides including biarylacetamides, heteroaryl-based biaryl carboxamides, arylheteroarylmethane, biaryl-based butyramides and related carboxamides and mono *ortho* arylated phenylglycine (biaryl glycine) derivatives. Independently biaryl-based small organic molecules, arylacetamide and arylacetic acid derivatives and pyridine-*N*-oxide unit-containing molecules are significant classes of compounds in organic synthesis and

pharmaceuticals. Thus, this work is a contribution toward enriching the libraries of these types of molecules.

Experimental Section

General information: The ^{1}H and $^{13}C\{H\}$ NMR spectra of all compounds have been recorded in 400 and ~101 MHz spectrometers by using TMS as an internal standard, respectively. The IR spectra of samples reported here were recorded as neat or thin films. The HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography purification of crude reaction mixtures/samples was carried out on silica gel (100-200 mesh). Thin layer chromatography (TLC) analysis was performed on alumina and silica plates, and components were visualized by observation under irradiation with UV lamp or iodine vapour. Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after workup were dried using anhydrous Na_2SO_4. Isolated yields of all of the products are reported and yields were not optimized. The compounds **13a,b, 14a,b** in this work are known compounds and their characterization data were reported in the literature.

General Procedure for the Synthesis of Carboxamides (2a): To a dry flask containing mixture of 2-aminopyridine 1-oxide (1 mmol), and Et_3N (1.2 equiv.), anhydrous DCM (4 mL) was added and then stirred for 5-10 min under a nitrogen atmosphere, followed by dropwise addition of phenylacetyl chloride (1 equiv.). The resulting mixture was stirred at rt for 24 h. After this period, the reaction mixture was diluted with dichloromethane and washed once with water and twice with saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo, and purification of the resulting reaction mixture was done by column chromatography to afford the carboxamide **2a**.

General Procedure for the Synthesis of Carboxamides (9b,d, 2b-e): To a dry flask containing mixture of appropriate carboxylic acid (1 mmol), and CDI (1.0 equiv.), anhydrous DMF (4 mL) was added and then stirred at rt for 1 h under a nitrogen atmosphere. After this period, 2-aminopyridine 1-oxide (1 equiv), was added to the reaction mixture and heated at 110 ^{o}C for 12-15 h. After completion, the solution was cooled to room temperature and then the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic

layers were washed with water and saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and purification of the resulting crude was done by column chromatography to afford the corresponding carboxamide.

General Procedure for the Synthesis of Carboxamides (9a,c): An appropriate carboxylic acid derivative (1 mmol), 2-aminopyridine 1-oxide (1 equiv.) and DMAP (0.1 equv.) were dissolved in anhydrous DCM (5 mL) in a round-bottom flask, followed by addition of EDC (1.2 equiv.) at 0 ^oC under nitrogen atmosphere. The resulting mixture was stirred at rt for overnight. After completion, the reaction was diluted with DCM, washed water and $NaHCO_3$ solution, and dried over $NaSO_4$. The organic solvent was removed by evaporation and purification of crude mixture was done by column chromatography.

General procedure for the Pd(II)-catalyzed, pyridine *N*-oxide-aided sp^2 C-H arylation of phenylacetamides, phenylglycine, thiophene/furan-2-carboxamide and benzothiophene/benzofuran-2-carboxamide systems (2a, 13a,b, 14a,b, 21a, 23a-d): A mixture of an appropriate carboxamide substrate (**2a-e, 13a,b, 14a,b, 21a, 23a-d**) (1 equiv, reaction scale range = 0.15-0.6 mmol), aryl iodide (4-6 equiv),$Pd(OAc)_2$ (10 mol%) and AgOAc (2.0 equiv) and anhydrous *t*-AmylOH(3-4 mL) were added to screw-cap seal tube and nitrogen was purged to the seal tube prior to the heated at 120 ^oC for 24-26 h. After the reaction period, the reaction mixture wascooled to rt and concentrated under reduced pressure to afford a crude reactionmixture, which was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to give the corresponding sp^2C-Harylated product (**5 / 6 / 7 / 8 / 15 / 16 / 17 / 18 / 24 / 31**).

General procedure for the Pd(II)-catalyzed, pyridine N-oxide-aided sp^3 C-H arylation of 3-methyl- thiophene/furan-2-carboxamide and 3-methyl- benzothiophene/benzofuran-2-carboxamide systems (9a-d): A mixture of an appropriate carboxamide (0.25 mmol, 1 equiv), an appropriate aryl iodide (4 equiv),$Pd(OAc)_2$ (10 mol%) and AgOAc (2.0 equiv) and $(BnO)_2PO_2H$ (20 mol%) in anhydrous toluene(3 mL) were added to screw-cap seal tube. Then, nitrogen was purged and the reaction mixture containing tube was sealed and the tube was submerged into a silicon oil bath preheated at 130 ^oC for 24-36 h under a nitrogen atm. After the reaction period, the reaction mixture wasconcentrated under reduced pressure to afford a crude

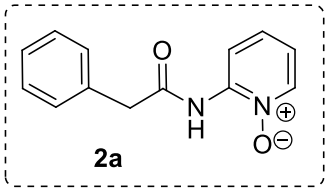
reactionmixture, which was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to furnish the corresponding arylheteroarylmethane derivative (**10 / 11 / 12**).

General procedure for the Pd(II)-catalyzed pyridine N-oxide-aided intramolecular amidation of the remote sp^2 δ-C-H bond of the arylated carboxamides 15, 16: A dry seal tube containing a mixture of an appropriate thiophene/furan-based biaryl carboxamides (**15** or **16**, 0.25 mmol), $Pd(OAc)_2$ (10 mol%), and $PhI(OAc)_2$ (2.5 equiv) in anhydrous toluene (1-2 mL) was heated at 110 °C for 24 h. After this period, the reaction mixture was cooled to rt and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (eluent = EtOAc:hexanes) to give the corresponding quinolones (**19** / **20**).

General procedure for the deoxygenation of the pyridine-N-oxide unit containing carboxamides 5a,f, 19a, and 24d: A mixture of an appropriate N-oxide unit containing quinolone or carboxamide (**5a,f** / **19a** / **24d**, 0.15-0.2 mmol) and phenylboronic acid (1.5 equiv.) was stirred in DCE (2 mL) at 120 ^oC in a sealed tube for 24 h. The progress of the reaction was monitored by using TLC. After completion, the solution was cooled to room temperature and then the reaction mixture was diluted with EtOAc (7-10 mL) and transferred into a separating funnel, the organic layers were washed with water (2 times) and NaOH solution. The combined organic layers were dried over anhydrous Na_2SO_4, Next, the solvent was evaporated to afford a crude reaction mixture, and subjected to the column chromatography to obtain the deoxygenated product (**35a-d**).

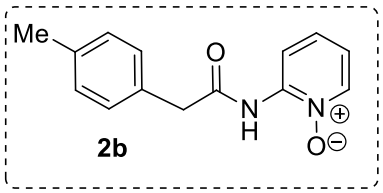
General Procedure for the Hydrolysis of C-H-Arylated Carboxamides 5a,j,f and 24l. A solution of the corresponding arylated carboxamide (**5a,j,f** / **24l**, 0.2-0.25 mmol) and NaOH (15 equiv) in ethanol (2-3 mL) were added to screw-cap seal tube. Then, the reaction mixture containing tube was sealed and the tube was submerged into a silicon oil bath preheated to 80 ^oC for 24 h. After this period, the reaction mixture was quenched with 2 N HCl to obtain pH ∼2. Then, resulting aqueous layer was extracted with DCM (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4 followed by the evaporation of the solvent in vacuo, resulting crude mixture was subjected to the column chromatography (eluent = EtOAc:hexanes) to obtain the corresponding pure carboxylic acids **36a-d**.

2-(2-Phenylacetamido)pyridine 1-oxide (2a): The compound **2a** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (736 mg, 5 mmol scale, 64%); R_f (100% EtOAc) 0.3; mp: 104-106 ^oC; IR (DCM): 3066, 1705, 1511, 1429, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.13 (1H, br. s), 8.44 (1H, dd, J_1 = 8.5, J_2 = 1.6Hz), 8.19 (1H, dd, J_1 = 6.6, J_2 = 0.8Hz), 7.44-7.30 (6H, m), 6.99-6.96 (1H, m), 3.86 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 144.0, 137.0, 133.3, 129.4, 129.2, 128.0, 127.8, 118.7, 114.6, 44.9; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0977 found 229.0984.



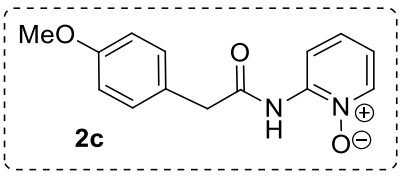
2a

2-(2-(*p*-Tolyl)acetamido)pyridine 1-oxide (2b): The compound **2b** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (230 mg, 2 mmol scale, 48%); R_f (100% EtOAc) 0.5; mp: 150-152 ^oC; IR (DCM): 2922, 1714, 1507, 1262, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.09 (1H, br. s), 8.44 (1H, dd, J_1 = 8.5, J_2 = 1.7Hz), 8.19 (1H, dd, J_1 = 6.5, J_2 = 1.0Hz), 7.35-7.31 (1H, m), 7.28-7.22 (4H, m), 6.99-6.95 (1H, m), 3.82 (2H, s), 2.37 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 144.1, 137.6, 137.0, 130.1, 129.9, 129.3, 128.0, 118.6, 114.6, 44.6, 21.1; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$ 243.1134 found 243.1124.



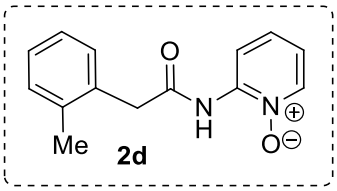
2b

2-(2-(4-Methoxyphenyl)acetamido)pyridine 1-oxide (2c): The compound **2c** was obtained after purification by column chromatography on silica gel (EtOAc) as a yellow color solid (71 mg, 2 mmol scale, 14%); R_f (100% EtOAc) 0.5; mp: 145-147 ^oC; IR (DCM): 3482, 2938, 1506, 1257, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.10 (1H, br. s), 8.44 (1H, d, J = 8.4 Hz), 8.19 (1H, d, J = 6.4 Hz), 7.34-7.28 (3H, m), 6.99-6.93 (3H, m), 3.82 (3H, s), 3.79 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.2, 159.2, 144.1, 137.0, 130.5, 128.1, 125.2, 118.6, 114.6, 114.6, 55.2, 44.1; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$ 259.1083 found 259.1079.



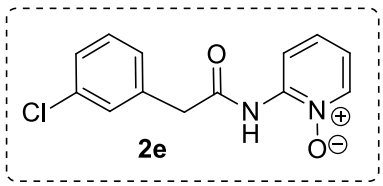
2c

2-(2-(*o*-Tolyl)acetamido)pyridine 1-oxide (2d):The compound **2d** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (459 mg, 2 mmol scale, 95%);R_f (100% EtOAc) 0.4; mp: 130-132 ^oC; IR (DCM): 2932, 1704, 1510, 1430, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.06 (1H, br. s), 8.43 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz),

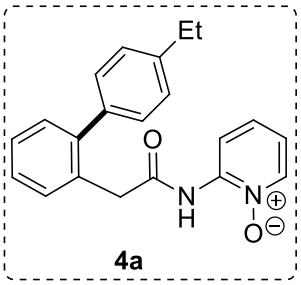


8.17 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.34-7.26 (5H, m), 6.98-6.94 (1H, m), 3.87 (2H, s), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 143.9, 136.9, 131.8, 130.9, 130.4, 128.2,128.1, 126.8, 118.6, 114.5, 42.8, 19.6; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_2$ $[M-H]^-$ 241.0977 found 241.0978.

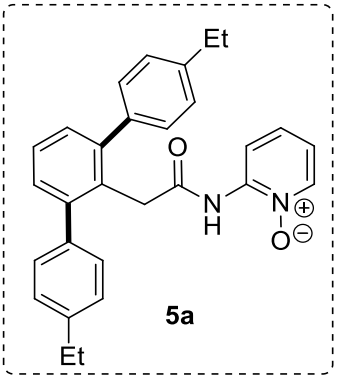
2-(2-(3-Chlorophenyl)acetamido)pyridine 1-oxide (2e): The compound **2e** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (228 mg, 2 mmol scale, 44%); R_f (100% EtOAc) 0.5; mp: 134-136 ^{o}C; IR (DCM): 3070, 1702, 1506, 1215, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.19 (1H, br. s), 8.43 (1H, d, J = 8.5 Hz), 8.22 (1H, d, J = 6.5 Hz), 7.37-7.31 (4H, m), 7.28-7.25 (1H, m), 7.00 (1H, t, J = 7.1 Hz), 3.84 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.0, 143.9, 137.0, 135.2, 134.8, 130.3, 129.5, 128.2, 128.0, 127.5, 118.9, 114.7, 44.3; HRMS (ESI) calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$ 263.0587 found 263.0581.



2-(2-(4'-Ethyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (4a): The compound **4a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown colour solid (33 mg, 0.25 mmol scale, 40%); R_f (100% EtOAc) 0.3; mp: 122-124 ^{o}C; IR (DCM): 2958, 1701, 1503, 1424, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.94 (1H, br. s), 8.40 (1H, d, J = 8.4 Hz), 8.19 (1H, d, J = 6.5 Hz), 7.46-7.24 (9H, m), 6.96 (1H, t, J = 7.0 Hz), 3.85 (2H, s), 2.70 (2H, q, J = 7.6 Hz), 1.28 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 144.0, 143.3, 142.8, 137.9, 137.0, 131.0, 130.7, 130.4, 129.0, 128.0, 127.9, 127.8, 118.6, 114.5, 42.4, 28.5, 15.4; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603 found 333.1619.

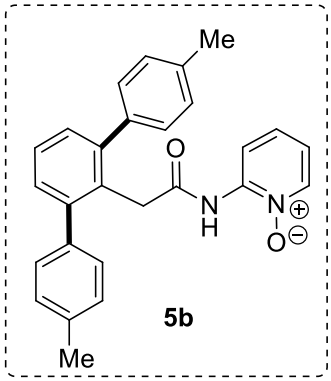


2-(2-(4,4''-Diethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5a): The compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (95 mg, 0.25 mmol scale, 87%); R_f (100% EtOAc) 0.4; mp: 76-78 ^{o}C; IR (DCM): 2968, 1702, 1509, 1424, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.59 (1H, br. s), 8.27 (1H, d, J = 8.4 Hz), 8.16 (1H, d, J = 6.4 Hz), 7.44 (1H, t, J =

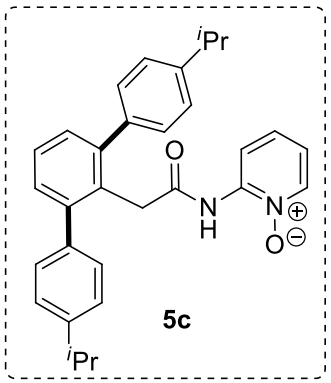


7.4 Hz), 7.34 (2H, d, *J* = 7.5 Hz), 7.30-7.26 (1H, m), 7.29 (H, d, *J* = 7.8 Hz), 7.20 (4H, d, *J* = 7.8 Hz), 6.94 (1H, t, *J* = 6.6 Hz), 3.81 (2H, s), 2.66 (4H, q, *J* = 7.6 Hz), 1.26 (6H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 143.9, 143.6, 143.2, 138.6, 136.9, 129.6, 129.4, 129.0, 127.9, 127.7, 127.3, 118.2, 114.3, 40.2, 28.4, 15.3; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_2$ $[M+H]^+$ 437.2229 found 437.2211.

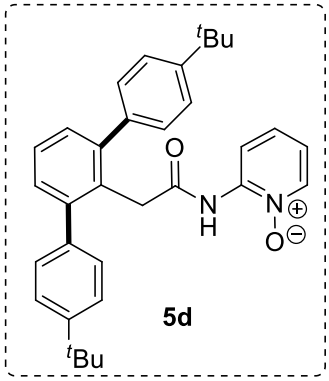
2-(2-(4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5b): The compound **5b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (87 mg, 0.25 mmol scale, 85%); R_f (100% EtOAc) 0.2; mp: 145-147 ^{o}C; IR (DCM): 2924, 1701, 1507, 1423, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.59 (1H, br. s), 8.28 (1H, dd, J_1 = 8.4, J_2 = 1.2Hz), 8.17-8.16 (1H, m), 7.43 (1H, t, *J* = 7.8 Hz), 7.34-7.25 (7H, m), 7.17 (4H, d, *J* = 7.8 Hz), 6.97-6.93 (1H, m), 3.78 (2H, s), 2.36 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 144.0, 143.7, 138.4, 137.0, 137.0, 129.7, 129.4, 129.1, 129.0, 128.0, 127.5, 118.3, 114.4, 40.2, 21.2; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_2$ $[M+H]^+$ 409.1916 found 409.1912.



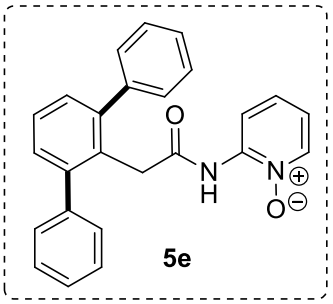
2-(2-(4,4''-Diisopropyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5c): The compound **5c** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (78 mg, 0.25 mmol scale, 67%); R_f (100% EtOAc) 0.4; mp: 100-102 ^{o}C; IR (DCM): 2962, 1506, 1422, 1208, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, br. s), 8.25 (1H, d, *J* = 8.4 Hz), 8.14 (1H, d, *J* = 6.4 Hz), 7.43 (1H, t, *J* = 7.7 Hz), 7.35-7.21 (11H, m), 6.93 (1H, t, *J* = 6.6 Hz), 3.82 (2H, s), 2.95-2.89 (2H, m), 1.25 (12H, d, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 147.8, 143.9, 143.6, 138.7, 136.8, 129.6, 129.5, 129.0, 127.8, 127.3, 126.3, 118.2, 114.2, 40.2, 33.7, 23.9; HRMS (ESI) calcd for $C_{31}H_{33}N_2O_2$ $[M+H]^+$ 465.2542 found 465.2551.



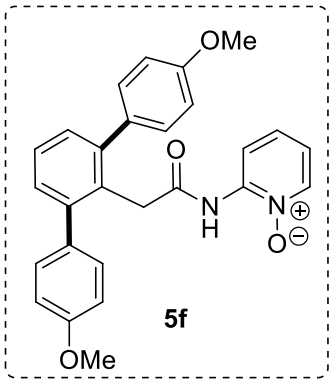
2-(2-(4,4''-Di-*tert*-butyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5d): The compound **5d** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (92 mg, 0.25 mmol scale, 75%); R_f (100% EtOAc) 0.4; mp: 118-120 ^oC; IR (DCM): 2961, 1506, 1423, 1268, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.55 (1H, br. s), 8.25 (1H, dd, J_1 = 8.5, J_2 = 1.6Hz), 8.14 (1H, dd, J_1 = 6.5, J_2 = 1.0Hz), 7.43 (1H, dd, J_1 = 8.3, J_2 = 6.9Hz), 7.38-7.25 (11H, m), 6.95-6.91 (1H, m), 3.82 (2H, s), 1.32 (18H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 150.1, 143.9, 143.6, 138.3, 136.8, 129.6, 129.6, 128.8, 127.8, 127.3, 125.2, 118.2, 114.3, 40.3, 34.5, 31.3; HRMS (ESI) calcd for $C_{33}H_{37}N_2O_2$ $[M+H]^+$ 493.2855 found 493.2850.



