Zinc - Mediated Nucleophilic Addition of Bromoacetonitrile to Isatin Ketimines

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A dissertation submitted for the partial fulfilment of BS-MS dual degree in Science

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Certificate of Examination

This is to certify that the dissertation titled "*Zinc-Mediated Nucleophilic Addition of Bromoacetonitrile to Isatin Ketimines*" submitted by Ms. Soniya Rani (Reg. No. MS10068) for the partial fulfilment of BS-MS dual degree programme of Indian Institute of Science Education and Research Mohali, has been examined by the thesis committee duly appointed by the institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. S. V. RamaSastry Sripada	Dr. R. Vijaya Anand	Dr. S. Arulananda Babu
Committee Member	Committee Member	(Supervisor)

Dated: April 24, 2015

Declaration

The work presented in this dissertation has been carried out by me under the guidance of **Dr. S. Arulananda Babu** at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Soniya Rani
(Candidate)

Dated : April 24, 2015

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

Dr. S. Arulananda Babu
(Supervisor)

Acknowledgement

It is my privilege to express my deep gratitude to my master thesis supervisor, **Dr. S. Arulananda Babu** for the continuous support in my BS-MS study and research, for his patience, motivation, enthusiasm and immense knowledge. I have learned many things since I joined Dr. S. Arulananda Babu's lab. I attribute the level of my master degree to his encouragement and effort and without him this thesis, too, would not have been possible. One could not wish for a better or friendlier supervisor.

It has been my privilege to work closely with Mr. Nayyar Ahmad Aslam and Mr. Rajkumar Vadla. I am extremely thankful to both of them for their help in learning the experimental techniques. I have enjoyed the opportunity to watch and learn from their knowledge and experience. Their frequent insights and patience with me are always appreciated. I am also thankful for my lab members Mr. Chennakesava Reddy, Mr. Naveen, Mr. Ramarao Parella, Mr. B. Gopalkrishnan, Mr. Narendra Bisht, Mr. Sankar R, Ms. Priyanka and Ms. Arya J. S. for giving me friendly environment in lab and helping me in working in lab.

I am also very thankful to my teachers in IISER Mohali Chemistry Department for always being helpful and supportive. I would like thank Prof. K. S. Viswanathan for teaching me Analytical chemistry which helped me a lot in my research project in analyzing the compounds. After that I would like to thank Dr. R. Vijaya Anand and Dr. Sugumar Venkataramani for teaching me Organic chemistry which helped me lot in the synthesis in my project work. I am also very thankful to Dr. Sripada S. V. Rama Sastry for teaching us separating technique in organic chemistry which also gives me great help in working in synthetic lab.

I am thankful to IISER Mohali for giving us funds for research and for X-Ray, NMR, HRMS facility and DST for providing us INSPIRE fellowship.

Personally I would like to thank my family for supporting me throughout the years financially, practically and with moral support especially my parents, brothers Mr. Rupinder Singh and Narender Kumar and sister in law Punam Rani.

Lastly I would like to thank Tanya Kaushal Srivastava for being my friend and for helping me throughout my BS-MS.

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Notations and Abbreviations

NMR	Nuclear magnetic resonace
IR	Infra-red
HRMS	High resolution mass spectroscopy
TLC	Thin layer chromatography
δ	Chemical shift in ppm
ppm	Parts per million
EtOAc	Ethyl acetate
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
br s	Broad singlet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
M.P	Melting point

Contents

Abstract

Formation of various oxindole derivatives via nucleophilic addition of bromoacetonitrile to different kinds of isatin ketimines is reported. Zinc-mediated nucleophilic addition of bromoacetonitrile to simple isatin ketimines and chiral isatin ketimines gave various oxindole derivatives with good yield and stereoselectivity.

Chapter 1

INTRODUCTION

Oxindole compounds are one of the special class of alkaloids, which are a group of biologically active natural products. Oxindole framework having spirocyclic quaternary stereocenter at C3 position found in many of the natural and pharmaceutical products.[1] Many of the oxindole derivatives have been reported for their biological properties such as cyclin-dependent kinases inhibition, anti-angiogenic properties,[2] antimicrobial,[3,4] anti-inflammatory,[5] anticonvulsant activity,[6,7] anticancer activity,[8] antiviral activity,[9,10] tyrosine kinase inhibitor,[11] etc. Additionally, isatin derivatives having oxindole fragment also shows fibrinolytic, muscle relaxant, anti-allergic, anti-thrombotic and immunosuppressant activity.[12]

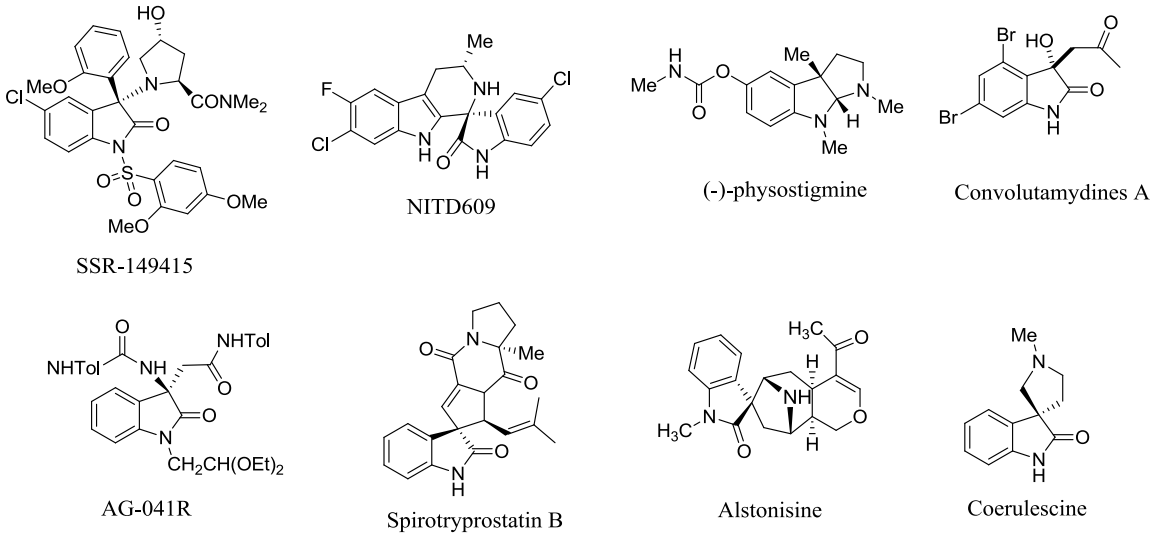


Figure 1. Representative examples of biologically important oxindole scaffolds.

Some of the synthetically derived oxindole derivatives showed above have some interesting biological activities. For example SSR-149415 is used for the treatment of anxiety and depression. NITD609 acts as an antimalarial drug. (-)-Physostigmine is used as a covalent inhibitor of acetyl cholinesterase. Cholinesterase is an enzyme which is responsible for the breakdown of acetylcholine. AG-041R has chondrogenic activity.[13] Spirotryprostatin B acts as an inhibitor of tubulin polymerization.[14]

Due to immense biological importance and use in pharmaceutical industries, synthetic chemists have been trying to develop new synthetic methods for the formation of

oxindole derivatives. Many research groups have already synthesized and tested a wide range of molecules, possessing 3-aminooxindole core unit, for their selective and potential bioactive properties and a significant number of such molecules are under clinical trials and will be ready for commercialization in near future.[15]

There have been methods reported for developing the new synthetic routes for the formation of novel oxindole derivatives, e.g. Knoevenagel condensation reaction,[16-18] Michael addition reaction,[19] *N*-alkylation,[20] nucleophilic addition reaction, acylation of oxindole,[21] etc. There are many reactive sites available on the oxindole scaffold, such as, carbonyl group, nitrogen atom, C-3 site and aromatic ring, on which different types of reaction can be performed (Figure 2).[22] All of these reactions can be carried out to synthesize the desirable oxindole derivatives. Because of the presence of stereogenic centers in the natural products having oxindole substructure,[23] various stereo selective processes such as asymmetric addition to isatin imines,[24] multicomponent reaction[25] and hydroxyamination reaction[26] have also been developed for preparing quaternary 3-amino-oxindole derivatives.

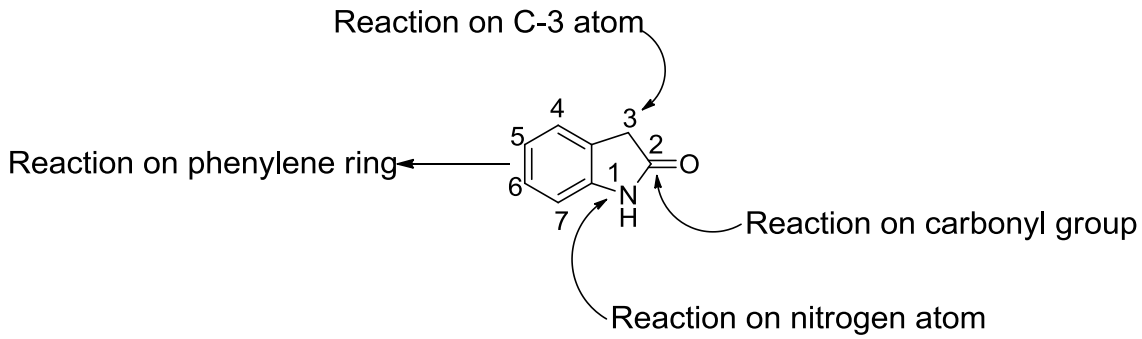


Figure 2. Sites of oxindole reactivity.

There have been numerous reports involving organometallic addition to isatin systems and one of the important organometallic reactions is Barbier-type nucleophilic addition to isatin systems. In recent years, the Barbier-type reaction is carried out in presence of a metal powder (e.g., In, Zn etc) in water or protogenic solvents. The Barbier-type reaction has the advantages of direct use of metal powder and alkyl halides and the prior preparation of nucleophilic reagents is not necessary. In literature several work are reported based on the use of Zn metal for the formation of chiral compounds having with stereoselectivity and yield.[27]

In continuation of our group's interest in metal-mediated nucleophilic addition to C=N systems[28] (imines, hydrazones, etc), we have developed a competitive synthetic methodology for the nucleophilic addition of bromoacetonitrile to C=N bond of isatin ketimines in the presence of zinc dust.

To the best of our knowledge the nucleophilic addition of bromoacetonitrile to C=N of isatin ketimines in presence of zinc dust has not been reported. By using this methodology we have prepared a various types of oxindole derivatives that can be functionalized to complex used to perform further functional group transformation to synthesize oxindole derivatives having the core structure similary to naturally occurring oxindoles.

Chapter 2

Experimental

General. Melting points are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers respectively with TMS as an internal or external standard. IR spectra were recorded as KBr pellets or thin films. Column chromatography was carried out on silica gel. Reactions were carried out in dry solvent under nitrogen atmosphere wherever required. Solutions were dried using anhydrous sodium sulphate. Reagents were added to the reaction flask with the help of syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products were reported (yields were not optimized). Ratios of diastereomers were determined from the ^{1}H and ^{13}C NMR spectra of crude reaction mixtures or after isolation.

Procedure A: *N*-Alkylation of isatins: According to reported procedure, NaH (20 mmol) was taken in a dry round bottom flask and washed with hexane. After that THF (50 mL) was added to the flask and the reaction mixture was cooled to 0 ^{o}C. Then isatin (10 mmol) was added to it in fractions at 0 ^{o}C and the reaction mixture was stirred for 30 min. under nitrogen atmosphere. After 30 min. alkyl halide (15 mmol) was added to the flask drop wise and the reaction was stirred at room temperature for 12-24 h. After confirming the disappearance of starting isatin by TLC, reaction mixture was quenched with water and transferred to a separating funnel and extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous sodium sulphate. Then the solvent was evaporated under vacuum. Purification of resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane) as eluent gave the product **3a**–**3d** (see Table 1 for individual entries). Products were confirmed with help of ^{1}H and ^{13}C NMR spectroscopy.

Procedure B: Synthesis of 3e and 3f: According to reported procedure, to the mixture of isatin (5 mmol) and trityl chloride (6 mmol) in DMF (6 mL), NaH (15 mmol) was added and the reaction mixture was stirred for 12-24 h under nitrogen atmosphere. After confirming the disappearance of starting isatin by TLC, reaction mixture was quenched with water and transferred to a separating funnel and extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous sodium sulphate. Then the

solvent was evaporated under vacuum. Purification of resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane) as eluent gave the product **3e** and **3f** as yellow solids (see Table 1 for individual entries). Products were confirmed with help of ^{1}H and ^{13}C NMR spectroscopy.

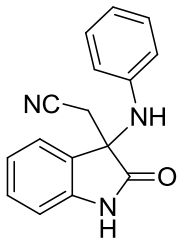
Procedure C: Preparation of isatin imines 5a-5h: To the solution of isatin (4 mmol) in ethanol (6 mL) the corresponding aniline (4 mmol) was added in one portion. Then, the reaction mixture was dipped in a pre-heated oil bath at 85 ^{o}C and stirred for 45 min. Once the solution becomes clear, the RB flask was removed from the heating and allowed to stand at r.t. The precipitated isatin ketimine was filtered out after cooling and washed with 10% ethanol/hexane mixture. Then, the solid product was air dried and used without further purification (see Tables 2 and 3 for individual entries). Products were confirmed with help of ^{1}H and ^{13}C NMR spectroscopy.

Procedure D: Preparation of sulfinyl ketimines of isatin 17a–17d: To the mixture of isatin (2 mmol), (*S* or *R*) 2-methylpropane-2-sulfinamide (**16**; 2.4 mmol) in dry DCM (6 mL) $Ti(O^{i}Pr)_4$ (4 mmol) was added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 12-24 h. After confirming the disappearance of starting isatin by TLC, saturated solution of $NaHCO_3$ was added to the reaction mixture and stirred for 15 min. After that, reaction mixture was filtered through a pad of celite and washed with DCM until the filtrate becomes colorless. Then the filtrate was transferred to a separating funnel and extracted with DCM (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane) as eluent gave the products **17a**–**17d** (see Table 9 for individual entries). Products were confirmed with help of ^{1}H and ^{13}C NMR spectroscopy.

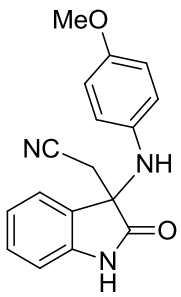
Procedure E: Zn-mediated nucleophilic addition of bromoacetonitrile (6a) or 2-bromopropanenitrile (6b) or bromoacetophenone (6c) to isatin ketimines 5a–5h and 17a–17d: To a vigorously stirring solution of the corresponding isatin ketimine **5/17** (0.25 mmol, 1 equiv.) and alkyl bromide (**6**; 0.75 mmol, 3 equiv.) in THF (2 mL) was added zinc dust (0.5 mmol, 2 equiv.) and the mixture was stirred vigorously at 30 ^{o}C till disappearance of starting material (as shown by TLC). Then, the reaction mixture was quenched with water and transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the

solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexanes) gave the corresponding products **7**, **8**, **9b** and **18** (see Tables 4–8, 10 and 11 for individual entries).

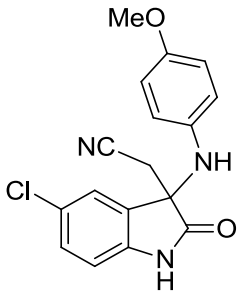
Procedure F: Deprotection of PMP for the synthesis of oxindole derivative 11 and 13: To the solution of corresponding oxindole derivative **7h**/**7i** (0.15 mmol) in CH_3CN (2 mL), a solution of CAN (0.015 mmol) and $(NH_4)_2S_2O_8$ (0.3 mmol) in water (0.5 mL) was added at 30 ^oC. The reaction mixture was stirred for 4 h at 30 ^oC. After completion of the reaction, the reaction mixture was transferred in to a separating funnel and extracted with DCM (3x5 mL). Water layer was neutralized using saturated solution of Na_2CO_3 and organic layer was extracted using DCM (5x2 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to get the product **11**/**13** (see Scheme 1 and 2).



