# Balasaheb Javle Thesis

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# Synthesis of Amino Acid Amide Based Ionic Liquids: Their Utilization in Asymmetric Transfer Hydrogenation

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By

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*Dedicated to*

*My Parents and Teachers*

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## Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled **Synthesis of Amino Acid Amide Based Ionic Liquids: Their Utilization in Asymmetric Transfer Hydrogenation** submitted by **Mr. Balasaheb Rajendra Javle** to Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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## Declaration by the Candidate

I hereby declare that the original research work embodied in this thesis entitled, **Synthesis of Amino Acid amide Based Ionic Liquids: Their utilization in Asymmetric Transfer Hydrogenation** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph. D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. A. K. Kinage**, Senior Scientist, Chemical Engineering & Process Development Division, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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*... Balasaheb*

| Abbreviation | Name |
|---|---|
| EDCI | *N*-(3-Dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride |
| EDC | *N*-(3-Dimethylaminopropyl)-*N'*-ethyl carbodiimide |
| Boc | Di-tert-butyl dicarbonate |
| Cbz | N carbonyloxy carboxy anhydride |
| Fmoc | 2-(9H-Fluoren-9-ylmethoxycarbonylamino)acetic acid |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| CDI | 1,1-carbonyl diimidazole |
| DMF | *N,N*-Dimethylformamide |
| HATU | 1-[Bis(dimethyl amino)methylene]-1H-1,2,3-triazolo[4,5] Pyridium 3-oxide hexafluorophosphate |
| TBTU | 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate |
| DIEPA | N,N-Diisopropylethylamine |
| MIBA | 5-Methoxy-2-iodophenylboronic acid |
| THF | Tetrahydrofuran |
| DCM | Dichloromethane |
| CD | Circular Dichroism |
| NMR | Nuclear Magnetic Resonance |
| HRMS (ESI) | High Resolution Mass Spectrometer (electron spray ionization) |
| CILs | Chiral ionic liquids |
| $NaBF_4$ | Sodium tetrafluoroborate |
| $NaBH_4$ | Sodium borohydride |

| | |
|---|---|
| $LiAlH_4$ | Lithium aluminum hydride |
| $Na_2SO_4$ | Sodium sulfate |
| $NaHCO_3$ | Sodium hydrogen carbonate |
| $CuSO_4$ | Copper sulfate |
| EtOAc | Ethyl acetate |
| $AgBF_4$ | Silver tetrafluoroborate |
| $LiNTf_2$ | Lithium trifluoro methane sulfonamide |
| $SOCl_2$ | Thionyl chloride |
| $BF_4$ | Tetrafluoro borate |
| $BF_3.Et_2O$ | Boron trifluoro etherate |
| TsCl | Tosyl chloride |
| HCl | Hydrochloric acid |
| $HNO_3$ | Nitric acid |
| $H_2SO_4$ | Sulfuric acid |
| MeOH | Methanol |
| MP | Melting Point |
| HPLC | High performance liquid chromatography |
| GC | Gas chromatography |
| TLC | Thin layer chromatography |
| ATH | Asymmetric transfer hydrogenation |
| CBS | Corey Bakshi and Cibata |
| *i*-PrOH | Isopropyl alcohol |
| TON | Turn over number |

| | |
|---|---|
| $Al(O\textit{i}\text{-}Pr)_3$ | Aluminum tri isopropoxide |
| TsDPEN | *N*-(p-toluene sulfonyl)-1,2-diphenylethylenediamine) |
| IPA | Isopropyl alcohol |
| FA | Formic acid |
| $Et_3N$ | Triethyl amine |
| PNNP | Phosphorous nitrogen nitrogen phosphorous |
| NADH | Nicotinamide adenine dinucleotide |
| NHC | *N*- hetero cyclic |

## GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60–80°C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatographic purifications were performed over silica gel (60–120 & 230–400 mesh).
5. TLC was performed on E-Merck pre-coated 60 $F_{254}$ plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol), phosphomolybdic acid (in ethanol) and ninhydrin (in ethanol).
6. IR Spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in $cm^{-1}$.
7. $^{1}H$ and $^{13}C$NMR and DEPT spectra were recorded on Brucker FT AC-200 MHz, Brucker Advance 400 MHz, 500 MHz and JEOL ECX 400 instruments using TMS or solvent residue as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiples, brs = broad singlet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, dq = doublet of quartet and app = apparent.
8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25°C using sodium D light.
9. Enantiomeric excess was determined on Agilent HPLC instrument equipped with a chiral column.
10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.
11. All melting points are uncorrected and the temperatures are in centigrade scale.
12. The compounds, scheme and reference numbers given in each chapter/section refers to that particular chapter/section only.

**Title of Thesis: Synthesis of amino acid amide based ionic liquids: Their utilization in asymmetric transfer hydrogenation**

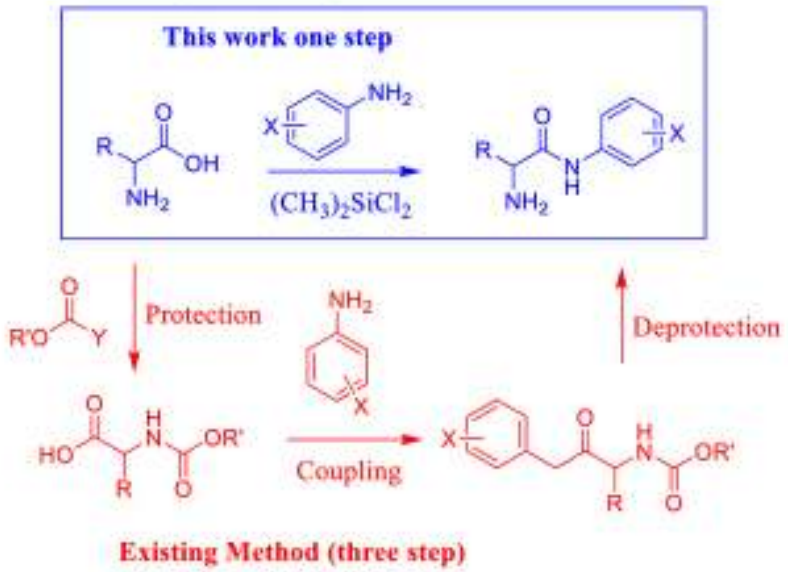
The thesis is mainly focused on the development of chiral ionic liquids of amino acid amides as organocatalyst for asymmetric transfer hydrogenation (ATH). This thesis is divided into three parts. The chapter first describes the protecting group free synthesis of N aryl (R) and (S) α amino acid amides from aliphatic natural amino acids and weakly nucleophilic substituted aryl amines as amine source using dichlorodialkyl silanes as simultaneous protecting and an activating agent. In the second chapter, we mainly focus on synthesis and characterization of CILs prepared from N aryl (R) and (S) α amino acid amides. For the synthesis of CILs of amino acid amides, perchloric acid was used as a protonating reagent. This work also described the simple and straightforward two-step atom economic synthetic methodology to the synthesis of CILs. And the third chapter consists of a synthesis of CILs of amino acid amides as asymmetric organocatalyst used in asymmetric transfer hydrogenation of ketones.

**Chapter I: One step synthesis of N aryl (R) and (S) chiral amino acid amides from unprotected aliphatic natural amino acids and weakly nucleophilic substituted aryl amines.**

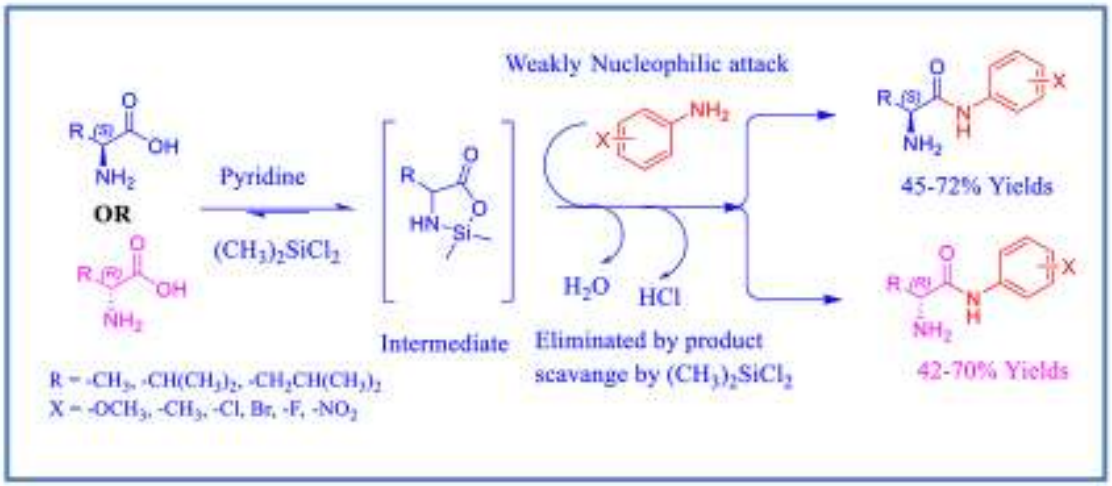
The amide bond is the significant building block of pharmaceuticals, agrochemicals, and biologically active natural products. Most of the biologically active natural products, chiral fine chemicals, pharmaceuticals as well as agrochemical compounds have important amide moiety such as endoderm, Vyvanse, Atlace, Cefprozil. Apart from these, amide bond serves as a synthetically important intermediate in organic synthesis[1-2], as well as organo catalyst[3] and chiral bidentate ligands[4] for stereoselective transformation. There is a number of methods existing in the literature involving three steps (protection, coupling, and deprotection) for the synthesis of the amino acid amides. However, problem is that, the epimerization occurs in product. There is one report in which, amino acid amides were synthesized in one step by using dichlorodimethyl silane as simultaneous protecting and activating agent from a free amino acid such as phenylalanine and strong nucleophilic benzylamine[5]. It was also reported that dichlorodimethyl silane is highly effective reagent to the synthesis of the amides. However, it is applicable only to phenylalanine and strongly nucleophilic benzylamines.

Therefore, in this chapter, we used series of naturally occurring amino acids (alanine, valine, leucine etc.) and weakly nucleophilic substituted aryl amines as amine to synthesis of amides.

We also proved that why dichlorodimethyl silane is highly efficient reagent in amide synthesis among the other dichlorodialkyl silane reagent.




**Scheme of present work:**




**Chapter II: Synthesis and characterization chiral ionic liquids of N aryl (R) and (S) α amino acid amides.**

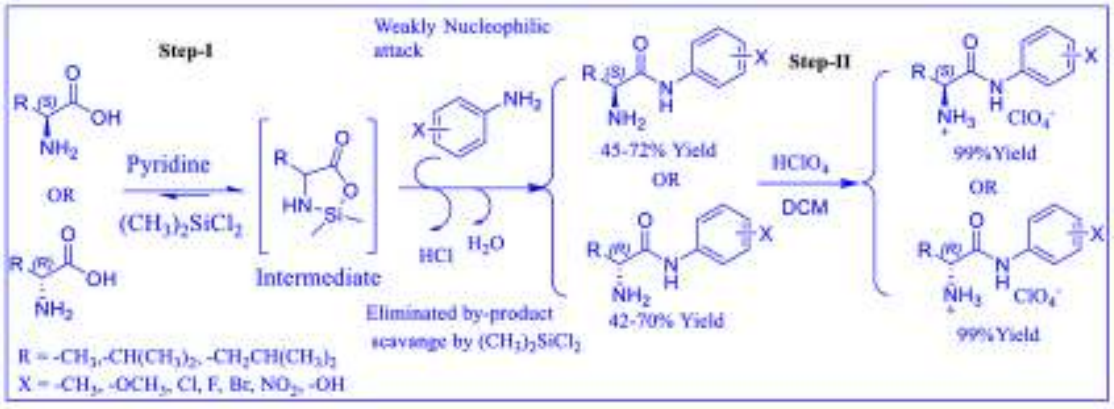
The chiral ionic liquids have wide applications in a chemical process for example as a solvent, catalyst, bio-catalyst, in synthetic chemistry, in electrochemistry, in separation and as extracting

agent. In literature, there are number of the reports available for the synthesis of chiral ionic liquids. Among the literature, one of the reported work reports synthesis of CILs using natural amino acids and aldehyde to from chiral imidazole as intermediates[6]. These CILs are used as chiral shift reagent for chiral discrimination of enantiomeric carboxylate salts in NMR. These CILs are used as chiral additives in transition metal catalyzed asymmetric organic transformation, n-hetetrocyclic carbene hydrido chiral ligands in transition metal based Schiff complexes, and in the dynamic kinetic resolution of racemic natural products and bioactive organic compounds.

In this chapter, we report two-step synthesis of novel chiral ionic liquids synthesized from naturally occurring amino acids and aryl amines. In first step, enantiopure α amino acid amides are synthesized from unprotected natural amino acids. The second step, amino acid amides are protonated by using perchloric acid to give chiral ionic liquids. Perchloric acid is used for protonation because chlorate anion of perchloric acid coordinates with amides and therefore, it does not affect the epimerization of chiral center of ionic liquid.

The synthesized chiral ionic liquids of the amino acid amides have melting point between 45-60 ℃. We report the confirmation of stereochemistry of stereo genic center of synthesized CILs of amino acid amides using CD spectroscopy and optical rotation. The mass of CILs was confirmed by HR-MS. We also confirm that epimerization dose not occurs in final product.

**Scheme of present work:**

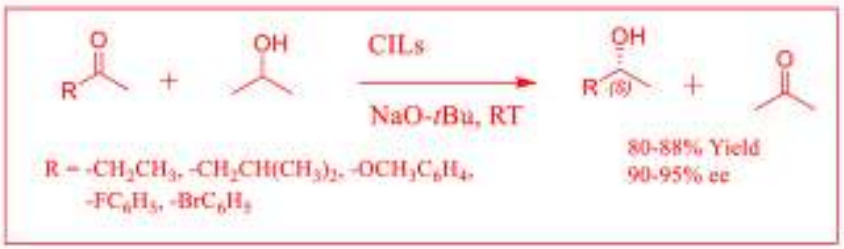


**Chapter III: Enantio pure CILs of amino acid amides as stereoselective organo-catalyst for asymmetric transfer hydrogenation of ketones at room temperature.**

Optically pure secondary alcohols are the important building block for preparation of chiral fine chemicals, pharmaceuticals, agrochemicals and bioactive natural products. For the synthesis of optically pure secondary alcohols, there are several catalytic methods are available in the literature. This was typically synthesized by hydrogenation of ketone by using transition metal catalyst and by using molecular hydrogen as well as different hydrogen donor viz. IPA, Formic acid, Hantzsch esters etc. The existing process has several drawbacks such as a hazardous chemical required in synthesis, difficulty in the separation of product, and requires elaborated set up which is not easy to handle.

Transfer hydrogenation reactions are divided according to catalyst type in Meerwein-Ponndrof-Verlay (MPV) reduction, late transition metal-catalyzed reactions, organo-catalyzed, enzyme-catalyzed, thermal, base-catalyzed and catalytic process. Herein, in this chapter, we show CILs of amino acid amides as stereoselective organo-catalyst for asymmetric transfer hydrogenation of ketone at room temperature[7]. These CILs are recyclable in ATH of ketones. We have synthesized both (R) & (S) aliphatic as well as aromatic secondary alcohols with moderate to good yield and with excellent enantio-selectivity using amino acid amide based (R) & (S) chiral ionic liquids as organo-catalyst. This also shows good activity and excellent enantioselectivity in ATH of Ketones after three recycles. We described the metal free ATH of ketone by using CILs of amino acid amide in IPA as hydrogen donor as well as solvent. This is the first report of metal free catalyzed ATH of ketone with moderate to excellent yield and ennatio-selectivity. It may be attractive alternatives method of ATH of ketone used without metal.

**Scheme of present work**:



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*Chapter 1*

# One step synthesis of *N* aryl *R* & *S* chiral amino acid amide from unprotected aliphatic natural amino acid and weakly nucleophilic substituted aryl amine

1.1 Introduction

1.2 Review of Literature

1.3 Present work

1.4 Conclusion

1.5 Experimental section

1.6 Spectral data

1.7 Reference

## 1.1 Introduction

The amide bonds are very important to every form of life, protein cannot be form without this, and life as we know it couldn't exists without protein based enzymes. Peptide bonds are formed by amino acids and amide bonds and these are the basic building blocks of protein[1][2]. Amino acid amide bond widely occurs in both natural and synthetic organic compounds[3]. There are many pharmaceuticals and medicinally relevant organic compounds containing amide bond with chirality[4][5][6]. Also the amide functionality is an important decorative design in polymers, natural products and agrochemicals[7][8]. The chiral amide bond is the key functional group in organic and biological chemistry. The drugs like Atovasartatin, Valsartin, Lisinoprine, Boscainide, Tocainide, Prilocaine, Lindocatine are the top selling agrochemicals and medicinal drugs involving *N*- hetero aryl amide bond as an active ingredient[4]. Tocainide is the amide derivatives of *D*-alanine used as antiarrhythmic agent[4]. Denagliptin drug is used for treatment for diabetes[9]. Cefprozil drug is an antibiotic called as antibacterial drug, which is used in the treatment and prevention of bacterial infection[5]. All these are the representative examples of chiral amino acid amide bond functionalities. Further, the compounds like Vyvanse, Altace and cefprozil are the example of biological active compounds containing amino acid amide bond functionality[5]. The compounds like sitaglimpltin, Ramipril and Lucosamide are DPP IV inhibitor, ACE inhibitor and anti-eliptic[6] having amino acid amide bond functionality.

Apart from these molecules, low molecular weight amino acid amides are used as solvents and intermediates in organic synthesis[10][11][12], organo-catalysis[13] and as well as chiral bi-dentate ligands in metal complexes for stereo-selective organic transformations[14].

## 1.2 Review of Literature

Numerous approaches have been reported for the synthesis of amides. The common method used for amide synthesis uses protected amines or amino acids and its deprotection. The Beckmann rearrangement is also used for preparation of amides. The most recognized method for preparation of amides is the reaction of amines with carboxylic acid derivatives like acid halides, acid anhydrides and esters. However, all these methods have limitations associated with the use of acid halide, acid anhydride and ester. Limitations are mostly due to stability of many acid chlorides and acid anhydrides, and reaction of esters required strong basic or acidic catalyst. Also

all these conventional methods of amide synthesis usually requires relatively high temperature and large amount of strongly acidic and dehydrating media ($H_2SO_4$, polyphosphoric acid, $P_2O_5$-methanesulfonic acid). The use of strong acidic media leads to large amount of waste products and not applicable to acid sensitive amide compounds.

### *1.2.1 Multistep synthesis of amino acid amide bond.*

In 2000 Shu Kobayashi and coworkers[15], reported multistep synthesis of amino acid amides. In this method initially aldehyde was condensed with amino phenol to form aldimine. Then aldimine was reacted with cyanide in presence of chiral Zr-catalyst to form chiral aminonitrile. Further aminonitrile was protected with iodomethane in acetone under basic condition at room temperature followed by oxidation of aminonitrile using $H_2O_2$ to form protected amino acid amide. The protected amino acid amide was then deprotected by Ce $(NH_4)_2(NO_3)_6$ in methanol to form amino acid amide. In 2003 Hyunik Shin and coworkers[16], reported the efficient synthesis of the HIV-I protease inhibitor LB71350 containing amino acid amide bond. In their multistep synthesis of HIV –I protease inhibitor, initially *N*-Cbz protected phenylalanine was reacted with ortho ester phosphonium salts in presence of KHMDS, followed by hydrolysis to form *N*-Cbz protected unsaturated acid. This unsaturated acid further reacted with chiral amine hydrochloride using various coupling reagents to form *N*-Cbz- protected amino amide bond. Which is epoxidized followed by deprotection to form amino acid amide bond containing HIV-I inhibitor. In 2005 Ormerod and coworkers[17], reported the synthesis of amide bond containing Gastrozole (JB95008) for the treatment of pancreatic cancer. In the multi-step synthesis of Gastrozole, first 2-flurophenylalanine was protected by Boc anhydride to form *N*-Boc protected 2-flurophenylalanine. That was reacted with substituted aniline in presence of coupling reagent to form *N*-Boc protected amino acid amide and simultaneously deprotected to obtained amino acid amide product. Further dipeptides and tripeptides were formed by reacting with amines to obtained Gastrozole (JB95008). In 2005 Richmond and coworkers[18], reported diamine containing modular ligands and during these synthesis amino acid amide bond is formed by protecting amino acid with *N*-Boc anhydride, this was then reacted with amine in presence of coupling reagent to form protected amino acid amide. In 2006 Vinod K. Singh and coworkers[19], reported chiral compound as asymmetric organo-catalyst for enantio-selective aldol reaction. The prolineamide was synthesized by multi-steps; in this synthesis initially proline is protected with

*N*-Boc anhydride and reacted with ethyl chloroformate and triethylamine. Further optically pure amino alcohol reacted to form protected prolineamide followed by deprotection. In 2008 Yugang Liu and coworkers[20], reported the synthesis of peptide defomylase inhibitor LCD320 containing amino acid amide bond. In this synthesis they reported an efficient amidation of proline derivatives with weakly nucleophilic 3-pyridizamine.The proline derivatives were synthesized by reacting proline with *t*-Boc anhydride to form *N*- Boc protected proline. During amidation of *N*-protected proline derivatives they observed epimerization of the C-2 center of Boc protected proline derivatives. To minimize the epimerization the reaction was further carried out at low temperature in DMF. In 2009 Gerald A Wiesenberger and coworkers[21], reported the αvβ3 integrin antagonist synthesis by carbonyl diimidazole (CDI) mediating peptide coupling. In the synthesis of peptide coupling, initially glycine reacted with *t*-Boc anhydride followed by addition of 1: 2 N-methyl pyrrolidine and CDI to generate activated glycine derivative containing amino acid amide bonds. That compound was used for further synthesis of integrin antagonist. In 2009 Paul D Shea and coworkers[22], reported the multi-steps synthesis of amide bond containing Cathepsin K inhibitor odanacatib. In the multistep synthesis of Cathepsin K inhibitor the amide bond was formed as follows, initially (S)-fluro-leucine ethyl ester was reacted with chiral trifluoromethylphenyl triflate to generate the *N*-protected (*S*) Fluro-leucine ethyl ester. Then *N* protected leucine ethyl ester was reacted with cyclopropylamine in presence of HATU and *i*-$Pr_2NEt$ as coupling reagent to obtained corresponding Cathepin K inhibitor containing amino acid amide. In 2009 Daniel Patterson and coworkers[9], reported the large scale synthesis of amide bond containing Denagliptin drug molecule. In multi-synthesis method first *N*-Boc protected proline was reacted with Boc anhydride to obtained double protected proline followed by reaction with $NH_4OH$ to form *N*-Boc protected prolinamide. The tosylated *N*-Boc protected prolinamide and (*S*) diflurophenyl amino acid reacted using coupling reagent in ethylacetate followed by deprotection of Boc group to obtain denagliptin drugs molecule containing amino acid amide. In 2009 Haun Wang and coworkers[23], reported the stereo-selective synthesis of SB-462795, a highly potent cathepsin K inhibitor with amide bond. In multi-synthesis of SB462795, *L*-leucine was reacted with heterocyclic carboxylic acid to form *N* protected *L*-leucine. Then *N*-protected *L*-leucine was further reacted with azepane amino alcohol in presence of coupling reagent EDCI to produced *N* protected amino acid amide bond containing SB-462795. The racemization of product was observed during use of EDCI as coupling reagent. In 2012 Harald

Groger and coworkers[24], reported the multi-step procedure for the preparation of Singh catalyst containing amide bond. In the synthesis of Singh catalyst, first Boc protected proline reacted with ethylchloroforamate to form mixed anhydride. Then proline mixed anhydride was condensed with *L*-diphenyl amino alcohol to form *N* –Boc protected prolinamide. That was then deprotected to obtained amino acid amide. In 2015 Michael A Schmidt and coworkers[25], reported the two step enantio-selective synthesis of amino alcohol drugs molecule containing amide. In first route, initially hydroxyl amino acid was protected with Boc anhydride that was then coupled with pyrrolidine to from Boc protected *β* hydroxyl amino acid amide. Then protected *β* hydroxyl amino acid amide was deprotected to obtained *β* hydroxyl amino acid amide. In second route chiral *β* hydroxyl amino acid was synthesized by enzymatic aldol reaction of pyridine aldehyde and glycine in presence of *D* threonine aldolase. Then *β* hydroxyl amino acid was reacted with dichlorodimethyl silane and pyrrolidine to obtain the *β* hydroxyl amino acid amide.

### *1.2.2 One step synthesis of amino acid amide compounds.*

In 1993 Roskamp and coworkers[26], reported the direct conversion of ester to secondary amide using Tin(II) reagent. The two synthetic routes were reported for direct conversion of esters to secondary amide. In the first route secondary amide was formed by the reaction between glycol ester and primary amine using $Sn[N(TMS)_2]_2$ via Tin (II) alkoxy amide as intermediate. In the second synthetic route reagent based approach was used, in this a phenylacetate and primary amine was reacted in presence of *N, N*- dimethylethanolamine and $Sn[N(TMS)_2]_2$. The tin (II) alkoxy amide was formed in-situ during amidation. In 2004 Anne-Marie Faucher and coworkers[27], reported the synthesis of amide bond containing BILN 2061 as HCV NS3 protease inhibitor. In this synthesis of HCV NS3 protease inhibitor involving amino acid amide bond, it was synthesized from reaction of (2R 3S)-3-vinyl-2-amino-2-cyclopropylcarboxylic acid methyl ester and trans-(2S 4R)-Boc protected hydroxyl proline in presence of TBTU and DIEPA as coupling reagent in DMF. In 2005 Liskamp and coworkers[28], reported amino acid amide synthesis procedure using boron trifluoride diethyl etherate as protecting and activating agent. In this procedure additional step was required to form the lithium salt of L-phenylalanine. The lithium salt of phenylalnine was then reacted with $BF_3.Et_2O$ to form cyclic intermediate, 2,2-difluoro-1,3,2-oxazaborolidin-5-one, which reacts with an amine to yield amino acid amide. The

method was suitable for only primary amines. In 2011 Matthias Beller and coworkers[5], reported the synthesis of α amino acid amides by reacting hydroxyl amide and aryl amine catalyzed by ruthenium. In 2012 Li and coworkers[29], showed amidation of L- and D-proline with p-anisidine, however, significant racemization was observed. This procedure requires anhydrous conditions. In 2011 Tom D Sheppard and coworkers[30][31][32][6][33], reported the amidation reaction of unprotected amino acid using borate ester $B(OCH_2CF_3)_3$. Borate ester as effective promoter for amide bond formation with variety of carboxylic acid and amine. Trans-amidation was also reported for the synthesis of primary and secondary amides. In 2013, they reported the $B(OCH_2CF_3)_3$- mediated synthesis of amino acid amide compound with Cbz or Boc protected amino acid and benzyl amine in solid phase. In 2015, they reported synthesis of amide compounds by reaction with benzylic acid and benzylamine using $B(OCH_2CF_3)_3$ coupling reagent to obtained the amide. In 2018, they reported the amidation of unprotected amino acid using variety of classical coupling reagents and using group (IV) metal salts as a catalyst. In 2012 Hans Adolfsson and coworkers[34], reported the direct amide formation from *N*-Boc protected amino acid and carboxylic acid with amine catalyzed by Zirconium (IV) chloride. In 2013 Shouxin Liu and coworkers[35], reported the direct amidation of amino acid derivatives catalyzed by arylboronic acid. The direct amidation reaction of *N*-Boc protected proline and strongly nucleophilic benzylamine in presence of catalytic amount of arylboronic acid was carried out to obtain *N*-Boc protected amino acid amide derivatives. They also synthesized dipepetide by reaction of *N* or *C* protected amino acid and amine in presence of flurobenzene solvent to avoid racemization. In 2015 Dennis G Hall and coworkers[36], reported preparation of amide using boronic acid as catalyst under ambient conditions to prevent epimerization of chiral amino acid derivatives. They carried out coupling reaction of N-Boc or Fmoc protected amino acid with strongly nucleophilic benzylamine in presence of MIBA catalyst to obtained *N*-Boc or Fmoc protected amino acid amide compounds. In 2015 Shinya Furukawa and coworkers[37], reported the reaction of amino acid ester hydrochlorides with tetrabutyl phosphonium amino acid ionic liquids to obtained the corresponding dipeptides and tripeptides. In 2017 Bert and coworkers[4], reported *N* arylamino acid amide as tocainide drug and it was synthesized by one step using*N-tert*-Butyl-*N*-2,6-dimethylphenyl-S-phenylisothiourea treated with *N*-Boc protected *D*- alanine in presence of iron acetate $(Fe(acac)_3$ as catalyst. In 2005 George A Olah and coworkers[38], reported the gallium (III) triflate catalyzed Beckmann rearrangement for synthesis

of amide. They reported rearrangement reaction of oxime using catalytic amount of $Ga(OTf)_3$ to obtained amide. In 2005 Youquan Deng and coworkers[39], reported Beckmann rearrangement of variety of ketoxime in the presence of chlorosulfonic acid to obtained amides. In 2006 Youquan Deng and coworkers[40], reported the Beckmann rearrangement of cyclohexanone oxime in presence of Bronsted acidic ionic liquids to synthesized amides. In 2001 Yamaguchi and coworkers[41], reported the Backman rearrangement of oximes catalyzed by $[RhCl(cod)_2]$, trifluoromethanesulfonic acid and tris (p-tolyl) phosphine to obtained corresponding amides. In 2009 Robert H Crabtree and coworkers[42], reported Beckmann rearrangement of aldoxime using $TerPyRu(PPh_3)Cl_2$as catalyst to obtained amide. In 2009 Anxin Wu and coworkers[43], reported Beckmann rearrangement in which the direct transformation of methyl ketone, or carbinol to primary amide by aqueous ammonia. The K Burger and coworkers in 1995[44][45], reported the hexafluoroacetone as simultaneous protecting and activating reagent in peptide synthesis. In this synthesis method aspartic acid was treated with hexafluoroacetone to form reactive cyclic bis (trifluoromethyl) substituted oxazolidin-5-one as an intermediate, which further reacted with L-phenylalanine methyl ester to generate the dipeptide. However, hexafluoroacetone is a very toxic gas and much care has to be taken during handling. In 2002 Liskamp and coworkers[46], reported a simultaneous protection and activation method for the synthesis of amino acid amides. This procedure utilized dichlorodialkyl silanes as a protecting group and coupling reagent. The unprotected phenylalanine and benzylamine in presence of dichlorodimethyl silane was reacted at room temperature in presence of pyridine to produced amino acid amide. This procedure is limited to primary amines with stronger nucleophiles.

## 1.3 Present work

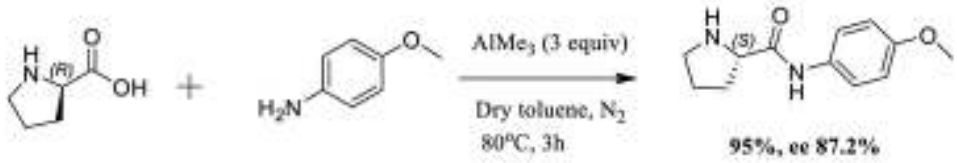
All above literature shows, the amidation reaction requires protection and deprotection of functional groups either from amino acids or amines to prevent any undesired side reaction **(Scheme 1).** Therefore, the protection and deprotection of either the amine or amino acid adds at least two extra steps in synthetic procedure. However, there are few reports that use simultaneous protecting and activating agents for amino acids in one step synthesis of amide.


**Scheme 1: One step synthetic amidation methods for unprotected amino acids.**

However, one step synthetic method[44][45] **(Scheme 2)** reported in literature uses hexafluoroacetone as a simultaneous protecting and activating agent, which is a very toxic gas and requires extra care to handle it.

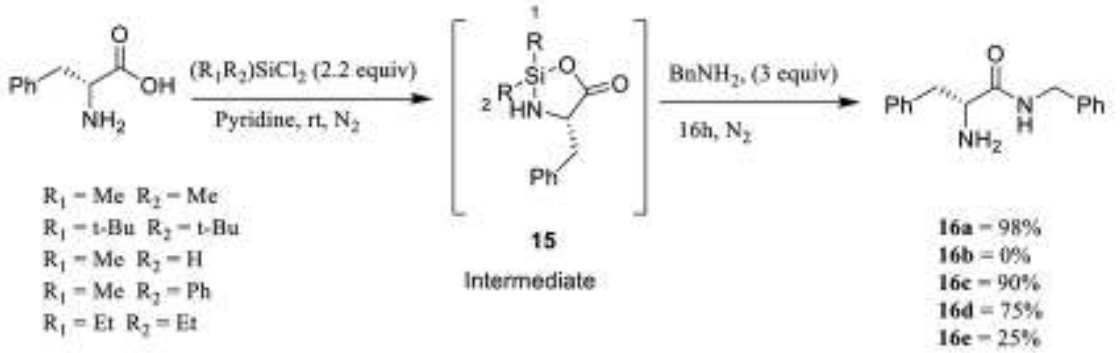

**Scheme 2: One step amidation reaction of amino acid with hexafluoroacetone as simultaneous protecting and activating agent.**

The other method[29] **(Scheme 3)** reported uses $AlMe_3$ as a simultaneous protecting and activating agent, however during this significant racemization in product was observed.




**Scheme 3: One step amidation reaction of amino acid with $AlMe_3$ as simultaneous protecting and activating agent.**

The another synthetic method[46] **(Scheme 4)** uses dichlorodialkyl silanes as a simultaneous protecting and activating agent, however, this procedure is limited to primary amines with stronger nucleophiles.




**Scheme 4: One step amidation reaction of amino acid with dichlorodialkyl silane as simultaneous protecting and activating agent.**

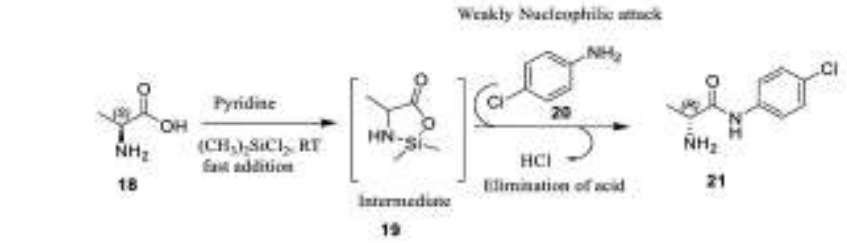
Therefore, there is scope to develop a one-step synthesis method for amidation reaction using amines (Aliphatic and aromatic) with weaker nucleophiles. We, therefore, report herein a synthetic method for amidation of unprotected amino acids with weaker nucleophilic amines (Aliphatic and aromatic) by using dichlorodialkyl silanes as a simultaneous protecting and activating agent as shown in **Figure 1**.


**Figure 1: Proposed synthesis scheme.**

### *1.3.1 Optimization of synthetic method for one step amidation of aliphatic unprotected amino acid using $(CH_3)_2SiCl_2$ as protecting and activating agent.*

Initially, one step synthesis of amino acid amide was carried out by reacting commercially available unprotected *L*-alanine (aliphatic natural amino acid) with chloroaniline (weakly nucleophilic arylamine) for optimization study. In literature, it was found that epimerization of amino acid amide product was observed in many synthetic methods. Here also we observed

epimerization of amide product and this may be due to formation of HCL during reaction of amino acid and dichlorodimethyl silane. This reaction is highly exothermic and due to formation of HCL and heat generated during reaction, active methylene group of amino acid forms enolates. Because of formation of enolates the active methylene carbon becomes $sp^2$ hybridized and hence chirality disappears and the epimerized amino acid amide product was obtained. This was confirmed by CD spectrophotometer as shown in **Figure 2**.



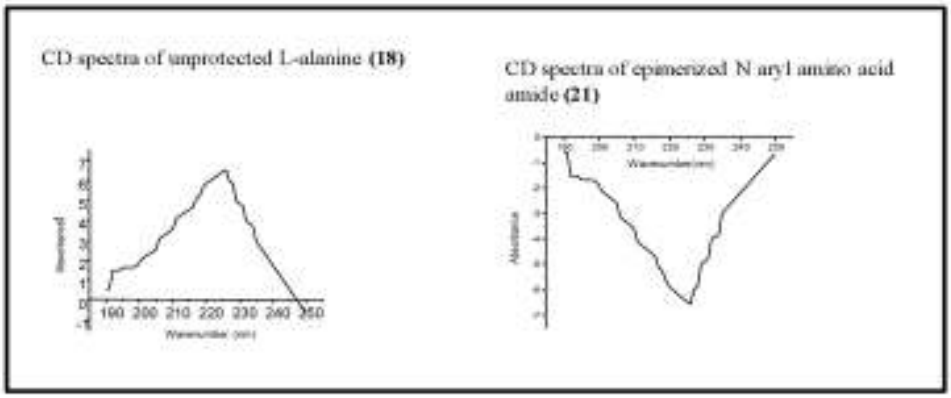




**Figure 2: CD spectral data of *N* aryl amino acid amide product with epimerization.**

To avoid epimerization, we carried out controlled experiment by first dissolving *L*-alanine completely in pyridine and then dichorodimethyl silane was added drop by drop (1 ml/min) followed by addition of chloroaniline. Because of slow addition of dichorodimethyl silane, heat generated during this step is dissipated and HCL formed during reaction was quenched in weak basic media. Thus enolate formation of active methylene group was avoided and the product obtained does not epimerize stereo-genic center of synthesized amino acid amide as shown in **Figure 3**. Therefore, for further all reactions were carried out using above producer to avoid epimerization of final amide product.

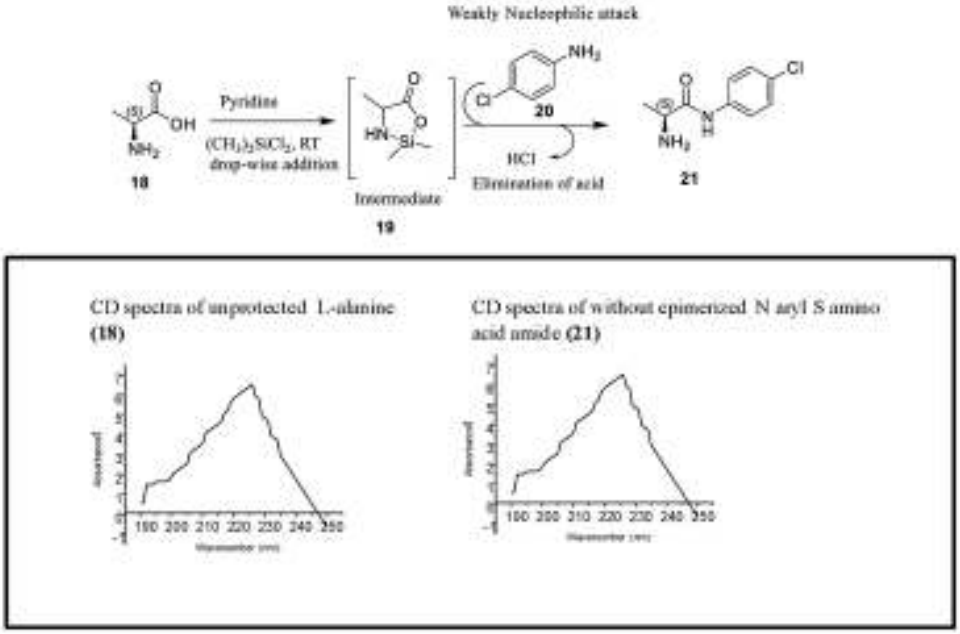
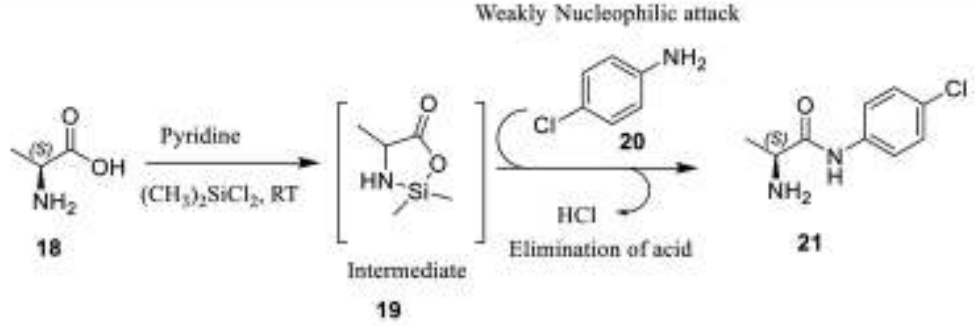



**Figure 3: CD spectral data of *N* aryl amino acid amide product without epimerization.**

Further optimization was carried out by using different solvents and different dichlorodimethyl silane ratios. The reaction was carried out using (1:1.2:4:2.5) equivalent ratio of *L*-alanine, dichlorodimethyl silane, 4-chloroaniline, and triethylamine in different solvents (acetonitrile, THF, DCM, DMF, toluene, 1,4-dioxane, and pyrrolidine) at room temperature for 48 h. The desired amino acid amide product was not obtained **(Table 1 entry 1-7)**. We observed that the desired product was not obtained because triethylamine reacts with dichlorodimethyl silane to form salt. Then amidation reaction with (1:0.5:4) equivalent ratio of *L*-alanine, dichlorodimethyl silane and 4-chloroaniline, was carried out at room temperature in pyridine as solvent as well as base for 48 h. The excepted desired product of amino acid amide was obtained **(Table 1, entry 8)**. Further we carried out reaction by varying different ratio of dichlorodimethyl silane and observed that an excellent yield of amino acid amide product was obtained at 1:1.2:4 ratios in 16 h. **(Table 1, entry 9-12)**. From above data we observed that (1:1.2) equivalent ratio of amino acid and dichlorodimethyl silane was ideal for one step amidation reaction of unprotected aliphatic amino acid and weakly nucleophilic aryl amine. Therefore, for further study we used same ratio of *L*-alanine and dichlorodimethyl silane.

**Table 1: Optimization of amidation reaction by varying L-alanine & dichlorodimethyl silane ratio and by using different solvents.**

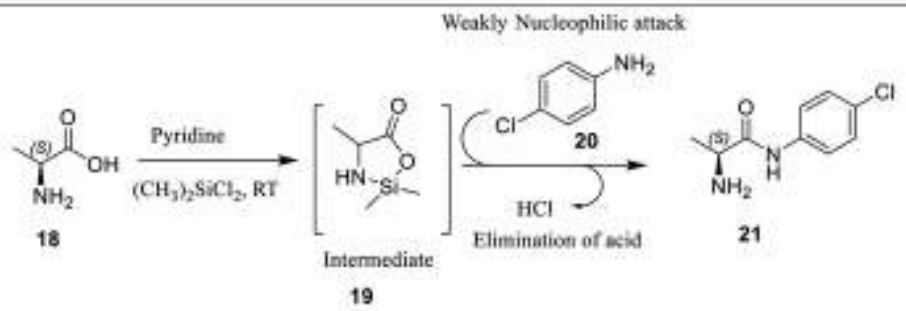



| Entry No. | L-alanine (equiv) | Dichlorodimethyl silane (equiv) | Choro aniline (equiv) | Solvent | Base | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1. | 1 | 1.2 | 4 | ACN | $Et_3N$ | 48 | - |
| 2. | 1 | 1.2 | 4 | THF | $Et_3N$ | 48 | - |
| 3. | 1 | 1.2 | 4 | DCM | $Et_3N$ | 48 | - |
| 4. | 1 | 1.2 | 4 | DMF | $Et_3N$ | 48 | - |
| 5. | 1 | 1.2 | 4 | Toluene | $Et_3N$ | 48 | - |
| 6. | 1 | 1.2 | 4 | 1,4-dioxane | $Et_3N$ | 48 | - |
| 7 | 1 | 1.2 | 4 | Pyrrolidine | $Et_3N$ | 48 | - |
| 8 | 1 | 0.5 | 4 | Pyridine | Pyridine | 48 | 35 |
| 9 | 1 | 1 | 4 | Pyridine | Pyridine | 48 | 50 |
| 10 | 1 | 1.2 | 4 | Pyridine | Pyridine | 16 | 72 |
| 11 | 1 | 1.5 | 4 | Pyridine | Pyridine | 16 | 72 |
| 12 | 1 | 2 | 4 | Pyridine | Pyridine | 16 | 72 |

Then for further optimization study we change the concentration of aryl amine (4-chloroaniline). Initially, amidation reaction was carried out with (1:1.2:1) equivalent ratio of *L*-alanine, dichlorodimethyl silane and 4-chloroaniline at room temperature in pyridine for 16h. No product was observed **(Table 2, entry 1)**. Further, we change the 4-chloroaniline concentration from 1.5 to 5 equivalent of L-alanine and it was observed that at 1.5 to 3 equivalent ratios of *L*-alanine and 4-chloroaniline, excepted desired amino acid amide product was obtained with lower yield

**(Table 2, entry 2-5)**. Then we change ratios of *L*-alanine to 4-chloroaniline from 3 to 5 equivalent, desired amino acid amide product was obtained with excellent yield **(Table 2, entry 7-9)**. From above screening data of amidation reaction, we observed that 4 or excess ratio of *L*-alanine and 4-chloroaniline gave excellent yield of amino acid amide product. It was then concluded that excess amount of 4-chloroaniline is required for amidation reaction. From above optimization study of amidation reaction we found that the 1:1.2:4 ratio of *L*-alanine, dichlorodimethyl silane and 4-chloroaniline, respectively, is the ideal ratio. Therefore, for all the further amidation reactions were carried out using above optimized condition.

**Table 2: Optimization of amidation reaction by varying arylamine concentration.**



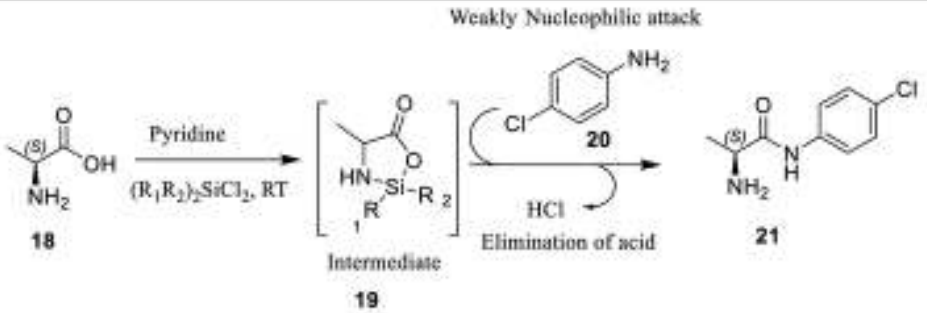

| Entry No. | L-alanine | Dichlorodimethylsilane | Chloroaniline | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1. | 1 | 1.2 | 1 | 16 | - |
| 2. | 1 | 1.2 | 1.5 | 16 | 16 |
| 3. | 1 | 1.2 | 2 | 16 | 20 |
| 4. | 1 | 1.2 | 2.5 | 16 | 40 |
| 5. | 1 | 1.2 | 3 | 16 | 50 |
| 6. | 1 | 1.2 | 3.5 | 16 | 55 |
| 7. | 1 | 1.2 | 4 | 16 | 72 |
| 8. | 1 | 1.2 | 4.5 | 16 | 72 |
| 9. | 1 | 1.2 | 5 | 16 | 72 |

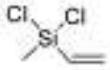
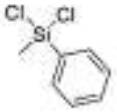
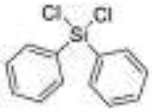
### *1.3.2 Effect of different silanes on one step amidation reaction.*

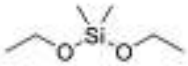
To see effect of different silanes, we carried out one step amidation reaction of *L*-alanine, dichlorodimethylsilane and 4-chloroaniline with 1:1.2:4 ratios at room temperature for 16h by

varying different silanes (Viz. dichloro-methyl-vinyl silane, dichloro-methyl-phenyl silane, dichloro-diphenyl silane, dichloro-methyl-octadecyl silane, and diethoxy-dimethyl silane). It was observed that using dichlorodimethyl silane gave corresponding amino acid amide product with excellent yield as compare to other silanes **(Table 3, entry 1)**. The use of other silane in amidation reaction gave moderate to good yield **(Table 3, entry 2-6)**. From above screening of dichlorodialkyl silane as protecting and activating reagent in one step amidation reaction of unprotected L-alanine and 4-chloroaniline it was observed that, by increase in the bulky moiety on silane, the rate of reaction decreased. This may be due to steric hindrance on silane. Screening of various dichlorodialkyl silane, we observed that dichlorodimethyl silane is highly effective reagent for one step amidation reaction.

**Table 3. Effect of different silane reagents on one step amidation reaction.**



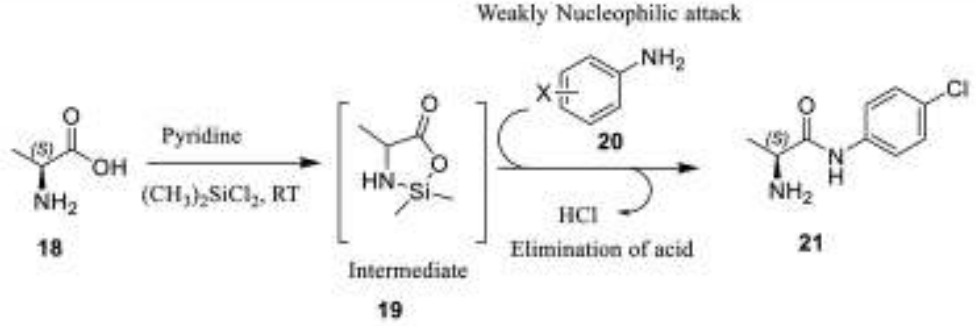

| Entry No. | $(R_1R_2)SiCl_2$ | Time (h) | Yield (%) |
|---|---|---|---|
| 1. |  | 16 | 72 |
| 2. |  | 16 | 62 |
| 3. |  | 16 | 35 |
| 4. |  | 16 | 30 |

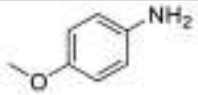
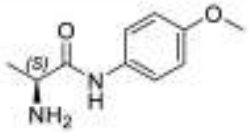
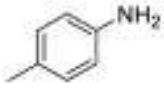
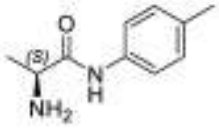
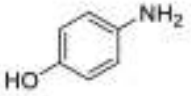
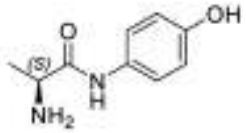
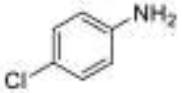
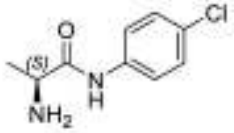
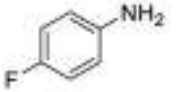
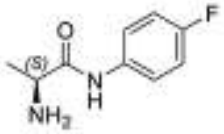
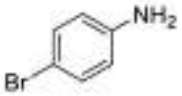
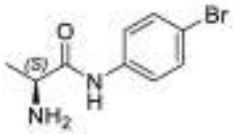
| | | | |
|---|---|---|---|
| 5. |  | 16 | 10 |
| 6. |  | 16 | - |

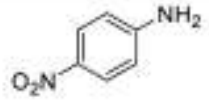
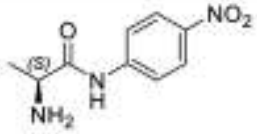
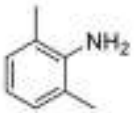
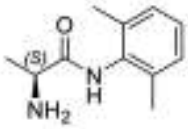
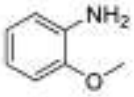
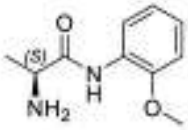
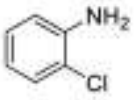
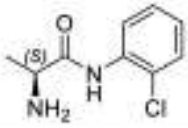
### *1.3.3 Effect of different substituted aryl amines with electron donating & withdrawing group on amidation reaction.*

Using above effective optimization study, further scope and efficiency of this method was explored for synthesis of different amino acid amides by using substituted aryl amines with electron donating and withdrawing group at ortho and para position. Initially, amidation reaction of unprotected *L*-alanine was carried out using electron donating substituted group of aryl amines at para position. The good to excellent yield of corresponding amino acid amide product was obtained **(Table 4, entry 1-2)** except hydroxyl group substituted aryl mine **(Table 4, entry 3)**. This may be because hydroxyl group in amino phenol has high affinity to react with dichlorodimethyl silane to form salt. Decreased in amino acid amide product was observed when chloroaniline, fluroaniline, bromoaniline and nitroaniline was used **(Table 4, entry 4-6)**. As the rate of reaction was decreased with increased in electron withdrawing strength of substituted group on aryl amine except nitro group. The nitro group is strong electron withdrawing group which withdraw the nucleophilic ability of aryl amine and thus reaction does not occur. However, when electron donating and withdrawing substituted group at ortho position of aryl amine was reacted with unprotected *L*-alanine, slight decreased yield of amide product was observed **(Table 4, entry 8-10)**. This may be because of steric hindrances to nucleophilic site of aryl amine.

**Table 4: Effect of different substituted electron donating & withdrawing group of aryl amine on amidation reaction.**




| Entry No. | Aryl amine | Products | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1. |  |  | 16 | 72 |
| 2. |  |  | 16 | 70 |
| 3. |  |  | 16 | - |
| 4 |  |  | 16 | 72 |
| 5. |  |  | 16 | 60 |
| 6. |  |  | 16 | 64 |

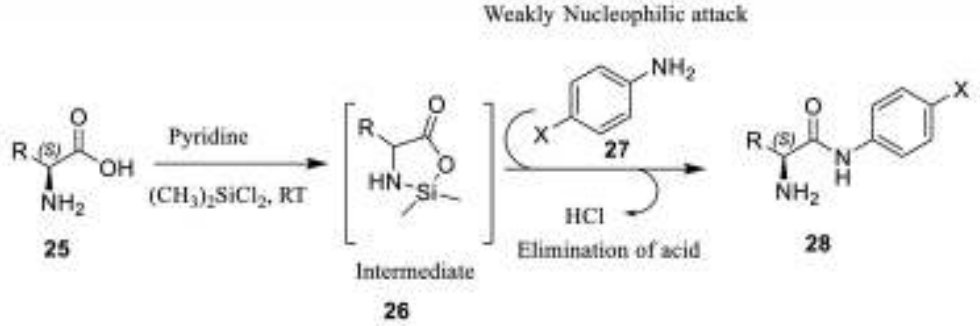
| | | | | |
|---|---|---|---|---|
| 7. |  |  | 16 | - |
| 8. |  |  | 16 | 58 |
| 9. |  |  | 16 | 60 |
| 10. |  |  | 16 | 55 |

### *1.3.4 The amidation reaction using different D and L-amino acids and different aryl amines.*

The different unprotected aliphatic *L*-amino acids like alanine, valine, and leucine was reacted with weakly nucleophilic substituted aryl amines like anisadine, chloroaniline, toludine, fluroaniline, and bromoaniline using dichlorodimethyl silane at room temperature for 16 h. The corresponding *N* aryl *S* amino acid amide product with good to excellent yield was obtained **(Table 5)**. All products were characterized by $^{1}H$ &$^{13}C$ NMR (200MHz, 400MHz, and 500MHz), HRMS, and optical rotation. The CD spectrum was recorded by JASCO-820 spectrophotometer and the data is shown in **Figure 4**.

