Organocatalytic Oxidative Kinetic Resolution of Racemic Benzoins

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Certificate of Examination

This is to certify that the dissertation titled **"Organocatalytic Oxidative Kinetic Resolution of Racemic Benzoins"** submitted by **Mr. Akhil V Gopal** (Reg. No. MS10036) for the partial fulfilment of BS-MS dual degree programme of the Institute, 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. Arulananda Babu Dr. Sugumar Venkataramani Dr. R. Vijaya Anand

(Supervisor)

Dated: April 24, 2015

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. R. Vijaya Anand 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 other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Akhil V Gopal (MS10036)

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Dated: April 24, 2015

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

Dr. R. Vijaya Anand

(Supervisor)

Acknowledgement

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Abbreviations

DBU	1, 8-Diazabicycloundec-7-ene
DMF	Dimethyl Formamide
THF	Tetrahydrofuran
TEMPO	2,2,6,6,Tetramethylpiperidinooxy
TLC	Thin Layer Chromatography
DCM	Dichloromethane
HPLC	High Performance Liquid Chromatography
NMR	Nuclear Magnetic Resonance
FT-NMR	Fourier Transform Nuclear Magnetic Resonance
DIAD	Diisopropyl azodicarboxylate.
DPPA	Diphenyl Phosphoryl Azide
KR	Kinetic Resolution
DKR	Dynamic Kinetic Resolution
BINAM	Binapthyldiamine
TFA	Trifluoroacetic acid

Contents

Abstract

An Organocatalytic protocol for the kinetic resolution of racemic benzoins has been attempted using chiral tertiary amine as a catalyst. A wide range of chiral non-racemic tertiary amine catalysts have been screened for this purpose. Out of many catalysts tried, cinchona alkaloid based catalysts were found to be better to effect this transformation. Although in most of the cases racemic benzoin was obtained after the reaction, a maximum of 30% ee was obtained for the *S*-isomer by using quinidine as a catalyst.

CHAPTER 1

Introduction

1.1 Overview

Benzoin and its derivatives are considered to be attractive targets because they possess a various biological properties.[1] For example, simple benzoin **1**, derived from homo dimerization of benzaldehyde or extracted from styrax benzoin tree, has been utilized as a cosmetic product to moisturize dry skin. It was found that benzoin tincture possesses antiseptic activities and thus can be used for the treatment of fungal irritations in the skin. Benzoin belongs to a class of compounds called acyloins or α-hydroxy ketones.

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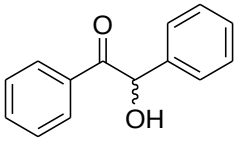

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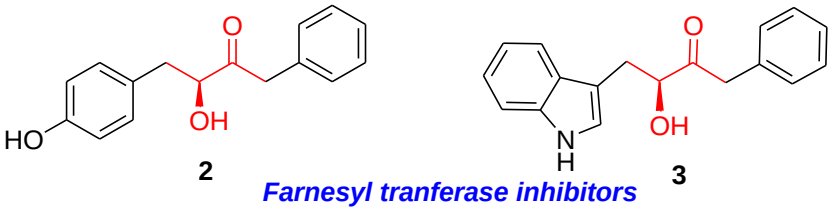
Fig.1 Benzoin

Enantiopure benzoins are very important building blocks in organic synthesis as well as pharmaceutical industry. Chiral Benzoins are involved in the synthesis of many natural products, heterocycles and drug molecules and some of them are useful as urease inhibitors.[2] Some of the chiral non-racemic cross acyloins (for e.g., **2** & **3**) derivatives are used as anticancer agents due to farnesyl transferase inhibition activity.[3] In addition to that benzoins or cross benzoins can be extended to different bioactive molecules like amino alcohols, diols etc. Because of their promising biological activities, many enantioselective methods have been developed so far.



2 **3**

Fig.2 Anticancer agents Kurasoin A and Kurasoin B

The methods for the synthesis of benzoins include α-hydroxylation of ketones by enamine catalysis using proline or proline derived organocatalysts[4], selective asymmetric oxidation of 1, 2 diols[5] and ketohydroxylation of alkenes (**Fig. 3**). The most employed methods for chiral benzoin, are asymmetric condensation and kinetic resolution of racemic benzoins.

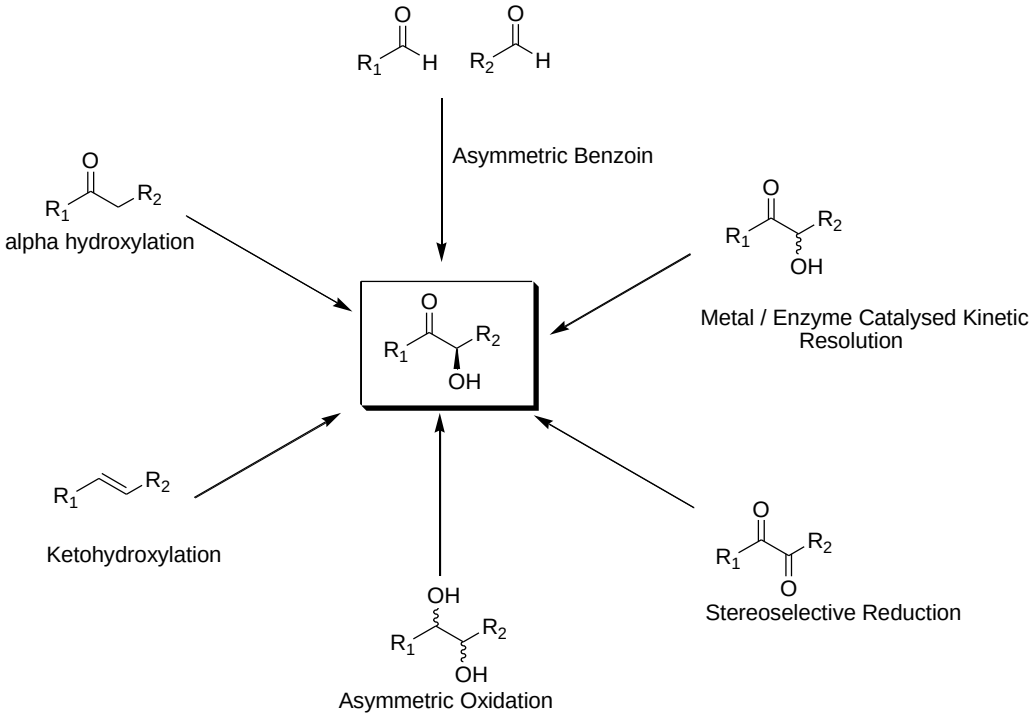


Fig.3 Synthetic Approaches towards Chiral Benzoin or acyloins

N-Heterocyclic carbene catalyzed enantioselective homo or cross benzoin condensation, which was developed recently, is the most popular method for the synthesis of enantiomerically pure benzoins.[7] Inspired from the biosynthetic mechanisms involving thiamine diphosphonate, N-heterocyclic carbenes became one of the most versatile organocatalysts. The first example of asymmetric benzoin condensation was reported by Sheehan and co-workers in 1966.[8] They reported the self-coupling of benzaldehyde using **4** as catalyst forming the benzoin product in 9% yield and 22% *ee*. Later in 1974 Sheehan modified the thiazolium catalyst **4** using a bulky naphthyl group. Using thiazolium salt **5** offered the product in 52% *ee* but the yield was only 6%.[9] This result was a milestone for the

enantioselective benzoin reaction for over 20 years. In 1996, Enders and co-workers reported triazolium salt **6** as an efficient carbene precursor. In their case the benzoin product was obtained in 75% yield and 66% *ee*.[10] In 1998 Leeper and co-workers developed a fused bicylcic triazolium **7** to give the product in a good enantiomeric excess of 80%.[11] In 2002, Enders and co- workers reported the more reactive triazolium salt **8**, which afforded the benzoin product in 90% *ee* and 83% yield.[12] Over the last decade a large number of chiral carbene precursors have been reported for enantioselective homo benzoin reaction as well as cross benzoin reactions.[13]

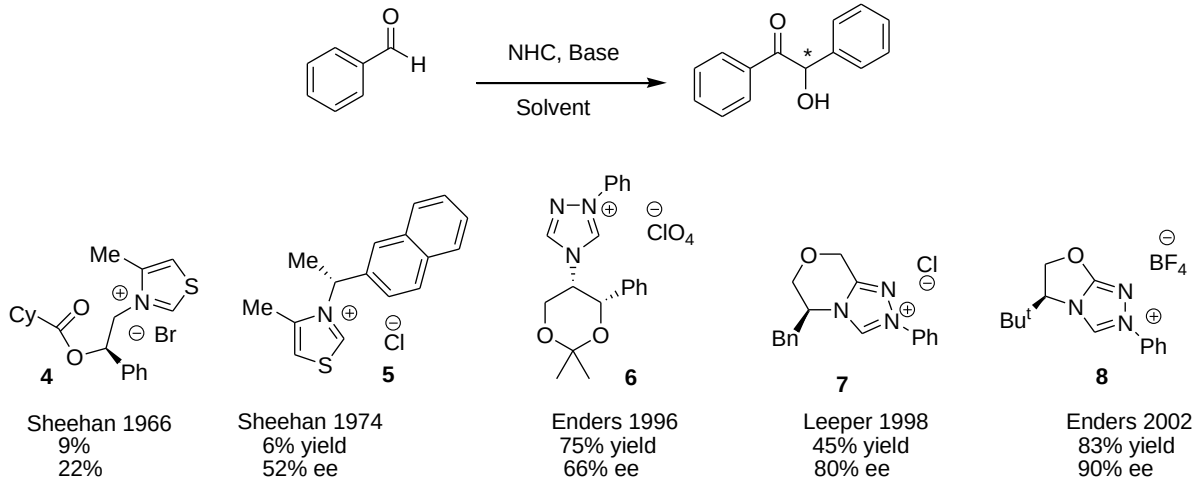


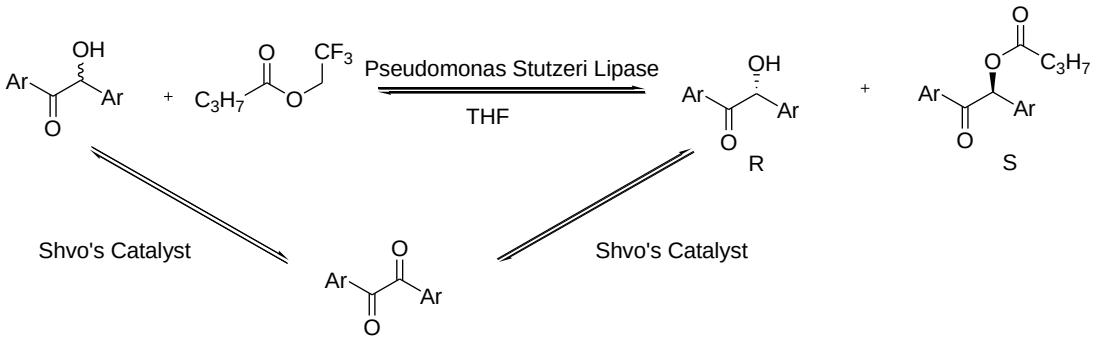
Fig.4. N-Heterocyclic carbenes developed for enantioselective benzoin condensation

Chiral benzoins or acyloins can also be obtained by enantioselective benzoin or acyloin condensation catalyzed by different thiamine diphosphate dependent enzymes such as pyruvate decarboxylase (PDC), benzoylformate decarboxylase (BFD), and benzaldehyde lyase (BAL).[14] Other enzymatic methods for the synthesis of enantiomerically pure benzoins are the enantioselective reduction of α-diketones[15] and the fungal deracemization.[16]

In spite of the progress in asymmetric synthesis, the dominant method to obtain a single enantiomer in industrial scale is based on the kinetic resolution of racemates.[17] In kinetic resolution, two enantiomers react with different reaction rates with the chiral catalyst, resulting in an enantio enriched sample of the less reactive enantiomer in the reaction. However, the major drawback of kinetic resolutions (KR) is that the required compound can

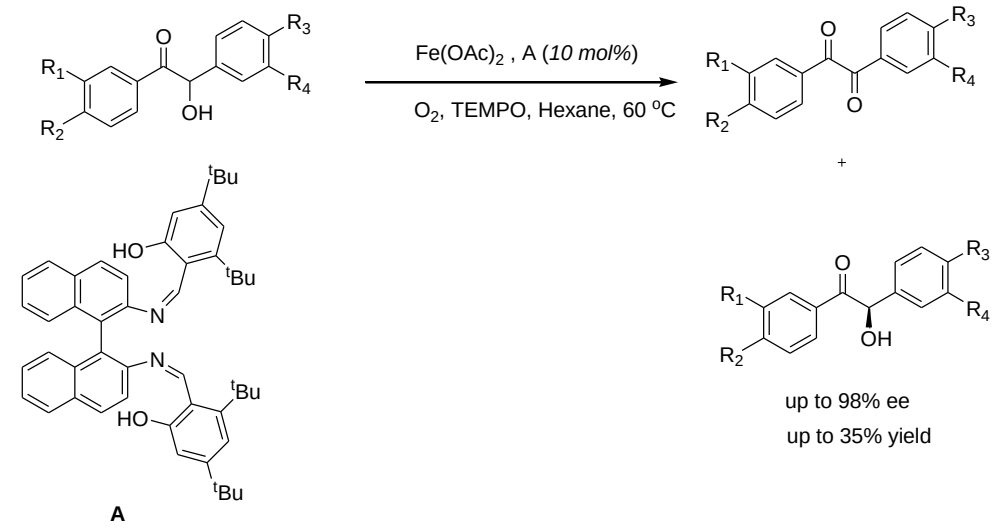
be obtained only in 50% yield. But it is possible to obtain a yield of 100% by carrying out the racemization of starting material under the resolution conditions in dynamic kinetic resolution (DKR) process.[18] The most employed method of doing DKR is combining an enzymatic resolution with a transition-metal catalyzed racemization *via* hydrogen transfer.[19] But the basic criteria for an efficient DKR is to develop an effective KR.

In 2006, Alcantara and co-workers reported an enzyme catalyzed kinetic resolution of racemic benzoins obtaining around 50% conversion and more than 99% *ee* in very short reaction times.[20] Out of various enzymes screened, lipase TL obtained from Pseudomonas Stutzeri was found to be more efficient. After developing an efficient KR they had reported dynamic kinetic resolution of racemic benzoins using a lipase ruthenium catalyzed transesterification for the first time (Scheme 1).



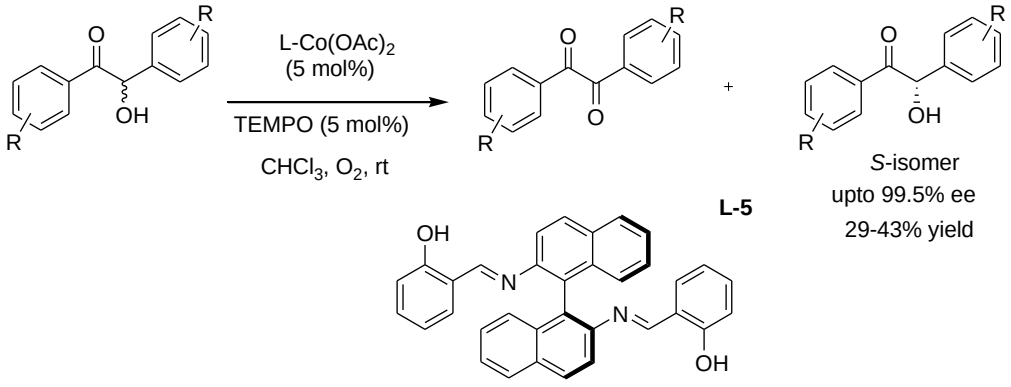
Scheme 1

In 2009, Sekar and co-workers reported the oxidative KR of racemic benzoins catalyzed by a chiral iron complex derived from (*R*)-BINAM, which provided enantio selectivities upto 98% for the recovered α-hydroxy ketones.[21] The reaction was performed in presence of 10 mol% of $Fe(OAc)_2$ combined with the (*R*)-BINAM-derived ligand with a catalytic amount of TEMPO in hexane at 60 ^{o}C using molecular oxygen as an oxidant (Scheme 2).



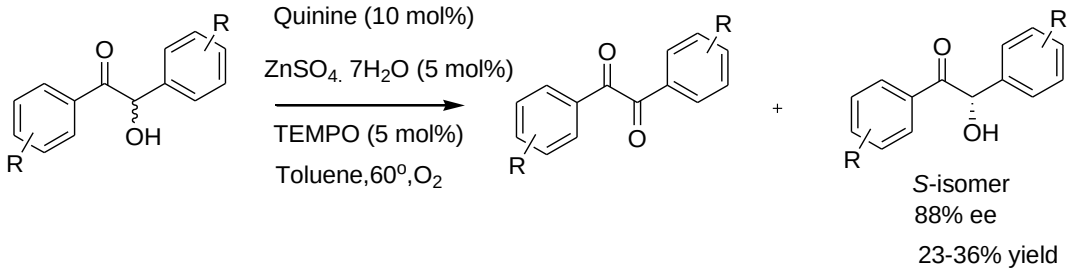
Scheme 2

The same group also reported a new chiral cobalt catalyzed oxidative kinetic resolution of racemic benzoins to get enatiomerically pure benzoins.[22] They used molecular oxygen as a stoichiometric oxidant and a cobalt complex derived from Schiff base. They were able to convert the *R*-isomer to benzil and *S*-isomer remain unreacted.



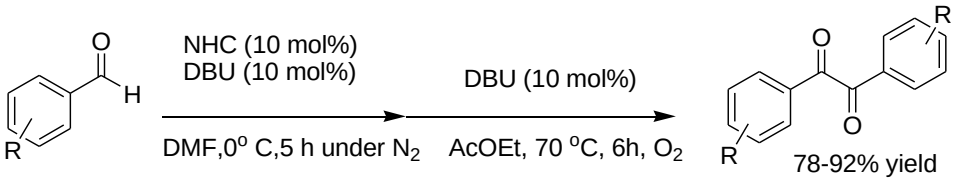
Scheme 3

In 2011, the same group reported another protocol for the synthesis of chiral α-hydroxyl ketones employing oxidative kinetic resolution process.[23] They accomplished the aerobic oxidative kinetic resolution of racemic α-hydroxy ketones using a chiral Zn–quinine complex as catalyst and molecular oxygen as oxidant (Scheme 4).



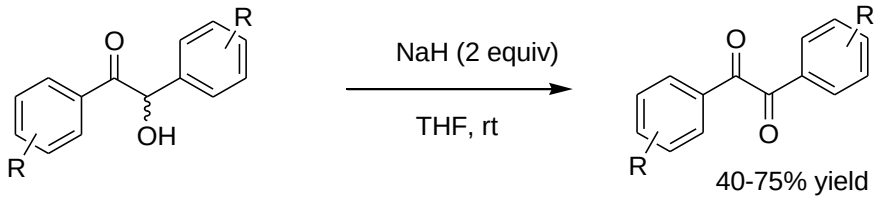
Scheme 4

In 2010, Sakaguchi and co-workers reported simple and efficient one-pot procedure for the synthesis of α-diketones from aldehydes *via* benzoin condensation.[24] They observed that in presence of excess base under heating conditions benzoin was completely converted to the diketone product in good to excellent yields. They proposed a mechanism of this oxidation by describing the abstraction of α-proton from benzoin by DBU to generate the carbanion. The generated carbanion will be trapped by molecular oxygen leading to a peroxy intermediate. Then the removal of phenolic proton by base followed by the elimination of hydrogen peroxide afforded the desired oxidized product benzil (Scheme 5).