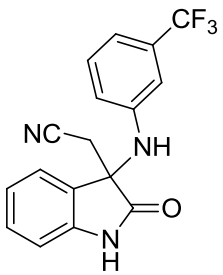
2-(2-Oxo-3-(phenylamino)indolin-3-yl)acetonitrile (7a): Following the general procedure E described above, **7a** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (55 mg, 84%); R_f (50% EtOAc/Hexane) 0.35; mp 171-176 °C; IR (thin film): υ_{max} 3353, 3060, 2256, 1717, 1624, 1499 and 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.49 (s, 1 H), 7.34 (d, J = 7.4 Hz, 1 H), 7.22 (td, J = 7.4, 1.2 Hz, 1 H), 6.96 (td, J = 7.4, 0.9 Hz, 1 H), 6.92-6.85 (m, 3 H), 6.57-6.54 (m, 1 H), 6.24 (d, J = 7.7 Hz, 2 H), 5.68 (d, J = 4.9 Hz, 1 H), 3.06 (d, J = 16.4 Hz, 1 H), 2.74 (d, J = 16.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 182.1, 150.0, 145.8, 134.8, 133.7, 132.7, 128.9, 127.6, 123.7, 120.6, 119.8, 115.9, 66.2, 33.3; HRMS (ESI): calcd. for $C_{16}H_{13}N_3O$ $[M + H]^+$ 264.1137; found 264.1132.



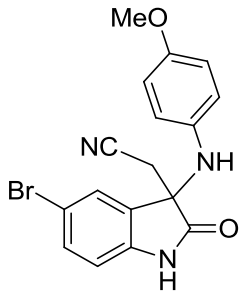
2-(3-((4-Methoxyphenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7b): Following the general procedure E described above, **7b** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (64 mg, 87%); R_f (50% EtOAc/Hexane) 0.35; mp 170-172 °C; IR (thin film): υ_{max} 3272, 2834, 2250, 1708, 1682, 1509, 1474 and 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.13 (br s, 1 H), 7.38 (dd, J = 7.3, 2.0 Hz, 1 H), 7.15 (td, J = 7.7, 2.2 Hz, 1 H), 6.93 (td, J = 7.7, 2.2 Hz, 1 H), 6.78 (dd, J = 7.7, 2.2 Hz, 1 H), 6.43-6.40 (m, 2 H), 6.31-6.29 (m, 2 H), 4.66 (br s, 1 H), 3.50 (s, 3 H), 2.94 (d, J = 16.5 Hz, 1 H), 2.65 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$+DMS0-d_6): δ 177.1, 153.8, 140.9, 137.6, 129.7, 127.4, 124.2, 122.4, 119.4, 115.5, 113.8, 110.7, 62.2, 55.0, 27.7; HRMS (ESI): calcd. for $C_{17}H_{15}N_3O_2$ [M + H]$^+$ 294.1243; found 294.1238.



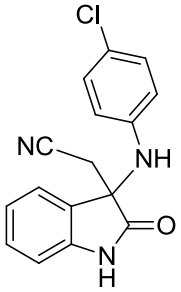
2-(5-Chloro-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7c): Following the general procedure E described above, **7c** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (76 mg, 92%); R_f (50% EtOAc/Hexane) 0.40; mp 181-183 °C; IR (thin film): υ_{max} 3331, 2952, 2259, 1712, 1620, 1511, 1333 and 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.17 (br s, 1 H), 7.30-7.21 (m, 2 H), 6.84-6.80 (m, 1 H), 6.57-6.54 (m, 2 H), 6.44-6.41 (m, 2 H), 4.54 (br s, 1 H), 3.62 (s, 3 H), 3.02 (d, J = 16.5 Hz, 1 H), 2.76 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 155.3, 138.5, 136.4, 130.6, 129.3, 129.1, 125.3, 121.3, 114.9, 114.4, 112.1, 63.3, 55.4, 27.9; HRMS (ESI): calcd. for $C_{17}H_{14}ClN_3O_2$ [M + H]$^+$ 328.0853; found 328.0847.



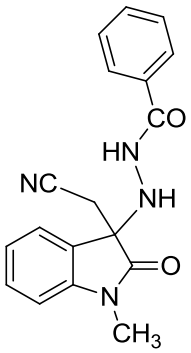
2-(2-Oxo-3-((3-(trifluoromethyl)phenyl)amino)indolin-3-yl)acetonitrile (7d): Following the general procedure E described above, **7d** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (72 mg, 95%); R_f (50% EtOAc/Hexane) 0.35; mp 187-189 °C; IR (thin film): υ_{max} 3315, 2958, 2260, 1713, 1616, 1473, 1447 and 996 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1 H), 7.37 (td, J = 7.6, 1.2 Hz, 1H), 7.33 (br s, 1 H), 7.19 (t, J = 8.2 Hz, 1 H), 7.07 (dd, J = 7.6, 1.2 Hz, 1 H), 7.03 (d, J = 8.2 Hz, 1 H), 6.87 (d, J = 7.6 Hz, 1 H), 6.46 (d, J = 8.9 Hz, 2 H), 3.24 (d, J = 16.6 Hz, 1 H), 3.14 (d, J = 16.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7, 146.7, 141.6, 130.7, 130.4, 129.7 (q, $J_{C\text{-}F}$ = 31.0 Hz), 127.8, 124.6 (q, $J_{C\text{-}F}$ = 270.6 Hz), 124.4, 123.0, 117.5, 116.9, 114.2, 114.2, 111.2, 109.9, 109.8, 61.1, 27.9; HRMS (ESI): calcd. for $C_{17}H_{12}F_3N_3O$ $[M + H]^+$ 332.1011; found 332.1015.



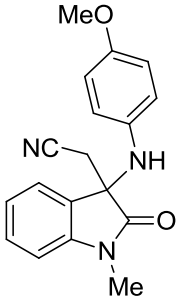
2-(5-Bromo-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7e): Following the general procedure E described above, **7e** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (77 mg, 82%); R_f (50% EtOAc/Hexane) 0.30; mp 198-200 °C; IR (thin film): υ_{max} 3332, 2955, 2259, 1712, 1511 and 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.32 (br s, 1H), 7.53 (br s, 1 H), 7.32 (dd, J = 8.3, 2.0 Hz, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 6.50 (dd, J = 6.8, 2.0 Hz, 2 H), 6.35 (dd, J = 6.8, 2.0 Hz, 2 H), 4.69 (br s, 1 H), 3.58 (s, 3 H), 2.99 (d, J = 16.5 Hz, 1 H), 2.73 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 176.9, 154.4, 140.4, 137.5, 133.0, 129.9, 127.5, 119.8, 115.4, 115.4, 114.3, 112.6, 62.7, 55.3, 27.9.



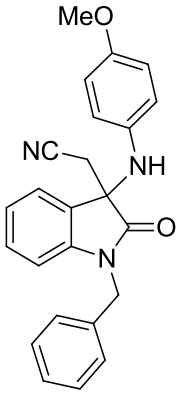
2-(3-((4-Chlorophenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7f): Following the general procedure E described above, **7f** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (60 mg, 80%); R_f (50% EtOAc/Hexane) 0.35; mp 192-194 °C; IR (thin film): υ_{max} 3303, 2962, 2257, 1711, 1623, 1495, 1472 and 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.92 (s, 1 H), 7.27-7.21 (m, 2 H), 6.96 (td, J = 7.5, 0.9 Hz, 1 H), 6.92-6.90 (m, 3 H), 6.80 (br s, 1 H), 6.13-6.09 (m, 2 H), 3.10 (d, J = 16.6 Hz, 1 H), 2.99 (d, J = 16.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.6, 149.9, 146.3, 135.3, 133.8, 132.9, 129.0, 127.7, 126.5, 121.7, 120.3, 116.0, 66.0, 32.8; HRMS (ESI): calcd. for $C_{16}H_{12}ClN_3O$ $[M + H]^+$ 298.0747; found 298.0742.



N'-(3-(Cyanomethyl)-1-methyl-2-oxoindolin-3-yl)benzohydrazide (7g): Following the general procedure E described above, **7g** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (20 mg, 24%); R_f (50% EtOAc/Hexane) 0.40; mp 183-191 °C; IR (thin film): υ_{max} 3309, 2937, 2259, 1706, 1610, 1460 and 1305 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (br s, 1 H), 7.69 (d, J = 7.1 Hz, 2 H), 7.53 (t, J = 7.6 Hz,1 H), 7.48-7.42 (m, 3 H), 7.20 (t, J = 7.6 Hz, 1 H), 6.94 (d, J = 7.8 Hz, 1 H), 3.26 (s, 3 H), 3.17 (d, J = 16.6 Hz, 1 H), 2.90 (d, J = 16.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 168.0, 143.8, 132.3, 131.8, 131.0, 128.8, 127.1, 125.4, 124.6, 123.6, 115.8, 109.1, 63.7, 26.6, 23.7; HRMS (ESI): calcd. for $C_{18}H_{16}N_4O_2$ $[M + H]^+$ 321.1352; found 321.1354.

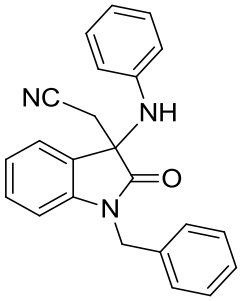


2-(3-((4-Methoxyphenyl)amino)-1-methyl-2-oxoindolin-3-yl)acetonitrile (7h): Following the general procedure E described above, **7h** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (52 mg, 64%); R_f (50% EtOAc/Hexane) 0.35; mp 142-144 °C; IR (thin film): υ_{max} 3336, 2927, 2260, 1721, 1613, 1511 and 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.4 Hz, 1 H), 7.41 (td, J = 7.8, 1.2 Hz, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 6.58 (d, J = 8.9 Hz, 2 H), 6.49 (d, J = 8.9 Hz, 2 H), 3.68 (s, 3 H), 3.20 (s, 3 H), 3.08 (d, J = 16.6 Hz, 1 H), 2.75 (d, J = 16.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 155.3, 143.1, 136.7, 130.5, 126.9, 124.8, 123.6, 122.0, 115.5, 114.1, 109.1, 62.8, 55.3, 27.8, 26.5; HRMS (ESI): calcd. for $C_{18}H_{17}N_3O_2$ $[M + H]^+$ 308.1399; found 308.1391.

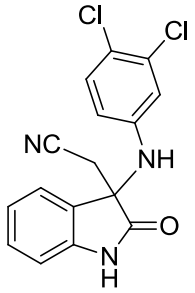


2-(1-Benzyl-3-((4-methoxyphenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7i): Following the general procedure E described above, **7i** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (73 mg, 85%); R_f (50% EtOAc/Hexane) 0.40; mp 146-155 °C; IR (thin film): υ_{max} 3341, 2929, 2250, 1721, 1614, 1510 and 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J = 7.4, 1.0 Hz, 1 H), 7.30-7.26 (m, 1 H), 7.24-7.16 (m, 4 H), 6.86 (d, J = 7.8 Hz, 2 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.59-6.53 (m, 2H), 6.55 (d, J = 6.5 Hz, 2H), 5.14 (d, J = 15.8 Hz, 1 H), 4.59 (d, J = 15.8 Hz, 1 H), 4.16 (br s, 1 H), 3.71 (s, 3 H), 3.15 (d, J = 16.5 Hz, 1 H), 2.83 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 155.8, 142.4, 136.6, 134.6,

130.5, 128.7, 127.7, 127.0, 126.9, 125.0, 123.6, 123.4, 115.5, 114.1, 110.2, 63.5, 55.3, 44.0, 27.7; HRMS (ESI): calcd. for $C_{24}H_{21}N_3O_2$ $[M + Na]^+$ 406.1531; found 406.1538.

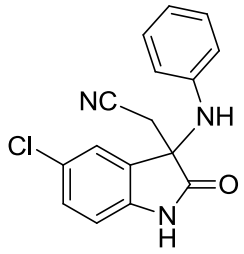


2-(1-Benzyl-2-oxo-3-(phenylamino)indolin-3-yl)acetonitrile (7j): Following the general procedure E described above, **7j** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (80 mg, 94%); R_f (50% EtOAc/Hexane) 0.45; mp 140-145 °C; IR (thin film): υ_{max} 3374, 3034, 2252, 1709, 1602, 1498 and 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.6 Hz, 1 H), 7.33 (td, J = 7.8, 1.3 Hz, 2H), 7.30-7.28 (m, 2 H), 7.18 (dd, J = 7.6, 0.8 Hz, 1 H), 7.15-7.13 (m, 2 H), 7.02-6.98 (m, 2H), 6.86-6.83 (m, 2 H), 6.41-6.38 (m, 2 H), 5.17 (d, J = 15.6 Hz, 1 H), 4.74 (d, J = 15.6 Hz, 1 H), 3.18 (d, J = 16.5 Hz, 1 H), 2.82 (d, J = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 143.9, 141.9, 134.8, 130.5, 129.1, 128.9, 127.9, 127.5, 127.0, 124.6, 123.9, 121.4, 118.0, 115.2, 110.4, 62.0, 44.3, 28.6; HRMS (ESI): calcd. for $C_{23}H_{19}N_3O$ $[M + H]^+$ 354.1606; found 354.1607.

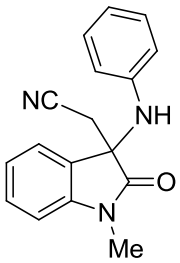


2-(3-((3,4-Dichlorophenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7k): Following the general procedure E described above, **7k** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (52 mg, 85%); R_f (50% EtOAc/Hexane) 0.30; mp 205-207 °C; IR (thin film): υ_{max} 3321, 2952, 2266, 1728, 1619, 1474 and 856 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1 H), 7.37 (td, J = 7.7, 1.0 Hz, 1 H), 7.34 (d, J = 7.4 Hz, 1 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.07 (td, J = 7.7, 1.0 Hz, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 6.31 (d, J = 2.6 Hz, 1 H), 6.23 (dd, J = 8.8, 2.7

Hz, 1 H), 3.22 (d, *J* = 16.6 Hz, 1 H), 3.13 (d, *J* = 16.6 Hz, 1 H); ^{13}C NMR (100 MHz, DMS0-d_6): δ 176.4, 146.3, 141.6, 131.5, 131.1, 130.8, 127.6, 124.4, 123.1, 119.4, 116.9, 114.9, 114.6, 111.3, 61.1, 27.8; HRMS (ESI): calcd. for $C_{16}H_{11}Cl_2N_3O$ $[M + H]^+$ 332.0357; found 332.0353.

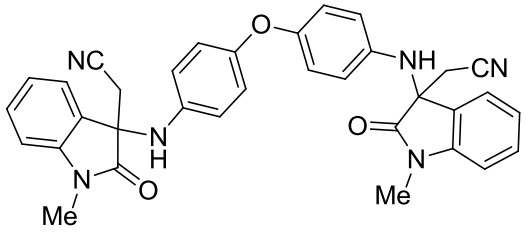


2-(5-Chloro-2-oxo-3-(phenylamino)indolin-3-yl)acetonitrile (7l): Following the general procedure E described above, **7l** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (65 mg, 92%); R_f (50% EtOAc/Hexane) 0.40; mp 200-210 °C; IR (thin film): υ_{max} 3337, 2957, 2259, 1714, 1603, 1499, 1478 and 815 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1 H), 7.35 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.28 (d, *J* = 2.1 Hz, 1 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.93 (t, *J* = 8.0 Hz, 2 H), 6.58 (t, *J* = 7.3 Hz, 1 H), 6.19 (d, *J* = 7.9 Hz, 2 H), 3.20 (d, *J* = 16.6 Hz, 1 H), 3.05 (d, *J* = 16.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 145.3, 140.2, 130.5, 130.4, 129.5, 127.5, 124.1, 119.1, 116.6, 114.1, 112.8, 61.6, 27.7; HRMS (ESI): calcd. for $C_{16}H_{12}ClN_3O$ $[M + H]^+$ 298.0747; found 298.0751.

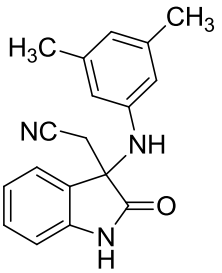


2-(1-Methyl-2-oxo-3-(phenylamino)indolin-3-yl)acetonitrile (7m): Following the general procedure E described above, **7m** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (51 mg, 79%); R_f (50% EtOAc/Hexane) 0.40; mp 166-168 °C; IR (thin film): υ_{max} 3339, 2919, 2248, 1713, 1615, 1497 and 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.4, 0.7 Hz, 1 H), 7.46 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.19 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.04-6.98 (m, 3 H), 6.78 (t, *J* = 7.4 Hz, 1 H), 6.35 (d, *J* = 7.6 Hz, 2 H), 3.30 (s, 3 H), 3.11 (d, *J* = 16.5 Hz, 1 H), 2.75 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 144.0, 142.6,

130.6, 129.1, 127.0, 124.4, 123.9, 120.8, 116.6, 115.2, 109.3, 61.5, 28.6, 26.7; HRMS (ESI): calcd. for $C_{17}H_{15}N_3O$ $[M + H]^+$ 278.1293; found 278.1291.