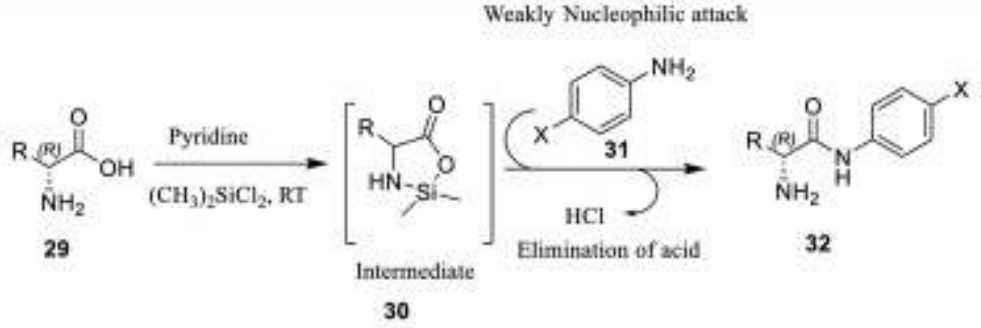
Similarly, *N* aryl *R* amino acid amides were synthesized using unprotected aliphatic *D* amino acids (alanine, valine, and leucine) and weakly nucleophilic aryl amines (anisadine, toludine, chloroaniline, fluroaniline, bromoaniline). The good to excellent yield of *N* aryl *R* amino acid amide was obtained **(Table 6)**. All the products were confirmed by $^{1}H$ &$^{13}C$ NMR (200Hz, 400MHz, and 500 MHz), HRMS, and optical rotation. The CD spectrum was recorded by JASCO-820 spectrophotometer and the data is shown in **Figure 4**.

**Table 5: One step synthesis of *N* aryl *S* amino acid amide.**




| Entry No | R | X | Amide products (22) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | -$CH_3$ | -$OCH_3$ | 28a | *S* | 72 |
| 2 | -$CH_3$ | -$CH_3$ | 28b | *S* | 70 |
| 3 | -$CH_3$ | -Cl | 28c | *S* | 68 |
| 4 | -$CH_3$ | -F | 28d | *S* | 64 |
| 5 | -$CH_3$ | -Br | 28e | *S* | 60 |
| 6 | -$CH(CH_3)_2$ | -$OCH_3$ | 28f | *S* | 71 |
| 7 | -$CH(CH_3)_2$ | -Cl | 28g | *S* | 68 |
| 8 | -CH(CH3)2 | -F | 28h | *S* | 61 |
| 9 | -$CH(CH_3)_2$ | -Br | 28i | *S* | 62 |
| 10 | -$CH_2CH(CH_3)_2$ | -$OCH_3$ | 28j | *S* | 70 |
| 11 | -$CH_2CH(CH_3)_2$ | -Cl | 28k | *S* | 67 |
| 12 | -$CH_2CH(CH_3)_2$ | -F | 28l | *S* | 63 |
| 13 | -$CH_2CH(CH_3)_2$ | -Br | 28m | *S* | 60 |
| 14 | -$CH_3$ | 2,6 –$CH_3$ | 28n | *S* | 58 |
| 15 | -$CH_3$ | 2-$OCH_3$ | 28o | *S* | 60 |
| 16 | -$CH_3$ | 2-Cl | 28p | *S* | 55 |

**Table 6: One step synthesis of *N* aryl *R* amino acid amide.**




| Entry No | R | X | Amide products (32) | Configuration | Yield (%) |
|---|---|---|---|---|---|
| 1 | -$CH_3$ | -$OCH_3$ | 32a | *R* | 71 |
| 2 | -$CH_3$ | -$CH_3$ | 32b | *R* | 69 |
| 3 | -$CH_3$ | -Cl | 32c | *R* | 68 |
| 4 | -$CH_3$ | -F | 32d | *R* | 64 |
| 5 | -$CH_3$ | -Br | 32e | *R* | 61 |
| 6 | -$CH(CH_3)_2$ | -$OCH_3$ | 32f | *R* | 71 |
| 7 | -$CH(CH_3)_2$ | -Cl | 32g | *R* | 66 |
| 8 | -CH(CH3)2 | -F | 32h | *R* | 62 |
| 9 | -$CH(CH_3)_2$ | -Br | 32i | *R* | 60 |
| 10 | -$CH_2CH(CH_3)_2$ | -$OCH_3$ | 32j | *R* | 72 |
| 11 | -$CH_2CH(CH_3)_2$ | -Cl | 32k | *R* | 65 |
| 12 | -$CH_2CH(CH_3)_2$ | -F | 32l | *R* | 61 |
| 13 | -$CH_2CH(CH_3)_2$ | -Br | 32m | *R* | 63 |
| 14 | -$CH_3$ | 2,6-$CH_3$ | 32n | *R* | 60 |

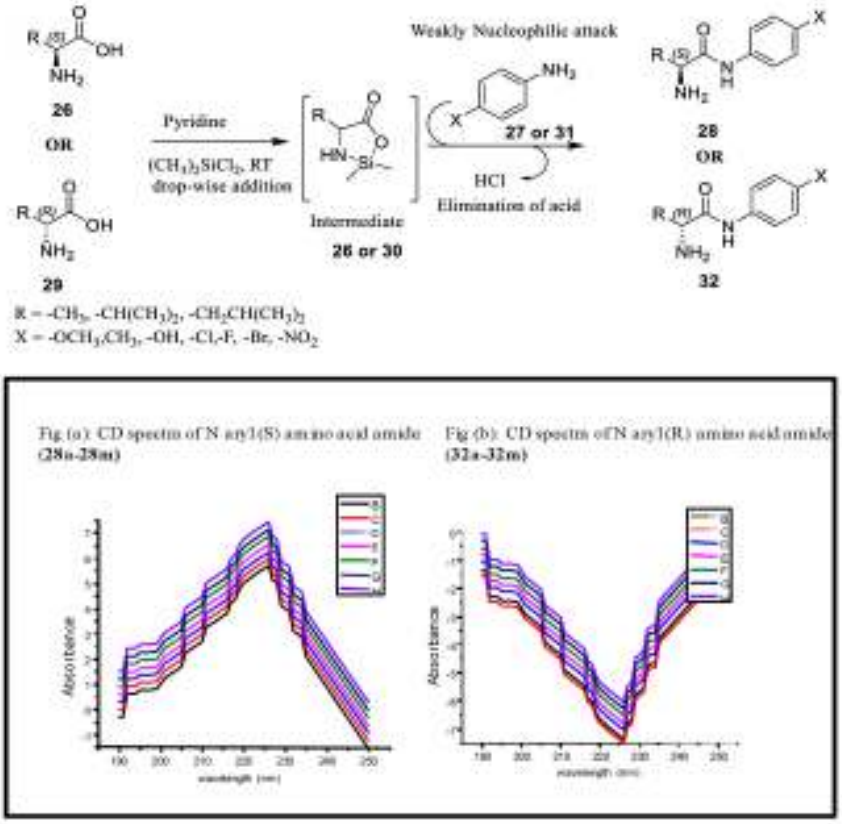
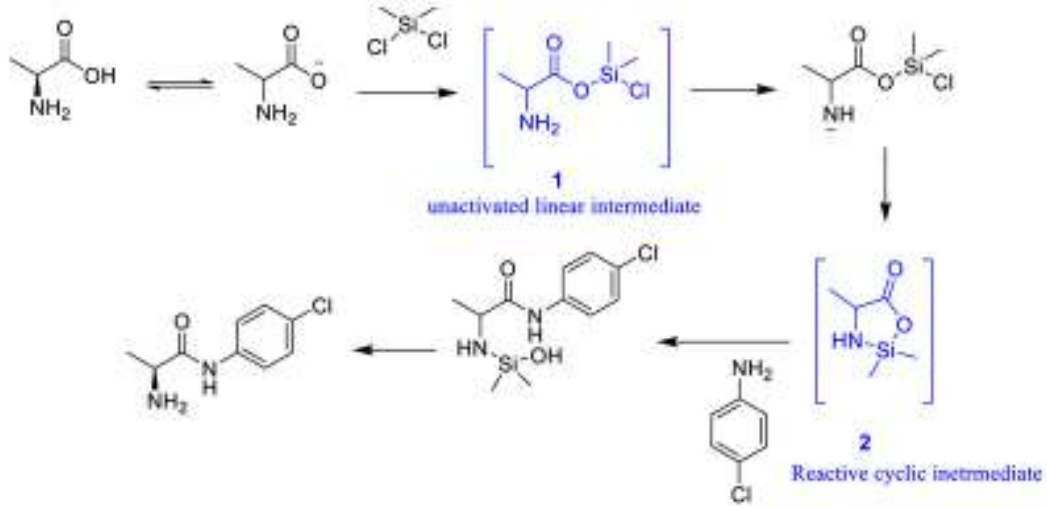



**Figure 4: CD spectra of *N* aryl *R* and *S* amino acid amides products using unprotected *D* & *L* amino acids.**

### *1.3.5 Proposed reaction mechanism of one step amidation reaction.*

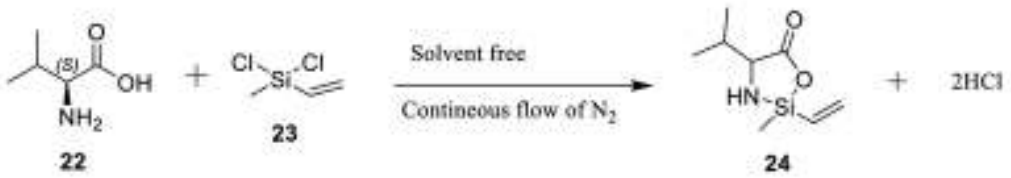
In proposed mechanism, initially carboxylate anion of *L*-alanine is formed in basic media. This carboxylate anion reacts with reactive dichlorodimethyl silane to form linear silane as intermediate **(1)** in situ. Then by simultaneous abstraction of proton from intermediate **(1)** under basic media followed by intramolecular cyclisation to form reactive cyclic silane intermediate **(2).** This reactive cyclic silane activate carbonyl carbon of L-alanine and reacts with 4-chloroanilinne to form amino acid amide product as shown in **Scheme 5.**




**Scheme 5: Postulated mechanism of amidation reaction using dichlorodimethyl silane under weakly basic media.**

### *1.3.6 Isolation of reactive intermediate of amidation reaction.*

For isolating the reactive intermediate, the controlled experiment using *L*-valine and dichloromethylvinyl silane was carried out under solvent free condition at room temperature. In controlled experimental set-up oven dried 50 ml two neck round bottom flask equipped with magnetic stirrer was charged with (11 mmole) of *L*-valine and (11 mmole) of dichloromethylvinyl silane and stirred at room temperature under continuous flow of nitrogen gas. The continuous flow of nitrogen gas was used for removal of HCl which was continuously quenched in aqueous $NH_3$ solution. After reaction 10 ml saturated solution of $NaHCO_3$ was added for removing the unreacted *L*-valine and silane. The product is isolated in DCM. The product was confirmed by $^{1}H$, $^{13}C$ and $^{29}Si$ NMR spectroscopy. Isolated reactive cyclic silane intermediate under solvent free method is shown in **Scheme 6**.




**Scheme 6: Isolation of reactive cyclic intermediate of amidation reaction.**

## 1.4 Conclusion

In conclusion, we have successively synthesized *N* aryl *R* & *S* amino acid amide in one step by using dichlorodimethyl silane as protecting and activating reagent by reacting unprotected aliphatic *D* & *L* amino acids with weakly nucleophilic aryl amines. We have shown that dichlorodimethyl silane is highly effective protecting and activating reagent for one step amidation reaction. By using this method the stereo-genic center of amide product does not epimerized and this was confirmed by CD spectrophotometer. This is one step method for synthesis of amino acid amide and in this method earlier three steps (viz. protection, coupling and deprotection) was reduced and also minimized toxic and hazardous byproducts formation. This method uses a simple reaction set up and it does not require specialized equipment. By using this method the amidation reaction is carried out at mild reaction condition and high yield of product is obtained.

## 1.5 Experimental Section

### *1.5.1 General information of chemicals and instrument.*

All the purified and dry distilled chemicals were purchased from reagent and solvent grade chemical company. All the 99% pure amino acid both *L* and *D* alanine, valine, leucine were purchased from sigma Aldrich chemical limited, aryl amine such as chloraniline, 4-methoxyaniline, 4-fluroaniline, 4-nitroaniline, pyridine, $Na_2SO_4$, $NaHCO_3$, $CuSO_4$ etc were received from Avra Pvt. Chemical limited. The solvents for chromatography and extraction were purchased from commercial suppliers and used without further purification. All reactions were performed in glass reactor equipped with a magnetic stirrer at an atmosphere pressure, unless otherwise stated. Thin layer chromatography (TLC) analysis was used to check reaction progress using Merck TLC plates (silica gel 60GF-254, 0.25mm) and visualized by using UV (254 nm). The products were purified by column chromatography on silica gel 60 (Merck, 230–400 mesh). Products were confirmed by $^{1}H$ & $^{13}C$ NMR (200MHz, 400MHz, 500MHz) Bruker NMR spectroscopy with solvent $CDCl_3$, MeOD-$_4$, $D_2O$, DMSO-$d_6$ as internal standard in chemical shift δ (7.26ppm,77.16 ppm, 3.31 ppm, 49 ppm, 4.79 ppm, 2.50 ppm, 39.52 ppm). Multiplicities are reported using following abbreviations - s= singlet, d= doublet, t= triplet, m= multiplets and br = broad, dd = doublet of doublet, dt = doublet of triplet etc. Optical rotation of product is

confirmed by JASCO Polarimeter and stereochemistry of product is confirmed by JASCO-820 series of circular dichroism Spectro photometer. Mass of the product is confirmed by HRMS. Elemental analysis was carried out by Thermo Finnigan EA1112 series Flash Elemental Analyzer.

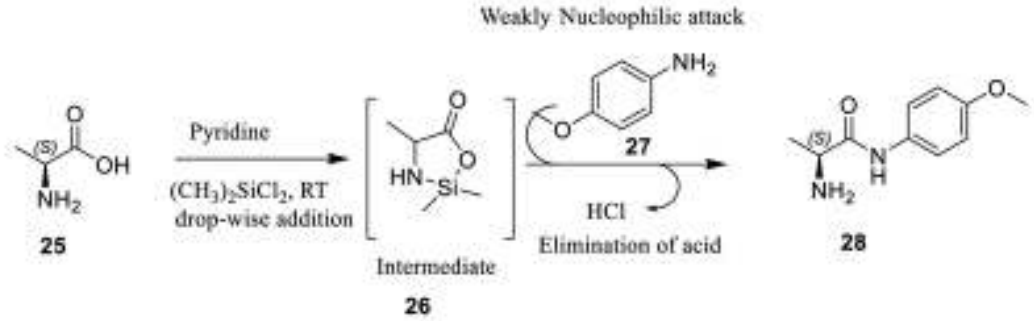
### *1.5.2 General experimental procedure for synthesis of amino acid amide.*

In oven dried 50ml round bottom flask equipped with magnetic stirrer, 11 mmole of amino acid in pyridine was charged and reaction was stir at room temperature to dissolved amino acid completely. Then 13.4 mmole of dichlorodimethyl silane was added and reaction was further stirred for 15 min to obtained clear solution at room temperature. Then corresponding amount of 44 mmole of aryl amine was added and reaction was continuously stirred at room temperature. The progress of reaction was monitored by TLC. The products were confirmed by $^{1}H$ &$^{13}C$ NMR. Mass is confirmed by HRMS. The optical property is confirmed by optical rotation and CD spectrophotometer.

### *1.5.3 Experimental procedure for synthesis of N aryl (S) amino acid amide.*

***28a. (S)-2-amino-N-(4-methoxyphenyl) propanamide:***

Reaction:




Procedure:

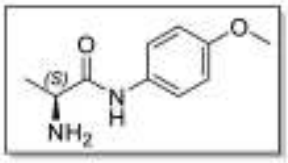
In oven dried 50ml round bottom flask equipped with magnetic stirrer 11mmoles of L-alanine in pyridine was charged and reaction was stirred at room temperature till complete dissolved L-alanine in pyridine. Then 13.5 mmole of dichlorodimethyl silane was added drop-wise and reaction was continuously stirred at 23°C-30°C until complete clear solution is obtained. Then 44 mmoles of anisadine was added and reaction was further stirred at room temperature for 16h.

The progress of reaction was monitored by TLC. After the reaction 25ml saturated solution of $NaHCO_3$ was added to quench the pyridine as well as silane and then 25ml of ethyl acetate was added. Two layer was formed. Both aqueous & organic layer were separated & organic layer was washed three time by saturated solution of $NaHCO_3$ and dried over $Na_2SO_4$ and concentrated under reduced pressure. Product was purified by silica gel column chromatography. Product was confirmed by $^1H$ & $^{13}C$ NMR (200MHz, 400MHz, 500MHz) spectroscopy, mass is confirmed by HRMS, stereochemistry is confirmed by JASCO-820 series of CD spectrophotometer and optical activity is confirmed by JASCO polarimeter. Similar procedure was used for synthesis of other *N* aryl *R* & *S* amino acid amides (28a-28p, 32a-32m).

## 1.6 Spectral data

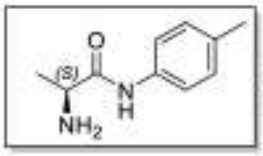
### *1.6.1 Spectral data of N aryl S amino acid amide.*

***28a. (S)-2-amino-N-(4-methoxyphenyl) propanamide:***



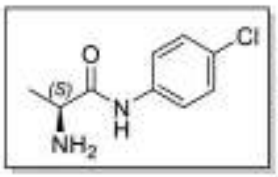
Solid products; Yield 72 %; $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 1.43 (d, *J*=6.71 Hz, 3 H) 2.57 (br. s., 2 H) 3.67 (q, *J*=6.51 Hz, 1 H) 3.79 (s, 3 H) 6.85 (d, *J*=8.55 Hz, 2 H) 7.51 (d, *J*=8.55 Hz, 2 H) 9.40 (br. s., 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ ppm 21.38, 51.01, 55.48, 114.10, 121.09, 131.08, 156.18, 173.14; $[\alpha]_D^{25} = -14.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 194.1055 found: 194.0995; Anal. Calculated C, 61.84; H, 7.27; N, 14.42; found C, 61.58; H, 6.96; N, 14.84;

***28b. (S)-2-amino-N-(p-tolyl) propanamide:***



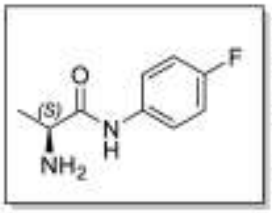
Solid products; Yield 70%; $^1$HNMR (200 MHz, $CDCl_3$) δ ppm 1.44 (d, *J*=6.69 Hz, 3 H) 2.27 (s, 3 H) 3.09 (br. s., 2 H) 3.79 (q, *J*=6.57 Hz, 1 H) 7.07 (d, *J*=8.08 Hz, 2 H) 7.46 (d, *J*=8.21 Hz, 2 H) 9.54 (br. s., 1 H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ ppm 20.09, 20.84, 50.83, 119.80, 129.42, 129.79, 133.84, 135.10, 171.52; $[\alpha]_D^{25} = -12.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O$: 178.1106 found: 178.2350; Anal calculated C, 61.84; H, 7.27; N, 14.42; found C, 61.58; H, 6.96; N, 14.84;

*28c.(S)-2-amino-N-(4-chlorophenyl) propanamide:*



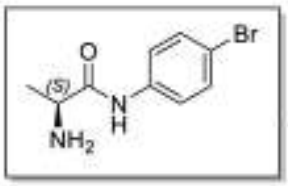

Solid products; Yield 68 %; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 1.42 - 1.47 (m, 3 H) 1.94 (br. s., 2 H) 3.65 (q, *J*=6.87 Hz, 1 H) 7.30 (d, *J*=8.77 Hz, 2 H) 7.57 (d, *J*=8.77 Hz, 2 H) 9.57 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$); δ ppm 21.49, 51.10, 120.59, 128.90, 128.96, 138.44, 173.68; $[\alpha]_D^{25} = -16.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}ClN_2O$: 198.0560; found: 198.153 Anal calculated C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*28d. (S)-2-amino-N-(4-flurorophenyl) propanamide:*



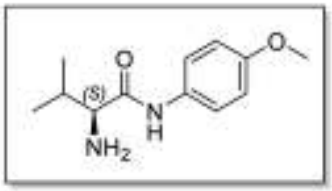

Solid products; Yield 64 %; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 1.41 - 1.44 (d, 3 H) 2.38 (br. s., 2 H) 3.58 (q, *J*=6.87 Hz, 1 H) 7.24 (d, *J*=8.77 Hz, 2 H) 7.53 (d, *J*=8.77 Hz, 2 H) 9.58 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$); δ ppm 21.49, 51.10, 120.59, 128.90, 128.96, 136s.44, 173.68; $[\alpha]_D^{25} = -15.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}FN_2O$: 182.0960; found: 182.153; Anal calculated $C_9H_{11}FN_2O$ : C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*28e. (S)-2-amino-N-(4-bromophenyl) propanamide:*



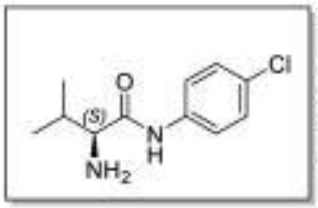

Solid products; Yield 60 %; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 1.44 - 1.45 (d, 3 H) 1.94 (br. s., 2 H) 3.63-3.67 (q, *J*=6.87 Hz, 1 H) 7.29 (d, *J*=8.77 Hz, 2 H) 7.57 (d, *J*=8.77 Hz, 2 H) 9.57 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$); δ ppm 21.49, 51.10, 120.59, 128.90, 128.96, 138.44, 173.68; $[\alpha]_D^{25} = -14.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}BrN_2O$: 182.0960; found: 182.153; Anal calculated $C_9H_{11}BrN_2O$ : C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*28f. (S)-2-amino-N-(4-methoxyphenyl)-3-methylbutnamide:*



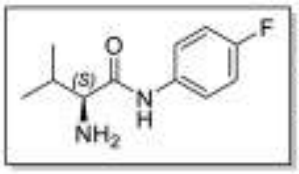
Solid products; Yield 71%; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 0.72-0.88 (d, *J*=6.87 Hz, 3 H) 0.91 (d, *J*=6.87 Hz, 3 H) 1.51 (br. s., 2 H) 2.19 (td, *J*=6.87, 3.81 Hz, 1 H) 3.19 (d, *J*=3.43 Hz, 1 H) 3.65 (s, 3 H) 6.70 (d, *J*=8.77 Hz, 2 H) 7.36 (d, *J*=9.16 Hz, 2 H) 9.28 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 16.04, 19.79, 30.79, 55.49, 60.33, 114.11, 121.99, 121.12, 131.06,156.17, 172.26; $[\alpha]_D^{25} = -16.600$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{18}N_2O_2$ calculated 222.1386 found 222.1296; Anal calculated $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8016; N, 12.60; found C, 62.50; H, 7.40; N, 13.10;

*28g. (S)-2-amino-N-(4-chlorophenyl)-3-methylbutnamide:*



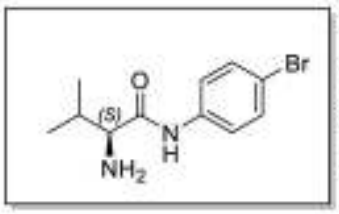
Solid products; Yield 68 %; $^1$H NMR (200 MHz, $CDCl_3$) δ ppm 0.86 (d, *J*=6.95 Hz, 3 H) 1.04 (d, *J*=7.07 Hz, 3 H) 1.68 (br. s., 2 H) 2.32 - 2.56 (m, 1 H) 3.38 (d, *J*=3.54 Hz, 1 H) 7.25 - 7.32 (d, 2 H) 7.53 - 7.60 (d, 2 H) 9.60 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 15.93, 19.82, 30.68, 60.34, 120.63, 128.96, 136.38, 172.66; $[\alpha]_D^{25} = -14.45$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}ClN_2O$ : 226.0873 found : 226.0974; Anal calculated $C_{11}H_{15}ClN_2O$ : C, 58.28; H, 6.67; N, 12.36; found C, 58.10; H, 6.20; N, 12.96;

*28h. (S)-2-amino-N-(4-flurorophenyl)-3-methylbutnamide:*



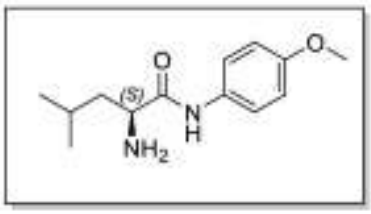
Solid products; Yield 61 %; $^1$H NMR (200 MHz, $CDCl_3$) δ ppm 0.85 (d, *J*=6.95 Hz, 3 H) 1.03 (d, *J*=7.07 Hz, 3 H) 2.37 (br. s., 2 H) 2.39 - 2.56 (m, 1 H) 3.37 (d, *J*=3.54 Hz, 1 H) 7.26 - 7.30 (d, 2 H) 7.53 - 7.59 (d, 2 H) 9.60 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 15.93, 19.82, 30.68, 60.34, 120.63, 128.86, 128.96, 136.38, 172.66; $[\alpha]_D^{25} = -15.45$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}FN_2O$ : 210.1283 found : 210.0974; Anal calculated $C_{11}H_{15}FN_2O$ : C, 58.28; H, 6.67; N, 12.36; found C, 58.10; H, 6.20; N, 12.96;

*28i. (S)-2-amino-N-(4-bromophenyl)-3-methylbutnamide:*



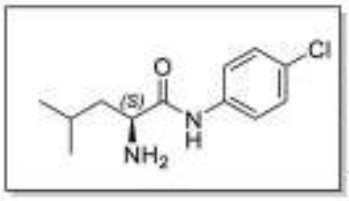
Solid products; Yield 62 %; $^{1}$H NMR (200 MHz, $CDCl_3$) δ ppm 0.85 (d, *J*=6.95 Hz, 3 H) 1.02 (d, *J*=7.07 Hz, 3 H) 1.84 (br. s., 2 H) 2.39 - 2.49 (m, 1 H) 3.37 (d, *J*=3.54 Hz, 1 H) 7.26 - 7.30 (d, 2 H) 7.54 - 7.59 (d, 2 H) 9.59 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 15.93, 19.82, 30.68, 60.34, 120.63, 128.80, 128.96, 136.38, 172.66; $[\alpha]_D^{25} = -11.450$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}BrN_2O$ : 270.0473 found : 270.0974; Anal calculated $C_{11}H_{15}BrN_2O$ : C, 58.28; H, 6.67; N, 12.36; found C, 58.10; H, 6.20; N, 12.96;

*28j. (S)-2-amino-N-(4-methoxyphenyl)-4-methylpentanamide:*



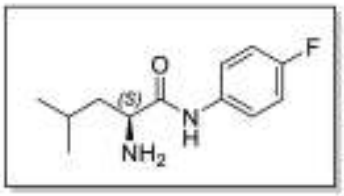
Solid products; Yield 70%; $^{1}$H NMR (500 MHz, $CDCl_3$) δ ppm 0.98 (d, *J*=6.49 Hz, 3 H) 1.01 (d, *J*=6.10 Hz, 3 H) 1.39 - 1.45 (m, 2 H) 1.81 - 1.85 (m, 3 H) 3.51 (dd, *J*=9.73, 3.62 Hz, 1 H) 3.81 (s, 3 H) 6.87 (d, *J*=8.77 Hz, 2 H) 7.52 (d, *J*=8.77 Hz, 2 H) 9.39 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.37, 23.44,25.01, 43.92, 53.86, 55.48, 114.12, 114.65, 120.95, 130.10, 131.23, 156.11, 173.30; $[\alpha]_D^{25} = -10.7$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{13}H_{20}N_2O_2$ calculated 236.1525 found 236.1498; Anal calculated $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; found C, 65.84; H, 8.10; N, 12.30;

*28k. (S)-2-amino-N-(4-chlorophenyl)-4-methylpentanamide:*



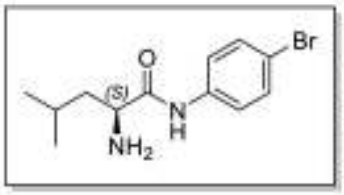
Solid products; Yield 67%; $^{1}$H NMR (500 MHz, $CDCl_3$) δ ppm 0.98 (d, *J*=6.10 Hz, 3 H) 1.01 (d, *J*=6.49 Hz, 3 H) 1.39 - 1.47 (m, 2 H) 1.76 - 1.86 (m, 3 H) 3.52 (dd, *J*=9.92, 3.43 Hz, 1 H) 7.29 (d, *J*=8.77 Hz, 2 H) 7.57 (d, *J*=8.77 Hz, 2 H) 9.61 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.31, 23.41, 24.94,43.82, 53.86, 116.21,120.55, 128.78, 128.94, 130.06, 136.54, 173.74; $[\alpha]_D^{25} = -14.7$ (C = 1 $CHCl_3$); HRMS(ESI) calculated $C_{12}H_{17}ClN_2O$ : 240.1029 found : 240.1109; Anal calculated $C_{12}H_{17}ClN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

### 28l. (S)-2-amino-N-(4-flurophenyl)-4-methylpentanamide:



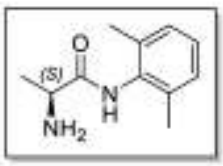
Solid products; Yield 63%; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 0.94 (dd, *J*=6.10 Hz, 6 H) 1.39 - 1.46 (m, 2 H) 1.73 - 1.83 (m, 3 H) 3.47-3.57 (dd, *J*=9.92, 3.43 Hz, 1 H) 7.29 (d, *J*=8.77 Hz, 2 H) 7.53 (d, *J*=8.77 Hz, 2 H) 9.60 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.31, 23.41, 24.94,43.82, 53.86, 116.21,120.55, 128.87, 128.94, 130.06, 136.54, 173.74; $[\alpha]_D^{25} = -12.7$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{17}FN_2O$ calculated 224.1329 found 224.1109; Anal calculated $C_{12}H_{17}FN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

### 28m. (S)-2-amino-N-(4-bromophenyl)-4-methylpentanamide:



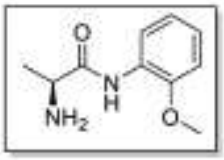
Solid products: Yield 60%; $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 0.95-1.00 (d, *J*=6.10 Hz, 3 H) 1.39 - 1.47 (m, 2 H) 1.64 - 1.90 (m, 3 H) 3.64-3.70 (dd, *J*=9.92, 3.43 Hz, 1 H) 7.25-7.30 (d, *J*=8.77 Hz, 2 H) 7.53-7.58 (d, *J*=8.77 Hz, 2 H) 9.59 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.31, 23.41, 24.99, 43.82, 54.86, 116.21,120.55, 128.78, 128.94, 130.06, 136.54, 173.74; $[\alpha]_D^{25} = -13.54$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{17}BrN_2O$ calculated 224.1329 found 224.1109; Anal calculated $C_{12}H_{17}BrN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

### 28n. (S)-2-amino-N-(2,6-dimethylphenyl)propanamide



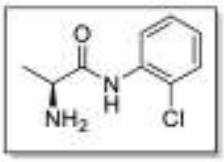
$^1$H NMR ($CDCl_3$, 200MHz): δ ppm = 8.48 (br. s., 1 H), 6.81 (d, *J*=7.3 Hz, 2 H), 6.35 - 6.59 (m, 1 H), 3.82 - 4.18 (m, 1 H), 3.34 (br. s., 2 H), 2.05 (s, 6 H), 0.99 - 1.21 (d, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm = 173.0, 136.2, 128.8, 123.4, 120.6, 50.8, 20.8, 20.4; $[\alpha]_D^{25} = -32.10$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 192.1263 found: 192.1195; Anal calculated $C_{11}H_{16}N_2O$ : C, 68.72; H, 8.39; N, 14.57; found C, 67.88; H, 7.96; N, 14.84;

*28o. (S)-2-amino-N-(2-methoxyphenyl)propanamide*



$^1$H NMR ($CDCl_3$, 200MHz): δ ppm = 8.45 (br. s., 1 H), 6.55 - 6.80 (m, 20 H), 3.71 (s, 3 H), 3.33 - 3.65 (m, 3 H), 1.06 - 1.19 ppm (d, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm = 174.6, 147.3, 136.0, 121.0, 118.4, 115.0, 110.4, 55.3, 29.6, 14.1; $[\alpha]_D^{25} = -12.23$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 194.1055 found: 194.0995 Anal calculated C, 61.84; H, 7.27; N, 14.42; found C, 61.58; H, 6.96; N, 14.84;

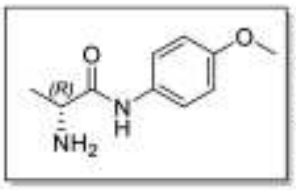
*28p. (S)-2-amino-N-(2-chlorophenyl) propanamide*



$^1$H NMR ($CDCl_3$, 200MHz): δ ppm = 8.43 (d, *J*=4.3 Hz, 1 H), 7.45 - 7.71 (m, 1 H), 7.06 - 7.28 (m, 1 H), 6.86 - 7.01 (m, 1 H), 6.38 - 6.67 (m, 1 H), 3.69 - 4.49 (m, 3 H), 1.06 - 1.24 ppm (d, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm = 171.2, 149.0, 136.3, 128.9, 123.8, 118.8, 116.1, 29.5, 14.0; $[\alpha]_D^{25} = -9.25$ (C = 1 $CHCl_3$), HRMS (ESI) calculated $C_9H_{11}ClN_2O$: 198.0560; found: 198.153 Anal calculated C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

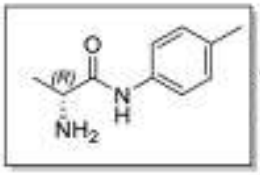
## *1.6.2 Spectral data of N aryl R amino acid amides.*

*32a. (R)-2-amino-N-(4-methoxyphenyl) propanamide:*



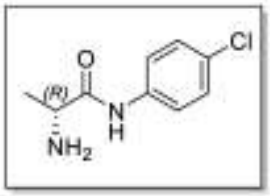
Solid products; Yield 71%; $^1$H NMR (400 MHz, $CHCl_3$-*d*) δ ppm 1.40 (d, *J*=6.87 Hz, 3 H) 2.53 (br. s., 2 H) 3.62-3.67 (q, *J*=6.87 Hz, 1 H) 3.76 (s, 3 H) 6.81 (d, *J*=9.16 Hz, 2 H) 7.47 (d, *J*=8.70 Hz, 2 H) 9.37 (s, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$-*d*) 21.38, 51.01, 55.46, 114.10, 121.09, 131.06, 156.18, 173.14; $[\alpha]_D^{25} = +14.600$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 194.1055 found: 194.0995; Anal calculated $C_{10}H_{14}N_2O_2$ : C, 61.84; H, 7.27; N, 14.42; found C, 61.58; H, 6.96; N, 14.84;

*32b. (R)-2-amino-N-(p-tolyl) propanamide:*



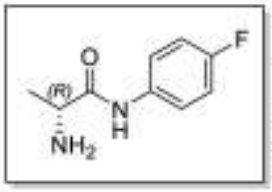
Solid products, Yield 69%; $^1$NMR (200 MHz, $CHCl_3$-*d*) δ ppm 1.43 (d, *J*=6.57 Hz, 3 H) 2.27 (s, 3 H) 3.20 (br. s., 2 H) 3.73 - 3.87 (m, 1 H) 7.07 (d, *J*=8.21 Hz, 2 H) 7.46 (d, *J*=8.34 Hz, 2 H) 9.54 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) 20.87, 29.72, 50.98, 119.61, 129.44, 133.73, 135.20, 172.58; $[\alpha]_D^{25} = +13.10$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 194.1055 found: 194.0995; Anal calculated $C_{10}H_{14}N_2O$ : C, 61.84; H, 7.27; N, 14.42; found C, 61.58; H, 6.96; N, 14.84;

*32c. (R)-2-amino-N-(4-chlorophenyl) propanamide:*



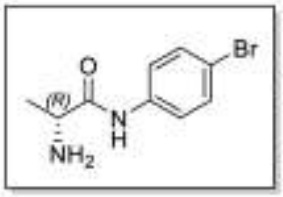
Solid products; Yield 68%; $^1$H NMR (200 MHz, $CDCl_3$-*d*) δ ppm 1.31 (d, *J*=6.95 Hz, 3 H) 1.76 (br. s., 2 H) 3.47 (q, *J*=6.99 Hz, 1 H) 7.16 - 7.20 (d, 2 H) 7.44 (d, *J*=8.72 Hz, 2 H) 9.28 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$-*d*) 21.38, 51.01,114.10, 121.09, 128.90, 131.06, 156.18, 173.14; $[\alpha]_D^{25} = +16.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}ClN_2O$: 198.0560; found: 198.153; Anal calculated $C_9H_{11}ClN_2O$ : C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*32d. (R)-2-amino-N-(4-flurophenyl) propanamide:*



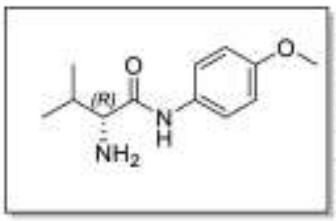
Solid products; Yield 64%; $^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.44 (d, *J*=6.95 Hz, 3 H) 1.94 (br. s., 2 H) 3.63 (q, *J*=6.99 Hz, 1 H) 7.29 - 7.30 (d, 2 H) 7.57 (d, *J*=8.72 Hz, 2 H) 9.57 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 21.49, 51.10, 120.59, 128.90, 128.96, 136.44, 173.68; $[\alpha]_D^{25} = +15.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}FN_2O$: 182.0960; found: 182.153; Anal calculated $C_9H_{11}FN_2O$ : C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*32e. (R)-2-amino-N-(4-bromophenyl) propanamide:*



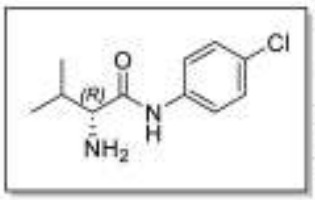
Solid products; Yield 61%; $^{1}$H NMR (200 MHz, $CDCl_3$-*d*) δ ppm 1.41 (d, *J*=6.95 Hz, 3 H) 2.38 (br. s., 2 H) 3.68 (q, *J*=6.99 Hz, 1 H) 7.24 - 7.29 (d, 2 H) 7.53 (d, *J*=8.72 Hz, 2 H) 9.58 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$-*d*) δ ppm 21.38, 51.01, 114.10, 121.09, 131.06, 156.18, 138.44, 173.14; $[\alpha]_D^{25} = +13.60$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_9H_{11}BrN_2O$: 242.0160; found: 242.153; Anal calculated $C_9H_{11}BrN_2O$ : C, 54.42; H, 5.58; N, 14.10; found C, 54.10; H, 5.25; N, 14.58;

*32f. (R)-2-amino-N-(4-methoxyphenyl) 3-methylbutanamide:*



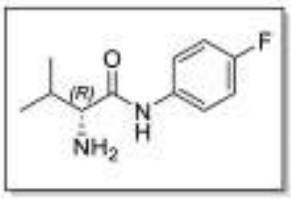
Solid products; Yield 71%; $^{1}$H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 0.89 (d, *J*=6.87 Hz, 3 H) 1.05 (d, *J*=6.87 Hz, 3 H) 1.90 (br. s., 2 H) 2.42 - 2.46 (m, 1 H) 3.39 (br. s., 1 H) 3.80 (s, 3 H) 6.87 (d, *J*=8.77 Hz, 2 H) 7.51 (d, *J*=8.77 Hz, 2 H) 9.39 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$-*d*) δ ppm 16.02, 19.79, 30.79, 55.49, 60.33, 114.11, 121.12, 131.06, 156.17, 172.2; $[\alpha]_D^{25} = +17.60$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{18}N_2O_2$ calculated 222.1386 found 222.1296; Anal calculated $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8016; N, 12.60; found C, 62.50; H, 7.40; N, 13.10;

*32g. (R)-2-amino-N-(4-chlorophenyl) 3-methylbutanamide:*



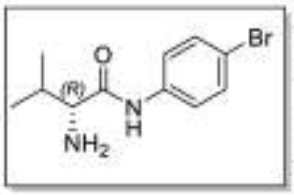
Solid products; Yield 66%; $^{1}$H NMR (200 MHz, $CDCl_3$-*d*) δ ppm 0.85 (d, *J*=6.95 Hz, 3 H) 1.02 (d, *J*=7.07 Hz, 3 H) 1.88 (br. s., 4 H) 2.49 (dtt, *J*=10.43, 6.96, 6.96, 3.49, 3.49 Hz, 1 H) 3.37 (d, *J*=3.41 Hz, 1 H) 7.26 (d, *J*=8.97 Hz, 2 H) 7.54 (d, *J*=8.84 Hz, 2 H) 9.59 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$-*d*) δ ppm 17.97, 18.98, 31.74, 60.50, 116.22, 122.67,130.04,130.86, 157.73, 168.03; $[\alpha]_D^{25} = +18.45$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}ClN_2O$: 226.0873 found: 226.0974; Anal calculated $C_{11}H_{15}ClN_2O$: C, 58.28; H, 6.67; N, 12.36; found C, 58.10; H, 6.20; N, 12.96;

***32h. (R)-2-amino N (4-flurophenyl)-3-methylbutanamide:***



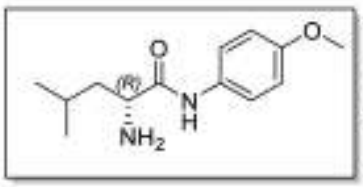
Solid products; Yield 62%; $^{1}$H NMR (200 MHz, $CDCl_3$) δ ppm 0.85 (d, *J*=6.95 Hz, 3 H) 1.03 (d, *J*=7.07 Hz, 3 H) 1.70 (br. s., 2 H) 2.38-2.50 (dtd, *J*=13.88, 6.92, 6.92, 3.60 Hz, 1 H) 3.36 (d, *J*=3.66 Hz, 1 H) 7.26 (d, *J*=8.84 Hz, 2 H) 7.54 (d, *J*=8.84 Hz, 2 H) 9.57 (br. s., 1 H); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ ppm 15.97, 19.78, 30.73, 60.38, 116.23, 120.67, 128.87, 128.95, 136.40, 172.67; $[\alpha]_D^{25} = +11.80$ (C= 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}FN_2O$: 210.1273 found : 210.2574 Anal. Calculated $C_{11}H_{15}FN_2O$: C, 62.84; H, 7.19; N, 13.32. Found: C, 62.57; H, 7.28; N, 13.50;

***32i. (R)-2-amino-N-(4-bromophenyl) 3-methylbutanamide:***



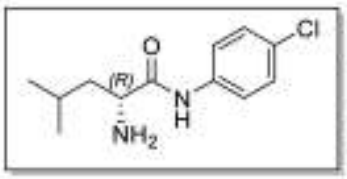
Solid products; Yield 60%; $^{1}$H NMR (200 MHz, $CDCl_3$) δ ppm 0.71 (d, *J*=6.95 Hz, 3 H) 0.88 (d, *J*=7.07 Hz, 3 H) 1.74 (br. s., 4 H) 2.22 (dtt, *J*=10.43, 6.96, 6.96, 3.49, 3.49 Hz, 1 H) 3.23 (d, *J*=3.41 Hz, 1 H) 7.11 (d, *J*=8.97 Hz, 2 H) 7.40 (d, *J*=8.84 Hz, 2 H) 9.45 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 15.93, 19.82, 30.68, 60.34, 116.22, 120.63, 128.86, 128.96, 136.38, 172.66; $[\alpha]_D^{25} = +18.450$ (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{11}H_{15}BrN_2O$: 270.0473 found: 270.0974; Anal calculated $C_{11}H_{15}BrN_2O$: C, 58.28; H, 6.67; N, 12.36; found C, 58.10; H, 6.20; N, 12.96;

***32j. (R)-2-amino-N-(4-methoxyphenyl)-4-methylpentanamide:***



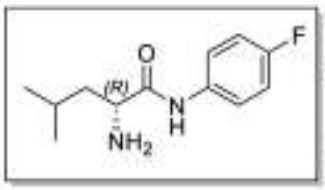
Solid products; Yield 72%; $^{1}$H NMR (200 MHz, $CDCl_3$) δ ppm 0.95 (t, *J*=5.75 Hz, 6 H) 1.37 - 1.40 (m, 1 H) 1.70 (br. s., 2 H)1.78 - 1.89 (m, 2 H) 3.47 (dd, *J*=9.92, 3.60 Hz, 1 H) 3.79 (s, 3 H) 6.84 (d, *J*=9.09 Hz, 2 H) 7.48 (d, *J*=9.09 Hz, 2 H) 9.37 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 18.21, 18.88, 30.40, 55.67, 74.86, 114.60, 121.65, 131.29, 156.36, 166.68; $[\alpha]_D^{25} = +10.7$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{13}H_{20}N_2O_2$ calculated 236.1525 found 236.1498; Anal calculated $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85; found C, 65.84; H, 8.10; N, 12.30;

***32k. (R)-2-amino-N-(4-chlorophenyl)-4-methylpentanamide:***



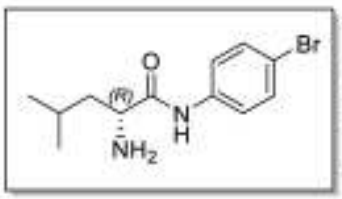
Solid products; Yield 65%; $^{1}$H NMR (200 MHz, $CDCl_3$) δ ppm 0.94 (m, *J*=5.68 Hz, 6 H) 1.37 - 1.46 (m, 2 H) 1.73-1.88 (m, 4H) 3.47-3.63 (dd, *J*=9.85, 3.03 Hz, 1 H) 7.25 (d, *J*=8.84 Hz, 2 H) 7.53 (d, *J*=8.72 Hz, 2 H) 9.60 (br. s., 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 22.24, 23.03, 24.14,49.04, 52.28,121.68, 128.78, 128.36, 129.39, 137.25, 16842; $[\alpha]_D^{25} = +12.7$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{17}ClN_2O$ calculated 240.1029 found 240.1109; Anal calculated $C_{12}H_{17}ClN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

***32l. (R)-2-amino-N-(4-flurophenyl)-4-methylpentanamide:***



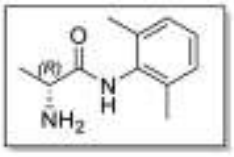
Solid products; Yield 61%; $^{1}$H NMR (500 MHz, $CDCl_3$) δ ppm 0.82 (d, *J*=6.10 Hz, 3 H) 0.85 (d, *J*=6.49 Hz, 3 H) 1.26 - 1.31 (m, 2 H) 1.76 - 1.86 (m, 3 H) 3.35 (dd, *J*=9.92, 3.43 Hz, 1 H) 7.13 (d, *J*=8.77 Hz, 2 H) 7.41 (d, *J*=8.77 Hz, 2 H) 9.46 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.37, 23.44, 25.09, 43.92, 53.86, 114.12,114.65, 120.95, 130.10, 130.23, 156.11, 173.30; $[\alpha]_D^{25} = +16.7$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_{12}H_{17}FN_2O$ calculated 224.1329 found 224.1109; Anal calculated $C_{12}H_{17}FN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

***32m. (R)-2-amino-N-(4-bromophenyl)-4-methylpentanamide:***



Solid products; Yield 63%; $^{1}$H NMR (500 MHz, $CDCl_3$) δ ppm 0.95 (m, *J*=6.10 Hz, 6 H) 1.39 - 1.47 (m, 2 H) 1.65 - 1.96 (m, 3 H) 3.64 (dd, *J*=9.92, 3.43 Hz, 1 H) 7.25 (d, *J*=8.77 Hz, 2 H) 7.53 (d, *J*=8.77 Hz, 2 H) 9.59 (br. s., 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ ppm 21.31, 23.41, 24.99, 43.82, 53.86, 116.21,120.55, 128.78, 128.94, 129.60, 130.06, 136.54, 173.74; $[\alpha]_D^{25} = +14.7$ (C = 1 $CHCl_3$), HRMS (ESI) of $C_{12}H_{17}BrN_2O$ calculated 224.1329 found 224.1109; Anal calculated $C_{12}H_{17}BrN_2O$: C, 59.87; H, 7.12; N, 11.64; found C, 59.20; H, 6.96; N, 12.10;

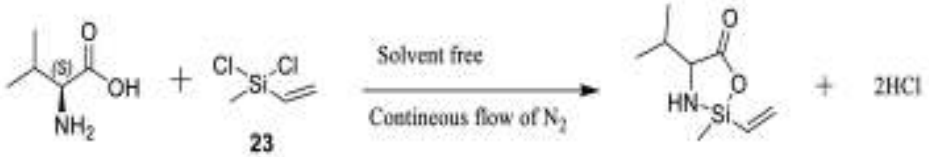
*32m. (R)-2-amino-N-(2,6-dimethylphenyl)propanamide*



$^1$H NMR ($CDCl_3$, 200MHz): δ ppm = 8.48 (br. s., 1 H), 6.81 (d, *J*=7.3 Hz, 2 H), 6.35 - 6.59 (m, 1 H), 3.82 - 4.18 (m, 1 H), 3.34 (br. s., 2 H), 2.05 (s, 6 H), 0.99 - 1.21 (d, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm = 173.0, 136.2, 128.8, 123.4, 120.6, 50.8, 20.8, 20.4 ; $[\alpha]_D^{25}$ = +32.10 (C = 1 $CHCl_3$); HRMS (ESI) calculated $C_{10}H_{14}N_2O_2$ : 192.1263 found: 192.1195; Anal calculated $C_{11}H_{16}N_2O$ : C, 68.72; H, 8.39; N, 14.57; found C, 67.88; H, 7.96; N, 14.84;

### *1.6.3 Experimental procedure for isolation cyclic silane intermediate.*

Reaction:

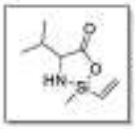



22 23 24

Procedure:

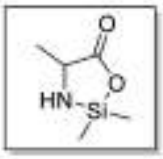
Oven dry 50 ml two neck round bottom flask equipped with magnetic stirrer was charged with 11 mmoles of L-valine and 11 mmoles of dichloromethylvinylsilane and reaction was stir at room temperature under solvent free condition. One neck of round bottom flask was connected to continuous flow of nitrogen gas line and another neck wass connected to pipe which was deep into the aqueous $NH_3$ solution. Wen white fume was started in aqueous solution of $NH_3$; formation of reactive cyclic silane intermediate is started then reaction was stoped. Reactive cyclic intermediate was isolated in DCM and was confirmed by $^1$H, $^{13}$C & $^{29}$Si NMR.