Scheme 5

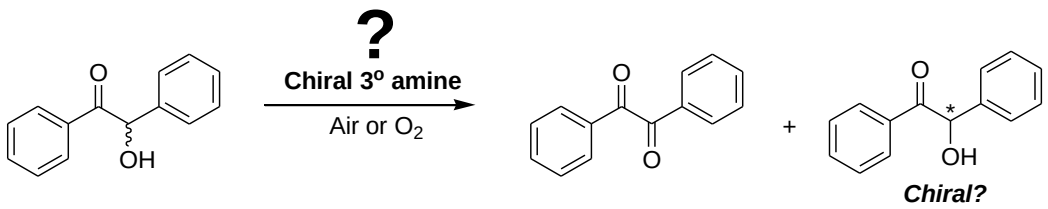
In the same year, Yang and co-workers reported a highly efficient and eco-friendly procedure for oxidation of benzoin to benzil using sodium hydride.[25] The protocol explained the importance of molecular oxygen forming a hydro peroxide intermediate by the trapping of hydride leading to the desired benzil product (Scheme 6).



Scheme 6

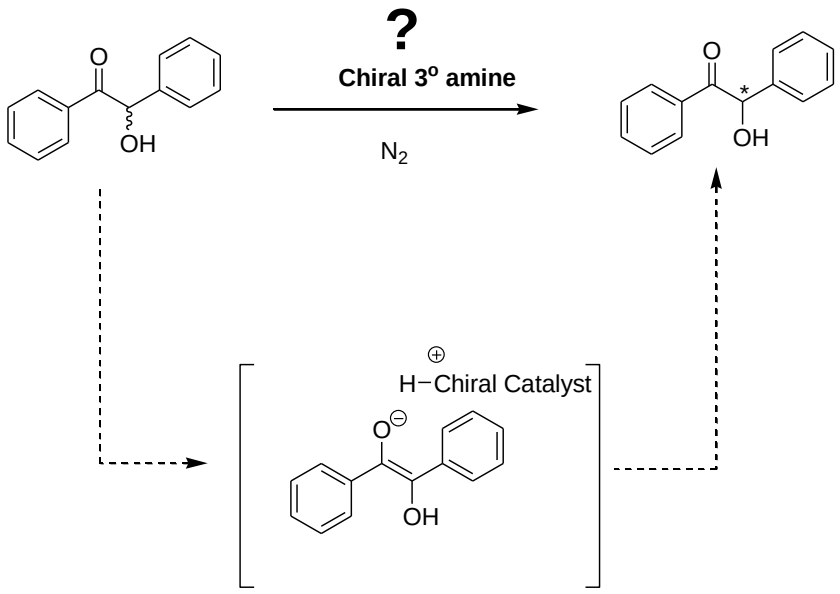
1.2 Our Approach

As a part of our research, employing N-heterocyclic carbenes in devepoing chemoselective cross benzoin reaction, we observed the formation of oxidized product benzil many times, while allowing the reaction mixture to stir for long time. Based on our own experience and the literature reports, we envisioned that it is possible to access enantiomerically pure benzoins through kinetic resolution of racemic benzoins using chiral tertiary amine as a catalyst. Although metal catalyzed kinetic resolution of benzoins are well studied under aerobic conditions, surprisingly, organocatalytic version of this transformation is still unprecedented in the literature, which prompted to investigate this transformation in detail.



Scheme 7

As per the mechanism suggested by Sakaguchi *et al*, the base will abstract the α-proton of benzoin and it will be in the form of enolate. Based on this we thought that using enantioselective protonation process we will be able to access enantiomerically pure benzoins using chiral tertiary amines through deprotonation followed by enantioselective protonation in the absence of oxygen. Although enantioselective protonation reactions are well studied, the enantioselective protonation of racemic benzoin using chiral teritiary amines is still unknown in the literature.



Scheme 8

CHAPTER 2

Results and Discussion

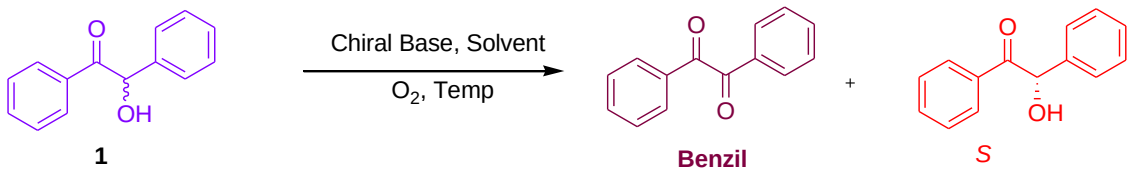
We began our investigation with simple benzoin (**1**) as a model substare and cinchona alkaloids as chiral tertiary amine base for oxidative kinetic resolution reaction. When benzoin was reacted with 20 mol% of Quinine as chiral tertiary amine in the presence of molecular oxygen at 60 ^{o}C and toluene as a solvent, the oxidation took 5 h for more than 50% conversion (by TLC) and provided 68% of benzil. In this asymmetric oxidation reaction, 30% of racemic benzoin was recovered. When the reaction was done with 20 mol% of quinidine in similar conditions, the oxidation took 5 hrs for more than 50% conversion and provided 73% benzil. This time 27% of benzoin was recovered with 10% enantiomeric excess (Table 1, entry 2). The same reaction with cinchonine and cinchonidine also provided racemic benzoin (Table 1, entries 3&4).

When the temperature was decreased from 60 ^{o}C to rt (25 ^{o}C), quinine catalyzed the oxidative kinetic resolution reaction of racemic benzoin and 65% of benzil and 35% of benzoin with an enantiomeric excess of 6%. Out of the four cinchona alkaloids screened quinidine gave better result in terms of selectivity. Encouraged by this preliminary result next we optimized catalyst loading. When benzoin was reacted with 10 mol% of quinidine in the presence of molecular oxygen at rt and toluene as a solvent, the oxidation took 24 hrs for more than 50% conversion (by TLC) provided 62% of benzil and 35% benzoin with 5% *ee*. After increasing the catalyst loading to 20 mol%, within 24 hrs the oxidation reaction showed more than 50% conversion on TLC gave 67% benzil and 32% benzoin was recovered with an *ee* of 30%.

To check whether the temperature is playing any role or not we performed the reaction at low temperature (Table1, entries 11&12). When the benzoin was reacted with 20 mol% of quinidine at -10 ^{o}C the oxidation took more than 48 hrs to show more than 50% conversion and gave 55% of benzil. The recovered benzoin (32%) showed an enantiomeric excess of

3%. Decreasing the temperature to -20 ^{o}C didn't give any fruitful result as the ee of the recovered benzoin was only 7%.

Table 1. Optimization Studies [a] of Oxidative Kinetic Resolution Of benzoins



1 Benzil S

Sl.no	Benzoin	Base	Mol%	Solvent	Temp(^{o}C)	Time(h)	Benzil Yield(%)	Benzoin Recovered(%)	*ee* [b]
1	1	Q	20	Toluene	60	5	68	30	racemic
2	1	QD	20	Toluene	60	5	73	27	10%
3	1	C	20	Toluene	60	5	55	41	racemic
4	1	CD	20	Toluene	60	5	52	48	racemic
5	1	Q	20	Toluene	rt	20	65	35	6%
6	1	QD	20	Toluene	rt	12	52	47	20%
7	1	C	20	Toluene	rt	24	64	36	racemic
8	1	CD	20	Toluene	rt	24	53	40	racemic
9	1	QD	10	Toluene	rt	24	62	35	5%
10	1	QD	20	Toluene	rt	24	65	29	20%
11	1	QD	50	Toluene	rt	24	67	32	30%
12	1	QD	20	Toluene	-10	>48	55	39	3%
13	1	QD	20	Toluene	-20	>48	63	31	7%
14	1	QD	20	DCM	rt	24	63	37	racemic
15	1	QD	20	THF	rt	36	60	36	5%
16	1	QD	20	Dioxane	rt	28	67	33	8%
17	1	QD	20	DiethylEther	rt	32	57	43	13%
18	1	QD	20	EthylAcetate	rt	36	61	37	11%
19	1	QD	20	Chloroform	rt	26	57	40	8%
20	1	QD	20	Toluene	33	12	59	37	25%
21	1	C1	10	Toluene	rt	8	NR	NR	NR
22	1	C2	10	Toluene	rt	16	63	33	racemic
23	1	C3	10	Toluene	rt	56	55	43	racemic
24	1	C4	10	Toluene	rt	56	59	40	5%
25	1	C5	5	Toluene	rt	60	53	45	9%
26	1	C6	5	Toluene	rt	60	58	42	7%
27	1	DBU(5+L1)	5+10	Toluene	rt	2.5	88	12	26%

[a] Reaction Conditions : 0.1mmol of benzoin, X mol% catalyst in 1mL solvent under O_2 atmosphere (O_2balloon), [b] : The % ee was determined by HPLC using Daicel Chiral-PAK IA column, rt = 25-27 ^{o}C.

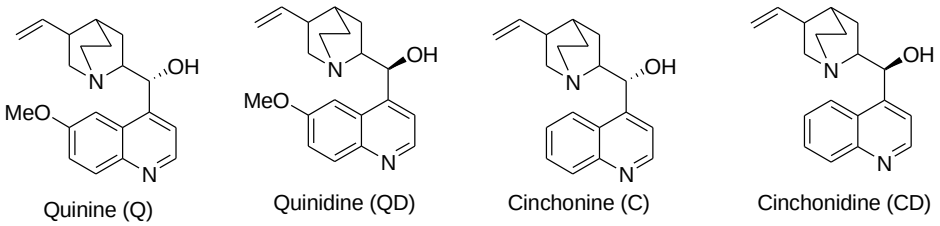


Fig.5. Cinchona Alkaloids Screened

Then we investigated the role of different solvents for the oxidative kinetic resolution reaction. A wide range of organic solvents like DCM, THF, 1,4-Dioxane, Diethyl Ether, Ethyl Acetate, MeOH, Toluene, Hexane etc were tried for this purpose. The reaction was a bit faster in the case of DCM but gave only racemic benzoin (Table1, entry 14). All the other solvents were able to resolute racemic benzoins with very less chiral purity (Table 1, entries15-19). When the oxidation reaction was carried out with toluene in slightly high temperature (33 ^{o}C) when compared to initial studies, the benzoin was obtained in 37% yield and 25% ee. Then we turned our studies using different tertiary amine catalysts. We investigated the reaction with two catalyst that contain tertiary amine moiety (**C-1** and **C-2** in **Fig.6**). These catalysts were prepared in our laboratory as a part of our ongoing research on pyrrolizidine alkaloids. The use of catalyst **C-1** for the oxidation reaction in presence of molecular oxygen and toluene was found to be ineffective.

Then we synthesized the catalyst **C-2** which is having a pyridine moiety attached to the bicyclic ring by aiming that the pyridine moiety attached to chiral carbon can catalyze the reaction. The catalyst was able to oxidise the benzoin but the recovered benzoin was racemic. Then our aim was to find out whether there is any involvement of hydrogen bonding between the hydroxyl group of cinchona based tertiary amine catalyst and benzoin. For that purpose we synthesized *O*-benzylated quinidine and quinine which are more bulky and have no hydrogen for hydrogen bonding. When we used *O*–benzylated quinine (**C-3**) as a catalyst for the resolution reaction in presence of oxygen and toluene as a solvent the reaction took 56 hrs for more than 50% conversion and gave 55 % of benzil. In this case the recovered benzoin was racemic. Then we attempted the reaction with *O*-benzylated quinidine as a catalyst. In that case the product was recovered with 5% ee. Then we synthesized the amine catalyst

epiquinine (**C-5**) and performed the reaction under the above mentioned conditions with 5mol % of the catalyst. The reaction was very slow and took more than two days to show more than 50% conversion on TLC. After HPLC analysis it was found that the recovered benzoin has only 9% *ee*.

The reaction was also tried with a few chiral thiourea catalysts, which is well known for its ability to act as a bifunctional catalyst. When we performed the oxidative kinetic resolution reactions with thiourea catalyst **C-6** benzoin was recovered only in 7% ee. Then we attempted the oxidative kinetic resolution reaction with a peptide **L-1** and 5 mol% of DBU as a base. The reaction was very fast which showed more than 80% conversion in 2.5 hrs provided 85 % benzil and 15 % benzoin was recovered with an ee of 26%. The result was not satisfactory due to the less *ee* even after more than 80% conversion.

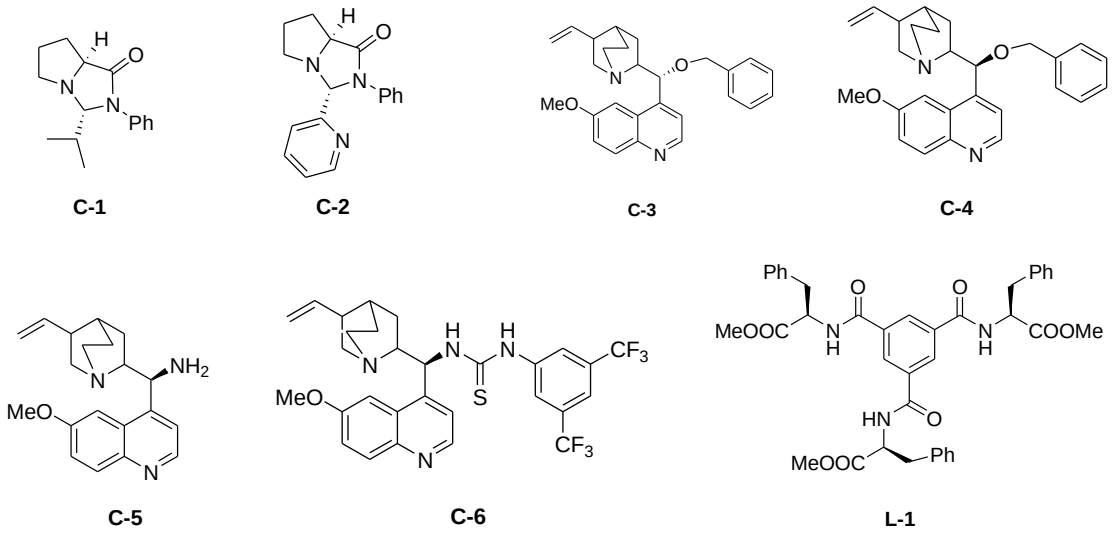


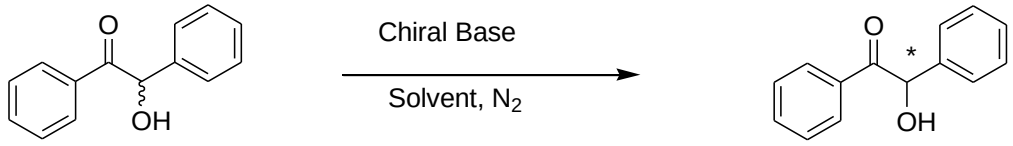
Fig.6 Different catalysts synthesized and screened

Enantioselective Protonation

The enantioselective protonation reaction of racemic benzoin was performed under N_2 atmosphere using commercially available cinchona alkaloids as chiral teritiary amine base. Optimization studies were performed using **1** as substrate and quinidine as catalyst. We were unable to get enantiomerically pure benzoins in all the cases (Table 2, entries 1-4). The

reaction was also tried using cinchonidine and quinine, but they failed to give the expected enantiomerically pure benzoin.

Table 2. Optimization Studies [a] of Enantioselective Protonation



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Sl.No	Benzoin	Base	Mol%	Solvent	*ee* [b]
1	1	Quinidine	5	THF	Racemic
2	1	Quinidine	5	DCM	Racemic
3	1	Quinidine	5	Toluene	Racemic
4	1	Quinidine	5	Ether	Racemic
5	1	Quinine	5	Toluene	Racemic
6	1	Cinchonidine	5	Toluene	Racemic

[a] Conditions: 5 mol% of base in 1ml solvent under N_2 atmosphere at room temperature (25 ^oC),

[b] The % ee was determined by HPLC using Daicel Chiral-PAK IA column

2.1 Conclusion

In conclusion, we have attempted an organocatalytic approach for the oxidative kinetic resolution of racemic benzoins using a few chiral tertiary amines as catalysts under aerobic conditions. By using quinidine as a catalyst, the unreacted *S*-benzoin was recovered with 30% ee, which is the maximum ee at this point of time. Further studies employing other chiral non-racemic tertiary amines will be investigated in near future.

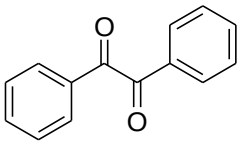
CHAPTER 3

Experimental Section

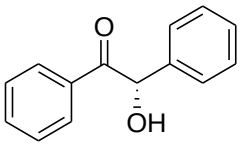
3.1 General Methods: All the reactions for catalyst preparation were performed under inert atmosphere. All the kinetic resolution reactions were performed under O_2 atmosphere using O_2 balloon. All the reagents used were purchased from the commercially available sources and used as such. ^{1}H, ^{13}C spectra were analyzed in deuteriated solvents using 400MHz and 100 MHz Bruker FT-NMR Spectrometers. Chemical Shift values are reported in parts per million keeping TMS as background reference. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Enantiomer ratios were determined by chiral HPLC analysis using a Waters 600 and Waters 996 Photodiode Array Detector with a Chiralpak IA column (0.46 cm × 25 cm) with a particle size of 5μm. The absolute stereochemistry of the recovered benzoin was confirmed by comparing with reported HPLC chromatogram.

3.2 Typical procedure for oxidative kinetic resolution reaction

Chiral tertiary amine catalyst (10-50 mol%) was added to a solution of racemic benzoin (0.1 mmol) in solvent (1 mL) at room temperature and the resulting solution was stirred under oxygen atmosphere until approximately 50% starting material was consumed (by TLC). The reaction mixture was directly loaded on a silica gel column (100-200 mesh) and eluted using 10-20% ethyl acetate in hexane mixture to get benzil and unreacted benzoin. The purified unreacted benzoin was subjected to HPLC analysis.