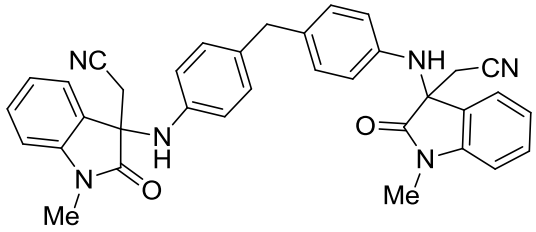


2,2'-(3,3'-((Oxybis(4,1-phenylene))bis(azanediyl))bis(1-methyl-2-oxoindoline-3,3-diyl))diacetonitrile (7n): Following the general procedure E described above, **7n** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 40 : 60) as colorless solid (89 mg, 63%); R_f (50% EtOAc/Hexane) 0.30; mp 121-128 °C; IR (thin film): υ_{max} 3349, 2925, 2257, 1715, 1613, 1498 and 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.6 Hz, 2 H), 7.42 (td, J = 7.8, 0.9 Hz, 2 H), 7.18 (t, J = 7.8 Hz, 2 H), 6.93 (d, J = 7.8 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 4 H), 6.31 (d, J = 8.8 Hz, 4 H), 4.38 (br s, 2 H), 3.24 (s, 3 H), 3.24 (s, 3 H), 3.08 (d, J = 16.6 Hz, 2 H), 2.73 (d, J = 16.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 152.0, 142.8, 139.2, 130.6, 126.9, 124.5, 123.8, 119.4, 119.2, 117.3, 109.3, 62.1, 28.3, 26.6; HRMS (ESI): calcd. for $C_{34}H_{28}N_6O_3$ $[M + Na]^+$ 591.2121; found 591.2123.

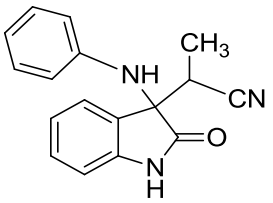


2-(3-((3,5-Dimethylphenyl)amino)-2-oxoindolin-3-yl)acetonitrile (7o): Following the general procedure E described above, **7o** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (39 mg, 53%); R_f (50% EtOAc/Hexane) 0.45; mp 217-222 °C; IR (thin film): υ_{max} 3380, 2919, 2254, 1724, 1600 and 1471 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.95 (s, 1 H), 7.35-7.30 (m, 2 H), 7.04 (td, J = 7.6, 0.8 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.50 (s, 1 H), 6.20 (s, 1 H), 5.84 (s, 2 H), 3.18 (d, J = 16.5 Hz, 1 H), 3.05 (d, J = 16.5 Hz, 1 H), 1.97 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.4. 146.2, 141.7, 137.9, 130.3, 128.9, 124.3, 122.7,

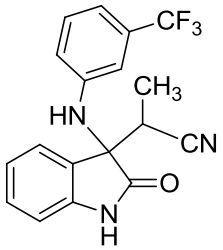
120.1, 117.2, 112.3, 110.8, 61.2, 28.0, 21.6; HRMS (ESI): calcd. for $C_{18}H_{17}N_3O$ $[M + H]^+$ 292.1450; found 292.1450.



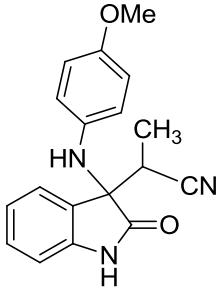
2,2'-(3,3'-((Methylenebis(4,1-phenylene))bis(azanediyl))bis(1-methyl-2-oxoindoline-3,3-diyl))diacetonitrile (7p): Following the general procedure E described above, **7p** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 40 : 60) as colorless solid (92 mg, 65%); R_f (50% EtOAc/Hexane) 0.30; mp 169-171 °C; IR (thin film): υ_{max} 3349, 2925, 2257, 1715, 1613, 1498 and 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 2 H), 7.43 (t, J = 7.5 Hz, 2 H), 7.17 (t, J = 7.5 Hz, 2 H), 6.96 (d, J = 7.8 Hz, 2 H), 6.71 (d, J = 8.3 Hz, 4 H), 6.21 (d, J = 8.3 Hz, 4 H), 4.45 (br s, 2 H), 3.58 (s, 2 H), 3.26 (s, 6 H), 3.07 (d, J = 16.5 Hz, 2 H), 2.72 (d, J = 16.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 142.6, 142.0,133.6, 130.5, 129.6, 127.1, 124.4, 123.9, 116.7, 115.2, 109.2, 61.6, 40.0, 28.6, 26.7; HRMS (ESI): calcd. for $C_{35}H_{30}N_6O_2$ $[M + Na]^+$ 589.2328; found 589.2326.



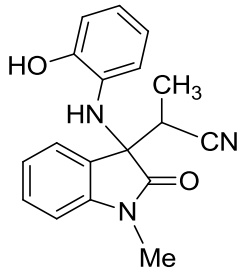
2-(2-Oxo-3-(phenylamino)indolin-3-yl)propanenitrile (8a): Following the general procedure E described above, **8a** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 25 : 75) as colorless solid (50 mg, 72%); R_f (50% EtOAc/Hexane) 0.40; mp 195-200 °C; IR (thin film): υ_{max} 3278, 2925, 2338, 1737, 1617 and 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.07 (s, 1 H), 7.30-7.24 (m, 2 H), 7.04-6.91 (m, 4 H), 6.70-6.64 (m, 1 H), 6.37-6.33 (m, 2 H), 4.83-4.80 (m, 1 H), 3.26-3.22 (m, 1 H), 1.40-1.35 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$+DMS0-d_6): δ 177.0, 144.6, 141.6, 130.2, 128.9, 126.6, 124.7, 122.8, 120.0, 118.9, 116.3, 111.1, 65.0, 34.7, 12.1; HRMS (ESI): calcd. For $C_{17}H_{15}N_3O$ $[M + Na]^+$ 300.1113; found 300.1111.



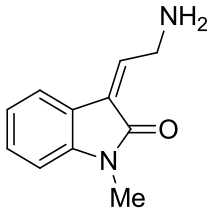
2-(2-Oxo-3-((3-(trifluoromethyl)phenyl)amino)indolin-3-yl)propanenitrile (8b): Following the general procedure E described above, **8b** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless sticky solid (52 mg, 60%); R_f (50% EtOAc/Hexane) 0.35; IR (thin film): υ_{max} 3358, 2925, 2247, 1728, 1619 and 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 10.50 (s, 1 H), 7.32-7.23 (m, 2 H), 7.06-6.97 (m, 3 H), 6.84 (d, J = 7.6 Hz, 1 H), 6.66 (br s, 1 H), 6.40 (d, J = 8.5 Hz, 1 H), 5.80 (br s, 1 H), 3.35-3.30 (m, 1 H), 1.40 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 176.2, 145.1, 141.4, 130.5 (q, $J_{C\text{-}F}$ = 35.5 Hz), 130.0, 129.1, 125.6, 123.71(q, $J_{C\text{-}F}$ = 273.5 Hz), 124.2, 122.5, 118.6, 117.5, 115.0, 111.8, 110.8; 64.3, 34.2, 11.8; HRMS (ESI): calcd. For $C_{18}H_{14}F_3N_3O$ $[M + Na]^+$ 330.1218; found 330.1227.



2-(3-((4-Methoxyphenyl)amino)-2-oxoindolin-3-yl)propanenitrile (8c): Following the general procedure E described above, **8c** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (66 mg, 77%); R_f (50% EtOAc/Hexane) 0.35; mp 182-187 °C; IR (thin film): υ_{max} 3303, 2927, 2250, 1723, 1620, 1511 and 1037 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1 H), 7.45 (br s, 1 H), 7.36 (td, J = 7.7, 1.2 Hz, 1 H), 7.10 (td, J = 7.7, 1.2 Hz, 1 H), 6.94 (t, J = 7.8 Hz, 1 H), 6.56 (d, J = 9.0 Hz, 2 H), 6.28 (d, J = 9.0 Hz, 2 H), 6.19 (br s, 1 H), 3.56 (s, 3 H), 3.44 (q, J = 7.2 Hz, 1 H), 1.31 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.3, 177.1, 153.0, 152.8, 142.6, 142.4, 139.8, 139.8, 130.61, 130.3, 127.6, 127.0, 125.1, 124.7, 122.9, 122.6, 120.9, 120.1, 117.4, 117.0, 114.6, 114.6, 110.9, 110.8, 65.6, 65.6, 55.5, 34.1, 34.0, 12.5, 12.4; HRMS (ESI): calcd. For $C_{18}H_{17}N_3O_2$ $[M + Na]^+$ 368.0987; found 368.0989.

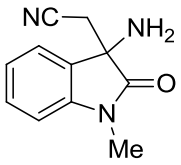


2-(3-((2-Hydroxyphenyl)amino)-1-methyl-2-oxoindolin-3-yl)propanenitrile (8d): Following the general procedure E described above, **8d** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (45 mg, 58%); R_f (50% EtOAc/Hexane) 0.35; mp 171-177 °C; IR (thin film): υ_{max} 3361, 2926, 2250, 1722, 1612, 1514 and 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 1 H), 7.45-7.41 (m, 1 H), 7.16-7.14 (m, 1 H), 6.91 (d, J = 7.8 Hz, 1 H), 6.83-6.81 (m, 2 H), 6.50 (s, 2 H), 6.31 (dd, J = 8.0, 1.2 Hz, 1 H), 4.11 (br s, 1 H), 3.41 (q, J = 7.1 Hz, 1 H), 3.25 (s, 3 H), 0.98 (d, J = 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 176.5, 151.4, 143.7, 143.4, 130.6, 130.6, 129.3, 126.1, 125.5, 124.9, 124.7, 124.4, 123.9, 123.9, 123.5, 123.2, 120.8, 120.3, 119.8, 118.8, 115.3, 115.1, 109.1, 108.7, 67.1, 66.1, 34.8, 34.6, 26.6, 12.6, 12.4 ; HRMS (ESI): calcd. For $C_{18}H_{17}N_3O_2$ $[M + Na]^+$ 330.1218; found 330.1221.

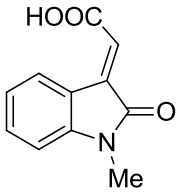


3-(2-Aminoethylidene)-1-methylindolin-2-one (10): To a solution of **7m** (0.2 mmol) in EtOH (6 mL), $NaBH_4$ (4.2 mmol) was added. Reaction mixture was stirred at room temperature till the disappearance of starting material **7m** as indicated by TLC. Then, the reaction mixture was quenched with water and transferred in to a separating funnel and extracted with EtOAc (3x15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (MeOH : EtOAc = 10 : 90) as colorless solid (7 mg, 19%); R_f (80% EtOAc/Hexane) 0.08; mp 180-182 °C; IR (thin film): υ_{max} 3343, 2928, 1661 and 1372 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.57 (dt, J = 7.9, 0.9 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.21-7.17 (m, 1 H), 7.12 (s, 1 H), 7.09-7.05 (m, 1 H), 3.79 (s, 3 H), 3.66 (s, 2 H), 3.34-3.32 (m, 2 H); ^{13}C NMR (100 MHz,

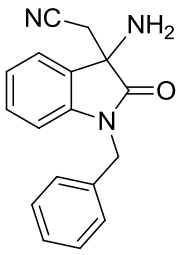
CD_3OD): δ 176.5, 137.2, 127.9, 127.6, 121.3, 118.6, 118.2, 108.9, 107.5, 31.9, 31.3; HRMS (ESI): calcd. for $C_{11}H_{12}N_2O$ $[M + H]^+$ 189.1028; found 189.1024.



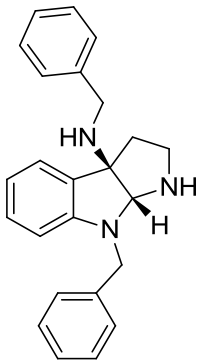
2-(3-Amino-1-methyl-2-oxoindolin-3-yl)acetonitrile (11): Following the general procedure G described above, **11** was obtained as colorless solid (20.2 mg, 67%); R_f (80% EtOAc/Hexane) 0.10; mp 95-97 °C; IR (thin film): υ_{max} 3362, 2935, 2253, 1715, 1614 and 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.7 Hz, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 6.91 (d, J = 7.7 Hz, 1 H), 3.22 (s, 3 H), 2.88 (d, J = 16.5 Hz, 1 H), 2.59 (d, J = 16.5 Hz, 1 H), 2.04 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 142.9, 130.4, 128.9, 124.0, 123.6, 116.2, 109.0, 57.8, 27.9, 26.5.



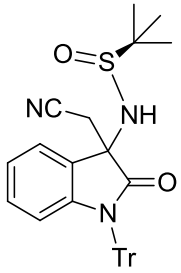
(E)-2-(1-methyl-2-oxoindolin-3-ylidene)acetic acid (12): To the the compound **11**, 3 mL of concentrated.HCl (6 M) was added and allowed to stir for overnight under open condition at 90 ^oC. After the reaction time, HCl was removed under vacuum that gave the product **12** as light brown solid (15 mg, 46%); mp 225-235 °C; IR (thin film): υ_{max} 3332, 2923, 1612 and 1669 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 8.40 (d, J = 8.4 Hz, 1 H), 7.75-7.71 (m, 1 H), 7.67 (d, J = 8.4 Hz, 1 H), 7.39 (t, J = 8.1 Hz, 1 H), 7.11 (s, 1 H), 3.80 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD): δ 167.2, 162.2, 140.1, 131.3, 127.0, 126.4, 122.7, 121.6, 117.6, 114.9, 29.0; HRMS (ESI): calcd. for $C_{11}H_9NO_3$ $[M + H]^+$ 204.0661; found 204.0668.



2-(3-Amino-1-benzyl-2-oxoindolin-3-yl)acetonitrile (13): Following the general procedure G described above, **13** was obtained as light brown sticky solid (15.3 mg, 37%); R_f (80% EtOAc/Hexane) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.4 Hz, 1 H), 7.37-7.29 (m, 6 H), 7.14 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 7.9 Hz, 1 H), 5.00 (d, J = 15.7 Hz, 1 H), 4.87 (d, J = 15.7 Hz, 1 H), 2.99 (d, J = 16.5 Hz, 1 H), 2.71 (d, J = 16.5 Hz, 1 H), 2.19 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 142.0, 135.1, 130.4, 129.0, 128.7, 128.0, 127.3, 124.2, 123.7, 116.0, 110.0, 51.9, 44.1, 27.9; HRMS (ESI): calcd. for $C_{17}H_{15}N_3O$ $[M + H]^+$ 278.1293; found 278.1295.

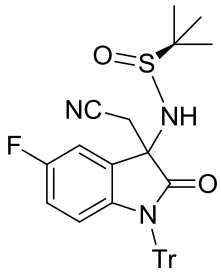


Synthesis of Pyrrolo[2,3-b]indoline (15): To a solution of oxindole derivative (**14**; 0.13 mmol) in THF (2 mL), $LiAlH_4$ (0.65 mmol) was added at 0 ^{o}C. Then the reaction mixture was stirred for 15 min. at 0 ^{o}C and then refluxed for 30 min. After completion of the reaction, the reaction mixture was filtered over celite pad and the celite pad was washed with EtOAc. Then the filtrate was transferred in to a separating funnel and extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexanes) gave the product **15** (22 mg, 47%). Characterization data (^{1}H and ^{13}C NMR and HRMS) of compound **14** and **15** matches with that of reported literature data.[29]

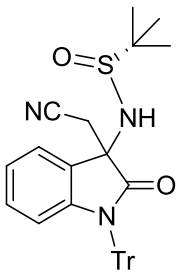


(*R*)-N-(3-(cyanomethyl)-2-oxo-1-tritylindolin-3-yl)-2-methylpropane-2-sulfinamide (18a): Following the general procedure E described above, **18a** was obtained after

purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (73 mg, 69%); R_f (50% EtOAc/Hexane) 0.40; mp 135-137 °C; IR (thin film): υ_{max} 3216, 2927, 2253, 1732, 1607, 1467 and 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.4 Hz, 7 H), 7.30 (t, J = 7.04 Hz, 6 H), 7.23 (t, J = 7.2 Hz, 3 H), 7.10-7.07 (m, 2 H), 6.51-6.48 (m, 1 H), 4.50 (br s, 1 H), 2.97 (d, J = 16.8 Hz, 1 H), 2.44 (d, J = 16.8 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 143.6, 141.4, 129.7, 129.4, 127.8, 127.1, 125.3, 124.4, 123.1, 117.1, 115.6, 75.1, 60.3, 56.9, 27.9, 22.8; HRMS (ESI): calcd. for $C_{33}H_{31}N_3O_2S$ $[M + Na]^+$ 556.2035; found 556.2049.