2-(2-([1,1':3',1''-Terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5e): The compound **5e** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (48 mg, 0.25 mmol scale, 50%); R_f (100% EtOAc) 0.3; mp: 158-160 ^oC; IR (DCM): 3063, 1702, 1508, 1428, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.58 (1H, br. s), 8.25 (1H, dd, J_1 = 8.4, J_2 = 1.2Hz), 8.16 (1H, d, J = 6.2Hz), 7.48-7.26 (14H, m), 6.97-6.93 (1H, m), 3.78 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.2, 143.9, 143.7, 141.2, 136.9, 129.6, 129.2, 129.1, 128.3, 128.0, 127.5, 127.3, 118.4, 114.3, 40.1; HRMS (ESI) calcd for $C_{25}H_{21}N_2O_2$ $[M+H]^+$ 381.1603 found 381.1602.

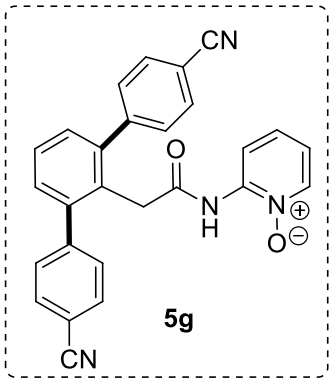


2-(2-(4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5f): The compound **5f** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (50 mg, 0.25 mmol scale, 45%); R_f (100% EtOAc) 0.2; mp: 126-128 ^oC; IR (DCM): 2954, 1699, 1508, 1255, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.60 (1H, br. s), 8.27 (1H, d, J = 8.4 Hz), 8.16 (1H, d, J = 6.4Hz), 7.42 (1H, t, J = 7.5Hz), 7.33-7.26 (7H, m), 6.97-6.92 (1H, m), 6.89 (4H, d, J = 8.5Hz), 3.82 (6H, s), 3.79 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.4, 158.8, 143.9, 143.3,

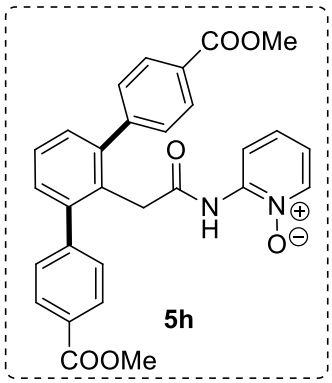


136.9, 133.7, 130.2, 129.8, 129.7, 127.9, 127.4, 118.3, 114.3, 113.7, 55.2, 40.2; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_4$ $[M+H]^+$ 441.1814 found 441.1803.

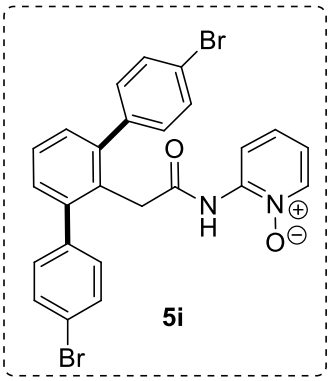
2-(2-(4,4''-Dicyano-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5g): The compound **5g** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (43 mg, 0.25 mmol scale, 40%); R_f (100% EtOAc) 0.2; mp: 160-162 ^oC; IR (DCM): 3061, 2230, 1507, 1424, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (1H, br. s), 8.23-8.18 (2H, m), 7.69 (4H, d, J = 8.3 Hz), 7.54-7.48 (1H, m), 7.49 (H, d, J = 8.3 Hz), 7.36-7.31 (3H, m), 7.04-7.00 (1H, m), 3.67 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.1, 145.5, 143.4, 142.1, 137.0, 132.3, 130.1, 129.9, 128.5, 128.2, 128.0, 118.9, 118.5, 114.2, 111.7, 39.8; HRMS (ESI) calcd for $C_{27}H_{19}N_4O_2$ $[M+H]^+$ 431.1508 found 431.1498.



2-(2-(4,4''-Bis(methoxycarbonyl)-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5h): The compound **5h** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (40 mg, 0.25 mmol scale, 32%); R_f (100% EtOAc) 0.2; mp: 146-148 ^oC; IR (DCM): 3059, 1701, 1507, 1424, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, br. s), 8.24 (1H, d, J = 8.3Hz), 8.15 (1H, d, J = 6.5Hz), 8.05 (4H, d, J = 8.0Hz), 7.49 (1H, t, J = 7.7Hz), 7.45 (H, d, J = 8.1Hz), 7.36 (2H, d, J = 7.6Hz), 7.33-7.28 (1H, m), 6.97 (1H, t, J = 7.2Hz), 3.93 (6H, s), 3.72 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.5, 166.7, 145.7, 143.7, 142.9, 137.0, 129.8, 129.7, 129.3, 129.2, 128.6, 128.2, 127.7, 118.6, 114.3, 52.2, 39.9; HRMS (ESI) calcd for $C_{29}H_{25}N_2O_6$ $[M+H]^+$ 497.1713 found 497.1722.

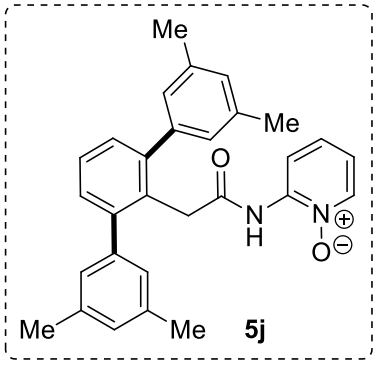


2-(2-(4,4''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5i): The compound **5i** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (78 mg, 0.25 mmol scale, 58%); R_f (100% EtOAc) 0.5; mp: 88-90 ^oC; IR (DCM): 3054, 1700, 1505, 1424, 759 cm^{-1}; ^1H NMR (400 MHz,



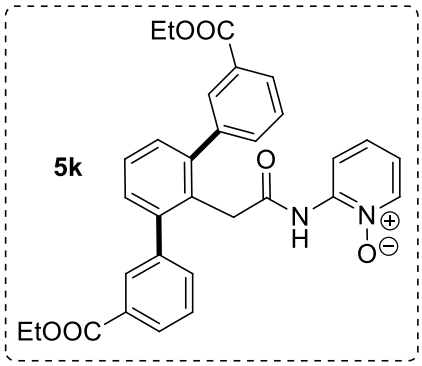
$CDCl_3$): δ_H 9.68 (1H, br. s), 8.26 (1H, dd, J_1 = 8.5, J_2 = 1.5Hz), 8.18 (1H, d, J = 6.4Hz), 7.49 (4H, d, J = 8.2Hz), 7.51-7.43 (1H, m), 7.32-7.28 (3H, m), 7.23 (4H, d, J = 8.3Hz), 6.98 (1H, t, J = 6.2Hz), 3.73 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 143.7, 142.5, 139.9, 137.0, 131.5, 130.7, 129.8, 128.9, 128.1, 127.6, 121.8, 118.6, 114.2, 39.9; HRMS (ESI) calcd for $C_{25}H_{19}Br_2N_2O_2$ $[M+H]^+$ 536.9813 found 536.9806.

2-(2-(3,3'',5,5''-Tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5j):

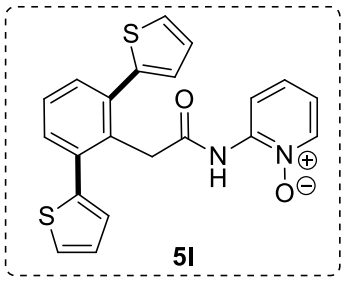


The compound **5j** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (60 mg, 0.25 mmol scale, 55%); R_f (100% EtOAc) 0.5; mp: 157-159 ^{o}C; IR (DCM): 2919, 1505, 1422, 1208, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.55 (1H, br. s), 8.28 (1H, dd, J_1 = 8.4, J_2 = 1.2Hz), 8.18 (1H, d, J = 6.1Hz), 7.41 (1H, dd, J_1 = 8.2, J_2 = 7.0Hz), 7.32-7.26 (3H, m), 6.98-6.93 (7H, m), 3.77 (2H, s), 2.27 (12H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 144.0, 143.8, 141.2, 137.7, 136.9, 129.3, 129.2, 128.8, 127.8, 127.2, 126.9, 118.2, 114.1, 40.3, 21.2; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_2$ $[M+H]^+$ 437.2229 found 437.2222.

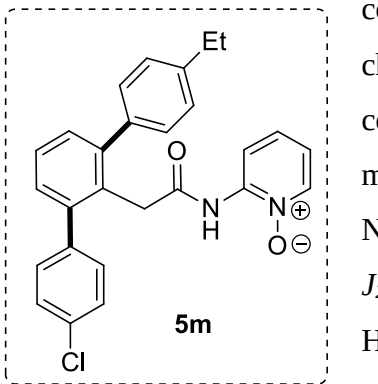
2-(2-(3,3''-Bis(ethoxycarbonyl)-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5k): The compound **5k** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (78 mg, 0.25 mmol scale, 60%); R_f (100% EtOAc) 0.4; mp: 82-84 ^{o}C; IR (DCM): 2975, 1714, 1510, 1246, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.60 (1H, br. s), 8.26 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.17-8.15 (1H, m), 8.05-8.02 (4H, m), 7.60 (2H, d, J = 7.6 Hz), 7.51-7.45 (3H, m), 7.38 (2H, d, J = 7.6 Hz), 7.30-7.26 (1H, m), 6.98-6.94 (1H, m), 4.33 (4H, q, J = 7.1 Hz), 3.72 (2H, s), 1.35 (6H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 166.2, 143.7, 142.8, 141.2, 136.9, 133.4, 130.6, 130.1, 129.9, 129.2, 128.7, 128.5, 127.9, 127.7, 118.5, 114.4, 61.0, 40.0, 14.2; HRMS (ESI) calcd for $C_{31}H_{29}N_2O_6$ $[M+H]^+$ 525.2026 found 525.2018.



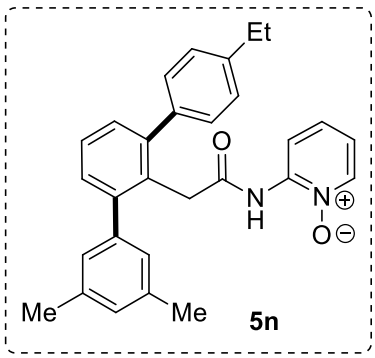
2-(2-(2,6-Di(thiophen-2-yl)phenyl)acetamido)pyridine 1-oxide (5l): The compound **5l** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (60 mg, 0.25 mmol scale, 61%); R_f (100% EtOAc) 0.2; mp: 170-172 ^oC; IR (DCM): 3096, 1699, 1506, 1422, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (1H, br. s), 8.40 (1H, d, J = 8.4 Hz), 8.19 (1H, d, J = 6.4 Hz), 7.51 (2H, d, J = 7.52 Hz), 7.44-7.40 (1H, m), 7.35-7.31 (3H, m), 7.07-7.03 (4H, m), 6.97 (1H, t, J = 7.0 Hz), 4.01 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.2, 144.0, 141.6, 137.0, 136.3, 131.6, 131.6, 128.1, 127.4, 127.3, 127.2, 126.1, 118.5, 114.5, 40.6; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_2S_2$ $[M+H]^+$ 393.0731 found 393.0738.



2-(2-(4-Chloro-4''-ethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5m): The compound **5m** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 70:30) as a brown color solid (44 mg, 0.15 mmol scale, 67%); R_f (100% EtOAc) 0.7; mp: 95-97 ^oC; IR (DCM): 2962, 1702, 1506, 1206, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, br. s), 8.26 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.16 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.44 (1H, t, J = 7.6 Hz), 7.37-7.26 (9H, m), 7.20 (2H, d, J = 8.1 Hz), 6.97-6.93 (1H, m), 3.77 (2H, s), 2.66 (2H, q, J = 7.6 Hz), 1.24 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.0, 143.8, 143.4, 142.3, 139.7, 138.3, 136.9, 133.4, 130.4, 130.0, 129.4, 129.2, 128.9, 128.5, 128.0, 127.8, 127.5, 118.4, 114.2, 40.0, 28.4, 15.3; HRMS (MALDI) calcd for $C_{27}H_{23}ClN_2NaO_2$ $[M+Na]^+$ 465.1346 found 465.1265.

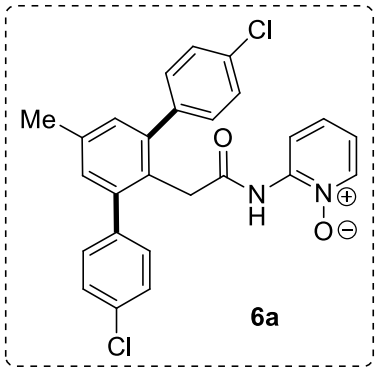


2-(2-(4''-Ethyl-3,5-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (5n): The compound **5n** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 70:30) as a brown color solid (40 mg, 0.15 mmol scale, 61%); R_f (100% EtOAc) 0.7; mp: 84-86 ^oC; IR (DCM): 2962, 1700, 1505, 1205, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, br. s), 8.28 (1H, dd, J_1 = 8.6, J_2 = 1.7 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 0.7 Hz), 7.43 (1H, t, J = 7.6 Hz), 7.35-7.26 (5H, m), 7.20 (2H, d, J =



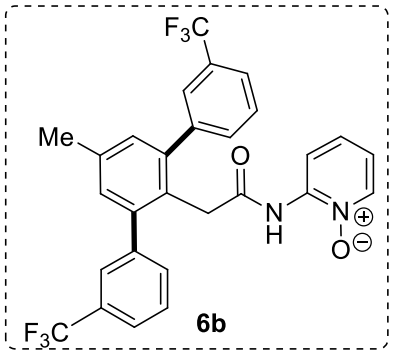
8.0 Hz), 6.97-6.93 (4H, m), 3.78 (2H, s), 2.67 (2H, q, J = 7.6 Hz), 2.26 (6H, s), 1.25 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 144.0, 143.9, 143.6, 143.2, 141.2, 138.6, 137.7, 136.9, 129.5, 129.4, 129.3, 129.1, 128.8, 127.9, 127.7, 127.3, 126.9, 118.2, 114.2, 40.3, 28.5, 21.2, 15.3; HRMS (MALDI) calcd for $C_{29}H_{28}N_2NaO_2$ $[M+Na]^+$ 459.2048 found 459.2060.

2-(2-(4,4''-Dichloro-5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (6a):



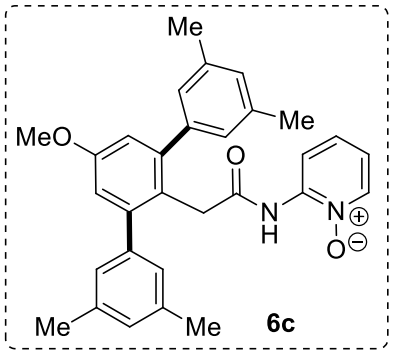
The compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (70 mg, 0.2 mmol scale, 76%); R_f (100% EtOAc) 0.7; mp: 128-130 ^{o}C; IR (DCM): 2924, 1700, 1503, 1210, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.67 (1H, br. s), 8.25 (1H, dd, J_1 = 8.8, J_2 =2.0 Hz), 8.17 (1H, dd, J_1 = 6.4, J_2 = 1.2 Hz), 7.36-7.32 (4H, m), 7.30-7.27 (5H, m), 7.14 (2H, s), 6.99-6.95 (1H, m), 3.69 (2H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 143.8, 142.4, 139.6, 137.4, 137.0, 133.5, 130.7, 130.4, 128.5, 128.0, 126.0, 118.6, 114.3, 39.6, 21.0; HRMS (ESI) calcd for $C_{26}H_{21}Cl_2N_2O_2$ $[M+H]^+$ 463.0980 found 463.0982.

2-(2-(5'-Methyl-3,3''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (6b):

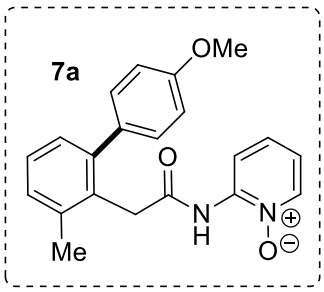


The compound **6b** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (54 mg, 0.2 mmol scale, 51%); R_f (100% EtOAc) 0.7; mp: 135-137 ^{o}C; IR (DCM): 2926, 1702, 1509, 1325, 1127, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, br. s), 8.24 (1H, dd, J_1 = 8.5, J_2 =2.1 Hz), 8.14 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.62-7.57 (6H, m), 7.52-7.48 (2H, m), 7.29-7.26 (1H, m), 7.18 (2H, s), 6.97-6.93 (1H, m), 3.59 (2H, s), 2.44 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 143.6, 142.3, 141.9, 137.7, 136.9, 132.3, 130.9, 130.7 (q, $J_{C\text{-}F}$ = 32.4 Hz), 128.9, 128.2, 126.2, 126.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.4 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.9 (q, $J_{C\text{-}F}$ = 271.1 Hz), 118.7, 114.5, 39.7, 21.0; HRMS (ESI) calcd for $C_{28}H_{21}F_6N_2O_2$ $[M+H]^+$ 531.1507 found 531.1519.

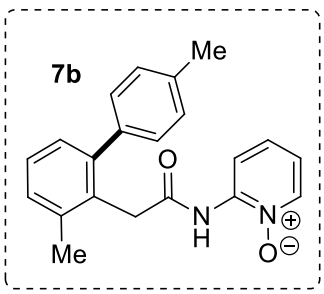
2-(2-(5'-Methoxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetamido)pyridine 1-oxide (6c): The compound **6c** was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (61 mg, 0.2 mmol scale, 65%); R_f (100% EtOAc) 0.7; mp: 152-154 ^oC; IR (DCM): 2924, 1702, 1507, 1204, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, br. s), 8.27 (1H, dd, J_1 = 8.4, J_2 =1.7 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.30-7.25 (1H, m), 6.97-6.92 (7H, m), 6.86 (2H, s), 3.84 (3H, s), 3.67 (2H, s), 2.27 (12H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.9, 158.0, 145.1, 144.1, 141.2, 137.7, 136.9, 128.9, 127.8, 126.8, 121.5, 118.2, 114.8, 114.2, 55.3, 39.7, 21.2, 21.2; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_3$ $[M+H]^+$ 467.2335 found 467.2346.



2-(2-(4'-Methoxy-3-methyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (7a): The compound **7a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (68 mg, 0.25 mmol scale, 78%); R_f (100% EtOAc) 0.3; mp: 136-138 ^oC; IR (DCM): 2926, 1700, 1506, 1423, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.92 (1H, br. s), 8.42 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.34-7.26 (5H, m), 7.21 (1H, dd, J_1 = 7.2, J_2 = 1.7 Hz), 6.99-6.93 (3H, m), 3.87 (2H, s), 3.84 (3H, s), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 158.7, 144.0, 143.1, 137.7, 137.0, 133.7, 130.1, 129.9, 129.7, 128.6, 128.0, 127.6, 118.5, 114.5, 113.7, 55.2, 39.7, 20.3; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1552 found 349.1541.

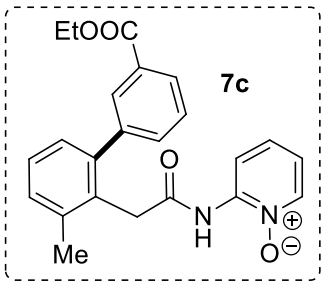


2-(2-(3,4'-Dimethyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (7b): The compound **7b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (60 mg, 0.25 mmol scale, 72%); R_f (100% EtOAc) 0.5; mp: 162-164 ^oC; IR (DCM): 2922, 1505, 1421, 1208, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (1H, br. s), 8.41 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.34-7.27 (4H, m), 7.25-7.20 (5H, m), 6.99-6.95 (1H, m), 3.86 (2H, s), 2.39 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 144.0,



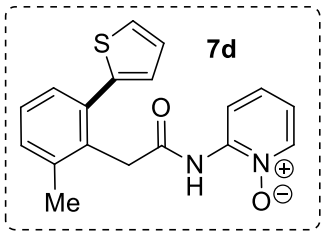
143.5, 138.4, 137.7, 137.0, 136.9, 129.8, 129.8, 129.0, 128.9, 128.5, 128.0, 127.6, 118.5, 114.5, 39.7, 21.1, 20.3; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603 found 333.1592.