Benzil Yield: 67%, R_f 0.48; (hexane : ethyl acetate, 90:10 v/v): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.98 (m, 4H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 194.7, 135.0, 133.0, 130.0, 129.1; IR (KBr) 3064.87, 1659.06, 1593.97 $cm^{-1.}$



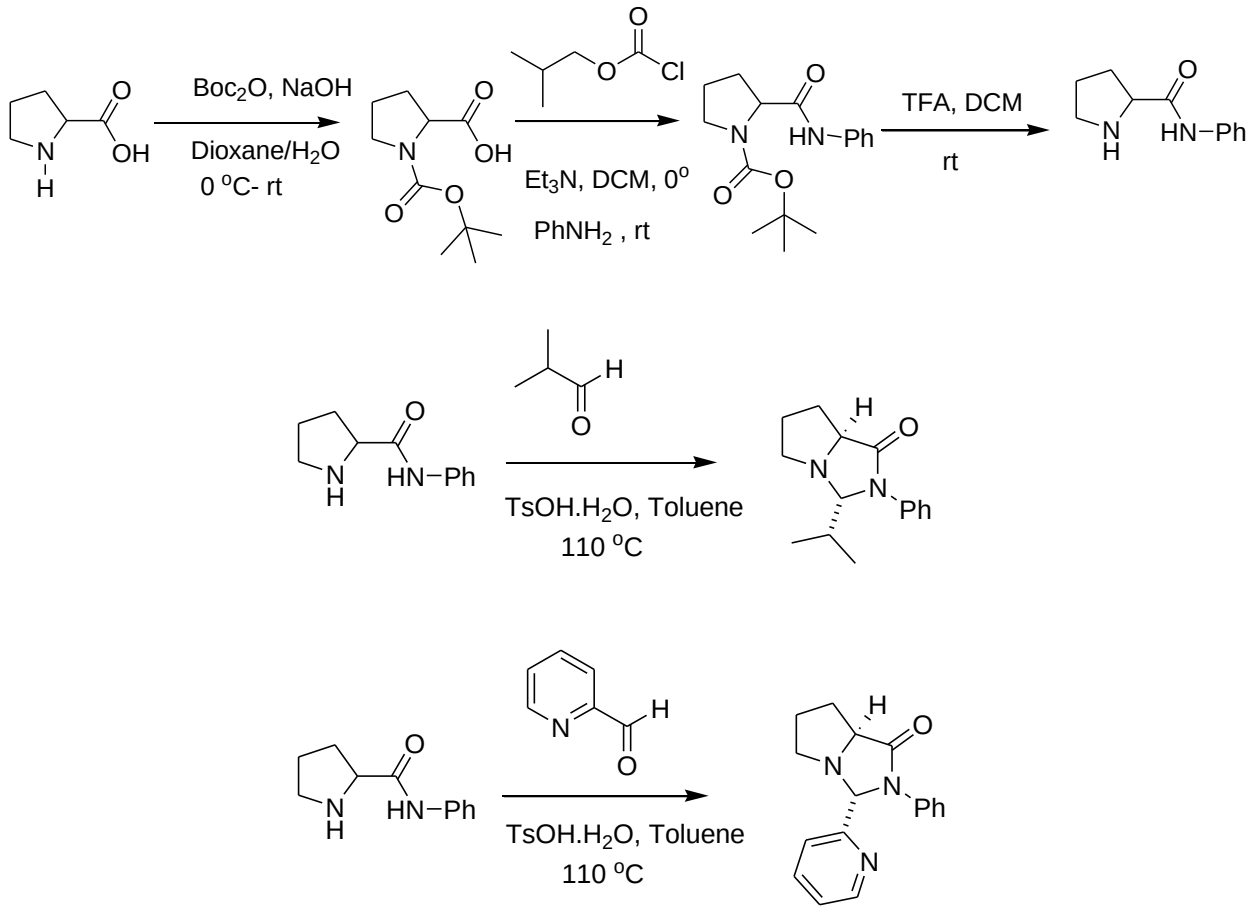
***S*-Benzoin** Yield: 32%, R_f 0.26 (hexane : ethyl acetate, 90:10 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.92 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.31-7.34 (m, 4H), 7.27-7.30 (m, 1H), 5.96 (d, *J* = 6.0 Hz, 1H), 4.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 199.0,134.0, 129.29, 128.8, 128.7, 127.9, 76.3; IR (KBr) 3418, 1679, 1261, 1068.

3.3 Typical procedure for enantioselective protonation

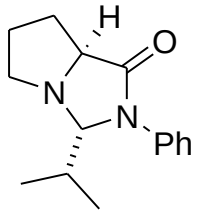
Chiral tertiary amine catalyst (5 mol%) was added to a solution of racemic benzoin (0.1 mmol) in solvent (1 mL) at room temperature under oxygen atmosphere. Stirred the reaction mixture under nitrogen atmosphere and monitored the reaction for 12 h. After 12 h filtered the reaction mixture through a short pad of silica. The purified benzoin was subjected to HPLC analysis.

3.4 General procedure for the synthesis of C-1 and C-2

The aminals are synthesized using the reported procedure.[27]

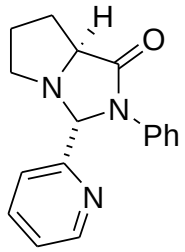


To a solution of amide in CH_2Cl_2 at rt was added TFA. The solution was stirred at rt for 1.5 h, and after the completion of reaction the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until became pH ~9. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford desired amino amide.



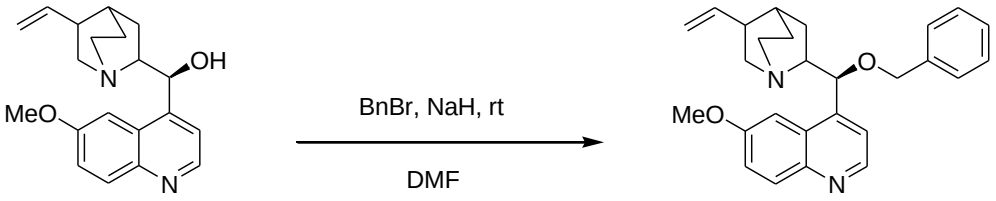
Yield: 86%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.7 Hz,2H), 7.19 (t, *J* = 7.1 Hz, 1H), 4.63 (s, 1H), 3.95 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.31-

3.26(m, 1H), 2.77 (q, *J* = 7.8 Hz, 1H), 2.23-2.15 (m, 1H), 2.06-1.97 (m, 1H), 1.90-1.86(m, 1H), 1.84-1.78 (comp m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 174.0,136.8, 129.1, 125.7, 123.4, 87.9, 66.4, 58.5, 31.3, 28.9,25.1, 18.4, 14.6.

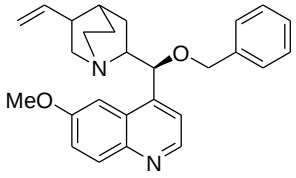


Yield: 82%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63-8.61(m, 1H), 7.65(td, *J* = 7.68, 1.68, 1H), 7.50(d, *J* = 7.60, 2H), 7.29(d, *J* = 7.60, 2H), 7.21(d, *J* = 7.68, 2H), 7.09(t, *J* =7.40, 1H), 5.78(s, 1H), 4.14(t, *J* = 6.8, 1H), 3.52-3.47(m, 1H), 3.02-2.93(m, 1H), 2.25-2.20(m, 2H), 1.94-1.87(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 158.3, 150.3, 137.6, 137.4, 129.1, 125.2, 123.6, 120.9, 120.1, 84.72, 64.8, 56.6, 27.8, 24.9.

3.5 General procedure for Synthesis of O-benzylated cinchona Alkaloid.



To the solution of corresponding Cinchona alkaloid (1 equiv) in dry DMF (8 mL) NaH was added (2.5 equiv) portion wise at 0 ^{o}C over a period of 1h. The resulting mixture was stirred at room temperature for 2h. Then BnBr (1.1 equiv) was added dropwise in 10 minutes. The resulting mixture was stirred overnight. When the reaction was completed, brine (20 mL) was added and the resulting mixture was extracted with EtOAc (50 mL). The organic phase was washed with brine (3 x 50 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by column chromatography (MeOH/EtOAc: 1/40) to give desired 9-*O*-Benzyl Ether.

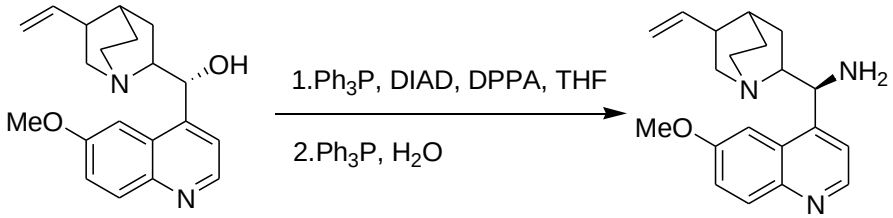


QD-Bn

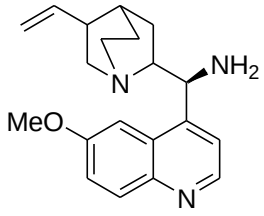
Quinidne–*O*-benzyl ether, Yield: 79%, ^{1}H NMR (400 MHz) δ 8.76 (d, *J* = 5.2 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 4.2 Hz, 1H), 7.40-7.26 (m, 7H), 6.00-5.90 (m, 1H), 5.30 (br, 1H), 5.00 (s, 1H), 4.97 (d, *J* = 5.56, 1H), 4.50-4.43 (m, 2H), 3.93 (s, 3H), 3.26(m, 1H), 3.1-2.72 (m, 5H), 2.36-2.13 (m, 3H), 1.75 (br, 1H), 1.51-1.44 (m, 2H), 1.29-1.24 (m, 1H).

3.6 General procedure for synthesis of 9-amino (9-deoxy) epiquinine.

Synthesis was carried out with slight modifications from the reported procedure.[28]



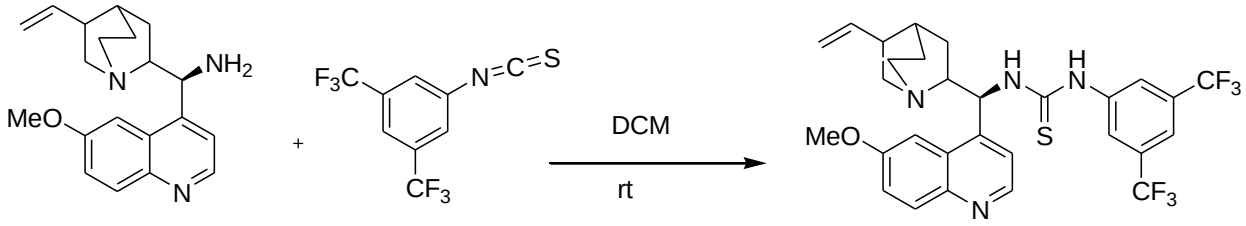
Quinine (1.00 g, 1equiv) and triphenylphosphine (1.21 g, 1.5 equiv) were dissolved in 17 mL of dry THF and the solution was cooled to 0 ^{o}C. Diisopropyl azodicarboxylate (0.91 mL, 1.5 equiv) was added all at once followed by the dropwise addition of a solution of diphenyl phosphoryl azide (1.0 mL, 1.5 equiv) in 8 mL of dry THF at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred overnight. After that the resulting solution was heated to 50 ^{o}C for 2 h. Then triphenylphosphine (2.02 g, 2.5 equiv) was added and heating was maintained until the gas evolution has ceased (2h). The solution was cooled to room temperature, and 1 mL of water was added and stirred for 3h. Solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and 10% hydrochloric acid (1:1,100 mL). The aqueous phase was washed with CH_2Cl_2 (4 × 50 mL) and made alkaline with excess aqueous ammonia and was washed with CH_2Cl_2 (4 × 50 mL). The combined organic phases was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/MeOH/cc. aq. NH_4OH = 50/50/1 as eluant) affording the desired amine compound.



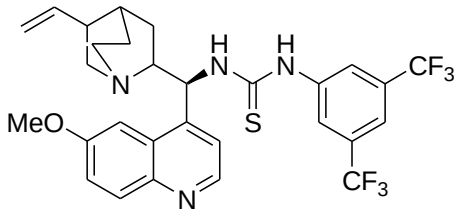
9-amino (9-deoxy) epiquinine**,** Yield; 58%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 3.7 Hz; 1H), 8.32 (br s; 1H), 8.11 (d, *J* = 8.4 Hz; 1H), 7.69 (t, *J* = 7.5 Hz; 1H), 7.57 (t, *J* = 7.5Hz; 1H), 5.81-5.72 (m, 1H), 5.00-5.93 (m, 2H), 4.70 (d, *J* = 6.6 Hz; 1H), 3.78 (br; 2H), 3.28-2.78 (m; 5H), 2.26 (br; 1H), 1.99-1.91 (m; 1H), 1.59-1.53 (m; 3H), 1.42-1.37 (m; 1H).

3.7 Synthesis of thiourea catalyst.

The desired thiourea has been prepared using the reported procedure.[29]



To a solution of 9-amino (9-deoxy) epi quinine (1equiv) in dry DCM (10 mL) was added a solution of 3, 5-bis (trifluoromethyl) phenyl isothiocyanate (1.2 equiv) in dry DCM (10 mL). After stirring the reaction overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH) to give the desired tertiary amine thiourea.



Yield: 88%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.88 (s, 2H), 7.68 (s, 1H), 7.40 (dd, *J* = 2.6, 9.2Hz, 1H), 7.29 (d, *J* = 4.4 Hz, 1H), 5.70-5.65 (m, 1H), 5.04 (d, *J* = 3.9 Hz, 1H), 4.99 (s, 1H), 3.97

(s, 3H), 3.44-3.42 (m, 2H), 3.23 (dd, *J* = 10.2, 13.5 Hz, 1H), 2.88-2.80 (m, 2H), 2.40-2.31 (m, 1H), 1.76 (br.s, 1H), 1.28-1.24 (m, 1H), 0.96 (br s, 1H).

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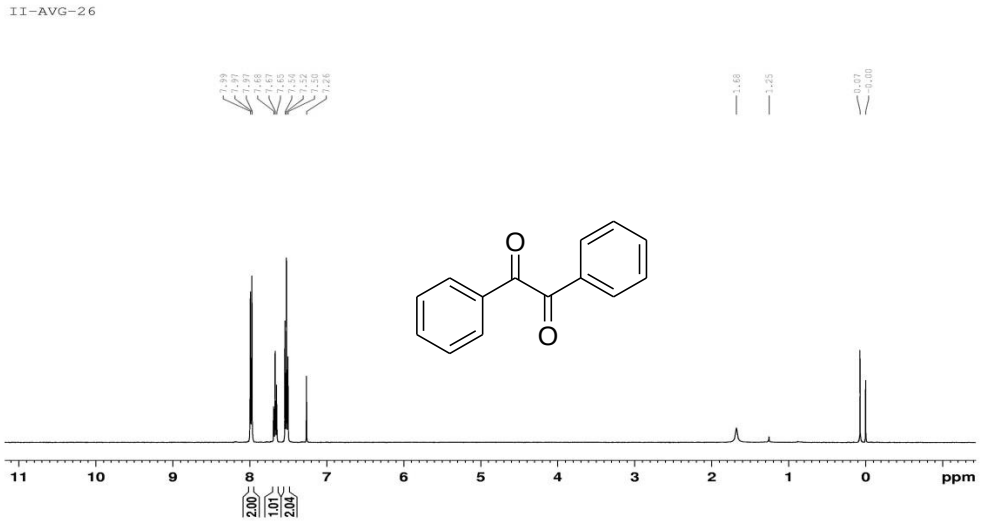
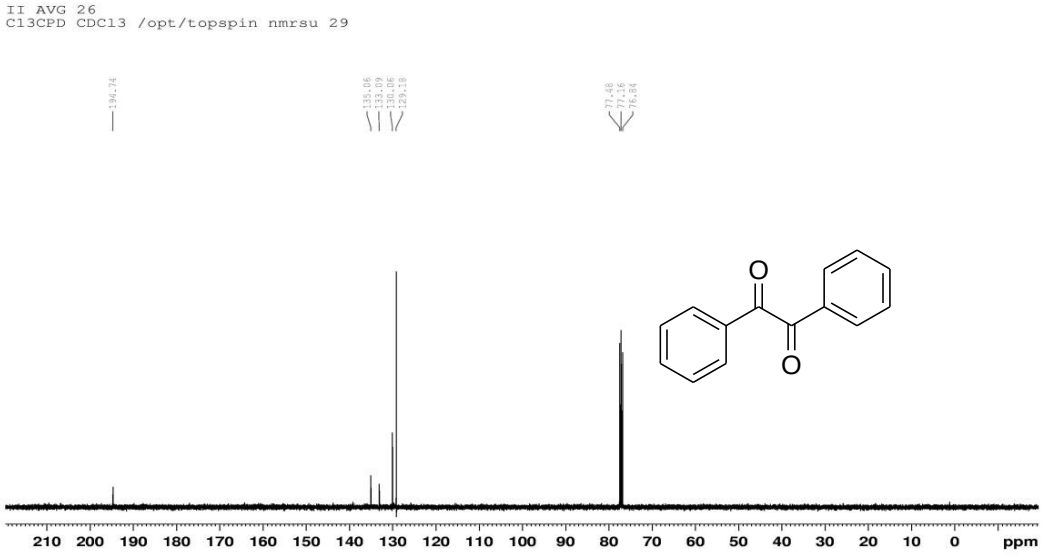
Appendix