(*R*)-N-(3-(cyanomethyl)-5-fluoro-2-oxo-1-tritylindolin-3-yl)-2-methylpropane-2-sulfinamide (18b): Following the general procedure E described above, **18b** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (112 mg, 81%); R_f (50% EtOAc/Hexane) 0.40; mp 132-134 °C; IR (thin film): υ_{max} 3211, 2927, 2253, 1731, 1613, 1482 and 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.0 Hz, 6 H), 7.32-7.28 (m, 7 H), 7.24 (t, J = 7.2 Hz, 3 H), 6.79 (td, J = 9.0, 2.8 Hz, 1 H), 6.43 (dd, J = 9.0, 4.2 Hz, 1 H), 4.42 (br s, 1 H), 2.94 (d, J = 16.8 Hz, 1 H), 2.45 (d, J = 16.8 Hz, 1 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 158.8 (d, $J_{C\text{-}F}$ = 242.9 Hz), 141.2, 139.5 (d, $J_{C\text{-}F}$ = 2.5 Hz), 129.4, 127.9, 127.2, 118.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 116.5 (d, $J_{C\text{-}F}$ = 22.7 Hz), 115.2, 112.9 (d, $J_{C\text{-}F}$ = 24.5 Hz), 75.2, 60.4, 57.0, 27.8, 22.7; HRMS (ESI): calcd. for $C_{33}H_{30}FN_3O_2S$ $[M + Na]^+$ 574.194; found 574.1933.



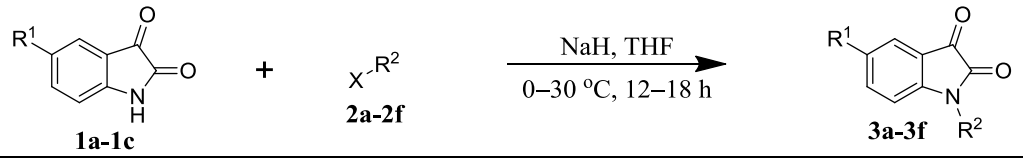
(*S*)-N-(3-(cyanomethyl)-2-oxo-1-tritylindolin-3-yl)-2-methylpropane-2-sulfinamide (18c): Following the general procedure E described above, **18c** was obtained after purification by silica gel column chromatography (EtOAc : Hexane = 30 : 70) as colorless solid (97 mg, 73%); R_f (50% EtOAc/Hexane) 0.40; mp 112-118 °C; IR (thin film): υ_{max} 3208, 2927, 2253, 1730, 1607, 1466 and 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 7 H), 7.29 (t, J = 7.08 Hz, 6 H), 7.23 (t, J = 7.2 Hz, 3 H), 7.10-7.08 (m, 2 H), 6.50-6.48 (m, 1 H), 4.35 (s, 1 H), 2.95 (d, J = 16.8 Hz, 1 H), 2.43 (d, J = 16.8 Hz, 1 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 143.6, 141.4, 129.7, 129.4, 127.8, 127.1, 125.3, 124.3, 123.0, 117.1, 115.6, 75.0, 60.2, 56.8, 27.9, 22.8; HRMS (ESI): calcd. for $C_{33}H_{31}N_3O_2S$ $[M + Na]^+$ 556.2035; found 556.2029.

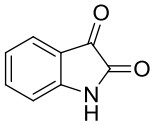
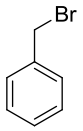
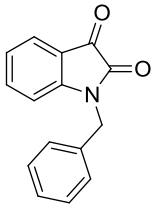
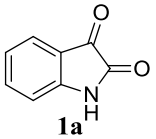
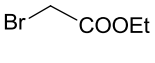
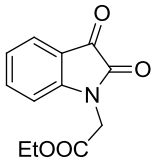
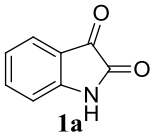
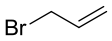
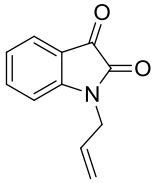
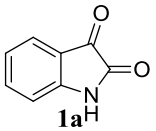
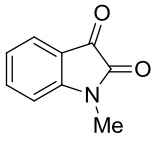
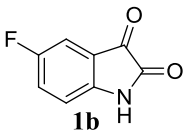
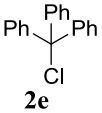
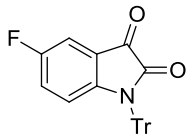
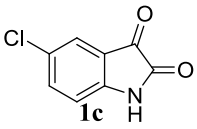
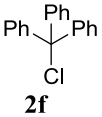
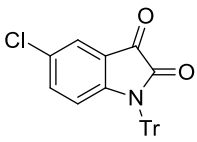
Chapter 2

Results and Discussion

At the outset, we synthesized the key starting materials, such as isatin ketimines for performing the Barbier-type nucleophilic addition reactions to prepare new oxindoles having the core unit similar to naturally occurring molecules.

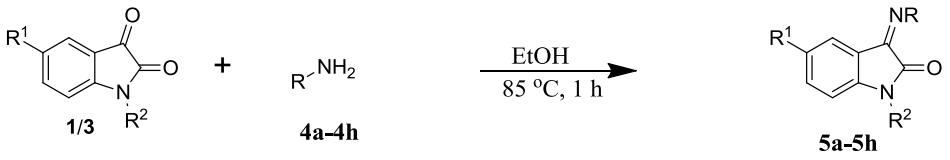
Table 1. *N*-alkylation of various isatins.

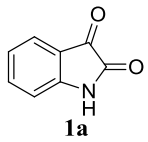
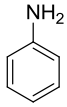
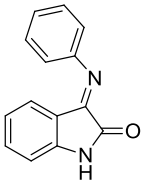
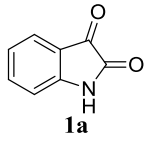
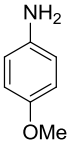
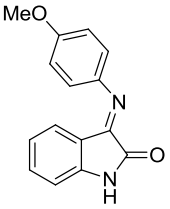
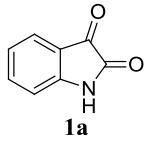
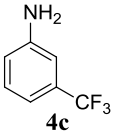
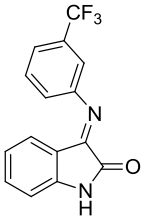
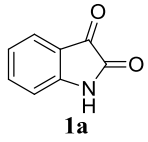
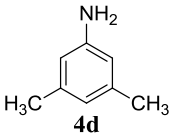
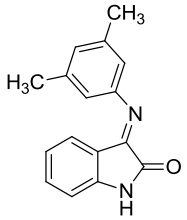
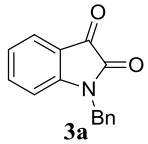
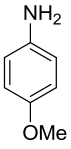
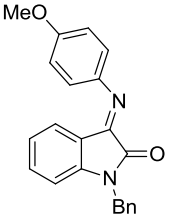
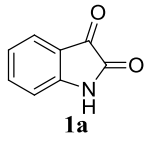
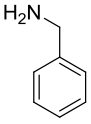
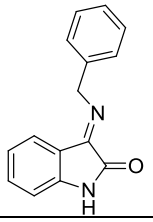


Entry	Oxindole	Alkyl halide	Product	**3;** Yield[a] (%)
1	 **1a**	 **2a**		**3a**; 81
2[b]	 **1a**	 **2b**		**3b**; 67
3	 **1a**	 **2c**		**3c**; 72
4	 **1a**	CH_3I **2d**		**3d**; 70
5[c,d]	 **1b**	 **2e**		**3e**; 60
6[c,d]	 **1c**	 **2f**		**3f**; 50

Reaction was performed using isatin (10 mmol), alkyl halide (15 mmol), NaH (20 mmol) and THF (40-50 mL). [a] Isolated yields are given. [b] NaI (15 mmol) has been used. [c] Trityl chloride (12 mmol) has been used. [d] DMF (8 mL) has been used

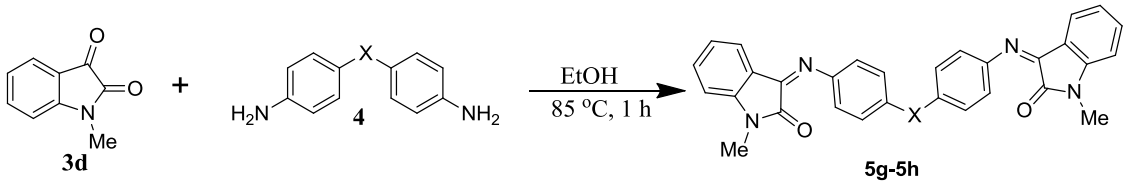
Table 2. Formation of isatin ketimines

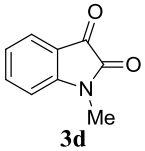
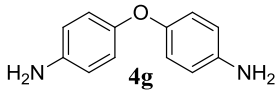
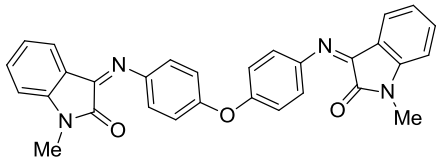
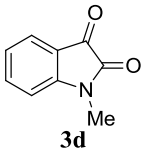
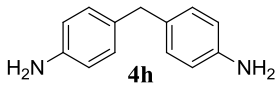
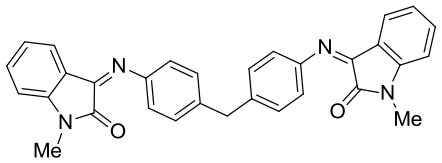


Entry	Oxindole	Amine	Product	**5;** Yield (%)
1	 **1a**	 **4a**		**5a**; 80
2	 **1a**	 **4b**		**5b**; 90
3	 **1a**	 **4c**		**5c**; 83
4	 **1a**	 **4d**		**5d**; 83
5	 **3a**	 **4e**		**5e**; 54
6	 **1a**	 **4f**		**5f;** 16

First of all, various *N*-alkylated isatins (**3a**–**3f**) have been synthesized from the corresponding isatins (**1a**–**1c**) and alkyl halide (**2a-2f**) using standard literature methods in average to good yield (Table 1).

Table 3. Formation of isatin ketimines



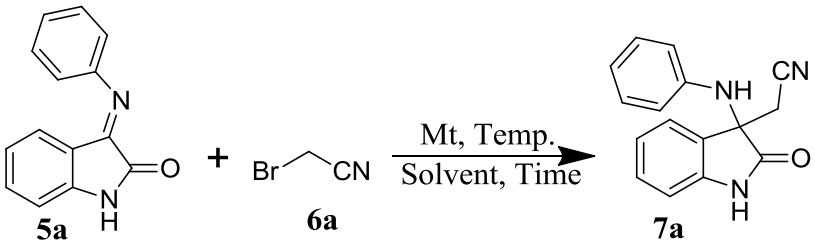
7				**5g**; 54
8				**5h**; 55

Reaction was performed using isatin (4 mmol), amine (2 mmol) and EtOH (6 mL).

Next, the synthesis of isatin ketimines (**5a**-**5f**) was achieved using from different types of isatins and amines (**4a**-**4f**) by using literature methods in average to good yield (Table 2 and 3). Some bis−isatin ketimines (**5g** and **5h**) were also synthesized by using the method adopted for synthesizing **5a**-**5f** average yield (Table 3).

After synthesizing the various isatin ketimines, we examined the reactivity of isatin ketimine with bromoacetonitrile in the presence of different types of metals and solvents to optimize the reaction condition. The results are shown in Table 4. Initially, the reaction of isatin ketimine (**5a**) with bromoacetonitrile (**6a**) was carried out in the presence of 0.37 mmol of indium metal powder and DMF solvent at 30 ^{o}C under nitrogen atmosphere for 1 h, which gave the compound **7a** in 65% yield (Table 4, entry 1). When the reaction was performed in the presence of 0.37 mmol zinc dust for 1 h, the desired product **7a** was formed in 61% yield (Table 4, entry 2). With increasing the equivalents of zinc dust to 0.5 mmol, the product **7a** was obtained in 85% yield in 1 h (Table 4, entry 3). No desired product was formed in the presence of Bi metal powder (Table 4, entry 4). The use of Sn powder gave the desired product **7a** in 56% yield after 5 h (Table 4, entry 5). After screening the reaction conditions, zinc dust was found to be the best and effective metal. Increasing or decreasing the temperature of the reaction of **5a** with **6a** gave the product **7a** in 85% and 81% yields, respectively (Table 4, entries 7 and 8).

Table 4. Nucleophilic addition of bromoacetonitrile (**6a**) to isatin ketimine (**5a**).



5a **6a** **7a**

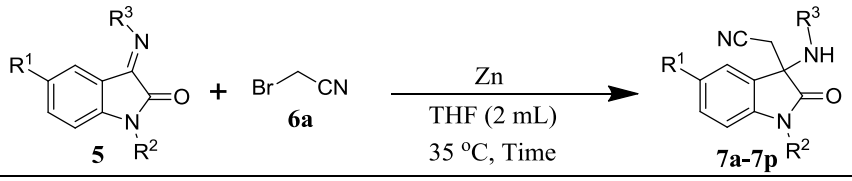
Entry	Mt (mmol)	Solvent (mL)	Temp. (^{o}C)	Time (h)	**7a**; Yield[a] (%)
1	In (0.37)	DMF (0.5)	30	1	65
2[b]	Zn (0.37)	DMF (0.5)	30	1	61
3[b]	Zn (0.5)	DMF (0.5)	30	1	85
4	Bi (0.37)	DMF (0.5)	30	4	0
5	Sn (0.37)	DMF (0.5)	30	5	56
6	Zn (0.5)	DMF (0.5)	30	1	62
7[b]	Zn (0.5)	DMF (0.5)	80	1	85
8[b]	Zn (0.5)	DMF (0.5)	0	1	81
9[b]	**Zn (0.5)**	**THF (2)**	**30**	**1**	**84**
10[b]	Zn (0.5)	Dioxane (2)	30	13	69
11[b]	Zn (0.5)	DMSO (1)	30	12	50
12[b]	Zn (0.5)	CH_3CN (1)	30	12	71
13[b]	Zn (0.5)	DCE (2)	30	12	0
14[b]	Zn (0.5)	EtOH (0.5)	33	6	0
15[b]	Zn (0.5)	THF (2)	85	4	53
16[b]	Zn (0.5)	THF (2)	0	4.5	44
17	Zn (0.5)	THF (2)	38	1.5	74
18	Mg (0.5)	THF (2)	30	9	34

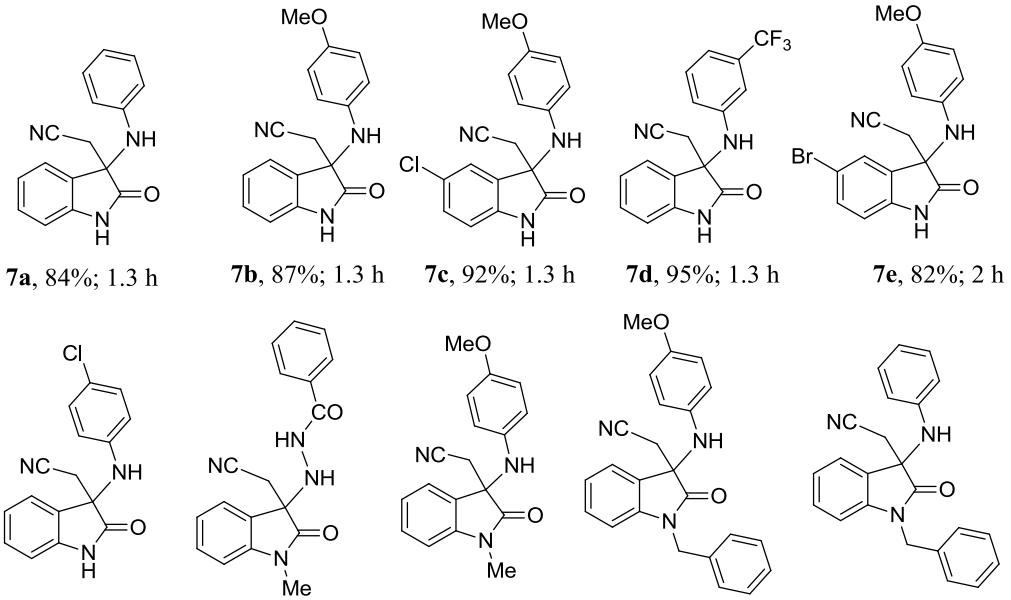
[a]Reaction was performed using isatin imine (0.25 mmol), bromoacetinitrile (0.5 mmol). Isolated yields are given. [b] Bromoacetonitrile (0.75 mmol) has been used. Mt - metal

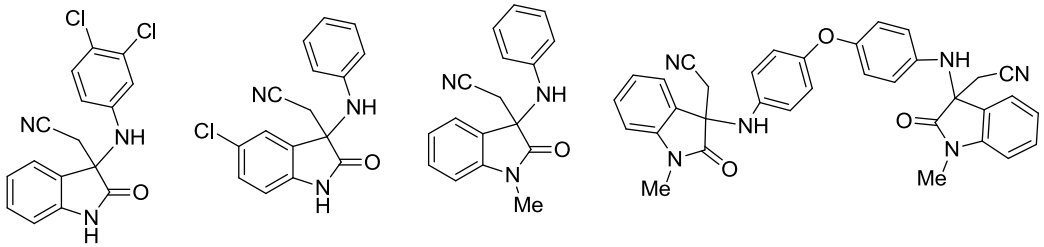
The reaction in THF gave the product **7a** in 85% yield (Table 4, entry 9) and when the reaction of isatin ketimine (**5a**) and bromoacetonitrile (**6a**) was performed in the presence of Zn in DMSO, 1,4-Dioxane and CH_3CN for 6-12 h gave the product **7a** in moderate

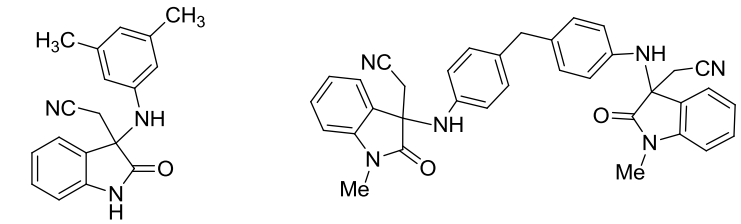
yields (50-71%; Table 4, entries 10-12). The reaction in DCE and EtOH, did not give the desired product **7a** (Table 4, entry 13 and 14).