2-(2-(3'-(Ethoxycarbonyl)-3-methyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (7c):

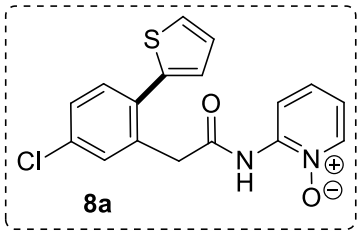


The compound **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (50 mg, 0.25 mmol scale, 51%); R_f (100% EtOAc) 0.2; mp: 86-88 ^oC; IR (DCM): 2926, 1710, 1508, 1251, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.96 (1H, br. s), 8.41 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 8.05 (1H, dt, J_1 = 7.8, J_2 = 1.5 Hz), 8.01 (1H, t, J = 1.6 Hz), 7.57 (1H, dt, J_1 = 7.7, J_2 = 1.6 Hz), 7.50-7.46 (1H, m), 7.37-7.30 (3H, m), 7.22-7.20 (1H, m), 7.00-6.96 (1H, m), 4.34 (2H, q, J = 7.2 Hz), 3.83 (2H, s), 2.41 (3H, s), 1.34 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.6, 166.3, 144.0, 142.6, 141.6, 138.0, 137.0, 133.5, 130.6, 130.4, 130.1, 129.7, 128.6, 128.5, 128.4, 128.1, 127.8, 118.7, 114.6, 61.0, 39.7, 20.4, 14.3; HRMS (ESI) calcd for $C_{23}H_{23}N_2O_4$ $[M+H]^+$ 391.1658 found 391.1653.

2-(2-(2-Methyl-6-(thiophen-2-yl)phenyl)acetamido)pyridine 1-oxide (7d): The compound **7d**



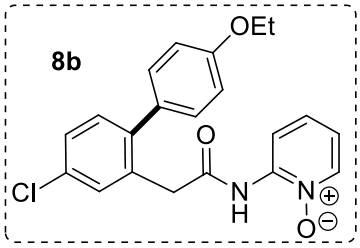
was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (55 mg, 0.25 mmol scale, 68%); R_f (100% EtOAc) 0.3; mp: 130-132 ^oC; IR (DCM): 2922, 1702, 1508, 1424, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.01 (1H, br. s), 8.44 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.19 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.37-7.30 (5H, m), 7.07-7.05 (2H, m), 7.00-6.96 (1H, m), 3.99 (2H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 143.9, 142.0, 138.0, 137.0, 135.6, 130.9, 130.7, 129.5, 128.0, 127.6, 127.2, 127.0, 125.8, 118.6, 114.6, 39.8, 20.4; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2S$ $[M+H]^+$ 325.1011 found 325.1000.



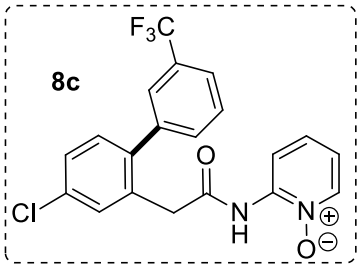
2-(2-(5-Chloro-2-(thiophen-2-yl)phenyl)acetamido)pyridine 1-oxide (8a): The compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (40 mg, 0.2 mmol scale, 58%); R_f (100%

EtOAc) 0.6; mp: 118-120 ^{o}C; IR (DCM): 2925, 1701, 1507, 1210, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.10 (1H, br. s), 8.40 (1H, dd, J_1= 8.4, J_2=1.6 Hz), 8.20 (1H, d, J= 5.8 Hz), 7.44-7.30 (5H, m), 7.07 (2H, d, J = 3.2 Hz), 7.00-6.96 (1H, m), 3.94 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.1, 143.9, 140.1, 137.0, 134.3, 133.8, 133.4, 132.7, 130.7, 128.2, 127.9, 127.5, 127.4, 126.4, 118.8, 114.7, 42.2; HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O_2S$ $[M+H]^+$ 345.0465 found 345.0475.

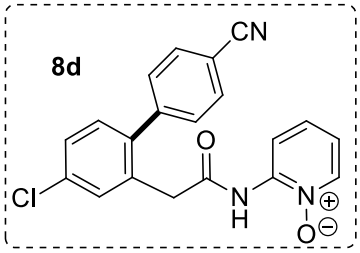
2-(2-(4-Chloro-3'-ethoxy-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (8b): The compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a light yellow color solid (25 mg, 0.2 mmol scale, 33%); R_f (100% EtOAc) 0.5; mp: 186-188 ^{o}C; IR (DCM): 2924, 1706, 1510, 1242, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.34 (1H, br. s), 8.39 (1H, dd, J_1= 8.5, J_2=1.8 Hz), 8.20 (1H, dd, J_1 = 6.0, J_2 = 0.4Hz), 7.42 (1H, d, J = 2.1 Hz) 7.36-7.20 (5H, m), 7.00-6.96 (1H, m), 6.92 (2H, dt, J_1 = 8.6, J_2 = 3.0 Hz), 4.06 (2H, q, J = 7.0 Hz), 3.81 (2H, s), 1.43 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.3, 158.5, 143.9, 140.9, 137.0, 133.3, 133.0, 131.9, 131.6, 130.2, 130.1, 128.1, 127.9, 118.7, 114.6, 114.5, 63.4, 42.0, 14.8; HRMS (ESI) calcd for $C_{21}H_{20}ClN_2O_3$ $[M+H]^+$ 383.1162 found 383.1163.



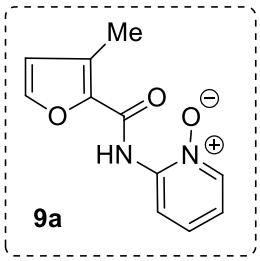
2-(2-(4-Chloro-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (8c): The compound **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (63 mg, 0.2 mmol scale, 78%); R_f (100% EtOAc) 0.4; mp: 60-62 ^{o}C; IR (DCM): 3198, 1511, 1430, 1265, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.98 (1H, br. s), 8.36 (1H, dd, J_1= 8.5, J_2=1.7 Hz), 8.21 (1H, dd, J_1= 6.5, J_2= 0.8 Hz), 7.65-7.63 (1H, m), 7.58-7.54 (3H, m), 7.46 (1H, d, J = 2.1 Hz), 7.41 (1H, dd, J_1= 8.2, J_2=2.2 Hz), 7.36-7.32 (1H, m), 7.28 (1H, s), 7.03-6.99 (1H, m), 3.76 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 143.7, 140.3, 139.6, 137.0, 134.4, 133.0, 132.4, 131.6, 130.9 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.7, 129.1, 128.2, 128.1, 125.9 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.8 (q, $J_{C\text{-}F}$ = 270.9 Hz), 118.9, 114.7, 41.9; HRMS (ESI) calcd for $C_{20}H_{15}ClF_3N_2O_2$ $[M+H]^+$ 407.0774 found 407.0785.



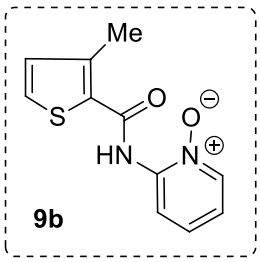
2-(2-(4-Chloro-3'-cyano-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (8d): The compound **8d** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (35 mg, 0.15 mmol scale, 64%); R_f (100% EtOAc) 0.4; mp: 178-180 °C; IR (DCM): 2926, 2230, 1508, 1426, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.01 (1H, br. s), 8.35 (1H, dd, J_1= 8.5, J_2=1.7 Hz), 8.22 (1H, dd, J_1= 6.5, J_2= 1.0 Hz), 7.72 (2H, dt, J_1 = 8.4, J_2 = 1.8 Hz), 7.49-7.46 (3H, m), 7.41 (1H, dd, J_1 = 8.2, J_2 = 2.2 Hz), 7.37-7.33 (1H, m), 7.25 (1H, d, J = 8.2 Hz), 7.04-7.00 (1H, m), 3.77 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 168.6, 144.4, 143.6, 139.2, 137.0, 134.8, 132.6, 132.4, 131.4, 130.8, 130.0, 128.3, 128.2, 119.0, 118.5, 114.6, 111.8, 41.8; HRMS (ESI) calcd for $C_{20}H_{15}ClN_3O_2$ $[M+H]^+$ 364.0853 found 364.0867.



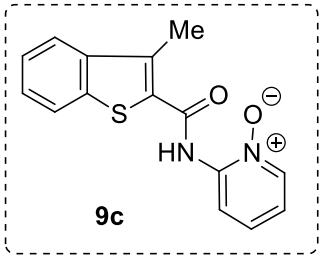
2-(3-Methylfuran-2-carboxamido)pyridine 1-oxide (9a): The compound **9a** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (225 mg, 1.1 mmol scale, 94%); R_f (100% EtOAc) 0.4; mp: 188-190 °C; IR (DCM): 3263, 1676, 1515, 1423, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.84 (1H, br. s), 8.55 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.29 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.47 (1H, d, J = 1.4 Hz), 7.38-7.33 (1H, m), 7.02-6.98 (1H, m), 6.43 (1H, d, J = 1.4 Hz), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 157.1, 144.3, 144.0, 141.3, 137.2, 131.1, 127.9, 118.4, 115.9, 114.5, 11.3; HRMS (ESI) calcd for $C_{11}H_{11}N_2O_3$ $[M+H]^+$ 219.0770 found 219.0766.



2-(3-Methylthiophene-2-carboxamido)pyridine 1-oxide (9b): The compound **9b** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (473 mg, 3 mmol scale, 67%); R_f (100% EtOAc) 0.5; mp: 125-127 °C; IR (DCM): 3258, 1667, 1512, 1424, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.70 (1H, br. s), 8.57 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.30 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.48 (1H, d, J = 5.0 Hz), 7.42-7.38 (1H, m), 7.05-7.01 (1H, m), 6.99 (1H, d, J = 5.0 Hz), 2.71 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.7, 144.4, 142.8, 136.9, 132.5, 130.9, 129.6, 128.2, 118.4, 114.7, 16.2; HRMS (ESI) calcd for $C_{11}H_{11}N_2O_2S$ $[M+H]^+$ 235.0541 found 235.0545.

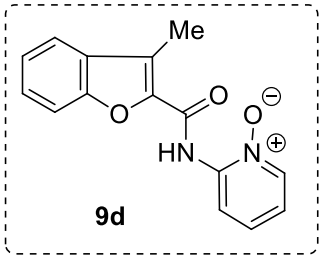


2-(3-Methylbenzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (9c): The compound **9c** was



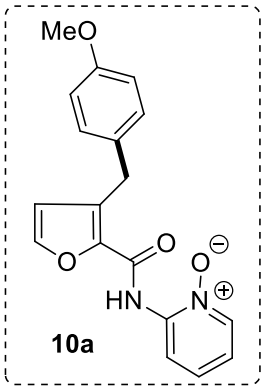
obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (700 mg, 3 mmol scale, 82%); R_f (100% EtOAc) 0.3; mp: 203-205 ^oC; IR (DCM): 2930, 1666, 1519, 1217, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.85 (1H, br. s), 8.60 (1H, d, J = 8.5 Hz), 8.33 (1H, dd, J_1 = 6.5, J_2 = 0.4 Hz), 7.91-7.89 (2H, m), 7.54-7.47 (2H, m), 7.44-7.40 (1H, m), 7.08-7.04 (1H, m), 2.89 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 161.4, 144.3, 140.3, 139.5, 138.2, 137.0, 130.2, 128.1, 127.3, 124.8, 123.7, 122.7, 118.7, 114.8, 13.4; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2S$ $[M+H]^+$ 285.0698 found 285.0705.

2-(3-Methylbenzofuran-2-carboxamido)pyridine 1-oxide (9d): The compound **9d** was



obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (529 mg, 3 mmol scale, 66%); R_f (100% EtOAc) 0.5; mp: 192-194 ^oC; IR (DCM): 3062, 1587, 1512, 1433, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.14 (1H, br. s), 8.63 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.35 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.68 (1H, d, J = 7.8 Hz), 7.61 (1H, d, J = 8.4 Hz), 7.54-7.50 (1H, m), 7.43-7.34 (2H, m), 7.08-7.04 (1H, m), 2.72 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 158.0, 153.6, 144.0, 141.5, 137.2, 129.3, 128.1, 127.8, 125.7, 123.3, 121.0, 118.7, 114.6, 112.1, 9.09; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_3$ $[M+H]^+$ 269.0926 found 269.0919.

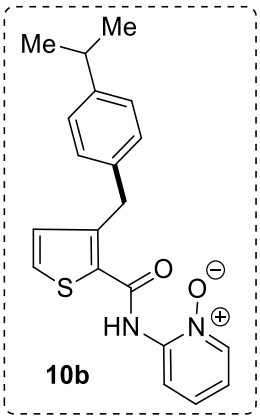
2-(3-(4-Methoxybenzyl)furan-2-carboxamido)pyridine 1-oxide (10a): The compound **10a**



was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (49 mg, 0.25 mmol scale, 60%); R_f (100% EtOAc) 0.4; mp: 98-100 ^oC; IR (DCM): 2921, 1509, 1429, 1251, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.92 (1H, br. s), 8.59 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.30 (1H, dd, J_1 = 6.6, J_2 = 1.2 Hz), 7.47 (1H, d, J = 1.7 Hz), 7.40-7.36 (1H, m), 7.23 (2H, m), 7.05-7.01 (1H, m), 6.86 (2H, dt, J_1 = 8.7, J_2 = 3.0 Hz), 6.36 (1H, d, J = 1.7 Hz), 4.25 (2H, s), 3.81 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 158.1, 157.0,

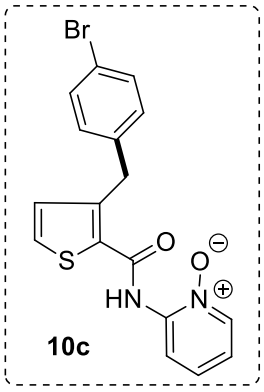
144.2, 144.1, 140.7, 137.2, 134.9, 131.3, 129.7, 128.1, 118.5, 114.9, 114.6, 113.9, 55.2, 30.5; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_4$ $[M+H]^+$ 325.1188 found 325.1177.

2-(3-(4-Isopropylbenzyl)thiophene-2-carboxamido)pyridine 1-oxide (10b): The compound



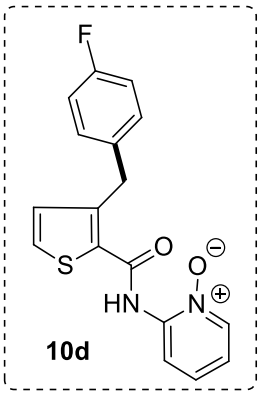
10b was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (47 mg, 0.25 mmol scale, 53%); R_f (100% EtOAc) 0.6; mp: 112-114 ^oC; IR (DCM): 2961, 1671, 1506, 1423, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.68 (1H, br. s), 8.56 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.31 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.44-7.37 (2H, m), 7.21-7.16 (4H, m), 7.05-7.01 (1H, m), 6.91 (1H, d, J = 5.0 Hz), 4.44 (2H, s), 2.93-2.86 (1H, s), 1.25 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.7, 148.2, 146.9, 144.4, 137.0, 136.8, 132.0, 129.6, 128.8, 128.7, 128.1, 126.6, 118.5, 114.8, 35.0, 33.6, 24.0; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_2S$ $[M+H]^+$ 353.1324 found 353.1308.

2-(3-(4-Bromobenzyl)thiophene-2-carboxamido)pyridine 1-oxide (10c): The compound **10c**



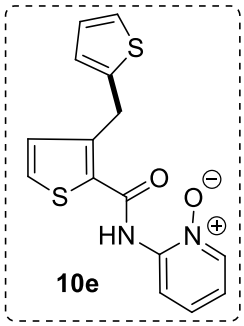
was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (35 mg, 0.25 mmol scale, 44%); R_f (100% EtOAc) 0.5; mp: 170-172 ^oC; IR (DCM): 2361, 1510, 1427, 1272, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.68 (1H, br. s), 8.53 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.30 (1H, dd, J_1 = 6.4, J_2 = 0.7 Hz), 7.46-7.37 (4H, m), 7.15 (2H, d, J = 8.3 Hz), 7.06-7.02 (1H, m), 6.89 (1H, d, J = 5.1 Hz), 4.42 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.5, 147.1, 144.3, 138.6, 137.0, 131.7, 131.6, 130.5, 129.8, 129.1, 128.1, 120.2, 118.6, 114.7, 34.7; HRMS (ESI) calcd for $C_{17}H_{14}BrN_2O_2S$ $[M+H]^+$ 388.9959 found 388.9954.

2-(3-(4-Fluorobenzyl)thiophene-2-carboxamido)pyridine 1-oxide (10d): The compound **10d** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (53 mg, 0.25 mmol scale, 65%); R_f (100% EtOAc) 0.3; mp: 102-104 ^oC; IR (DCM): 1674, 1509, 1427, 1228, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.68



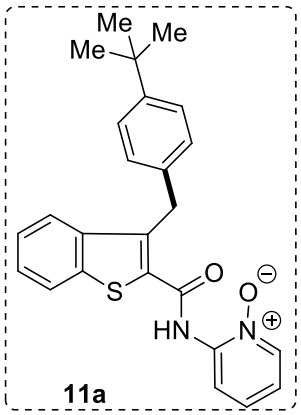
(1H, br. s), 8.54 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.31 (1H, dd, J_1 = 6.5, J_2 = 0.7 Hz), 7.45 (1H, d, J = 5.1 Hz), 7.42-7.37 (1H, m), 7.25-7.22 (2H, m), 7.06-6.98 (3H, m), 6.89 (1H, d, J = 5.0 Hz), 4.43 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 161.5 (d, $J_{C\text{-}F}$ = 243.0 Hz), 160.6, 147.7, 144.4, 137.0, 135.3 (d, $J_{C\text{-}F}$ = 3.4 Hz), 131.8, 130.2 (d, $J_{C\text{-}F}$ = 7.8 Hz), 129.8, 129.1, 128.2, 118.6, 115.3 (d, $J_{C\text{-}F}$ = 21.1 Hz), 114.8, 34.6; HRMS (ESI) calcd for $C_{17}H_{14}FN_2O_2S$ $[M+H]^+$ 329.0760 found 329.0753.

2-(3-(Thiophen-2-ylmethyl)thiophene-2-carboxamido)pyridine 1-oxide (10e): The compound



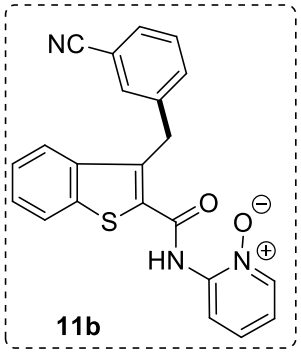
10e was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a black color solid (35 mg, 0.25 mmol scale, 44%); R_f (100% EtOAc) 0.3; mp: 96-98 ^{o}C; IR (DCM): 2924, 1508, 1425, 1272, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.67 (1H, br. s), 8.56 (1H, dd, J_1 = 8.5, J_2 = 1.5 Hz), 8.31 (1H, d, J = 6.4 Hz), 7.46 (1H, d, J = 5.1 Hz), 7.41-7.37 (1H, m), 7.18 (1H, d, J = 5.1 Hz), 7.06-7.02 (2H, m), 6.96-6.94 (2H, m), 6.92-6.91 (1H, m), 4.65 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.5, 147.2, 144.4, 142.0, 137.0, 131.7, 129.6, 129.0, 128.2, 126.8, 125.6, 124.2, 118.6, 114.8, 29.6; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2S_2$ $[M+H]^+$ 317.0418 found 317.0424.