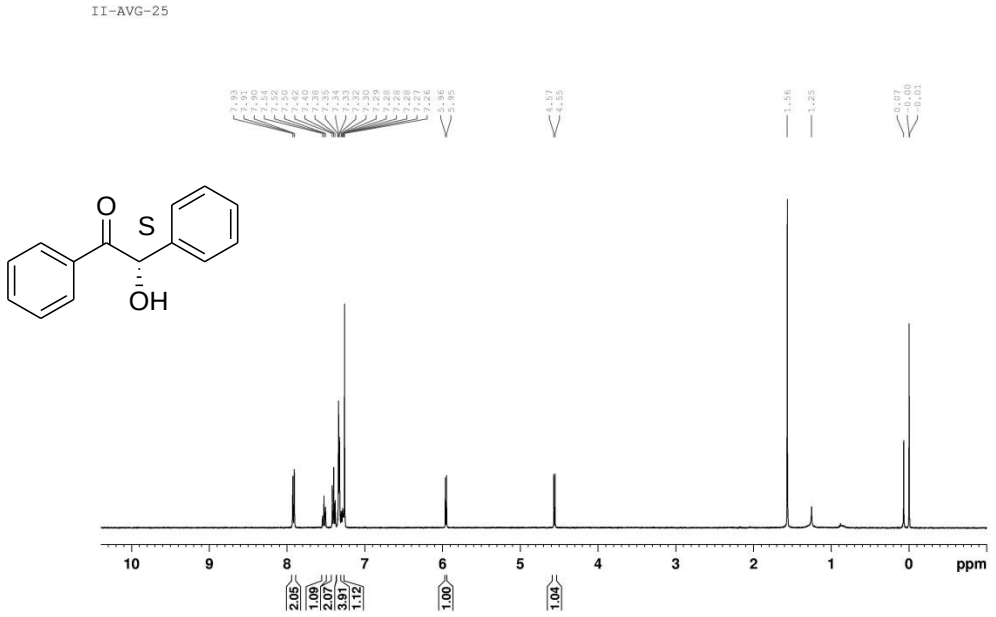
Spectral Data

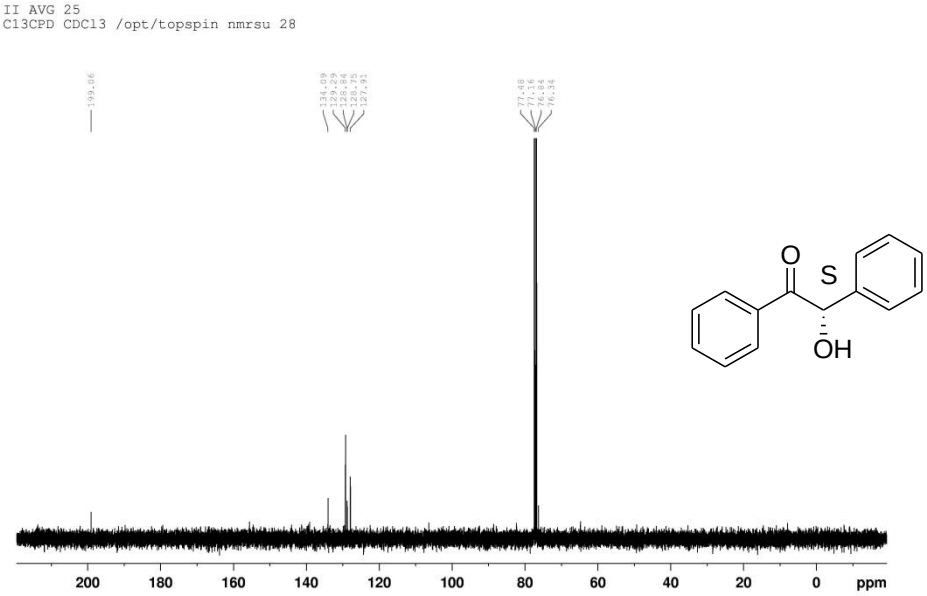
^{1}H and ^{13}C NMR spectra of Benzil



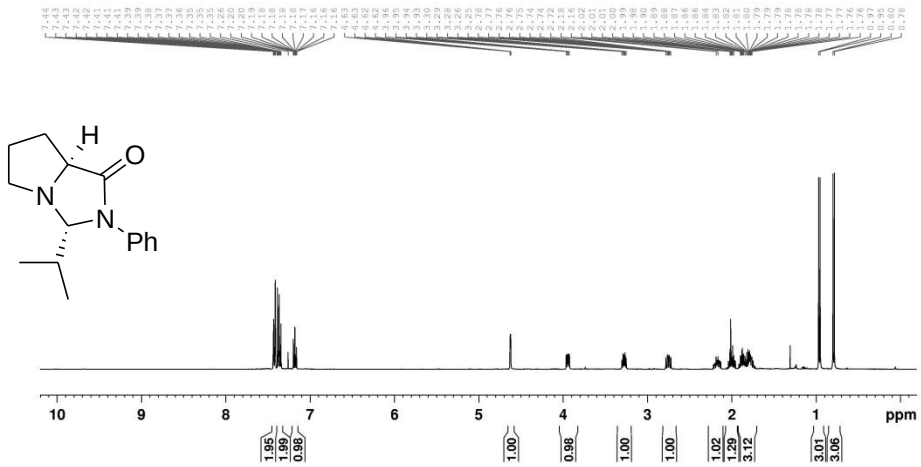


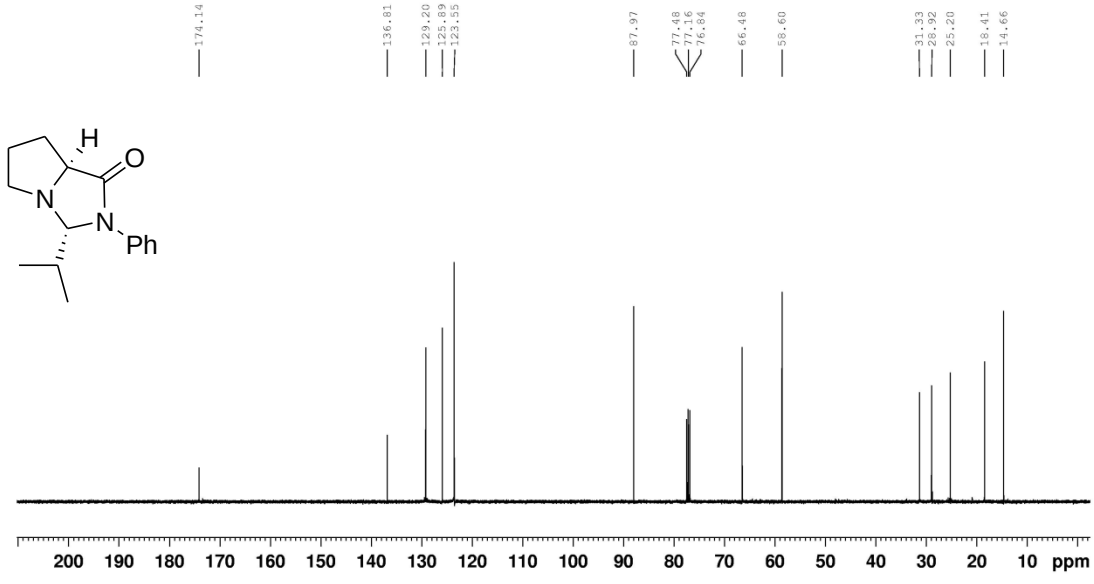
^{1}H and ^{13}C NMR Spectra of Recovered Benzoin



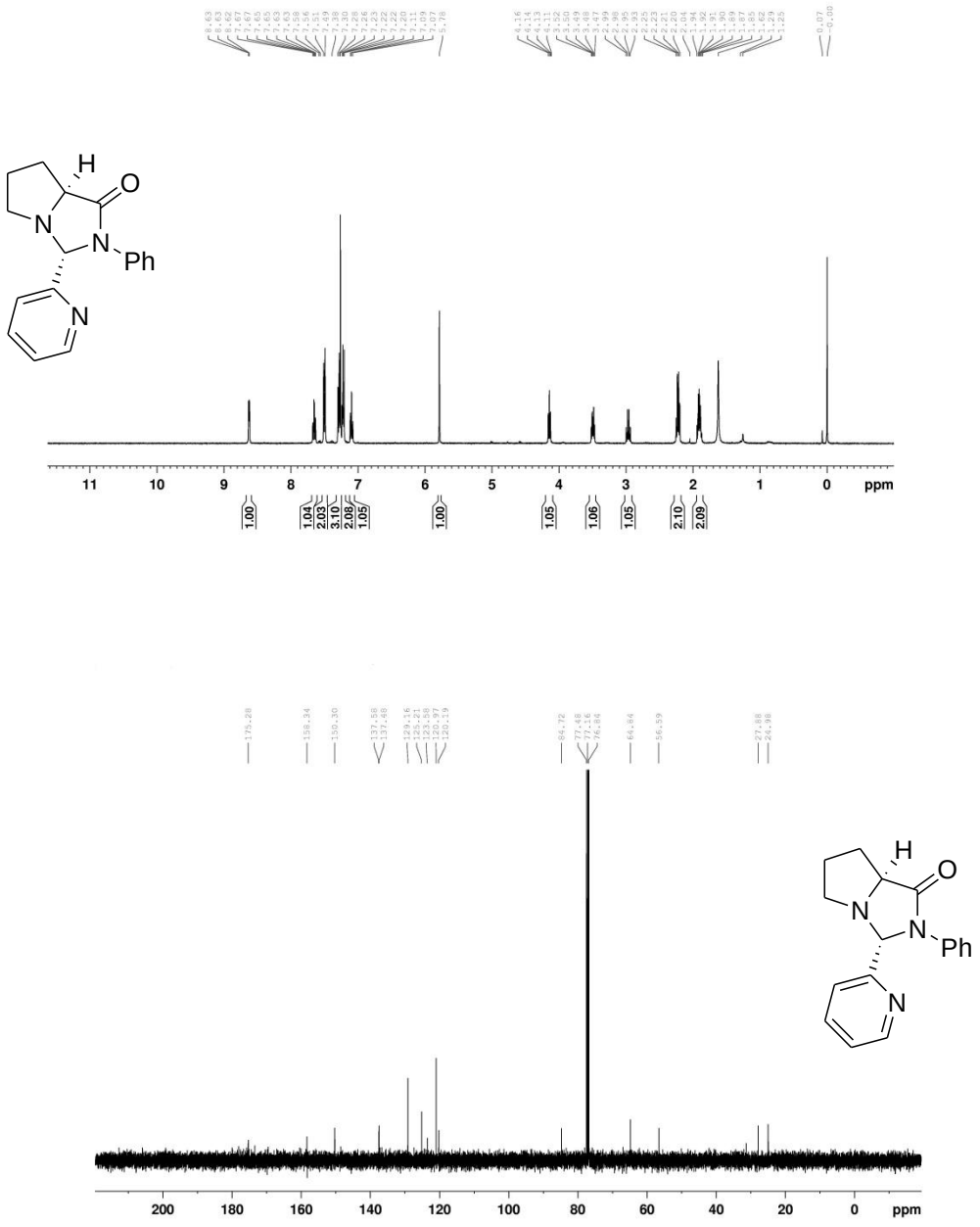


^{1}H and ^{13}C spectra of C 1

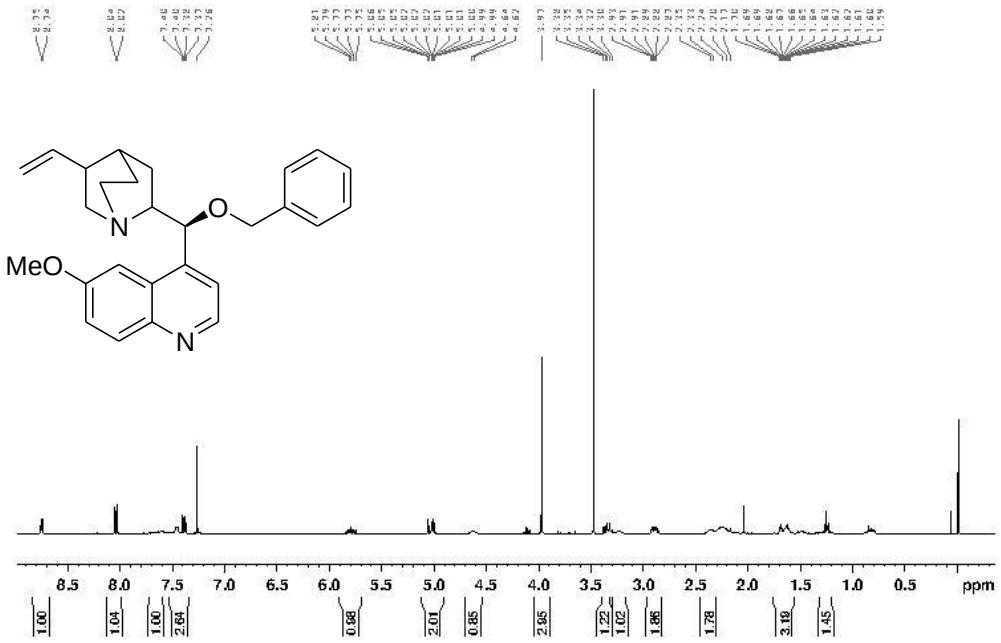




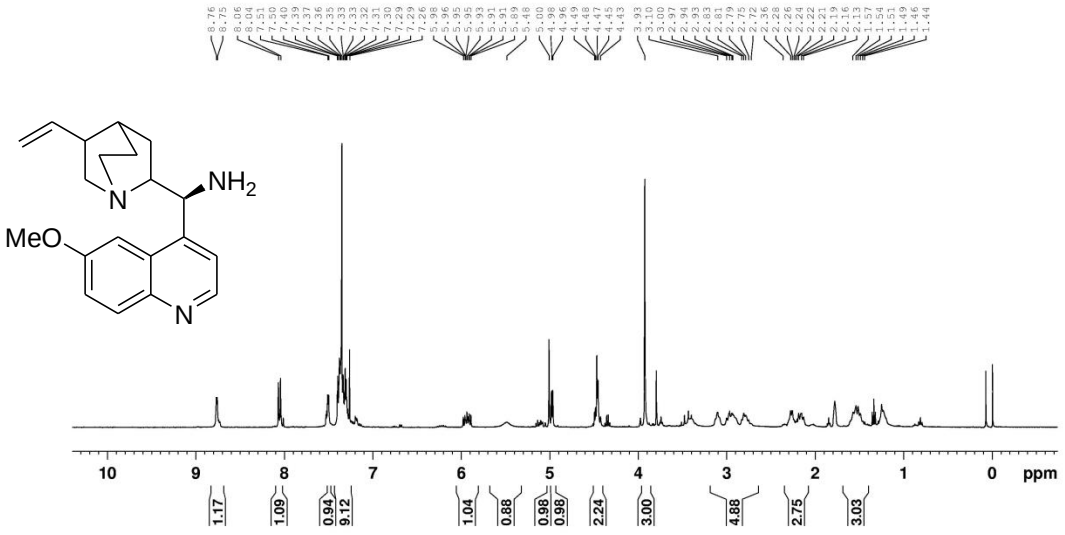
^{1}H and ^{13}C Spectra of C 2



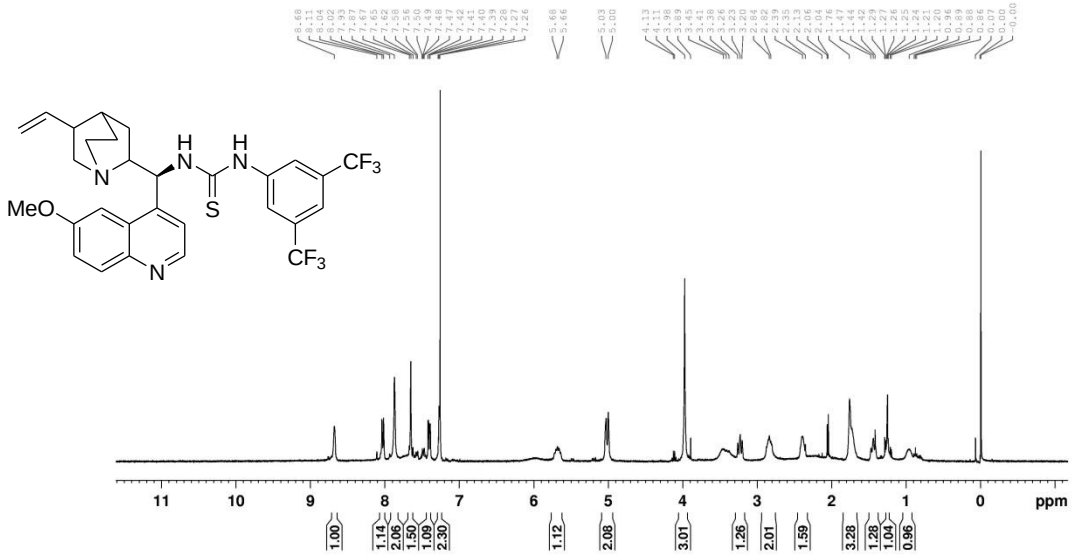
^{1}H NMR Of C 3

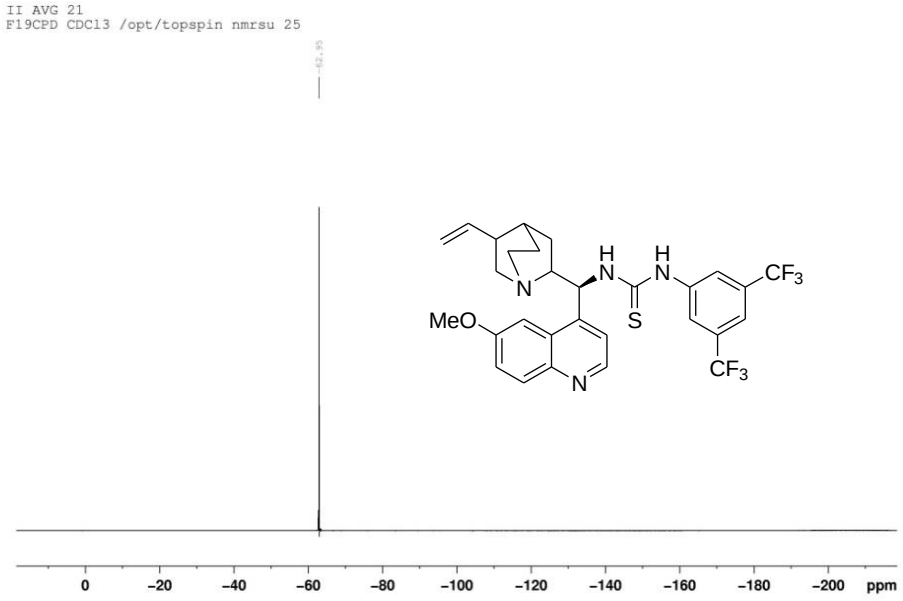


^{1}H NMR of C 5



^{1}H and ^{19}F NMR spectra of C6

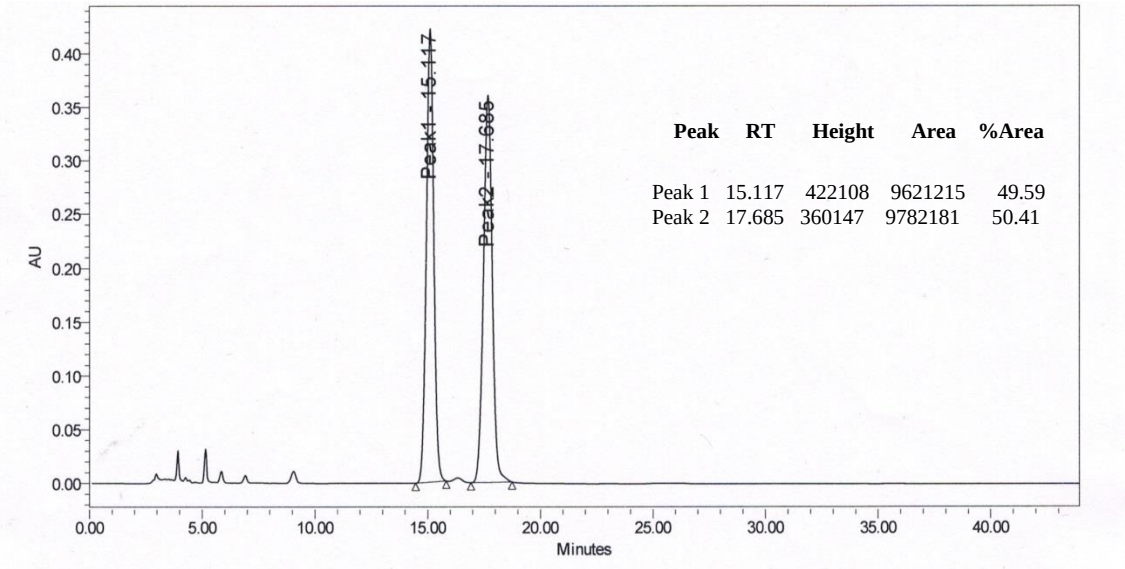




HPLC Data

Sample : Racemic Benzoin Column used : Chiral Pak® IA (4.6mm x 250mm)
Mobile Phase : 10% Isopropanol : Hexane Flow rate : 1ml/min Wave Length :254nm