Table 5. Nucleophilic addition of bromoacetonitrile (**6a**) to various isatin ketimines (**5**).









Reaction was performed using isatin imine (0.25 mmol), bromoacetonitrile (0.75 mmol) and Zn (0.5 mmol).
[a] Isolated yields are given.

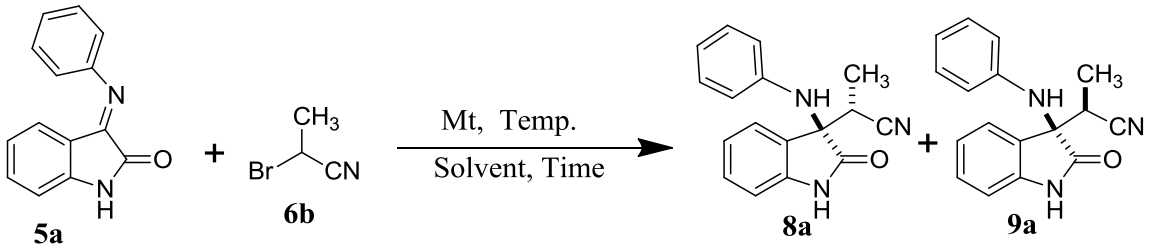
Further, the reaction of isatin ketimine (**5a)** and bromoacetonitrile (**6a)** at high and low temperature gave the product **7a** in moderate yields (53% and 44%, Table 4, entries 15

and 16). When the reaction of isatin ketimine (**5a**) and bromoacetonitrile (**6a**) was carried out in the presence of magnesium metal powder instead of zinc dust, the product **7a** was obtained in low yield (34%; Table 4, entry 18). Since in presence of zinc metal and THF solvent, the desired product **7a** was obtained in good yield, this reaction condition was chosen as a standard condition.

The scope of the Barbier-type addition of bromoacetonitrile (**6a**) was tested using various isatin ketimines and the synthesis of a number of examples of nitrile containing 3-aminooxindoles was accomplished (Table 5). The zinc-mediated addition of bromoacetonitrile (**6a)** to various isatin ketimines derived from various substituted anilines and isatins in THF gave the corresponding quaternary 3-aminooxindoles (**7a-7p**) in average to good yield (Table 5). Benzoyl hydrazone of isatin resulted in the formation of oxindole derivative **7g** in only 24% yield (Table 5). Compounds shown in Table 4 were confirmed by ^{1}H and ^{13}C-NMR and HRMS analysis.

We also examined the reactivity of 2-bromopropanenitrile with isatin ketimine **5a** in the presence of different metals and solvents and the results are shown in Table 5. Initially, we performed the reaction with 0.5 mmol of zinc dust, 0.75 mmol of 2-bromopropanenitrile (**6b**) and DMF solvent for 1 h at room temperature under nitrogen atmosphere, which gave the desired product **8a** in 67% yield with poor diastereoselectivity (53:47; Table 6, entry 1). When reaction was carried out in THF for 14 h, the desired product **8a** was obtained in 72% yield and with slightly improved diastereoselectivity (65:35; Table 6, entry 2). Since in THF solvent the diastereoselectivity got improved, we next performed the reaction in THF using indium metal powder instead of zinc dust for 16 h, which gave the product **8a** in 80% yield without diastereoselectivity (51:49; Table 6, entry 3). Further, we also performed the reaction in different solvents to improve the diastereoselectivity. When reaction was performed in toluene and DCE, the desired product was not obtained (Table 6, entries 5 and 6). The reaction in CH_3CN gave the product **8a** in 90% yield with moderate diastereoselectivity (60:40; Table 6, entry 4). The product **8a** was formed in 38% yield with very less diastereoselectivity when we performed the reaction in DMSO (49:51; Table 6, entry 7).

Table 6. Nucleophilic addition of 2-bromopropanenitrile (**6b**) to isatin ketimine (**5a**).



5a **6b** **8a** **9a**

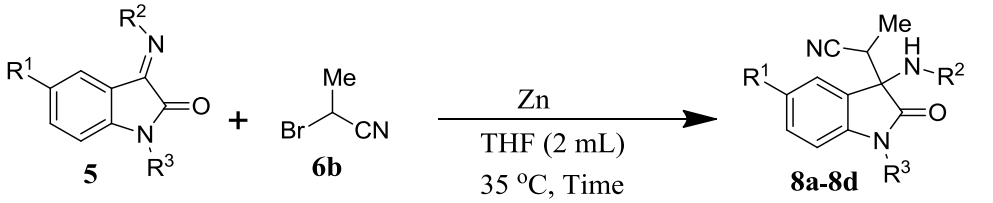
Entry	Mt (mmol)	Solvent (mL)	Temp. (°C)	Time (h)	**8a/9a**; Yield[a] (%, dr)
1	Zn (0.5)	DMF (0.5)	32	1	67 (53:47)
2	**Zn (0.5)**	**THF (2)**	**32**	**14**	**72 (65:35)**
3	In (0.5)	THF (2)	32	16	80 (51:49)
4	Zn (O.5)	CH_3CN (1)	30	1.5	90 (60:40)
5	Zn (0.5)	Toluene (2)	32	18	0
6	Zn (0.5)	DCE (2)	28	24	0
7	Zn (0.5)	DMSO (0.7)	28	24	38 (49:51)
8	Zn (0.5)	DMF (0.5)	26	17	45 (51:49)
9	In (0.5)	EtOH (2.0)	28	52	24 (58:42)
10	In (0.5)	CH_3CN (1.5)	28	17	53 (50:50)
11[b]	In (0.5)	CH_3CN (1.5)	28	25	17 (52:48)
12[b]	Zn (0.5)	CH_3CN (1.5)	28	0.5	80 (59:41)
13	Zn (0.5)	THF (3)	80	1	91 (53:47)
14	Sn (0.5)	THF (3)	30	4	92 (52:48)
15	Bi (0.5)	THF (2)	30	23	63 (64:36)

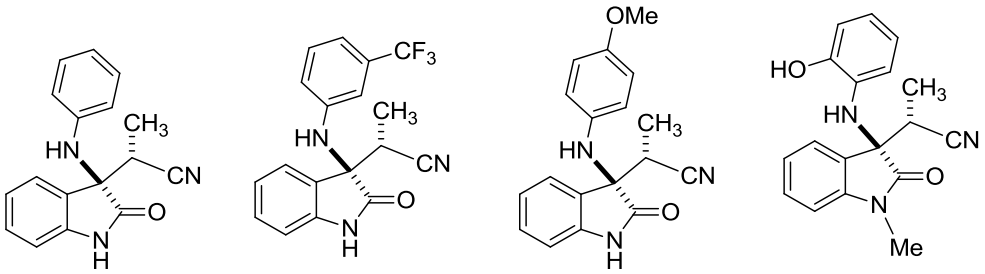
Reaction was performed using isatin imine (0.25 mmol), and 2-bromopropanenitrile (0.75 mmol). [a] Isolated yield are given. [b] N-Me has been used as starting material.
Mt-metal

When reaction was carried with *N*-methyl isatin ketimine in presence of indium or zinc metal, the product was obtained in 17% and 80% yields respectively with no improvement in diastereoselectivity (Table 6, entries 11 and 12). We found that increasing the reaction temperature to 80 °C gave the product in 91% yield with less diastereoselectivity (53:47; Table 6, entry 13). The reaction of **5a** with **6b** in the presence

of Sn metal in THF gave the product **8a** in 92% yield without diastereoselectivity (Table 6, entry 14). When reaction was carried out uisng Bi metal, the product **8a** was obtained in 63% yield with moderate diastereoselectivity (64:36; Table 6, entry 15). From the screening of reaction conditions, we found that zinc dust and THF solvent were found to be only suitable reaction conditions for performing the reaction of **5a** with **6b**.

Table 7. Diastereoselective addition of 2-bromopropanenitrile (**6b)** to various isatin ketimines (**5**).





8a, 72%; 14 h (dr; 65:35) | **8b**, 60%; 20 h (dr; 59:41) | **8c**, 77%; 2.3 h (dr; 63:37) | **8d**, 58%; 1.5 h (dr; 59:41)

Reaction was performed using isatin imine (0.25 mmol), 2-bromopropanenitrile (0.75 mmol), zinc (0.5 mmol). Isolated yields are given. Diastereoselectivity was calculated from ^{1}H NMR of crude reaction mixture.

Next, we performed the reaction of **6b** with different types of isatin ketimines using the available best reaction condition and results are shown in table 7. The reaction of **6b** with an isatin imine **5c** having CF_3 substituted aniline part gave the desired product **8b** in 65% yield with 59:41 diastereoselectivity. Similarly, the reaction of **6b** with an isatin imine **5b** containing the OMe group at the *para* position gave the desired product **8c** in 77% yield with 63:47 diastereoselectivity (Table 7). The reaction of **6b** isatin ketimine having an free OH group afforded the desired product **8d** in 58% yield with 59:41 diastereoselectivity (Table 7). There was no big difference in diastereoselectivity when different positions of phenyl ring are substituted with different types of functionality. Further work to be done to improve the diastereoselectivity in these reactions.

Crystal structure of compound **8a** Crystal structure of compound **8b**

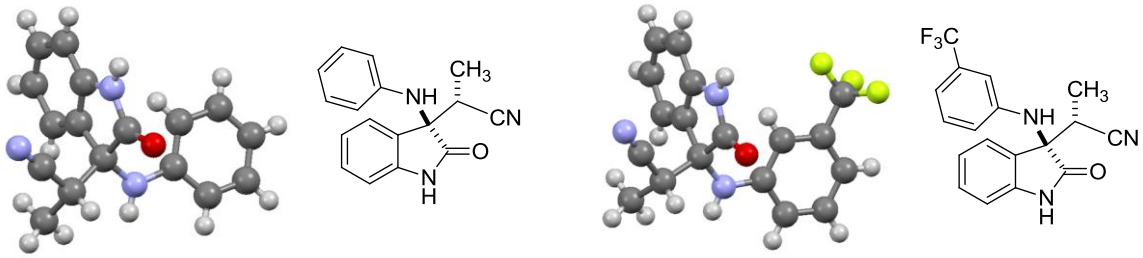
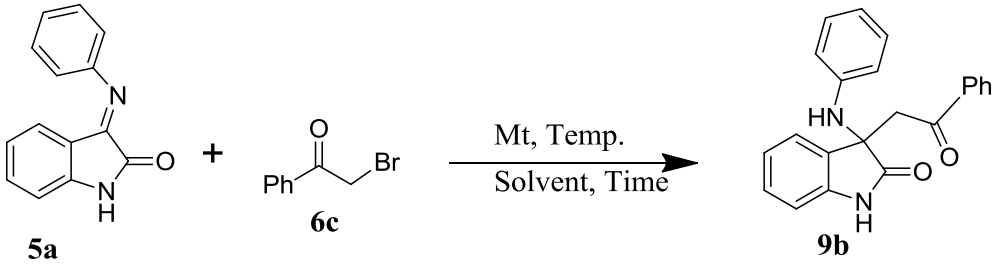


Figure 3. X-ray crystal structure of **8a** and **8b**.

The corresponding major diastereoisomers were separated in pure form in cases of the compounds **8a** and **8b**. The stereochemistry of the major diastereoisomer was confirmed from the single-crystal X-ray structure analysis (Figure 3).

Table 8. Nucleophilic addition of bromoacetophenone (**6c**) to isatin ketimine (**5**).



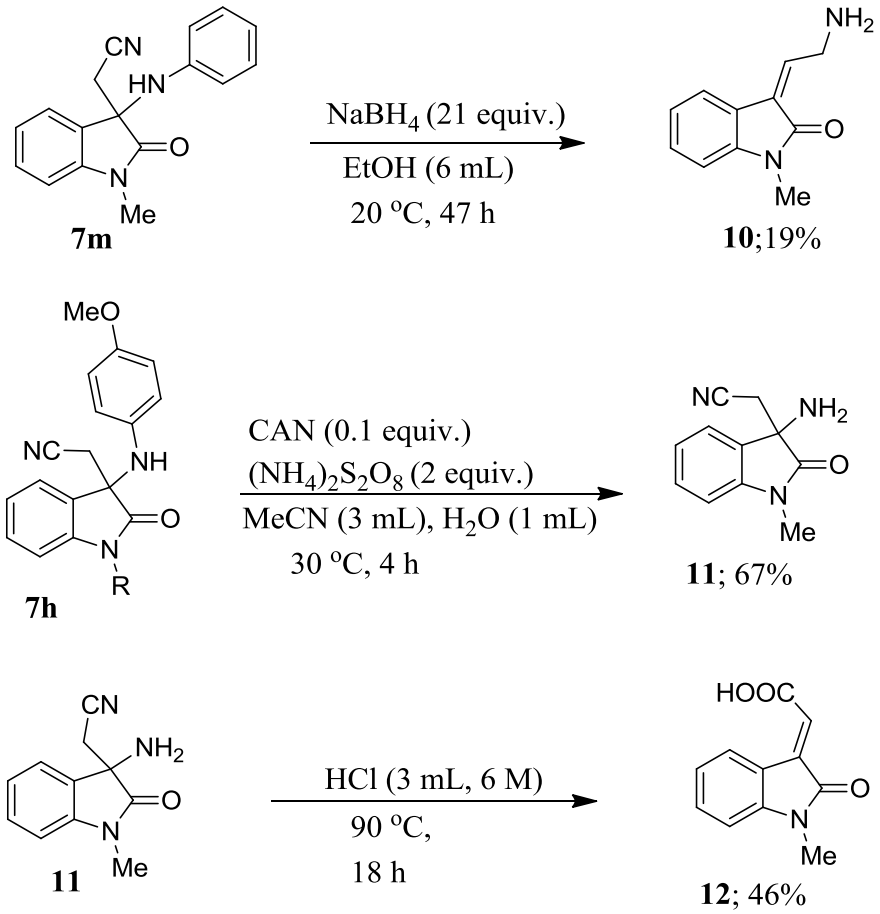
5a **6c** **9b**

Entry.	Mt (mmol)	Solvent (mL)	Temp. (°C)	Time (h)	**9b;** Yield[a] (%)
1	In (0.5)	THF (2)	28	12	60
2	Zn (0.5)	DMF (1)	28	13	0
3	Zn (0.5)	THF (2)	28	22	0
4[b]	Zn (0.5)	THF (2)	28	24	0

Reaction was performed by using isain imine (0.75 mmol), bromoacetophenone (0.75 mmol). [a] Isolated yields are given. [b] N-methyl isatin imine is used as a starting material. Mt - metal