*4-isopropyl-2-methyl-2-vinyl-1,3,2-oxazasilolidin-5-one:*



$^1$H NMR (400 MHz, MeOH-*d*$_4$) δ ppm 0.17 (br. s., 2 H) 1.57 (d, *J*=6.71 Hz, 6 H) 2.29-2.37 (m, *J*=7.32 Hz, 1 H) 3.88 (d, *J*=8.55 Hz, 1 H) 6.00 (dd, *J*=6.10 Hz, 3 H); $^{13}$C NMR (100 MHz, MeOH-*d*$_4$) δ ppm 2.09, 15.02, 132.81, 132.82, 135.90, 136.50, 171.10; $^{29}$Si NMR (s, -32.44);

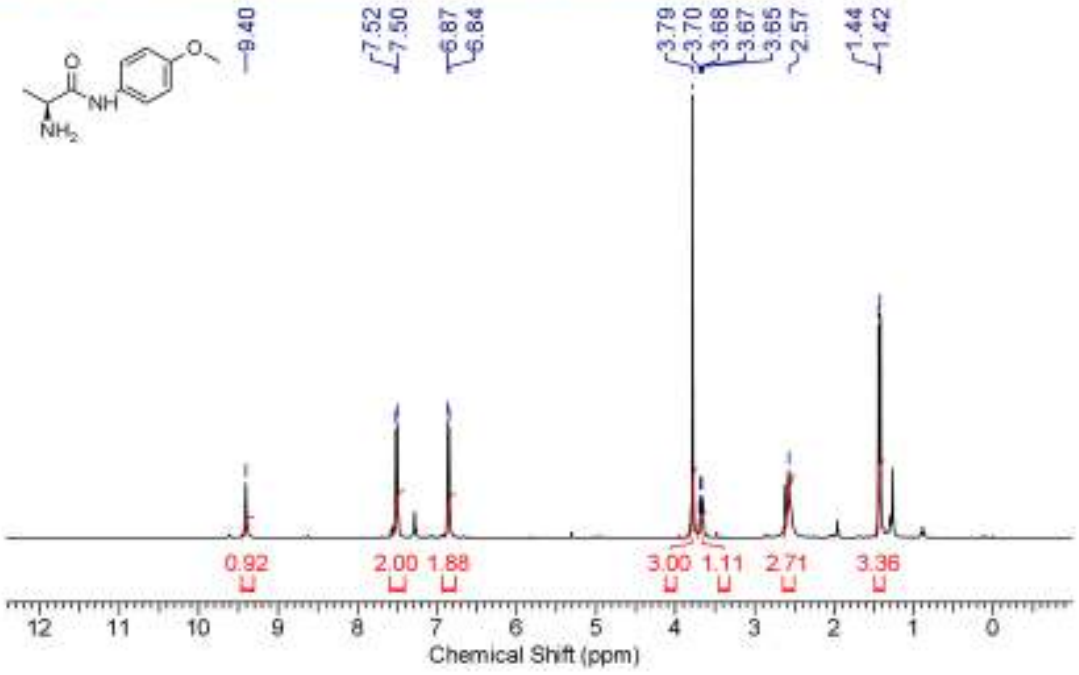
*2,2,4-trimethyl-1,3,2-oxazasilolidin-5-one:*

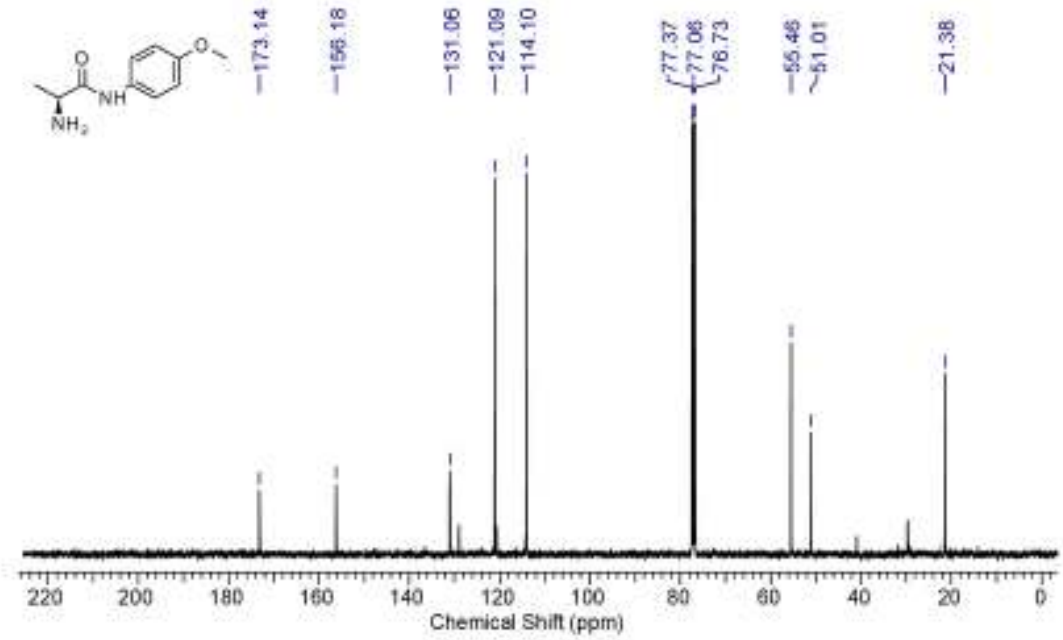



$^{1}$H NMR (DMSO-$d_6$, 200MHz): δ = 3.60 - 3.88 (m, 1 H), 1.32 (d, *J*=7.2 Hz, 3 H), -0.10 ppm (br. s., 6 H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ ppm -0.6, 0.6, 23.5, 61.3, 179.10;

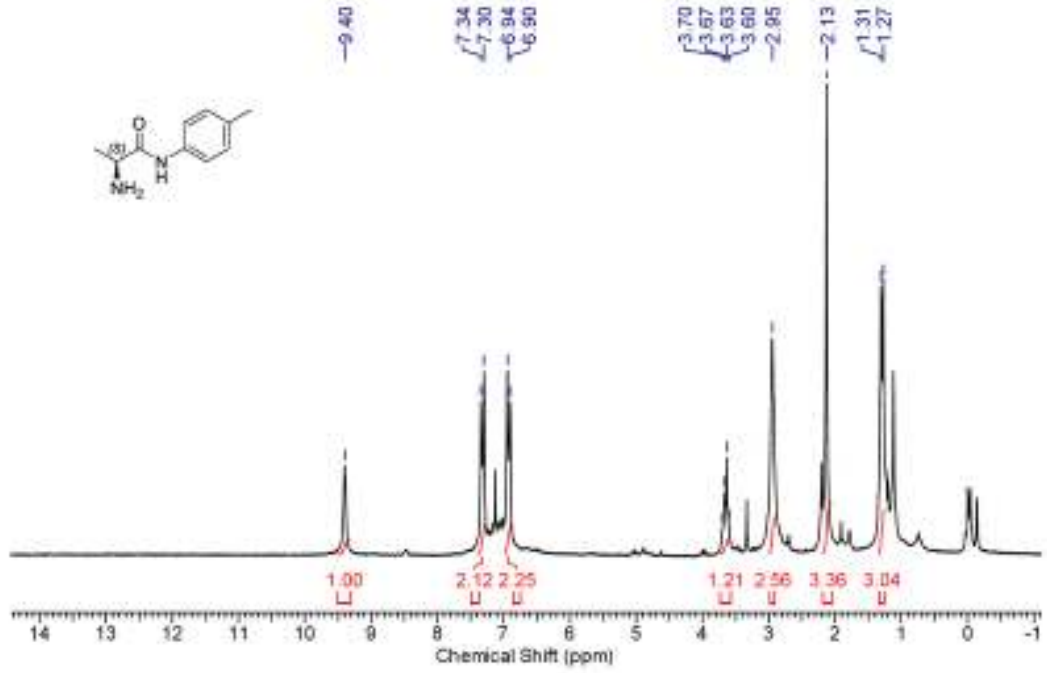
## 1.6 $^{1}H$ & $^{13}C$ NMR spectra of *N* aryl *S* amino acid amides

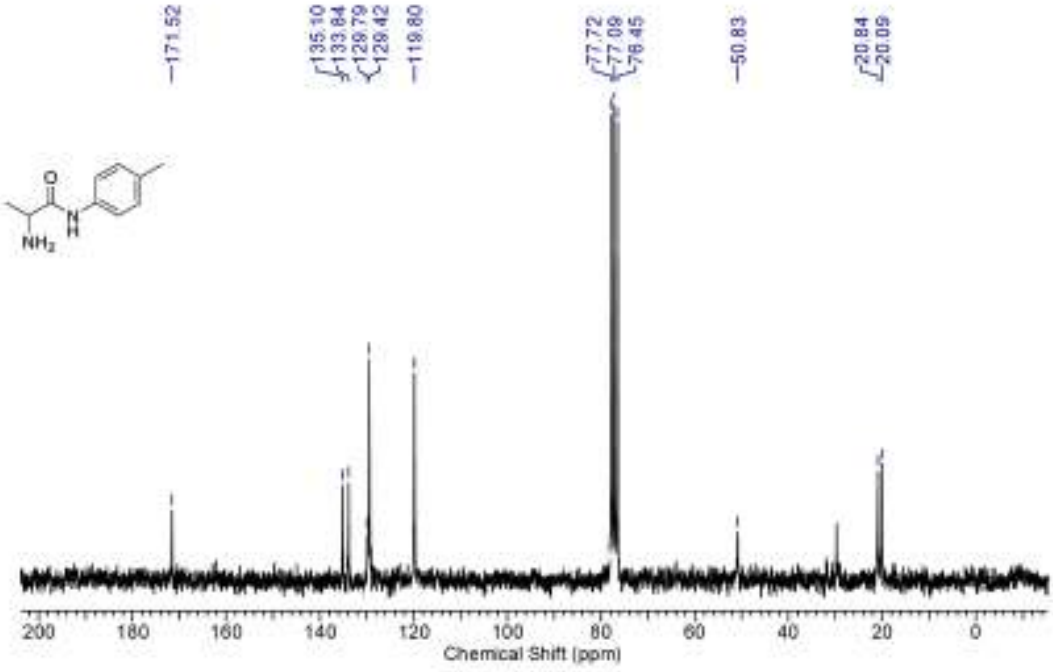
*28a. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(4-methoxyphenyl) propanamide:*



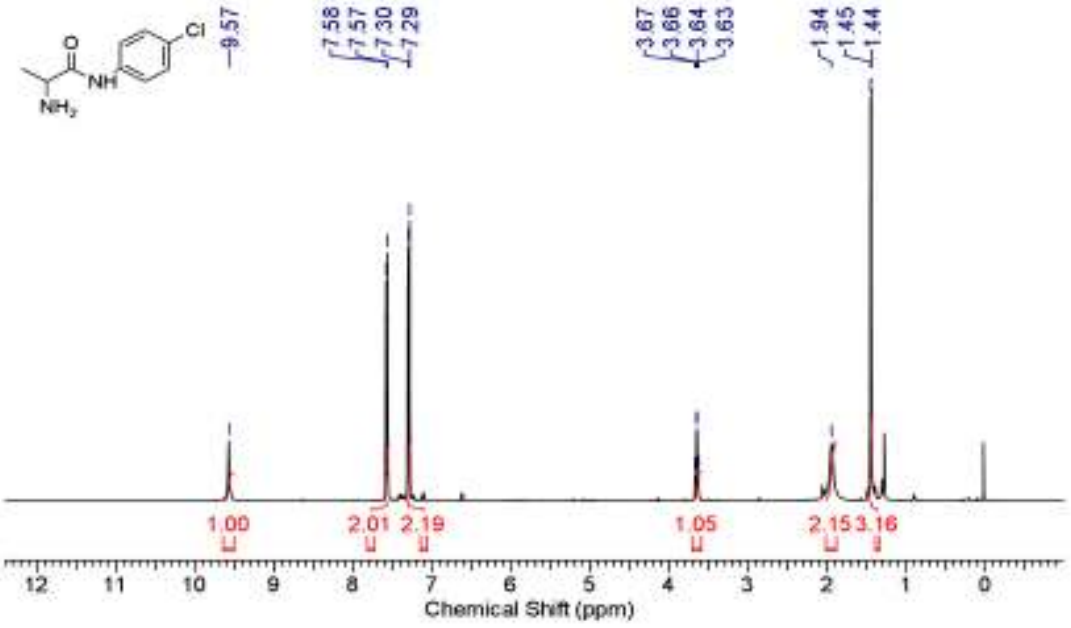



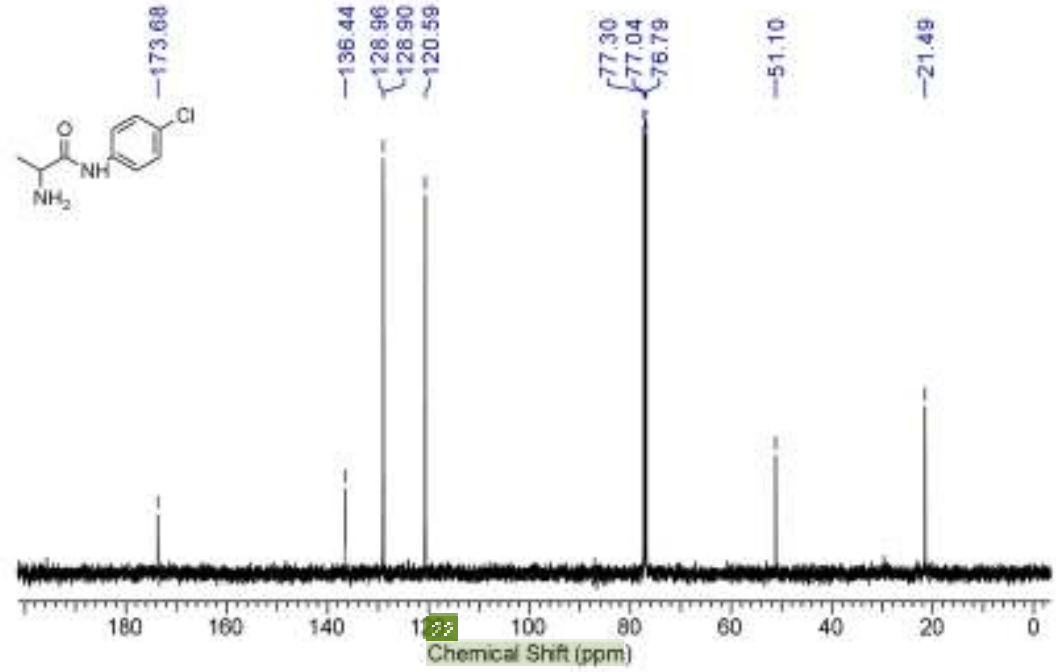
*28b. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(p-tolyl)propanamide:*



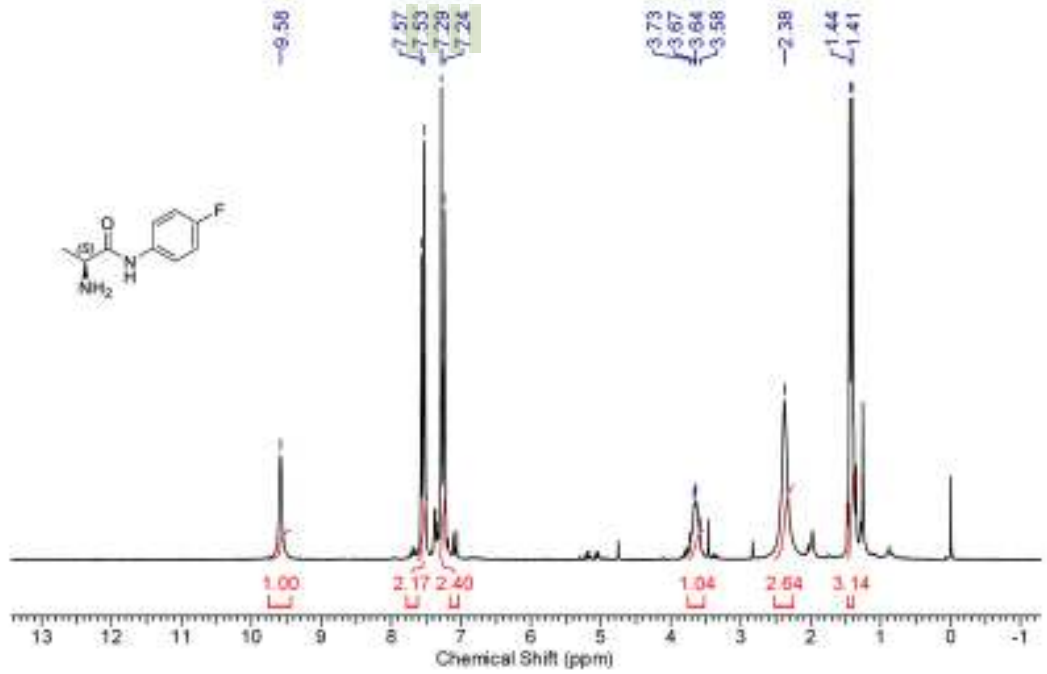



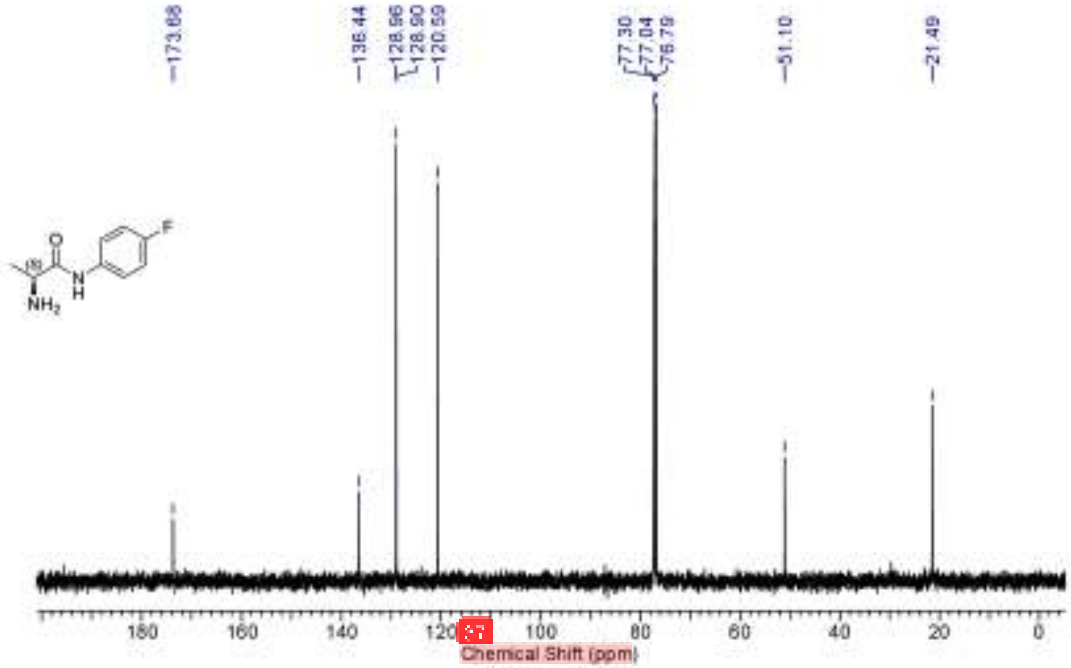
*28c. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(4-chlorophenyl) propanamide:*



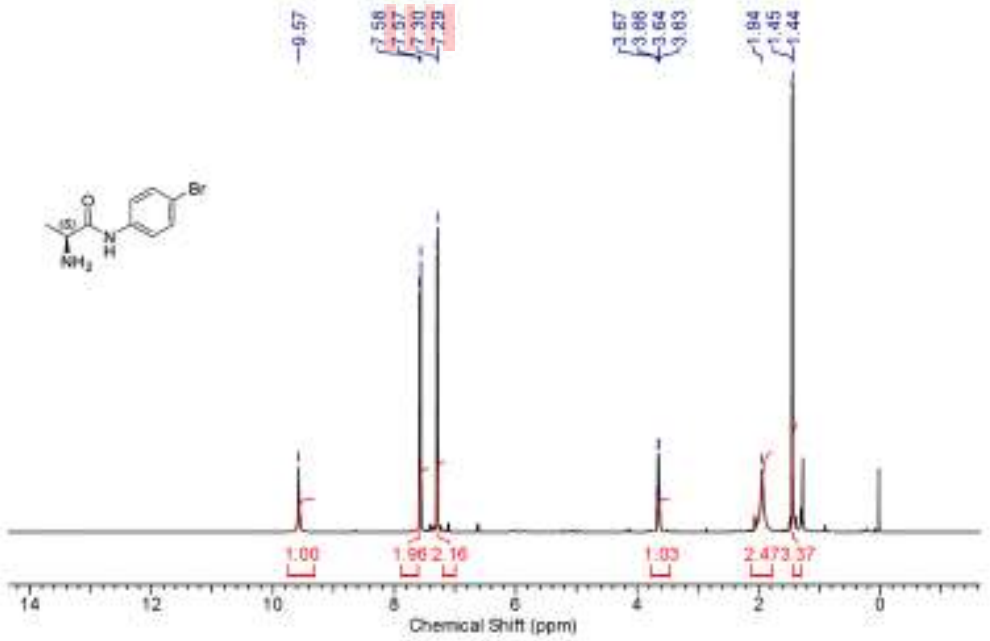



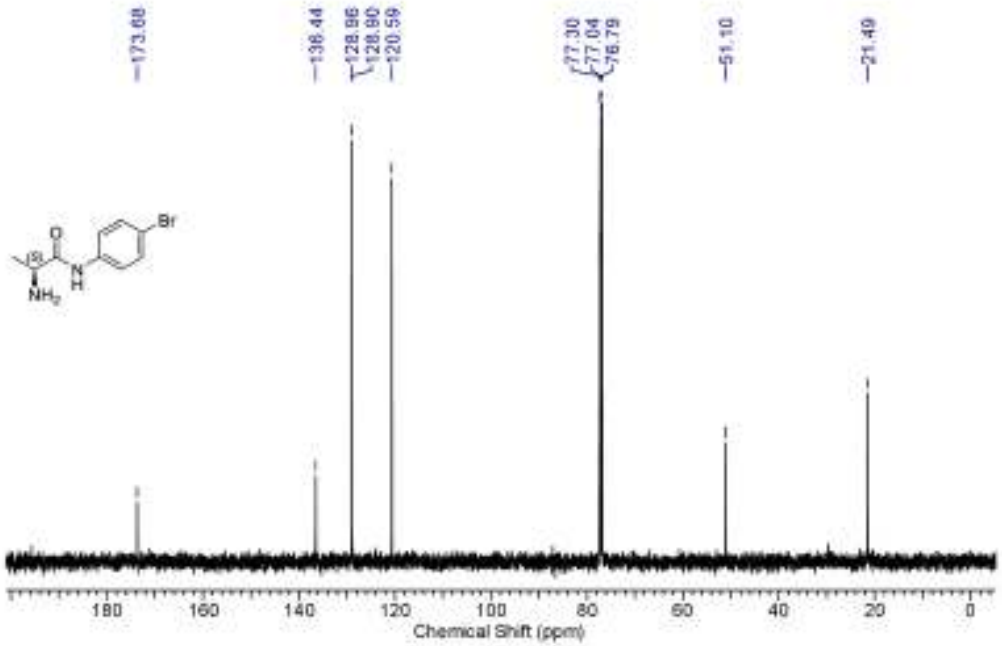
*28d.$^{1}$H & $^{13}$C NMR(S)-2-amino-N-(4-flurophenyl) propanamide:*



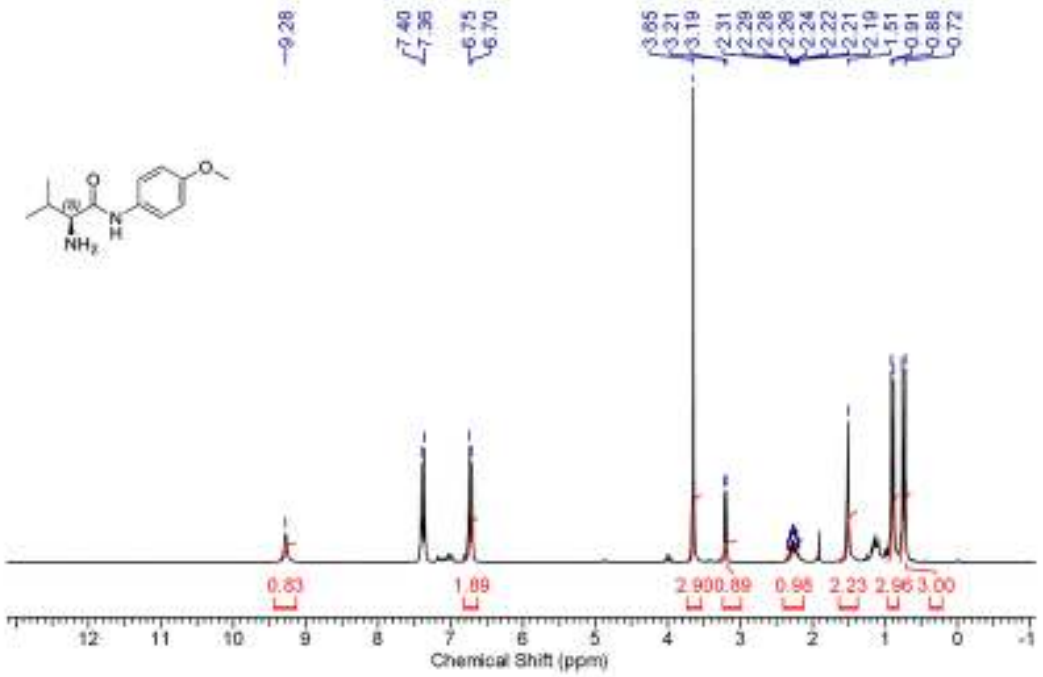



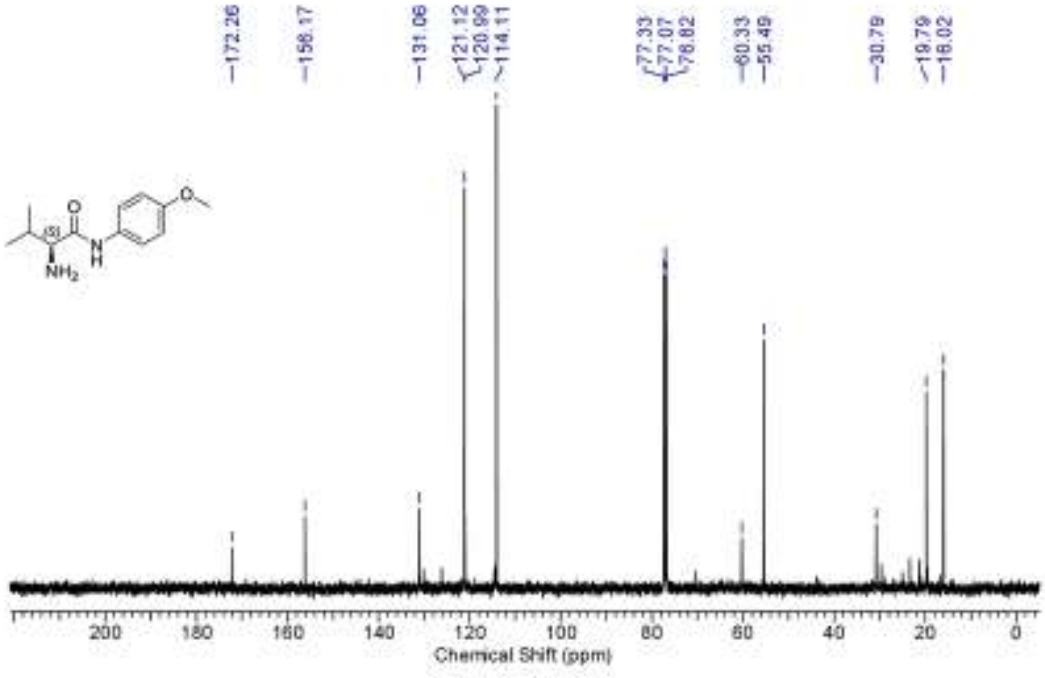
*28e.$^{1}H$ & $^{13}C$ NMR(S)-2-amino-N-(4-bromophenyl) propanamide:*



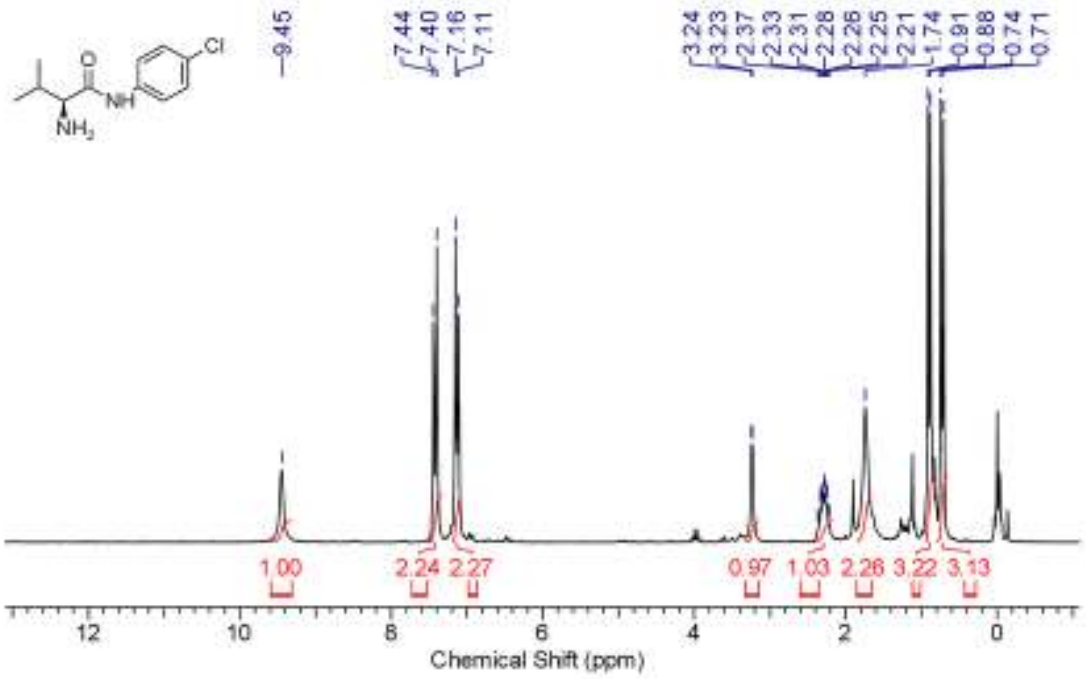



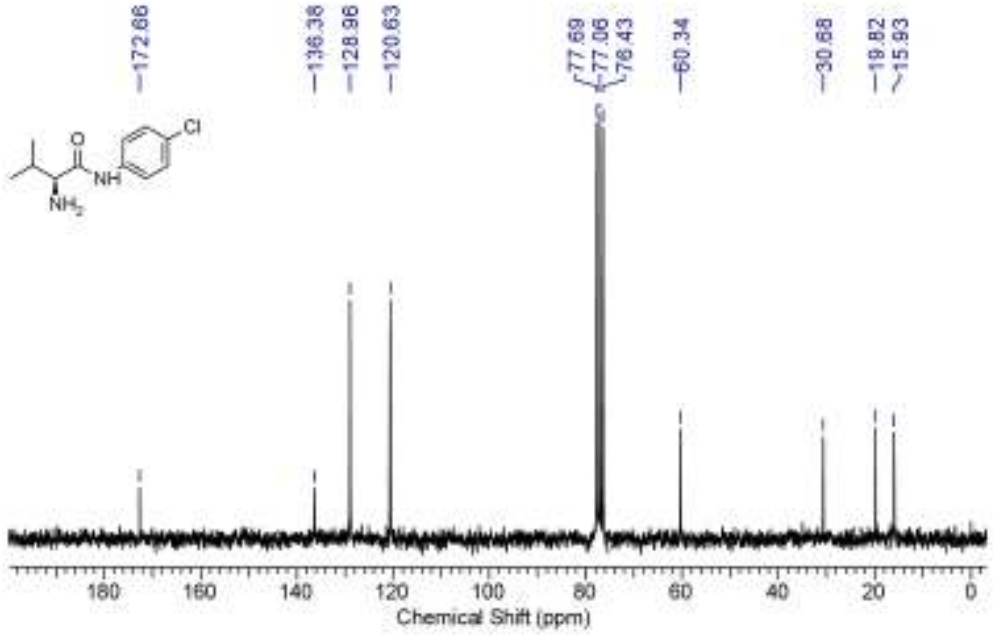
*28f.$^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(4-methoxyphenyl) butanamide:*



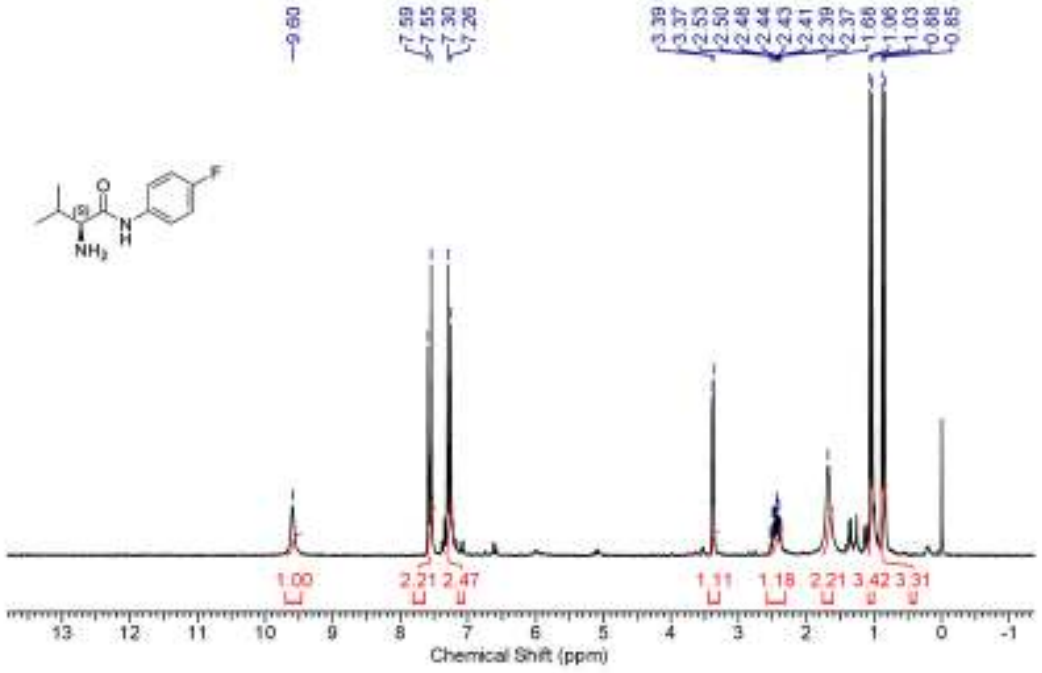



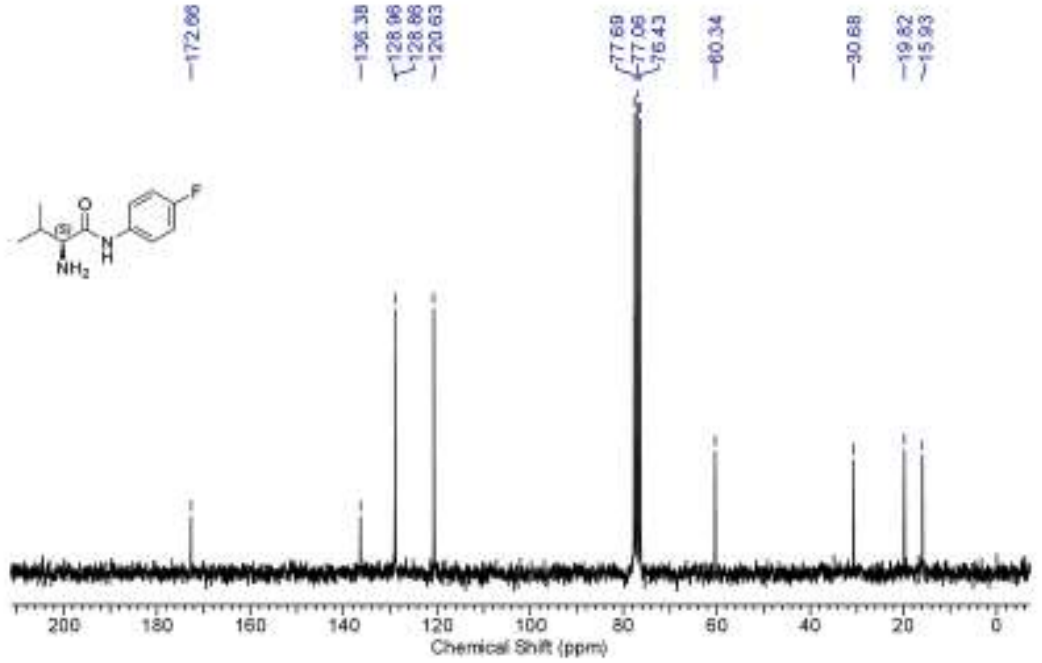
*28g.$^{1}H$ & $^{13}C$ NMR(S)-2-amino-N-(4-chlorophenyl)-3-methylbutnamide:*



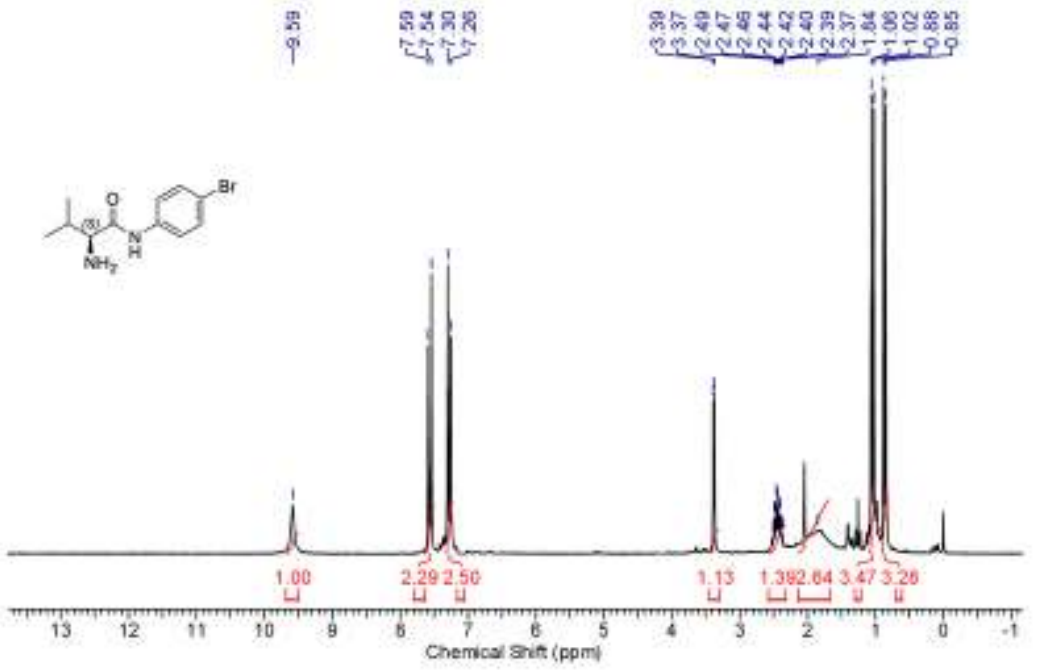



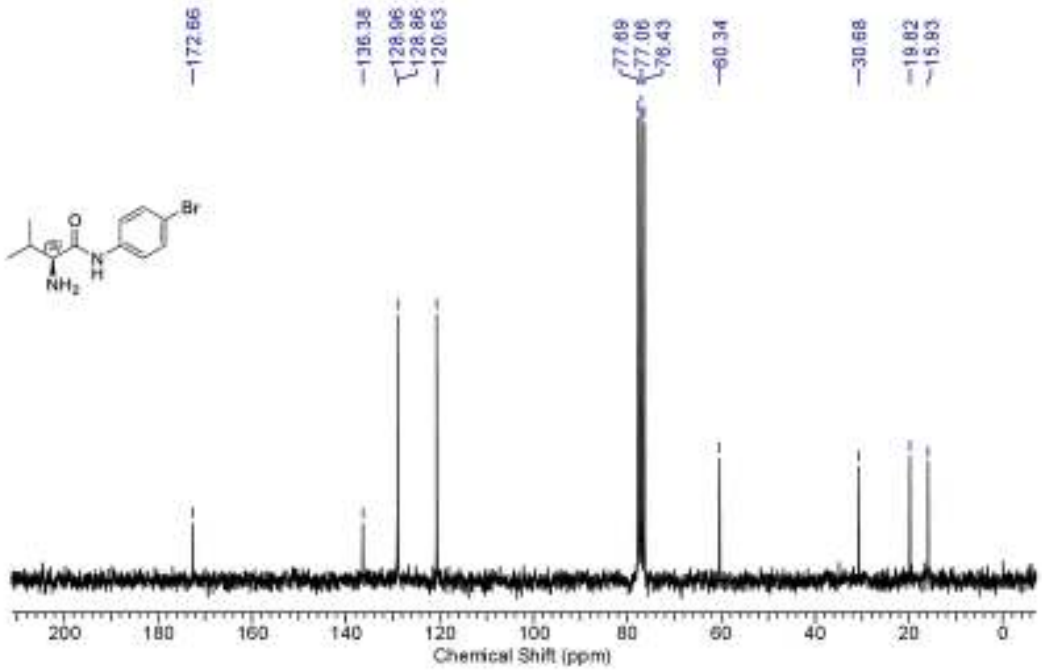
*28h.[1]H & [13]C NMR(S)-2-amino-N-(4-flurophenyl)-3-methylbutnamide:*



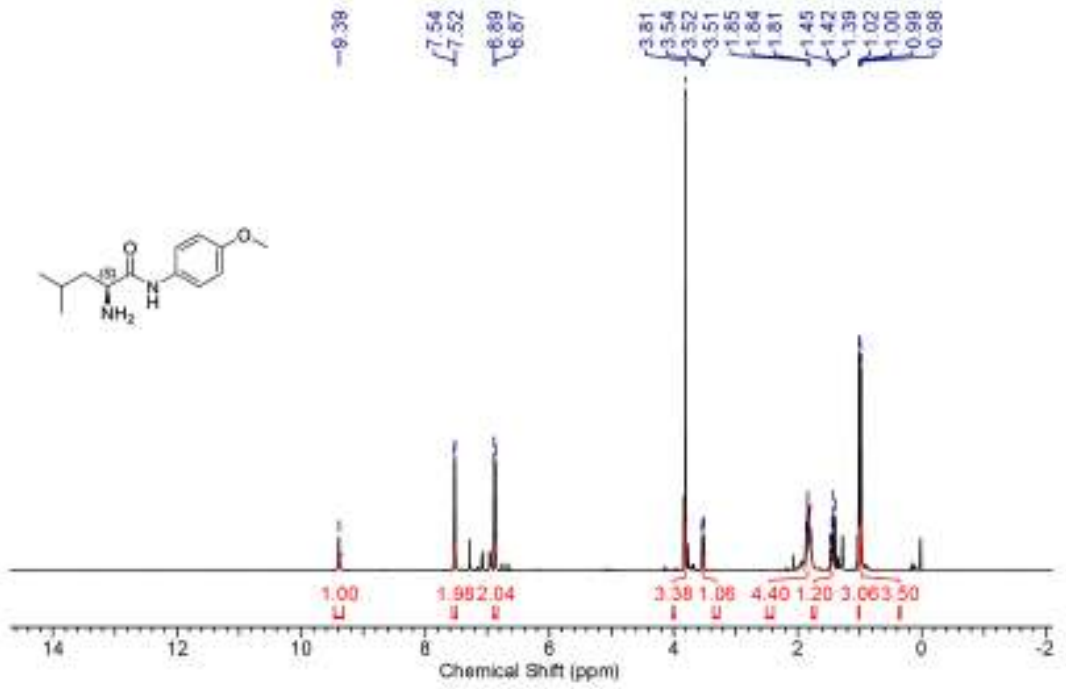



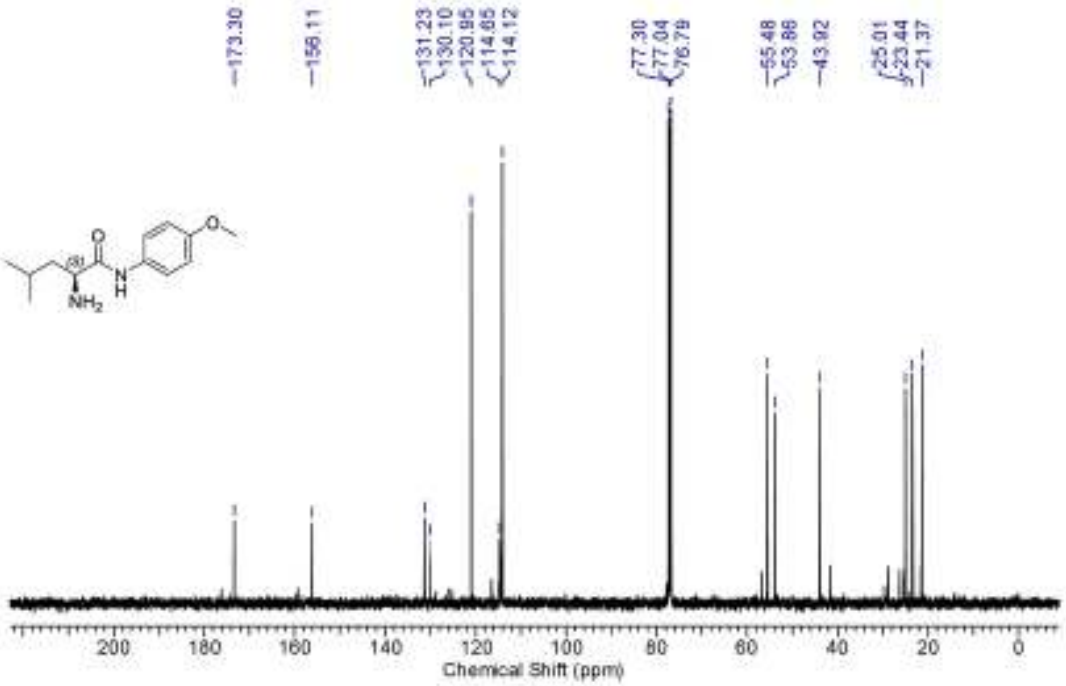
*28i.$^{1}H$ & $^{13}C$ NMR(S)-2-amino-N-(4-bromophenyl)-3-methylbutnamide:*



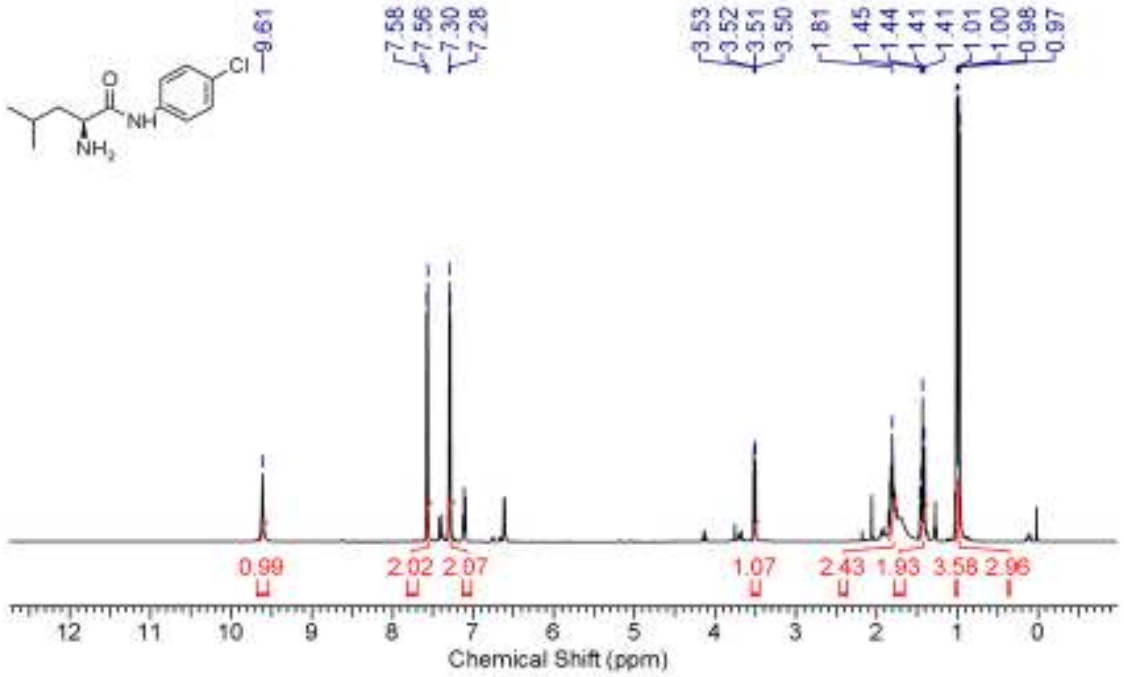



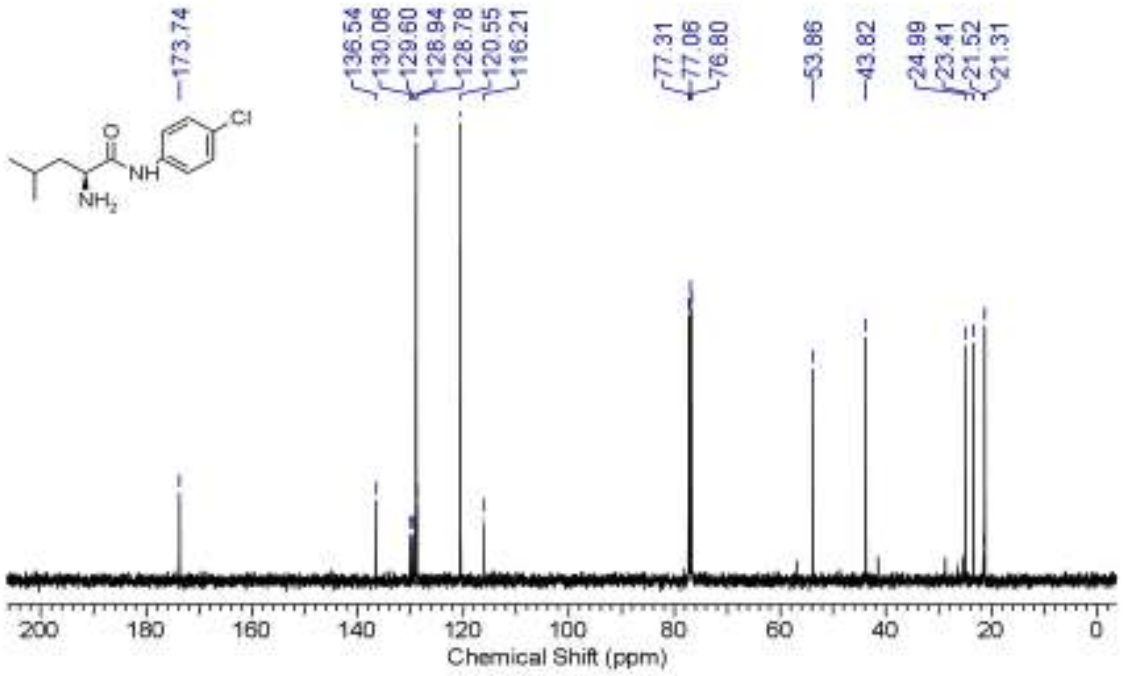
*28j.[1]H & [13]C NMR(S)-2-amino-N-(4-methoxyphenyl)-3-methylpentamide:*



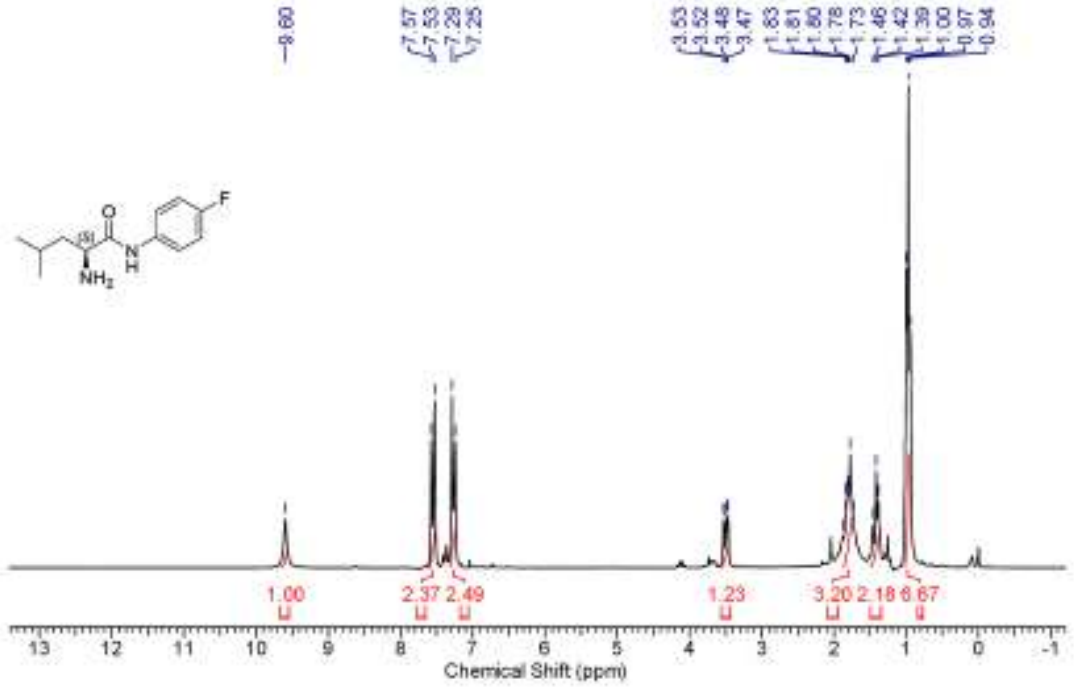



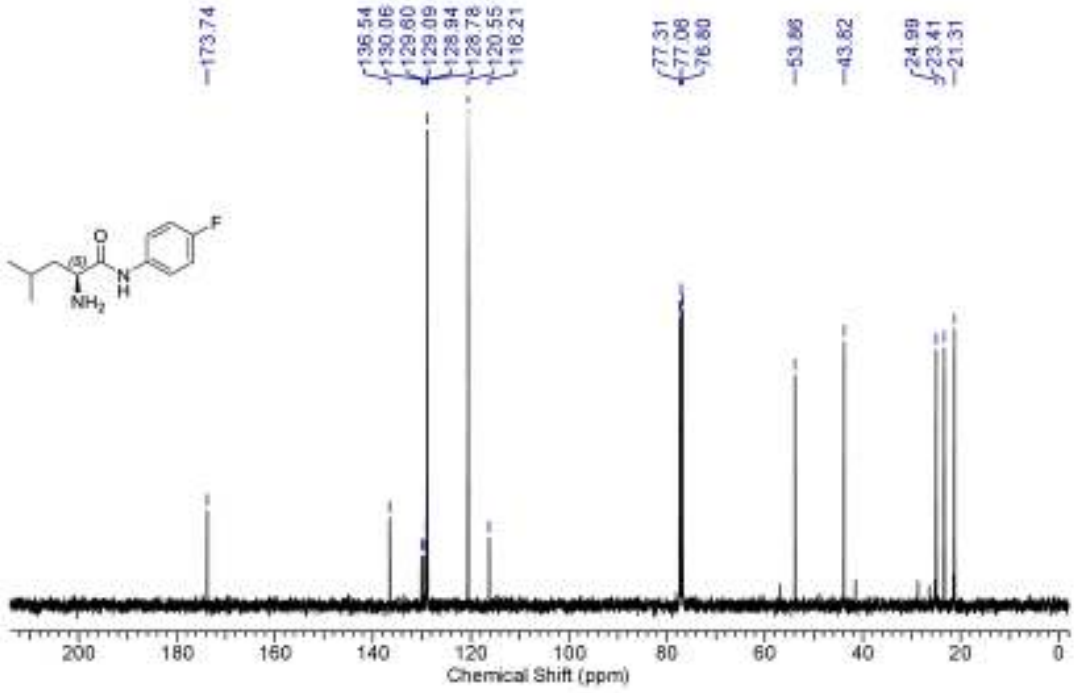
*28k.$^{1}H$ & $^{13}C$ NMR(S)-2-amino-N-(4-chlorophenyl)-4-methylpentanamide:*



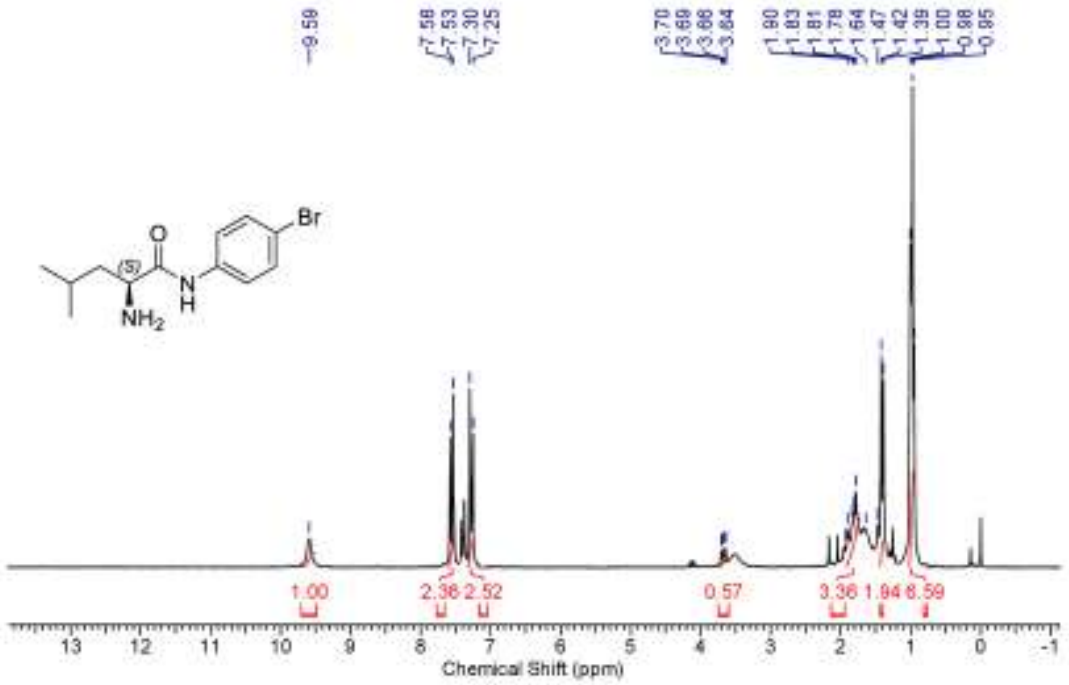



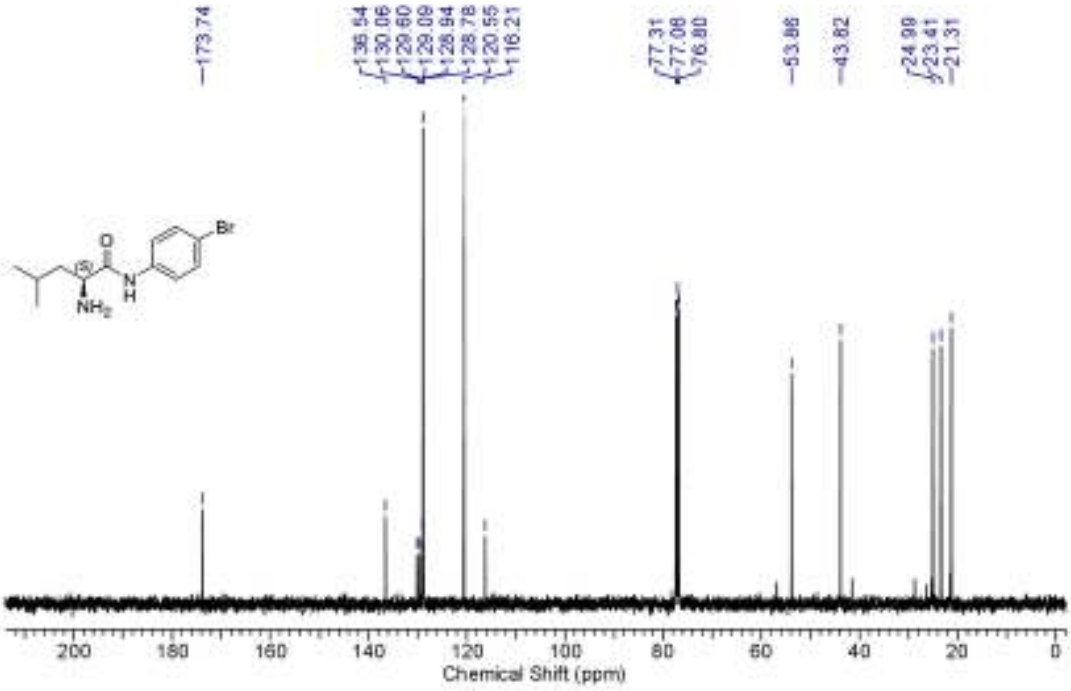
*28l.$^{1}$H & $^{13}$C NMR(S)-2-amino-N-(4-fluorophenyl)-4-methylpentanamide:*