HPLC Chromatogram of Racemic Benzoin



HPLC Chromatogram for Table 1, Entry 11

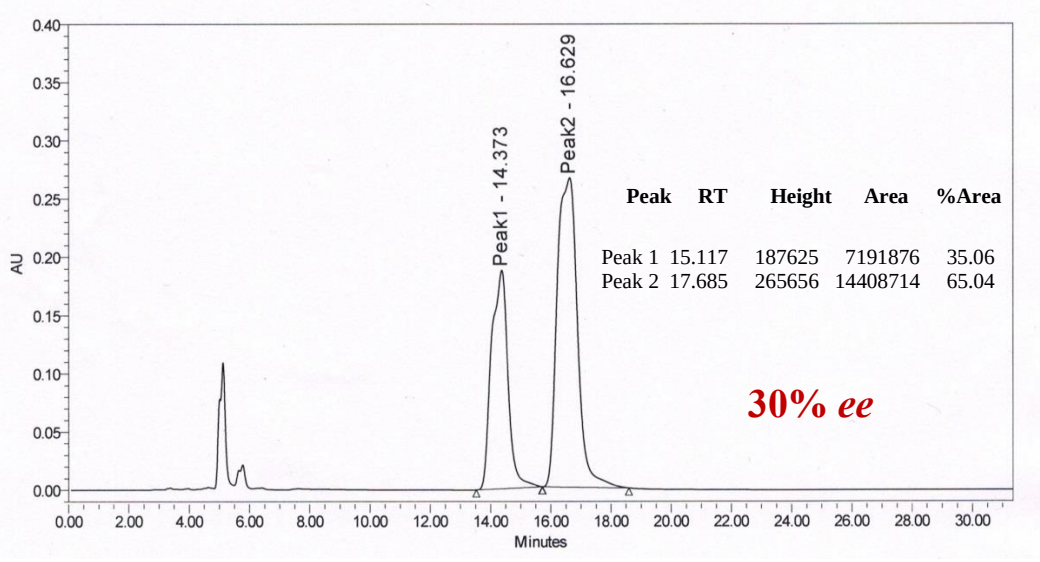
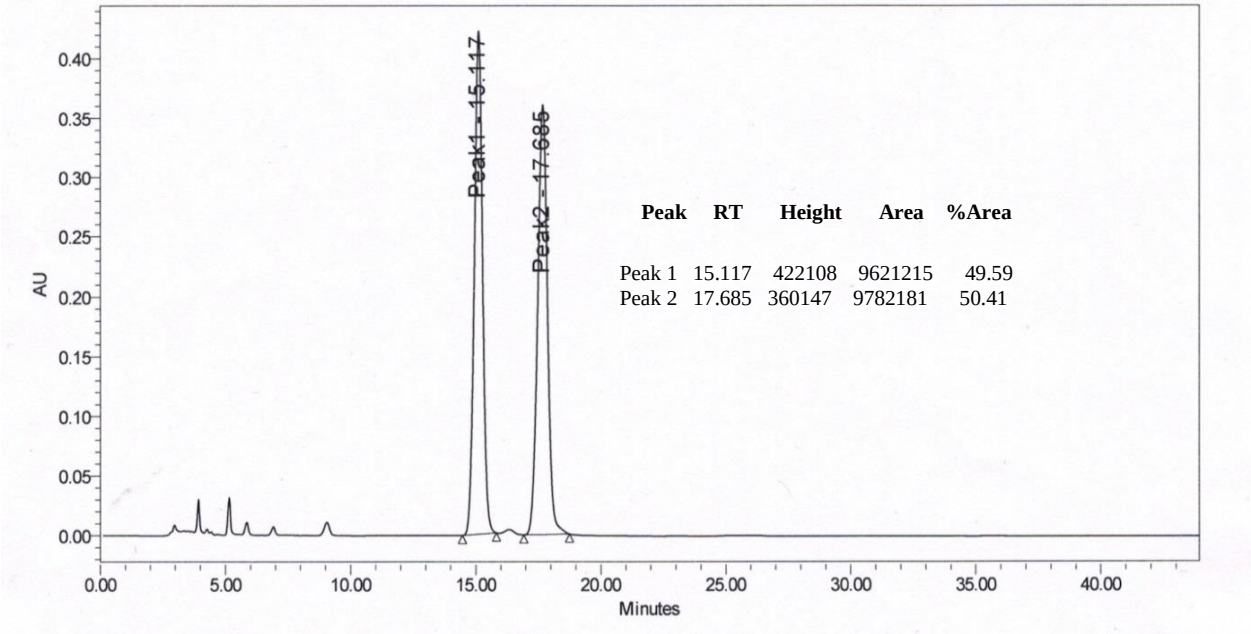


Table 1, Entry 1



Peak	RT	Height	Area	%Area
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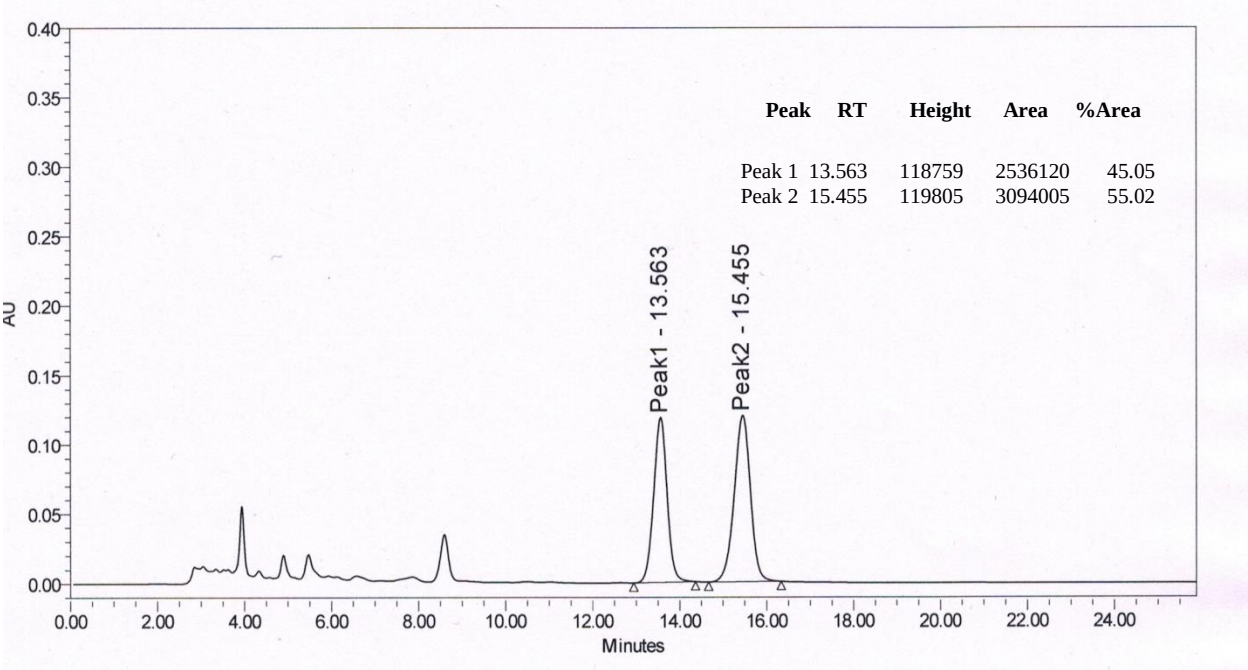
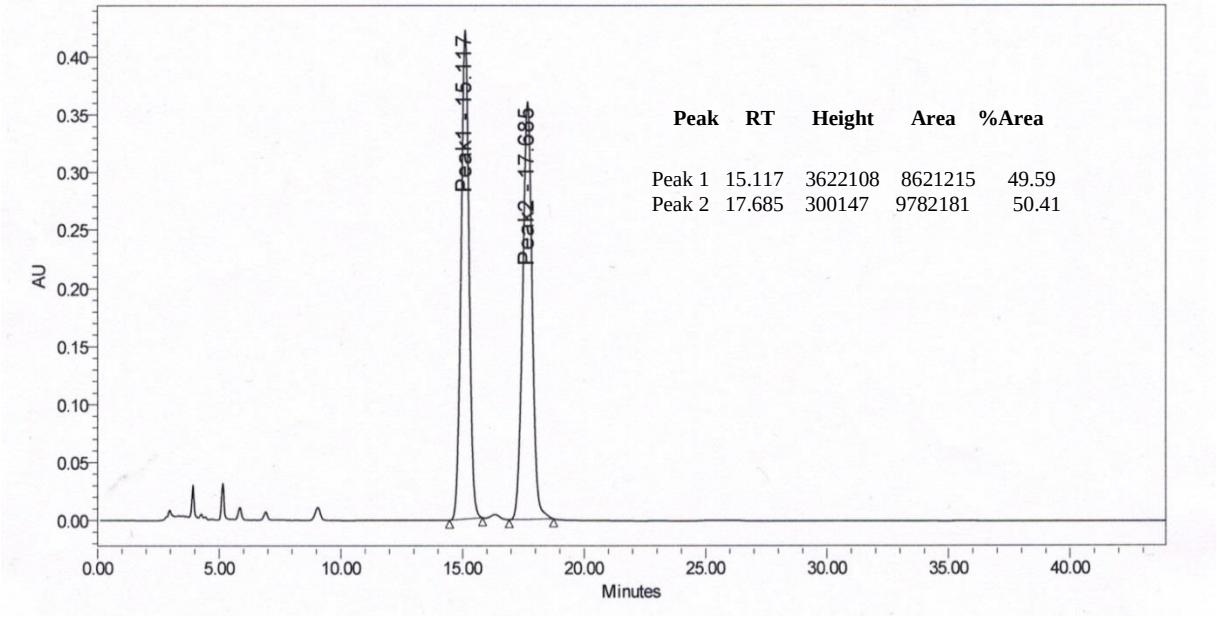
Peak 2	17.685	360147	9782181	50.41

Table 1, Entry 2



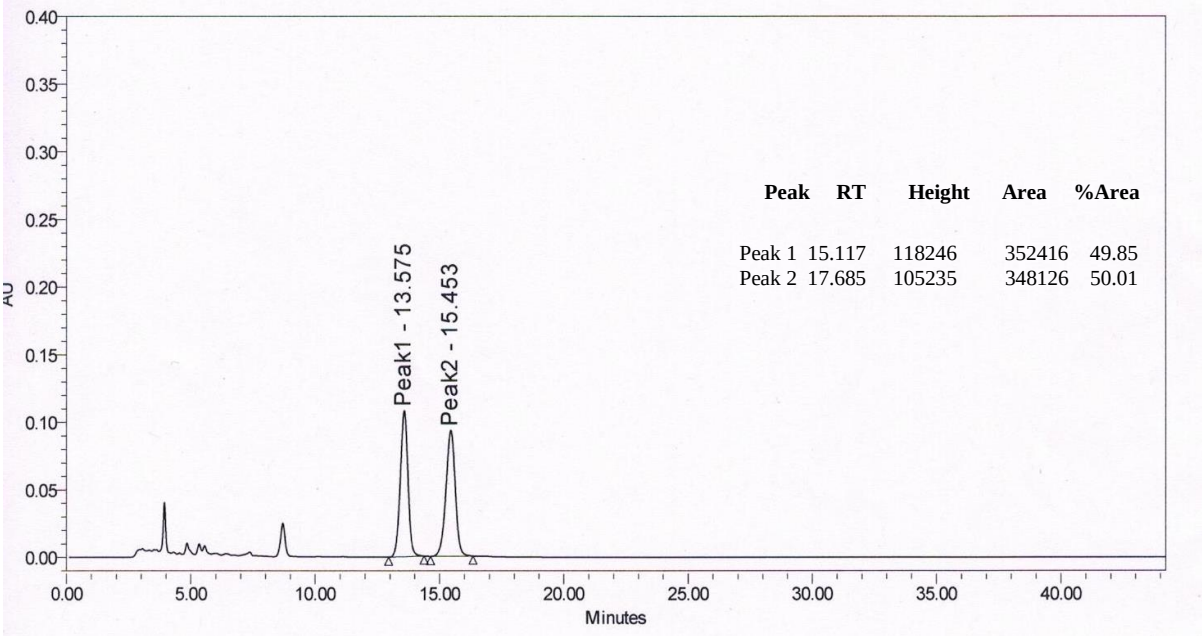
Peak	RT	Height	Area	%Area
Peak 1	13.563	118759	2536120	45.05
Peak 2	15.455	119805	3094005	55.02

Table 1, Entry 3



Peak	RT	Height	Area	%Area
Peak 1	15.117	3622108	8621215	49.59
Peak 2	17.685	300147	9782181	50.41

Table 1, Entry 4



Peak	RT	Height	Area	%Area
Peak 1	15.117	118246	352416	49.85
Peak 2	17.685	105235	348126	50.01