2-(3-(4-(*Tert*-butyl)benzyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (11a): The

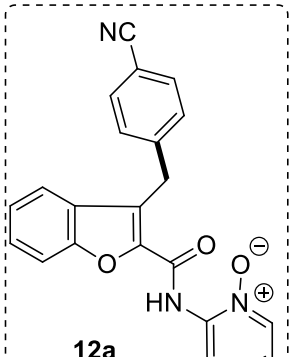


compound **11a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (45 mg, 0.22 mmol scale, 49%); R_f (100% EtOAc) 0.5; mp: 186-188 ^{o}C; IR (DCM): 2960, 1502, 1425, 1270, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.83 (1H, br. s), 8.58 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.36-8.32 (1H, m), 7.91-7.86 (2H, m), 7.52-7.48 (1H, m), 7.44-7.37 (2H, m), 7.28 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.07-7.03 (1H, m), 4.73 (2H, s), 1.28 (9H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 161.3, 149.0, 144.3, 142.1, 140.0, 139.3, 137.0, 135.7, 129.9, 128.1, 127.9, 127.3, 125.4, 125.1, 124.4, 122.8, 118.8, 115.0, 34.3, 32.3, 31.3; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_2S$ $[M+H]^+$ 417.1637 found 417.1645.

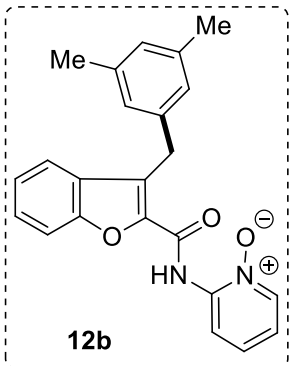
2-(3-(3-Cyanobenzyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (11b): The compound **11b** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (38mg, 0.22 mmol scale, 45%); R_f (100% EtOAc) 0.5; mp: 104-106 ^oC; IR (DCM): 2923, 2231, 1508, 1429, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.85 (1H, br. s), 8.55 (1H, dd, J_1 = 8.5, J_2 = 1.5 Hz), 8.34 (1H, d, J = 6.5 Hz), 7.94 (1H, d, J = 8.1 Hz), 7.77 (1H, d, J = 8.1 Hz), 7.60 (1H, s), 7.56-7.36 (6H, m), 7.09-7.05 (1H, m), 4.77 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 161.0, 144.1, 140.5, 140.4, 139.4, 139.3, 137.1, 132.9, 131.9, 130.5, 130.2, 129.3, 128.2, 127.7, 125.5, 123.7, 123.1, 119.0, 118.9, 114.9, 112.5, 32.4; HRMS (ESI) calcd for $C_{22}H_{16}N_3O_2S$ $[M+H]^+$ 386.0963 found 386.0968.



2-(3-(4-Cyanobenzyl)benzofuran-2-carboxamido)pyridine 1-oxide (12a): The compound **12a** was obtained after purification by column chromatography on silica gel (Acetone:Hexane = 50:50) as a colourless solid (45 mg, 0.25 mmol scale, 49%); R_f (40% Acetone/hexane) 0.4; mp: 238-240 ^oC; IR (DCM): 2921, 2224, 1510, 1429, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.23 (1H, br. s), 8.61 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.37 (1H, dd, J_1 = 6.5, J_2 = 1.2 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.59 (2H, d, J = 8.3 Hz), 7.55-7.48 (4H, m), 7.44-7.39 (1H, m), 7.34-7.30 (1H, m), 7.11-7.07 (1H, m), 4.67 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 157.7, 153.9, 144.4, 143.9, 142.1, 137.3, 132.4, 129.3, 128.5, 128.2, 128.0, 126.6, 124.0, 121.2, 119.1, 118.8, 114.9, 112.6, 110.4, 29.9; HRMS (ESI) calcd for $C_{22}H_{16}N_3O_3$ $[M+H]^+$ 370.1192 found 370.1202.

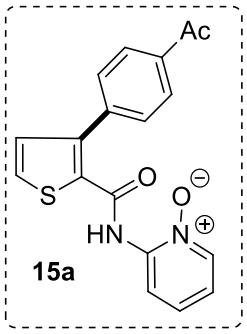


2-(3-(3,5-Dimethylbenzyl)benzofuran-2-carboxamido)pyridine 1-oxide (12b): The compound **12b** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (38 mg, 0.25 mmol scale, 41%); R_f (100% EtOAc) 0.5; mp: 176-178 ^oC; IR (DCM): 2920, 1510, 1428, 1268, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.21 (1H, br. s), 8.66 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.36 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.62 (1H, d, J = 8.4 Hz), 7.56 (1H, d, J =

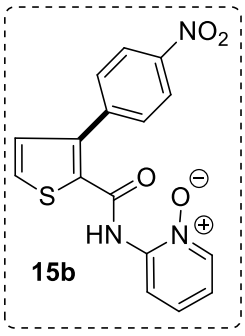


7.9 Hz), 7.50-7.46 (1H, m), 7.43-7.39 (1H, m), 7.30-7.26 (1H, m), 7.09-7.05 (1H, m), 6.98 (2H, s), 6.85 (1H, s), 4.56 (2H, s), 2.27 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 158.0, 153.9, 144.1, 141.7, 138.6, 138.0, 137.3, 128.8, 128.6, 128.1, 128.1, 127.9, 126.4, 123.6, 121.9, 118.8, 115.0, 112.3, 29.8, 21.3; HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3$ $[M+H]^+$ 373.1552 found 373.1538.

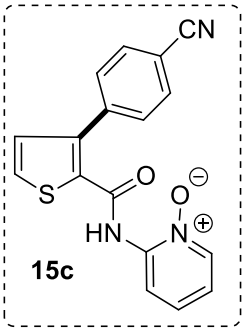
2-(3-(4-Acetylphenyl)thiophene-2-carboxamido)pyridine 1-oxide (15a): The compound **15a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (28 mg, 0.1 mmol scale, 82%); R_f (100% EtOAc) 0.2; mp: 168-170 ^{o}C; IR (DCM): 3081, 1673, 1505, 1270, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.30 (1H, br. s), 8.46 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.12-8.08 (3H, m), 7.64-7.60 (3H, m), 7.33-7.28 (1H, m), 7.13 (1H, d, J = 5.0 Hz), 6.98-6.94 (1H, m), 2.68 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 197.6, 160.1, 144.0, 139.2, 137.0, 136.9, 133.1, 131.4, 130.5, 129.3, 129.0, 127.9, 118.7, 114.9, 26.7; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_3S$ $[M+H]^+$ 339.0803 found 339.0792.



2-(3-(4-Nitrophenyl)thiophene-2-carboxamido)pyridine 1-oxide (15b): The compound **15b** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (35 mg, 0.25 mmol scale, 41%); R_f (100% EtOAc) 0.5; mp: 192-194 ^{o}C; IR (DCM): 2923, 1665, 1508, 1426, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.30 (1H, br. s), 8.44 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 8.81-8.79 (2H, m), 7.66-7.62 (3H, m), 7.36-7.32 (1H, m), 7.12 (1H, d, J = 5.1 Hz), 7.01-6.97 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C 159.8, 147.9, 143.8, 143.0, 141.3, 136.9, 133.3, 131.2, 130.6, 130.1, 128.0, 124.1, 118.9, 114.8; HRMS (ESI) calcd for $C_{16}H_{12}N_3O_4S$ $[M+H]^+$ 342.0549 found 342.0547.

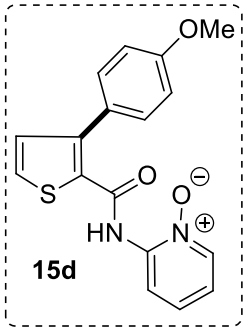


2-(3-(4-Cyanophenyl)thiophene-2-carboxamido)pyridine 1-oxide (15c): The compound **15c** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (42 mg, 0.25 mmol scale, 52%); R_f (100% EtOAc) 0.6; mp: 208-210 ^{o}C; IR (DCM): 2926, 1670, 1512, 1349, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.34 (1H, br. s), 8.44 (1H,



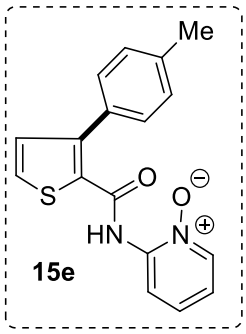
dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.36 (2H, dt, J_1 = 8.8, J_2 = 2.3 Hz), 8.16 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.69 (2H, dt, J_1 = 8.8, J_2 = 2.3 Hz), 7.67 (1H, d, J = 5.1 Hz), 7.36-7.31 (1H, m), 7.16 (1H, d, J = 5.0 Hz), 7.01-6.97 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 159.9, 144.0, 143.4, 139.4, 137.0, 133.4, 132.8, 131.3, 130.7, 129.9, 128.0, 118.9, 118.6, 115.0, 112.7; HRMS (ESI) calcd for $C_{17}H_{12}N_3O_2S$ $[M+H]^+$ 322.0650 found 322.0656.

2-(3-(4-Methoxyphenyl)thiophene-2-carboxamido)pyridine 1-oxide (15d): The compound



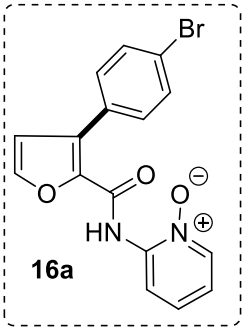
15d was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a colourless solid (35 mg, 0.2 mmol scale, 54%); R_f (100% EtOAc) 0.2; mp: 172-174 ^{o}C; IR (DCM): 2922, 1503, 1424, 1250, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.34 (1H, br. s), 8.50 (1H, dd, J_1 = 8.6, J_2 = 1.7 Hz), 8.12 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.59 (1H, d, J = 5.0 Hz), 7.45 (2H, dt, J_1 = 8.8, J_2 = 2.9 Hz), 7.32-7.27 (1H, m), 7.10-7.06 (3H, m), 6.95-6.91 (1H, m), 3.91 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.7, 160.2, 144.9, 144.3, 137.0, 132.6, 132.1, 130.4, 130.3, 127.6, 126.5, 118.4, 115.1, 114.7, 55.4 ; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3S$ $[M+H]^+$ 327.0803 found 327.0798.

2-(3-(*p*-Tolyl)thiophene-2-carboxamido)pyridine 1-oxide (15e): The compound **15e** was



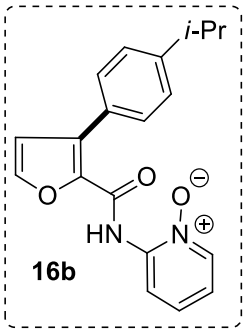
obtained after purification by column chromatography on silica gel (Acetone:hexane = 50:50) as a brown color solid (40 mg, 0.2 mmol scale, 64%); R_f (50% Acetone/hexane) 0.5; mp: 120-122 ^{o}C; IR (DCM): 2924, 1505, 1426, 1277, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.32 (1H, br. s), 8.50 (1H, dd, J_1 = 8.6, J_2 = 1.7 Hz), 8.12 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.60 (1H, d, J = 5.0 Hz), 7.42-7.36 (4H, m), 7.31-7.27 (1H, m), 7.07 (1H, d, J = 5.0 Hz), 6.94-6.90 (1H, m), 2.48 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.7, 145.1, 144.3, 139.0, 137.1, 132.9, 132.1, 131.4, 130.5, 130.0, 128.9, 127.6, 118.4, 115.1, 21.4; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2S$ $[M+H]^+$ 311.0854 found 311.0842.

2-(3-(4-Bromophenyl)furan-2-carboxamido)pyridine 1-oxide (16a): The compound **16a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a cplourless solid (48 mg, 0.25 mmol scale, 53%); R_f (100% EtOAc) 0.3; mp: 184-186 ^{o}C; IR

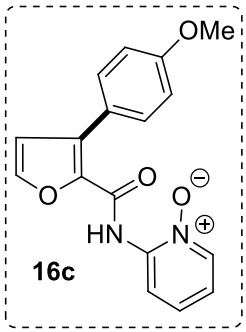


(DCM): 2931, 1570, 1430, 1271, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.01 (1H, br. s), 8.52 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.32 (1H, d, J = 6.3 Hz), 7.65-7.58 (5H, m), 7.37-7.33 (1H, m), 7.05-7.01 (1H, m), 6.71 (1H, d, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 156.3, 144.5, 144.2, 140.4, 137.3, 133.4, 131.4, 131.0, 130.1, 128.1, 123.0, 118.7, 114.9, 114.8; HRMS (ESI) calcd for $C_{16}H_{12}BrN_2O_3$ $[M+H]^+$ 359.0031 found 359.0037.

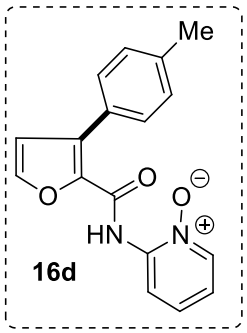
2-(3-(4-Isopropylphenyl)furan-2-carboxamido)pyridine 1-oxide (16b): The compound **16b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (47 mg, 0.25 mmol scale, 59%); R_f (100% EtOAc) 0.5; mp: 150-152 ^oC; IR (DCM): 2956, 1693, 1512, 1432, 775cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.97 (1H, br. s), 8.56 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.32 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.69 (2H, d, J = 8.2 Hz), 7.63 (1H, d, J = 1.8 Hz), 7.37-7.32 (3H, m), 7.03-6.99 (1H, m), 6.73 (1H, d, J = 1.8 Hz), 3.02-2.95 (1H, m), 1.31 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 156.5 149.6, 144.4, 144.3, 140.1, 137.3, 134.8, 129.3, 128.5, 128.2, 126.4, 118.5, 115.3, 114.9, 34.0, 23.9; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1396 found 323.1401.



2-(3-(4-Methoxyphenyl)furan-2-carboxamido)pyridine 1-oxide (16c): The compound **16c** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a colourless solid (58 mg, 0.25 mmol scale, 75%); R_f (100% EtOAc) 0.4; mp: 168-170 ^oC; IR (DCM): 2922, 1684, 1511, 1246, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.98 (1H, br. s), 8.56 (1H, d, J = 8.2 Hz), 8.30 (1H, d, J = 6.4 Hz), 7.72 (2H, d, J = 8.7 Hz), 7.62 (1H, d, J = 0.6 Hz), 7.35-7.31 (1H, m), 7.02-6.99 (3H, m), 6.71 (1H, d, J = 0.6 Hz), 3.89 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 159.8, 156.4, 144.3, 144.2, 139.7, 137.1, 134.3, 130.6, 128.0, 123.3, 118.4, 114.9, 114.7, 113.6, 55.2; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_4$ $[M+H]^+$ 311.1032 found 311.1039.

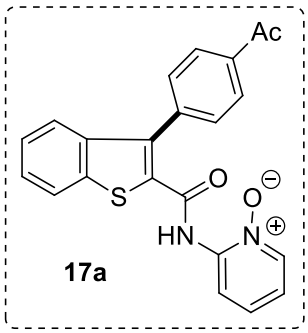


2-(3-(*p*-Tolyl)furan-2-carboxamido)pyridine 1-oxide (16d): The compound **16d** was obtained after purification by column chromatography on silica gel (Acetone:Hexane = 50:50) as a



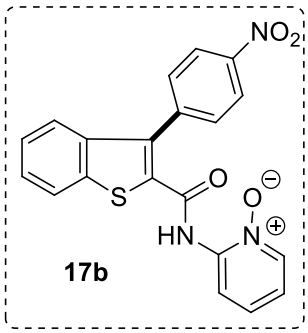
colourless solid (45 mg, 0.25 mmol scale, 61%); R_f (50% Acetone/hexane) 0.5; mp: 180-182 ^oC; IR (DCM): 3093, 1685, 1505, 1428, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.97 (1H, br. s), 8.56 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.31-8.29 (1H, m), 7.64-7.62 (3H, m), 7.35-7.28 (3H, m), 7.02-6.98 (1H, m), 6.72 (1H, d, J = 1.7 Hz), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 156.4, 144.3, 144.2, 140.0, 138.6, 137.1, 134.6, 129.1, 128.9, 128.1, 127.9, 118.4, 115.1, 114.7, 21.3; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3$ $[M+H]^+$ 295.1083 found 295.1078.

2-(3-(4-Acetylphenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17a): The



compound **17a** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 90:10) as a brown color solid (47 mg, 0.2 mmol scale, 61%); R_f (100% EtOAc) 0.2; mp: 170-172 ^oC; IR (DCM): 2923, 2856, 1667, 1506, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.36 (1H, br. s), 8.48 (1H, dd, J_1= 8.5, J_2=1.6 Hz), 8.22 (2H, d, J= 8.2 Hz), 8.11 (1H, d, J = 6.5 Hz), 7.97 (1H, d, J = 8.1 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.56-7.52 (1H, m), 7.44-7.41 (2H, m), 7.33-7.28 (1H, m), 6.98-6.94 (1H, m), 2.74 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.8, 160.6, 144.0, 140.2, 140.1, 139.1, 137.9, 137.7, 137.0, 133.9, 130.1, 129.4, 127.9, 127.5, 125.3, 124.9, 122.6, 118.9, 115.1, 26.9; HRMS (ESI) calcd for $C_{22}H_{17}N_2O_3S$ $[M+H]^+$ 389.0960 found 389.0959.

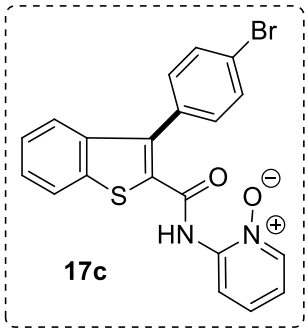
2-(3-(4-Nitrophenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17b):The



compound **17b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (14 mg, 0.18 mmol scale, 30%); R_f (100% EtOAc) 0.5; mp: 210-212 ^oC; IR (DCM): 2925, 1664, 1513, 1350, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.39 (1H, br. s), 8.49 (2H, dt, J_1 = 8.8, J_2 = 2.2 Hz), 8.45 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.14 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.72 (2H, dt, J_1 = 8.8, J_2 = 2.3 Hz), 7.59-7.55 (1H, m), 7.45-43 (2H, m), 7.35-7.31 (1H, m), 7.01-6.97 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.2, 148.4, 143.8, 140.1, 140.0, 139.7, 138.0, 137.0, 134.0, 131.0,

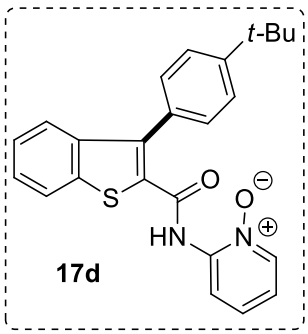
127.9, 127.7, 125.6, 124.6, 124.5, 122.8, 119.1, 114.9; HRMS (ESI) calcd for $C_{20}H_{14}N_3O_4S$ $[M+H]^+$ 392.0705 found 392.0703.

2-(3-(4-Bromophenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17c): The



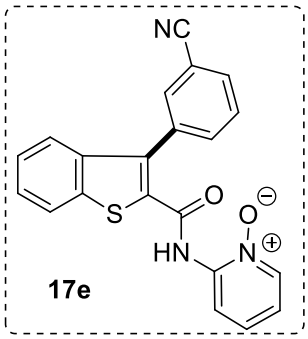
compound **17c** was obtained after purification by column chromatography on silica gel (EtOAc) as a grey color solid (24 mg, 0.2 mmol scale, 28%); R_f (100% EtOAc) 0.7; mp: 238-240 ^oC; IR (DCM): 2935, 1676, 1519, 1276, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.38 (1H, br. s), 8.49 (1H, dd, J_1= 8.5, J_2=1.7 Hz), 8.16 (1H, dd, J_1= 6.5, J_2=1.0 Hz), 7.95 (1H, d, J = 8.1 Hz), 7.80 (2H, dt, J_1 = 8.4, J_2 = 2.3 Hz), 7.55-7.51 (1H, m), 7.45-7.38 (4H, m), 7.34-7.29 (1H, m), 6.99-6.95 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.7, 144.1, 140.5, 140.1, 138.9, 137.1, 134.0, 132.8, 131.8, 131.4, 127.6, 127.4, 125.2, 125.0, 123.9, 122.6, 118.8, 118.1; HRMS (ESI) calcd for $C_{20}H_{14}BrN_2O_2S$ $[M+H]^+$ 424.9959 found 424.9957.