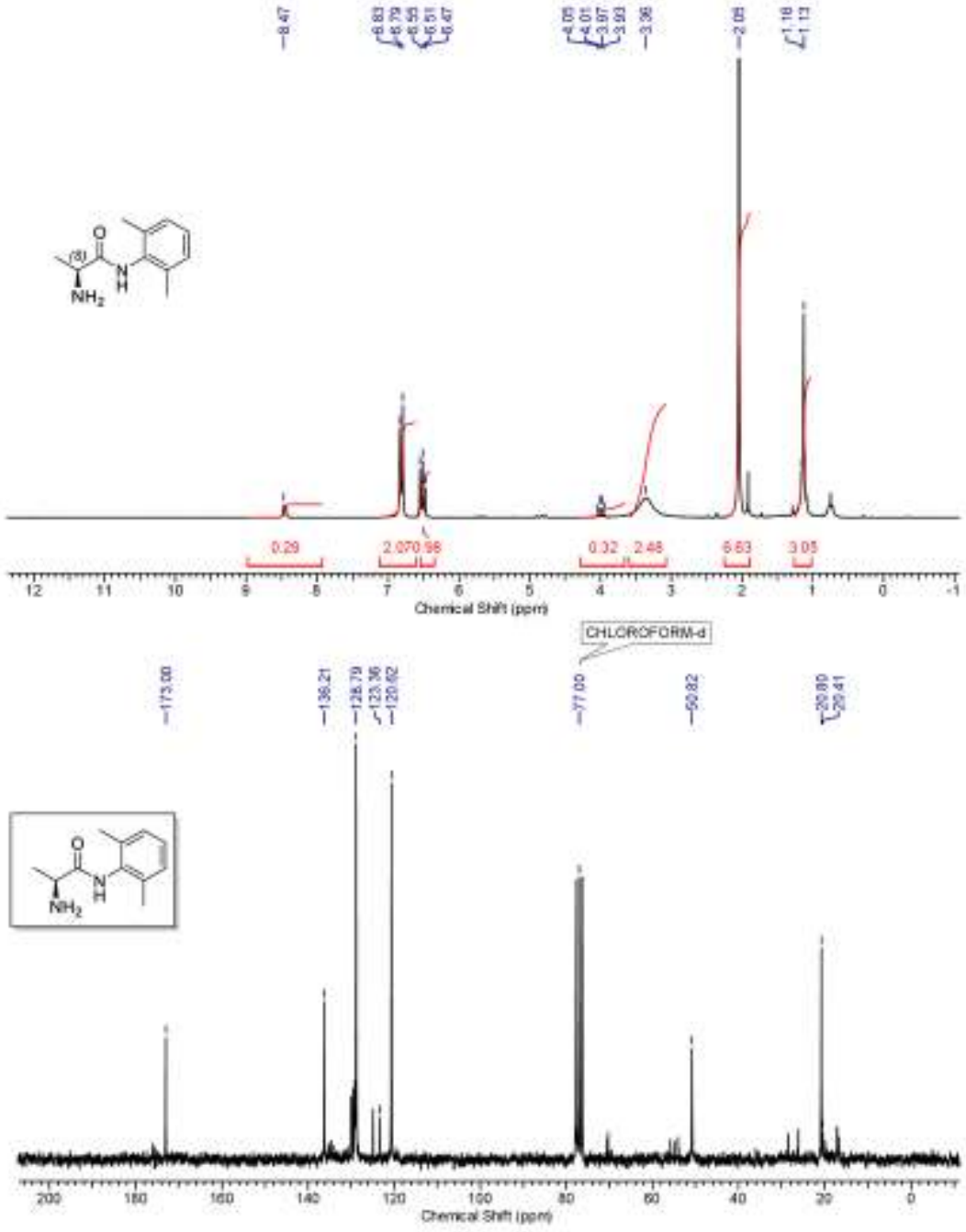



*28m. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(4-bromophenyl)-4-methylpentanamide:*

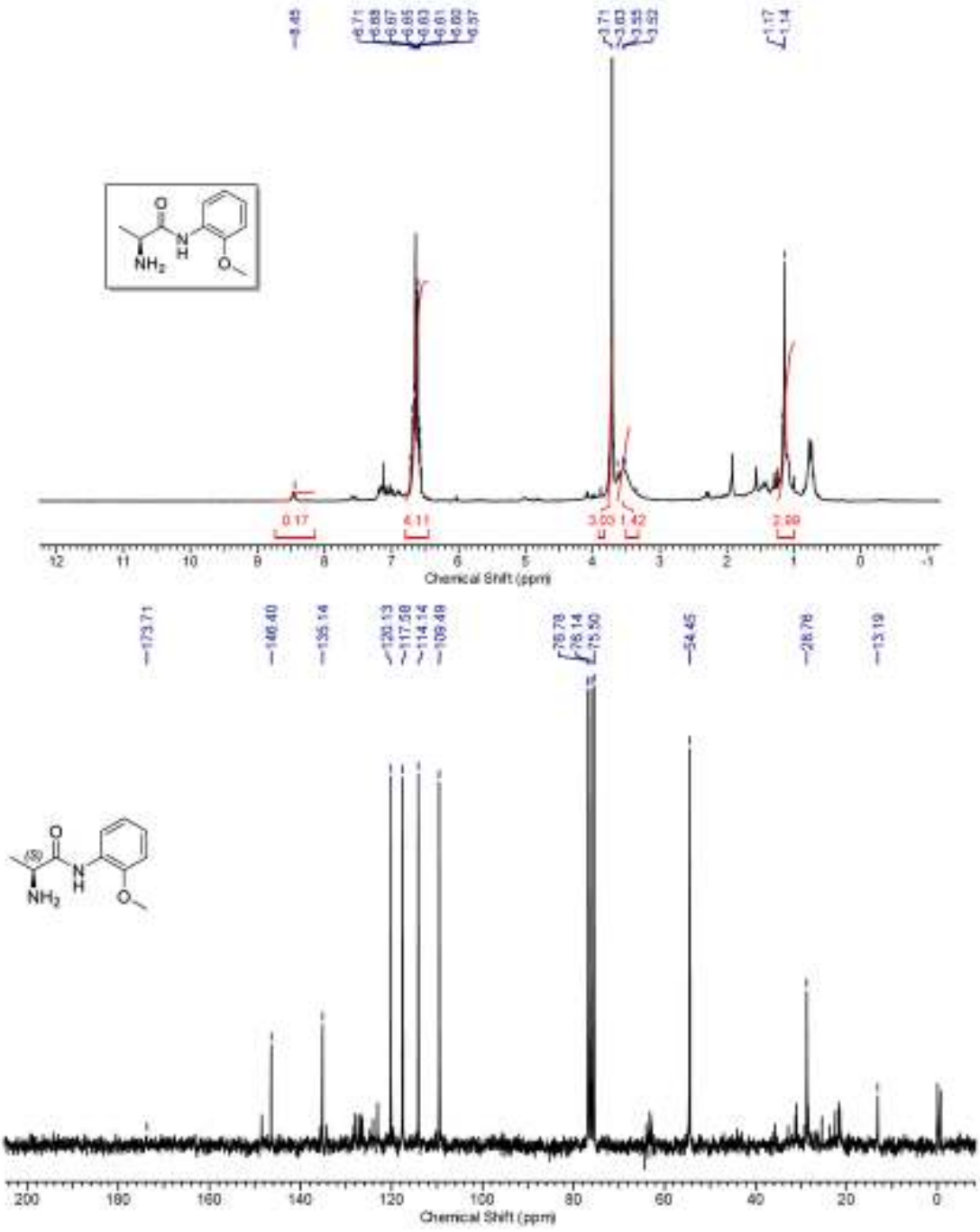


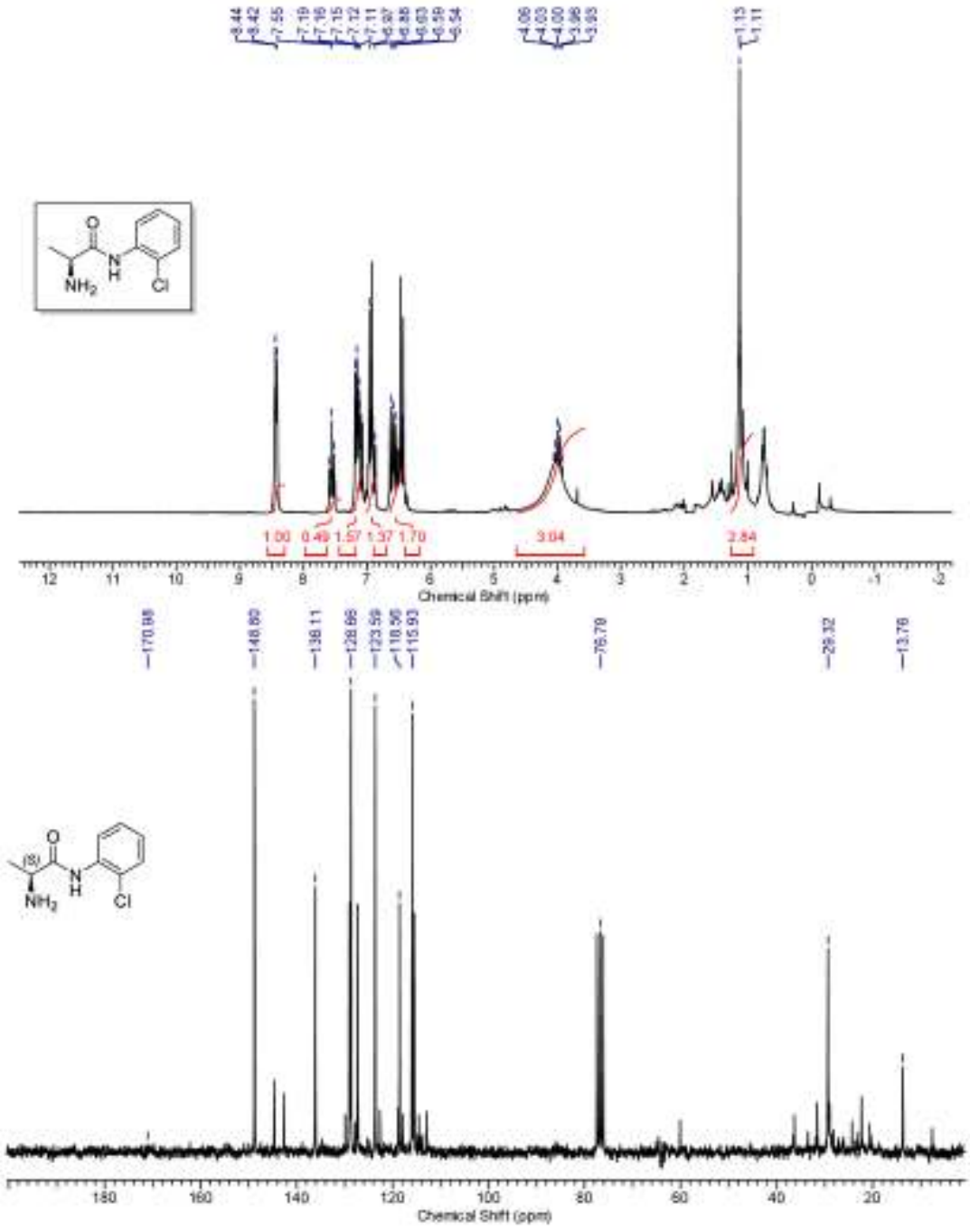
*28n. $^{1}H$ & $^{13}C$ NMR of (S)-2-amino-N-(2,6-dimethylphenyl)propanamide*



## 28o. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(2-methoxyphenyl)propanamide

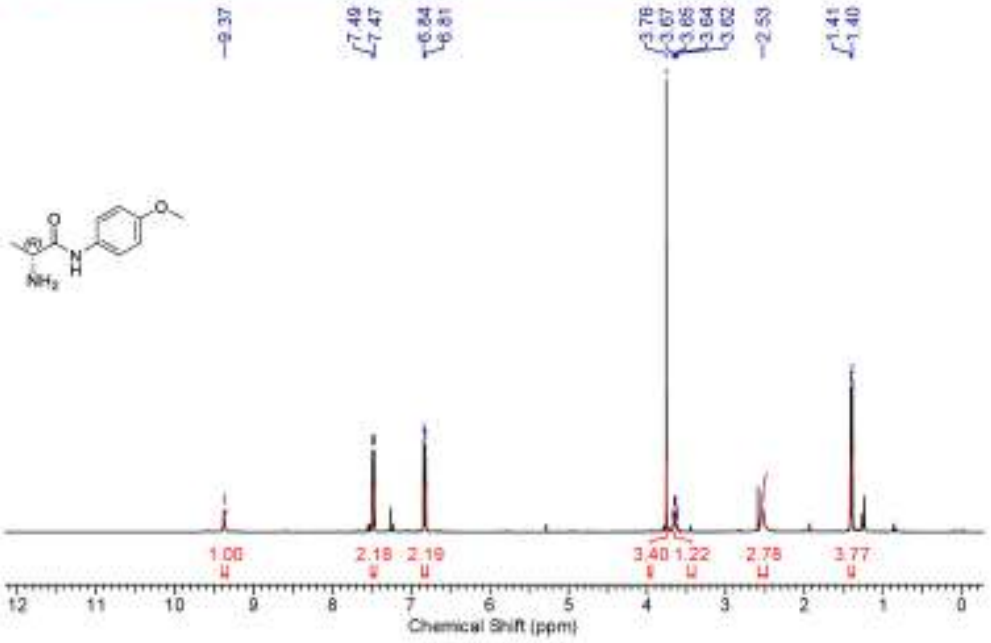


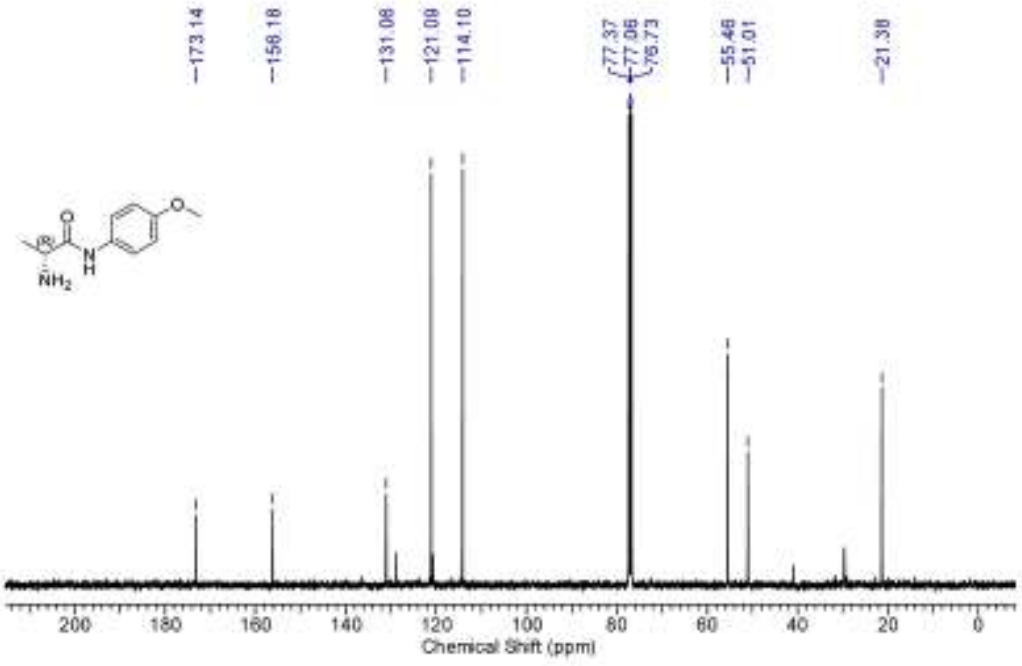
*28o. $^{1}H$ & $^{13}C$ NMR (S)-2-amino-N-(2-chlorophenyl)propanamide*



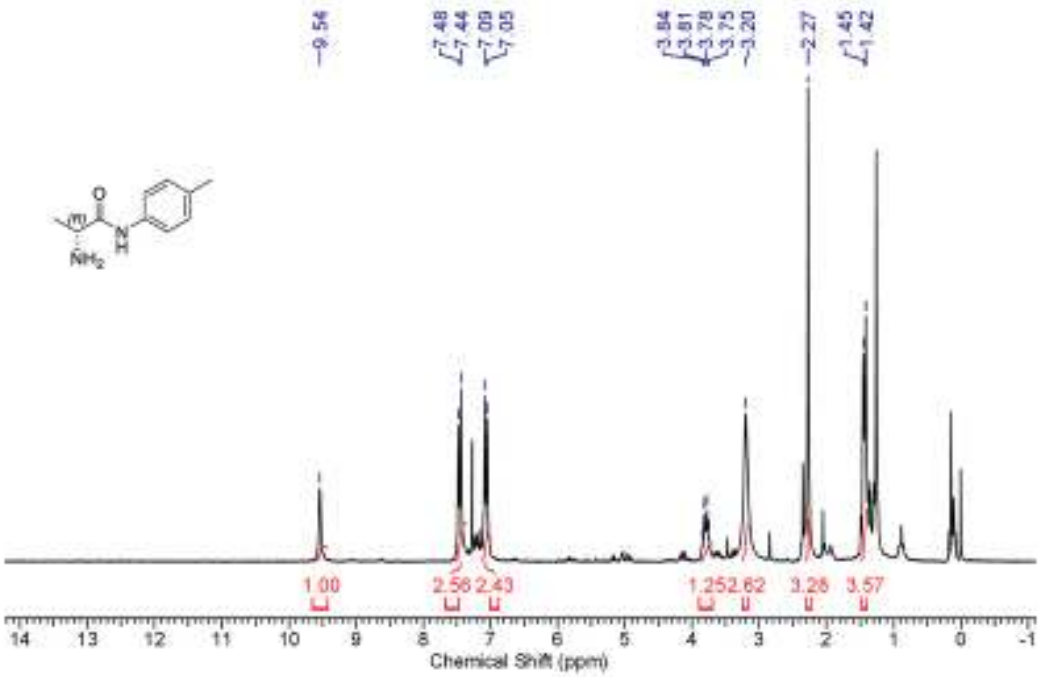
## 1.6.5 $^{1}H$ & $^{13}C$NMR spectra of *N* aryl *R* amino acid amide

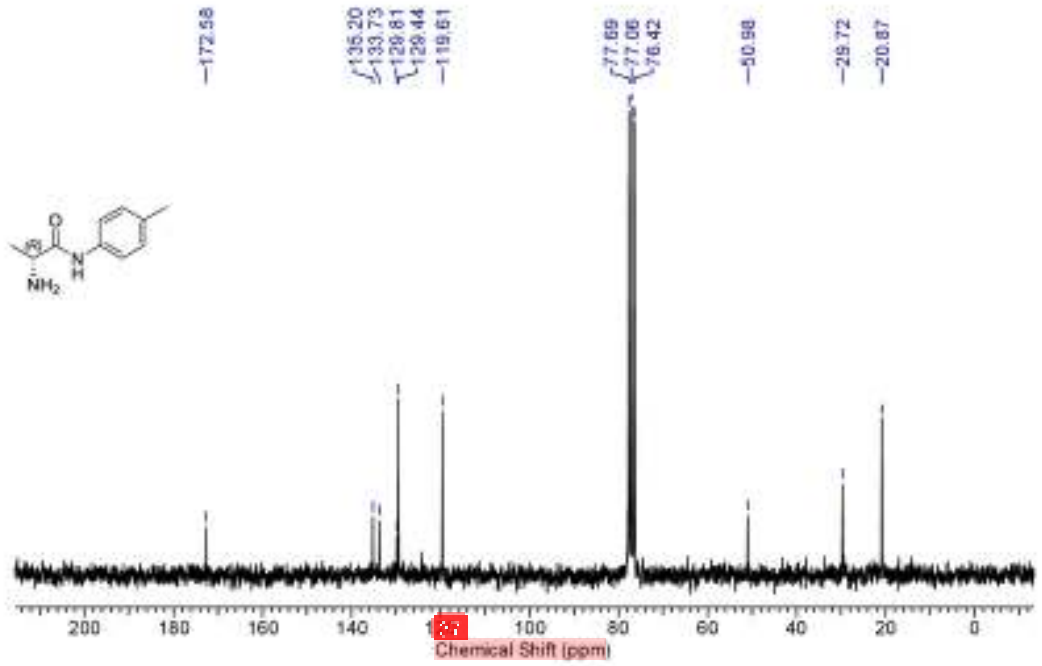
*32a. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-N-(4-methoxyphenyl) propanamide:*



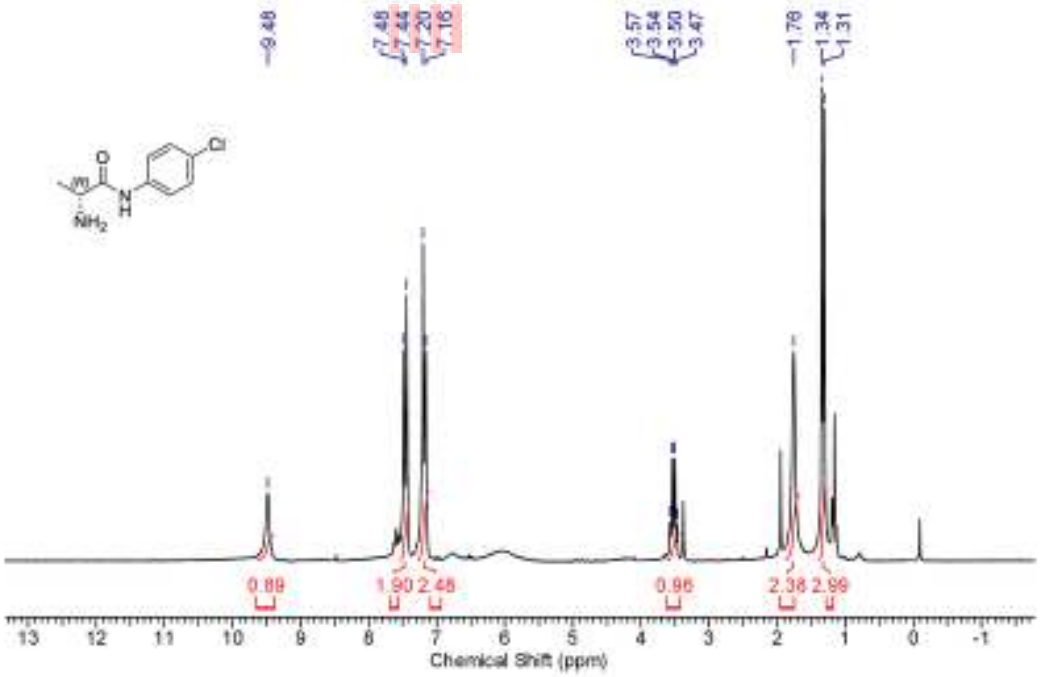



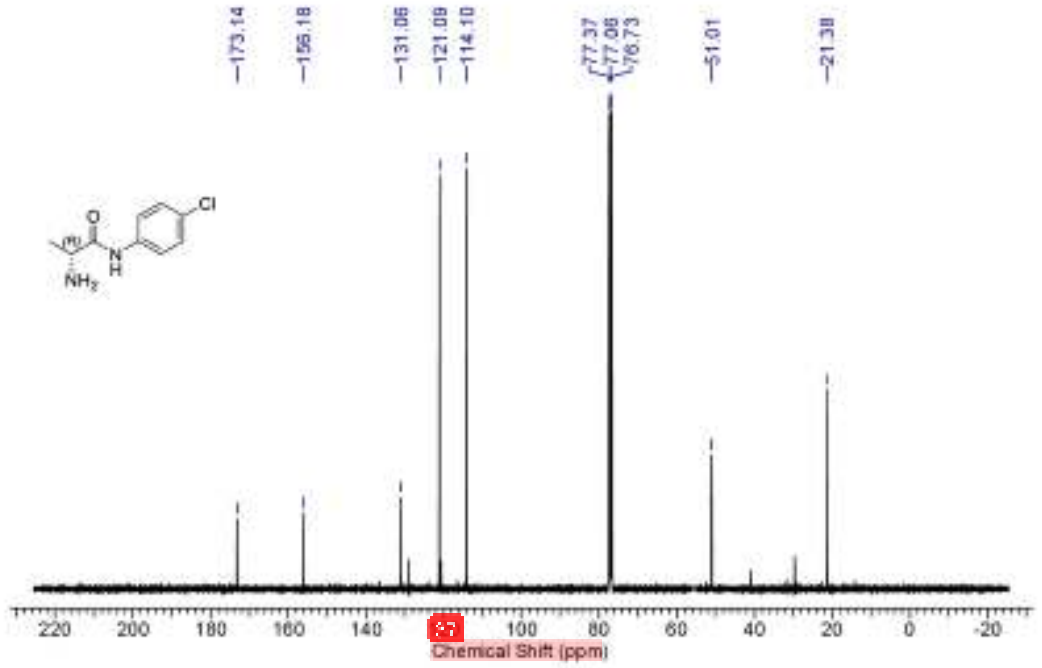
*32b. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-(p-tolyl)propanamide:*



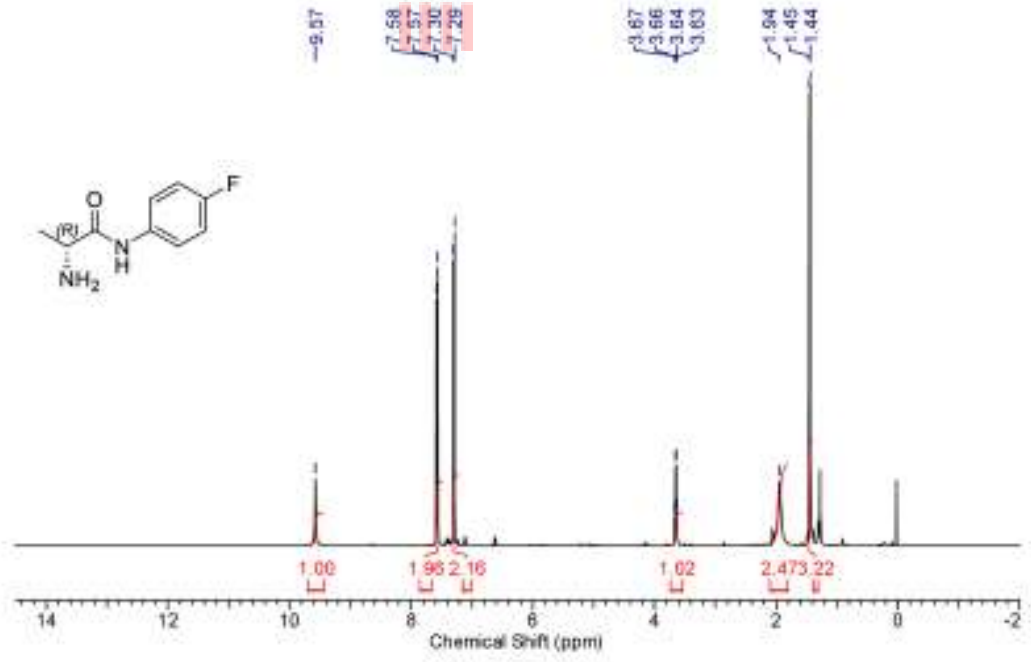



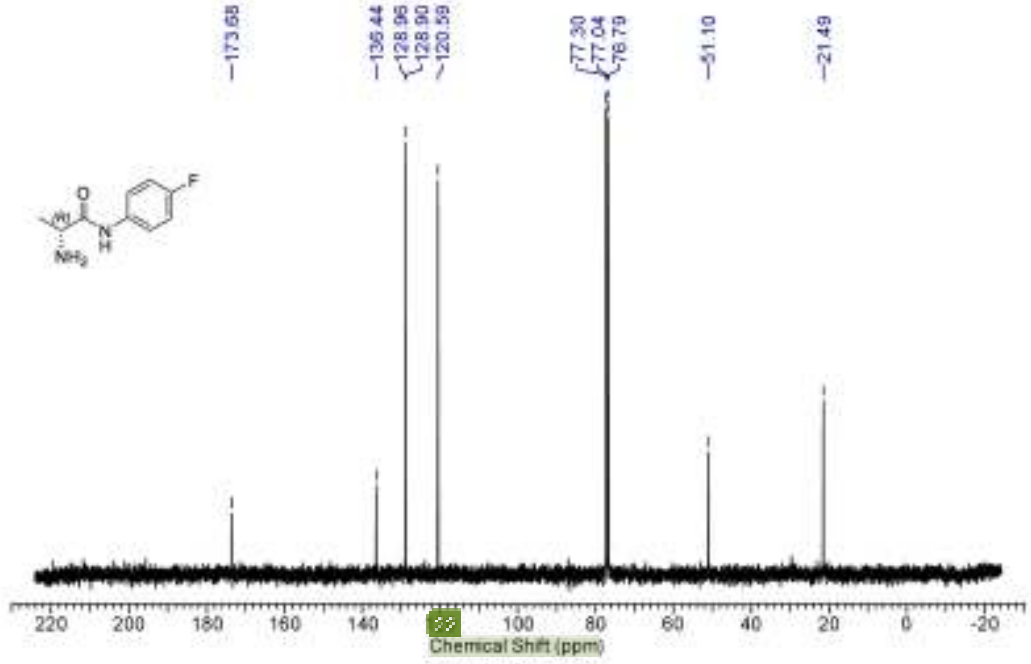
*32c. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-N-(4-chlorophenyl) propanamide:*



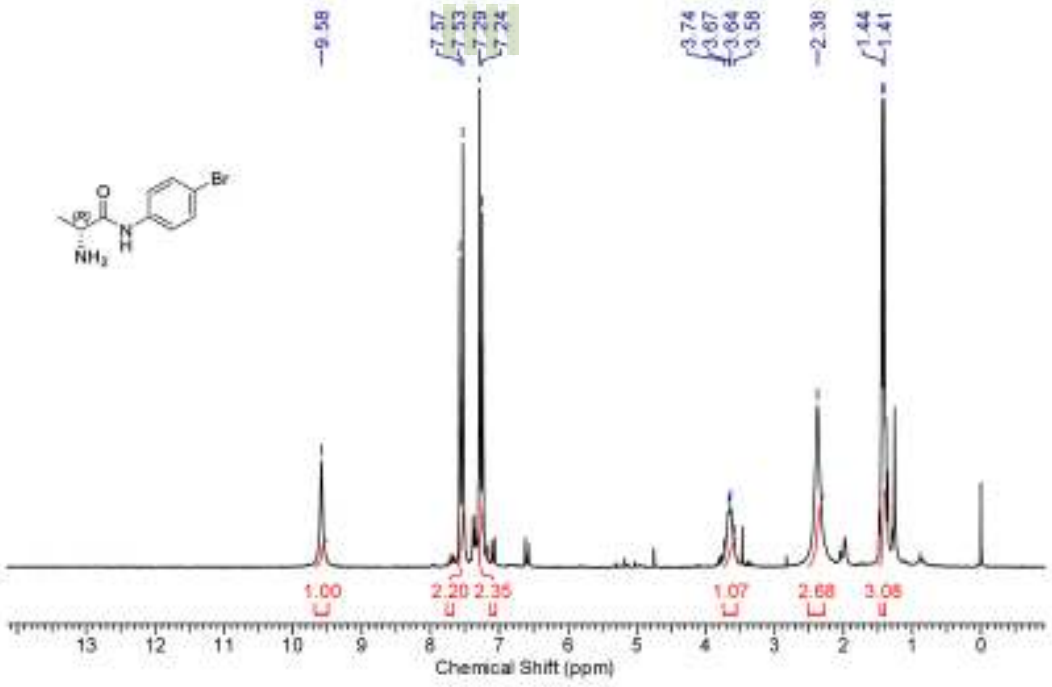



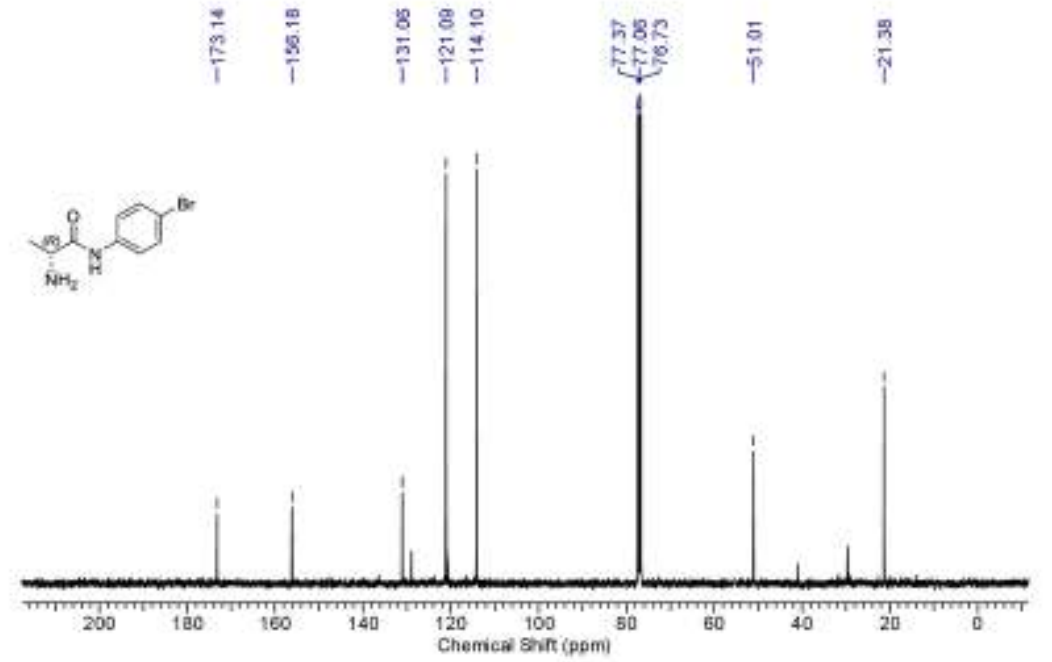
*32d.$^{1}$H & $^{13}$C NMR(R)-2-amino-N-(4-flurophenyl) propanamide:*



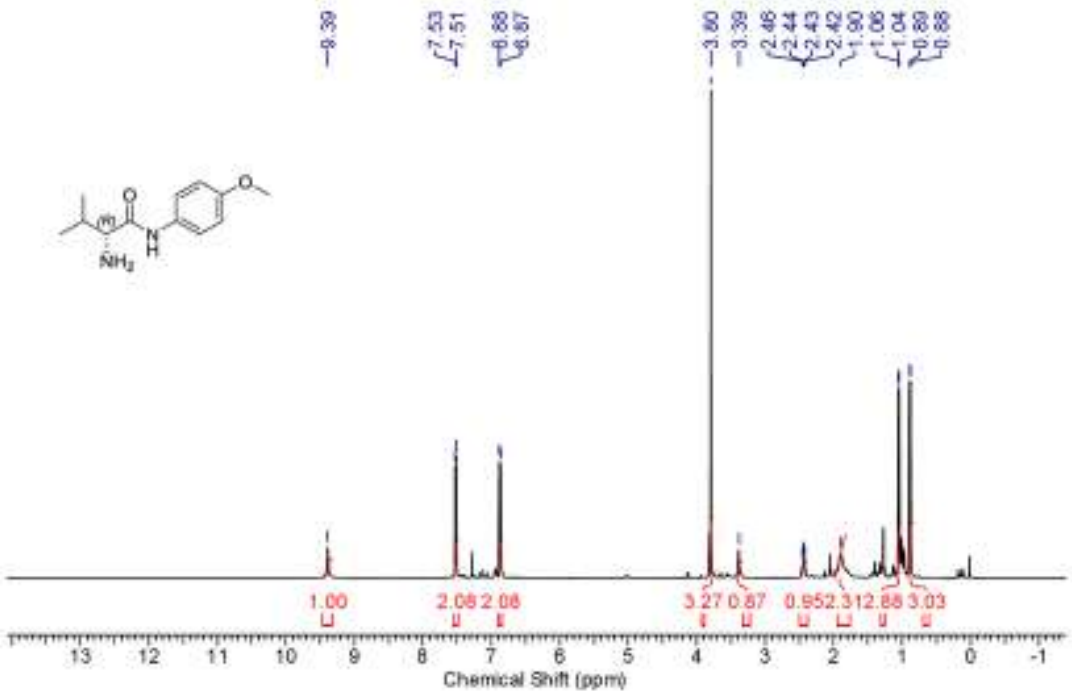



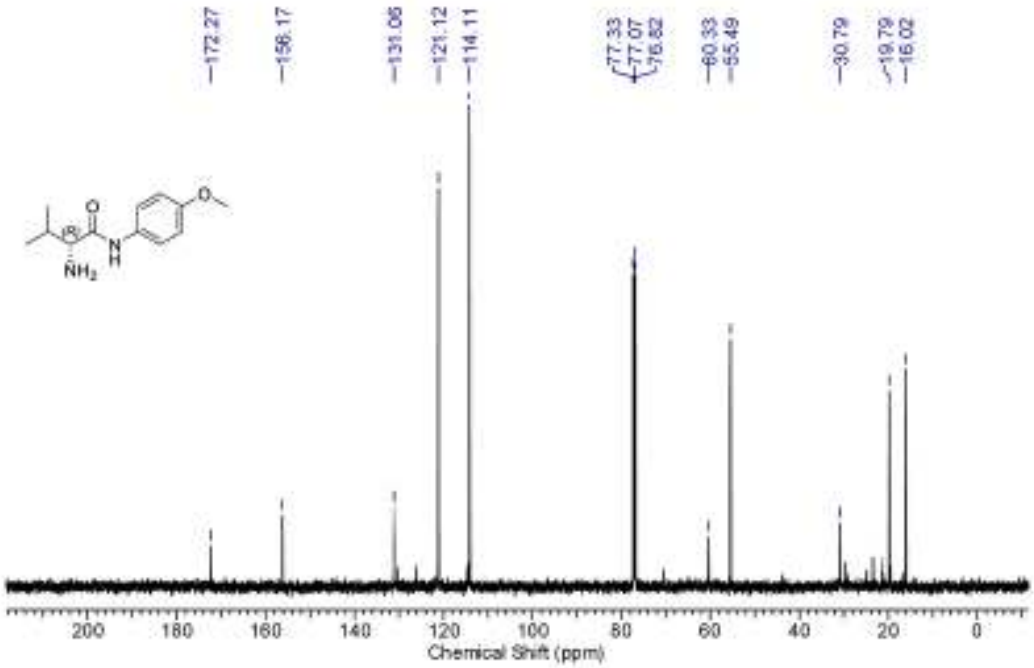
*32e.$^{1}H$ & $^{13}C$ NMR(R)-2-amino-N-(4-bromophenyl) propanamide:*



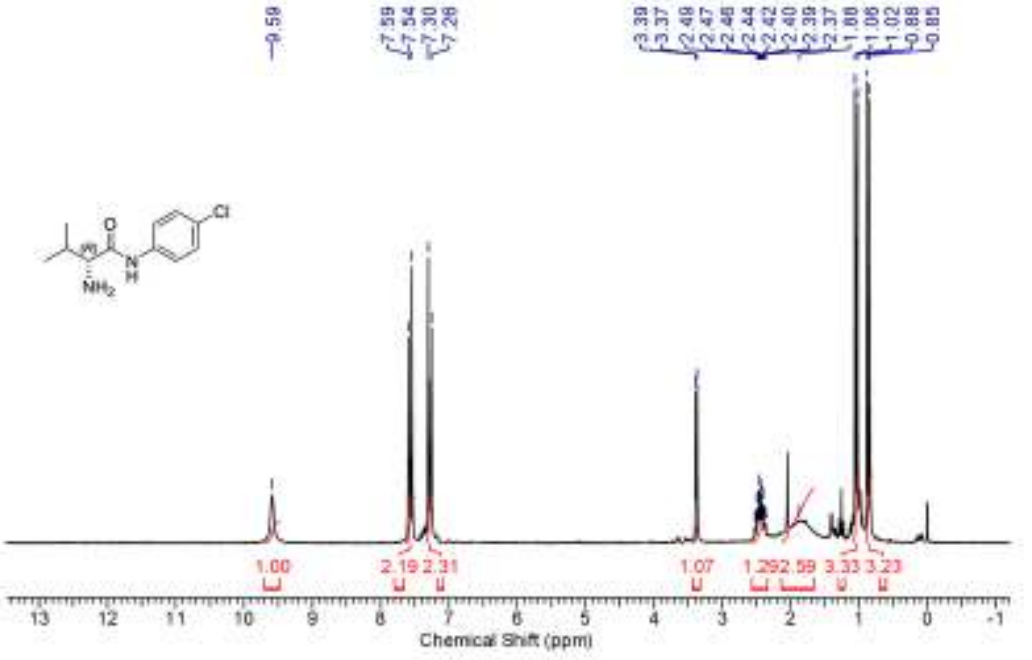



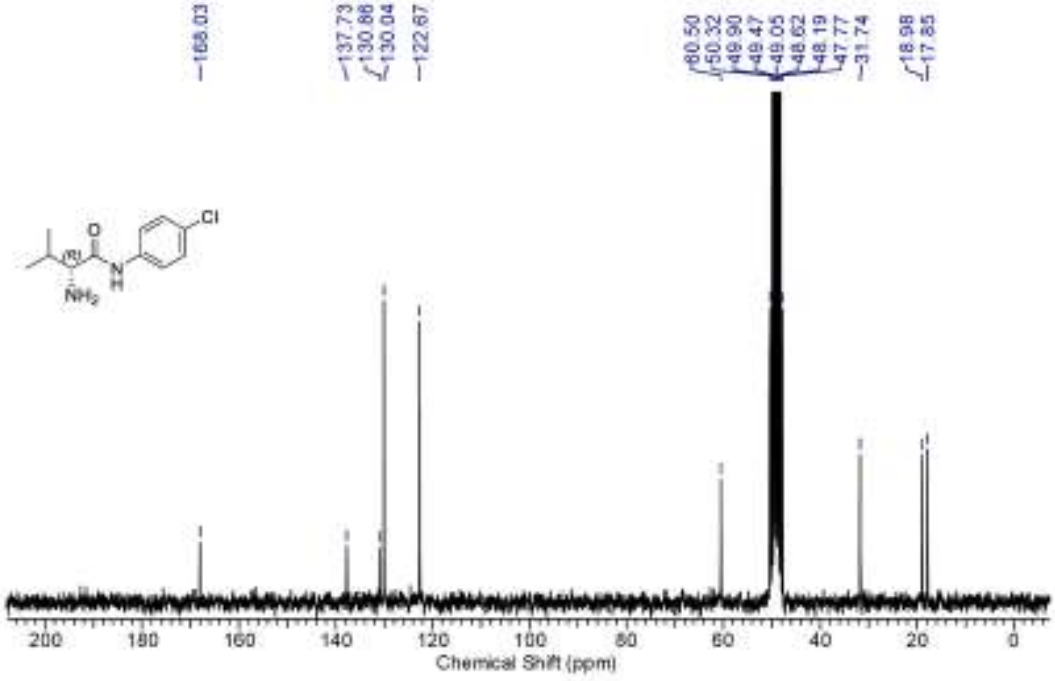
*32f.[1]H & [13]C NMR(R)-2-amino-N-(4-methoxyphenyl) 3-methylbutanamide:*



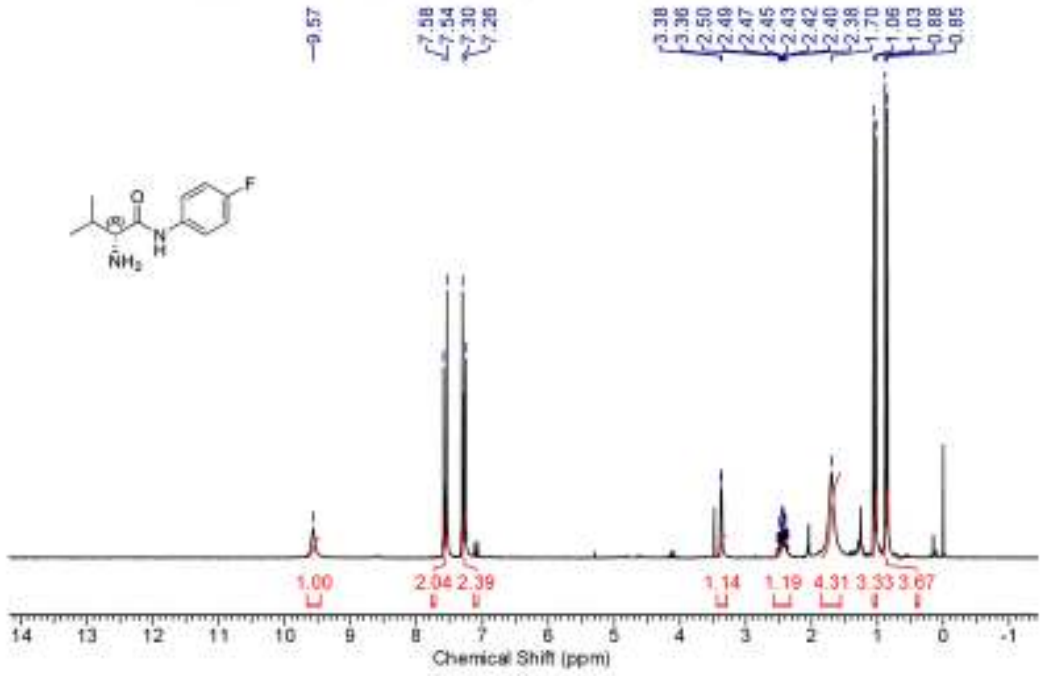



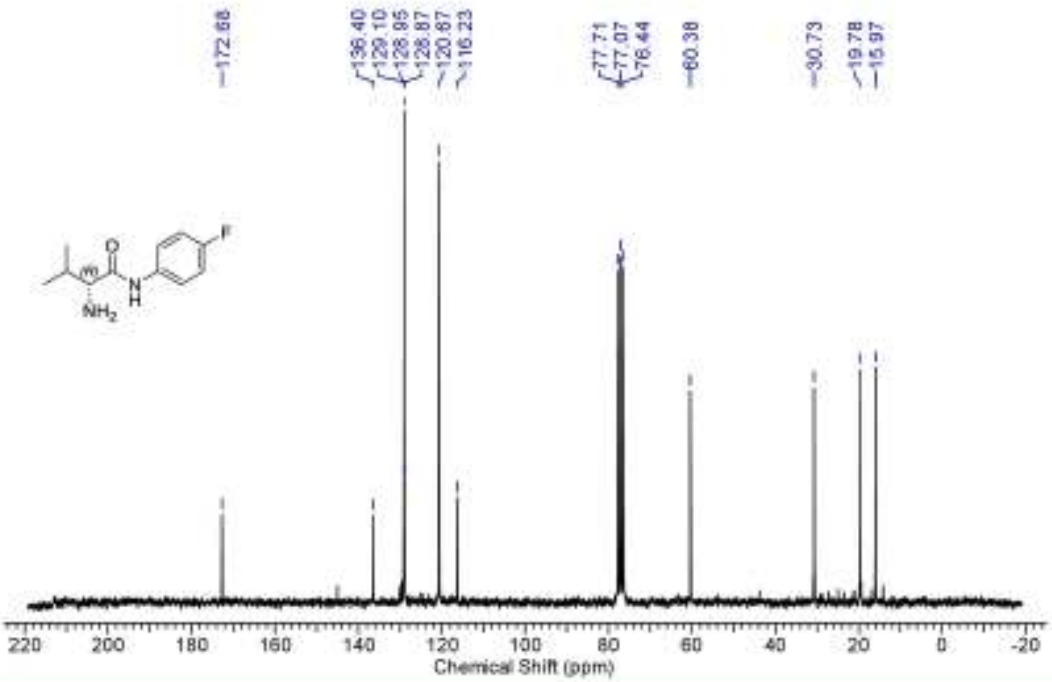
*32g.[1]H & [13]C NMR (R)-2-amino-N-(4-chlorophenyl) 3-methylbutanamide:*



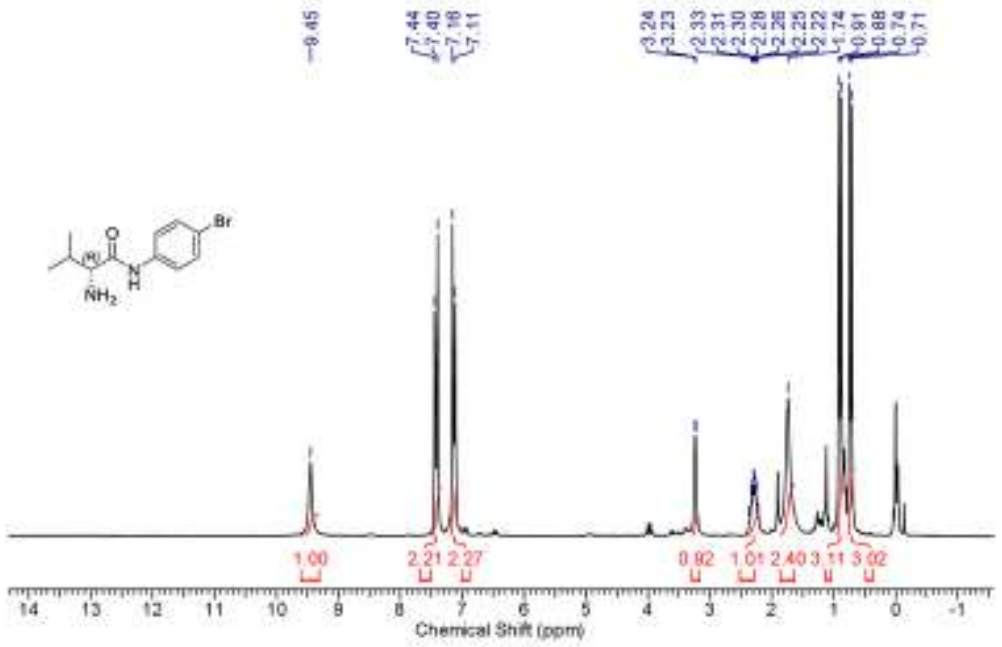



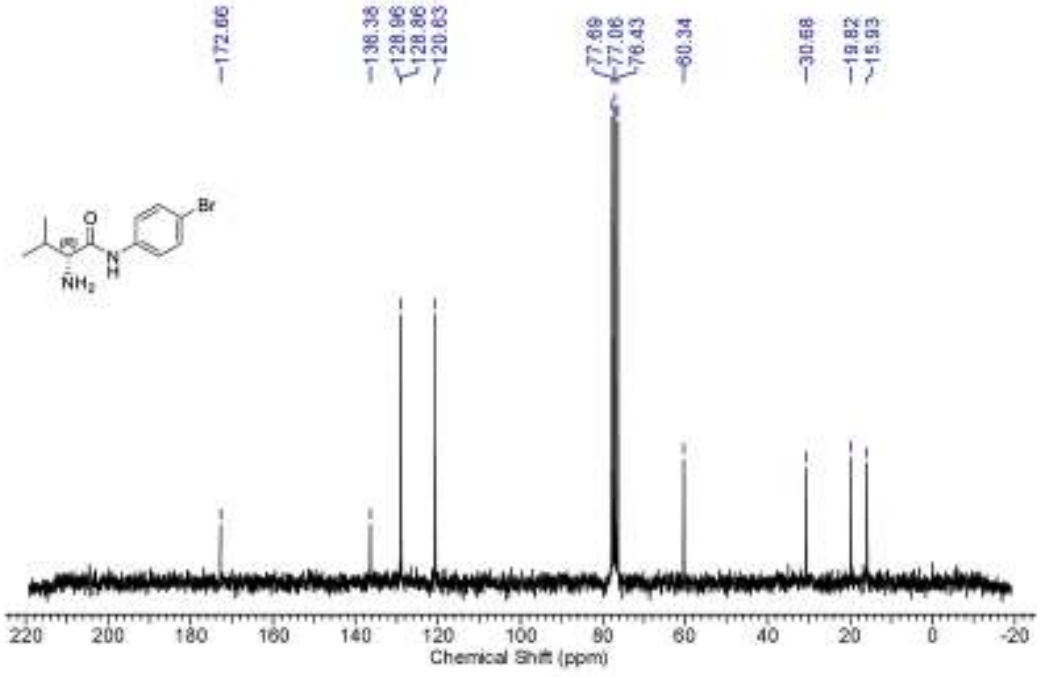
*32h.$^{1}H$ & $^{13}C$ NMR(R)-2-amino N (4-flurophenyl)-3-methylbutanamide:*