Table 1, Entry 5

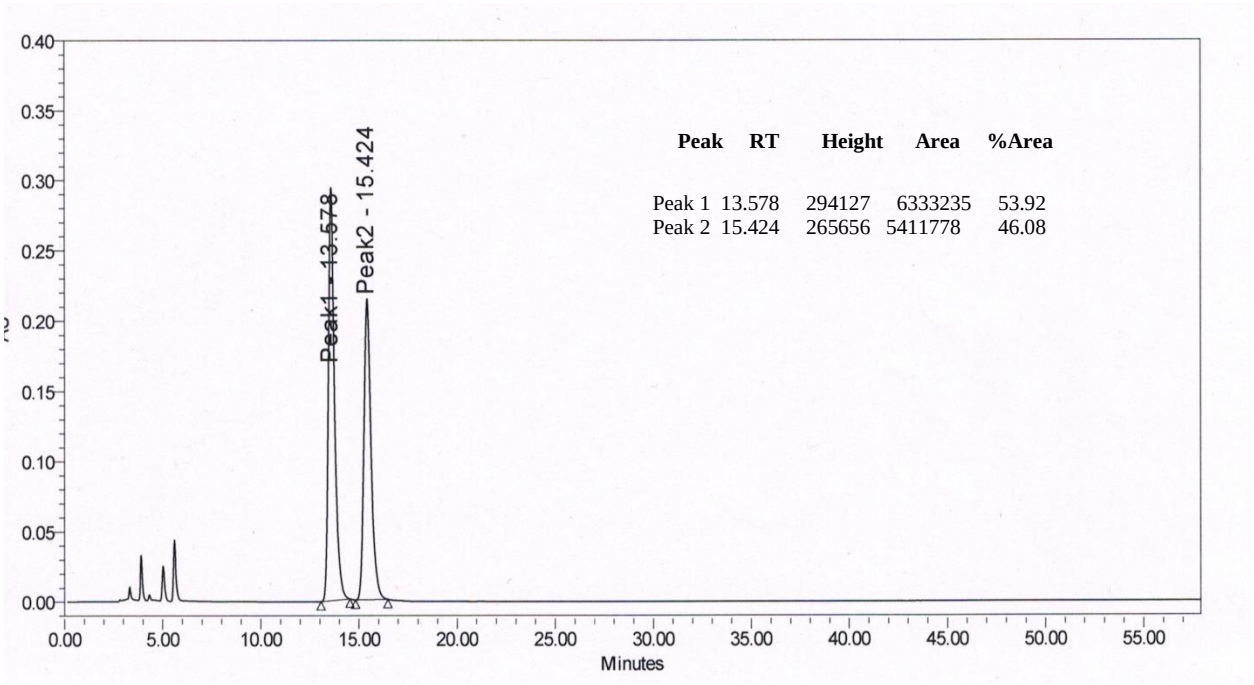


Table 1, Entry 6

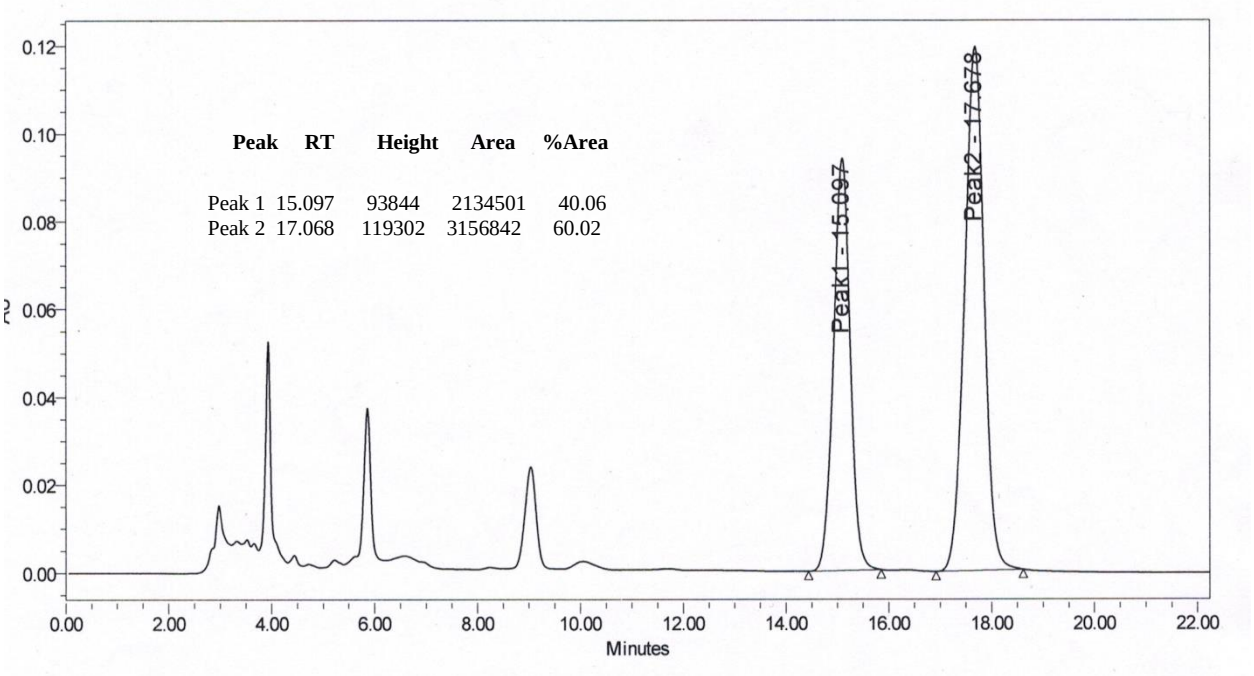


Table 1, Entry 7

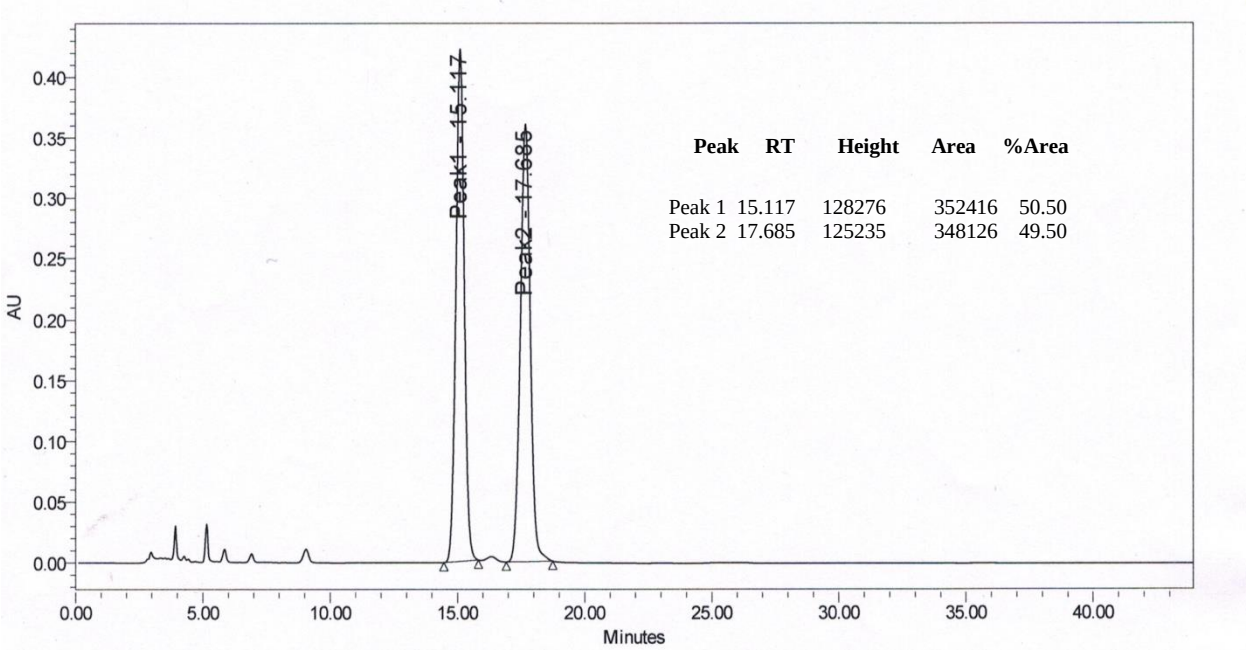


Table 1, Entry 8

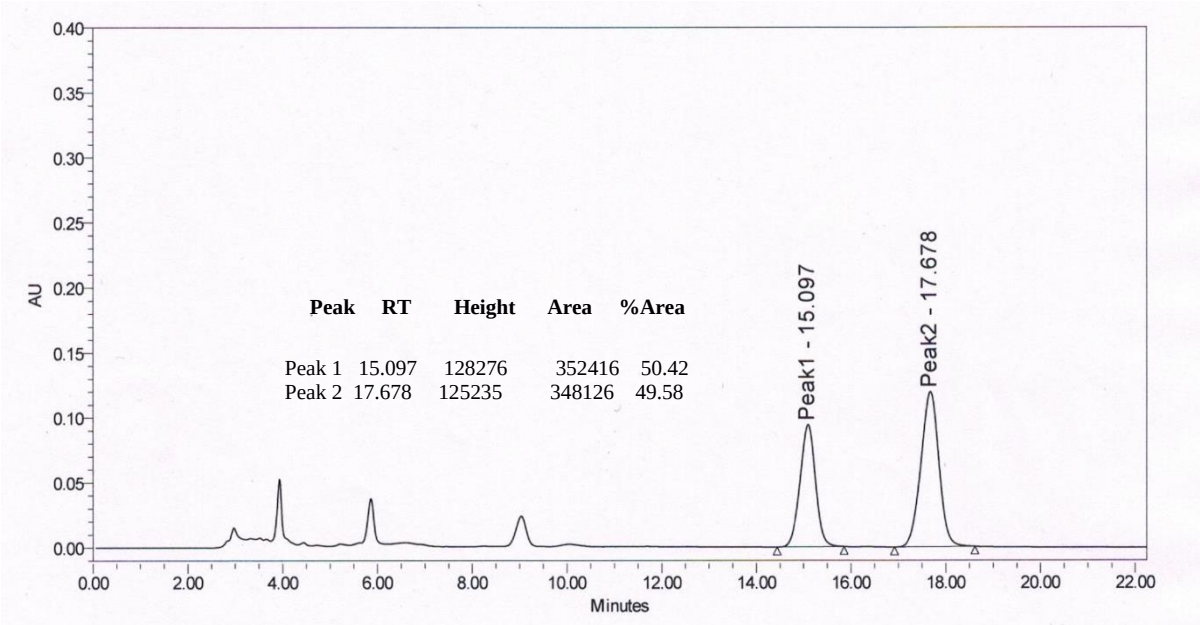


Table 1, Entry 9

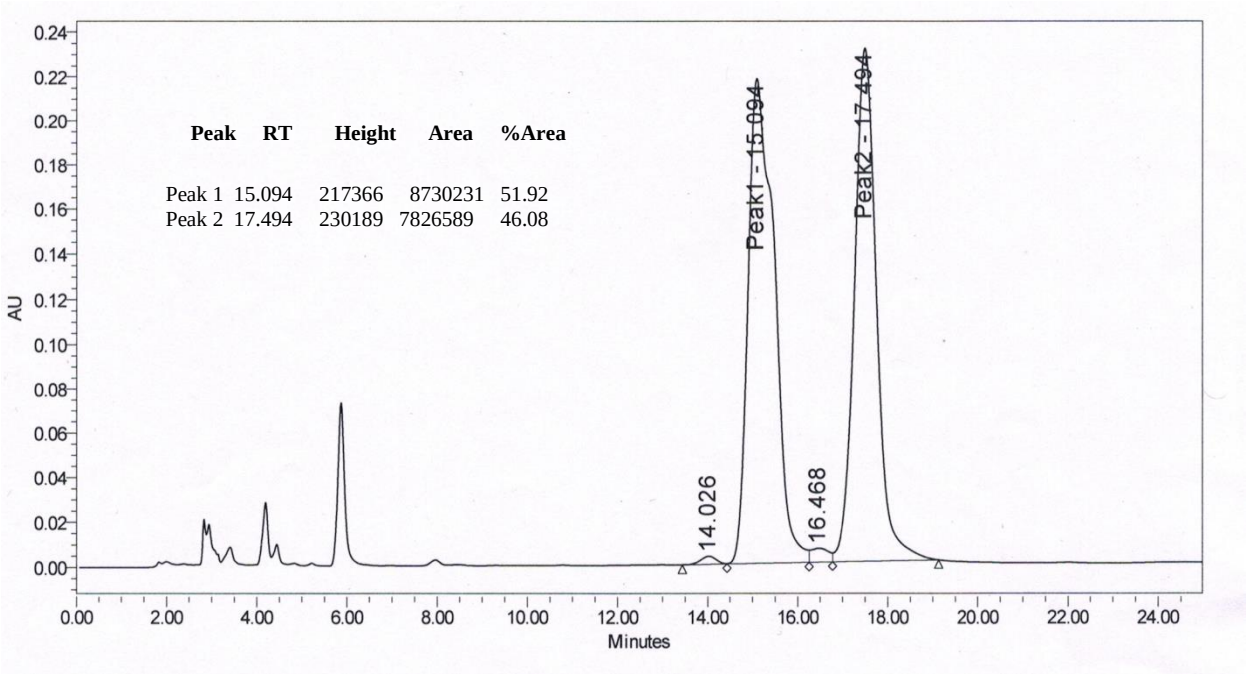


Table 1, Entry 10

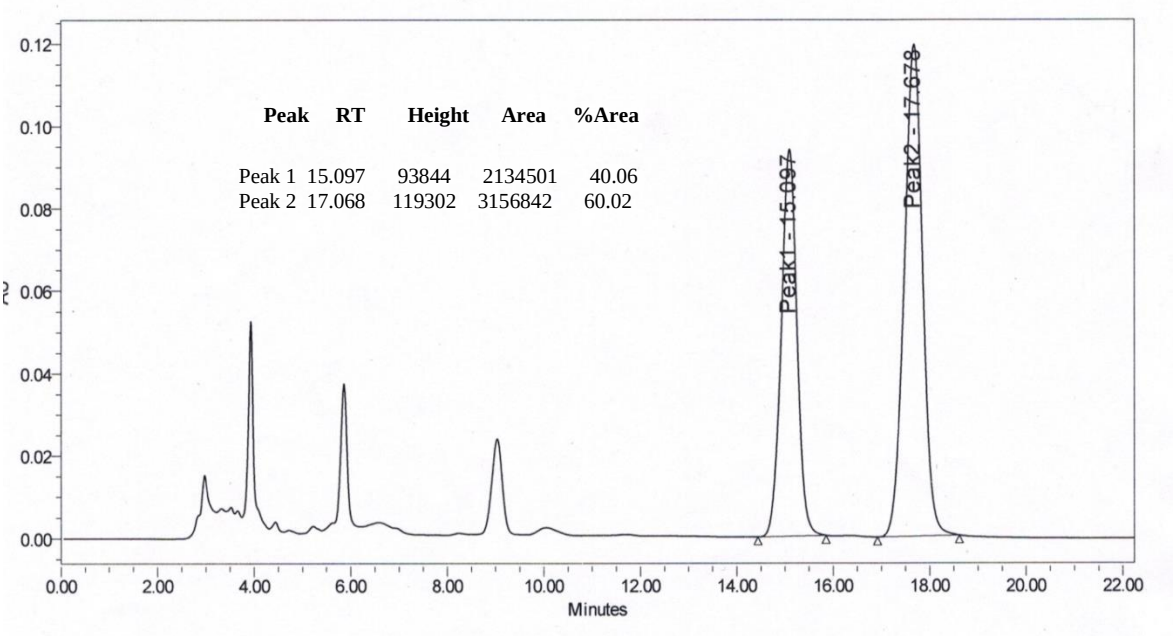


Table 1, Entry 12

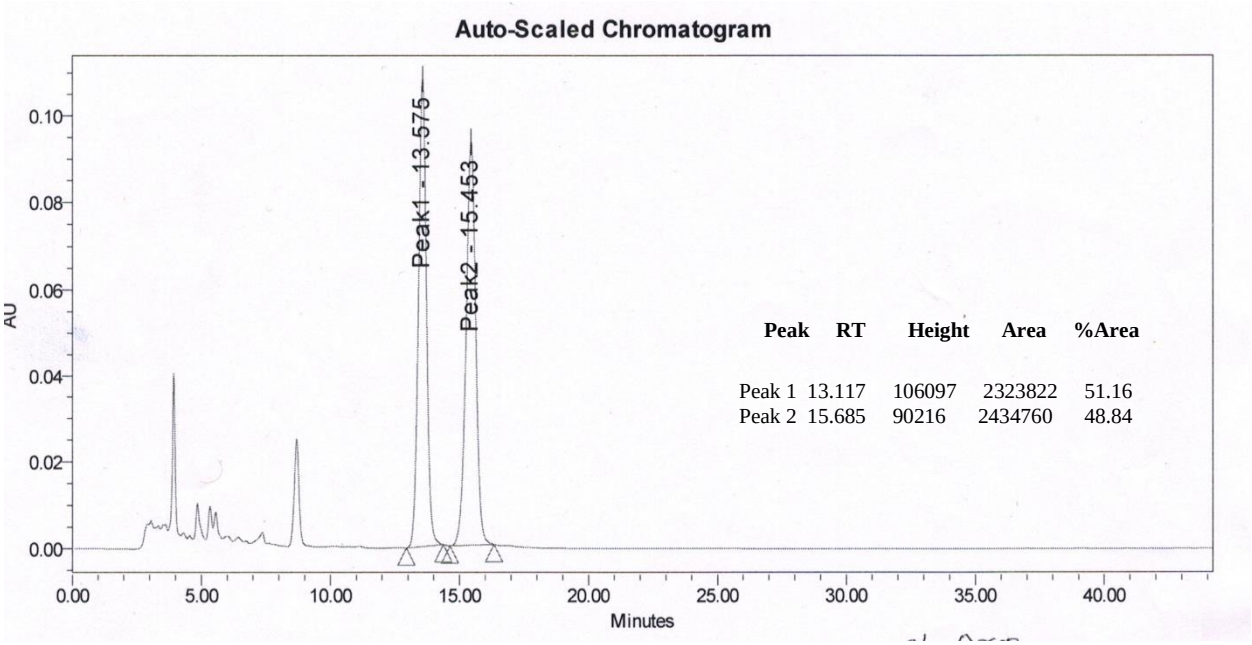


Table 1, Entry 13

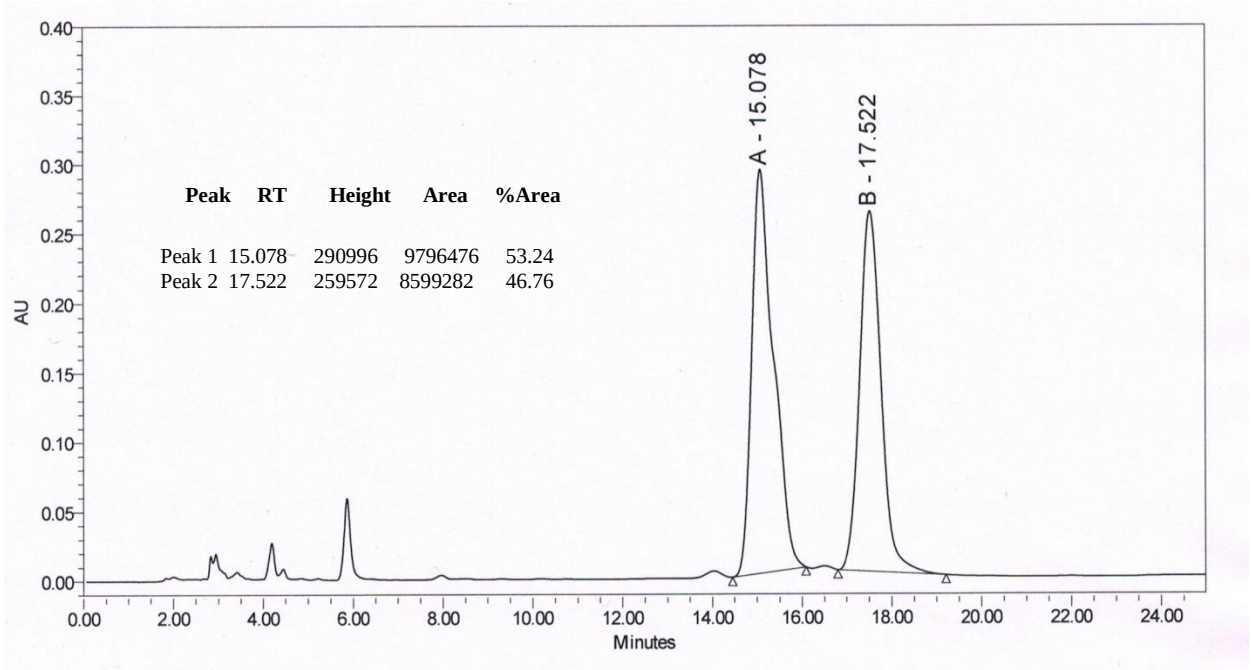


Table 1, Entry 14

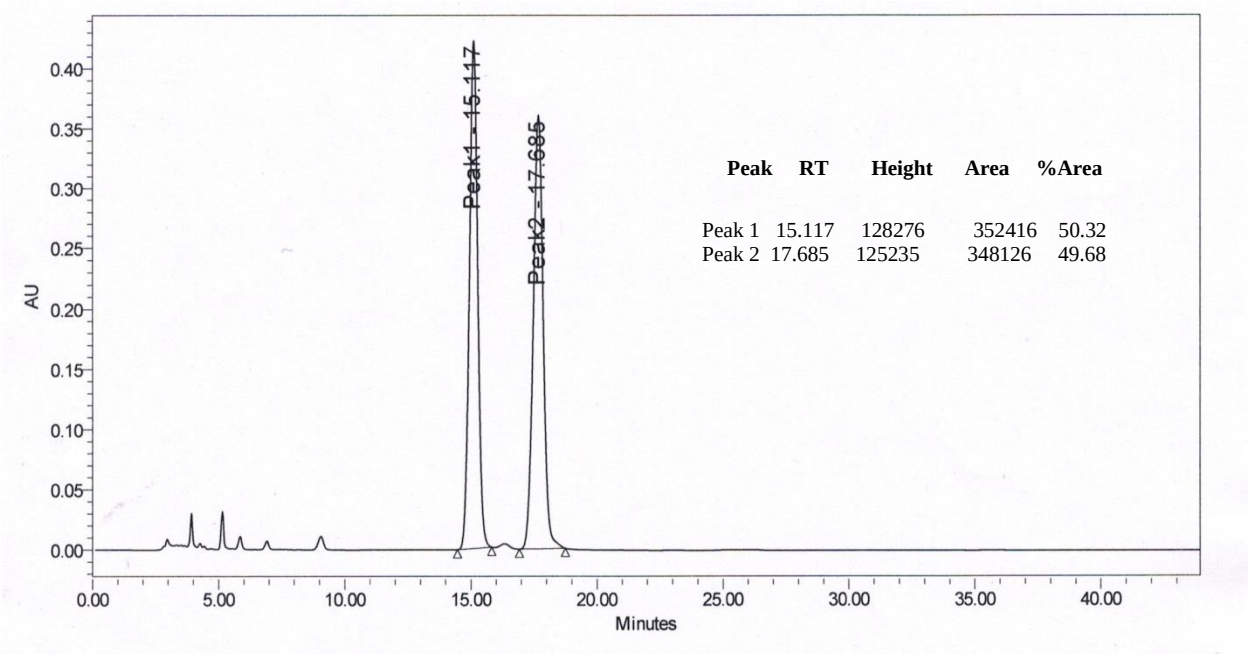


Table 1, Entry 15

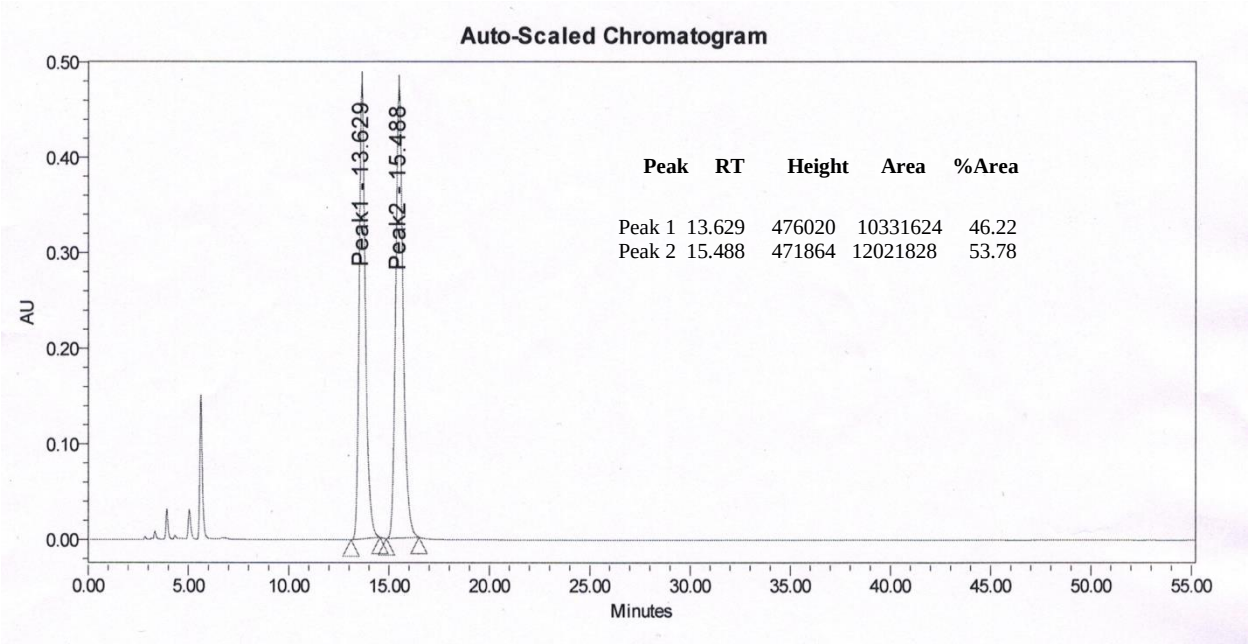