2-(3-(4-(*Tert*-butyl)phenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17d): The



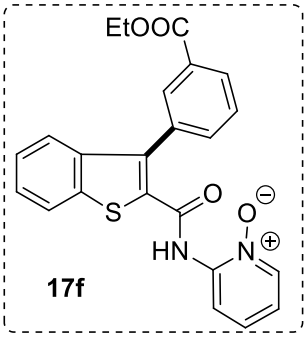
compound **17d** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a colorless solid (37 mg, 0.2 mmol scale, 48%); R_f (100% EtOAc) 0.5; mp: 198-200 ^oC; IR (DCM): 2961, 1690, 1509, 1265, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.24 (1H, br. s), 8.59 (1H, dd, J_1= 8.5, J_2=1.7 Hz), 8.33 (1H, dd, J_1 = 6.7, J_2 = 1.1 Hz), 7.74-7.67 (4H, m), 7.60-7.54 (3H, m), 7.38-7.32 (2H, m), 7.06-7.02 (1H, m), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C 157.2, 153.9, 151.7, 144.1, 140.6, 137.2, 129.7, 129.2, 128.7, 128.3, 127.9, 126.8, 125.3, 123.9, 122.4, 118.8, 115.0, 112.3, 34.8, 31.3; HRMS (ESI) calcd for $C_{24}H_{22}N_2NaO_2S$ $[M+Na]^+$ 425.1300 found 425.1310.

2-(3-(3-Cyanophenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17e): The compound **17e** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 90:10) as a colorless solid (42 mg, 0.2 mmol scale, 57%); R_f (100% EtOAc) 0.4; mp: 177-179 ^oC; IR (DCM): 3061, 2231, 1642, 1512, 761 cm^{-1}; ^1H NMR (400 MHz,

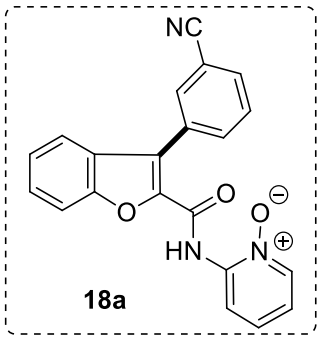


$CDCl_3$): δ_H 10.29 (1H, br. s), 8.49 (1H, d, J = 7.7 Hz), 8.16 (1H, d, J = 6.3 Hz), 7.98-7.92 (2H, m), 7.82-7.78 (3H, m), 7.58-7.54 (1H, m), 7.46-7.39 (2H, m), 7.36-7.32 (1H, m), 6.99 (1H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.2, 140.1, 140.0, 137.4, 137.0, 137.0, 136.9, 134.5, 134.2, 133.4, 132.9, 130.5, 128.0, 127.7, 125.5, 124.6, 122.7, 119.0, 118.2, 115.1, 114.0; HRMS (ESI) calcd for $C_{21}H_{14}N_3O_2S$ $[M+H]^+$ 372.0807 found 372.0821.

2-(3-(3-(Ethoxycarbonyl)phenyl)benzo[*b*]thiophene-2-carboxamido)pyridine 1-oxide (17f): The compound **17f** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 90:10) as a colorless solid (55 mg, 0.2 mmol scale, 65%); R_f (100% EtOAc) 0.4; mp: 234-236 ^{o}C; IR (DCM): 2930, 1720, 1510, 1278, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.29 (1H, br. s), 8.50 (1H, dd, J_1 = 8.5, J_2 = 1.5 Hz), 8.35-8.33 (1H, m), 8.20 (1H, s), 8.11-8.10 (1H, m), 7.95 (1H, d, J = 8.1 Hz), 7.80-7.75 (2H, m), 7.54-7.50 (1H, m), 7.41-7.39 (2H, m), 7.31-7.27 (1H, m), 6.95-6.91 (1H, m), 4.39 (2H, q, J= 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 165.9, 160.6, 144.0, 140.6, 140.2, 138.9, 136.9, 134.3, 134.0, 133.1, 131.9, 130.9, 130.5, 129.8, 127.6, 127.4, 125.2, 125.0, 122.5, 118.7, 115.1, 61.2, 14.2; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_4S$ $[M+H]^+$ 419.1066 found 419.1071.

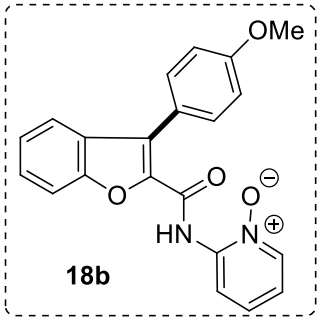


2-(3-(3-Cyanophenyl)benzofuran-2-carboxamido)pyridine 1-oxide (18a): The compound **18a** was obtained after purification by column chromatography on silica gel (Acetone:hexane = 50:50) as a colorless solid (48 mg, 0.2 mmol scale, 68%); R_f (40% Acetone/hexane) 0.4; mp: 243-245 ^{o}C; IR (DCM): 2924, 1683, 1508, 1263, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.27 (1H, br. s), 8.51 (1H, dd, J_1= 8.5, J_2= 1.7 Hz), 8.34-8.33 (1H, m), 8.00 (1H, s), 7.94 (1H, d, J = 7.8 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.72 (1H, d, J = 8.7 Hz), 7.66 (1H, t, J = 8.7 Hz), 7.61-7.57 (2H, m), 7.42-7.34 (2H, m), 7.08-7.04 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 156.7, 153.9, 143.8, 141.3, 137.3, 134.5, 133.5, 132.1, 131.6, 129.2, 128.8, 128.0, 127.8, 126.6, 124.6, 121.4,



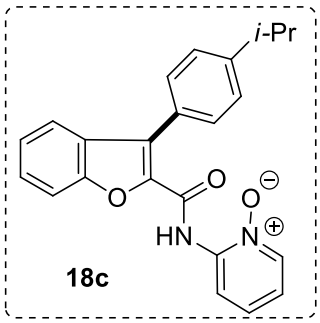
119.2, 118.5, 115.0, 112.7, 112.6; HRMS (ESI) calcd for $C_{21}H_{14}N_3O_3$ $[M+H]^+$ 356.1035 found 356.1028.

2-(3-(4-Methoxyphenyl)benzofuran-2-carboxamido)pyridine 1-oxide (18b): The compound



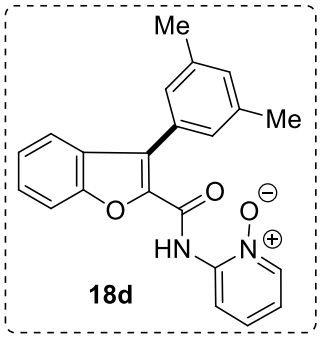
18b was obtained after purification by column chromatography on silica gel (Acetone:hexane = 80:20) as a light yellow color solid (60 mg, 0.2 mmol scale, 84%); R_f (40% Acetone/hexane) 0.2; mp: 210-212 ^oC; IR (DCM): 2951, 1756, 1510, 1187, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.21 (1H, br. s), 8.58 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.33 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.70-7.66 (4H, m), 7.58-7.53 (1H, m), 7.38-7.32 (2H, m), 7.10 (2H, dt, J_1 = 8.8, J_2 = 2.8 Hz), 7.05-7.01 (1H, m), 3.92 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 160.0, 157.2, 153.9, 144.1, 140.6, 137.2, 131.3, 129.0, 128.7, 128.4, 127.9, 124.0, 122.2, 122.0, 118.8, 115.0, 113.9, 112.4, 55.3; HRMS (ESI) calcd for $C_{21}H_{17}N_2O_4$ $[M+H]^+$ 361.1188 found 361.1197.

2-(3-(4-Isopropylphenyl)benzofuran-2-carboxamido)pyridine 1-oxide (18c): The compound



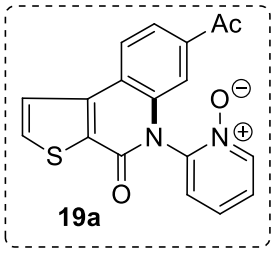
18c was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a yellow color solid (25 mg, 0.2 mmol scale, 33%); R_f (100% EtOAc) 0.5; mp: 192-194 ^oC; IR (DCM): 2963, 1685, 1509, 1263, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.23 (1H, br. s), 8.59 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.33 (1H, d, J = 6.4 Hz), 7.72-7.65 (4H, m), 7.58-7.54 (1H, m), 7.43 (2H, d, J = 8.2 Hz), 7.38-7.32 (2H, m), 7.06-7.02 (1H, m), 3.07-3.00 (1H, m), 1.36 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 157.2, 153.9, 149.5, 144.1, 140.7, 137.2, 129.9, 129.3, 128.7, 128.3, 127.9, 127.2, 126.5, 123.9, 122.4, 118.8, 115.0, 112.3, 34.0, 23.9; HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3$ $[M+H]^+$ 373.1552 found 373.1557.

2-(3-(3,5-Dimethylphenyl)benzofuran-2-carboxamido)pyridine 1-oxide (18d): The compound **18d** was obtained after purification by column chromatography on silica gel (Aetone:hexane = 60:40) as a colourless solid (40 mg, 0.2 mmol scale, 56%); R_f (40% Acetone/hexane) 0.5; mp: 224-226 ^oC; IR (DCM): 3250, 1686, 1508, 1266, 750 cm^{-1}; ^1H NMR



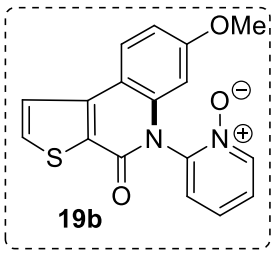
(400 MHz, $CDCl_3$): δ_H 11.15 (1H, br. s), 8.58 (1H, dd, J_1 = 8.4, J_2 = 1.1 Hz), 8.32 (1H, d, J = 6.4 Hz), 7.68 (1H, d, J = 8.5 Hz), 7.64 (1H, d, J = 8.0 Hz), 7.54 (1H, t, J = 7.7 Hz), 7.37-7.29 (2H, m), 7.29 (2H, s), 7.15 (1H, s), 7.04-7.00 (1H, m), 2.44 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 157.0, 153.9, 144.1, 140.9, 138.0, 137.2, 130.6, 129.7, 129.2, 128.8, 128.2, 127.8, 127.5, 123.9, 122.3, 118.7, 115.0, 112.2, 21.4, 21.4; HRMS (ESI) calcd for $C_{22}H_{19}N_2O_3$ $[M+H]^+$ 359.1396 found 359.1385.

2-(7-Acetyl-4-oxothieno[2,3-*c*]quinolin-5(*4H*)-yl)pyridine 1-oxide (19a): The compound **19a**



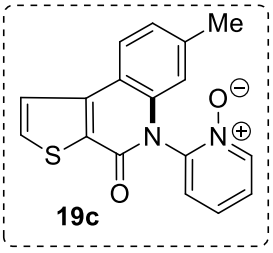
was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (25 mg, 0.15 mmol scale, 50%); R_f (100% EtOAc) 0.3; mp: 264-266 ^{o}C; IR (DCM): 3085, 1672, 1508, 1266, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.61 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 8.50 (1H, d, J = 8.2 Hz), 8.39 (1H, d, J = 5.2 Hz), 8.29 (1H, d, J = 5.2 Hz), 8.01 (1H, dd, J_1 = 8.2, J_2 = 1.5 Hz), 7.96 (1H, dd, J_1 = 7.8, J_2 = 2.04 Hz), 7.75-7.71 (1H, m), 7.67-7.63 (1H, m), 6.98 (1H, d, J = 1.3 Hz), 2.57 (3H, s); ^{13}C NMR (DMSO-d_6, 101 MHz): δ_C 197.8, 157.0, 143.0, 142.3, 140.9, 137.7, 137.2, 137.0, 131.1, 129.3, 128.2, 127.3, 126.1, 124.7, 124.3, 121.6, 114.1, 27.3; HRMS (ESI) calcd for $C_{18}H_{13}N_2O_3S$ $[M+H]^+$ 337.0647 found 337.0656.

2-(7-Methoxy-4-oxothieno[2,3-*c*]quinolin-5(4*H*)-yl)pyridine 1-oxide (19b): The compound



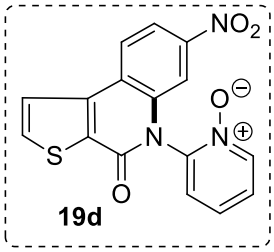
19b was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 90:10 as a yellow color solid (30 mg, 0.2 mmol scale, 46%); R_f (100% EtOAc) 0.2; mp: 135-137 ^{o}C; IR (DCM): 2969, 1672, 1440, 1273, 758 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 +$CDCl_3$): δ_H 8.57 (1H, dd, J_1 = 6.5, J_2= 1.0 Hz), 8.29-8.26 (2H, m), 8.09 (1H, d, J = 5.2 Hz), 7.89 (1H, dd, J_1 = 7.8, J_2= 2.0 Hz), 7.67 (1H, td, J_1 = 7.7, J_2 = 2.1 Hz), 7.60 (1H, td, J_1 = 7.8, J_2 = 1.2 Hz), 7.05 (1H, dd, J_1 = 8.8, J_2= 2.3 Hz), 5.94 (1H, d, J = 2.3 Hz), 3.71 (3H, s); ^{13}C NMR (DMSO-d_6 +$CDCl_3$, 101 MHz): δ_C 160.7, 157.2, 144.2, 142.7, 140.9, 139.4, 136.4, 129.1, 127.8, 127.1, 126.8, 126.7, 124.0, 112.2, 110.4, 100.4, 55.9; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_3S$ $[M+H]^+$ 325.0647 found 325.0660.

2-(7-Methyl-4-oxothieno[2,3-*c*]quinolin-5(4*H*)-yl)pyridine 1-oxide (19c): The compound **19c**



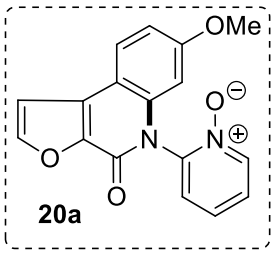
was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 80:20) as a brown color solid (50 mg, 0.2 mmol scale, 81%); R_f (100% EtOAc) 0.1; mp: 265-267 ^oC; IR (DCM): 3404, 1654, 1262, 994, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 +$CDCl_3$): δ_H 8.57 (1H, dd, J_1 = 6.4, J_2 = 1.0 Hz), 8.30 (1H, d, J = 5.2 Hz), 8.21 (1H, d, J = 8.0 Hz), 8.13 (1H, d, J = 5.2 Hz), 7.88 (1H, dd, J_1 = 7.8, J_2= 2.0 Hz), 7.67 (1H, td, J_1 = 7.7, J_2 = 2.2 Hz), 7.60 (1H, td, J_1 = 7.8, J_2= 1.4 Hz), 7.22 (1H, dd, J_1 = 7.8, J_2= 0.6 Hz), 6.38 (1H, s), 2.30 (3H, s); ^{13}C NMR (DMSO-d_6 +$CDCl_3$, 101 MHz): δ_C 157.0, 144.1, 142.8, 140.9, 140.2, 138.1, 136.3, 129.2, 128.4, 127.7, 126.7, 125.4, 125.1, 124.1, 115.9, 115.4, 21.8; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_2S$ $[M+H]^+$ 309.0698 found 309.0699.

2-(7-Nitro-4-oxothieno[2,3-*c*]quinolin-5(4*H*)-yl)pyridine 1-oxide (19d): The compound **19d**



was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 95:05) as a brown color solid (48 mg, 0.32 mmol scale, 44%); R_f (100% EtOAc) 0.3; mp: 260-262 ^oC; IR (DCM): 1682, 1345, 1255, 867, 739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ_H 8.65-8.61 (2H, m), 8.44 (1H, d, J = 5.2 Hz), 8.31 (1H, d, J = 5.3 Hz), 8.21 (1H, d, J = 8.6 Hz), 8.01 (1H, d, J = 7.7 Hz), 7.77-7.74 (1H, m), 7.71-7.66 (1H, m), 7.25 (1H, s); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 101 MHz): δ_C 156.8, 147.6, 142.3, 141.8, 141.1, 137.9, 137.5, 132.1, 129.3, 128.4, 127.2, 127.1, 125.0, 123.0, 118.5, 110.5; HRMS (ESI) calcd for $C_{16}H_{10}N_3O_4S$ $[M+H]^+$ 340.0392 found 340.0381.

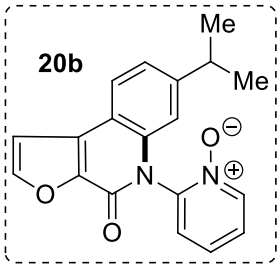
2-(7-Methoxy-4-oxofuro[2,3-*c*]quinolin-5(*4H*)-yl)pyridine 1-oxide (20a): The compound **20a**



was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 90:10) as a brown color solid (36 mg, 0.175 mmol scale, 67%); R_f (5% Methanol/EtOAc) 0.3; mp: 246-248 ^oC; IR (DCM): 2931, 1686, 1431, 1268, 762 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.57 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 8.32 (1H, d, J = 2.0 Hz), 8.12 (1H, d, J = 8.7 Hz), 7.88 (1H, dd, J_1 = 7.8, J_2 = 2.0 Hz), 7.70-7.66 (1H, m), 7.62-7.58 (1H, m), 7.56 (1H, d, J = 2.0 Hz), 7.08 (1H, dd, J_1 = 8.7, J_2 = 2.4 Hz), 5.94 (1H, d, J = 2.3 Hz), 3.70 (3H, s); ^{13}C NMR (DMSO-d_6, 101 MHz): δ_C 160.5 152.5, 150.9, 142.5, 141.0, 140.0, 138.9, 132.1, 129.2,

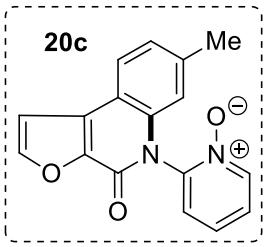
127.8, 127.0, 126.7, 110.6, 110.0, 107.3, 100.5, 55.9; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_4$ $[M+H]^+$ 309.0875 found 309.0871.

2-(7-Isopropyl-4-oxofuro[2,3-*c*]quinolin-5(4*H*)-yl)pyridine 1-oxide (20b): The compound **20b**



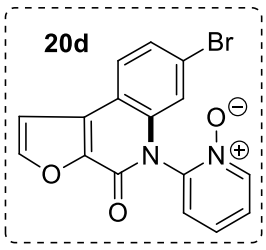
was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 80:20) as a brown color solid (20 mg, 0.2 mmol scale, 32%); R_f (100% EtOAc) 0.1; mp: 130-132 ^oC; IR (DCM): 2960, 1688, 1434, 1266, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.58 (1H, dd, J_1 = 6.3, J_2= 0.8 Hz), 8.34 (1H, d, J = 1.9 Hz), 8.10 (1H, d, J = 8.1 Hz), 7.88 (1H, dd, J_1 = 7.8, J_2= 2.0 Hz), 7.68 (1H, td, J_1 = 7.8, J_2 = 2.2 Hz), 7.63-7.58 (2H, m), 7.33 (1H, dd, J_1 = 8.2, J_2= 1.2 Hz), 6.35 (1H, d, J = 0.7 Hz), 2.91-2.81 (1H, m), 1.13-1.10 (6H, m);^{13}C NMR (DMSO-d_6, 101 MHz):δ_C 152.4, 150.8, 150.4, 142.6, 141.0, 140.9, 137.5, 131.8, 129.2, 127.8, 126.7, 125.6, 122.2, 114.3, 113.0, 107.4, 34.0, 24.2, 24.0; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ 321.1239 found 321.1230.