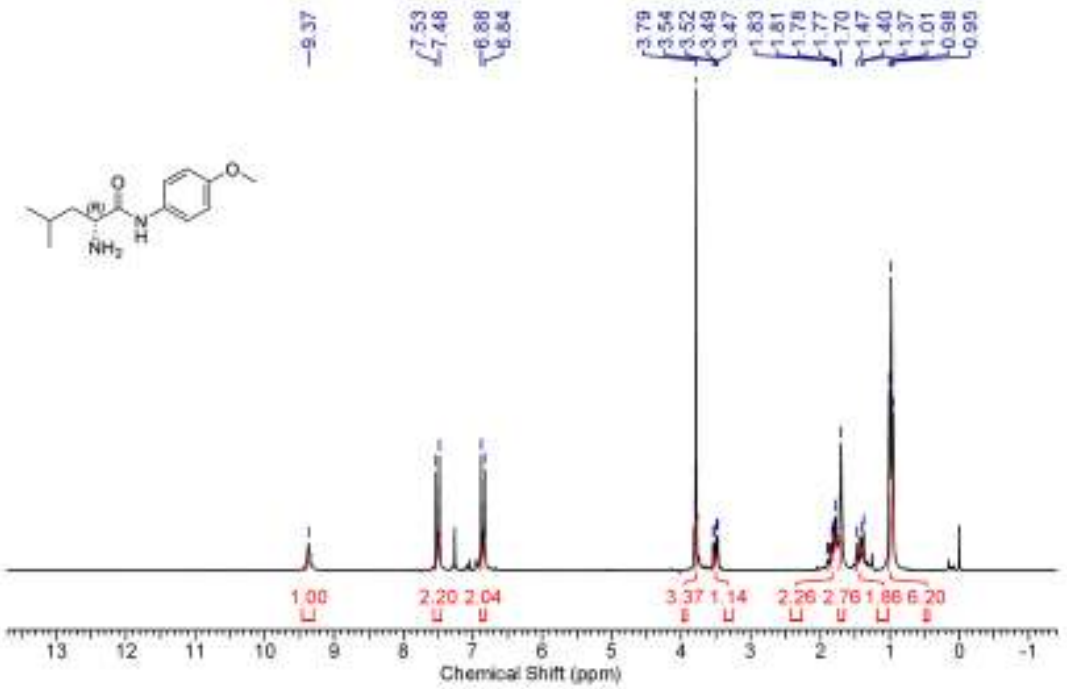



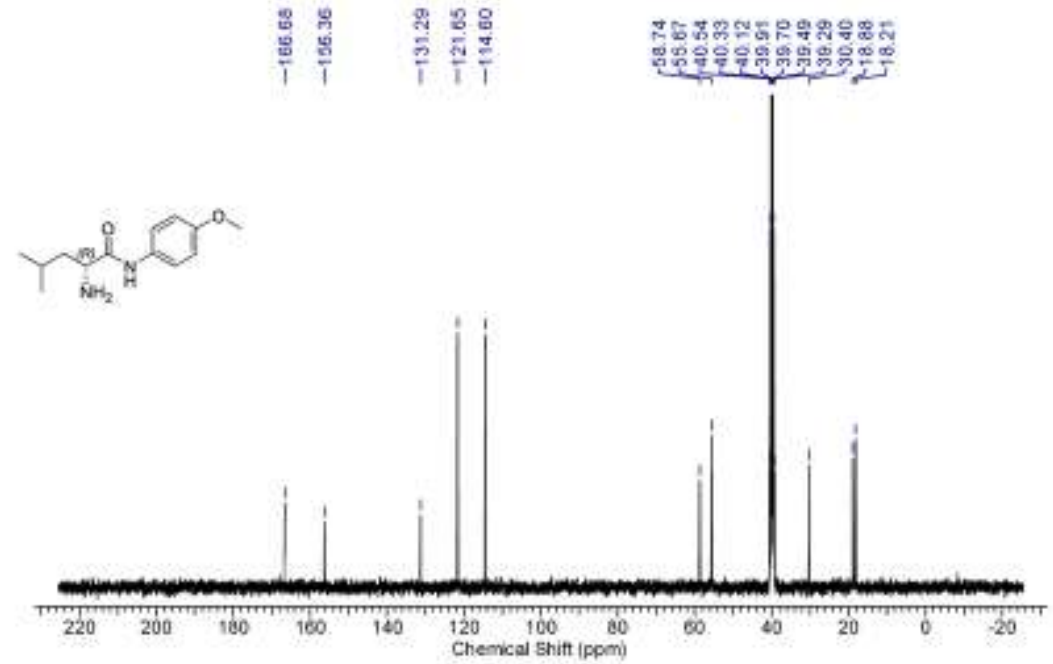
*32i.[1]H & [13]C NMR(R)-2-amino-N-(4-bromophenyl) 3-methylbutanamide:*



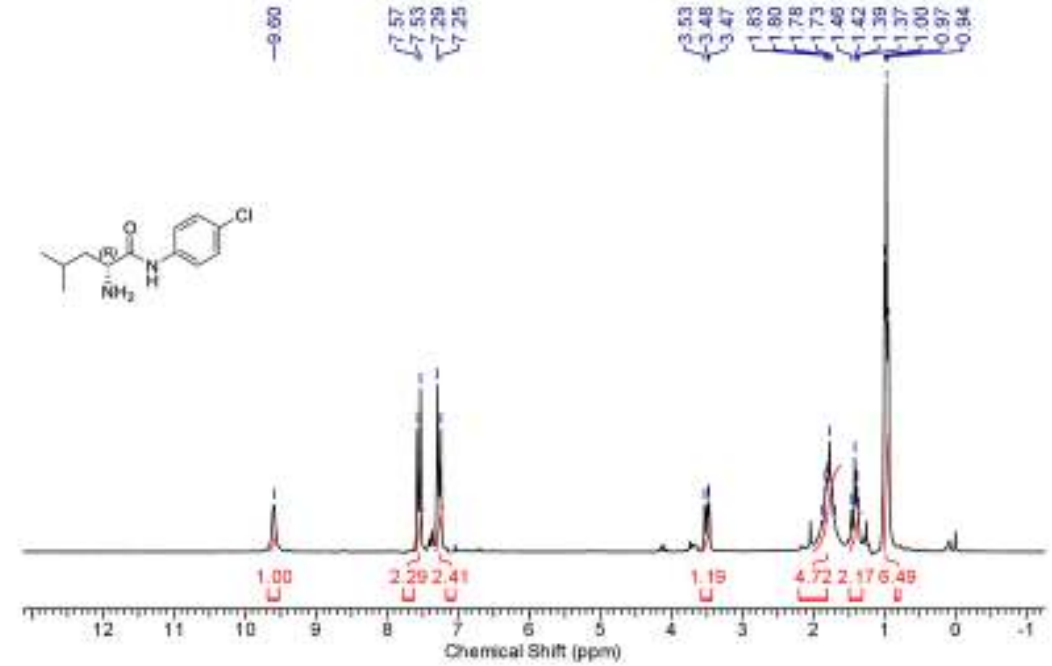



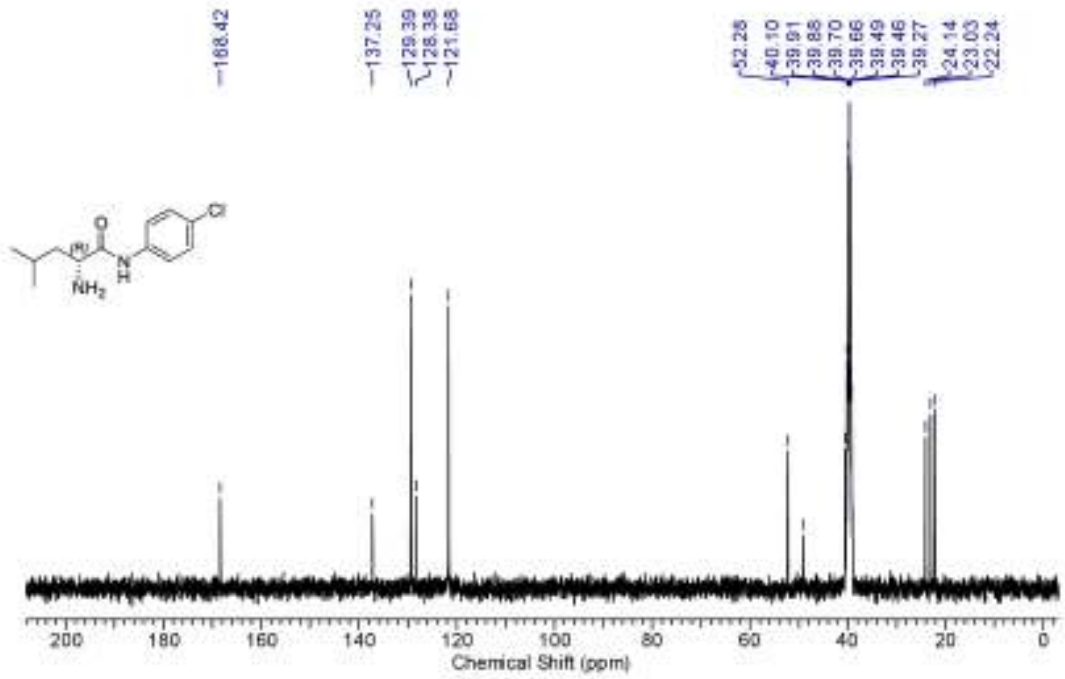
*32j. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-N-(4-methoxyphenyl)-4-methylpentanamide:*



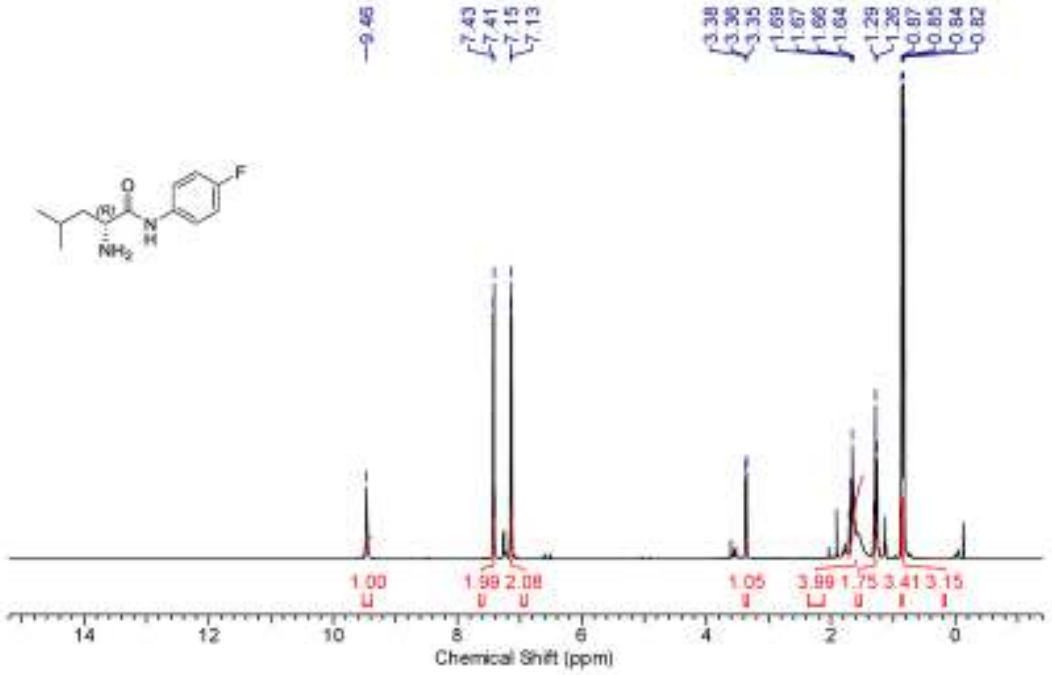



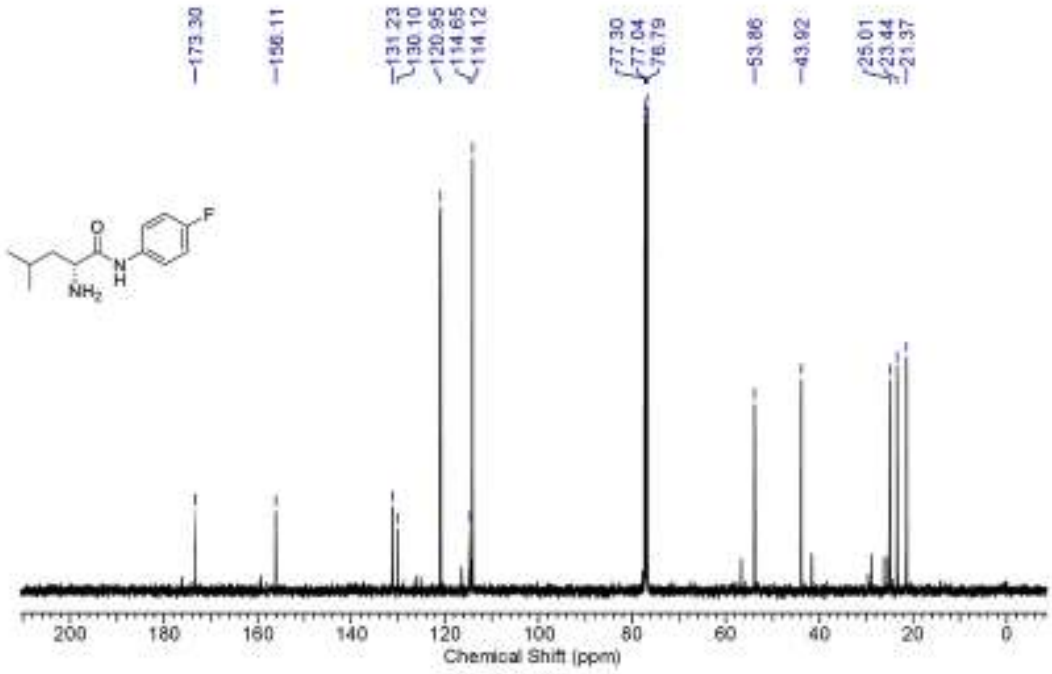
*32k.$^{1}$H & $^{13}$C NMR (R)-2-amino-N-(4-chlorophenyl)-4-methylpentanamide:*



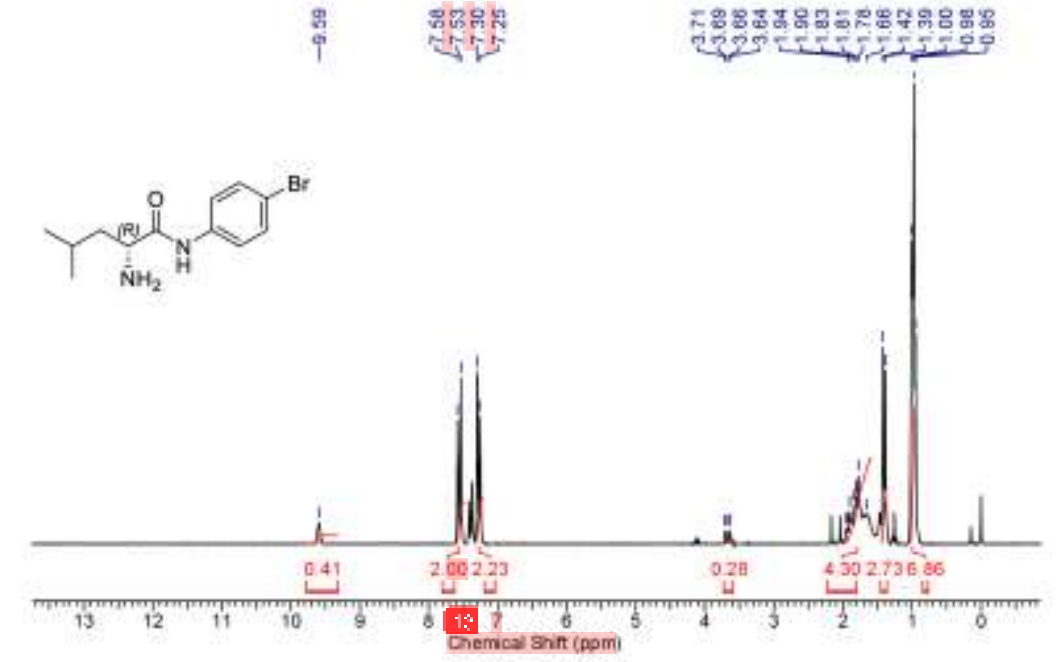



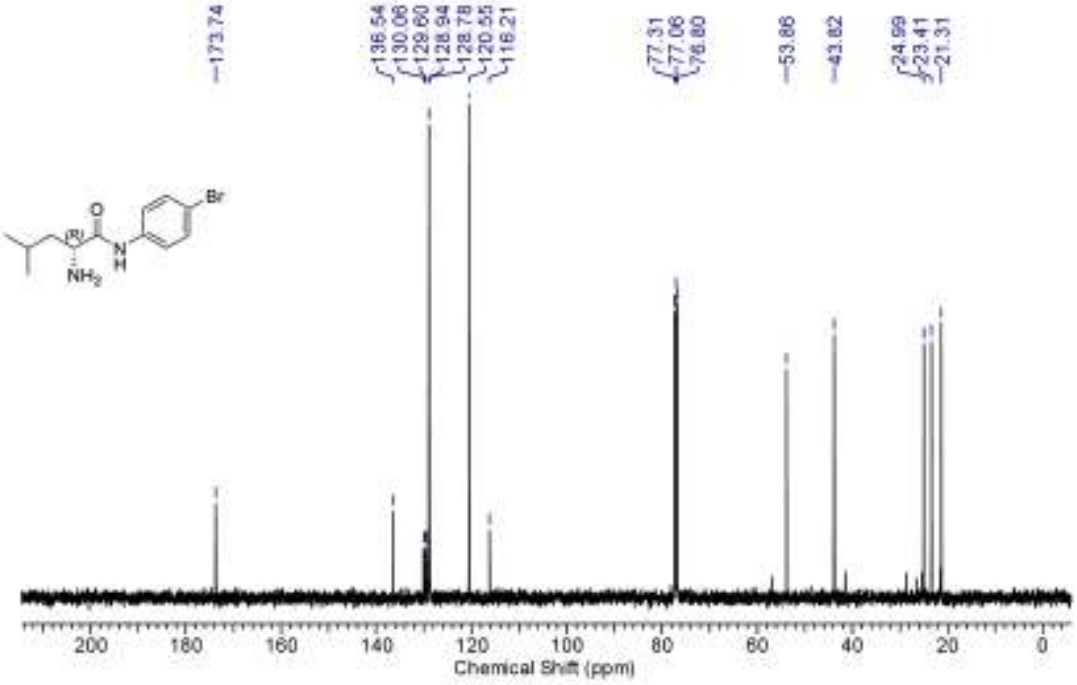
### 32l. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-N-(4-flurophenyl)-4-methylpentanamide:



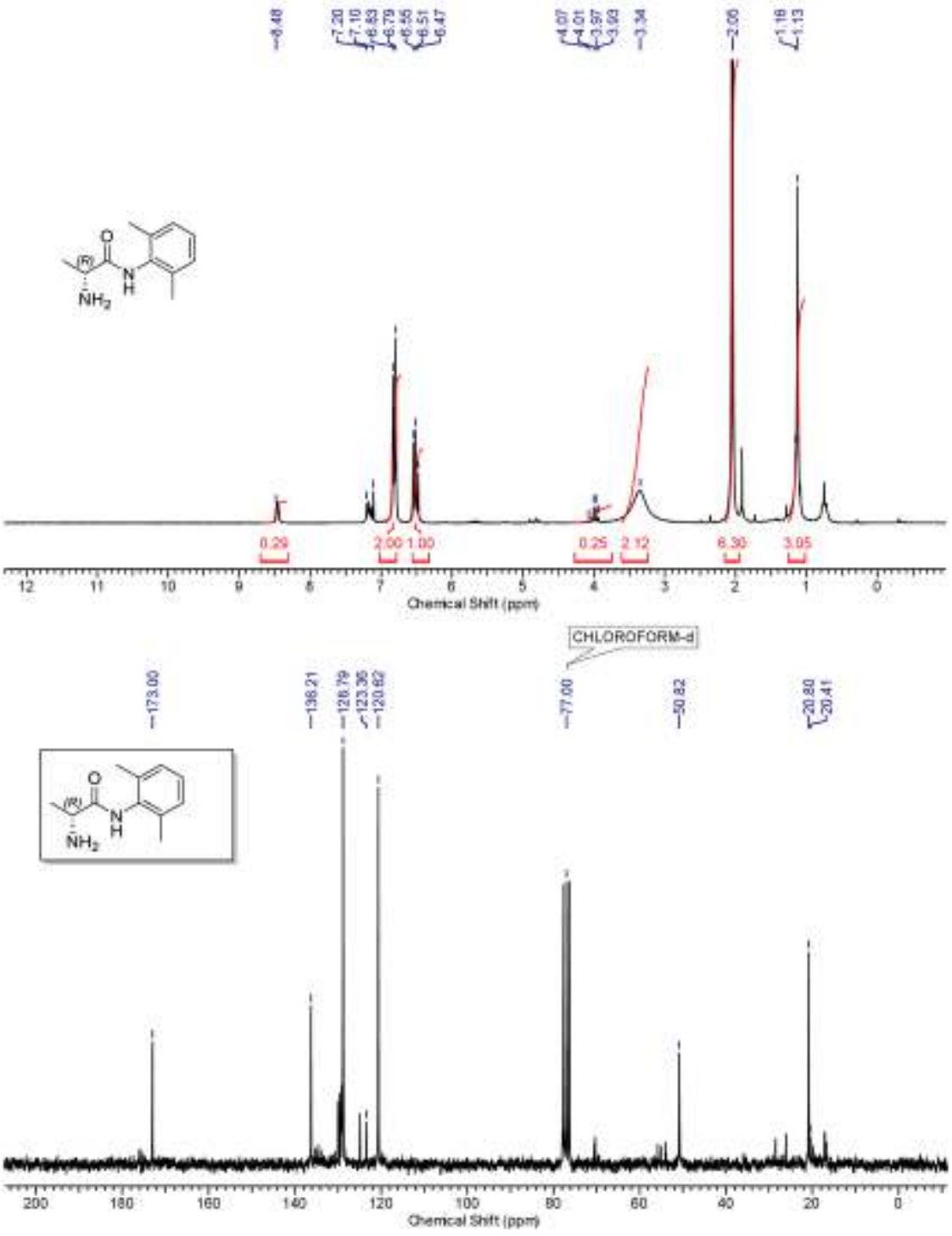



*32m. $^{1}H$ & $^{13}C$ NMR (R)-2-amino-N-(4-bromophenyl)-4-methylpentanamide:*

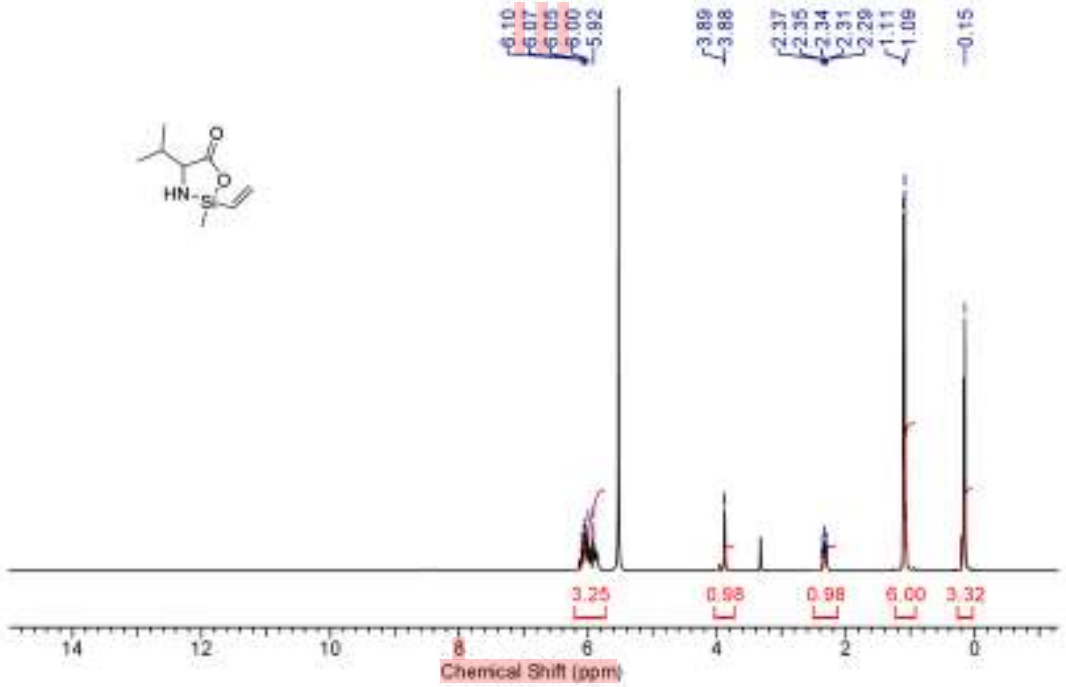


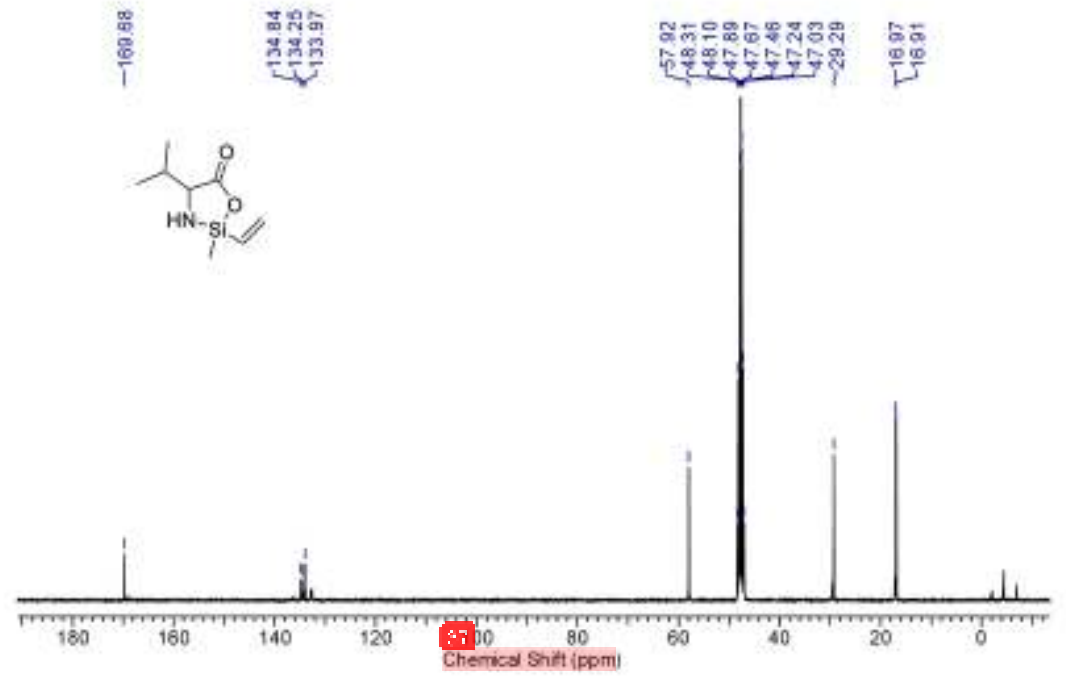



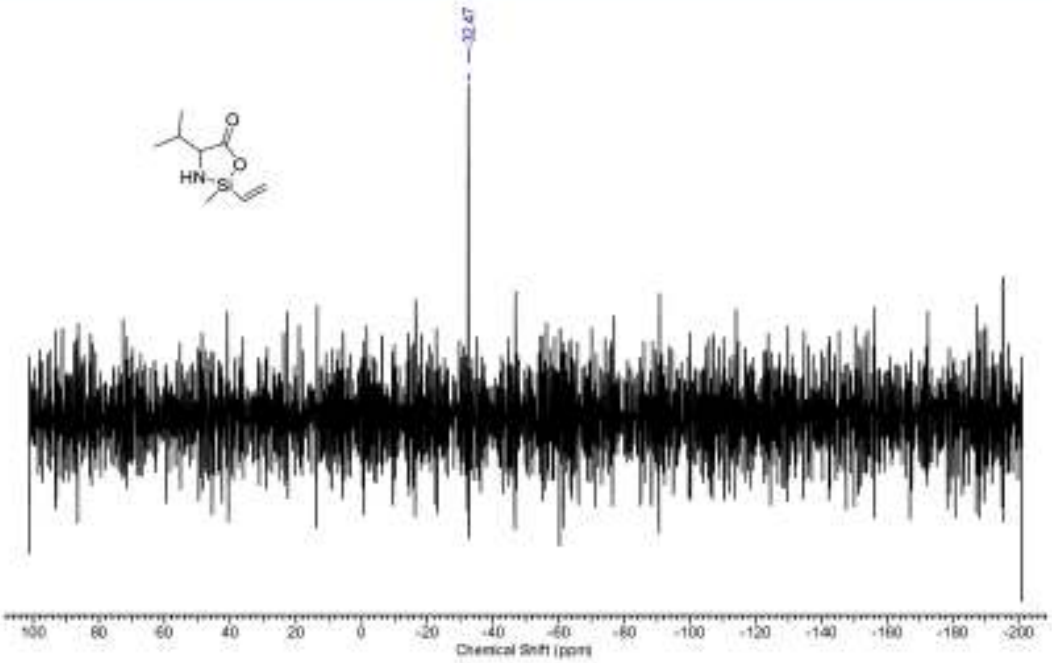
*32m. $^{1}H$ & $^{13}C$ NMR of (S)-2-amino-N-(2,6-dimethylphenyl)propanamide*



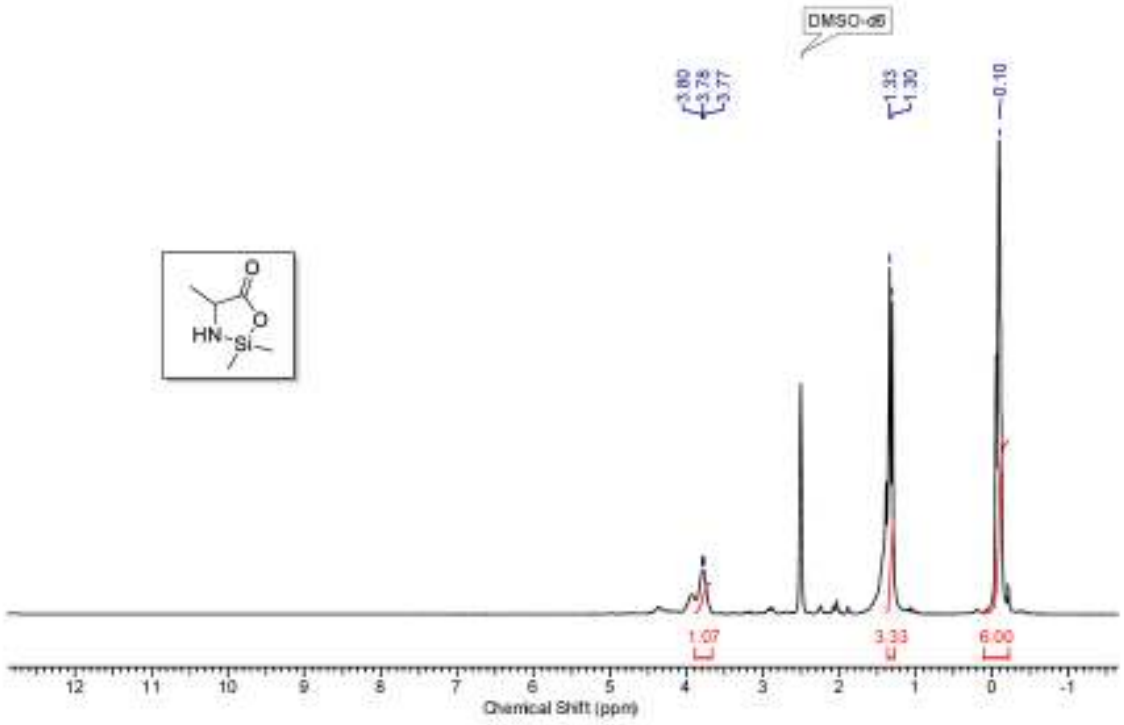
*$^{1}H$ , $^{13}C$ & $^{29}Si$ NMR 2,4-dimethyl-2-vinyl-1,3,2-oxazasilolidin-5-one:*






*$^{1}$H NMR of 2,2,4-trimethyl-1,3,2-oxazasilolidin-5-one*



## 1.7 References


[1] B. S. Davidson, *Chem. Rev.* **1993**, *93*, 1771–1791.

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*Chapter 2*

# Synthesis and characterization of Chiral Ionic Liquids of *N* aryl *R* & *S* amino acid amide

## 2.1 Introduction

The term Ionic liquid is now commonly known for the salts with melting point below 373K or below the boiling point of water (100°C). Ionic liquids (ILs) pauses either cations, anions or both. They have, generally, insignificant vapor pressure, high thermal and chemical stability, wide liquid range and good solvation behavior. They are potential environmental friendly alternatives to conventional volatile organic solvents. One of their notable features is the wide variation in their physicochemical properties, including viscosity, polarity, density, melting point and stability. These benefits make ILs as an attractive choice in the area of solvents[1][2], catalysts[3][4][5], bio-catalysts[6], electrochemistry[7][8][9][10], chemical separations[11], solid supports[12], chemical fixation of carbon dioxide[13] etc. Over the past few decades, catalysis by ionic liquids (ILs) has gained much attention due to clean media for green chemistry, especially in synthetic and catalytic transformations. ILs have several advantages, one of the advantage is they are used as alternative solvents in catalytic reactions as they have lower vapor pressure.

ILs having chiral center is called as Chiral Ionic liquids (CILs). A lot of efforts are made to develop CILs and finding their suitable applications. The successful application of CILs as solvents in enantio-selective synthesis is recently reported. Wasserscheid and coworkers,[14] and Warner and coworkers,[15] showed that CILs can be enantiomeric recognition as shift reagents in solution NMR spectroscopy. In both the references it was showed that the center of chirality was located within the IL cation. The another application shows the anion-directed chirality transfer[16]. In this it was showed that the hydrogenation of an IL composed of a prochiral cation and a chiral anion gave hydrogenated cation with 80%ee. Recently, the development of chiral ionic liquids and their applications in asymmetric synthesis has attracted much attention as these reactions have widespread applications in pharmaceutical industries. This chapter focus on synthesis and characterization of CILs.

## 2.2 Literature Review

Numerous synthesis methods for CILs are reported in literature. Many synthesis methods uses amino acid as starting material. This is mainly due to their easy availability, low cost and excellent enantiomeric purity. Amino acid derived CILs are considered bio-renewable and greener class of solvents as compare to imidazolium and quaternary ammonium salts, which are

derived from fossil feedstock[17]. In 2002 Wasserchcid and coworker[14], reported the CIL having oxazolinium cation derived from amino acid. In their synthesis initially oxazolinium cation was synthesized by reduction of valine methyl ester using $NaBH_4$- $H_2SO_4$ in THF to obtained amino alcohol followed by cyclisation of amino alcohol to oxazoline in presence of propionic acid. Then oxazoline was alkylated using alkyl halide to obtained salts. The salt anion was metatheses using $HPF_6$ to obtained oxazolinium cation based CILs. In 2003 Bao and coworkers[18], reported chiral imidazolium ionic liquids. In their synthesis L-alanine was reacted with formaldehyde, glyoxal, and aqueous ammonia under basic condition to form imidazole ring followed by esterification to obtained imidazoylakonic ester. The ester was further reduced using $LiAlH_4$ followed by alkylation to obtained imidazole based CILs. In 2003 Gaumont and coworker[19], reported the thiozoliunium based CILs. In their synthesis dithioester was reacted with amino alcohol followed by cyclisation in presence of triethylamine and mesyl chloride to obtained thiozoline. Further, thiozoline was alkylated using alkyl halide followed by anion exchange with $LiNTf_2$, $HPF_6$, $BF_4$ to thiozoline based CILs. In 2004 Jean Claude Guillemin and coworkers[20], reported the imidazolium derived CILs. In their synthesis of chiral imidazolium salts, N- Boc protected Valine was reacted with substituted aniline followed by hydrolysis to obtained corresponding amino acid amide. This was then reduced by using $LiAlH_4$ to obtained chiral diamine. Further chiral diamine was condensed with trimethyl orthoformate in toluene to obtained chiral imidazoline. The imidazoline was then reacted with alkyl halide followed by anion exchange to obtained chiral imidazole based CILs. In 2004 Vo-Thanh and coworkers[21], reported the ephedrinium based CILs having variable alkyl chain length on nitrogen group. In their synthesis initially ephedrine was reduced by using Eschweiler–Clarck procedure to obtained (1R 2S) N-methylephedrine salt. Then the salt was alkylated using different chain length of alkyl halide followed by anion metathesis to obtained corresponding CILs. The alkylation and metathesis step was carried out under solvent free condition using microwave activation. In 2004 Guillemin and coworker[20], reported the imidazole based CILs. In their synthesis, initially, protected valine was reacted with t-butylaniline followed by deprotection under acidic condition to amino acid amide. Further amino acid amide was reduced by using $LiAlH_4$ to diamine. Then in acidic condition diamine was reacted with triethyl orthoformate to imidazole ring. Further, alkylation of imidazole ring using alkyl halide followed by anion exchange with trifluromethane sulfonamide lithium hydroxide to imidazole based CILs. In 2004

Jodry J and coworkers[22], reported the imidazole based CILs. In their synthesis (S) ethyl lactate was reacted with 1-methylimidazole in presence of triflic acid anhydride and 2,6-lutadine in diethyl ether to obtained corresponding salt. Then salt was further anion exchanged with trifluoromethanesulfonic amide lithium hydroxide to CILs. In 2005 Ohno and coworkers[23], reported series of CILs using amino acid and 1 ethyl-3-methyl imidazolium. A similar synthetic route was followed in 2006 by the same group[24] and they introduced CILs with tetra butyl phosphonium (amino acid reacted with [TBP][OH]) as common cation and deprotonated amino acid anions. In 2005 Weiliang Bao and coworker[25], reported synthesis of CILs by using enantio-selective Michael addition reaction. In their synthesis D tartrate was reacted with benzyl bromide to form benzyl protected tartrate which was then reduced using $LiAlH_4$ to produced benzyl protected alcohol. Then this was reacted with tosyl chloride followed by N-methylimidazole bromide to form salt, salt was then refluxed in acetone to form CILs. In 2005 Yuan Kou and coworkers[26], reported easy synthesis of CILs. In their synthesis procedure, amino acid was protonated using acid to obtained CILs. Also amino acid ester hydrochloride was reacted with bis (trifluromethane sulfonamide) to obtained CILs. In 2006 Jin Pei Cheng and coworkers[27], reported functionalized CILs and which was used as organo catalyst for Michael addition reaction to nitroolefin. In their synthesis proline was reduced using $LiAlH_4$ in THF to obtained prolinol, which was further reacted with Boc anhydride followed by tosyl chloride to obtained N-Boc protected tosylted proline. This was then reacted with imidazole under basic condition to obtained N-Boc protected proline imidazole. This was further reacted with alkyl halide to obtained Boc deprotected CILs. In 2006 Zhen-Yuan Xu and coworker[28], reported the synthesis of CILs. In their synthesis procedure, initially, chiral amino acid was reduced using $NaBH_4$ to formed chiral amino alcohol. Then chiral amino alcohol was reacted with HBr followed by N-methyl imidazole to form imidazole salts. This salt was then anion exchanged using $AgBF_4$ to obtained CILs. In 2006 Baltas M and coworkers [29], reported the imidazole based CILs. In their synthesis procedure, imidazole was condensed with chiral phenylethylamine, formaldehyde, glyoxal aqueous ammonia to chiral imidazole. Then it was alkylated by using alkyl halide followed by anion metathesis using $NaBF_4$ to obtained CILs. In 2007 Giancarlo Francio and coworker[30], reported the amino acid based CILs. In their synthesis procedure, proline was esterified in presence of $SOCl_2$ followed by anion exchange with $LiNTf_2$ to obtained amino acid based CILs. In 2007 Allen D Headley and coworkers[31], reported the pyrrolidine based CILs

which was used as organo catalyst in asymmetric Michael addition of nitrostyrenes. In their synthesis chloropropylsulfonyl chloride was reacted with (S)-2-amino-1-N-Boc pyrrolidine to obtained N-Boc pyrrolidine sulfonamide which was then converted to imidazolium iodide using NaI in acetone. Then alkylation of pyrrolidine sulfonamide with 1-methylimidazole in acetonitrile to obtained Boc deprotected CILs followed by anion exchange with $NTf_2$. In 2007 Jin Pei Cheng and coworkers[32], reported the FILs incorporated with chiral pyrrolidine unit and which was used as reusable organo-catalysts for direct Aldol reaction. In their synthesis initially prolinol was reacted with Boc anhydride followed by tosylation to obtain Boc protected tosylated prolinol. This was reacting with imidazole to obtained pyrrolidine imidazole. This was then further quaternate with alkyl halide followed by anion exchange with $BF_4$ to obtained functionalized CILs. In 2007 Lei Wang and coworker[33], reported the CILs containing proline. In their synthesis procedure, N-methyl imidazole was reacted with 1,2-dibromoethane to 2-bromo ethane N-methylimidazole. This was then reacted with proline derivative to form corresponding salt which was reduced using $H_2$, Pd/C in methanol to CILs. In 2007 Allan D. Headley and coworkers[34], reported the fused ring CILs. In their synthesis procedure, N-methyl-2-carbaldehyde imidazole was reacted with chiral amino alcohol to imidazole imine. This was reduced using $NaBH_4$ to chiral amine imidazole followed by intramolecular cyclisation of amine imidazole to fused ring CILs. In 2008 Chieu D. Tran and coworkers[35], reported the CILs based on imidazolium. In their synthesis procedure, hydroxyl acid was reacted with boric acid and lithium carbonate to lithiated borate salt. This was then reacted with chiral imidazolinium cation to chiral imidazole based borate ion with spiral structure and chiral substituent. In 2008 Guanwu Wang and coworkers[36], reported silica supported CILs. In their synthesis procedure, initially, silica gel was reacted with 3-chloropropyl trimetoxysilane to obtain silica gel supported 3-chloropropylsilane. Then secondly Boc protected proline was reduced using $NaBH_4$ in $BF_3.Et_2O$ to obtain Boc protected prolinol. This was reacted with TsCl in pyridine and imidazole to obtained Boc protected proline imidazole. This Boc protected proline imidazole was reacted with silica gel supported 3-chloropropyl silane to obtained silica supported CILs. In 2009 Giang Vo-Thanh and coworkers[37], reported imidazole based CILs. CILs was synthesized using isosorbide as starting materials. In their synthesis procedure, initially, isosorbide was reacted with phenylsulfonyl chloride to obtained phenylsulfonated isosorbide. This was further reacted with amine to obtained aminated isosorbide, which was then reacted with formaldehyde in

formic acid to obtained N-alkylated isosorbide. This was reacted with methyl iodide to obtained isosorbide salt. The salt was anion exchanged with triflic acid and trifluromethansulfonamide to obtained CILs. In 2009 Giang Vo-Thanh and coworker[38], reported the imidazole based CILs obtained from isosorbide which was used in asymmetric Dial Alder reaction. In their synthesis procedure, isosorbide was reacted with acetic anhydride to acylated isosorbide. This was treated with triflic anhydride followed by reaction with N-methyl imidazole to obtained imidazole based isosorbide triflate salts. The salt was then refluxed in methanol to obtained imidazole based CILs. In 2009 Isiah M. Warner and coworkers[39], reported the synthesis of magnetic CILs, in their synthesis amino acid ester hydrochloride was reacted with ferric chloride hexa-hydrated in methanol to obtained magnetic CILs. In 2012 Shantiago and coworkers[40], reported the imidazole base CILs. In their synthesis procedure, initially, imidazole was formed by condensation reaction between amino acid amide, formaldehyde, glyoxal and aqueous ammonia. This chiral imidazole was alkylated by alkyl halide followed by anion metathesis with trifluoromethane sulfonyl amide lithium hydroxide to obtained CILs. In 2013 Katharina Bica and coworkers[41], reported the coordinating CILs based on amino alcohol. In their synthesis procedure, chiral amino alcohol (prolinol or valinol) was reacted with pyridine carbaldehyde to obtained pyridine prolinol. This was then alkylated by using alkyl halide followed by anion exchange with trifluoromethane sulfonamide to obtained pyridinium based CILs. In 2013 Jian Li and coworker[42] , reported the synthesis of CILs which was used for asymmetric Michael addition. In their synthesis procedure, initially, Boc protected amino methyl pyrrolidine was reacted with para tolyl sufonyl chloride imidazole salts to form Boc protected amino methyl pyrrolidine imidazole salt. This salt was then treated with trifluoro acetic acid to obtained CILs. In 2014 Yuki Yammamato [43], reported pyrrolidine based CILs. In their synthesis procedure, prolinol was react with tosyl chloride in excess of pyrrolidine followed by alkylation with alkyl halide to obtained chiral salt. The chiral salt was then anion exchanged with trifluorosulfonamide lithium hydroxide to obtained pyrrolidine base CILs. In 2015 Katharina Bica and coworkers[44], reported the amino alcohol derived CILs which was used as structural investigation toward chiral recognition. In their synthesis procedure, (1R 2S) ephedrine, (S) prolinol, (S) phenylalaninol are used as chiral starting materials. Initially, chiral amino alcohol (1R 2S) was reacted with chloroacetyl chloride under anhydrous condition in presence of triethyl amine to obtained corresponding carboxyamide compound. This was reacted with N-methylimidazole to obtained

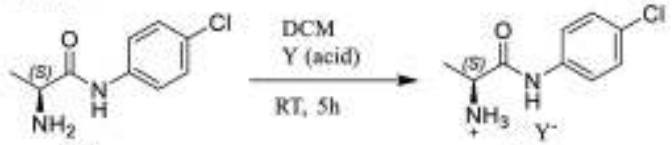
imidazole based salt. The salt was then anion metathesed with trimethyl sulfonamide lithium salts to obtained amino alcohol (1R 2S) ephedrine based CILs. In 2015 Katharina Bica and coworker[45], reported the coordinating CILs. In their synthesis procedure, chiral amino alcohol was reacted with pyridine aldehyde followed by reduction using $NaBH_4$ to form tri coordinated pyridine amino alcohol compound, which was alkylated using alkyl halide to obtained CILs. In 2016 Harish Kumar Chopra and coworkers[46], reported the benzimidazole based CILs, in their synthesis procedure, chloroacetic acid and methanol was reacted to obtained menthol. This was then reacted with N-methylbenzimidazole to obtained salt which was further anion exchanged with $HBF_4$ to obtained benzimidazole based CILs. In 2017 Irene W. Kimaru and coworkers[47], reported the synthesis of CILs and which was used for gas chromatography as stationary phase. In their synthesis procedure, L-phenylalanine methyl ester hydrochloride was reacted with trifluoromethyl sulfonyl amide lithium hydroxide to obtained corresponding CILs. In 2017 C. Hardacre and coworkers[48], reported the CILs as additive for asymmetric induction in Dial Alder reaction. In their synthesis procedure, (1R 2S) ephedrine was reacted with bromobutane to form (1R 2S)- 1-(−)-(phenylhydroxylethyl)methyl-butylamine. This was then alkylated by using iodomethane to obtained corresponding salt. This salts was then reacted with bis(trifluoromethane sufonyl) imide to obtained CILs. In 2018 Giang Vo-Thanh and coworkers[49], reported the reversible CILs from amino acid. In their synthesis procedure, salt of chiral ammonium carbamate was reacted with silylated amine at atmospheric $CO_2$ to obtained reversible CILs.

## 2.3 Present work

### *2.3.1 Synthesis of CILs of N aryl S amino acid amide by using different protonating agents.*

The synthesis of CILs of amino acid amide was optimized by changing counter anion. For this study amino acid amides was protonated using various 1:1 equivalent of acids (HCL, $HNO_3$, $H_2SO_4$ Perchloric acid etc.) in DCM for 5h. The desired product of CILs was obtained with excellent yield **(Table entry 1-4)**. However, protonated CILs obtained by using HCL, $H_2SO_4$ and $HNO_3$ were hydroscopic compared to perchloric acid. Therefore, perchloric acid was used for further to synthesis of all CILs of *N* aryl *R* & *S* amino acid amides.

**Table 1: Synthesis CILs of *N* aryl *S* amino acid amide by changing various acids as protonating agent.**




**28**
***N* aryl *S* amino acid amide**

**33**
**CILs**

| Entry no | Amide | Acid (Y) | Solvent | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 28a | HCl | DCM | 5 | 90 |
| 2 | 28a | $HNO_3$ | DCM | 5 | 92 |
| 3 | 28a | $H_2SO_4$ | DCM | 5 | 94 |
| 4 | 28a | $HClO_4$ | DCM | 5 | 99 |

### *2.3.2 Synthesis of CILs in different solvents.*

In synthesis of CILs, unprotected *L*-alanine (aliphatic natural amino acid) and chloroaniline (weakly nucleophilic aryl amine) was protonated by perchloric acid. Here we observed epimerization of CILs and this may be due to sudden formation of acidic condition during addition of perchloric acid and heat generated during this reaction. Because of acidic condition and heat generated active methylene group forms enolate and due to formation of enolate the active methylene carbon becomes $sp^2$ hybridized. Therefore, the epimerized CIL was obtained. This was confirmed by CD spectrophotometer shown in **Figure 1.**

To avoid epimerization, we carried out protonation by first dissolving amino acid amide completely in DCM and then perchloric acid was added drop by drop. By drop wise addition of perchloric acid heat generated was dissipated and sudden formation of acidic condition is avoided. Thus the product obtained does not epimerized and stereo-genic center of CIL retained as per original amino acid amide as shown in **Figure 2**. Therefore, for further all reactions were carried out using above producer to avoid epimerization in final CILs.

Further in optimization study, the protonation was carried out using (1:1) equivalent ratio of *N* aryl *S* amino acid amides and perchloric acid in different solvents (acetonitrile, THF, DMF, MeOH DCM) at room temperature for 5h. The corresponding CILs of amino acid amides were obtained with excellent yield **(Table 2, entry 1-5).** The all CILs except protonation carried out in

DCM products were purified by silica gel column chromatography using 20 % MeOH in DCM as solvent. As DCM is moderate polar solvent, CIL formed does not need purification by silica gel column, it was purified by decantation and drying. All CILs were confirmed by NMR. Therefore further all CILs were protonated by perchloric acid and in DCM carried.

**Figure 1: CD spectrum of epimerized CILs of *N* aryl amino acid amide.**

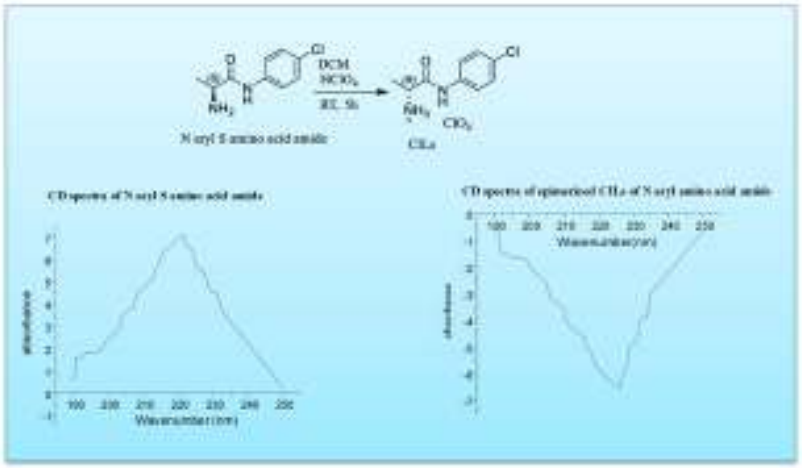


**Figure 2: CD spectrum of without epimerized CILs of *N* aryl *S* amino acid amide.**

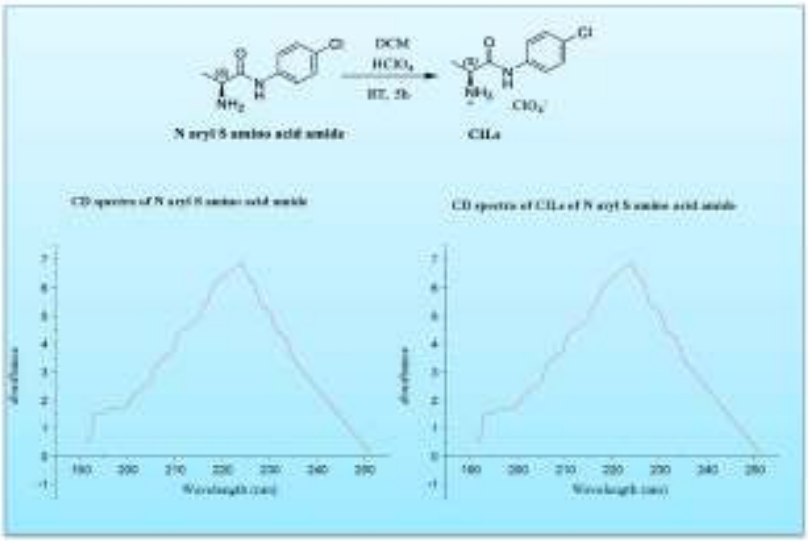
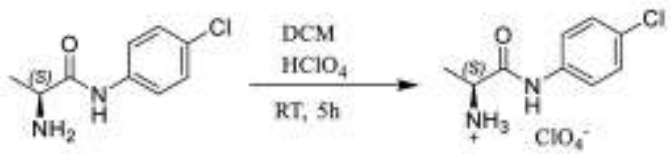


**Table 2: Synthesis of CILs in different solvents.**




**28**
***N* aryl *S* amino acid amide**

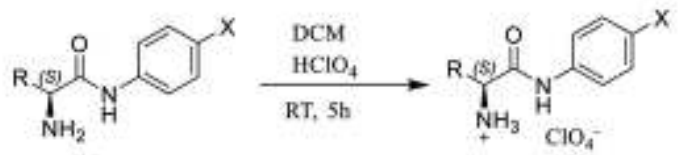
**33**
**CILs**

| Entry No | Solvent | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | ACN | 5 | 70 |
| 2 | THF | 5 | 80 |
| 3 | DMF | 5 | 60 |
| 4 | MeOH | 5 | 85 |
| 5 | DCM | 5 | 99 |

### *2.3.3 Synthesis of CILs using different N aryl R & S amino acid amides.*

The corresponding CILs of *N* aryl *S* amino acid amides were synthesized by protonating different amino acid amides **(33)** by using perchloric acid in DCM for 5 h. The excellent yield was obtained as shown in **Table 3 entry 1-11.** The melting point of CILs was measured by MP I apparatus. The melting point of CILs was in the range of 45 - 65°C. All CILs were characterized by $^{1}H$ & $^{13}C$ (200MHz, 400MHz, 500MHz) NMR spectroscopy. The mass of CILs was confirmed by HRMS. The chirality was confirmed by optical rotation and CD Spectro-photometer and shown in **Figure 3**. The purity of CILs was confirmed by HPLC.