Table 1, Entry 16

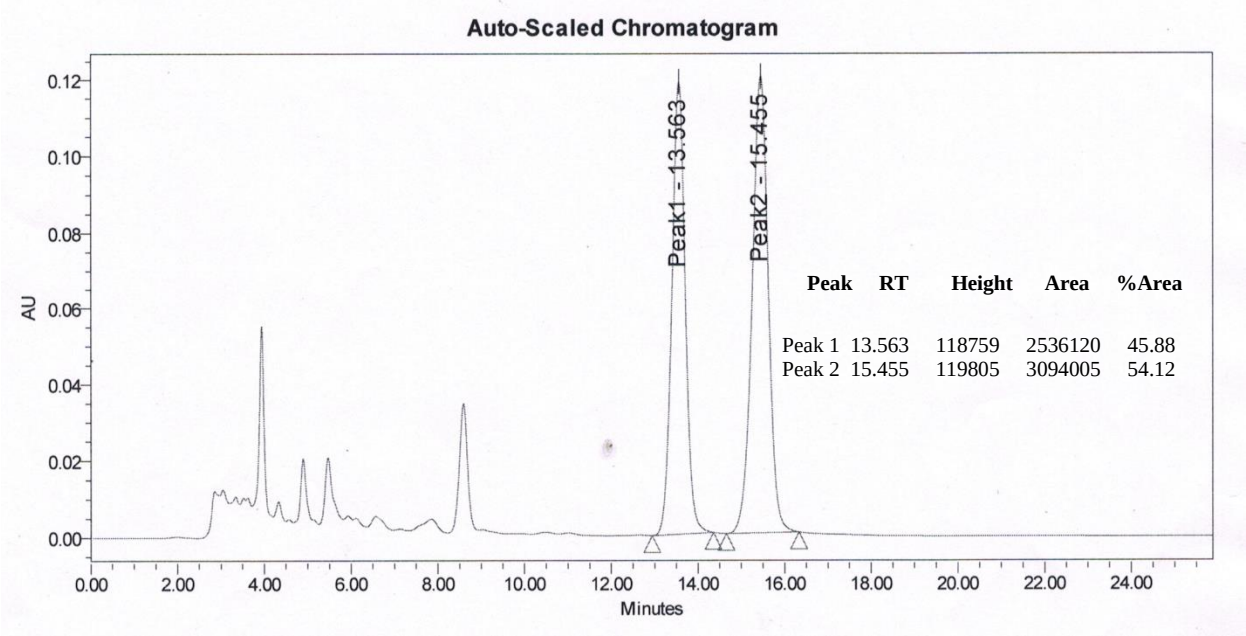


Table 1, Entry 17

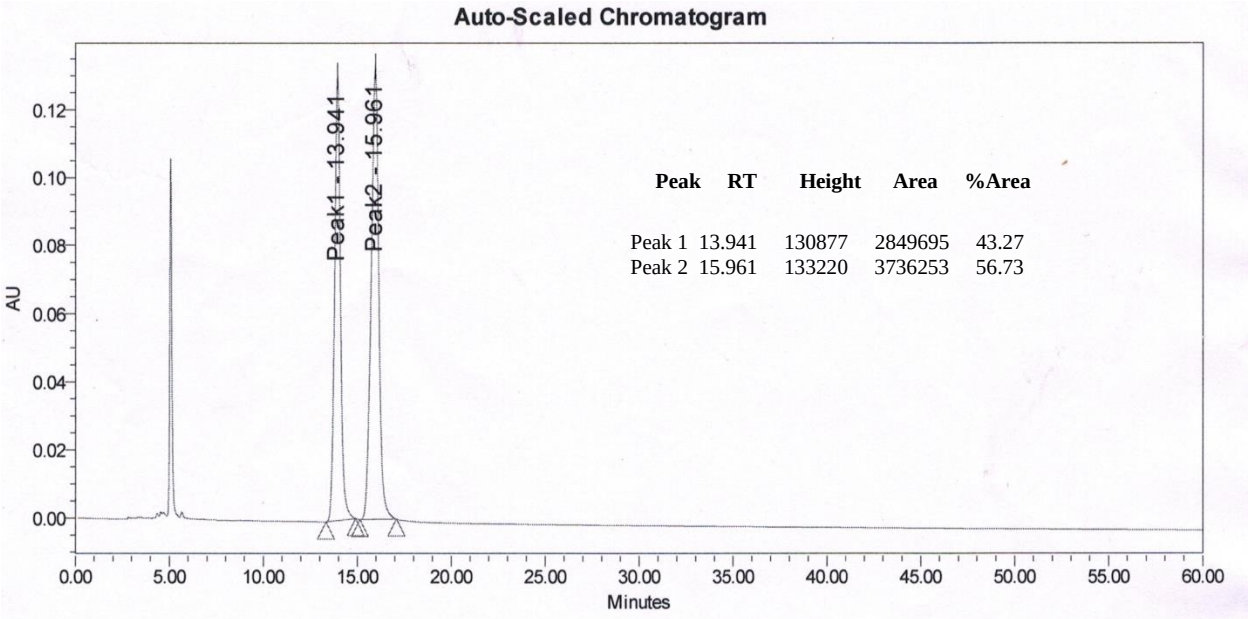


Table 1, Entry 18

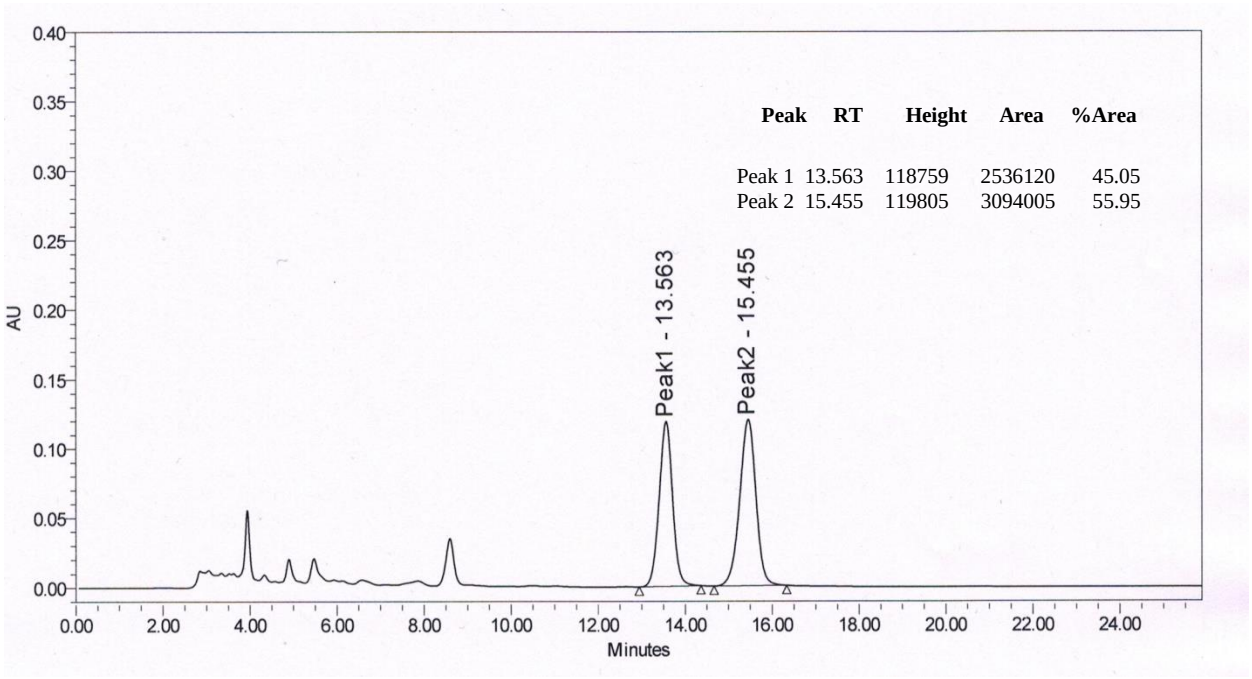


Table 1, Entry 19

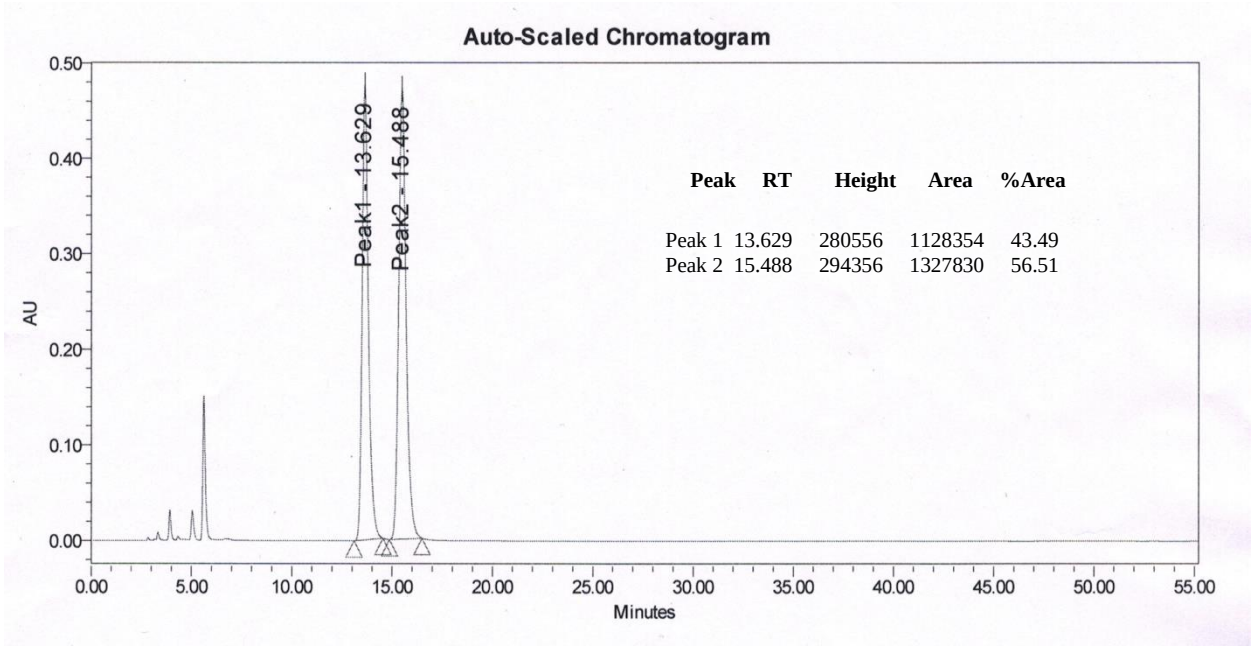


Table 1, Entry 20

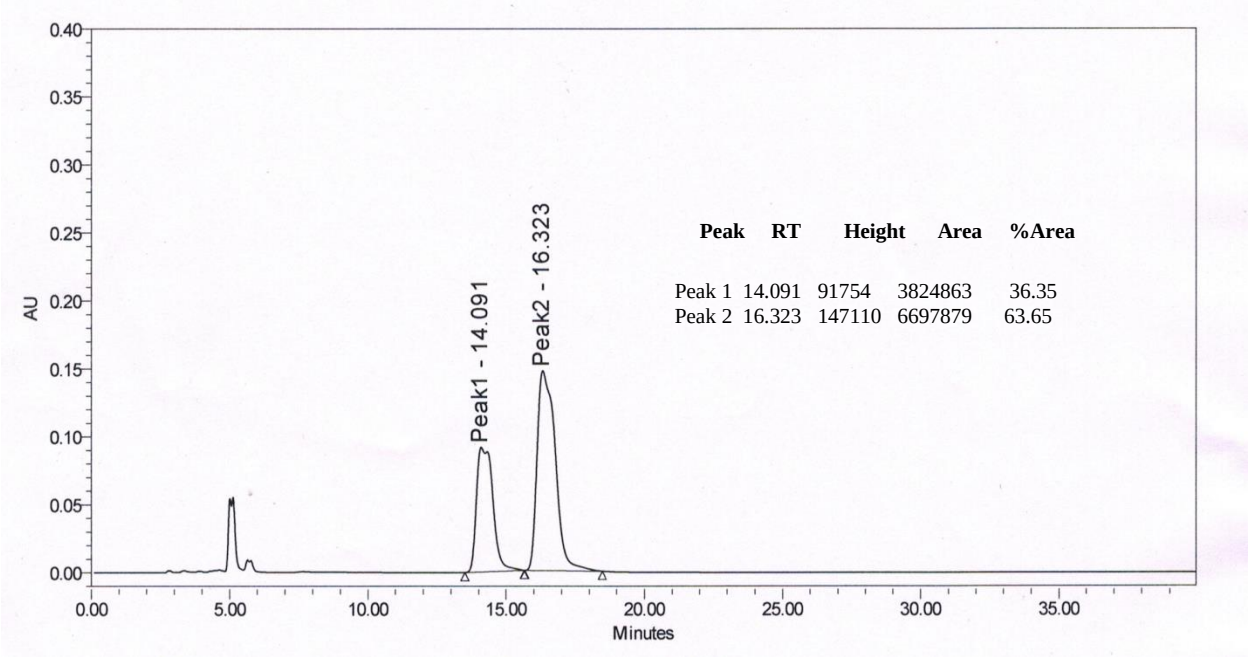


Table 1; Entry 24

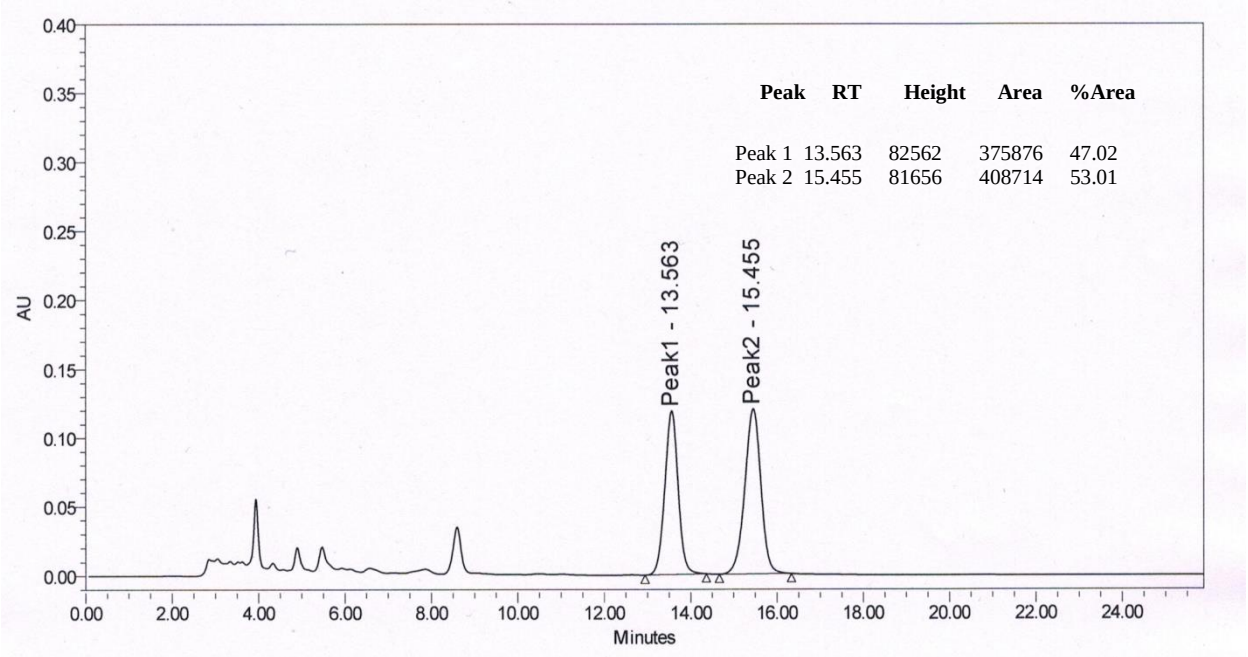


Table 1, Entry 25

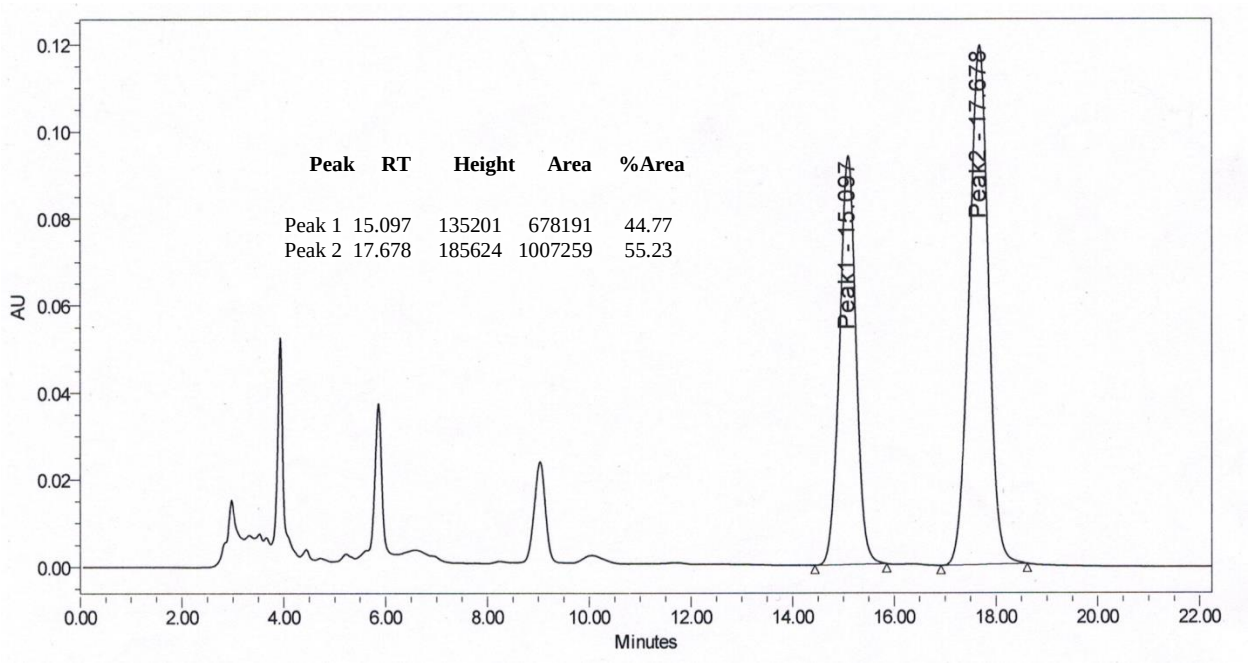


Table 1, Entry 26

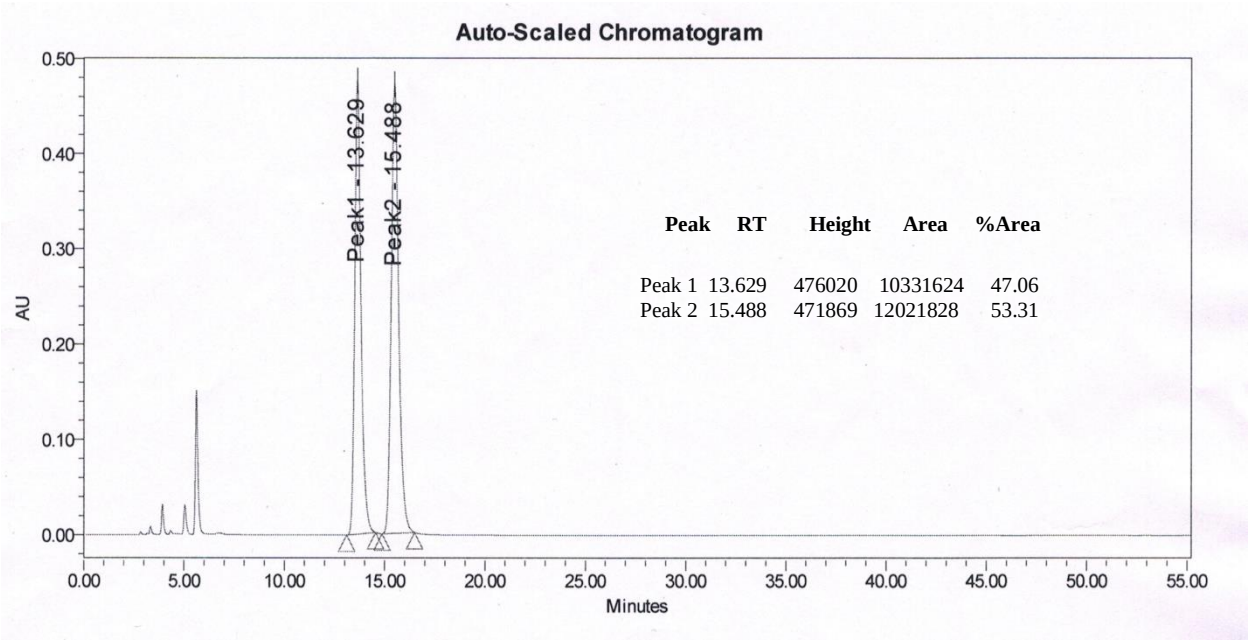


Table 1, Entry 27

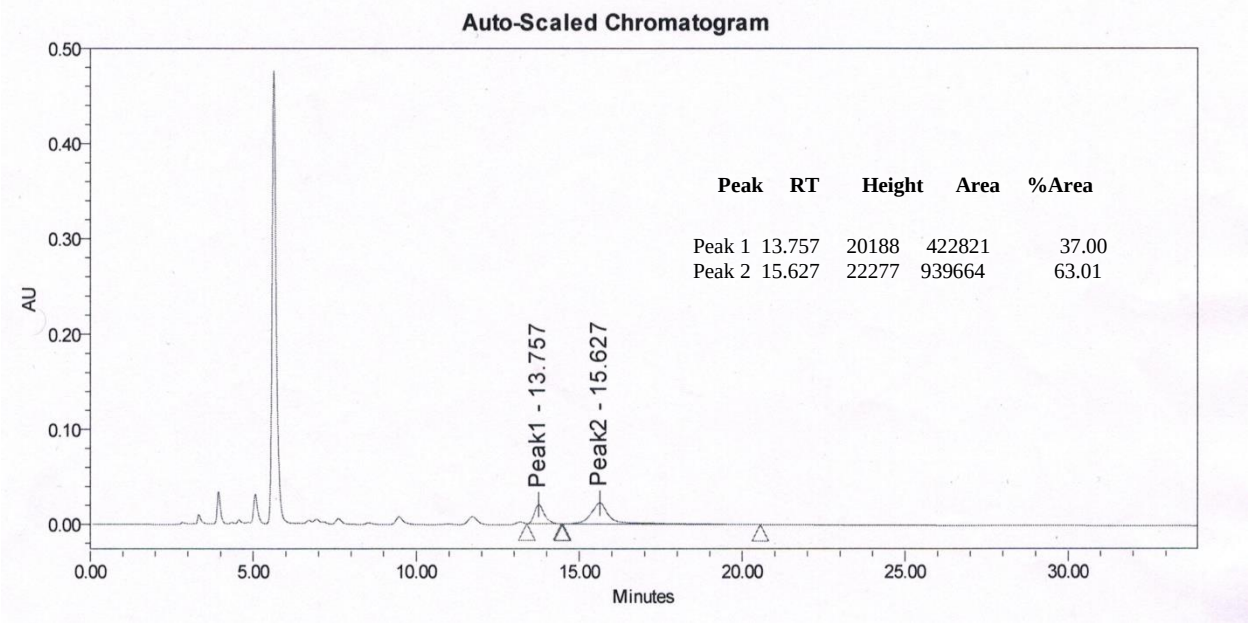


Table 2; Entry 1

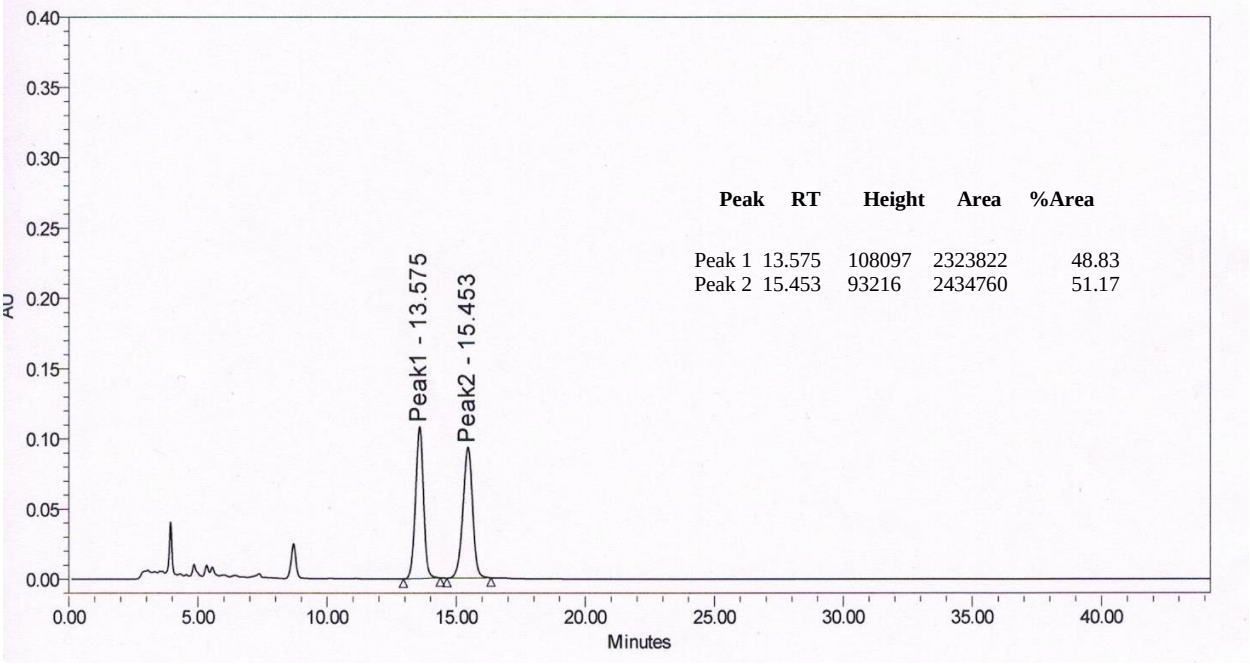