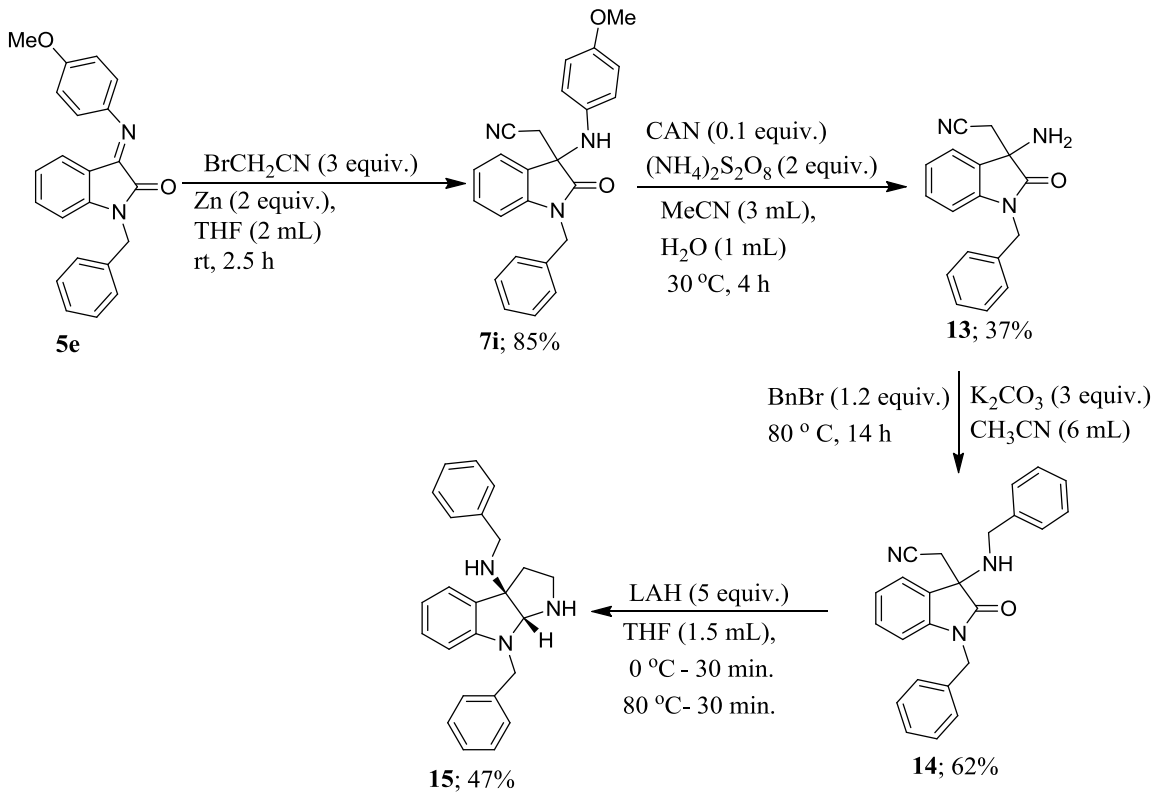
The reactivity of bromoacetophenone (**6c**) with isatin ketimine (**5a**) was also examined in the presence of different metals and solvents at room temperature and the results are shown in Table 8. Initially, we performed the reaction of bromoacetophenone (**6c**) with **5a** in the presence of indium metal in THF for 12 h at room temperature under nitrogen atmosphere, which gave the product **9b** in 60% yield (Table 8, entry 1). The reaction in presence of zinc metal in DMF or THF did not give the desired product **9b** (Table 8,

entries 2 and 3). Further, the reaction of **6c** with *N*-methyl isatin ketimine in presence of zinc in THF also did not give the desired product 9a (Table 8, entry 4).



Scheme 1. Functional group transformation of amino nitrile oxindole derivatives.

Subsequently, having amino nitrile containing oxindole derivatives in our hand, then we performed some functional group transformations. The reduction of nitrile group can generate 3-amino-3-alkyl oxindole derivatives[26] and accordingly, the reduction of nitrile group in **7m** was performed by using $NaBH_4$ as reducing agent under well-known literature methodology, this reaction gave the compound **10** instead of the desired product **(**Scheme 1**)**. Deprotection of PMP group was done by using the literature method, which resulted in the formation of the desired product **11** from compound **7h (**Scheme 1**).** Hydrolysis of nitrile group present in the compound **11** was also performed in aqueous HCl using the standard condition known in the literature, which resulted in the formation of the product **12** in 46% yield (Scheme 1). Then, we carried out the synthesis of pyrrolo[2,3-b]indoline (**15)** in the presence of $LiAlH_4$, a strong reducing agent via a one pot reductive cyclization of the compound **14**, and this reaction gave the product **15** with 47% yield (Scheme 2).[27]



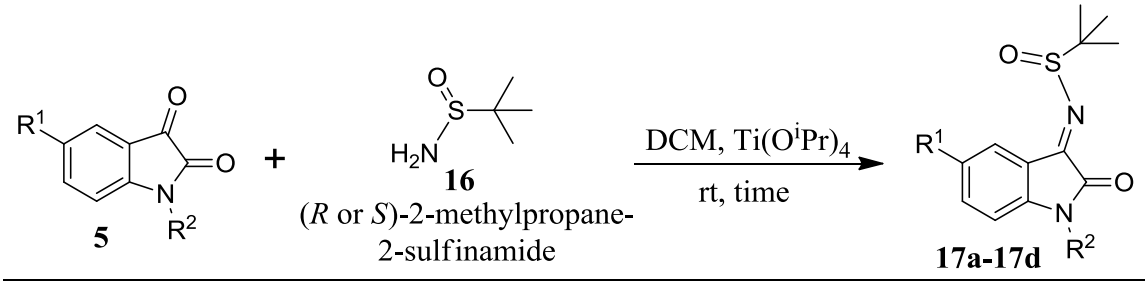
Scheme 2. Synthesis of pyrrolo[2,3-b]indoline from **5e**.

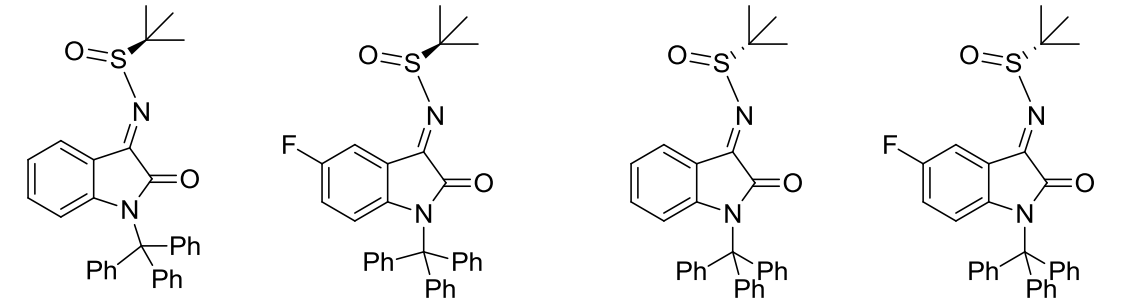
Furthermore, we prepared some chiral starting materials (**17a-17d**) by using the literature methods (Table 9). After synthesizing the various chiral isatin ketimines **17a-17d**, we examined the reactivity of isatin ketimine (**17a**) with bromoacetonitrile (**6a**) in the presence of different metals and solvents under nitrogen atmosphere and the results are shown in Table 10. Initially, the reaction of isatin ketimine (**17a**) with 0.6 mmol bromoacetonitrile (**6a**) in the presence of 0.4 mmol zinc in THF for 26 h at 30 ^{o}C under nitrogen atmosphere gave the desired product **18a** in 69% yield with good diastereoselectivity (75:25; Table 10, entry 1). The reaction in DMF solvent gave the product **18a** in 45% yield with less diastereoselectivity (57:43; Table 10, entry 2).

Then, the reaction was carried out in other solvents, such as, 1,4-dioxane, EtOH, DCM, CH_3CN, which were not effective (Table 10, entry 3-6). Successively, when reaction of **17a** and **6a** was performed in the presence of other metals, such as, In, Sn and Bi, the desired product was not obtained (Table 10, entry 7-9). Decreasing the reaction temperature to 0 ^{o}C gave was not effective (Table 10, entry 11) and however, the reaction at 80 ^{o}C gave the desired product **18a** in 71% yield with moderate diastereoselectivity (65:35; Table 10, entry 10). When reaction of **17a** with **6a** was performed with lesser equivalents (0.2 mmol) of bromoacetonitrile **6a** and 0.15 mmol of zinc, the product **18a**

was obtained in 37% and 66% yield, respectively (dr; 75:25; Table 10, entry 12 and 13). We also found that the zinc and indium metals could not promote the reaction of **17a** and **6a** in aqueous medium (Table 10, entries 14 and 15).

Table 9. Synthesis of chiral isatin ketimines.

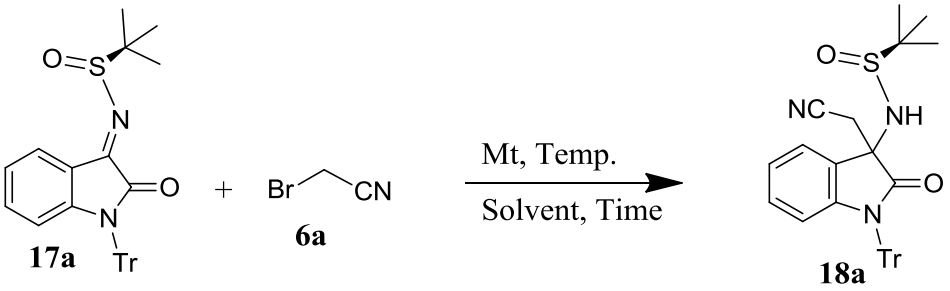




Reaction was performed by using isatin (2 mmol), 2-methylpropane-2-sulfinamide (2.4 mmol), $Ti(O^iPr)_4$ (4 mmol) and DCM (6 mL). Isolated yields are given.

After establishing the optimal reaction conditions, the addition of **6a** with various chiral isatin ketimines (**17a**-**17c**) gave various chiral nitrile substituted oxindole derivatives (**18a**-**18c**) in good yields with diastereoselectivity and the results are shown in Table 11. The reaction of isatin ketimine (**17b**) with **6a** for 12 h under a nitrogen atmosphere gave the product **18b** in 81% yield with good diastereoselectivity (dr; 83:17; Table 11). Similarly, the reaction of the isatin ketimine (**17c**) derived from *S*-*tert*-butylsulfinamide with **6a**, afforded the product **18c** in 73% yield with good diastereoselectivity (dr; 81:19, Table 11).

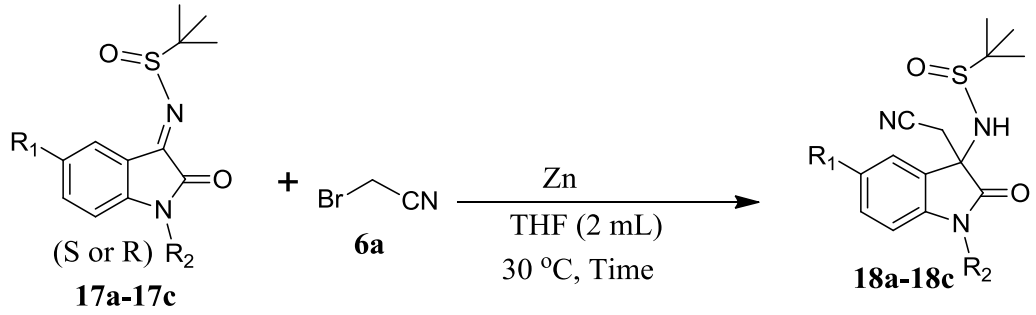
Table 10. Nucleophilic addition of bromoacetonitrile (**6a**) to chiral Isatin Ketimine (**17a**).

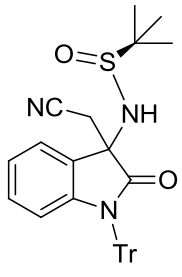


Entry	Mt (mmol)	Solvent (mL)	Temp. (°C)	Time (h)	**18a;** Yield[a] (%, dr)
1[b]	**Zn (0.4)**	**THF (2)**	**30**	**26**	**69 (75:25)**
2	Zn (0.2)	DMF (1)	30	12	45 (57:43)
3	Zn (0.2)	Dioxane (2)	30	22	0
4	Zn (0.2)	EtOH (2)	30	22	0
5	Zn (0.2)	DCM (2)	30	24	0
6	Zn (0.2)	CH_3CN (2)	30	24	0
7	In (0.2)	THF (2)	30	24	0
8	Sn (0.2)	THF (2)	30	20	0
9	Bi (0.2)	THF (2)	30	24	0
10	Zn (0.2)	THF (2)	80	2	71 (65:35)
11	Zn (0.2)	THF (2)	0	21	0
12[c]	Zn (0.2)	THF (2)	30	38	37 (75:25)
13	Zn (0.15)	THF (2)	30	38	66 (73:27)
14	Zn (0.2)	THF/H_2O (3)	30	24	0
15	In (0.2)	THF/H_2O (3)	30	24	0

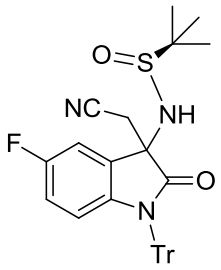
Reaction was performed by using isatin imine (0.1 mmol), bromoacetonitrile (0.3 mmol). [a] Isolated yield are given. [b] Starting material (0.2 mmol) has been used. [c] Bromoacetonitrile (0.2 mmol) has been used.

Table 11. Diastereoselective Nucleophilic addition of bromoacetonitrile (**6a**) to chiral isatin ketimine (**17**).

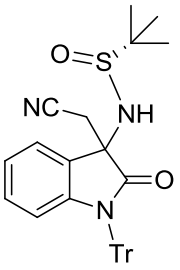




18a, 69%; 14 h
(dr; 75:25)



18b, 81; 12 h
(dr; 83:17)



18c, 73%; 6 h
(dr; 81:19)

Reaction was performed by using isatin imine (0.25 mmol), bromoacetonitrile (0.75 mmol) and zinc (0.5 mmol). Isolated yields are given. Diastereoselectivity was calculated from ^{1}H NMR of crude reaction mixture.

Summary

In summary, we have reported a highly efficient and stereoselective zinc-mediated Barbier-type C-C bond formation synthetic protocol and addition of bromoacetonitriles to the C=N bond of isatin ketimines. We have shown the synthesis of several new examples of 3-substituted 3-aminooxindoles and these molecules are expected to be used as synthetic building blocks. We have also shown the representative synthetic transformations using the oxindole derivatives obtained in this work.