**Table 3: Synthesis of CILs of *N* aryl *S* amino acid amides.**



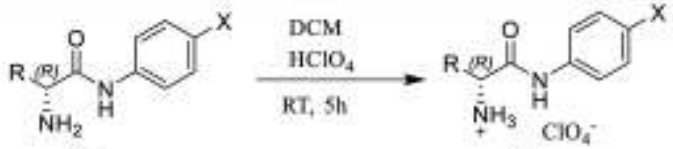

**28**
***N* aryl *S* amino acid amide**

**33**
**CILs**

| Entry No | R | X | Amide | CILs | MP (°C) | Configuration | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | -$CH_3$ | -$OCH_3$ | 28a | 33a | 55 | S | 98 |
| 2 | -$CH_3$ | -Cl | 28b | 33b | 65 | S | 98.5 |
| 3 | -$CH_3$ | -F | 28c | 33c | 60 | S | 99 |
| 4 | -$CH_3$ | -Br | 28d | 33d | 50 | S | 98 |
| 5 | -$CH(CH_3)_2$ | -$OCH_3$ | 28e | 33e | 62 | S | 99 |
| 6 | -$CH(CH_3)_2$ | -Cl | 28f | 33f | 44 | S | 99 |
| 7 | -$CH(CH_3)_2$ | -F | 28g | 33g | 45 | S | 98 |
| 8 | -$CH(CH_3)_2$ | -Br | 28h | 33h | 47 | S | 99 |
| 9 | -$CH_2CH(CH_3)_2$ | -$OCH_3$ | 28i | 33i | 48 | S | 99 |
| 10 | -$CH_2CH(CH_3)_2$ | -Cl | 28j | 33j | 41 | S | 98.5 |
| 11 | -$CH_2CH(CH_3)_2$ | -Br | 28k | 33k | 63 | S | 99 |

Also the corresponding CILs of *N* aryl *R* amino acid amides **(34)** were obtained by protonating with perchloric acid in DCM for 5h. The good to excellent yield was obtained **(Table 4 entry 1-11)**. The melting point of CILs was measured by MP I apparatus. The melting point of CILs was in the range of 45 - 65°C. The all CILs were characterized by $^{1}H$ & $^{13}C$ (200MHz, 400MHz, 500MHz) NMR spectroscopy. The mass of CILs was confirmed by HRMS. The chirality was confirmed by optical rotation and CD Spectro-photometer and shown in **Figure 3**. The purity of CILs was confirmed by HPLC.

**Table 4: Synthesis of CILs of *N* aryl *R* amino acid amide.**




**32**

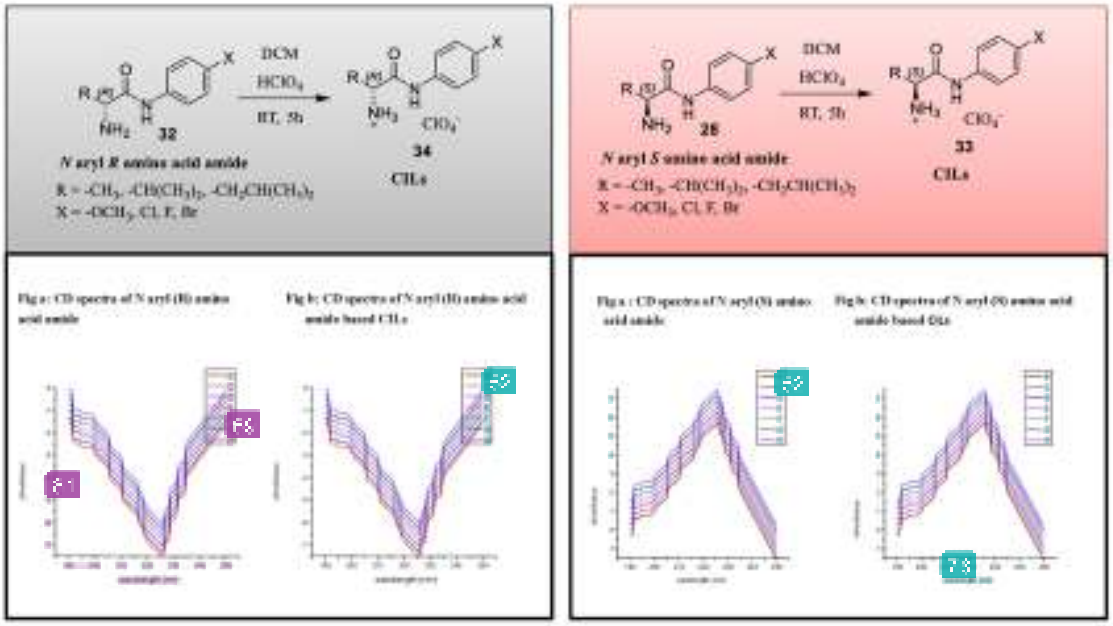
***N* aryl *R* amino acid amide**

**34**

**CILs**

| Entry No | R | X | Amide | CILs | MP (°C) | Configuration | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | -$CH_3$ | -$OCH_3$ | 32a | 34a | 52 | R | 98 |
| 2 | -$CH_3$ | -Cl | 32b | 34b | 63 | R | 98 |
| 3 | -$CH_3$ | -F | 32c | 34c | 58 | R | 99 |
| 4 | -$CH_3$ | -Br | 32d | 34d | 48 | R | 98 |
| 5 | -$CH(CH_3)_2$ | -$OCH_3$ | 32e | 34e | 60 | R | 99 |
| 6 | -$CH(CH_3)_2$ | -Cl | 32f | 34f | 45 | R | 99 |
| 7 | -$CH(CH_3)_2$ | -F | 32g | 34g | 44 | R | 98 |
| 8 | -$CH(CH_3)_2$ | -Br | 32h | 34h | 46 | R | 99 |
| 9 | -$CH_2CH(CH_3)_2$ | -$OCH_3$ | 32i | 34i | 50 | R | 99 |
| 10 | -$CH_2CH(CH_3)_2$ | -Cl | 32j | 34j | 40 | R | 98 |
| 11 | -$CH_2CH(CH_3)_2$ | -Br | 32k | 34k | 61 | R | 99 |

**Figure 3: CD spectrum of CILs of *N* aryl *R* & *S* amino acid amide.**




## 2.4 Conclusion

In conclusion we successively synthesized CILs of *N* aryl *R* & *S* amino acid amides with excellent yield by protonating corresponding amides using perchloric acid in DCM for 5h. By using above synthesis method CILs formed does not epimerized the stereo genic center and it was confirmed by CD Spectro-photometer. The synthesized CILs of *N* aryl *R* & *S* amino acid amide have melting point in the range of 45-65°C.

## 2.5 Experimental section

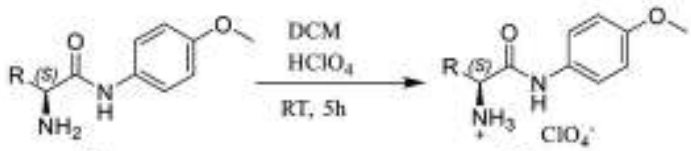
### *2.5.1 General information of chemicals, reagents and instruments.*

All the 99% pure amino acids *L* and *D* alanine, valine, leucine were purchased from sigma Aldrich chemical limited. Aryl amines (chloro aniline, 4-methoxyaniline, 4-fluroaniline), 4-nitroaniline, pyridine, $Na_2SO_4$, $NaHCO_3$, and $CuSO_4$ were purchased from Avra chemical limited. The solvents for chromatography and extraction were purchased from commercial suppliers and used without further purification. All reactions were performed in glass reactor

equipped with a magnetic stirrer at an atmosphere pressure, unless otherwise stated. Thin layer chromatography (TLC) analysis was used to monitor reaction progress using Merck TLC plates (silica gel 60GF-254, 0.25mm) and visualized under UV (254 nm). The products were purified by column chromatography on silica gel 60 (Merck, 230-400 mesh). Products were confirmed by $^{1}H$ & $^{13}C$ NMR (200MHz, 400MHz, 500MHz) using Bruker NMR spectrometer with solvent ($CDCl_3$, MeOD-$_4$, DMSO-$d_6$) as internal standard in chemical shift δ (7.26ppm,77.16 ppm, 3.31 ppm, 49 ppm, 2.50 ppm, 39.52 ppm). Multiplicities are reported using following abbreviations - s= singlet, d= doublet, t= triplet, m= multiplets and br = broad, dd = doublet of doublet, dt = doublet of triplet etc. Rotation of product is confirmed by JASCO. Stereochemistry of product is confirmed by JASCO-820 series of circular dichroism Spectro photometer. Mass of the product is confirmed by HRMS. Elemental analysis was carried out by Thermo Finnigan EA1112 series Flash Elemental Analyzer.

### *2.5.2 Experimental procedure for synthesis CILs of N aryl (R) & (S) amino acid amide.*

***Reaction:***



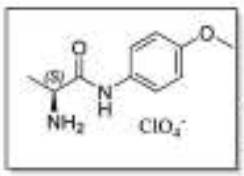

**28** **33**

***N* aryl *S* amino acid amide** **CILs**

The 50 ml of oven dried round bottom flask equipped with magnetic stirrer was charged with 1.7 mmoles of *N* aryl (*S*) amino acid amide and under stirring in this 1:1 equivalent perchloric acid was added drop-wise in DCM at room temperature. Reaction was monitored by TLC. The reaction was stop after 5h and excess DCM solvent was decanted. The solid product was washed three times by DCM and DCM was decanted. The remaining DCM was dried on reduced pressure. Products were confirmed by $^{1}H$ & $^{13}C$ NMR. The mass of product is confirmed by HRMS. Optical purity is confirmed by JASCO polarimeter.

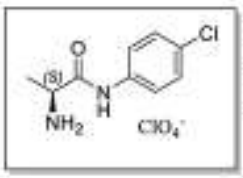
## 2.6 Spectral Data

### *33a. (S)-1-((4-methoxyphenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



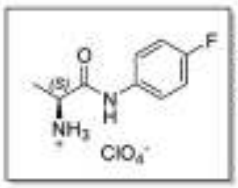
Yield 98 %; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.45 (d, $J$=7.25 Hz, 3 H) 3.74 (s, 3 H) 3.90 - 3.99 (m, 1 H) 6.94 (d, $J$=8.77 Hz, 2 H) 7.51 (d, $J$=8.77 Hz, 2 H) 8.13 (br. s., 3 H) 10.21 (s, 1 H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) δ ppm 17.66, 49.41, 55.67, 121.49, 131.58, 156.25, 168.10; $[\alpha]_D^{25} = -12.40$ (C= 1 in MeOH) ; HRMS (ESI) calculated $C_{10}H_{15}N_2O_2$ [M$^+$]: 195.1128 found : 195.1133 & calculated $ClO_4$ [M$^-$] : 98.9491 found : 98.9477;

### *33b. (S)-1-((4-chlorophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



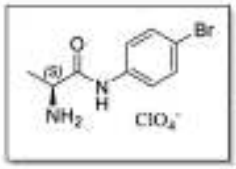
Yield 98.5 %; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.42 - 1.50 (m, 3 H) 3.98 (d, $J$=5.34 Hz, 1 H) 7.43 (d, $J$=8.77 Hz, 2 H) 7.63 (d, $J$=8.77 Hz, 2 H) 8.16 (br. s., 3 H) 10.49 (s, 1 H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) δ ppm 17.53, 49.53, 121.50, 128.23, 137.48, 168.29; $[\alpha]_D^{25} = -18.10$ (C= 1 in MeOH) ; HRMS (ESI) calculated $C_9H_{11}ClN_2O$ [M$^+$]: 199.0633 found : 199.0637 & calculated $ClO_4$ [M$^-$] : 98.9491 found : 98.9477;

### *33c. (S)-1-((4-flurophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



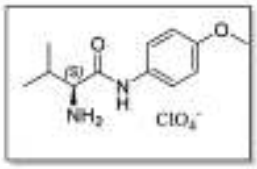
Yield 99%, $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.42 - 1.50 (m, 3 H) 3.98 (d, $J$=5.34 Hz, 1 H) 7.43 (d, $J$=8.77 Hz, 2 H) 7.63 (d, $J$=8.77 Hz, 2 H) 8.16 (br. s., 3 H) 10.49 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 17.53, 49.53, 121.50, 128.23, 137.48, 168.29; $[\alpha]_D^{25} = -16.60$ (C = 1 MeOH), HRMS (ESI) of $C_9H_{11}FN_2O^+$ calculated 183.0633 found 183.0637 & $ClO_4^-$calculated 98.9491 found 98.9477;

*33d. (S)-1-((4-bromophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



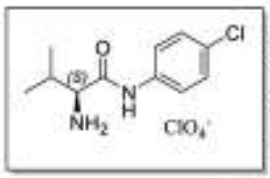
Yield 98% $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.41 (d, *J*=6.87 Hz, 3 H) 3.86 - 3.96 (m, 1 H) 7.34 (d, *J*=8.77 Hz, 2 H) 7.50 - 7.60 (m, 2 H) 8.10 (br. s., 3 H) 10.35 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 17.42, 49.54, 121.63, 127.70, 129.30, 137.21, 168.64; $[\alpha]_D^{25} = -15.60$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_9H_{11}ClN_2O^+$ calculated 199.0633 found 199.0637 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*33e. (S)-1-((4-methoxyphenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



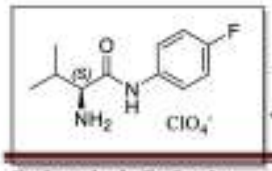
Yield 99%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.89 - 1.03 (m, 6 H) 2.08 - 2.22 (m, 1 H) 3.65 (br. s., 1 H) 3.72 (s, 3 H) 6.93 (d, *J*=8.55 Hz, 2 H) 7.50 (d, *J*=8.54 Hz, 2 H) 8.16 (br. s., 3 H) 10.23 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.21, 18.88, 30.39, 55.66, 58.73, 114.58,121.64, 131.29, 156.35, 166.68; $[\alpha]_D^{25} = -20.600$ (C = 1 MeOH); HRMS (ESI) of $C_{12}H_{19}N_2O_2^+$ calculated 223.1441 found in 223.1438 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*33f. (S)-1-((4-chlorophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



Yield 99 %; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.86 - 1.03 (m, 6 H) 2.07 - 2.22 (m, 1 H) 3.69 (br. s., 1 H) 7.40 (d, *J*=8.54 Hz, 2 H) 7.61 (d, *J*=8.54 Hz, 2 H) 8.19 (br. s., 3 H) 10.49 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.07, 18.85, 3034, 58.83, 121.63, 128.39, 129.40, 137.15, 167.40; $[\alpha]_D^{25} = -21.50$ (C = 1 in MeOH) ; HRMS (ESI) calculated $C_{11}H_{16}ClN_2O$ [$M^+$] : 227.0946 found : 227.0943 & calculated $ClO_4$ [$M^-$] : 98.9491 found : 98.9477;

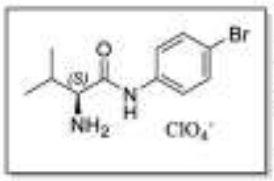
*33g. (S)-1-((4-flurophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



Yield 98%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.86 - 1.03 (m, 6 H) 2.07 - 2.22 (m, 1 H) 3.69 (br. s., 1 H) 7.40 (d, *J*=8.54 Hz, 2 H) 7.61 (d, *J*=8.54 Hz, 2 H) 8.19 (br. s., 3 H) 10.49 (br. s., 1 H); $^{13}$C NMR (100

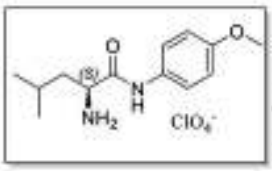
MHz, DMSO-$d_6$) δ ppm 18.07, 18.85, 3034, 58.83, 121.63, 128.39, 129.40, 137.15, 167.40; $[\alpha]_D^{25} = -18.450$ (C = 1 MeOH); HRMS (ESI) of $C_{11}H_{16}FN_2O^+$ calculated 211.0946 found 211.0943 & $ClO_4^-$ calculated 98.9491 found 98.9477;

### *33h. (S)-1-((4-bromophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



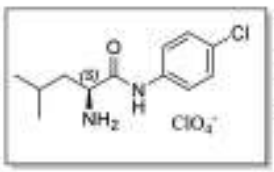

Yield 99%, $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.85 - 1.12 (dd, 6 H) 2.03 - 2.32 (m, 1 H) 3.69 (d., 1 H) 7.30 - 7.50 (d, 2 H) 7.53 - 7.70 (d, 2 H) 8.19 (br. s., 3 H) 10.31 - 10.64 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.09, 18.88, 30.34, 58.84, 121.64, 128.40, 129.42, 137.18, 167.42; $[\alpha]_D^{25} = -17.57$ (C = 1 MeOH); HRMS (ESI) of $C_{11}H_{16}ClN_2O^+$ calculated 227.0946 found 227.0943 & $ClO_4^-$ calculated 98.9491 found 98.9477;

### *33i. (S)-1-((4-methoxyphenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



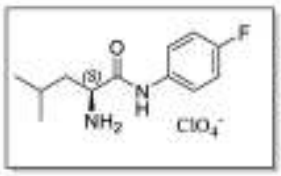

Yield 99%; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.85 - 0.98 (m, 6 H) 1.47 - 1.73 (m, 3 H) 3.67 - 3.74 (m, 3 H) 3.83 (d, $J$=4.96 Hz, 1 H) 6.91 (d, $J$=8.77 Hz, 2 H) 7.48 (d, $J$=8.77 Hz, 2 H) 8.17 (br. s., 3 H) 10.25 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 22.35, 22.99, 24.18, 49.06, 52.18, 55.63, 114.55, 121.71, 137.32, 156.34, 167.66; $[\alpha]_D^{25} = -5.7$ (C = 1 MeOH); HRMS (ESI) of $C_{13}H_{21}N_2O_2^+$ calculated 237.1598 found 237.1594 & $ClO_4^-$ calculated 98.9491 found 98.9477;

### *33j. (S)-1-((4-chlorophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



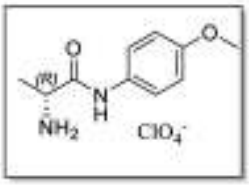

Yield 98.5 %; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.92 (d, $J$=2.67 Hz, 6 H) 1.66 (br. s., 3 H) 3.88 (d, $J$=4.20 Hz, 1 H) 7.42 (d, $J$=8.77 Hz, 1 H) 7.62 (d, $J$=8.77 Hz, 2 H) 8.21 (br. s., 3 H) 10.55 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 22.27, 23.07, 24.15, 49.06, 52.30, 121.68, 128.39, 129.92, 137.29, 168.46; $[\alpha]_D^{25} = -11.40$ (C= 1 in MeOH); HRMS (ESI) calculated $C_{12}H_{18}ClN_2O$ [M$^+$] : 241.1102 found : 241.1097 & calculated $ClO_4$ [M$^-$] : 98.9491 found : 98.9477;

*33k. (S)-1-((4-flurophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



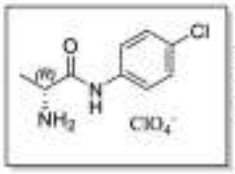
Yield 99%; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.92 (d, *J*=2.67 Hz, 6 H) 1.66 (br. s., 3 H) 3.88 (d, *J*=4.20 Hz, 1 H) 7.42 (d, *J*=8.77 Hz, 1 H) 7.62 (d, *J*=8.77 Hz, 2 H) 8.21 (br. s., 3 H) 10.55 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 22.27, 23.07, 24.15, 49.06, 52.30,121.68, 128.39, 129.92, 137.29, 168.46; $[\alpha]_D^{25} = -14.7$ (C = 1 MeOH), HRMS (ESI) of $C_{12}H_{18}FN_2O^+$ calculated 225.1102 found 225.1097 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34a. (R)-1-((4-methoxyphenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



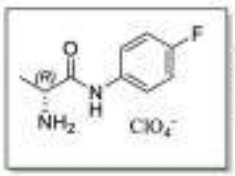
Yield 98%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 1.41 (d, *J*=6.10 Hz, 3 H) 3.66 (s, 3 H) 3.90 (br. s., 1 H) 6.77 - 6.94 (m, 2 H) 7.44 (d, *J*=8.54 Hz, 2 H) 8.11 (br. s., 3 H) 10.13 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 17.56, 49.38, 55.56, 114.49, 121.64, 125.03, 127.71, 130.28, 156.24, 168.03; $[\alpha]_D^{25} = +15.60$ (C = 1 MeOH),.HRMS (ESI) of $C_{10}H_{15}N_2O_2^+$ calculated 195.1128 found 195.1133 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34b. (R)-1-((4-Chlorophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



Yield 98%; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.41 (d, *J*=6.87 Hz, 3 H) 3.86 - 3.96 (m, 1 H) 7.34 (d, *J*=8.77 Hz, 2 H) 7.50 - 7.60 (m, 2 H) 8.10 (br. s., 3 H) 10.35 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 17.42, 49.54, 121.63, 127.70, 129.30, 137.21, 168.64; $[\alpha]_D^{25} = +15.60$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_9H_{11}ClN_2O^+$ calculated 199.0633 found 199.0637 & $ClO_4^-$ calculated 98.9491 found 98.9477.

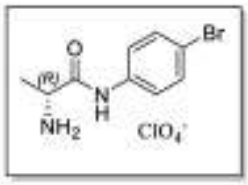
*34c. (R)-1-((4-flurophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



Yield 99%, $^1$H NMR (200 MHz, DMSO-$d_6$) δ ppm 1.49 (d, *J*=6.95 Hz, 3 H) 3.85 - 4.21 (m, 1 H) 7.43 (d, *J*=8.84 Hz, 2 H) 7.55 - 7.73 (m, 2 H) 8.18 (br. s., 3 H) 10.46 (s, 1 H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) δ ppm 17.42, 49.54,

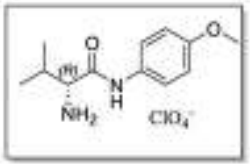
121.63, 127.70, 129.30, 137.21, 168.64; $[\alpha]_D^{25} = +15.60$ (C = 1 $CHCl_3$); HRMS (ESI) of $C_9H_{11}FN_2O^+$ calculated 183.0633 found 183.1637 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34d. (R)-1-((4-bromophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



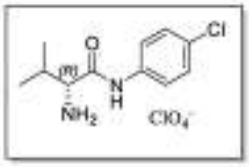

Yield 98%; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.42 - 1.50 (m, 3 H) 3.98 (d, *J*=5.34 Hz, 1 H) 7.43 (d, *J*=8.77 Hz, 2 H) 7.63 (d, *J*=8.77 Hz, 2 H) 8.16 (br. s., 3 H) 10.49 (s, 1 H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ ppm 17.53, 49.53, 121.50, 128.23, 137.48, 168.29; $[\alpha]_D^{25} = +16.60$ (C = 1 MeOH), HRMS (ESI) of $C_9H_{11}FN_2O^+$ calculated 183.0633 found 183.0637 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34e. (R)-1-((4-methoxyphenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



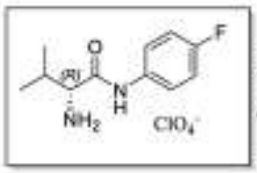

Yield 99%, $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.90 - 1.03 (dd, 6 H) 2.08 - 2.23 (m, 1 H) 3.61 - 3.68 (d, 1 H) 3.73 (s, 3 H) 6.93 (d, *J*=9.16 Hz, 2 H) 7.50 (d, *J*=8.54 Hz, 2 H) 8.16 (br. s., 3 H) 10.23 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm18.21, 18.88, 3040, 55.67, 58.74, 114.60, 121.65, 131.74, 156.36, 166.68; $[\alpha]_D^{25} = +18.20$ (C = 1 MeOH); HRMS (ESI) of $C_{12}H_{19}N_2O_2^+$ calculated 223.1441 found 223.1438 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34f. (R)-1-((4-chlorophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



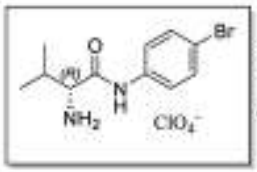

Yield 99%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.85 - 1.12 (dd, 6 H) 2.03 - 2.32 (m, 1 H) 3.69 (d., 1 H) 7.30 - 7.50 (d, 2 H) 7.53 - 7.70 (d, 2 H) 8.19 (br. s., 3 H) 10.31 - 10.64 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.09, 18.88, 30.34, 58.84, 121.64, 128.40, 129.42, 137.18, 167.42; $[\alpha]_D^{25} = +17.57$ (C = 1 MeOH); HRMS (ESI) of $C_{11}H_{16}ClN_2O^+$ calculated 227.0946 found 227.0943 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34g. (R)-1-((4-flurophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



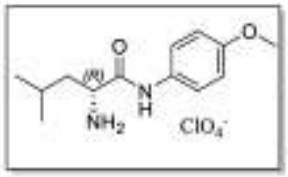
Yield 98%, $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.92 - 1.03 (m, 6 H) 2.05 - 2.26 (m, 1 H) 3.69 (br. s., 1 H) 7.42 (d, *J*=8.54 Hz, 2 H) 7.62 (d, *J*=7.93 Hz, 2 H) 8.19 (br. s., 3 H) 10.50 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.09, 18.88, 30.34, 58.84, 121.64, 128.40, 129.42, 137.17, 167.42 ; $[\alpha]_D^{25} = +17.57$ (C = 1 MeOH); HRMS (ESI) of $C_{11}H_{16}FN_2O^+$ calculated 309.0659 found 309.0943 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34h. (R)-1-((4-bromophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



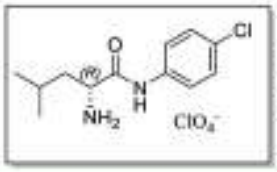
Yield 98%, $^{1}$H NMR (400 MHz, DMSO-$d_6$) d ppm 0.87 - 1.06 (m, 6 H) 2.07 - 2.28 (m, 1 H) 3.69 (br. s., 1 H) 7.40 (d, *J*=8.54 Hz, 2 H) 7.61 (d, *J*=8.54 Hz, 2 H) 8.19 (br. s., 3 H) 10.49 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 18.07, 18.85, 30.58, 58.83, 12103, 128.39, 129.40, 137.15, 67.40; $[\alpha]_D^{25} = +17.57$ (C = 1 MeOH); HRMS (ESI) of $C_{11}H_{16}BrN_2O^+$ calculated 368.6898 found 368.7095 & $ClO_4^-$ calculated 98.9491 found 98.9477;

*34i. (S)-1-((4-methoxyphenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



Yield 99%; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.84 (d, 6 H) 1.47 - 1.65 (m, 3 H) 3.63 (s, 3 H) 3.78 (t, 1 H) 6.85 (d, *J*=8.54 Hz, 2 H) 7.30 - 7.48 (d, 2 H) 8.09 (br. s., 3 H) 10.10 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 22.18, 22.83, 24.12, 30.94, 52.18, 55.52, 114.49, 121.85, 131.09, 156.35, 167.58; $[\alpha]_D^{25} = +9.52$ (C = 1 MeOH); HRMS (ESI) of $C_{13}H_{21}N_2O_2^+$ calculated 237.1598 found 237.1594 & $ClO_4^-$ calculated 98.9491 found 98.9477;

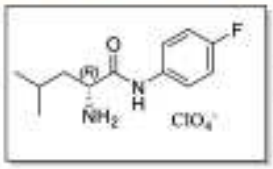
*34j. (R)-1-((4-chlorophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



Yield 98%, $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ ppm 0.90 (dd, 6 H) 1.64 (m, 3 H) 3.87 (t., 1 H) 7.39 (d, *J*=8.55 Hz, 2 H) 7.60 (d, *J*=8.54 Hz, 2 H) 8.19 (br. s., 3 H) 10.51 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 22.24, 23.03, 24.13, 49.04, 52.28, 121.68, 128.38, 129.39, 137.25,

168.42; $[\alpha]_D^{25} = +13.60$ (C = 1 MeOH); HRMS (ESI) of $C_{12}H_{18}ClN_2O^+$ calculated 241.1102 found 241.1097 & $ClO_4^-$ calculated 98.9491 found 98.9477;

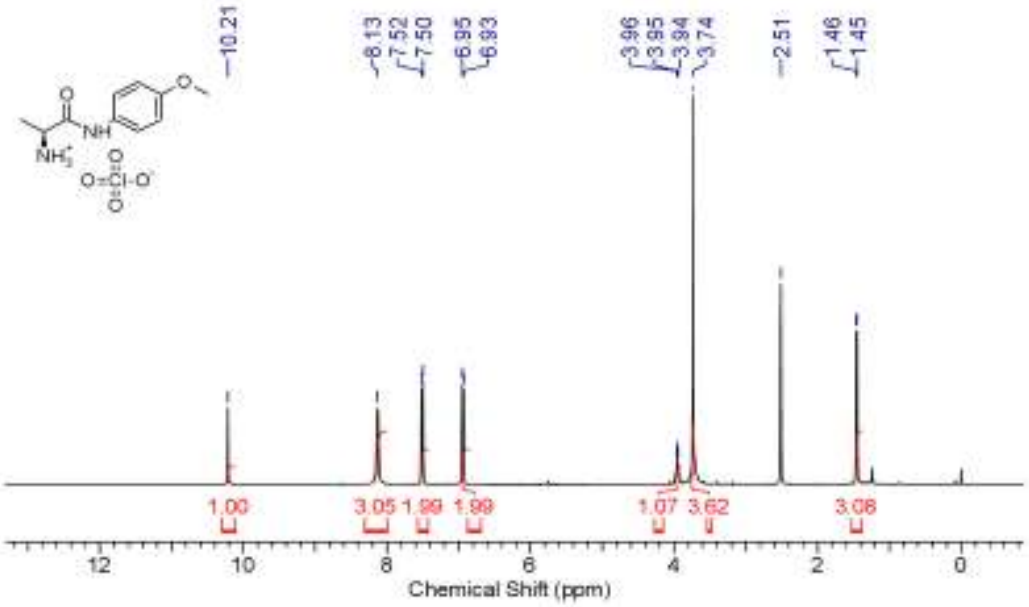
*34k. (R)-1-((4-flurophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*

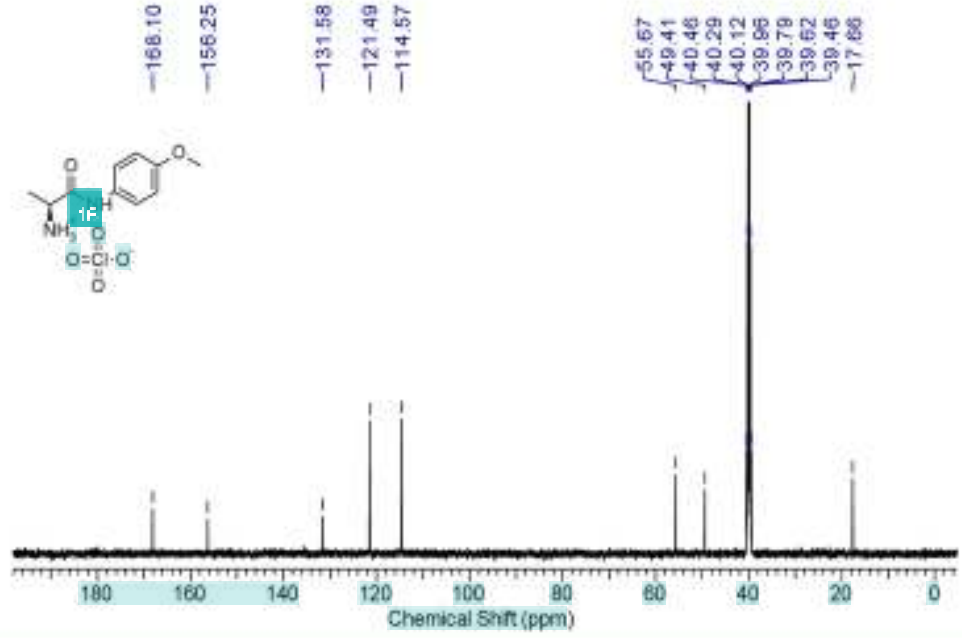



Yield 99%; $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.92 (d, *J*=2.67 Hz, 6 H) 1.66 (br. s., 3 H) 3.88 (d, *J*=4.20 Hz, 1 H) 7.42 (d, *J*=8.77 Hz, 1 H) 7.62 (d, *J*=8.77 Hz, 2 H) 8.21 (br. s., 3 H) 10.55 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 22.24, 23.03, 24.14, 49.04, 52.28, 121.68, 128.38, 129.39, 137.25, 168.42; $[\alpha]_D^{25} = +13.60$ (C = 1 MeOH); HRMS (ESI) of $C_{12}H_{18}FN_2O^+$ calculated 323.0816 found 323.0991 & $ClO_4^-$ calculated 98.9491 found 98.9477;

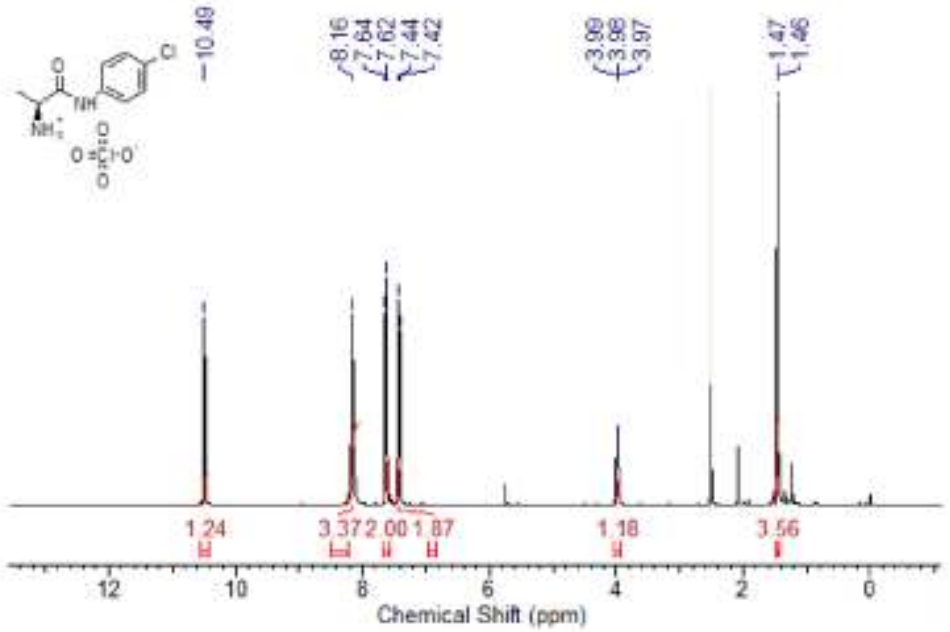
## 2.6.1 $^{1}H$ & $^{13}C$ NMR spectra CIL of N aryl R & S amino acid amide.

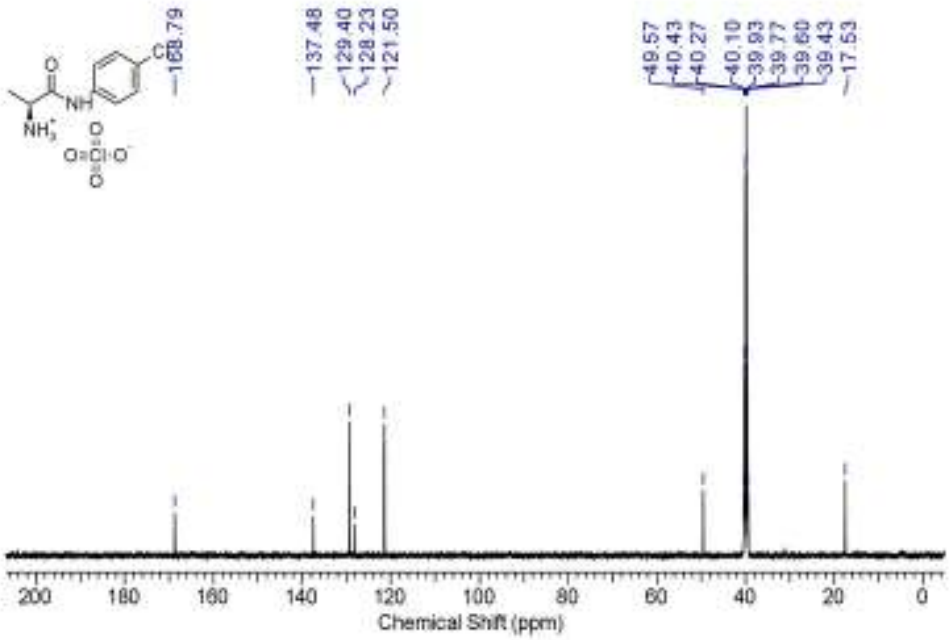
### 33a. (S)-1-((4-methoxyphenyl) amino)-1-oxozopropan-2-amminium perchlorate:



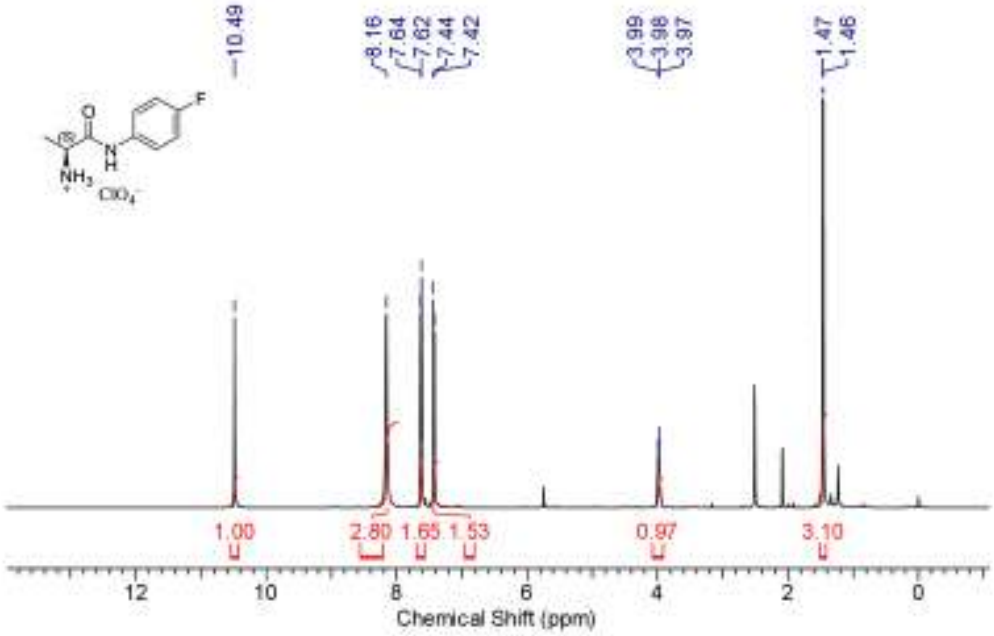



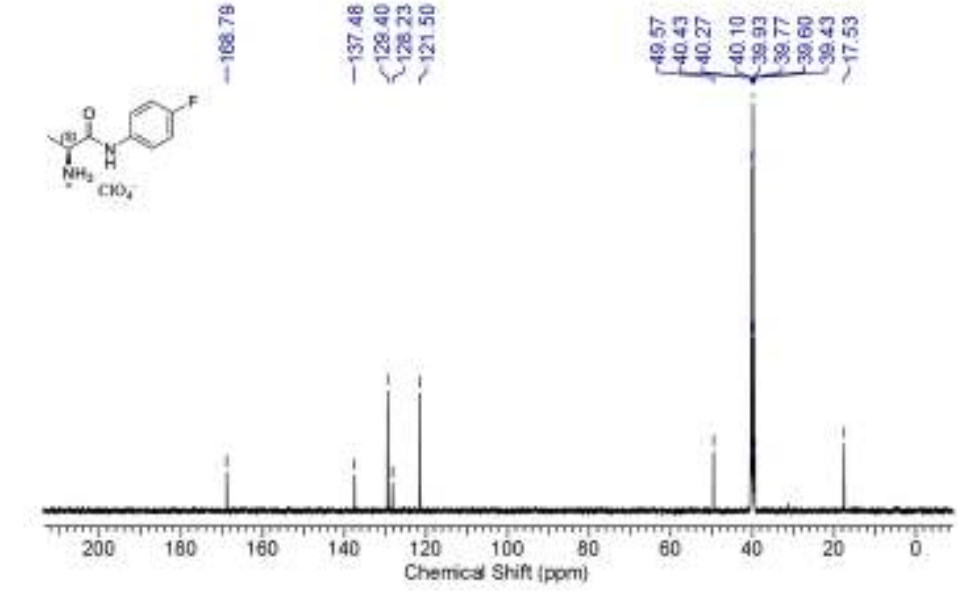
*33b. (S)-1-((4-chlorophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



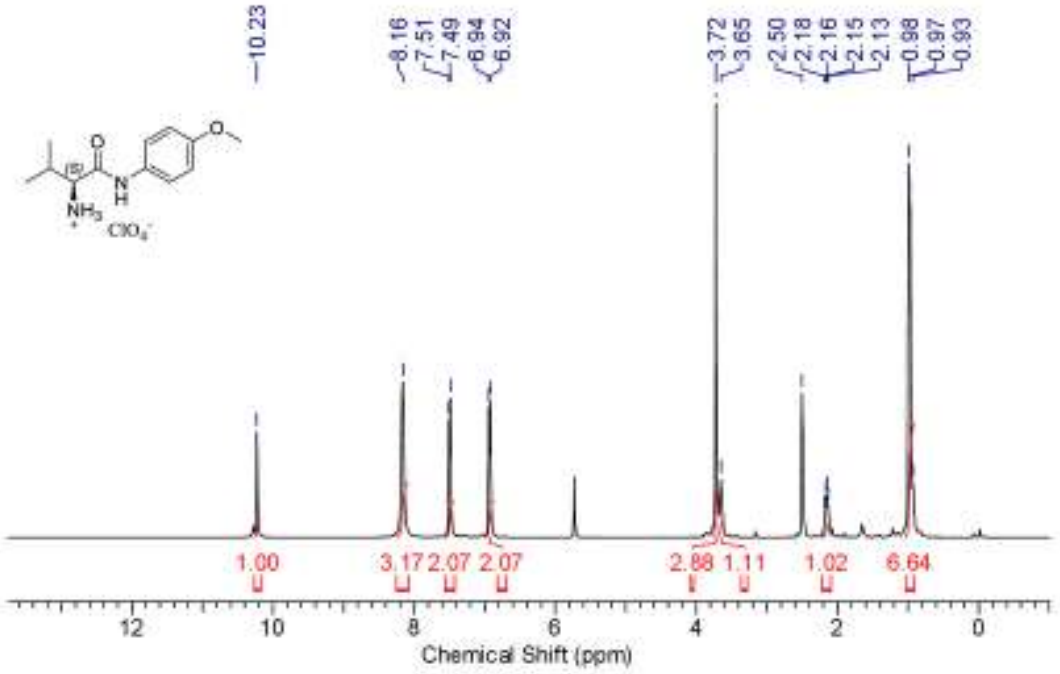



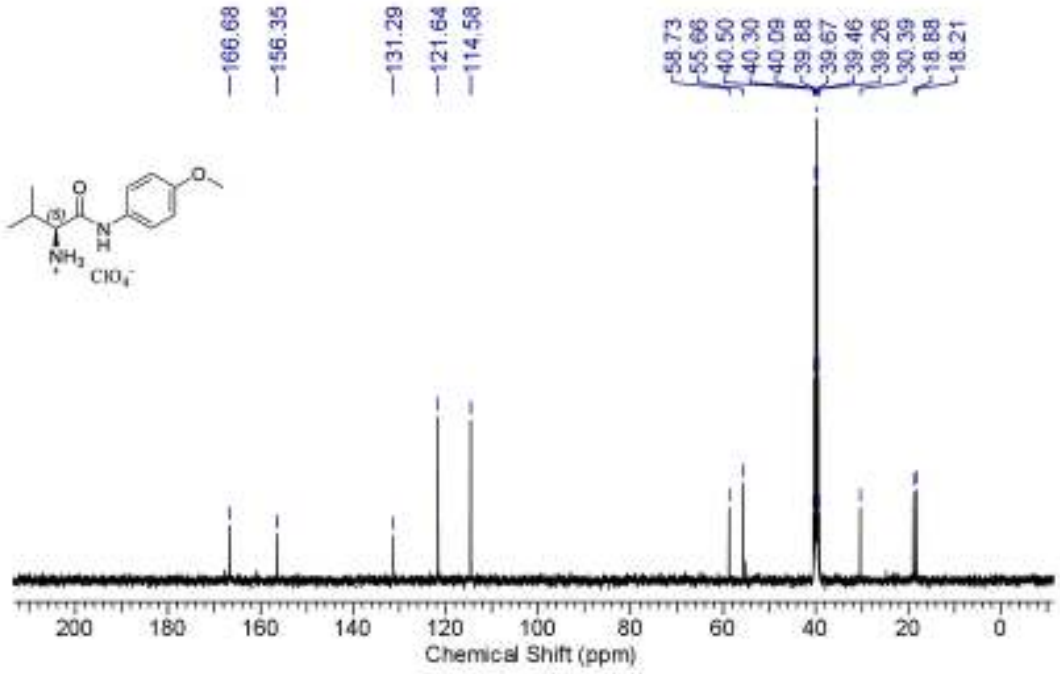
*33c. (S)-1-((4-flurophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



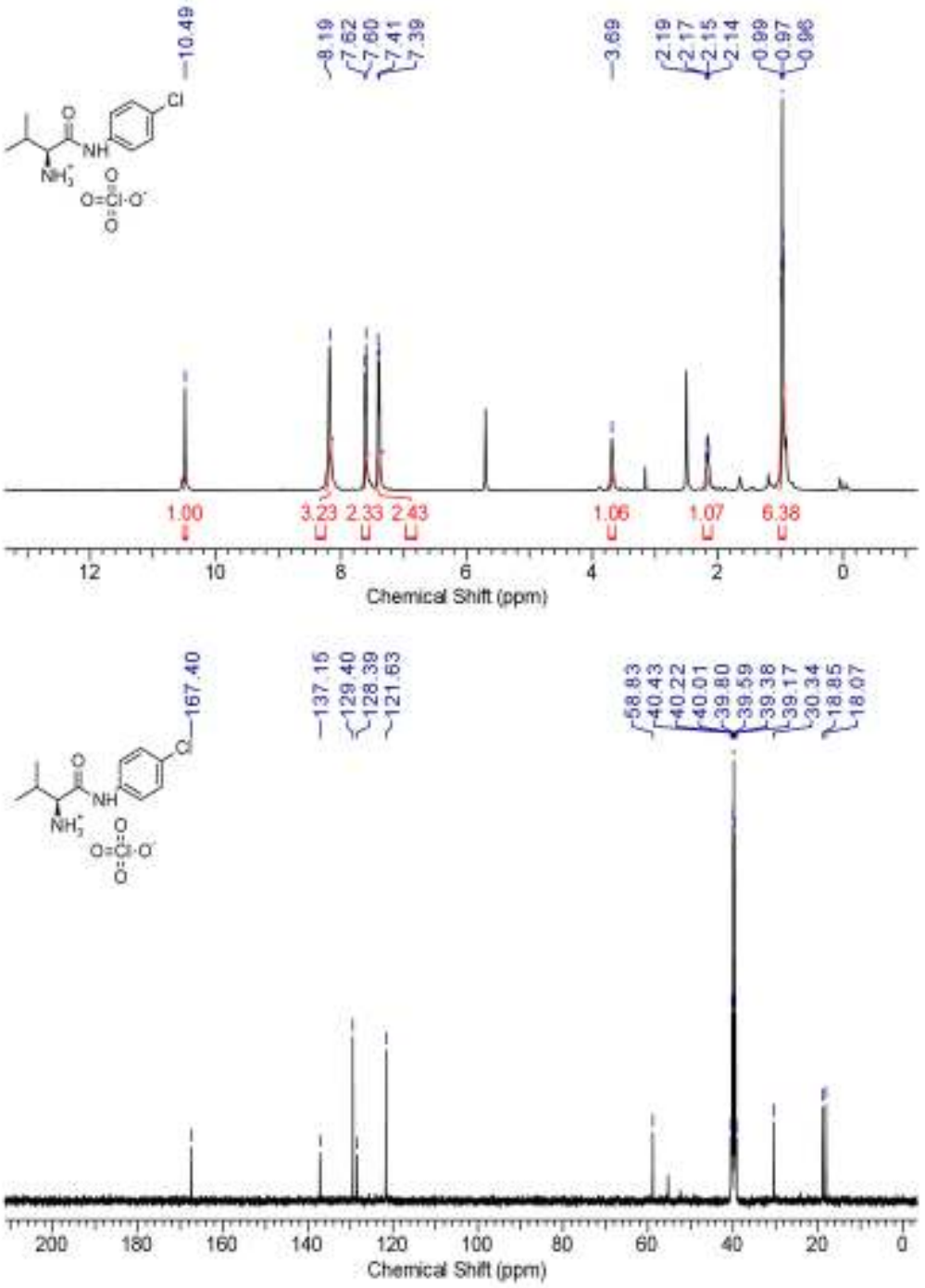



*33e. (S)-1-((4-methoxyphenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*

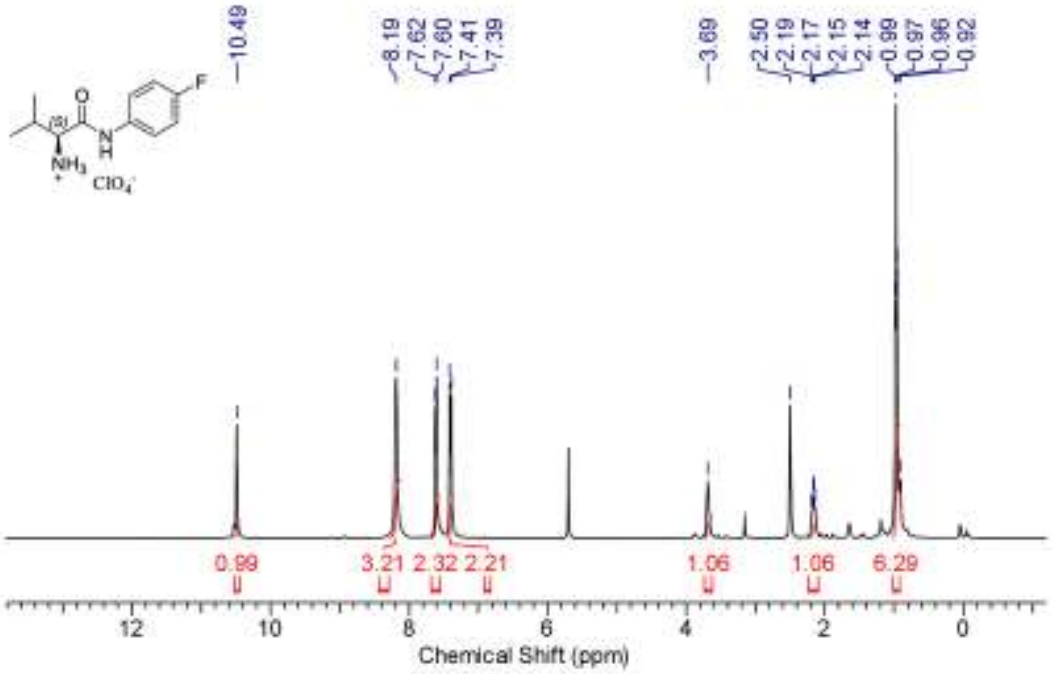


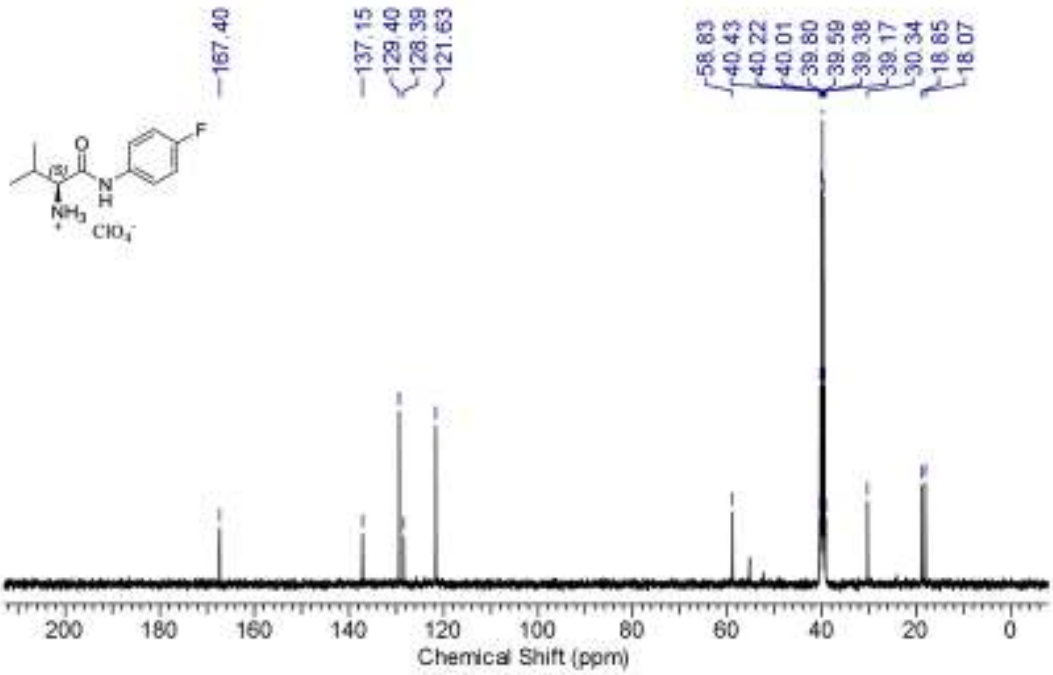



*33f. (S)-1-((4-chlorophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*

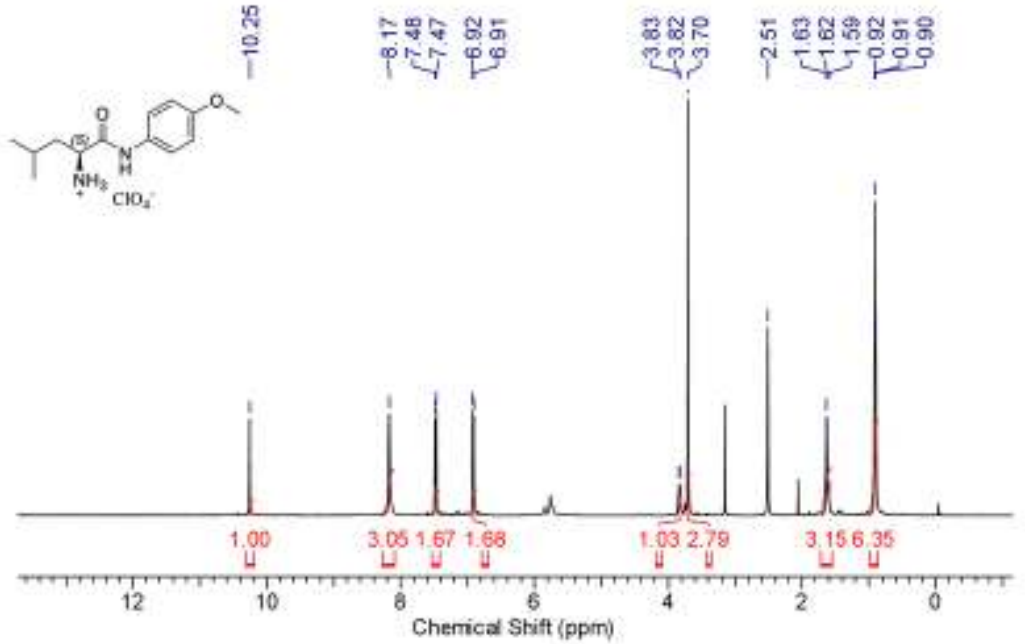


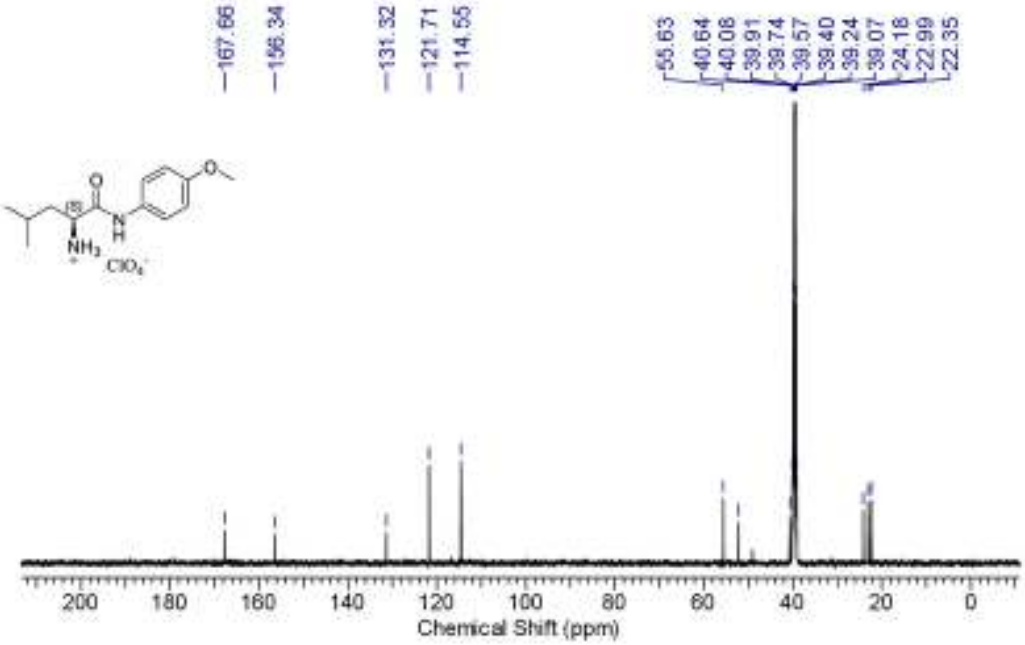
*33g. (S)-1-((4-flurophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