2-(7-Methyl-4-oxofuro[2,3-c]quinolin-5(4*H*)-yl)pyridine 1-oxide (20c): The compound **20c**



was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 80:20) as a brown color solid (52 mg, 0.25 mmol scale, 71%); R_f (100% EtOAc) 0.1; mp: 110-112 ^oC; IR (DCM): 2968, 1687, 1499, 1266, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.56 (1H, dd, J_1 = 6.4, J_2 = 0.8 Hz), 8.34-8.32 (1H, m), 8.06 (1H, d, J = 8.0 Hz), 7.86 (1H, dd, J_1 = 7.8, J_2= 2.0 Hz), 7.68 (1H, td, J_1 = 7.7, J_2 = 2.1 Hz), 7.62-7.57 (2H, m), 7.23 (1H, d, J = 7.7 Hz), 6.38 (1H, s), 2.30 (3H, s);^{13}C NMR (DMSO-d_6, 101 MHz):δ_C 152.4, 150.8, 142.6, 141.0, 139.8, 137.6, 131.9, 129.2, 127.8, 126.7, 125.3, 125.1, 115.4, 113.9, 107.4, 21.8; HRMS (ESI) calcd for $C_{17}H_{13}N_2O_3$ $[M+H]^+$ 293.0926 found 293.0922.

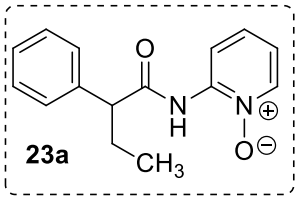
2-(7-Bromo-4-oxofuro[2,3-*c*]quinolin-5(4*H*)-yl)pyridine 1-oxide (20d): The compound **20d**



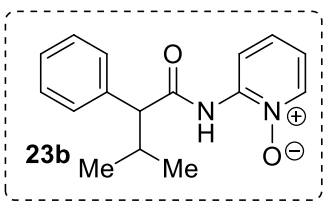
was obtained after purification by column chromatography on silica gel (Acetone:Hexane = 50:50) as a brown color solid (40 mg, 0.3 mmol scale, 37%); R_f (40% Acetone/hexane) 0.3; mp: 266-268 ^oC; IR (DCM): 2927, 1730, 1293, 1077, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$): δ_H 8.58 (1H, dd, J_1 = 6.4, J_2 = 1.0 Hz), 8.39 (1H, d, J = 1.9 Hz), 8.16 (1H, d, J = 8.4 Hz), 7.91 (1H, dd, J_1 = 7.8, J_2 = 2.1 Hz), 7.72-7.68 (1H, m), 7.64-7.60 (3H,

m), 6.68 (1H, d, J = 1.7 Hz); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 101 MHz): δ_C 152.1, 151.2, 141.9, 141.4, 141.1, 138.4, 131.4, 129.2, 128.1, 127.5, 127.0, 126.9, 122.7, 117.8, 115.6, 107.6; HRMS (ESI) calcd for $C_{16}H_{10}BrN_2O_3$ $[M+H]^+$ 356.9875 found 356.9865.

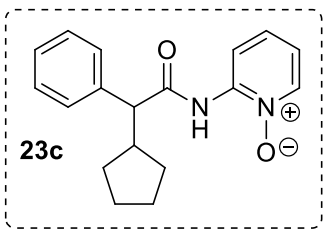
2-(2-Phenylbutanamido)pyridine 1-oxide (23a): The compound **23a** was obtained after purification by column chromatography on silica gel (EtOAc) as a yellow color solid (697 mg, 3 mmol scale, 91%); R_f (100% EtOAc) 0.5; mp: 144-146 ^{o}C; IR (DCM): 2942, 1704, 1507, 1434, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.09 (1H, br. s), 8.45 (1H, d, J = 8.4 Hz), 8.19 (1H, d, J = 6.4 Hz), 7.41-7.28 (6H, m), 6.95 (1H, t, J = 6.7 Hz), 3.58 (1H, t, J = 7.6 Hz), 2.33-2.23 (1H, m), 2.00-1.89 (1H, m), 0.97 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.5, 144.1, 138.4, 137.0, 129.0, 128.1, 127.9, 127.7, 118.5, 114.6, 56.4, 26.1, 12.2; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ 257.1290 found 257.1291.



2-(3-Methyl-2-phenylbutanamido)pyridine 1-oxide (23b): The compound **23b** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (183 mg, 1 mmol scale, 68%); R_f (100% EtOAc) 0.5; mp: 136-138 ^{o}C; IR (DCM): 3160, 2959, 1700, 1502, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.13 (1H, br. s), 8.47 (1H, d, J = 8.4 Hz), 8.21 (1H, d, J = 6.5 Hz), 7.42 (2H, d, J = 7.5 Hz), 7.37-7.34 (2H, m), 7.31-7.27 (2H, m), 6.97 (1H, t, J = 7.2 Hz), 3.23 (1H, d, J = 10.4 Hz), 2.59-2.49 (1H, m), 1.13 (3H, d, J = 6.5 Hz), 0.79 (3H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.4, 144.0, 137.9, 136.9, 128.7, 128.2, 128.0, 127.5, 118.5, 114.6, 63.0, 31.5, 21.5, 20.2; HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_2$ $[M+Na]^+$ 293.1266 found 293.1256.

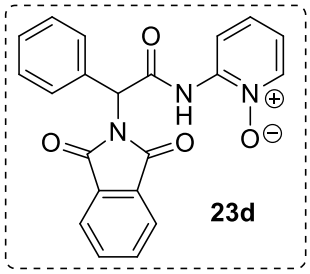


2-(2-Cyclopentyl-2-phenylacetamido)pyridine 1-oxide (23c): The compound **23c** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (189 mg, 1 mmol scale, 64%); R_f (100% EtOAc) 0.5; mp: 110-112 ^{o}C; IR (DCM): 2944, 1700, 1503, 1428, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.08 (1H, br. s), 8.52-8.50 (1H, m), 8.30-8.28 (1H, m), 7.46-7.27 (6H, m), 7.03 (1H, t, J = 6.6 Hz), 3.42 (1H, d, J = 10.9 Hz), 2.79-2.68 (1H, m), 2.05-1.97 (1H, m), 1.75-1.47 (5H, m), 1.39-1.29 (1H, m), 1.11-1.05 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.4, 144.1, 138.5,



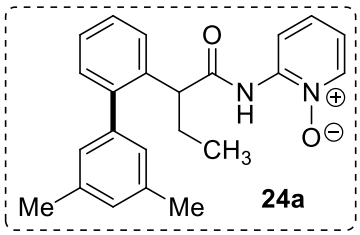
137.0, 128.8, 128.4, 128.0, 127.5, 118.4, 114.7, 60.9, 43.0, 31.6, 30.8, 25.1, 24.7; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ 297.1603 found 297.1599.

2-(2-(1,3-Dioxoisoindolin-2-yl)-2-phenylacetamido)pyridine 1-oxide (23d): The compound



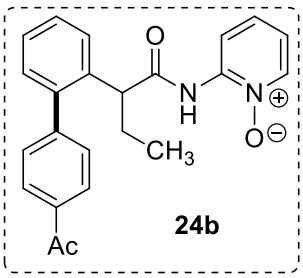
23d was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 50:50) as a light yellow colour solid (561 mg, 2 mmol scale, 75%); R_f (100% EtOAc) 0.8; mp: 190-192 ^oC; IR (DCM): 3150, 1719, 1513, 1379, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.36 (1H, br. s), 8.46 (1H, d, J= 8.4 Hz), 8.16 (1H, d, J = 6.4 Hz), 7.90 (2H, dd, J_1 = 5.1, J_2 = 3.2 Hz), 7.78-7.72 (4H, m), 7.52-7.44 (3H, m), 7.34 (1H, t, J = 8.2 Hz), 7.00 (1H, t, J = 7.1 Hz), 6.17 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.4, 166.1, 143.7, 136.9, 134.3, 133.4, 131.7, 129.8, 129.8, 129.5, 128.0, 123.7, 119.2, 114.6, 58.6; HRMS (ESI) calcd for $C_{21}H_{16}ClN_3O_4$ $[M+H]^+$ 374.1141 found 374.1139.

2-(2-(3',5'-Dimethyl-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24a): The compound



24a was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (40 mg, 0.2 mmol scale, 56%); R_f (80% EtOAc/hexane) 0.4; mp: 144-146 ^oC; IR (DCM): 2924, 1510, 1427, 1208, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.81 (1H, br. s), 8.46 (1H, d, J = 8.4 Hz), 8.22 (1H, d, J = 6.4 Hz), 7.53 (1H, d, J = 8.0 Hz), 7.38 (1H, td, J_1 = 7.8, J_2 = 2.1 Hz), 7.34-7.27 (3H, m), 7.07 (1H, s), 7.01-6.94 (3H, m), 3.75 (1H, t, J = 7.4 Hz), 2.42 (6H, s), 2.23-2.16 (1H, m), 1.94-1.83 (1H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.9, 144.2, 142.9, 140.8, 138.2, 137.0, 136.3, 130.2, 129.1, 128.4, 128.0, 127.1, 127.0, 126.6, 118.4, 114.7, 51.0, 26.6, 21.3, 12.1; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$ 361.1916 found 361.1926.

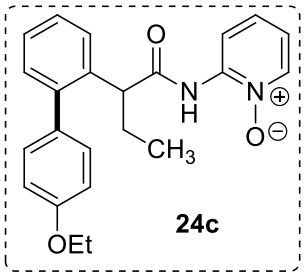
2-(2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24b): The compound **24b**



was obtained after purification by column chromatography on silica gel (EtOAc) as a clourless solid (50 mg, 0.2 mmol scale, 67%); R_f (80% EtOAc/hexane) 0.2; mp: 125-127 ^oC; IR (DCM): 2949, 1693, 1503, 1268, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.80 (1H, br. s), 8.43 (1H, dd, J_1 = 8.5, J_2 = 1.4 Hz), 8.22 (1H, d, J = 6.4 Hz), 8.11

(2H, d, J = 8.5 Hz), 7.57-7.51 (3H, m), 7.45 (1H, td, J_1 = 7.8, J_2 = 1.5 Hz), 7.38-7.33 (2H, m), 7.30-7.27 (1H, m), 7.00-6.96 (1H, m), 3.64 (1H, t, J = 7.5 Hz), 2.69 (3H, s), 2.28-2.17 (1H, m), 1.95-1.84 (1H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.7, 172.2, 145.8, 144.0, 141.5, 136.9, 136.2, 136.0, 129.9, 129.6, 128.8, 128.6, 128.2, 127.3, 126.9, 118.5, 114.5, 51.2, 26.7, 26.4, 12.0; HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3$ $[M+H]^+$ 375.1709 found 375.1721.

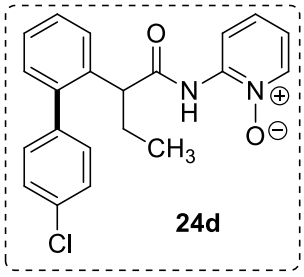
2-(2-(4'-Ethoxy-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24c): The compound **24c**



24c

was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a yellow color solid (40 mg, 0.2 mmol scale, 53%); R_f (100% EtOAc) 0.5; mp: 116-118 ^{o}C; IR (DCM): 2971, 1704, 1503, 1249, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.78 (1H, br. s), 8.45 (1H, d, J = 8.4 Hz), 8.21 (1H, d, J = 6.1 Hz), 7.51 (1H, d, J = 7.6 Hz), 7.40-7.28 (6H, m), 7.04 (2H, d, J = 8.6 Hz), 6.96 (1H, t, J = 7.1 Hz), 4.15-4.09 (2H, m), 3.77 (1H, t, J = 7.4 Hz), 2.25-2.18 (1H, m), 1.91-1.84 (1H, m), 1.47 (3H, t, J = 7.0 Hz), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.8, 158.4, 144.2, 142.4, 136.9, 136.6, 133.0, 130.6, 130.4, 128.2, 128.0, 127.1, 126.6, 118.4, 114.6, 114.5, 63.4, 51.0, 26.4, 14.8, 12.1; HRMS (ESI) calcd for $C_{23}H_{24}N_2NaO_3$ $[M+Na]^+$ 399.1685 found 399.1682.

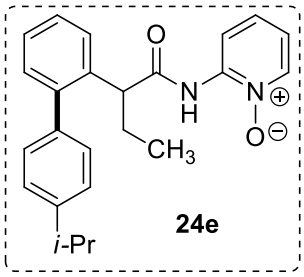
2-(2-(4'-Chloro-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24d): The com pound **24d**



24d

was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (90 mg, 0.6 mmol scale, 41%); R_f (100% EtOAc) 0.6; mp: 130-132 ^{o}C; IR (DCM): 3256, 1703, 1504, 1211, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.83 (1H, br. s), 8.42 (1H, dd, J_1= 8.5, J_2= 1.4 Hz), 8.19 (1H, d, J = 6.3 Hz), 7.55-7.48 (3H, m), 7.42 (1H, td, J_1 = 7.8, J_2 = 1.4 Hz) 7.36-7.26 (5H, m), 6.98-6.94 (1H, m), 3.66 (1H, t, J = 7.5 Hz), 2.26-2.19 (1H, m), 1.92-1.85 (1H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.3, 144.0, 141.4, 139.2, 136.8, 136.3, 133.6, 130.6, 130.2, 128.7, 128.6, 128.0, 127.2, 126.8, 118.4, 114.4, 51.0, 26.4, 12.0; HRMS (ESI) calcd for $C_{21}H_{19}ClN_2NaO_2$ $[M+Na]^+$ 389.1033 found 389.1029.

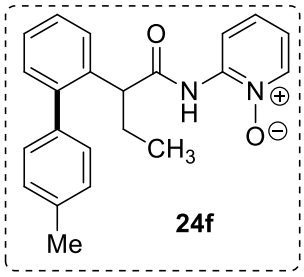
2-(2-(4'-Isopropyl-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24e): The compound



24e

24e was obtained after purification by column chromatography on silica gel (EtOAc) as a light brown colour viscous (44 mg, 0.2 mmol scale, 59%); R_f (80% EtOAc/hexane) 0.5; IR (DCM): 2951, 1709, 1502, 1209, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.79 (1H, br. s), 8.46 (1H, d, J = 8.2 Hz), 8.24 (1H, d, J = 6.0 Hz), 7.52 (1H, d, J = 7.8 Hz), 7.41-7.27 (8H, m), 6.96 (1H, t, J = 6.4 Hz), 3.77 (1H, t, J = 7.5 Hz), 3.04-2.97 (1H, m), 2.25-2.18 (1H, m), 1.93-1.86 (1H, m), 1.33 (6H, d, J = 6.9 Hz), 0.85 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.8, 148.0, 142.8, 138.2, 137.1, 136.3, 130.5, 129.5, 129.2, 128.9, 128.9, 128.1, 127.1, 126.6, 118.4, 114.7, 51.0, 33.8, 26.5, 24.0, 23.9, 12.1; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_2$ $[M+H]^+$ 375.2073 found 375.2075.

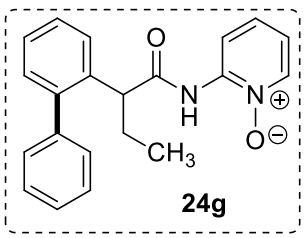
2-(2-(4'-Methyl-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24f): The compound **24f**



24f

was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (53 mg, 77%); R_f (100% EtOAc) 0.5; mp: 130-132 ^oC; IR (DCM): 3257, 2962, 1703, 1501,758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.84 (1H, br. s), 8.42 (1H, dd, J_1= 8.5, J_2 = 1.8 Hz), 8.19 (1H, dd, J_1= 6.5, J_2= 1.4 Hz), 7.53 (1H, dd, J_1= 8.3, J_2= 0.9 Hz), 7.41-7.37 (1H, m), 7.34-7.28 (7H, m), 6.96-6.92 (1H, m), 3.74 (1H, t, J = 7.5 Hz), 2.45 (3H, s), 2.27-2.16 (1H, m), 1.94-1.83 (1H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz):δ_C 172.8, 144.2, 142.7, 137.9, 137.2, 136.9, 136.5, 130.4, 129.3, 129.2, 128.1, 128.0, 127.1, 126.6, 118.4, 114.6, 51.0, 26.5, 21.2, 12.1; HRMS (ESI) calcd for $C_{22}H_{22}N_2NaO_2$ $[M+Na]^+$ 369.1579 found 369.1573

2-(2-([1,1'-Biphenyl]-2-yl)butanamido)pyridine 1-oxide (24g): The compound **24g** was

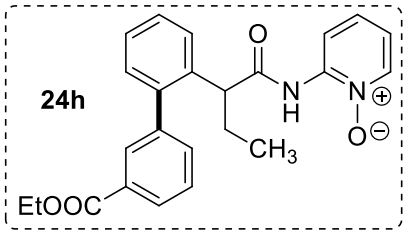


24g

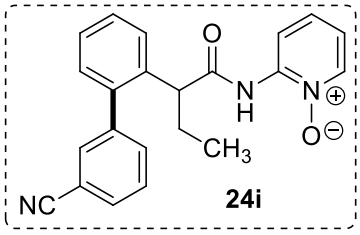
obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (46 mg, 0.2 mmol scale, 71%); R_f (100% EtOAc) 0.6; mp: 102-104 ^oC; IR (DCM): 2964, 1701, 1503, 1202, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.84 (1H, br. s), 8.42 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.55-7.50 (3H, m), 7.46-7.39 (4H, m), 7.36-7.28 (3H, m), 6.96-6.92 (1H, m), 3.72 (1H, t, J = 7.5 Hz), 2.27-2.16 (1H, m), 1.95-1.84 (1H, m), 0.85 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101

MHz): δ_C 172.7, 144.1, 142.7, 140.9, 136.9, 136.3, 130.3, 129.3, 128.6, 128.3, 127.9, 127.5, 127.1, 126.7, 118.4, 114.5, 51.0, 26.5, 12.1; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603 found 333.1611.

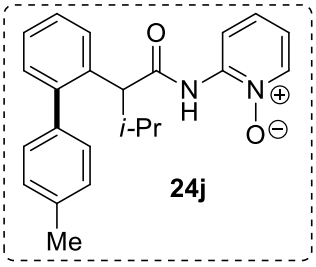
2-(2-(3'-(Ethoxycarbonyl)-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24h): The compound **24h** was obtained after purification by column chromatography on silica gel (EtOAc) as a light brown color viscous (55 mg, 0.2 mmol scale, 68%); R_f (EtOAc) 0.5; IR (DCM): 2967, 1708, 1498, 1228, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, br. s), 8.45 (1H, d, J = 8.5 Hz), 8.24 (1H, d, J = 4.3 Hz), 8.12 (1H, dt, J_1 = 7.4, J_2 = 1.6 Hz), 8.02 (1H, s), 7.68-7.61 (2H, m), 7.56 (1H, dd, J_1 = 7.9, J_2 = 1.0 Hz), 7.45 (1H, td, J_1 = 7.8, J_2 = 1.5 Hz), 7.39-7.35 (2H, m), 7.31 (1H, dd, J_1 = 7.6, J_2 = 1.5 Hz), 6.99 (1H, t, J= 6.8 Hz), 4.44-4.36 (2H, m), 3.69 (1H, t, J = 7.5 Hz), 2.29-2.19 (1H, m), 2.00-1.89 (1H, m), 1.39 (3H, t, J = 7.1 Hz), 0.89 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.4, 166.3, 144.0, 141.6, 140.9, 136.9, 136.1, 133.7, 130.7, 130.4, 130.3, 128.8, 128.7, 128.5, 128.5, 127.4, 126.9, 118.5, 114.6, 61.0, 51.2, 26.4, 14.2, 12.1; HRMS (ESI) calcd for $C_{24}H_{25}N_2O_4$ $[M+H]^+$ 405.1814 found 405.1808.