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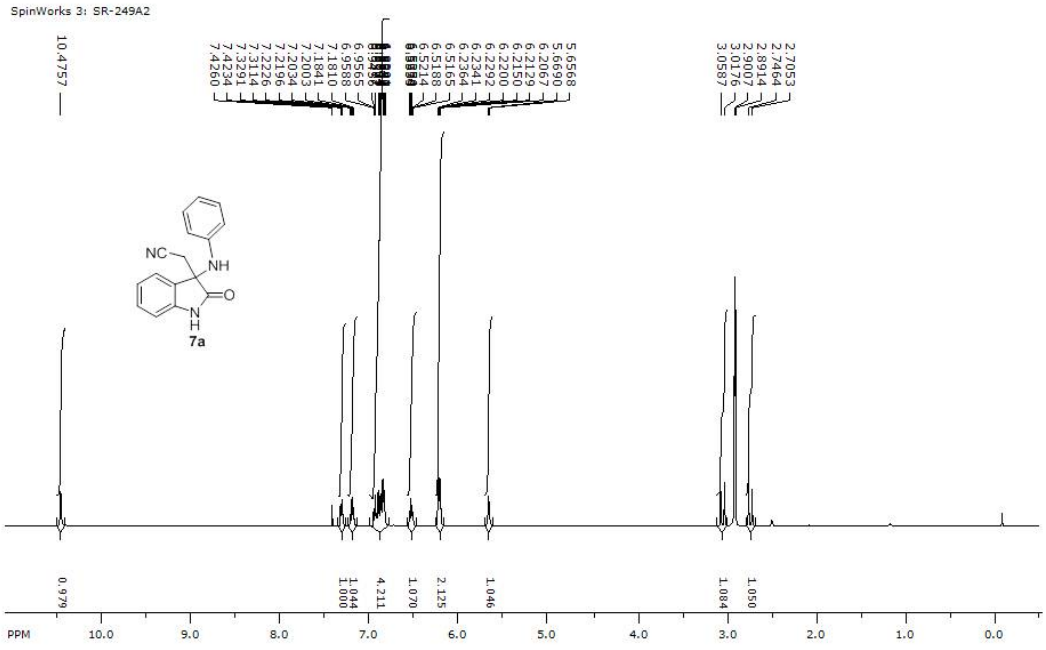
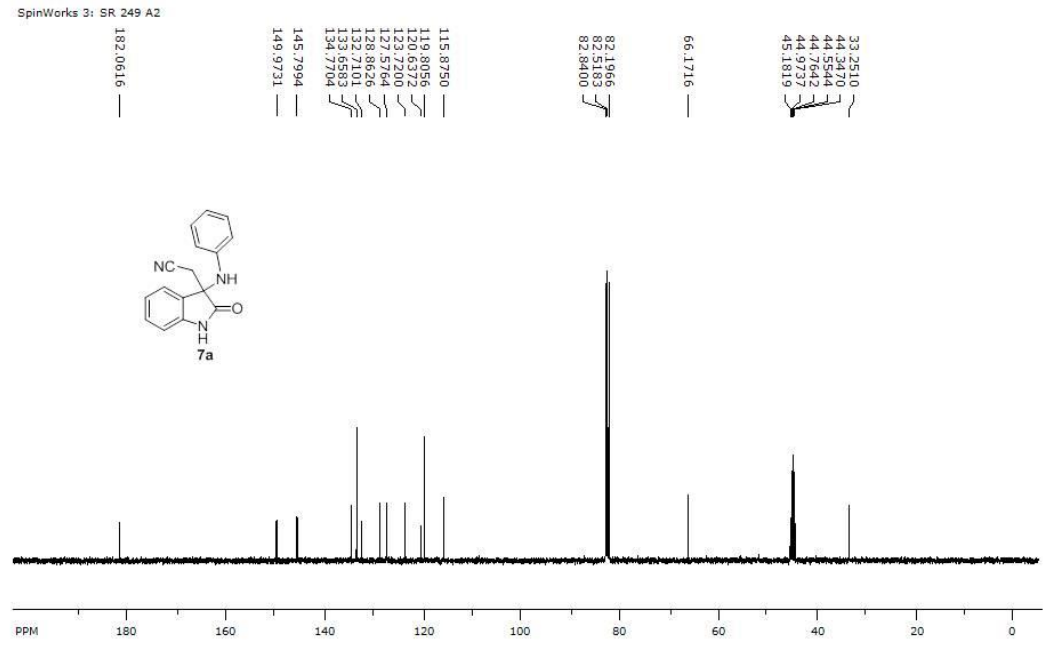
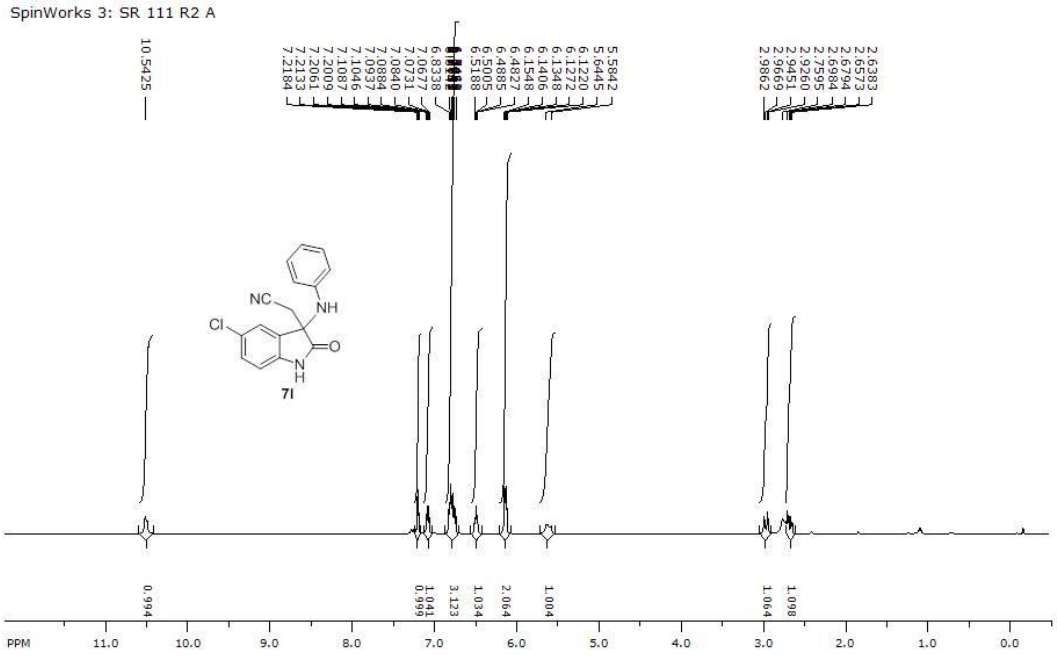
Appendix

NMR Spectra of Representative Compounds



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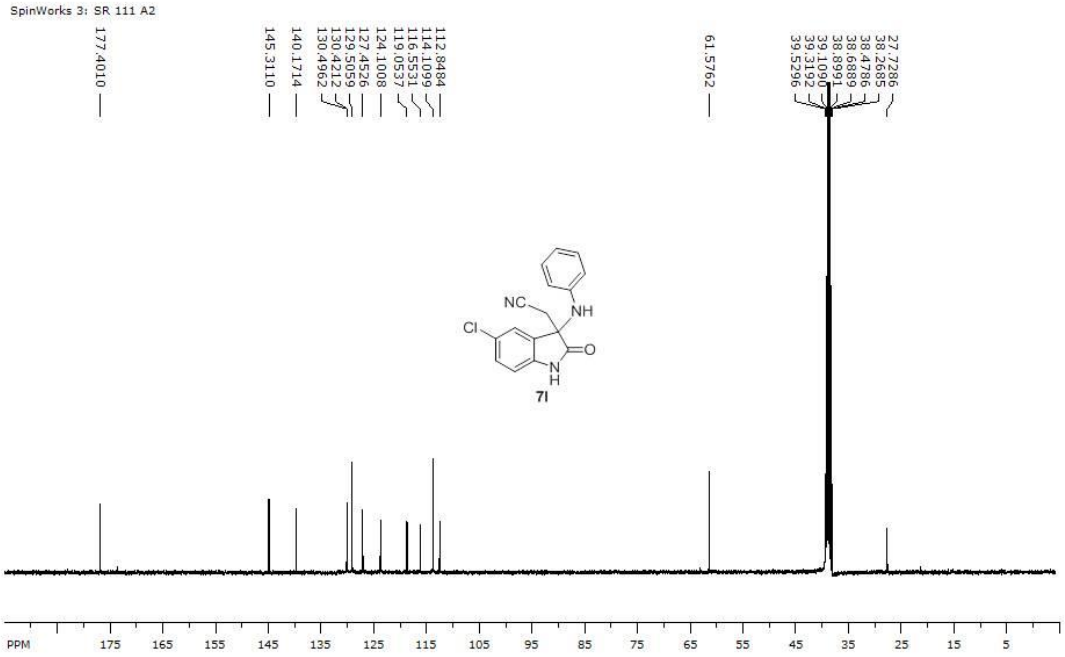
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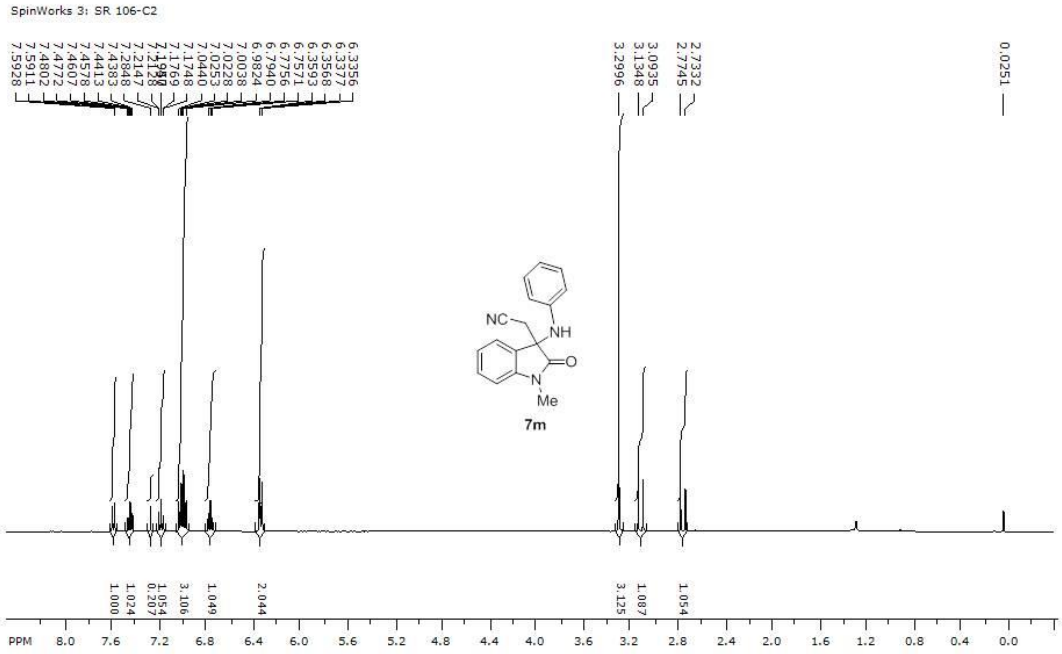
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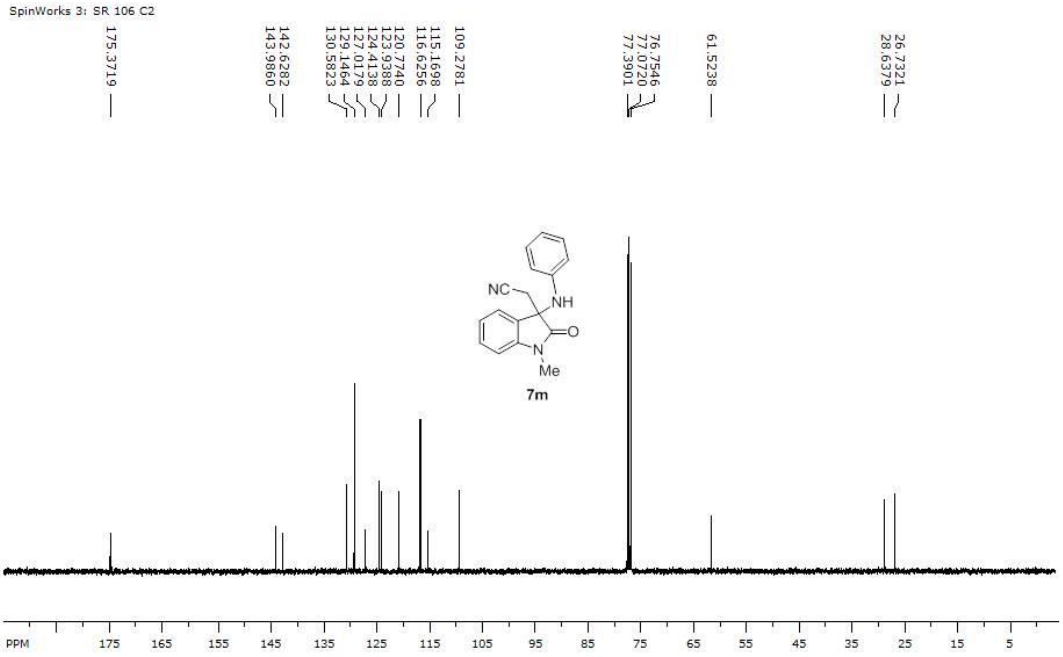
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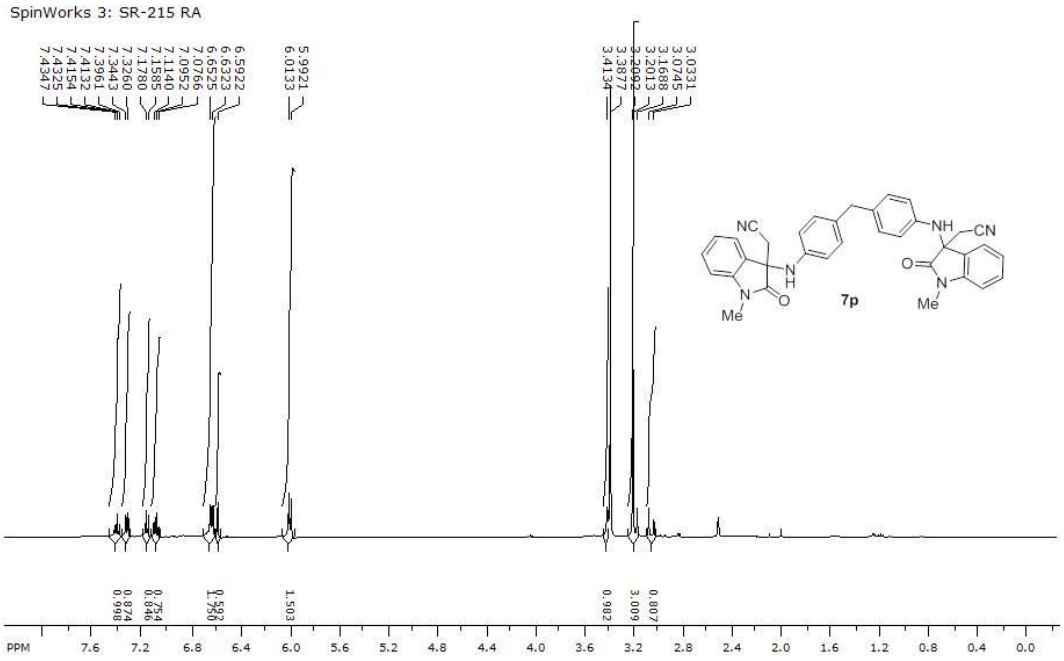
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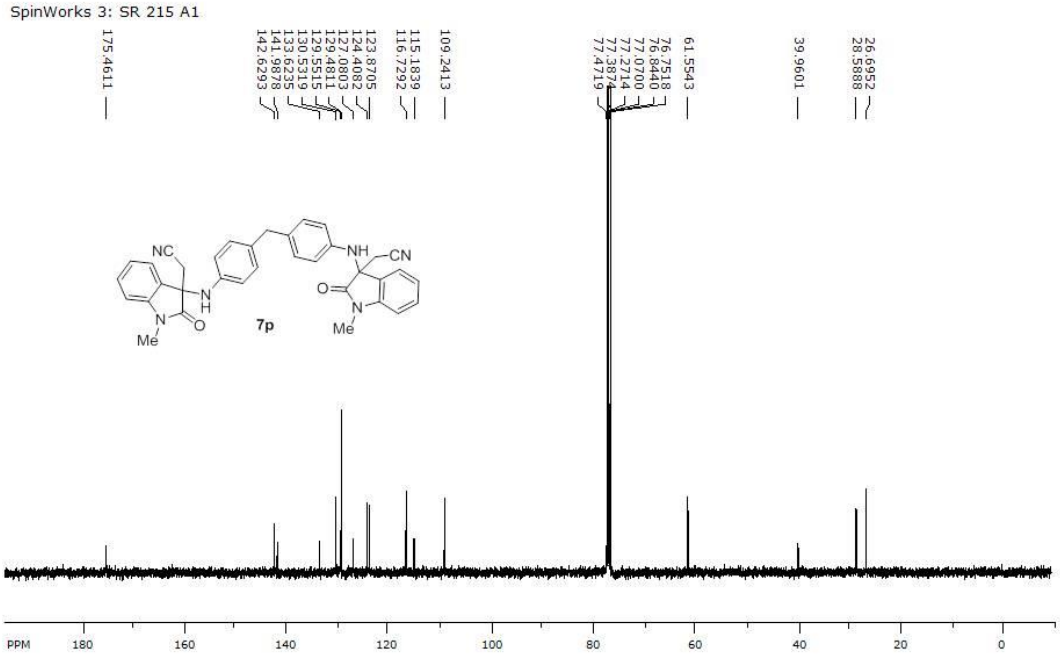
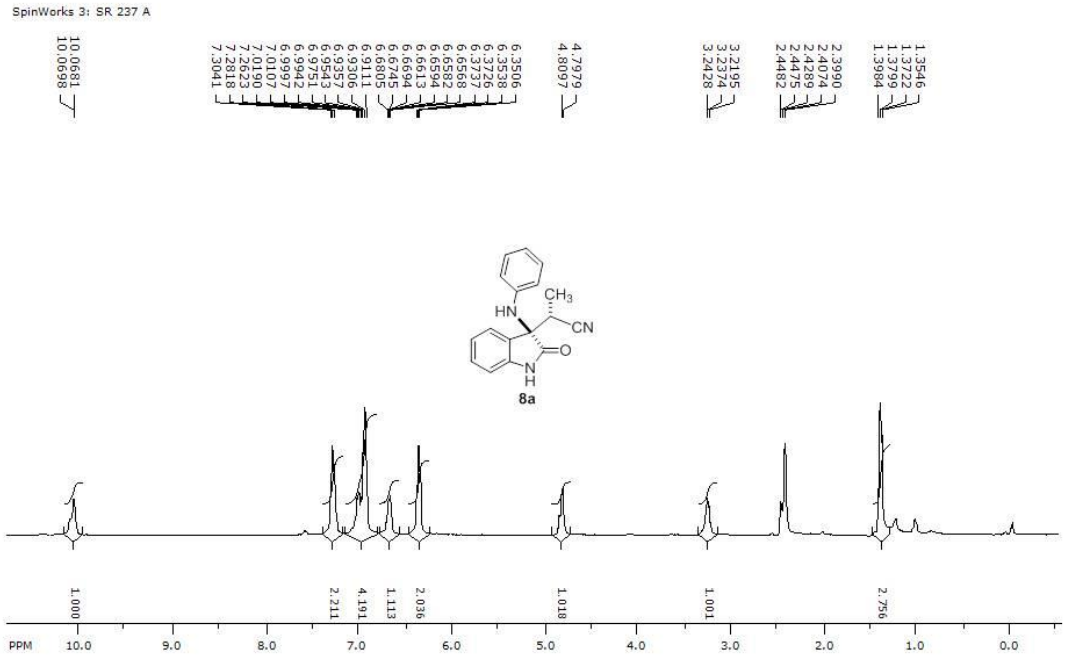
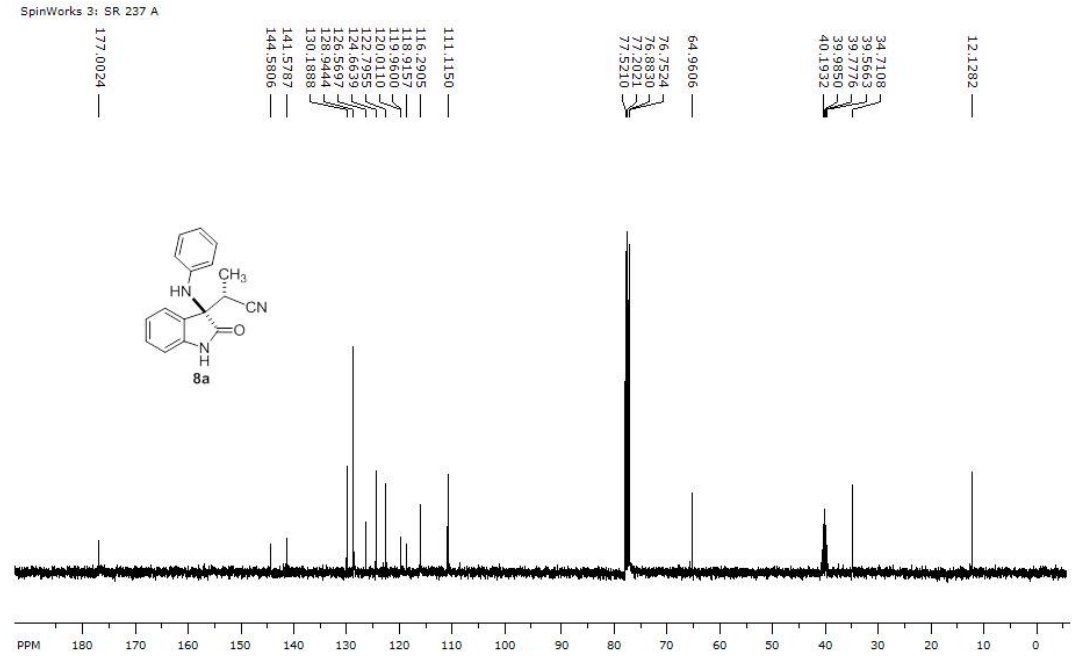
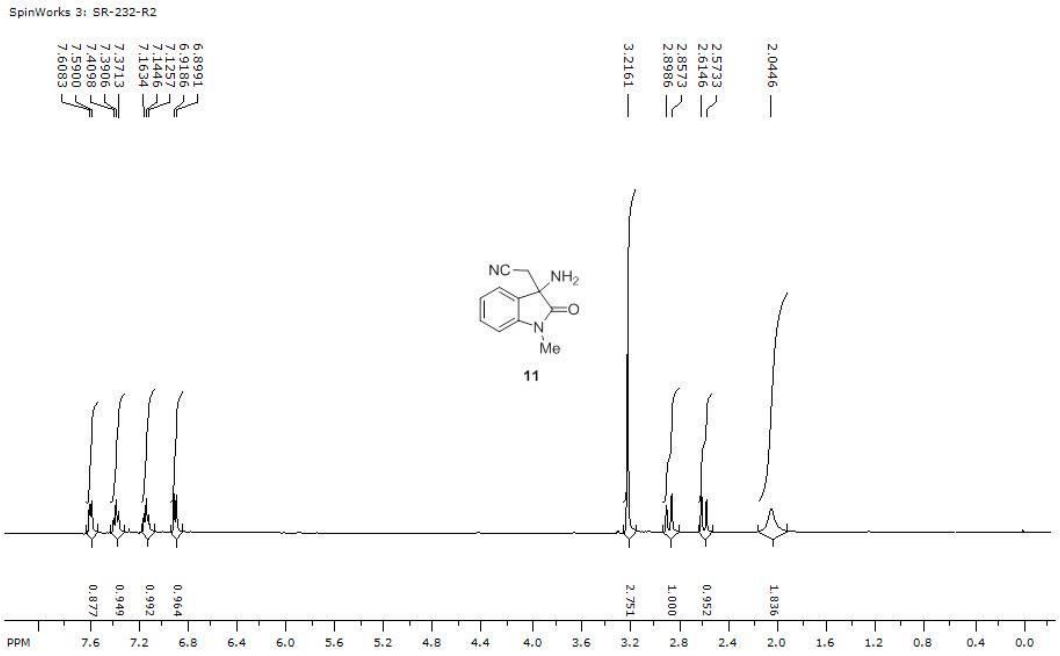
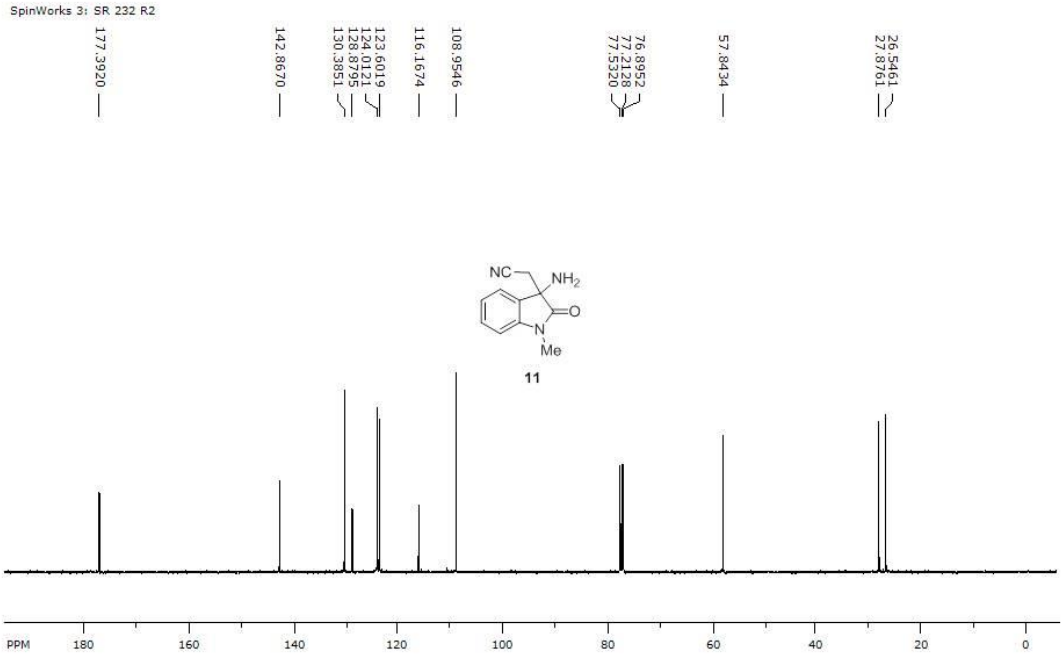
6.5922
6.0133
5.9921
3.4134
3.3877
3.2992
3.2013
3.1688
3.0745
3.0331
0.998
0.874
0.646
0.754
1.950
0.592
1.503
0.982
3.009
0.807
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0
NC
NH
CN
O
N
H
Me
7p