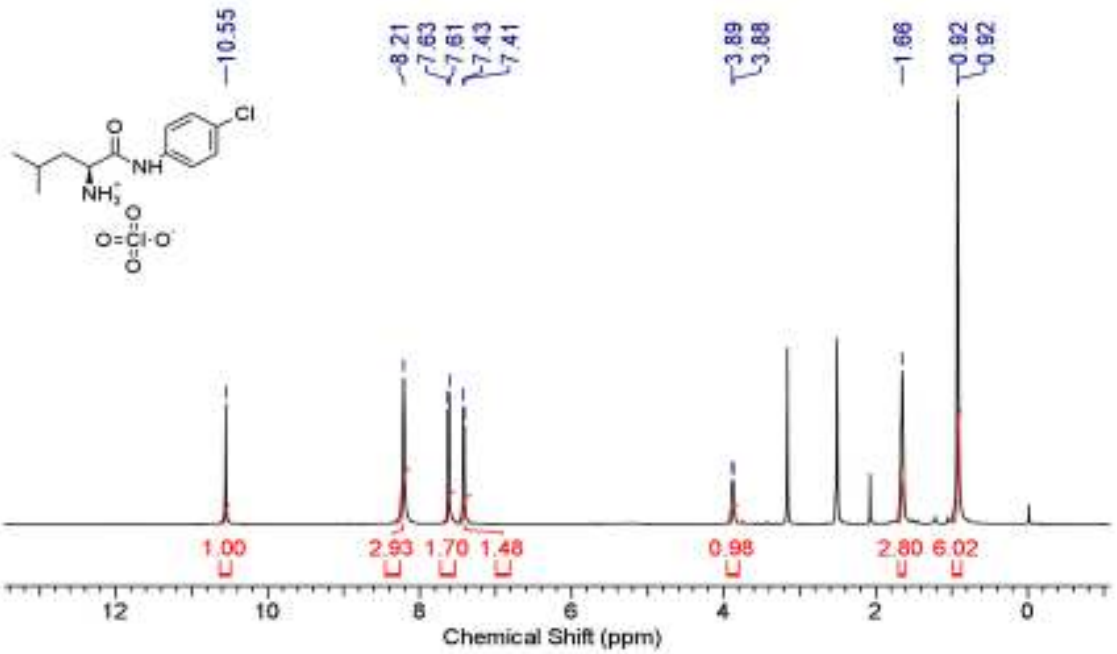



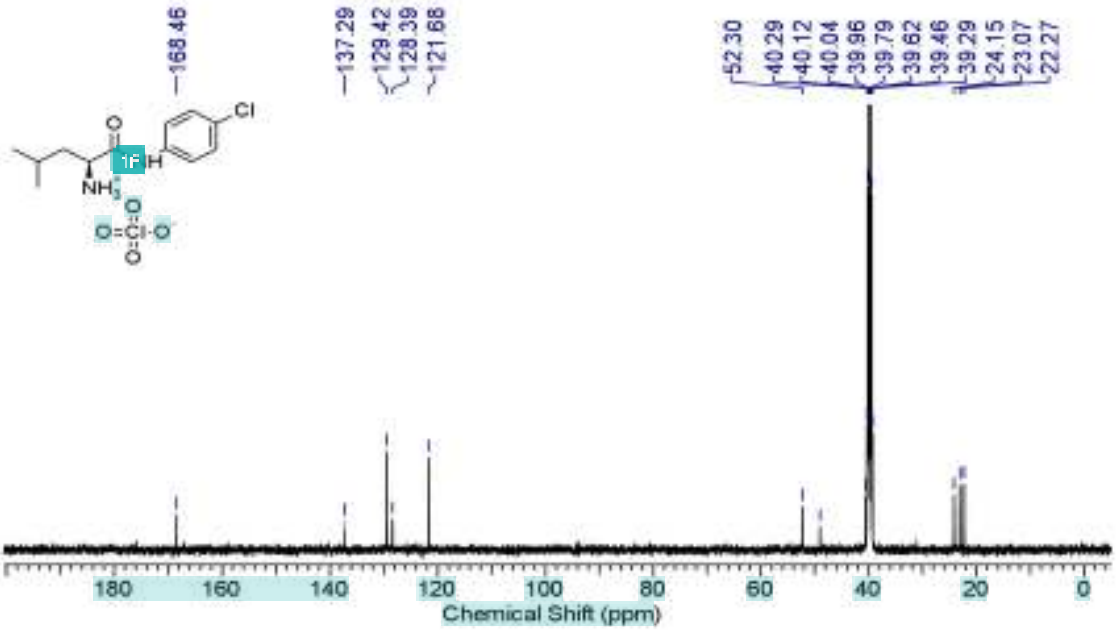
*33i. (S)-1-((4-methoxyphenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



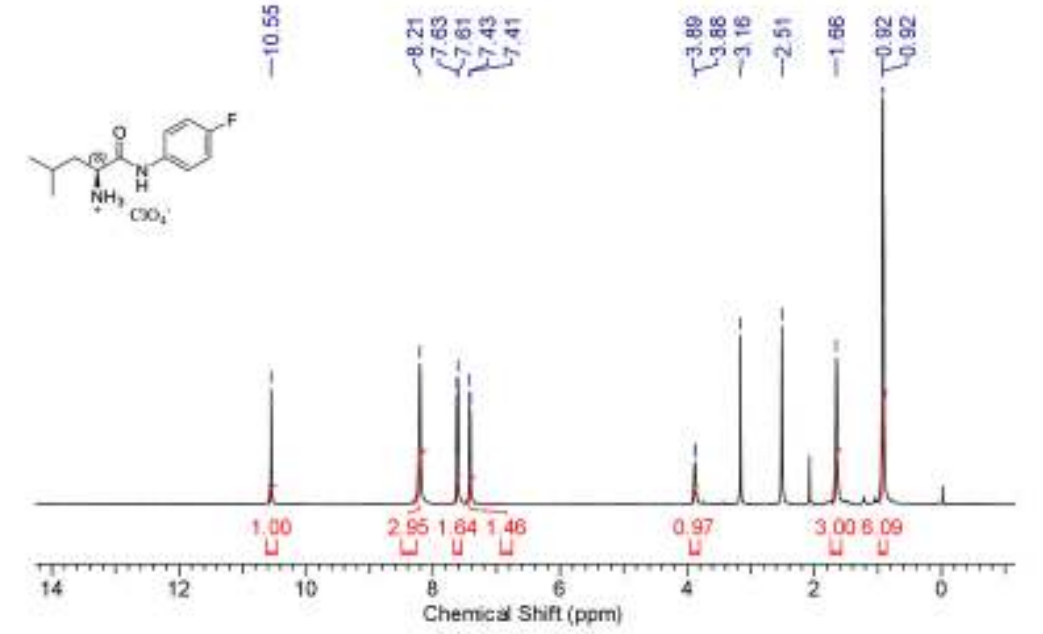



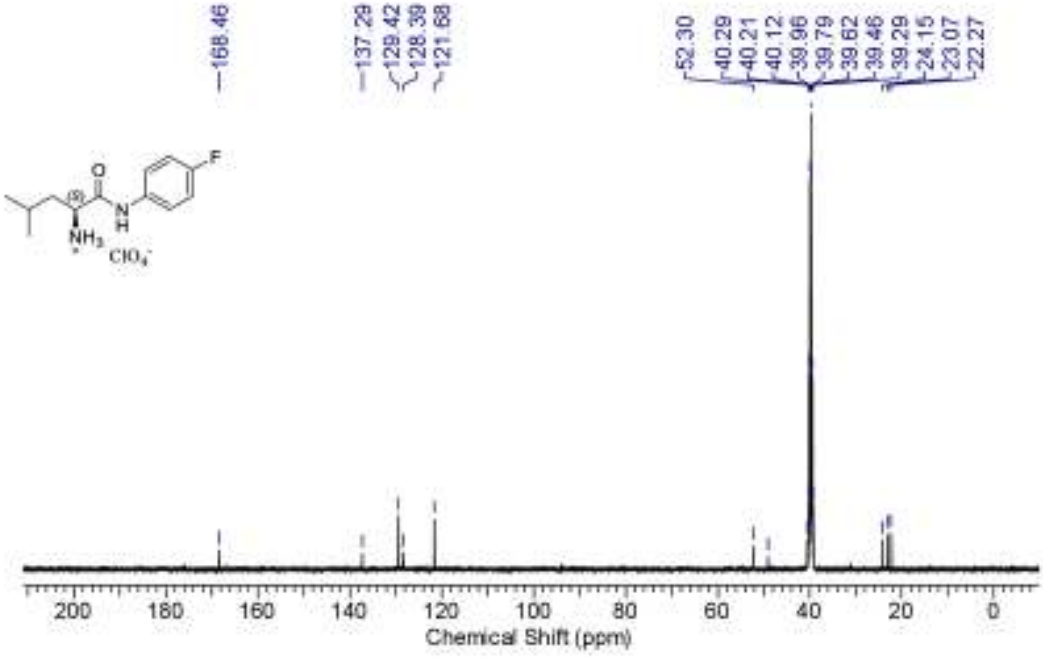
*33j. (S)-1-((4-chlorophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



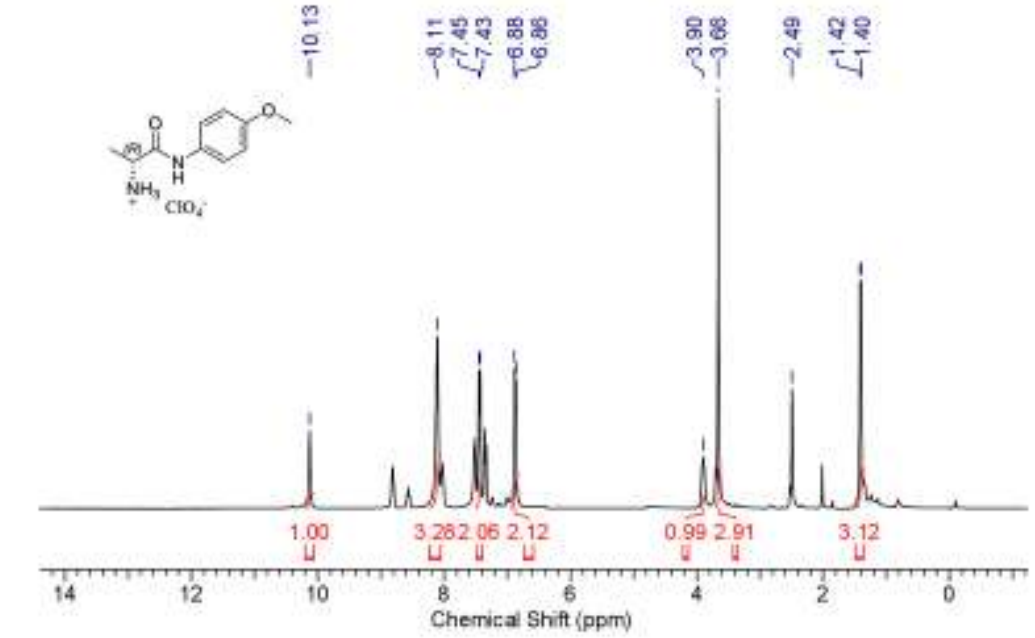



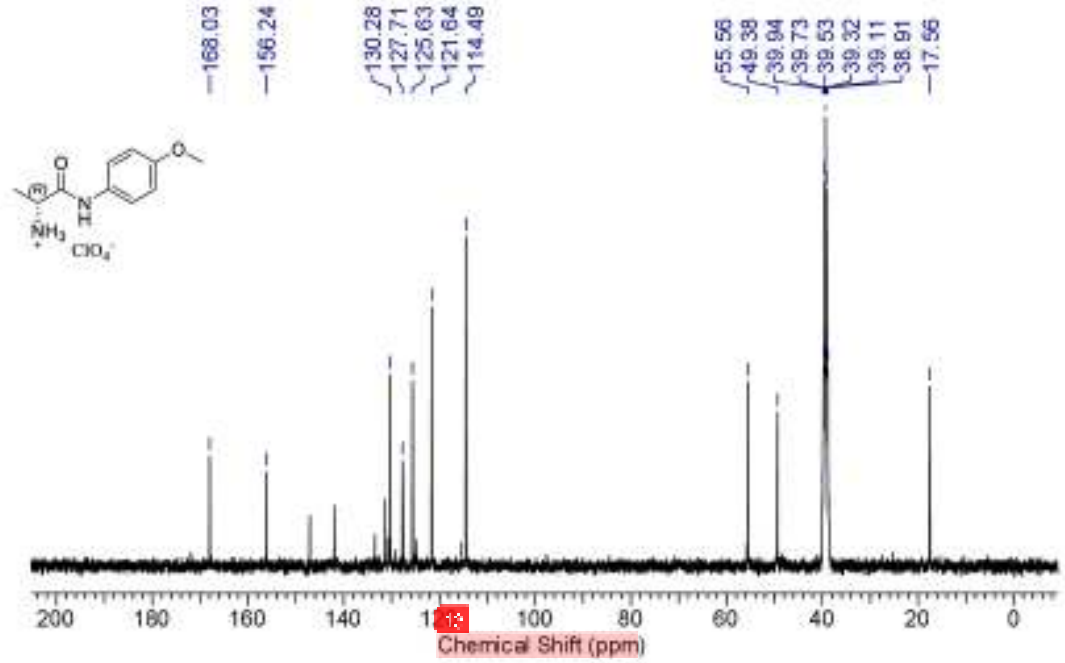
*33k. (S)-1-((4-flurophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



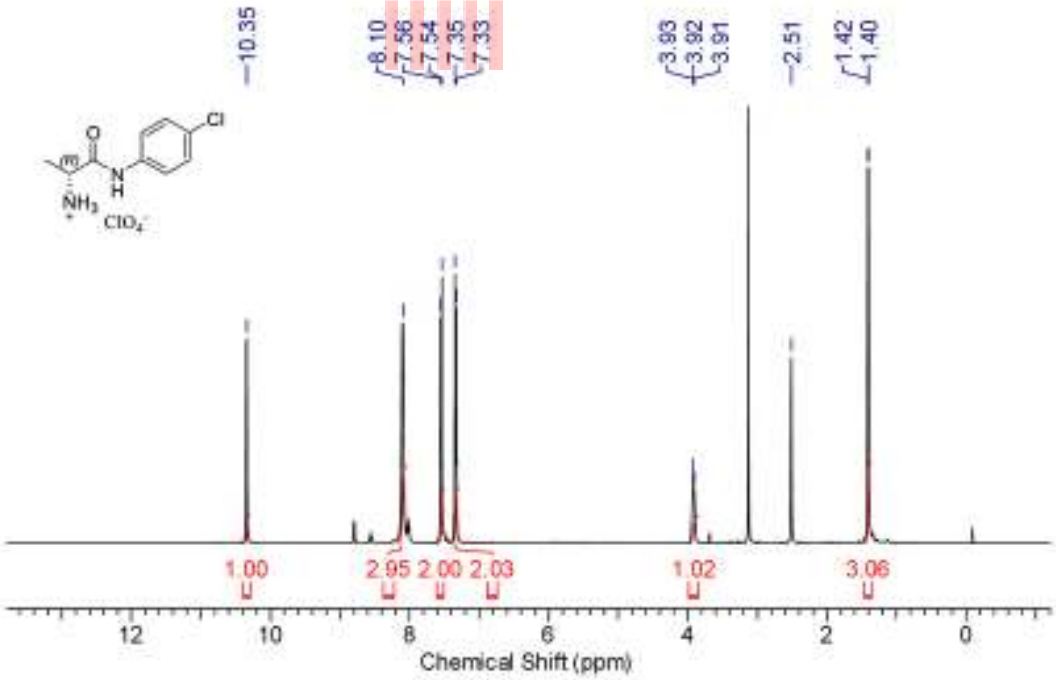



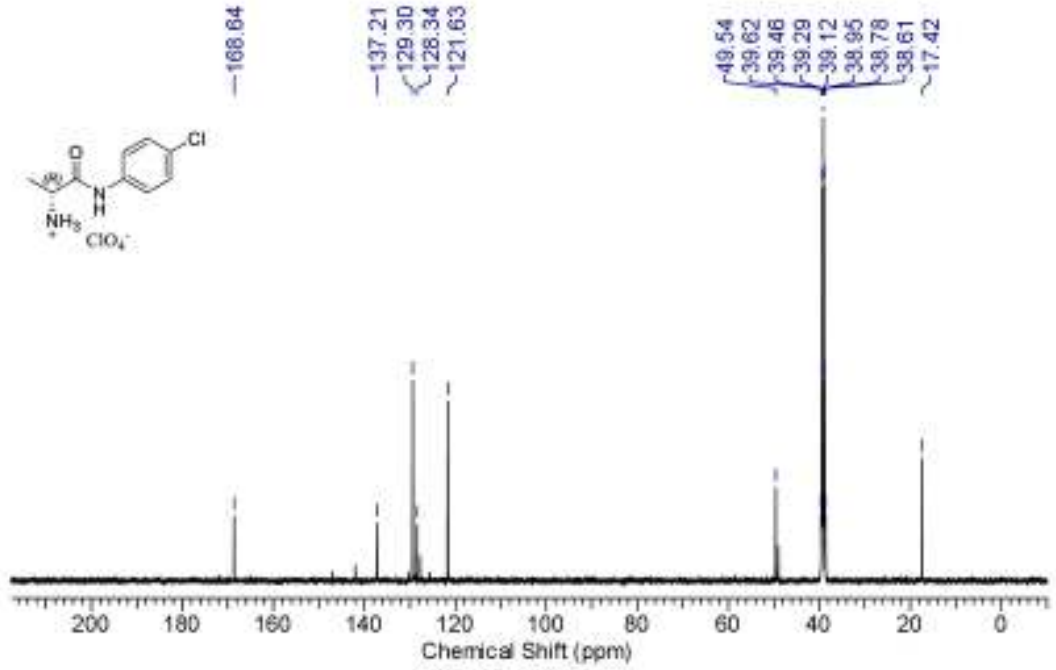
*34a. (R)-1-((4-methoxyphenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



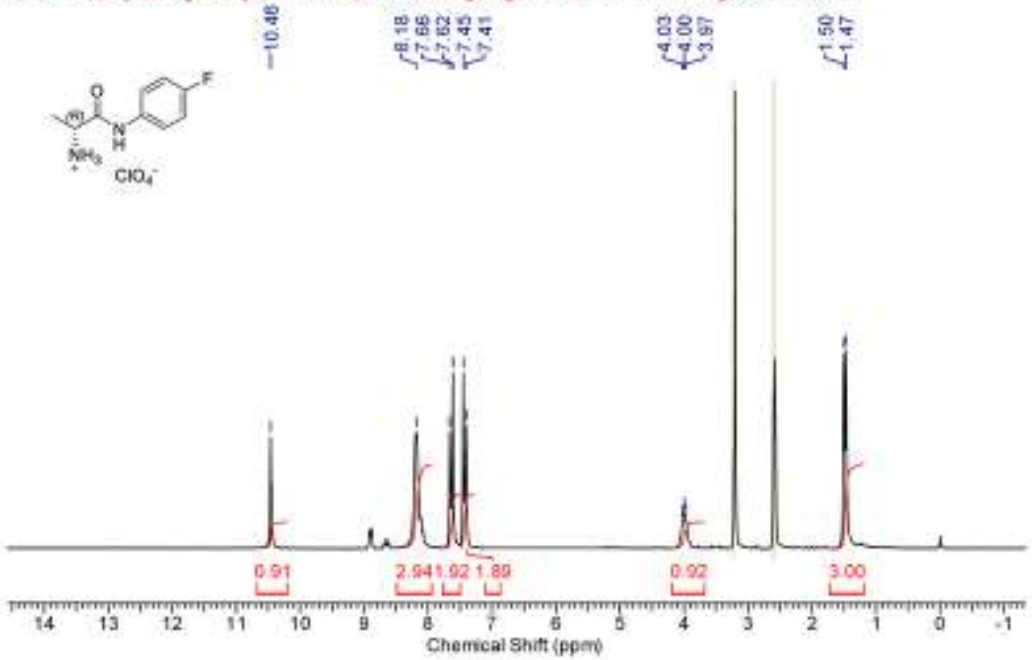



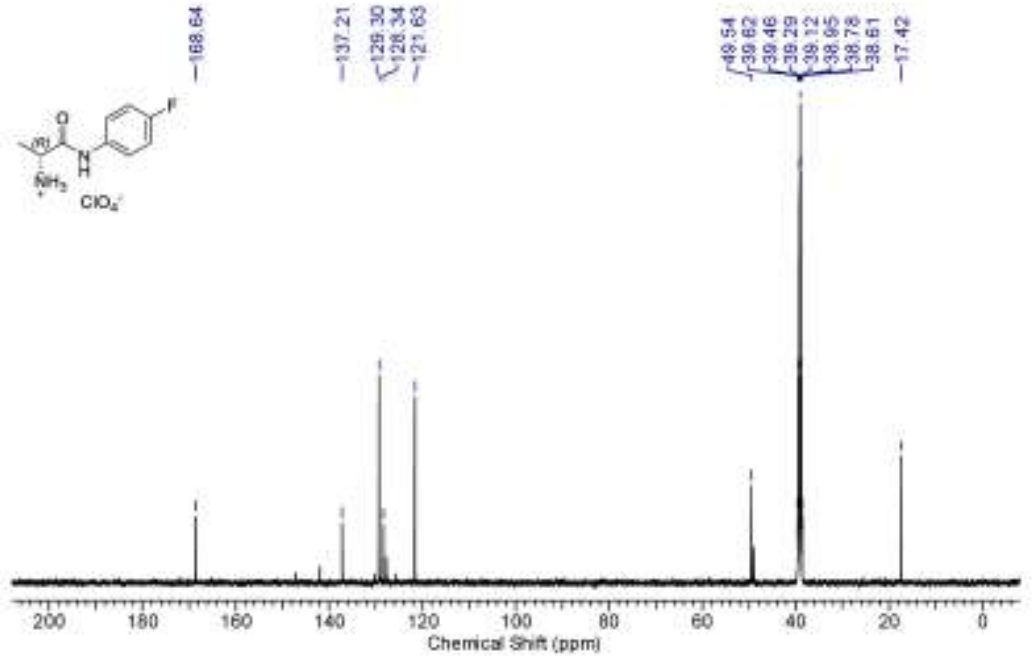
*34b. (R)-1-((4-Chlorophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*



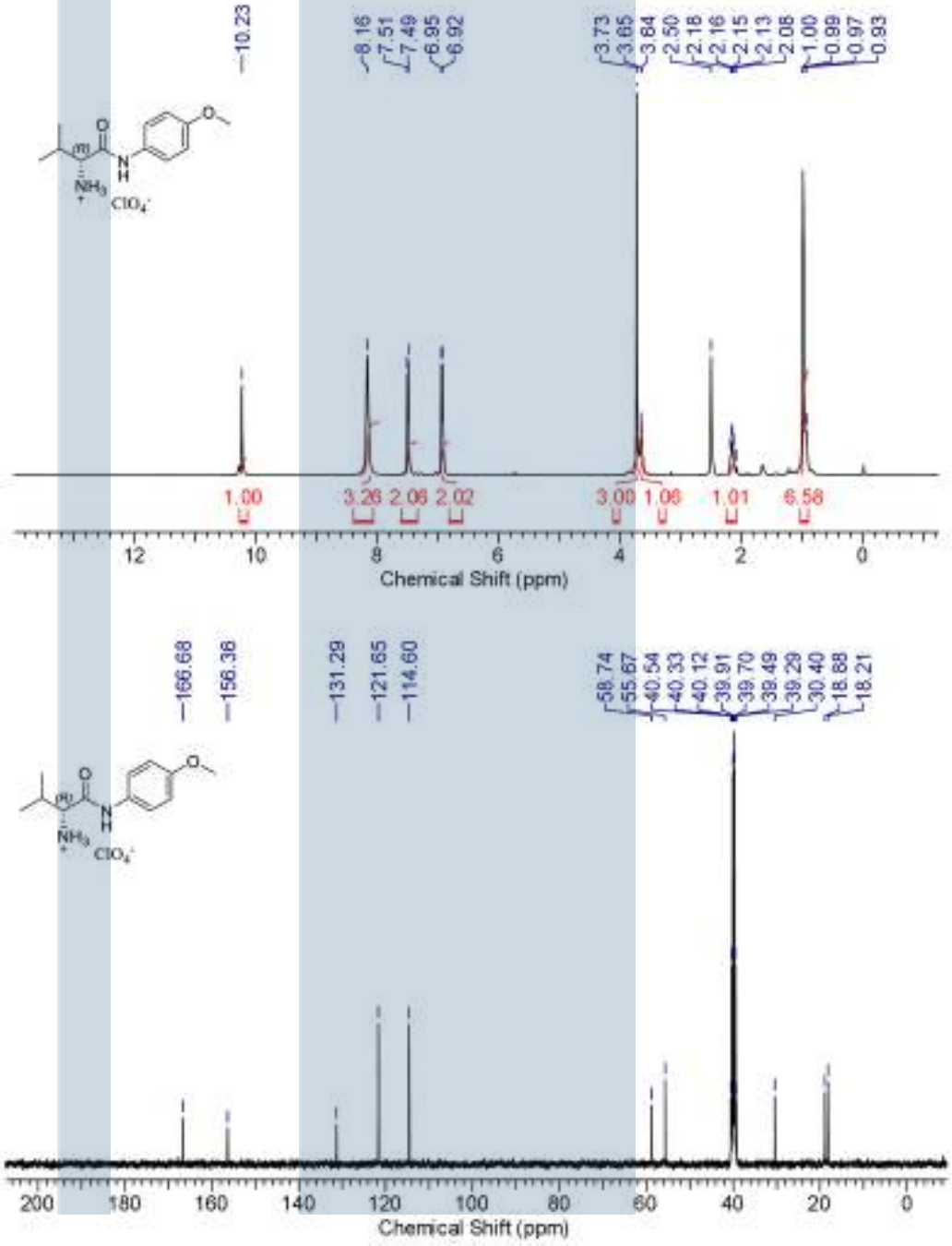



*34c. (R)-1-((4-flurophenyl) amino)-1-oxozopropan-2-amminium perchlorate:*

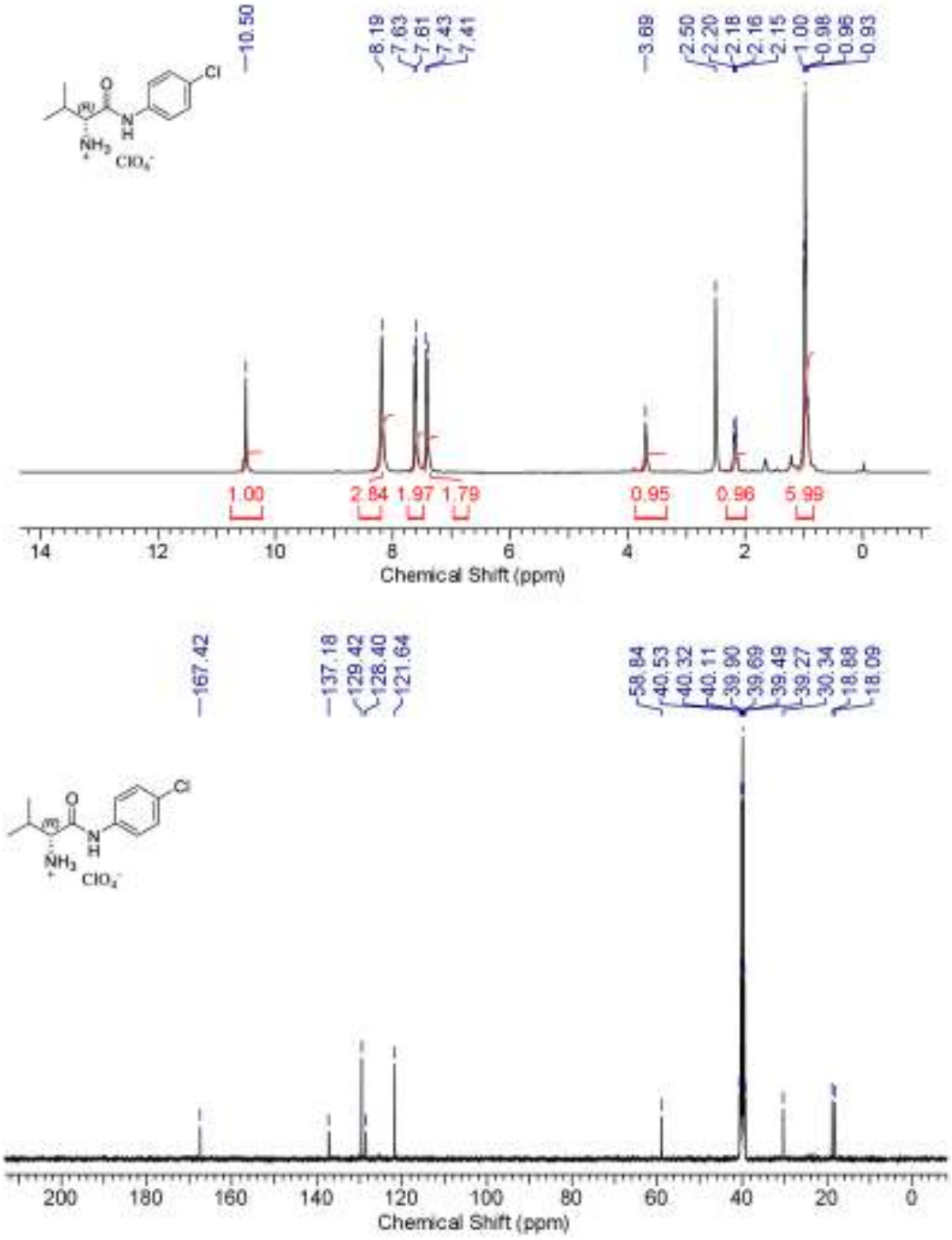


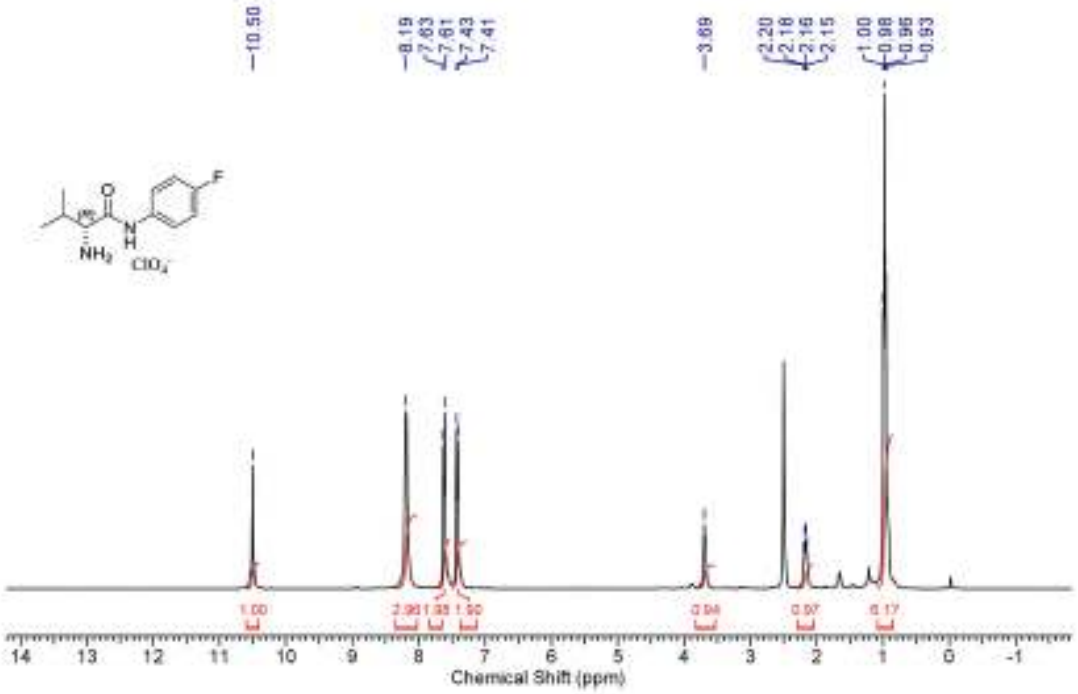
*34e. (R)-1-((4-methoxyphenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*

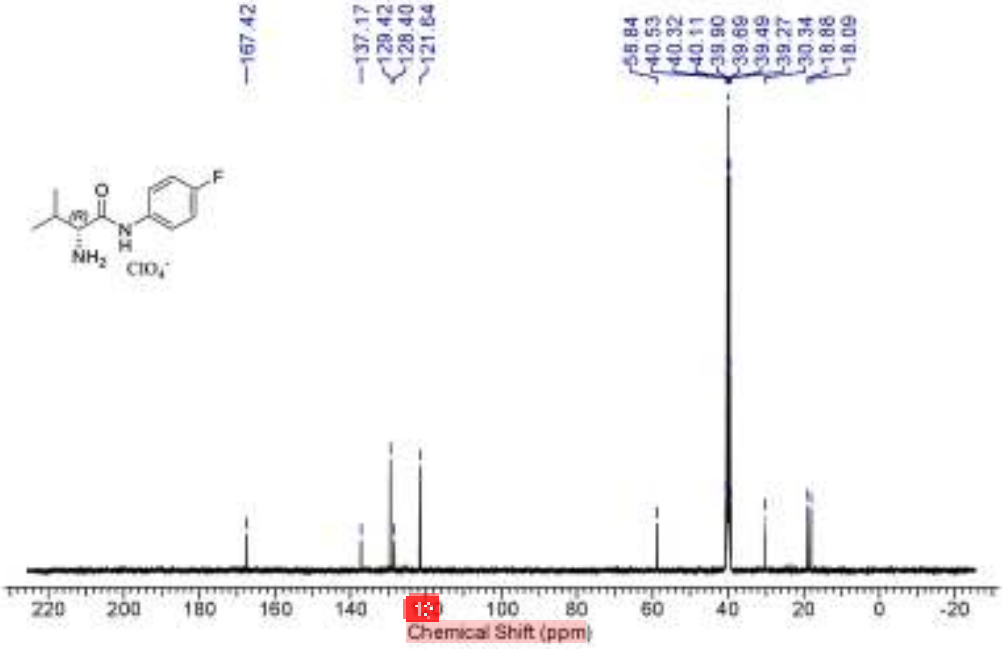


*34f. (R)-1-((4-chlorophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*

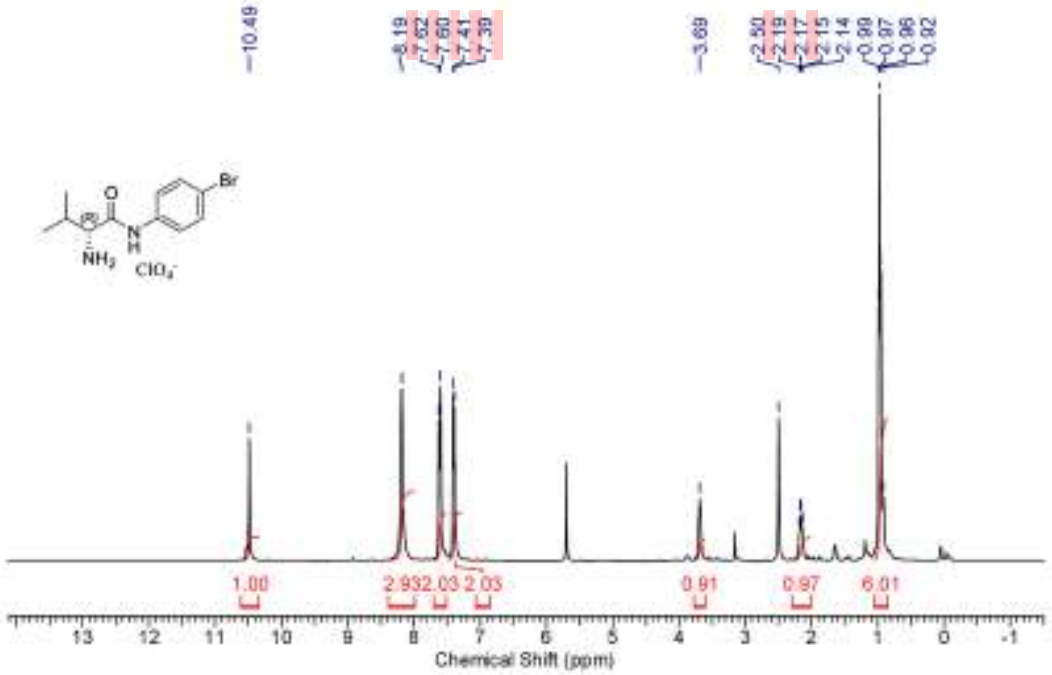


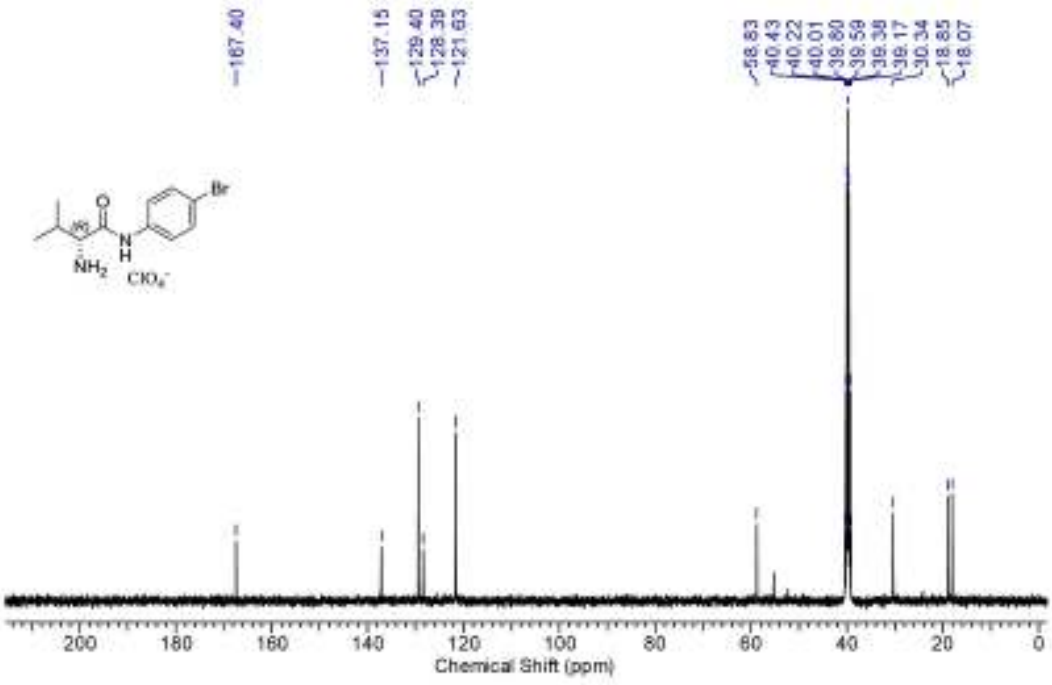
*34g. (R)-1-((4-flurophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



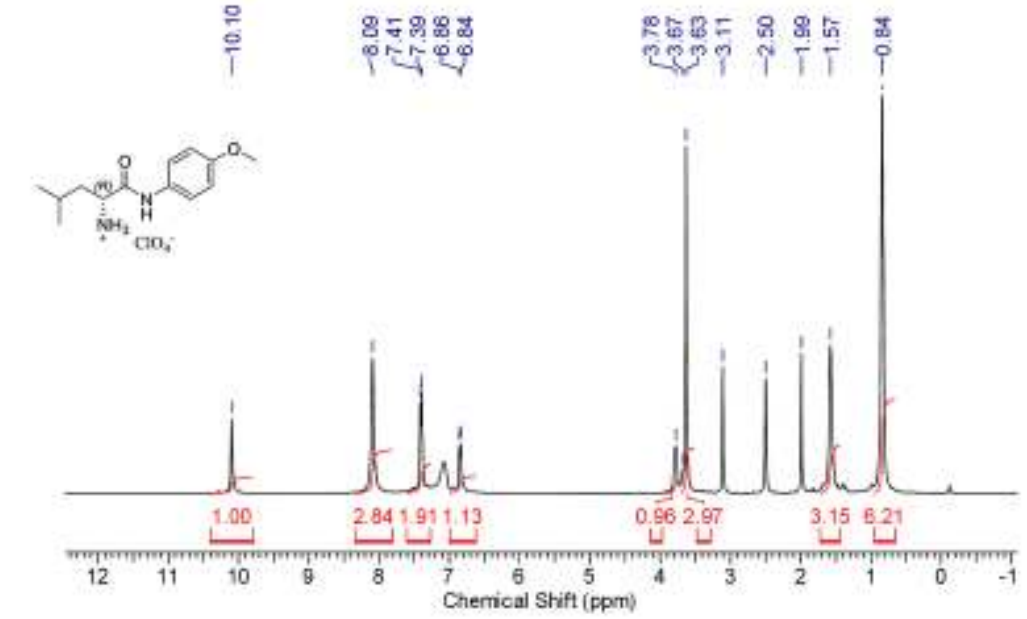



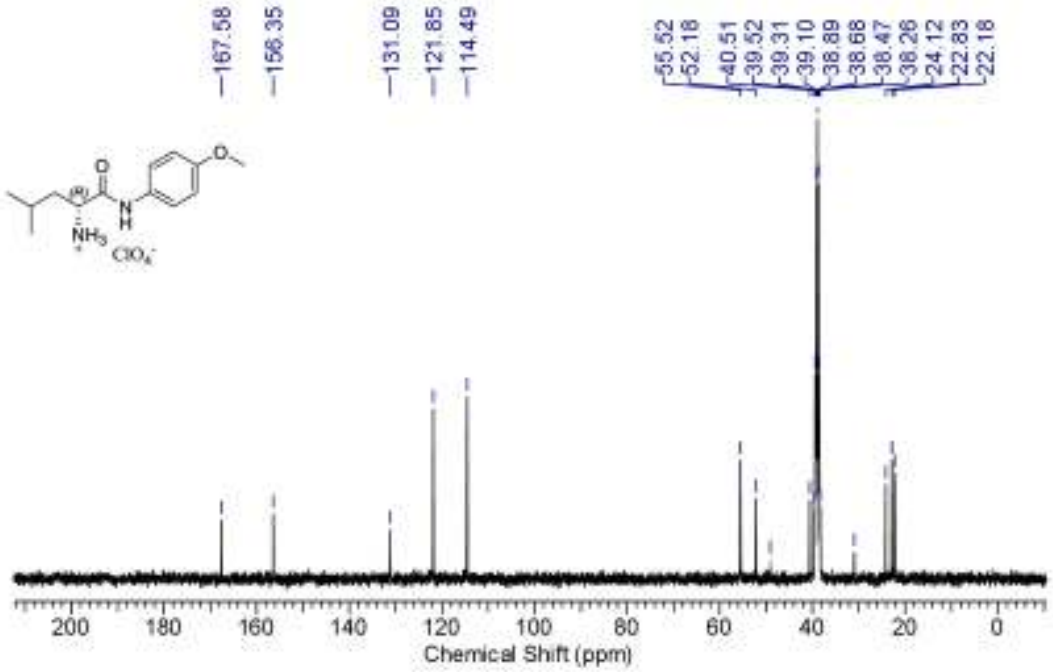
*34h. (R)-1-((4-bromophenyl) amino)-3-methyl-1-oxobutan-2-amminium perchlorate:*



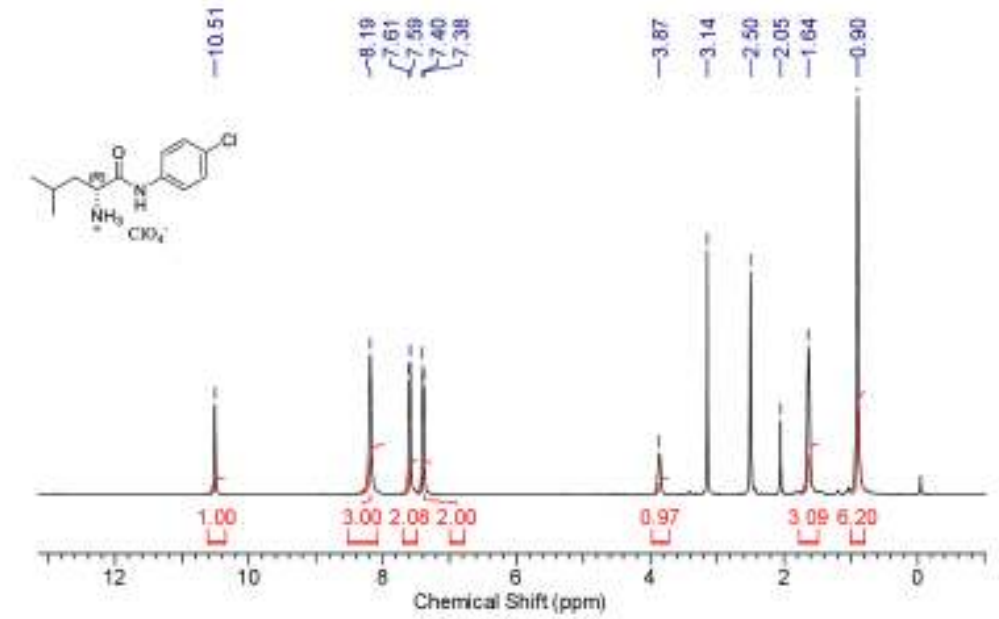



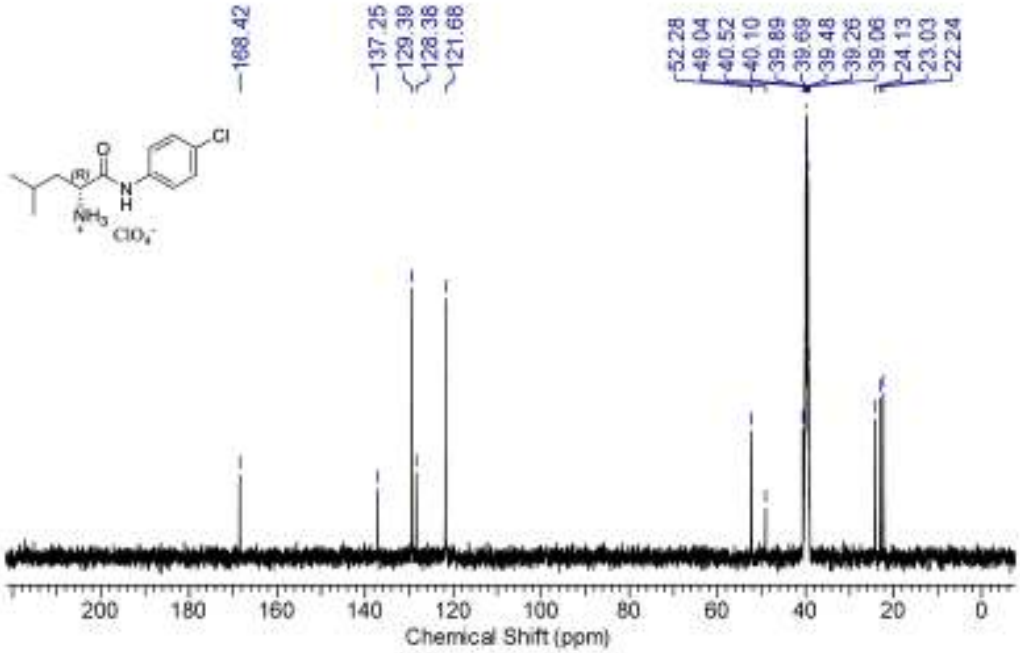
*34i. (S)-1-((4-methoxyphenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



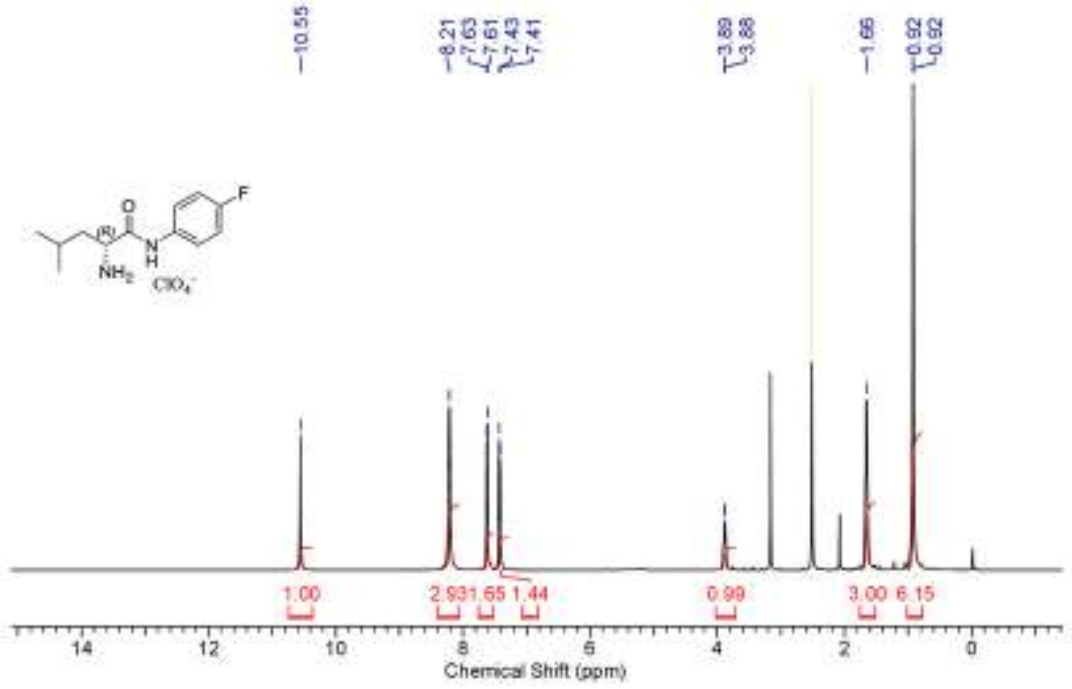



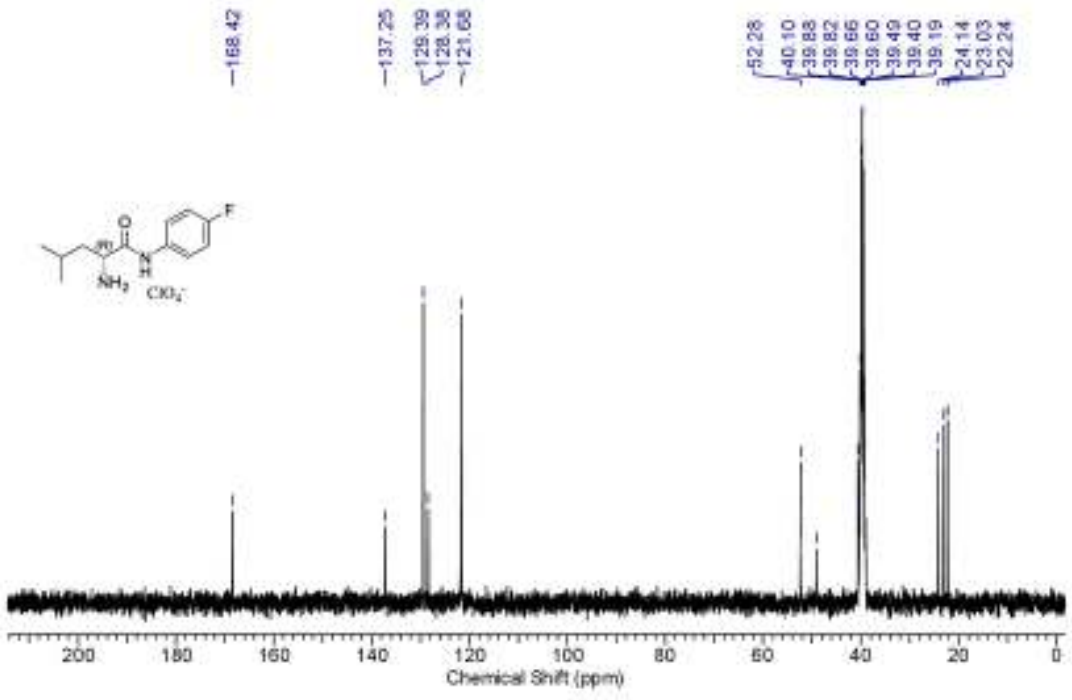
*34j. (R)-1-((4-chlorophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



*34k. (R)-1-((4-flurophenyl) amino)-4-methyl-1-oxopentan-2-amminium perchlorate:*



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*Chapter 3*

# Enantiopure CILs of amino acid amides as stereo-selective organo-catalyst for asymmetric transfer hydrogenation of ketone at room temperature

## 3.1 Introduction

Asymmetric reduction of unsaturated organic compound is a valuable synthetic tool which has been fundamental importance in the area of pharmaceutical, fragrance, flavoring, agrochemical and chiral fine chemical industries. Therefore, growing demand for enantio pure chiral compounds needs more environmentally acceptable process in the chemical industry. Most of these valuable compounds are synthesized by hydrogenation of pro-chiral substrate. The asymmetric hydrogenation of pro-chiral substrate is divided in different types depending on hydrogen donor source along with catalyst and the catalyst is either transition metal based or organo-catalyst.