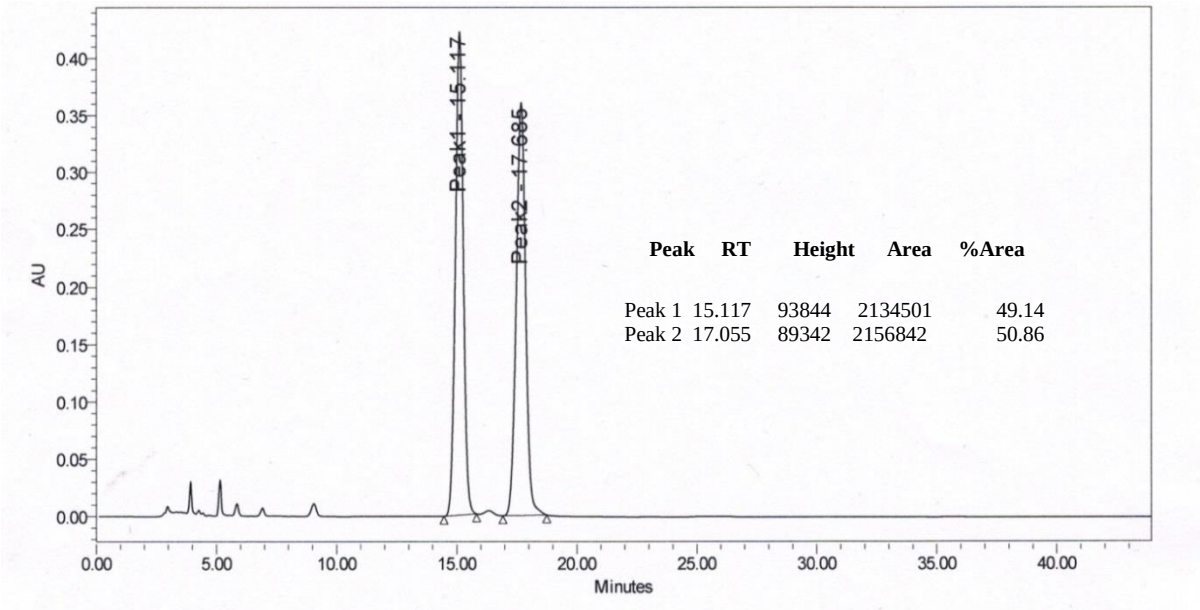
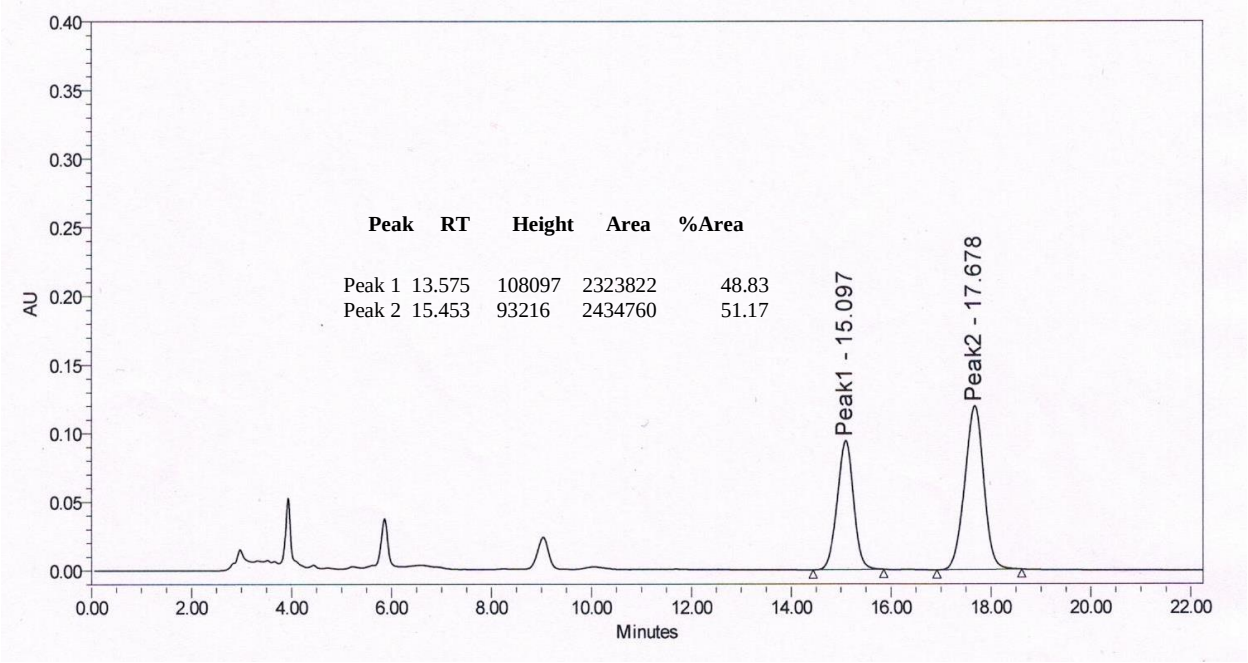


Table 2, Entry 2



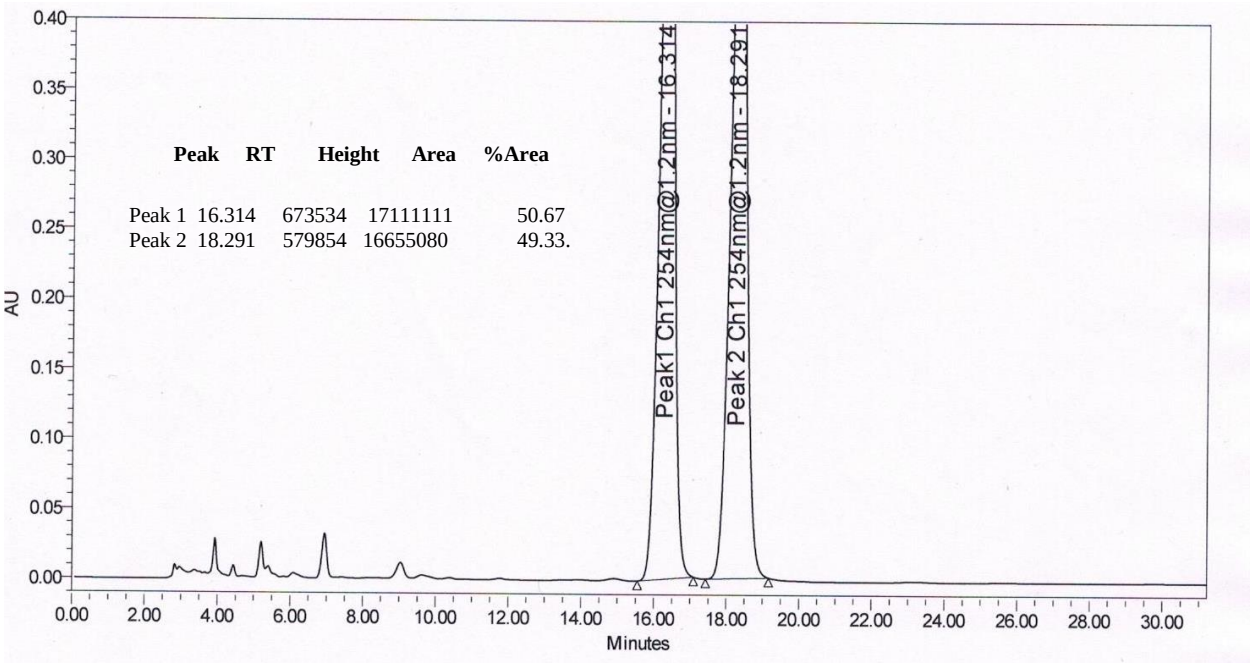
Peak	RT	Height	Area	%Area
Peak 1	15.117	93844	2134501	49.14
Peak 2	17.055	89342	2156842	50.86

Table 3, Entry 3



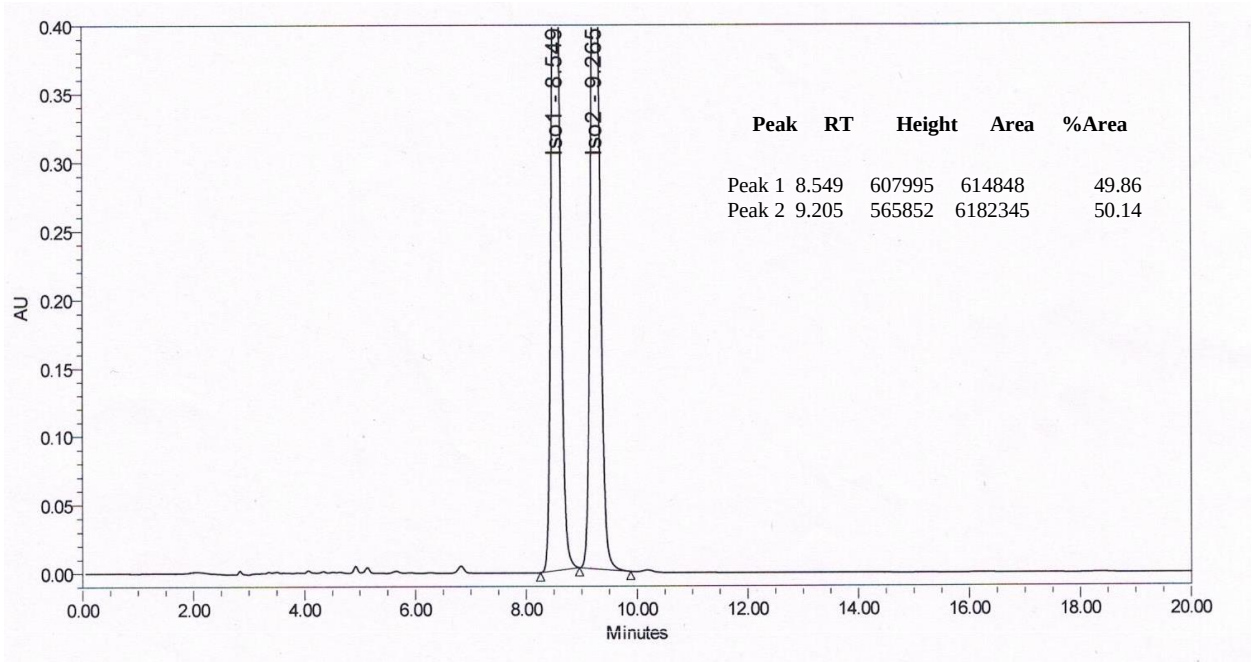
Peak	RT	Height	Area	%Area
Peak 1	13.575	108097	2323822	48.83
Peak 2	15.453	93216	2434760	51.17

Table 2, Entry 5



Peak	RT	Height	Area	%Area
Peak 1	16.314	673534	17111111	50.67
Peak 2	18.291	579854	16655080	49.33.

Table 2,Entry 7



Peak	RT	Height	Area	%Area
Peak 1	8.549	607995	614848	49.86
Peak 2	9.205	565852	6182345	50.14