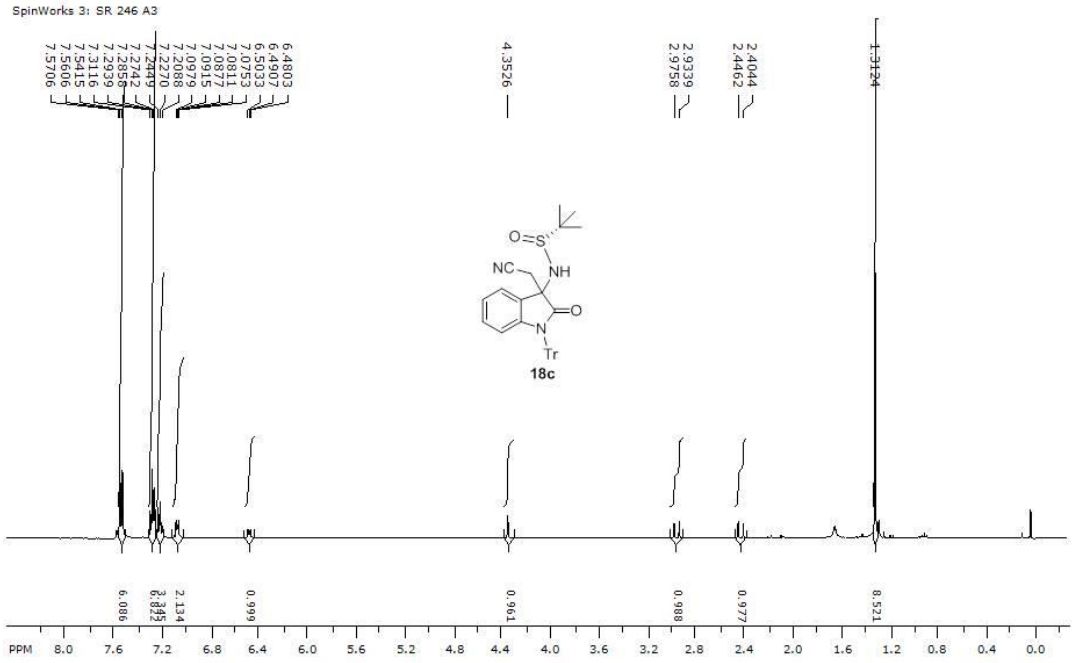

SpinWorks 3: SR 215 A1
175.4611
142.6293
141.6838
133.6235
130.5319
129.5511
129.4811
127.0803
124.4082
123.8705
116.7292
115.1839
109.2413
77.4719
77.3374
77.2700
77.0840
76.7518
61.5543
39.9601
28.5888
26.6952
PPM
180
160
140
120
100
80
60
40
20
0
NC
NH
CN
O
N
H
Me
7p

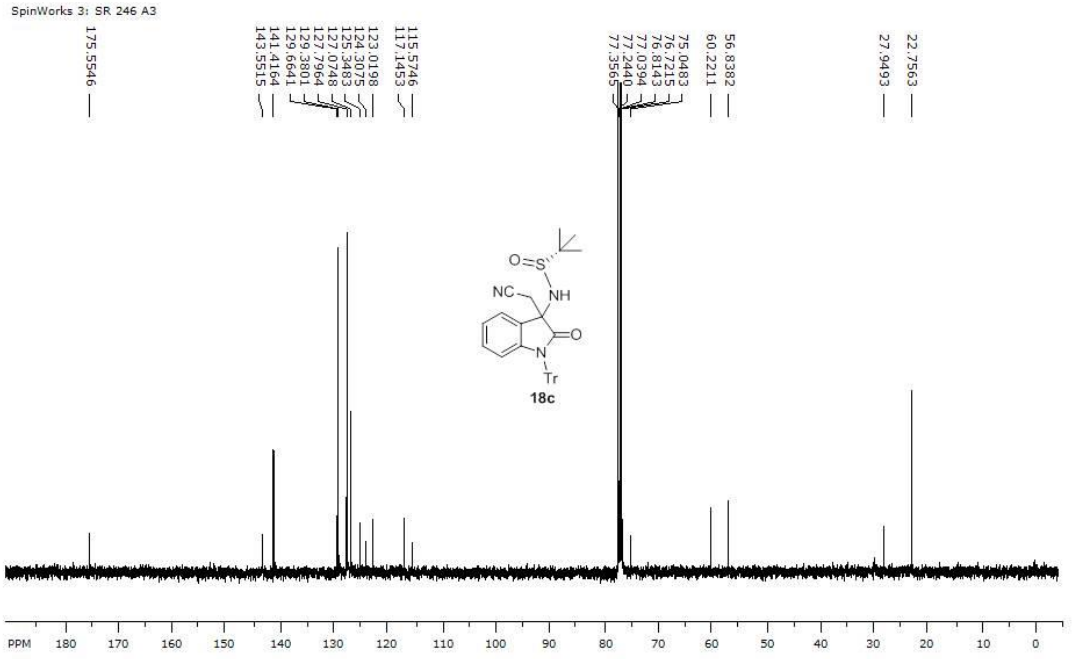

SpinWorks 3: SR 237 A
10.0681
10.0698
7.3041
7.2818
7.2623
7.0190
7.0107
6.9997
6.9942
6.9751
6.9543
6.9357
6.9306
6.9111
6.6805
6.6745
6.6694
6.6613
6.6594
6.6568
6.6528
6.3723
6.3528
6.3506
4.8097
4.7979
3.2428
3.2374
3.2195
2.4482
2.4475
2.4289
2.4074
2.3990
1.3984
1.3799
1.3722
1.3546
HN
CH3
CN
O
N
H
8a
1.000
2.211
4.191
1.113
2.036
1.018
1.001
2.756
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SpinWorks 3: SR 237 A
177.0024
144.5806
141.5787
130.1888
128.9444
126.5697
124.6639
122.7955
120.0110
118.9157
119.9600
116.2905
111.1150
77.5210
77.2021
76.8830
76.7524
64.9606
40.1932
39.9850
39.7776
39.5669
34.7108
12.1282
HN
CH3
CN
O
N
H
8a
PPM
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


SpinWorks 3: SR-232-R2
7.6083
7.5900
7.4098
7.3906
7.3713
7.1634
7.1446
7.1257
6.9186
6.8991
3.2161
2.8986
2.8573
2.6146
2.5733
2.0446
NC
NH2
O
N
Me
11
0.877
0.949
0.992
0.964
2.751
1.000
0.952
1.836
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


SpinWorks 3: SR 232 R2
177.3920
142.8670
130.3851
128.8795
124.0121
123.6019
116.1674
108.9546
77.5320
77.2128
76.8952
57.8434
27.8761
26.5461
NC
NH2
O
N
Me
11
PPM
180
160
140
120
100
80
60
40
20
0


SpinWorks 3: SR 246 A3
7.5706
7.5606
7.5415
7.3116
7.2939
7.2858
7.2742
7.2449
7.2270
7.2088
7.0979
7.0915
7.0877
7.0811
7.0753
6.5033
6.4907
6.4803
4.3526
2.9758
2.9339
2.4462
2.4044
1.3124
6.086
8.822
2.134
0.999
0.961
0.988
0.977
8.521
PPM 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
O=S
NC
NH
O
N
Tr
18c


SpinWorks 3: SR 246 A3
175.5546
143.5515
141.4164
129.6641
129.3801
127.7964
127.0748
125.3483
124.3075
123.0198
115.5746
117.1453
77.3565
77.2440
77.0394
76.8143
76.2215
75.0483
60.2211
56.8382
27.9493
22.7563
PPM 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
O=S
NC
NH
O
N
Tr
18c