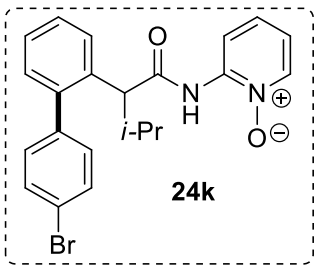
2-(2-(3'-Cyano-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24i): The compound **24i** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a colorless solid (50 mg, 0.2 mmol scale, 70%); R_f (100% EtOAc) 0.5; mp: 130-132 ^oC; IR (DCM): 2967, 2229, 1506, 1206, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.85 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.19 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.74 (1H, dt, J_1 = 7.4, J_2 = 1.6 Hz), 7.71-7.63 (2H, m), 7.58 (1H, dd, J_1 = 7.9, J_2 = 1.0 Hz), 7.48 (1H, dt, J_1 = 7.8, J_2 = 1.4 Hz), 7.40-7.30 (3H, m), 7.26 (1H, dd, J_1 = 7.7, J_2 = 1.4 Hz), 6.99-6.95 (1H, m), 3.56 (1H, t, J = 7.7 Hz), 2.30-2.19 (1H, m), 1.97-1.86 (1H, m), 0.86 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.0, 143.9, 142.2, 140.3, 136.9, 136.1, 133.9, 132.7, 131.3, 130.2, 129.5, 129.3, 128.1, 127.6, 127.2, 118.6, 118.5, 114.5, 112.8, 51.4, 26.3, 12.1; HRMS (ESI) calcd for $C_{22}H_{20}N_3O_2$ $[M+H]^+$ 358.1556 found 358.1541.



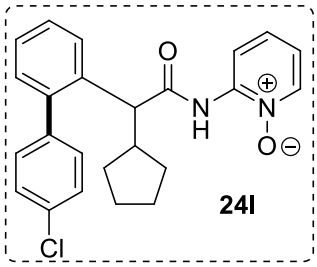
2-(3-Methyl-2-(4'-methyl-[1,1'-biphenyl]-2-yl)butanamido)pyridine 1-oxide (24j): The compound **24j** was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (40 mg, 0.2 mmol scale, 56%); R_f (100% EtOAc) 0.5; mp: 128-130 ^oC; IR (DCM): 2958, 1705, 1502, 1210, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.91 (1H, br. s), 8.48 (1H, dd, J_1= 8.5, J_2= 1.3 Hz), 8.25 (1H, d, J= 6.5 Hz), 7.67 (1H, dd, J_1= 8.0, J_2= 0.8 Hz), 7.40-7.24 (8H, m), 6.99-6.95 (1H, m), 3.37 (1H, d, J= 10.7 Hz), 2.57-2.45 (1H, m), 2.46 (3H, s), 0.97 (3H, d, J= 6.4 Hz), 0.69 (3H, d, J= 6.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.8, 144.1, 143.0, 138.1, 137.2, 137.0, 136.1, 130.1, 129.3, 129.3, 128.3, 127.9, 126.8, 126.7, 118.5, 114.8, 57.2, 32.3, 21.5, 21.2, 20.0; HRMS (ESI) calcd for $C_{23}H_{24}N_2NaO_2$ $[M+Na]^+$ 383.1735 found 383.1732.



2-(2-(4'-Bromo-[1,1'-biphenyl]-2-yl)-3-methylbutanamido)pyridine 1-oxide (24k): The compound **24k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 80:20) as a brown color solid (40 mg, 0.2 mmol scale, 47%); R_f (100% EtOAc) 0.6; mp: 130-132 ^oC; IR (DCM): 3259, 2963, 1499, 1208, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.94 (1H, br. s), 8.45 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.23 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.69-7.67 (3H, m), 7.43-7.39 (1H, m), 7.33-7.28 (4H, m), 7.21 (1H, dd, J_1 = 7.6, J_2 = 1.4 Hz), 6.99-6.95 (1H, m), 3.29 (1H, d, J = 10.7 Hz), 2.57-2.48 (1H, m), 0.99 (3H, d, J = 6.4 Hz), 0.68 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.4, 144.0, 141.7, 140.0, 136.9, 136.0, 131.8, 131.2, 129.9, 128.5, 128.0, 127.0, 126.9, 121.8, 118.6, 114.7, 57.3, 32.4, 21.5, 20.1; HRMS (ESI) calcd for $C_{22}H_{21}BrN_2NaO_2$ $[M+Na]^+$ 447.0684 found 447.0696.

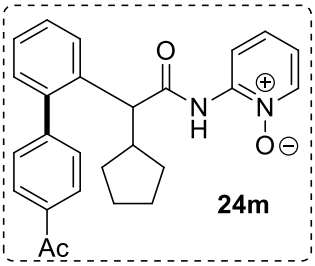


2-(2-(4'-Chloro-[1,1'-biphenyl]-2-yl)-2-cyclopentylacetamido)pyridine 1-oxide (24l): The compound **24l** was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (50 mg, 0.2 mmol scale, 62%); R_f (100% EtOAc) 0.6; mp: 96-98 ^oC; IR (DCM): 2952, 1698, 1505, 1208, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.94 (1H, br. s), 8.44 (1H, d, J= 8.5 Hz), 8.23 (1H, d, J= 6.5 Hz), 7.68 (1H, dd, J_1= 7.9, J_2= 1.0 Hz), 7.52 (2H, d, J= 8.2 Hz), 7.43-7.28 (5H, m), 7.22



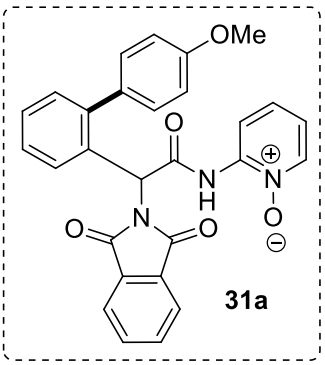
(1H, dd, J_1= 7.6, J_2= 1.2 Hz), 6.99-6.96 (1H, m), 3.45 (1H, d, J = 10.9 Hz), 2.77-2.66 (1H, m), 1.98-1.90 (1H, m), 1.60-1.54 (2H, m), 1.50-1.41 (3H, m), 1.17-1.07 (1H, m), 0.95-0.85 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.4, 144.1, 141.2, 139.5, 136.9, 136.5, 133.6, 130.9, 130.1, 128.8, 128.4, 128.4, 127.3, 126.9, 118.5, 114.7, 55.3, 44.0, 31.5, 30.6, 24.9, 24.6; HRMS (ESI) calcd for $C_{24}H_{24}ClN_2O_2$ $[M+H]^+$ 407.1526 found 407.1533.

2-(2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)-2-cyclopentylacetamido)pyridine 1-oxide (24m): The compound **24m** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (56 mg, 0.2 mmol scale, 68%); R_f (100% EtOAc) 0.4; mp: 170-172 ^{o}C; IR (DCM): 2955, 1694, 1504, 1270, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.92 (1H, br. s), 8.46 (1H, dd, J_1= 8.5, J_2= 1.6 Hz), 8.27 (1H, d, J= 6.4 Hz), 8.14 (2H, d, J= 8.4 Hz), 7.70 (1H, dd, J_1= 7.9, J_2= 0.6 Hz), 7.54-7.53 (2H, m), 7.43 (1H, td, J_1= 7.9, J_2= 1.3 Hz), 7.37-7.30 (2H, m), 7.23 (1H, dd, J_1= 7.6, J_2= 1.3 Hz), 7.01-6.97 (1H, m), 3.43 (1H, d, J = 10.9 Hz), 2.74-2.65 (1H, m), 2.70 (3H, s), 1.96-1.88 (1H, m), 1.57-1.52 (2H, m), 1.49-1.41 (3H, m), 1.14-1.05 (1H, m), 0.93-0.87 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.9, 172.3, 146.1, 144.0, 141.4, 137.0, 136.3, 136.2, 130.0, 129.7, 128.7, 128.7, 128.1, 127.3, 127.0, 118.6, 114.8, 55.4, 44.0, 31.5, 30.6, 26.8, 24.9, 24.6; HRMS (ESI) calcd for $C_{26}H_{26}N_2NaO_3$ $[M+Na]^+$ 437.1841 found 437.1862.



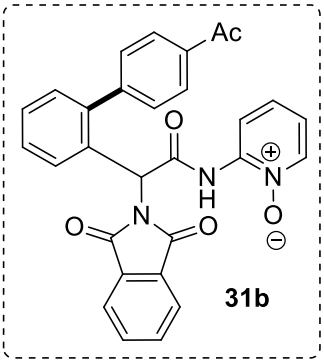
24m

2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-methoxy-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31a): The compound **31a** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (38 mg, 0.15 mmol scale, 53%); R_f (100% EtOAc) 0.5; mp: 202-204 ^{o}C; IR (DCM): 3153, 1721, 1510, 1261, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.28 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.16 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.93-7.90 (1H, m), 7.87 (2H, dd, J_1= 5.5, J_2= 3.1 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.51-7.38 (5H, m), 7.34-7.29 (1H, m), 7.01-6.97 (3H, m), 6.39 (1H, s), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.6, 166.4, 159.2, 143.6, 143.3, 137.0, 134.3, 131.9, 131.7, 131.4, 130.5, 129.5, 129.1, 128.6, 127.9, 123.6, 119.2, 114.5, 114.0, 56.0, 55.3; HRMS (ESI) calcd for $C_{28}H_{22}N_3O_5$ $[M+H]^+$ 480.1559 found 480.1565.

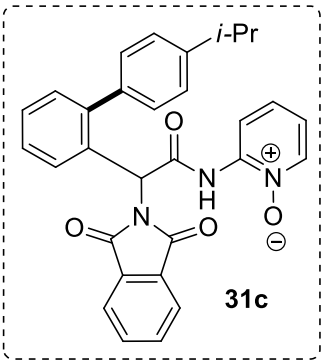


31a

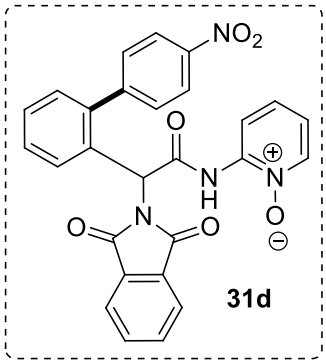
2-(2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamido)pyridine 1-oxide (31b): The compound **31b** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a brown color solid (37 mg, 0.15 mmol scale, 50%); R_f (100% EtOAc) 0.4; mp: 225-227 °C; IR (DCM): 2933, 1711, 1508, 1376, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.30 (1H, br. s), 8.39 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.17 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 8.06 (2H, d, J = 8.3 Hz), 7.97-7.94 (1H, m), 7.87 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.61 (2H, d, J = 8.4 Hz), 7.55-7.51 (2H, m), 7.40-7.37 (1H, m), 7.35-7.31 (1H, m), 7.04-7.00 (1H, m), 6.25 (1H, s), 2.66 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 197.7, 167.5, 165.9, 144.5, 143.5, 142.4, 136.9, 136.4, 134.4, 131.6, 131.3, 130.7, 129.7, 129.7, 129.4, 128.6, 128.1, 123.7, 119.3, 114.6, 55.8, 26.7; HRMS (ESI) calcd for $C_{29}H_{22}N_3O_5$ $[M+H]^+$ 492.1559 found 492.1563.



2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-isopropyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31c): The compound **31c** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 90:10) as a brown color solid (38 mg, 0.15 mmol scale, 52%); R_f (100% EtOAc) 0.6; mp: 110-112 °C; IR (DCM): 2940, 1714, 1502, 1371, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.29 (1H, br. s), 8.41 (1H, dd, J_1 = 8.5, J_2 = 1.8 Hz), 8.17 (1H, dd, J_1 = 6.5, J_2 = 1.1 Hz), 7.92-7.89 (1H, m), 7.87 (2H, dd, J_1= 5.3, J_2= 3.1 Hz), 7.75 (2H, dd, J_1 = 5.6, J_2 = 3.1 Hz), 7.51-7.46 (2H, m), 7.42-7.39 (3H, m), 7.34-7.29 (3H, m), 7.02-6.98 (1H, m), 6.38 (1H, s), 3.03-2.92 (1H, m), 1.31 (6H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.6, 166.5, 148.3, 143.6, 143.6, 136.9, 136.9, 134.3, 131.7, 131.5, 131.2, 129.4, 129.2, 129.0, 128.6, 127.9, 126.6, 123.6, 119.1, 114.5, 56.1, 33.8, 23.9, 23.9; HRMS (ESI) calcd for $C_{30}H_{26}N_3O_4$ $[M+H]^+$ 492.1923 found 492.1925.

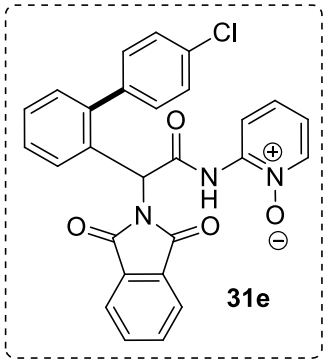


2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-nitro-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31d): The compound **31d** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a light yellow color solid (15 mg, 0.15 mmol scale, 20%); R_f (100% EtOAc) 0.5; mp: 112-114 °C; IR (DCM): 2932, 1717, 1512, 1365, 741 cm^{-1}; ^1H NMR

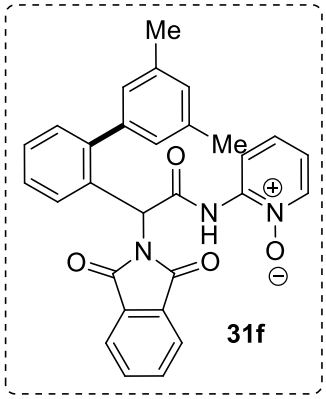


(400 MHz, $CDCl_3$): δ_H 10.30 (1H, br. s), 8.39 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.34 (2H, dt, J_1= 8.7, J_2= 2.3 Hz), 8.18 (1H, dd, J_1 = 6.6, J_2 = 1.0 Hz), 8.01-7.98 (1H, m), 7.88 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.78 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.70 (2H, dt, J_1= 8.8, J_2= 2.2 Hz), 7.59-7.54 (2H, m), 7.39-7.33 (2H, m), 7.06-7.02 (1H, m), 6.18 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.5, 165.6, 147.6, 146.4, 143.5, 141.2, 137.0, 134.5, 131.6, 131.3, 130.6, 130.5, 129.9, 129.8, 129.7, 128.2, 123.8, 123.8, 119.4, 114.7, 55.7; HRMS (ESI) calcd for $C_{27}H_{19}N_4O_6$ $[M+H]^+$ 495.1305 found 495.1281.

2-(2-(4'-Chloro-[1,1'-biphenyl]-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamido)pyridine 1-oxide (31e): The compound **31e** was obtained after purification by column chromatography on silica gel (EtOAc) as a colourless solid (38 mg, 0.15 mmol scale, 48%); R_f (100% EtOAc) 0.5; mp: 172-174 ^{o}C; IR (DCM): 2931, 1712, 1500, 1371, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.27 (1H, br. s), 8.39 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.16 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.95-7.93 (1H, m), 7.88 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.53-7.49 (2H, m), 7.44 (4H, s), 7.38-7.30 (2H, m), 7.03-6.99 (1H, s), 6.27 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.6, 166.0, 143.5, 142.3, 138.0, 136.9, 134.4, 134.1, 131.6, 131.5, 131.0, 130.8, 129.6, 129.3, 129.2, 128.8, 128.0, 123.7, 119.3, 114.6, 55.9; HRMS (ESI) calcd for $C_{27}H_{19}ClN_3O_4$ $[M+H]^+$ 484.1064 found 484.1054.

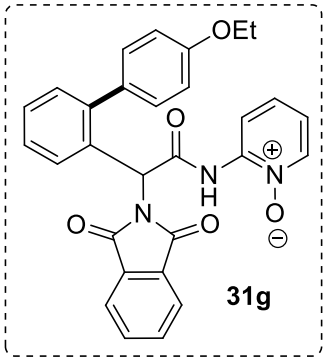


2-(2-(3',5'-Dimethyl-[1,1'-biphenyl]-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamido)pyridine 1-oxide (31f): The compound **31f** was obtained after purification by column chromatography on silica gel (EtOAc:Methanol = 98:02) as a colourless solid (39 mg, 0.15 mmol scale, 55%); R_f (100% EtOAc) 0.5; mp: 248-250 ^{o}C; IR (DCM): 1720, 1509, 1383, 722, 568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.30 (1H, br. s), 8.41 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.90-7.87 (1H, m), 7.86 (2H, dd, J_1= 5.5, J_2= 3.1 Hz), 7.75 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.50-7.45 (2H, m), 7.38-7.35 (1H, m), 7.34-7.30 (1H, m),

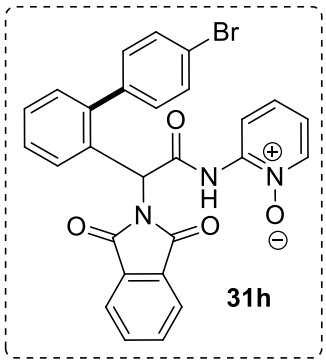


7.03-6.98 (4H, m), 6.37 (1H, s), 2.31 (6H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.4, 166.7, 143.8, 143.7, 139.5, 138.1, 137.0, 134.2, 131.7, 131.1, 130.8, 129.3, 128.3, 127.9, 127.1, 127.0, 123.5, 119.1, 114.5, 56.2, 21.3; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_4$ $[M+H]^+$ 478.1767 found 478.1758.

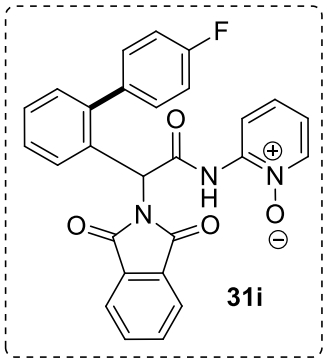
2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-ethoxy-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31g): The compound **31g** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (45 mg, 0.2 mmol scale, 46%); R_f (100% EtOAc) 0.6; mp: 85-87 ^{o}C; IR (DCM): 2929, 1715, 1507, 1243, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.27 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.17 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.92-7.89 (1H, m), 7.85 (2H, dd, J_1= 5.5, J_2= 3.1 Hz), 7.75 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.51-7.44 (2H, m), 7.42-7.38 (3H, m), 7.33-7.28 (1H, m), 7.01-6.96 (3H, m), 6.40 (1H, s), 4.09 (2H, q, J = 7.0 Hz), 1.45 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.7, 166.5, 158.7, 143.7, 143.4, 137.0, 134.3, 131.8, 131.7, 131.4, 130.5, 129.6, 129.1, 128.6, 128.0, 123.7, 119.2, 114.6, 114.5, 63.4, 56.1, 14.9; HRMS (ESI) calcd for $C_{29}H_{24}N_3O_5$ $[M+H]^+$ 494.1716 found 494.1711.



2-(2-(4'-Bromo-[1,1'-biphenyl]-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamido)pyridine 1-oxide1-oxide (31h): The compound **31h** was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (60 mg, 0.5 mmol scale, 23%); R_f (100% EtOAc) 0.6; mp: 120-122 ^{o}C; IR (DCM): 1718, 1509, 1384, 1004, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.27 (1H, br. s), 8.39 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.16 (1H, dd, J_1 = 6.6, J_2 = 1.1 Hz), 7.95-7.91 (1H, m), 7.88 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.59 (2H, dt, J_1= 8.4, J_2= 2.3 Hz), 7.53-7.49 (2H, m), 7.38 (2H, dt, J_1= 8.4, J_2= 2.0 Hz), 7.36-7.30 (2H, m), 7.03-6.99 (1H, m), 6.27 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.5, 166.0,143.5, 142.2, 138.4, 136.9, 134.4, 131.7, 131.6, 131.4, 131.0, 130.9, 129.6, 129.2, 129.2, 128.0, 123.6, 122.2, 119.2, 114.5, 55.8; HRMS (ESI) calcd for $C_{27}H_{18}BrN_3NaO_4$ $[M+Na]^+$ 550.0378 found 550.0383.

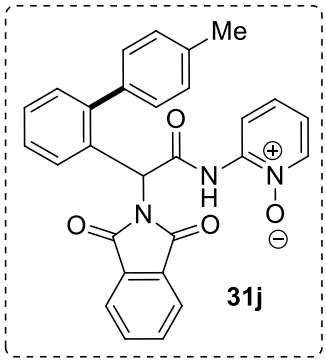


2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-fluoro-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide



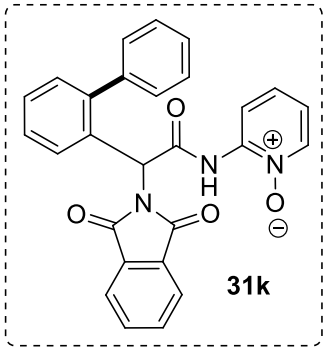
(31i): The compound **31i** was obtained after purification by column chromatography on silica gel (EtOAc) as a light yellow color solid (50 mg, 0.2 mmol scale, 54%); R_f (100% EtOAc) 0.5; mp: 192-194 ^oC; IR (DCM): 2925, 1713, 1508, 1381, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.27 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.4 Hz), 8.17 (1H, d, J = 6.4 Hz), 7.95-7.93 (1H, m), 7.88 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.52-7.45 (4H, m), 7.39-7.31 (2H, m), 7.16 (2H, t, J = 8.6 Hz), 7.03-6.99 (1H, m), 6.29 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.6, 166.1, 162.5 (d, J_{C-F} = 245.7 Hz), 143.6, 142.5, 137.0, 135.5 (d, J_{C-F} = 3.5 Hz), 134.4, 131.7, 131.6, 131.2 (d, J_{C-F} = 2.9 Hz), 131.1, 129.6, 129.3, 129.0, 128.0, 123.7, 119.2, 115.6 (d, J_{C-F} = 21.3 Hz), 114.6, 55.9; HRMS (ESI) calcd for $C_{27}H_{19}FN_3O_4$ $[M+H]^+$ 468.1360 found 468.1348.

2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-methyl-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide



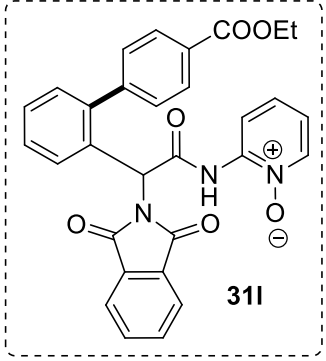
(31j): The compound **31j** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (41 mg, 0.2 mmol scale, 45%); R_f (100% EtOAc) 0.6; mp: 105-107 ^oC; IR (DCM): 2852, 1719, 1385, 1214, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.29 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.17 (1H, dd, J_1 = 6.4, J_2 = 0.6 Hz), 7.94-7.92 (1H, m), 7.87 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.75 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.52-7.46 (2H, m), 7.24-7.37 (3H, m), 7.34-7.23 (3H, m), 7.02-6.98 (1H, m), 6.36 (1H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.6, 166.4, 143.7, 143.6, 137.5, 136.9, 136.7, 134.3, 131.7, 131.5, 131.1, 129.5, 129.2, 129.2, 129.1, 128.6, 127.9, 123.6, 119.1, 114.5, 56.0, 21.2; HRMS (ESI) calcd for $C_{28}H_{22}N_3O_4$ $[M+H]^+$ 464.1610 found 464.1610.

2-(2-([1,1'-Biphenyl]-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamido)pyridine 1-oxide (31k): The compound **31k** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (48 mg, 0.2 mmol scale, 53%); R_f (100% EtOAc) 0.6; mp: 92-94 ^oC; IR (DCM): 2926, 1714, 1381, 1205, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.32 (1H,

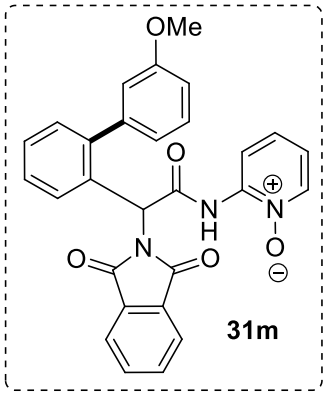


br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 1.0 Hz), 7.96-7.93 (1H, m), 7.86 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.75 (2H, dd, J_1 = 5.5, J_2 = 3.0 Hz), 7.53-7.39 (8H, m), 7.34-7.30 (1H, m), 7.02-6.98 (1H, m), 6.35 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.5, 166.4, 143.6, 143.6, 139.6, 137.0, 134.3, 131.7, 131.4, 131.0, 129.5, 129.3, 129.3, 128.8, 128.5, 128.0, 127.8, 123.6, 119.2, 114.6, 55.9; HRMS (ESI) calcd for $C_{27}H_{20}N_3O_4$ $[M+H]^+$ 450.1454 found 450.1448.

2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(4'-(ethoxycarbonyl)-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31l): The compound **31l** was obtained after purification by column chromatography on silica gel (EtOAc) as a brown color solid (62 mg, 0.2 mmol scale, 60%); R_f (100% EtOAc) 0.6; mp: 84-86 ^{o}C; IR (DCM): 2929, 1712, 1505, 1100, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.31 (1H, br. s), 8.39 (1H, dd, J_1 = 8.5, J_2 = 1.7 Hz), 8.18-8.14 (1H, m), 8.15 (2H, d, J = 8.3 Hz), 7.98-7.94 (1H, m), 7.87 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.76 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.55-7.50 (2H, m), 7.41-7.38 (1H, m), 7.35-7.31 (1H, m), 7.04-7.00 (1H, m), 6.26 (1H, s), 4.42 (2H, q, J = 7.1 Hz), 1.44 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C; 167.5, 166.3, 166.0, 144.2, 143.5, 142.6, 136.9, 134.4, 131.6, 131.3, 130.7, 130.0, 129.8, 129.6, 129.5, 129.4, 129.3, 128.0, 123.7, 119.3, 114.6, 61.0, 55.8, 14.3; HRMS (ESI) calcd for $C_{30}H_{24}N_3O_6$ $[M+H]^+$ 522.1665 found 522.1666.

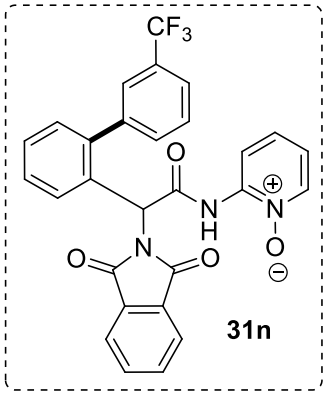


2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(3'-methoxy-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31m): The compound **31m** was obtained after purification by column chromatography on silica gel (EtOAc) as a colorless solid (40 mg,0.2 mmol scale, 42%); R_f (100% EtOAc) 0.6; mp: 98-100 ^{o}C; IR (DCM): 2935, 1714, 1381, 1209, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.29 (1H, br. s), 8.40 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.17 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.91-7.89 (1H, m), 7.87 (2H, dd, J_1= 5.5, J_2= 3.1 Hz), 7.75 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.52-7.46 (2H, m), 7.42-7.40 (1H, m), 7.38-7.29 (2H, m), 7.06-7.05

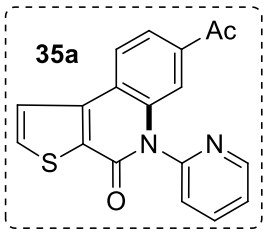


(2H, m), 7.02-6.94 (2H, m), 6.39 (1H, s), 3.82 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.5, 166.4, 159.5, 143.6, 143.4, 140.9, 136.9, 134.3, 131.7, 131.4, 130.9, 129.7, 129.5, 129.1, 128.8, 128.0, 123.6, 121.7, 119.2, 114.5, 114.4, 114.0, 56.0, 55.2; HRMS (ESI) calcd for $C_{28}H_{22}N_3O_5$ $[M+H]^+$ 480.1559 found 480.1566.

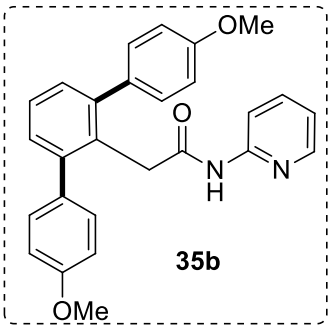
2-(2-(1,3-Dioxoisoindolin-2-yl)-2-(3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetamido)pyridine 1-oxide (31n): The compound **31n** was obtained after purification by column chromatography on silica gel (EtOAc) as a colorless solid (40 mg, 0.2 mmol scale, 39%); R_f (100% EtOAc) 0.6; mp: 96-98 ^{o}C; IR (DCM): 2928, 1717, 1334, 1125, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.33 (1H, br. s), 8.38 (1H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 8.18 (1H, dd, J_1 = 6.5, J_2 = 0.9 Hz), 7.95-7.91 (1H, m), 7.87 (2H, dd, J_1 = 5.5, J_2 = 3.1 Hz), 7.76 (2H, dd, J_1 = 5.4, J_2 = 3.1 Hz), 7.72-7.68 (3H, m), 7.62-7.58 (1H, m), 7.56-7.51 (2H, m), 7.40-7.36 (1H, m), 7.35-7.31 (1H, m), 7.04-7.00 (1H, m), 6.18 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 167.4, 166.0, 143.5, 141.9, 140.4, 136.9, 134.4, 132.6, 131.6, 131.4, 130.9(q, $J_{C\text{-}F}$ = 32.4 Hz), 130.9, 129.7, 129.5, 129.3, 129.1, 128.0, 126.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.7, 123.6 (q, $J_{C\text{-}F}$ = 270.8 Hz), 119.3, 114.6, 55.9; HRMS (ESI) calcd for $C_{28}H_{19}F_3N_3O_4$ $[M+H]^+$ 518.1328 found 518.1337.



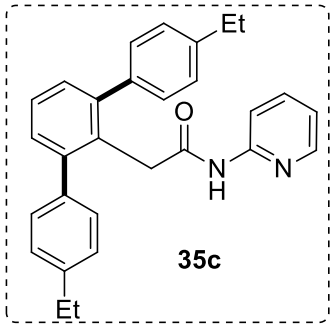
7-Acetyl-5-(pyridin-2-yl)thieno[2,3-*c*]quinolin-4(*5H*)-one (35a): The compound **35a** was obtained after purification by column chromatography on silica gel (EtOAc:Heaxane = 40:60) as a brown color solid (25 mg, 0.15 mmol scale, 52%); R_f (50% EtOAc/heaxane) 0.6; mp: 233-235 ^{o}C; IR (DCM): 2925, 1653, 1436, 1400, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.84 (1H, d, J = 3.7 Hz), 8.12-8.08 (2H, m), 7.92 (1H, d, J = 5.2 Hz), 7.87-7.83 (2H, m), 7.62-7.54 (2H, m), 7.22 (1H, d, J = 1.4 Hz), 2.52 (3H, s); ^{13}C NMR ($CDCl_3$ 101 MHz): δ_C 196.9, 157.9, 150.4, 150.3, 141.9, 139.8, 138.8, 136.6, 134.5, 132.2, 125.1, 124.7, 124.6, 122.8, 122.6, 121.5, 116.4, 26.6; HRMS (ESI) calcd for $C_{18}H_{13}N_2O_2S$ $[M+H]^+$ 321.0698 found 321.0690.



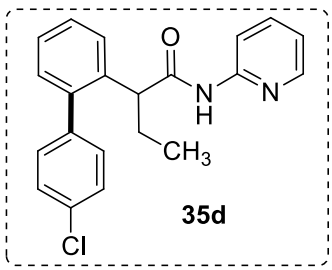
2-(4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(pyridin-2-yl)acetamide (35b): The compound **35b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless solid (33 mg, 0.15 mmol scale, 52%); R_f (40% EtOAc/hexane) 0.6; mp: 120-122 ^oC; IR (DCM): 2937, 1693, 1520, 1258, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.12 (1H, d, J = 4.7 Hz), 8.11 (1H, d, J = 8.4 Hz), 8.00 (1H, br. s), 7.69 (1H, t, J = 7.5 Hz), 7.40 (1H, dd, J_1= 8.2, J_2= 7.0 Hz), 7.31-7.28 (6H, m), 7.05-7.01 (1H, m), 6.89 (4H, dt, J_1= 8.6, J_2= 2.3 Hz), 3.80 (6H, s), 3.71 (2H, m); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.3, 158.8, 150.9, 146.4, 143.3, 138.9, 133.7, 130.3, 130.2, 129.7, 127.3, 119.4, 114.0, 113.7, 55.2, 55.2, 40.1; HRMS (ESI) calcd for $C_{27}H_{25}N_2O_3$ $[M+H]^+$ 425.1865 found 425.1874.



2-(4,4''-Diethyl-[1,1':3',1''-terphenyl]-2'-yl)-*N*-(pyridin-2-yl)acetamide (35c): The compound **35c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow color solid (35 mg, 0.2 mmol scale, 42%); R_f (30% EtOAc/hexane) 0.8; mp: 180-182 ^oC; IR (DCM): 2956, 1695, 1522, 1170, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.15 (1H, dd, J_1 = 5.0, J_2 = 1.0 Hz), 8.08 (1H, d, J = 8.4 Hz), 7.85 (1H, br. s), 7.70-7.66 (1H, m), 7.43(1H, dd, J_1 = 8.3, J_2 = 6.8 Hz), 7.34-7.28 (6H, m), 7.21-7.19 (4H, d, J = 8.1 Hz), 7.03-6.99 (1H, m), 3.72 (2H, s), 2.66 (4H, q, J = 7.6 Hz), 1.24 (6H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 170.2, 151.0, 146.8, 143.7, 143.2, 138.6, 138.6, 129.9, 129.6, 129.0, 127.8, 127.2, 119.4, 113.8, 40.1, 28.5, 15.4; HRMS (ESI) calcd for $C_{29}H_{29}N_2O$ $[M+H]^+$ 421.2280 found 421.2297.

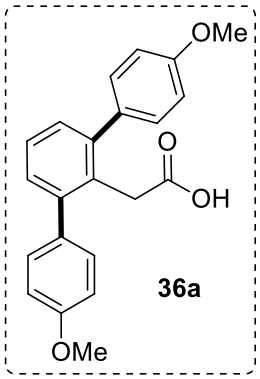


2-(4'-Chloro-[1,1'-biphenyl]-2-yl)-*N*-(pyridin-2-yl)butanamide (35d): The compound **35d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow color solid (30 mg, 0.2 mmol scale, 43%); R_f (80% EtOAc/hexane) 0.8; mp: 116-118 ^oC; IR (DCM): 2950, 1697, 1449, 1297, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.26 (1H, d, J = 8.5 Hz), 8.19-8.17 (1H, m), 8.13 (1H,

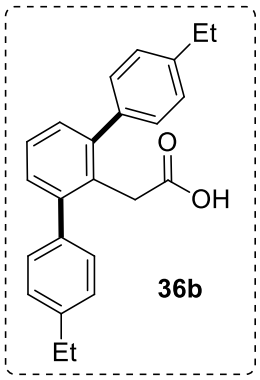


br. s), 7.76-7.72 (1H, m), 7.63 (1H, dd, J_1 = 7.9, J_2 = 1.0 Hz), 7.45-7.41 (3H, m), 7.33 (1H, td, J_1 = 7.4, J_2 = 1.3 Hz), 7.26-7.22 (3H, m), 7.06-7.03 (1H, m), 3.58 (1H, t, J = 7.4 Hz), 2.31-2.21 (1H, m), 1.92-1.81 (1H, m), 0.87 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 172.2, 150.9, 146.3, 141.2, 139.4, 139.2, 136.6, 133.5, 130.6, 130.3, 128.7, 128.6, 127.2, 127.1, 119.6, 114.4, 51.3, 27.0, 12.3; HRMS (ESI) calcd for $C_{21}H_{20}ClN_2O$ $[M+H]^+$ 351.1264 found 351.1266.

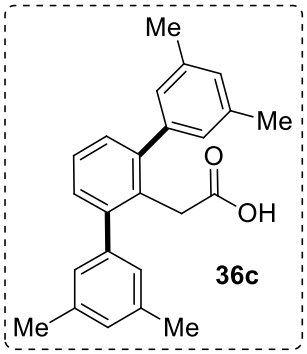
2-(4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)acetic acid (36a): The compound **36a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless solid (79 mg, 0.24 mmol scale, 95%); R_f (100% EtOAc) 0.7; mp: 133-135^{o}C; IR (DCM): 2946, 1707, 1513, 1246, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.38 (1H, t, J = 7.6 Hz), 7.27 (6H, d, J = 7.9 Hz), 6.96 (4H, d, J = 8.5 Hz), 3.86 (6H, s), 3.59 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 178.4, 158.8, 143.1, 133.9, 130.1, 129.9, 129.4, 126.9, 113.6, 55.2, 55.2, 36.8; HRMS (ESI) calcd for $C_{22}H_{20}NaO_4$ $[M+Na]^+$ 371.1259 found 371.1243. (In the proton NMR the COOH proton could not be detected correctly).



2-(4,4''-Diethyl-[1,1':3',1''-terphenyl]-2'-yl)acetic acid (36b): The compound **36b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (67 mg, 0.25 mmol scale, 78%); R_f (100% EtOAc) 0.8; mp: 138-140 ^{o}C; IR (DCM): 2955, 1708, 1429, 1233, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40 (1H, dd, J_1= 8.2, J_2 = 7.0 Hz), 7.30-7.22 (10H, m), 3.59 (2H, s), 2.73 (4H, q, J = 7.6 Hz), 1.31 (6H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 178.8, 143.4, 143.1, 138.8, 129.5, 129.3, 129.0, 127.7, 126.9, 36.8, 28.5, 15.4; HRMS (ESI) calcd for $C_{24}H_{24}NaO_2$ $[M+Na]^+$ 367.1674 found 367.1660. (In the proton NMR the COOH proton could not be detected correctly).

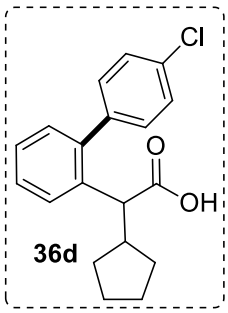


2-(3,3'',5,5''-Tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetic acid (36c): The compound **36c** was obtained after purification by column chromatography on silica gel (EtOAc/hexane = 40:60) as a yellow color solid (60 mg, 0.25 mmol scale, 70%); R_f (50% EtOAc:hexane) 0.7; mp: 160-



162 °C; IR (DCM): 2929, 1711, 1432, 1224, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.37 (1H, dd, J_1 = 8.2, J_2 = 6.9 Hz), 7.28-7.25 (2H, m), 7.00 (2H, s), 6.97-6.95 (4H, m), 3.56 (2H, s), 2.32 (12H, s); ^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 178.2, 143.6, 141.4, 137.6, 129.1, 129.0, 128.7, 126.9, 126.8, 36.6, 21.3; HRMS (ESI) calcd for $C_{24}H_{23}O_2$ $[M-H]^+$ 343.1698 found 343.1708. (In the proton NMR the COOH proton could not be detected correctly).

2-(4'-chloro-[1,1'-biphenyl]-2-yl)-2-cyclopentylacetic acid (36d): The compound **36d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a light brown color solid (31 mg, 0.12 mmol scale, 82%); R_f (50% EtOAc/hexane) 0.7; mp: 180-182 °C; IR (DCM): 2957, 1702, 1280, 1090, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.63 (1H, dd, J_1= 8.0, J_2= 1.0 Hz), 7.44-7.28 (6H, m), 7.23 (1H, dd, J_1= 7.6, J_2= 1.4 Hz), 3.52 (1H, d, J = 11.1 Hz), 2.56-2.5 (1H, m), 1.96-1.88 (1H, m), 1.57-1.49 (2H, m), 1.40-1.25 (4H, m), 1.16-1.06 (1H, m), 0.74-0.65 (1H, m);^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 180.5, 141.4, 139.5, 136.3, 133.2, 131.2, 130.0, 128.3, 128.1, 127.5, 126.9, 52.1, 44.3, 31.4, 30.2, 24.9, 24.5; HRMS (ESI) calcd for $C_{19}H_{18}ClO_2$ $[M-H]^+$ 313.0995 found 313.0999.



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