Asymmetric transfer hydrogenation (ATH): Less well known is the possibility to achieving the reduction of multiple bonds with the support of organic molecules as the hydrogen donor in the presence of chiral catalyst. This process is known as catalytic asymmetric transfer hydrogenation in which 1) Hydrogen migration takes place within the molecule, 2) Hydrogen transfer between identical donor and acceptor unit, 3) transfer hydrogen between different donor and acceptor unit. Mainly such ATH is further divided into two types:

- ATH of pro-chiral substrate using transition metal catalysts
- ATH of pro-chiral substrate using organo catalysts.

There are several catalytic methods suitable for enantio-selective hydrogenation of pro-chiral substrate, but the ATH of ketone is considered particularly useful because reaction proceed under mild condition and needs no sophisticated equipment. The operational simplicity and favorable properties of the reductant[1][2][3][4]. Furthermore intensive investigation in the last three decade has afforded abroad knowledge about ATH reaction mechanism, the useful hydrogen donor and development of highly active and enantio-selective catalysts. *i*-Propyl alcohol is generally used as hydrogen donor as it is non-hazardous, cheap, stable and acetone is the only by-product of the reaction, which can be easily to separable.

Thus the objective of this chapter is to evaluate and study strengths and weaknesses of synthesized chiral amino acid amide based ionic liquids as organo-catalyst in potential application of ATH processes at laboratory scales. Therefore, aim of this chapter is to study in details of ATH reaction of ketones to complete understanding of how the reaction conditions

determine catalyst performance and reaction mechanism. Also to study efficient recyclability of catalytic system.

## 3.2 Literature Review

### *3.2.1 ATH of pro-chiral substrate using transition metal catalysts.*

The biological active synthetic compounds are synthesized from optically active alcohols. Theses optically active alcohols are obtained from asymmetric hydrogenation of ketones. In 1976 Descotes and coworkers[5], reported the first feasibility of chiral transition metal catalyst to achieve asymmetric transfer hydrogenation by combining $[RuCl_2(PPh_3)_3]$ with chiral monophosphine ligand. In 1998 E J Corey[6], reported the enantio-selective ATH of ketone with protected proline based CBS catalyst to obtain chiral alcohol with excellent enantio-selectivity. K Itoh and coworkers[7] and Buchwald and coworkers[8], have reported the hydrosilylation of ketone with high enantio-selectivity using rhodium and titanium complexes. In 1998 Matsuda and coworkers[9], reported the enzymatic ATH of ketone using *i*-PrOH as reducing agent with good enantio-selectivity. The Meerwein-Pondorff-Verley reduction[10] and the Oppenauer oxidation[11] were carried out using $Al(Oi\text{-}Pr)_3$ as catalyst. The equilibrium of oxidation and reduction depend on donor or acceptor present in excess. In 1992 S. Giadiali and co-worker[12], reported ATH using Phosphine and pyridine ligands in amalgamation with ruthenium, iridium and rhodium complexes. However, lower activity and enantio-selectivity was observed and the also reaction required high temperature. This effect was overcome by C. Bolm and coworkers[13], added base in reaction and found that the activity increases significantly and then later addition of base in reaction media become common practice. Pfaltz[14], Lemaire[15] Evans[16] and Zhang[17] used iridium, rhodium, samarium and ruthenium complexes with chiral nitrogen containing ligands and found most remarkable impact on activity and enatio-selectivity in ATH. Later, Noyori and co-workers[18][19][20], made the most important innovation by using $[RuCl_2(arene)]_2$-complexes grouped with a chiral amino alcohol or monotosylated diamine as ligand to catalyzed the ATH of aromatic ketones with excellent enantio-selectivity and reaction rates. They have used different hydrogen donor like *i*-PrOH and 5:2 formic acid:triethylamine azeotrope to obtain excellent enantio-selectivity and conversion of wide range substrates including imines[21] and acetylenic ketones[22]. This innovation later led to the investigation of catalysts involving of N-H

ligands with $[RuCl_2(arene)]_2$ complexes as precursor[23][24][25][26]. Then after, many chiral catalytic system have been developed for ATH such as Pfaltzs; Ir(I) dihydrooxazole complexe[27] and Genets; chiral diphophane Ru(II) catalyst[28]. In 2010 Kelker and coworkers[29], reported the chiral amino alcohol based [Ru(p-cymene)Cl2] complex for ATH of ketone using IPA as hydrogen donor to obtain enantio-enriched alcohol. In 2012 F G Fontaine and coworkers[30], reported the ATH of ketone using homogeneous ruthenium catalyst anchor on chitosan for ATH of ketone. In 2013 M Gamsa and coworkers[31], reported the chiral Pybox based Osmium (II) complexes for the ATH of ketone to produce chiral alcohol with good enantio-selectivity. In 2015 Bica and coworkers[32], reported the chiral ionic liquids (CILs) based ruthenium catalyst for ATH of ketone to obtained chiral alcohol with good enantio-selectivity. In 2007 John Blacker and coworkers[33], reported the ATH of bifunctional aromatic ketone using transition metal based molecular bifunctional catalyst to obtained chiral alcohol with good enantioselectivity. In 2015 Zhou and coworker[34], reported the SpiroPAP ligand based chiral Ir complexes for ATH of ketone and used ethanol as hydrogen donor to obtain the chiral alcohol with good enantio-selectivity. In 2013 Robert H Morris and coworker[35], reported the ATH of ketones and imines using amine (imine) diphosphine iron catalyst and IPA as hydrogen dono to obtain chiral alcohol with good selectivity. In 2015 Jing Xing Gao and coworkers[36], reported the ATH of ketones and ketoesters using chiral PNNP based iron, cobalt, nickel complexes as catalyst to obtain chiral alcohol in good enantioselectivity. In 2005 Martin Wills and coworker[37], reported the ATH of aromatic ketones using chiral diamine derivative based ruthenium complex as catalyst to obtain chiral alcohol with good enantio-selectivity. In 2009 Robert H Morris and coworker[38], reported the ATH of ketones by using ethylene diamine derived diaminophosphine ligand based chiral iron complexes to obtained corresponding chiral alcohol with good enantio-selectivity. In 2014 Robert H Morris and coworkers[39], reported the asymmetric hydrogenation using molecular hydrogen and ATH of aromatic and heroaromatic ketones using amino(imine) diphosphine complex as catalyst to obtain corresponding chiral alcohol with good enantio-selectivity. In 2011 Erick M. Carreira and coworker[40], reported the ATH of alpha cyano and alpha nitro aromatic ketones using chiral diamine based iridium catalyst to obtain optically active alcohol with good enantio-selectivity. In 2016 Robert H Morris and coworker[41], reported the iron catalyzed ATH of aromatic ketones using aqueous biphasic iron complexes to obtain corresponding chiral alcohol with good enantio-selectivity. In 2007 Jianliang Xiao and coworkers[42], reported the

ATH of ketones by using transition metal based bidentate phopharous nitrogen ligand in aqueous phase to obtain chiral alcohol. In 2006 Benjamin List and coworker[43], reported the ATH of alpha ketoesters using chiral copper(II) bisoxazoline complex as catalyst with hantzsch ester as hydrogen donor to obtain corresponding chiral alcohol. In 2015 Akira Yanagisawa and coworker[44], reported the ATH of ketones using chiral bicyclic NHC/ iridium complexes as chiral catalyst to obtain chiral alcohols. In 2018 Qiao-Feng Wang and coworkers[45], reported the ATH of ketones using chiral ferrocene ligand based ruthenium complexes as catalyst to obtain chiral alcohols.

The above ATH reaction of pro-chiral ketones using transition metal based chiral complexes as catalyst have some good features, however, it has few limitations. Usually, these complexes are homogeneous complexes made up of chiral organic ligands and these are very difficult to separate from reaction mixture. The organic ligands are expensive and many of transition metals are toxic. Nowadays, metal-free products are preferred. Also the reuse of the catalyst is highly desired to reduce cost and improve the environmental impact on the process. To overcome these limitations heterogeneous catalysts are preferred as heterogeneous catalysts can be easily separated from the reaction mixture by virtue of its physical state. However, hetereogeneous catalyst has low activity and selectivity as compare to homogeneous catalyst, therefore, till homogeneous catalyst is favorable. To overcome above drawbacks of heterogeneous and homogeneous catalyst biphasic stereo-selective organo-catalyst is favorable. This organo-catalyst has important advantages like easy to separat from product and easily reusable for further reaction without losing their activity as well as selectivity. This organo-catalyst is cheap, non-toxic and its electron and stereo genic properties can be modified.

### *3.2.2 ATH of pro-chiral substrate using stereo-selective organo catalyst.*

Therefore, in the last decade, organo-catalysis has emerged as a powerful alternative for the enantio-selective synthesis of chiral compounds. The enantio-selective transfer hydrogenation of β-unsaturated aldehydes[46][47][48][49] have been carried out over chiral Bronsted acid organo catalyst using Hantzsch esters as the hydrogen source. Also Ionic liquids have been widely used as organo-catalysts in organic synthesis and they also can be used as solvents[50][51] because they are useful and have environmentally benign chemical and physical properties[52]. However, till

date, there is no report on ionic liquid used as ATH catalyst. Therefore, we report in this chapter amino acid amide based CILs as organo-catalyst in ATH of ketones.

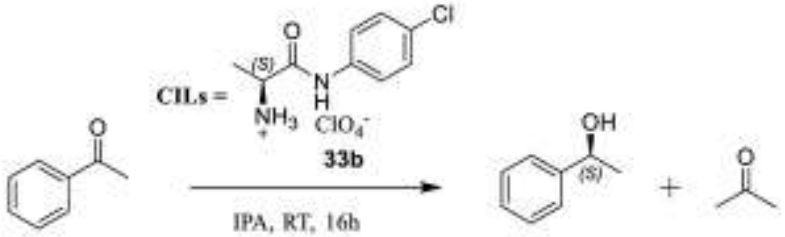
## 3.3 Present work

In this chapter we discussed the ATH of aromatic and aliphatic ketones using CILs of *N* aryl *R* & *S* amino acid amides as stereo-selective organo-catalyst at room temperature. The detail synthesis of CILs of *N* aryl *R* & *S* amino acid amides was reported in chapter 2 is shown in **Figure 1**.

### *3.3.1 Effect of base on ATH of acetophenone reaction.*

Initially, ATH of acetophenone reaction was carried out in the absence of CIL as catalyst **(33b)** under strong basic condition at room temperature in IPA for 24h. The trace amount of corresponding racemic alcohol was obtained **(Table 1, entry 1)**. Then ATH of acetophenone reaction was carried out under strong basic condition in presence of amino acid amide in IPA for 24h. The corresponding alcohol product was not obtained **(Table 1, entry 2)**. And then ATH of acetophenone reaction was carried out in presence of CIL of *N* aryl *S* amino acid amide as catalyst **(33b)** and in absence of base in IPA at room temperature for 24h. We did not observe desired ATH product **(Table 1, entry 3)**. From the above three entry it is clear that amino acid amide and CIL of amino acid amide **(33b)** themselves does not have any activity in ATH. Then ATH reaction of acetophenone was carried out in presence of CIL as catalyst **(33b)** and 0.5 equivalent of base in IPA for 16h. The corresponding ATH product was obtained with moderate yield & excellent enantio-selectivity **(Table 1, entry 4)**. Then we realized that, for activation of CIL of amino acid amide **(33b)** required base in ATH reaction. Then we explored the effect of base concentration on ATH reaction of acetophenone. ATH of acetophenone reaction was carried out in presence of CIL as catalyst **(33b)** & by varying concentration of base in IPA at room temperature for 16h. The desired ATH product was obtained with excellent yield & enantio-selectivity **(Table 1, entry 5-8)**. From this it is clear that 1:1 equivalent of acetophenone to base is required as ideal ratio for ATH reaction.

**Table 1: Effect of base concentration in ATH of acetophenone reaction.**

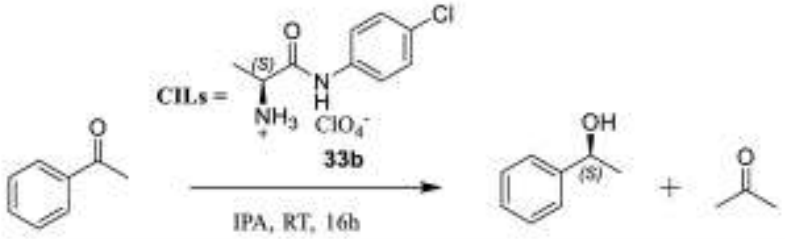



| Entry No | Acetophenone | CILs (catalyst) | Base (NaO*t*-Bu) | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | 1 | - | 1 | 24 | trace | - |
| 2 | 1 | amide | 1 | 24 | - | - |
| 3 | 1 | 0.05 | - | 24 | - | - |
| 4 | 1 | 0.05 | 0.5 | 16 | 40 | 98.9 |
| 5 | 1 | 0.05 | 1 | 16 | 80 | 98 |
| 6 | 1 | 0.05 | 1.2 | 16 | 80 | 98 |
| 7 | 1 | 0.05 | 1.5 | 16 | 80 | 98 |
| 8 | 1 | 0.05 | 2 | 16 | 80 | 98 |

### *3.3.2 Effect of catalyst concentration on ATH reaction of acetophenone.*

The ATH reaction of acetophenone was carried out in presence of base and by varying concentration of CILs as catalyst **(33b)** at room temperature in IPA for 16h. The corresponding desired ATH product was obtained with moderate to excellent yield and also excellent enantio-selectivity of desired product was obtained **(Table 2, entry 1-7)**. The maximum yield of desired product **(Table 2, entry 5)** was obtained when the acetophenone to CIL ratio was 1:0.05. Further increasing CILs **(33b)** concentration up to 1:0.2 the yield of product was not changed **(Table 2, entry 6-7)**. From this study it is clear that 1:0.05:1 equivalent of acetophenone, CILs and base ratio is required as ideal ratio for ATH reaction of acetophenone.

**Table 2: Effect of CILs concentration on ATH of acetophenone reaction.**

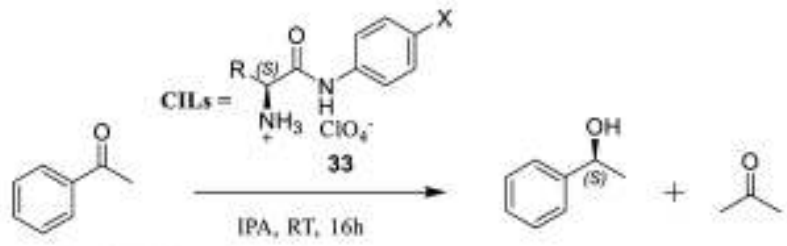



| Enrty No | Acetophenone | CILs (Catalyst) | Base (NaOtBu) | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | 1 | 0.05 | - | 16 | - | - |
| 2 | 1 | 0.01 | 1 | 16 | 20 | 98 |
| 3 | 1 | 0.02 | 1 | 16 | 35 | 98 |
| 4 | 1 | 0.03 | 1 | 16 | 45 | 98 |
| 5 | 1 | 0.05 | 1 | 16 | 80 | 98 |
| 6 | 1 | 0.07 | 1 | 16 | 80 | 98 |
| 7 | 1 | 0.1 | 1 | 16 | 80 | 98 |
| 8 | 1 | 0.2 | 1 | 16 | 80 | 98 |

### *3.3.3 ATH of acetophenone reaction over different CILs of N aryl S amino acid amide.*

With optimized ATH reaction conditions, we explored the use of different CILs of *N* aryl *S* amino acid amide as organo catalyst in ATH reaction of acetophenone. Initially, for preparation of racemic ATH product, reduction of acetophenone reaction was carried out by $NaBH_4$ in methanol for 1h. The desired racemic product was obtained with excellent yield **(Table 3, entry 1)**. Then ATH reaction of acetophenone was carried out at ideal reaction conditions using different CILs of *N* aryl *S* amino acid amide at room temperature. The desired ATH product obtained with excellent yield & enantio-selectivity **(Table 3, entry 2-12)**. Highest yield (81 %) and highest enantio- selectivity of product (97%) was obtained in above reactions. Product was confirmed by $^{1}H$ $^{13}C$ NMR (200MHz, 400MHz, and 500MHz) Brucker NMR Spectro-meter. Optical purity and configuration was confirmed by optical rotation (JASCO polarimeter). Mass of product is confirmed by HRMS. Enantiomeric excess is confirmed by GC having CYDEX-β chiral column.

**Table 3: ATH of acetophenone over different CILs of *N* aryl *S* amino acid amide.**



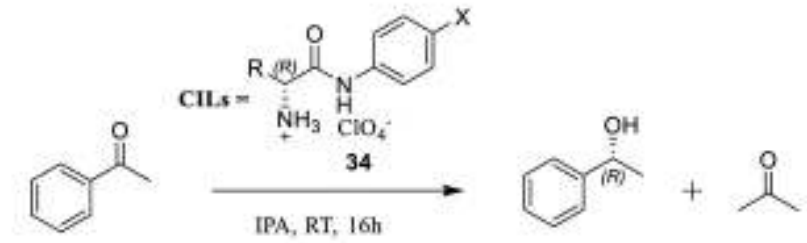

R = -$CH_3$, -$CH(CH_3)_2$, -$CH_2CH(CH_3)_2$
X = -$OCH_3$, F,Cl, Br,

| Entry No | CILs | Base (NaO*t*Bu) | Yield (%) | Configuration | Enantiomeric excess (%) | |
|---|---|---|---|---|---|---|
| | | | | | Optical rotation | GC |
| 1 | $NaBH_4$ | - | 100 | - | - | - |
| 2 | 33a | NaO*t*Bu | 80 | *S* | 97 | 98 |
| 3 | 33b | NaO*t*Bu | 81 | *S* | 97 | 99 |
| 4 | 33c | NaOtBu | 80 | *S* | 95 | 96 |
| 5 | 33d | NaO*t*Bu | 79 | *S* | 96 | 98 |
| 6 | 33e | NaO*t*Bu | 78 | *S* | 94 | 97 |
| 7 | 33f | NaOtBu | 80 | *S* | 97 | 98 |
| 8 | 33g | NaO*t*Bu | 80 | *S* | 95 | 96 |
| 9 | 33h | NaO*t*Bu | 79 | *S* | 97 | 98 |
| 10 | 33i | NaO*t*Bu | 80 | *S* | 96 | 97 |
| 11 | 33j | NaO*t*Bu | 80 | *S* | 94 | 95 |
| 12 | 33k | NaO*t*Bu | 80 | *S* | 96 | 98 |

### *3.3.4 ATH of acetophenone reaction over different CILs of N aryl R amino acid amide.*

The ATH reaction of acetophenone was carried out at ideal reaction conditions using different CILs of *N* aryl *R* amino acid amide at room temperature. The desired ATH product obtained with excellent yield & enantio-selectivity **(Table 4, entry 1-11)**. Highest yield (90 %) and highest enantio- selectivity of product (97%) was obtained in above reactions. Product was confirmed by $^{1}H$ $^{13}C$ NMR (200MHz, 400MHz, and 500MHz) Brucker NMR Spectro-meter. Configuration was confirmed by optical rotation (JASCO polarimeter). Mass of product is confirmed by HRMS. Enantiomeric excess is confirmed by GC having CYDEX-β chiral column.

**Table 4: ATH of acetophenone over different CILs of N aryl R amino acid amide.**




R = -$CH_3$, -$CH(CH_3)_2$, -$CH_2CH(CH_3)_2$
X = -$OCH_3$, F,Cl, Br,

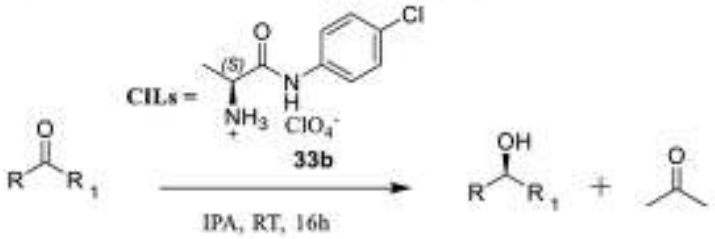
| Entry No | CILs | Base | Yield (%) | Configuration | Enantiomeric excess (%) | |
|---|---|---|---|---|---|---|
| | | | | | Optical rotation | GC |
| 1 | 34a | NaO*t*Bu | 80 | *R* | 94 | 96 |
| 2 | 34b | NaO*t*Bu | 90 | *R* | 96 | 97 |
| 3 | 34c | NaO*t*Bu | 82 | *R* | 88 | 90 |
| 4 | 34d | NaO*t*Bu | 81 | *R* | 96 | 97 |
| 5 | 34e | NaO*t*Bu | 83 | *R* | 94 | 93 |
| 6 | 34f | NaO*t*Bu | 85 | *R* | 89 | 91 |
| 7 | 34g | NaO*t*Bu | 87 | *R* | 86 | 88 |
| 8 | 34h | NaO*t*Bu | 80 | *R* | 91 | 91 |
| 9 | 34i | NaO*t*Bu | 86 | *R* | 95 | 96 |
| 10 | 34j | NaO*t*Bu | 82 | *R* | 95 | 94 |
| 11 | 34k | NaO*t*Bu | 81 | *R* | 89 | 92 |

### *3.3.5 ATH reaction of different ketones over CIL of N aryl S amino acid amide (33b).*

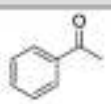
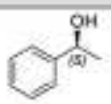
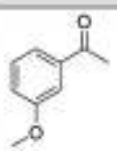
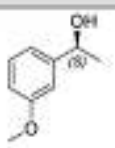
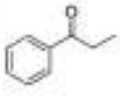
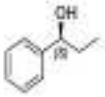
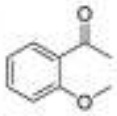
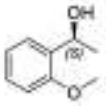
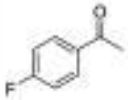
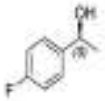
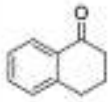
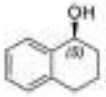
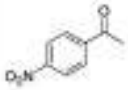
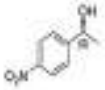
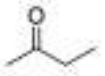
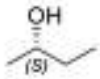
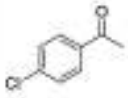
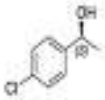
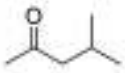
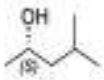
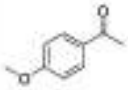
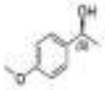
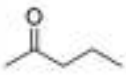
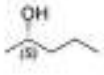
Using optimized ATH reaction condition, we explored the different substrate scope of ketones involving aromatic, aliphatic acyclic and cyclic ketone over CIL of *N* aryl *S* amino acid amide **(33b)**. The ATH reaction of different ketones (8mmole) was carried out by using 0.5 mmole of CIL **(33b)** as catalyst with 160 mmole of IPA as hydrogen source and base. The corresponding ATH product was obtained with good yield (88%) and excellent enantio-selectivity (99%) **(Table 5, entry 1-12)**. The substrate scope study shows that the activity of CIL was not affected by electron donating or withdrawing group on aryl ring. It states that electronic effect does not

influence on yield and enantio-selectivity of ATH product. All the products were confirmed by $^{1}H$ & $^{13}C$ NMR Spectrometer. Stereochemistry is confirmed by optical rotation. Mass was confirmed by HRMS. Enantiomeric excess is calculated by optical rotation.

**Table 5: Substrate scope of ATH of ketone over CILs (33b).**




R = -$CH_3$, -Ph
R1 = -$CH_3$, -$CH_2CH_3$,-$CH_2CH_2CH_3$,-$CH(CH_3)_2$,

| Entry no | Substrate | Product | Yield (%) | ee (%) | Entry no | Substrate | Product | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  |  | 88 | 97 | 7 |  |  | 75 | 80 |
| 2 |  |  | 84 | 95 | 8 |  |  | 77 | 78 |
| 3 |  |  | 79 | 89 | 9 |  |  | 72 | 88 |
| 4 |  |  | 84 | 84 | 10 |  |  | 75 | 88 |
| 5 |  |  | 78 | 88 | 11 |  |  | 78 | 88 |
| 6 |  |  | 78 | 85 | 12 |  |  | 80 | 89 |

### *3.3.6 ATH reaction of different ketones over CILs of N aryl R amino acid amide (34b).*

Using optimized ATH reaction condition, we explored the different substrate scope of ketones involving aromatic, aliphatic acyclic and cyclic ketone over CIL of *N* aryl *S* amino acid amide **(33b)**. The ATH reaction of different ketones (8mmole) was carried out by using 0.5 mmole of CIL **(33b)** as catalyst with 160 mmole of IPA as hydrogen source and base. The corresponding ATH product was obtained with good yield (88%) and excellent enantio-selectivity (99%) **(Table 6, entry 1-12)**. The substrate scope study shows that the activity of CIL was not affected by electron donating or withdrawing group on aryl ring. It states that electronic effect does not influence on yield & enantio- selectivity of ATH products. All the products were confirmed by $^{1}H$ & $^{13}C$ NMR Spectrometer. Stereochemistry is confirmed by optical rotation. Mass was confirmed by HRMS. Enantiomeric excess is calculated by optical rotation.

**Figure 1: CILs of N aryl R & S amino acid amide.**

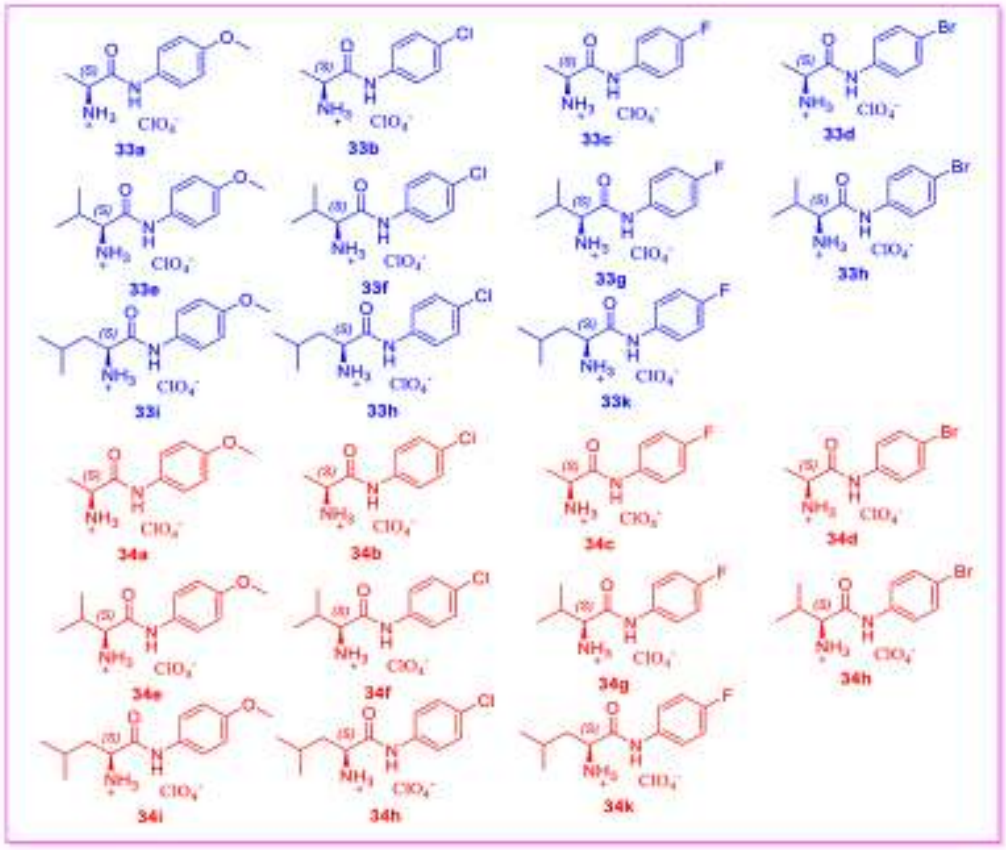
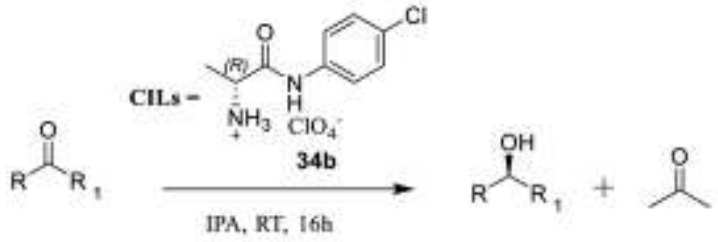
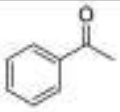
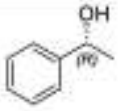
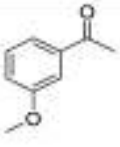
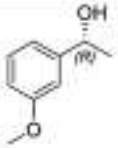
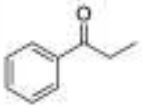
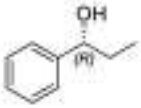
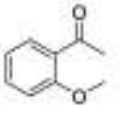
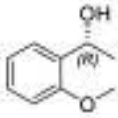
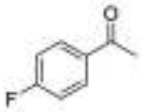
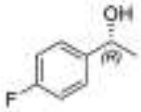
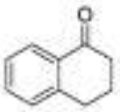
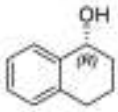
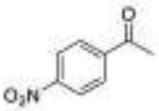
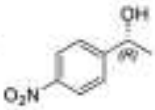
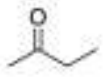
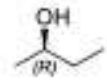
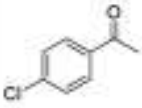
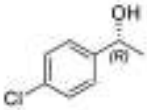
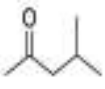
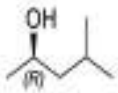
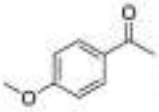
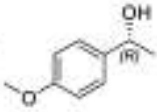
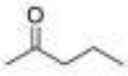
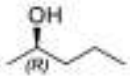


**Table 6: Substrate scope in ATH of ketone over CILs of *N* aryl *R* amino acid amide (34b).**




R = -$CH_3$, -Ph
R1 = -$CH_3$, -$CH_2CH_3$,-$CH_2CH_2CH_3$,-$CH(CH_3)_2$,

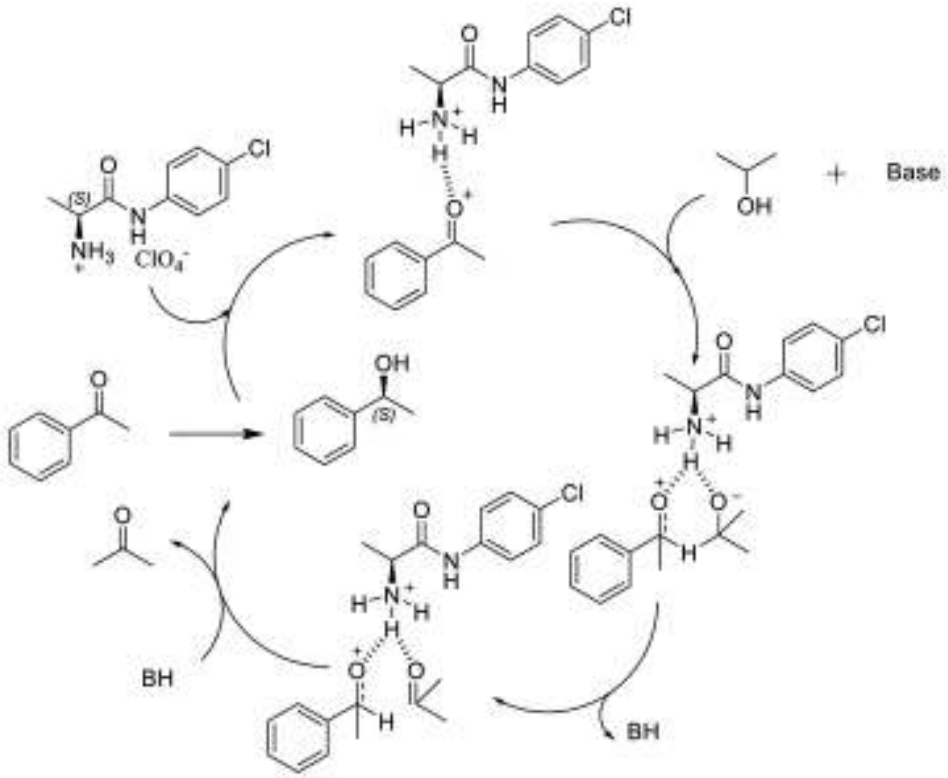
| Entry No | Substrate | Product | Yield (%) | ee (%) | Entry no | Substrate | Product | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  |  | 87 | 97 | 7 |  |  | 76 | 81 |
| 2 |  |  | 83 | 94 | 8 |  |  | 77 | 78 |
| 3 |  |  | 80 | 90 | 9 |  |  | 75 | 88 |
| 4 |  |  | 84 | 88 | 10 |  |  | 75 | 88 |
| 5 |  |  | 78 | 88 | 11 |  |  | 80 | 87 |
| 6 |  |  | 79 | 85 | 12 |  |  | 81 | 88 |

### *3.3.7 Postulated mechanism of ATH reaction over CILs of amino acid amide.*

Based on result obtained we proposed a postulated mechanism of the reaction as shown in **Scheme 1**. In the ATH reaction the positively charged nitrogen atom from CILs of amino acid

amide (adjusting to chiral carbon) donate proton to the oxygen atom of carbonyl group of ketone and carbonyl carbon becomes highly electrophilic, simultaneously proton from iso propyl alcohol is abstracted by base and oxygen atom. IPA becomes negatively charged and in alkaline medium hydride anion is transfer to carbonyl carbon to form unstable cyclic intermediate in-situ. Further stereochemistry of prochiral ketone changes due to partially hydrogen bonding between oxygen atom of carbonyl group of ketone and nitrogen atom of CILs which is adjusting to chiral carbon to form chiral secondary alcohol via cyclic intermediate. The structural stereochemistry of product is retained as per stereo-chemistry of CILs[53].

**Scheme 1: Postulated mechanism of ATH reaction over CILs of amino acid amide**.

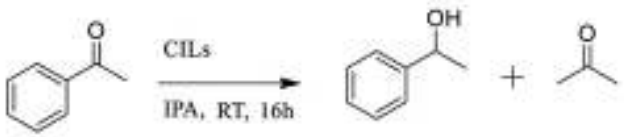



### *3.3.8 Recycle study of CILs of N aryl R & S amino acid amide in ATH of acetophenone.*

The reusability of CIL of amino acid amide was evaluated in ATH of acetophenone and results are shown in Table 7. After completion of first reaction, 10 ml 1N HCL solution was added and 10 ml ethyl acetate was added. Two layers are formed. Both layers were separated. From ethyl

acetate layer product was recovered by column chromatography. The aqueous layer was evaporated under reduced pressure to recovered CIL and same is used for ATH reaction by adding fresh acetophenone and base. By using this recycle procedure we have evaluated the CILs of amino acid amides **(33a, 33b, and 34b).** Initially recycle study of CIL **(33a)** in ATH of acetophenone reaction was carried out with ideal reaction condition. The desired ATH product was obtained with good and excellent enantioselectivity **( Table 7, entry 1-4)**. Secondly we have recycle CIL **(33b)** in ATH reaction. The excepted ATH product was obtained with excellent yield andexcellent enantio-selectivity **(Table 7, entry 5-8)**. Then finally recycle study of CIL **(34b)** in ATH reaction of acetophenone with ideal condition was carried out. The desired product was obtained with excellent yield and excellent enantio-selectivity **(Table 7, entry 9-12)**. From the recycle study it is clear that, there is no significant change in the yield and enantio-selectivity when CILs were reused three times.

**Table 7: Recycle study of CILs in ATH of acetophenone.**




| Entry No | CILs | Configuration | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 33a | *S* | 84 | 93 |
| 2 | 33a | *S* | 82 | 93 |
| 3 | 33a | *S* | 80 | 93 |
| 4 | 33a | *S* | 78 | 93 |
| 5 | 33b | *S* | 88 | 97 |
| 6 | 33b | *S* | 87 | 97 |
| 7 | 33b | *S* | 86 | 97 |
| 8 | 33b | *S* | 86 | 97 |
| 9 | 34b | *R* | 83 | 91 |
| 10 | 34b | *R* | 82 | 91 |
| 11 | 34b | *R* | 80 | 91 |
| 12 | 34b | *R* | 80 | 91 |

## 3.4. Conclusion

In conclusion, we successfully used CILs of *N* aryl *R* & *S* amino acid amide as stereo-selective organo-catalyst along with base in ATH reaction of ketones. The excellent enantio-selectivity and excellent yield of corresponding product was obtained. This is the first example to use CILs of amino acid amide as metal free organo-catalyst in ATH reaction. The CIL catalyst is an easy to recover and reuse without losing its activity and enantio-selectivity. Therefore, these CILs of amino acid amides may provide an attractive alternative to conventional asymmetric metal catalyzed ATH reaction of ketones.

## 3.5 Experimental details

### *3.5.1 General information of chemicals and instruments.*

Starting materials were purchased from Sigma Aldrich, Across Organic, Merck Chem, Spectrochem, Chemlab, and used as supplied. All solvents were purified by standard method prior to use. All NMR spectra was recorded on a Brucker 200 MHz, 400 MHz and 500 MHz spectrometer. High resolution mass spectra (HRMS) of compounds was recorded on a Thermo LTQ orbitrap XL (ESI). Optical rotation of compounds was confirmed on JASCO-700 Polarimeter. The enantiomeric separation of compounds was carried out using Nucon make Gas Chromatograph (GC) equipped with chiral CYDEX-β (25 m x 0.22 mm x 0.25 µm) column. The enantiomeric excess was calculated by GC and also by optical rotation data.

### *3.5.2 Procedure for asymmetric transfer hydrogenation of acetophenone.*

The asymmetric transfer hydrogenation was carried out in 50 ml of two neck round bottom flask equipped with magnetic stirrer. Acetophenone (8 mmole) and iso-propylalcohol (160 mmoles) was charged in round bottom flask and under stirring catalyst CIL of amino acid amide (0.5 mmoles) and base sodium tertiary butoxide (8 mmoles) was added and reaction is continued at room temperature (25-35° C) for 15 h. The completion of reaction was monitor by TLC. After reaction 50 ml 1N HCl was added for quenching the base and then 50 ml of ethyl acetate was added for isolation of product. Ethyl acetate extract was dried over anhydrous $Na_2SO_4$ and concentrated. Product was purified by silica gel column chromatography (5% petroleum ether &

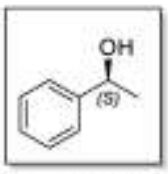
ethyl acetate) as solvent system. The product was then confirmed by $^{1}H$ and $^{13}C$ NMR spectra recorded on a Brucker spectrometer. High resolution mass spectra (HRMS) was recorded on a Thermo LTQ orbitrap XL (ESI) to confirm mass of the product. Optical activity was measured on JASCO-700 Polarometer and enantio meric excess of the product was calculated. Enantiomeric excess was also calculated from gas chromatogram having CYDEX-B (25m X 0.22mm, X 0.25µm) column.

### *3.5.3 Recycling of CILs in asymmetric transfer hydrogenation of acetophenone.*

After completion of first reaction, 10 ml 1N HCL and 10 ml ethyl acetate was added. Two layer form was separated. From ethyl acetate layer product was recovered by column chromatography. The aqueous layer was evaporated under reduced pressure to recovered CILs and same is used for ATH reaction by adding fresh acetophenone and base. The recycling study of CILs was carried out three times.

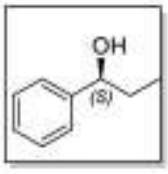
## 3.6 Spectral data

### *2a. (S)-1-phenyl ethanol:*



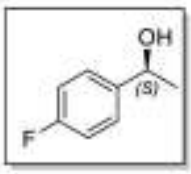

$^{1}H$ NMR (200 MHz, $CDCl_3$) δ ppm 1.40 (d, *J*=6.57 Hz, 3 H) 2.95 (br. s., 1 H) 4.76 (q, *J*=6.44 Hz, 1 H) 7.15 - 7.34 (m, 5 H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ ppm 25.19, 70.23, 125.50, 127.06, 127.23, 127.39, 128.47, 145.99; Enantiomeric excess is 97.63% [α] = -42.96, C= 1 in $CHCl_3$; Elemental analysis by HRMS(ESI) calculated mass 122.0732 and found 122.0651;

### *2b. (S)-1-Phenyl propan-1-ol:*



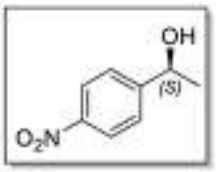

$^{1}H$ NMR (200 MHz, $CDCl_3$) δ ppm 0.72 (t, *J*=7.45 Hz, 3 H) 1.36 - 1.73 (m, 2 H) 2.99 (br. s., 1 H) 4.32 (t, *J*=6.57 Hz, 1 H) 6.93 - 7.32 (m, 5 H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ ppm 10.22, 31.91, 75.85, 126.15, 127.37, 128.02, 128.35, 144.81; Enantiomeric excess is 95% [α] = -44.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS(ESI) calculated mass 136.0888 and found 136.0838;

*2c. (S)-1-(-4-flurophenyl) ethan-1-ol:*



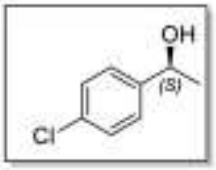

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.55 (br. s., 1 H) 4.65 (q, *J*=5.81 Hz, 1 H) 6.74 - 6.99 (d, 2 H) 7.13 (d, *J*=8.46 Hz, 2 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.16, 69.44, 114.87, 115.29, 126; Enantiomeric excess is 89% [α] = -44.3, C= 1 in $CHCl_3$. Elemental analysis by HRMS (ESI) calculated mass 140.0637 and found 140.0262;

*2d. (S)-1-(4-nitrophenyl) ethan-1-ol:*



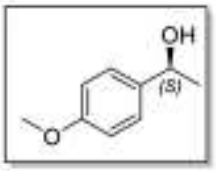

$^1$H NMR ($CDCl_3$, 200MHz): δ = 8.12 (d, *J*=8.7 Hz, 2 H), 7.52 (d, *J*=8.6 Hz, 2 H), 5.00 (q, *J*=6.4 Hz, 1 H), 3.73 (br. s., 1 H), 1.50 ppm (d, *J*=6.6 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm= 144.1, 132.6, 128.3, 126.6, 69.2, 24.9; Enantiomeric excess 84% [α] = -42.32, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 167.0582 and found 167.0707;

*2e. (S)-1-(4-chlorophenyl) ethan-1-ol:*



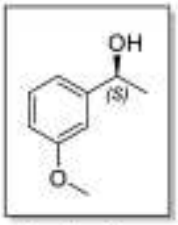

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.09 (s, *J*=13.26 Hz, 1 H) (q, *J*=6.44 Hz, 1 H) 7.08-7.19 (dd, *J*=8.59 Hz, 4 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.17, 69.44, 113.75, 126.86, 128.48, 132.86, 144.34; Enantiomeric excess is 88.40% [α] = -42.32, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 156.0342 and found 156.0807;

*2f. (S)-1-(4-methoxyphenyl) ethan-1-ol:*




$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.09 (s, *J*=13.26 Hz, 1 H) 3.61 (s, 3 H) 4.61 (q, *J*=6.44 Hz, 1 H) 6.70 (d, *J*=8.59 Hz, 2 H) 7.10 (d, *J*=8.59 Hz, 2 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.11, 55.22, 69.65, 113.75, 125.48, 126.73, 128.40, 138.29, 156.78; Enantiomeric excess is 85% [α] = -47.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 152.0837 and found 152.0832;

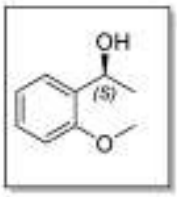
*2g. (S)-1-(3-methoxyphenyl) ethan-1-ol:*



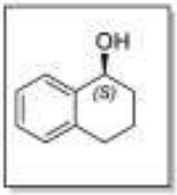

$^1$H NMR (200 MHz, $CDCl_3$) d ppm 1.41 (d, *J*=6.44 Hz, 3 H) 2.96 (br. s., 1 H) 3.74 (s, 3 H) 4.76 (q, *J*=6.36 Hz, 1 H) 6.76 (dd, *J*=8.65, 2.97 Hz, 2 H) 6.88 (d, *J*=4.67 Hz, 2 H) 7.09 - 7.34 (s, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) d ppm 25.18, 55.17, 70.11, 110.96, 112.77, 117.79, 129.47, 147.80, 159.69; Enantiomeric excess is 80% [α] = -44.3, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass is 152.0837 and found in 152.0832;

*2h. (S)-1-(2-methoxyphenyl) ethan-1-ol:*

$^1$H NMR ($CDCl_3$ ,200MHz): δ = 7.10 - 7.43 (m, 2 H), 6.69 - 7.03 (m, 2 H), 5.08 (q, *J*=6.4 Hz, 1 H), 3.82 (s, 3 H), 2.89 (br. s., 1 H), 1.47 ppm (d, *J*=6.6 Hz, 3 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm= 158.5, 138.0, 126.4, 113.4, 69.3, 54.9, 24.8; Enantiomeric excess is 88% [α] = -40.3, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 152.0837 and found 152.0832;

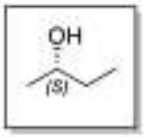



*2i. (S)-1,2,3.4-tetrahydronapthalen-1-ol:*



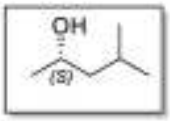

$^1$H NMR ($CDCl_3$, 200MHz): δ = 6.88 - 7.60 (m, 4 H), 4.67 (dd, *J*=4.4, 0.6 Hz, 1 H), 2.25 - 2.93 (m, 3 H), 1.61 - 2.08 ppm (m, 4 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm= 138.7, 136.9, 128.8, 128.5, 127.3, 125.9, 67.8, 32.1, 29.1, 18.7; Enantiomeric excess is 88.20% [α] = -11.41, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 148.0888 and found 148.0807;

*2j. (S)-butan-2-ol:*



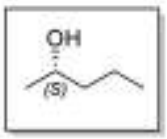

$^1$H NMR ($CDCl_3$, 200MHz): δ = 3.66 (sxt, *J*=6.1 Hz, 1 H), 1.98 (br. s., 1 H), 1.26 - 1.51 (m, 2 H), 1.11 (d, *J*=6.2 Hz, 3 H), 0.75 - 0.98 ppm (m, 3 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm = 69.4, 32.0, 22.8, 9.9; Enantiomeric excess is 88.30% [α] = -11, (C= 1 in $CHCl_3$); Elemental analysis by HRMS (ESI) calculated mass 74.0732 and found 74.0854;

*2k. (S)-4-methylpentan-2-ol:*



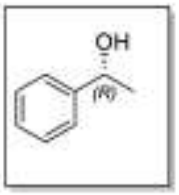

$^1$H NMR ($CDCl_3$ ,200MHz): δ = 3.69 - 3.96 (m, 1 H), 1.59 - 1.99 (m, 2 H), 1.32 - 1.51 (m, 2 H), 1.18 (d, *J*=6.1 Hz, 3 H), 0.91 ppm (d, *J*=6.6 Hz, 6 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm= 65.9, 48.5, 24.7, 23.8, 23.0, 22.2; Enantiomeric excess is 88.10% [α] = -4.39, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 88.0888 and found 88.0756;

*2l. (S)-pentan-2-ol:*



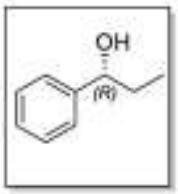

$^1$H NMR ($CDCl_3$ ,200MHz): δ = 3.65 - 3.96 (m, 1 H), 2.32 (br. s., 1 H), 1.30 - 1.57 (m, 4 H), 1.17 (d, *J*=6.2 Hz, 3 H), 0.79 - 1.06 ppm (m, 3 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm= 67.4, 41.3, 23.2, 18.8, 13.9; Enantiomeric excess is 88.70% [α] = -10.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 88.0888 and found 88.0985.

*4a. (R)-1-phenyl ethanol:*



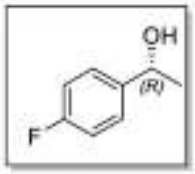

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.40 (d, *J*=6.57 Hz, 3 H) 2.95 (br. s., 1 H) 4.89 (q, *J*=6.44 Hz, 1 H) 7.15 - 7.34 (m, 5 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.19, 70.23, 125.50, 127.06, 127.23, 127.39, 128.47, 145.99; Enantiomeric excess is 97.63% [α] = +42.96, C= 1 in $CHCl_3$; Elemental analysis by HRMS(ESI) calculated mass 122.0732 and found 122.0651.

*4b. (R)-1-Phenyl propan-1-ol:*



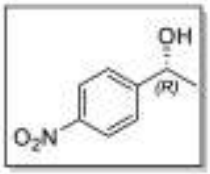

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 0.72 (t, *J*=7.45 Hz, 3 H) 1.36 - 1.73 (m, 2 H) 2.99 (br. s., 1 H) 4.32 (t, *J*=6.57 Hz, 1 H) 6.93 - 7.32 (m, 5 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 10.22, 31.91, 75.85, 126.15, 127.37, 128.02, 128.35, 144.81; Enantiomeric excess is 94.68% [α] = +44.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS(ESI) calculated mass 136.0888 and found 136.0838;

*4c. (R)-1-(-4-flurophenyl) ethan-1-ol:*



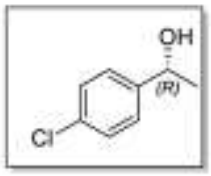

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.55 (br. s., 1 H) 4.65 (q, *J*=5.81 Hz, 1 H) 6.74 - 6.99 (d, 2 H) 7.13 (d, *J*=8.46 Hz, 2 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.16, 69.44, 114.87, 115.29, 126.01, 141.61, 159.58, 164.44; Enantiomeric excess is 90.40% [α] = +44.3, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 140.0637 and found 140.0262;

*4d. (R)-1-(4-nitrophenyl) ethan-1-ol:*



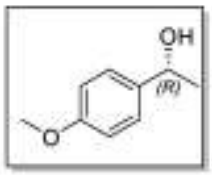

$^1$H NMR (CDCl3, 200MHz): δ = 8.12 (d, *J*=8.7 Hz, 2 H), 7.52 (d, *J*=8.6 Hz, 2 H), 5.00 (q, *J*=6.4 Hz, 1 H), 3.73 (br. s., 1 H), 1.50 ppm (d, *J*=6.6 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm= 144.1, 132.6, 128.3, 126.6, 69.2, 24.9; Enantiomeric excess is 88% [α] = +42.32, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 167.0582 and found 167.0707.

*4e. (R)-1-(4-chlorophenyl) ethan-1-ol:*



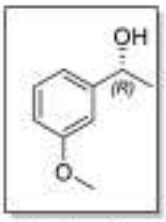

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.09 (s, *J*=13.26 Hz, 1 H) (q, *J*=6.44 Hz, 1 H) 7.08-7.19 (dd, *J*=8.59 Hz, 4 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.17, 69.44, 113.75, 126.86, 128.48, 132.86, 144.34; Enantiomeric excess is 88.10% [α] = +42.32, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 156.0342 and found 156.0807;

*4f. (R)-1-(4-methoxyphenyl) ethan-1-ol:*



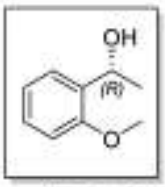

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.28 (d, *J*=6.44 Hz, 3 H) 3.09 (s, *J*=13.26 Hz, 1 H) 3.61 (s, 3 H) 4.61 (q, *J*=6.44 Hz, 1 H) 6.70 (d, *J*=8.59 Hz, 2 H) 7.10 (d, *J*=8.59 Hz, 2 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.11, 55.22, 69.65, 113.75, 125.48, 126.73, 128.40, 138.29, 156.78; Enantiomeric excess is 84.94% [α] = +47.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 152.0837 and found 152.0832;

*4g. (R)-1-(3-methoxyphenyl) ethan-1-ol:*



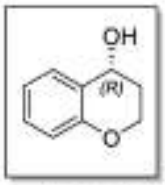

$^1$H NMR (200 MHz, $CDCl_3$) δ ppm 1.41 (d, *J*=6.44 Hz, 3 H) 2.96 (br. s., 1 H) 3.74 (s, 3 H) 4.76 (q, *J*=6.36 Hz, 1 H) 6.76 (dd, *J*=8.65, 2.97 Hz, 2 H) 6.88 (d, *J*=4.67 Hz, 2 H) 7.09 - 7.34 (s, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ ppm 25.18, 55.17, 70.11, 110.96, 112.77, 117.79, 129.47, 147.80, 159.69; Enantiomeric excess is 81% [α] = +44.3, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 152.0837 and found 152.0832;

*4h. (R)-1-(2-methoxyphenyl) ethan-1-ol:*



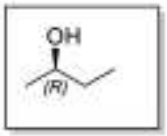

$^1$H NMR ($CDCl_3$ ,200MHz): δ = 7.10 - 7.43 (m, 2 H), 6.69 - 7.03 (m, 2 H), 5.08 (q, *J*=6.4 Hz, 1 H), 3.82 (s, 3 H), 2.89 (br. s., 1 H), 1.47 ppm (d, *J*=6.6 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm= 158.5, 138.0, 126.4, 113.4, 69.3, 54.9, 24.8; Enantiomeric excess is 78% [α] = +40.3, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 152.0837 and found 152.0832;

*4i. (R)-1,2,3.4-tetrahydronapthalen-1-ol:*



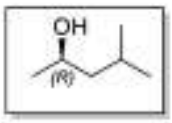

$^1$H NMR ($CDCl_3$, 200MHz): δ = 6.88 - 7.60 (m, 4 H), 4.67 (dd, *J*=4.4, 0.6 Hz, 1 H), 2.25 - 2.93 (m, 3 H), 1.61 - 2.08 ppm (m, 4 H); $^{13}$C NMR ($CDCl_3$, 50MHz): δ ppm= 138.7, 136.9, 128.8, 128.5, 127.3, 125.9, 67.8, 32.1, 29.1, 18.7; Enantiomeric excess is 88.20% [α] = +11.41, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 148.0888 and found 148.0807;

*4j. (R)-butan-2-ol:*



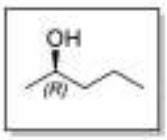

$^1$H NMR ($CDCl_3$, 200MHz): δ = 3.66 (sxt, *J*=6.1 Hz, 1 H), 1.98 (br. s., 1 H), 1.26 - 1.51 (m, 2 H), 1.11 (d, *J*=6.2 Hz, 3 H), 0.75 - 0.98 ppm (m, 3 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm = 69.4, 32.0, 22.8, 9.9; Enantiomeric excess is 88.50% [α] = +11, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 74.0732 and found 74.0854;

*2k. (R)-4-methylpentan-2-ol:*




$^{1}$H NMR ($CDCl_3$ ,200MHz): δ = 3.69 - 3.96 (m, 1 H), 1.59 - 1.99 (m, 2 H), 1.32 - 1.51 (m, 2 H), 1.18 (d, *J*=6.1 Hz, 3 H), 0.91 ppm (d, *J*=6.6 Hz, 6 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm= 65.9, 48.5, 24.7, 23.8, 23.0, 22.2; Enantiomeric excess is 87% [α] = +4.39, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 88.0888 and found 88.0756;

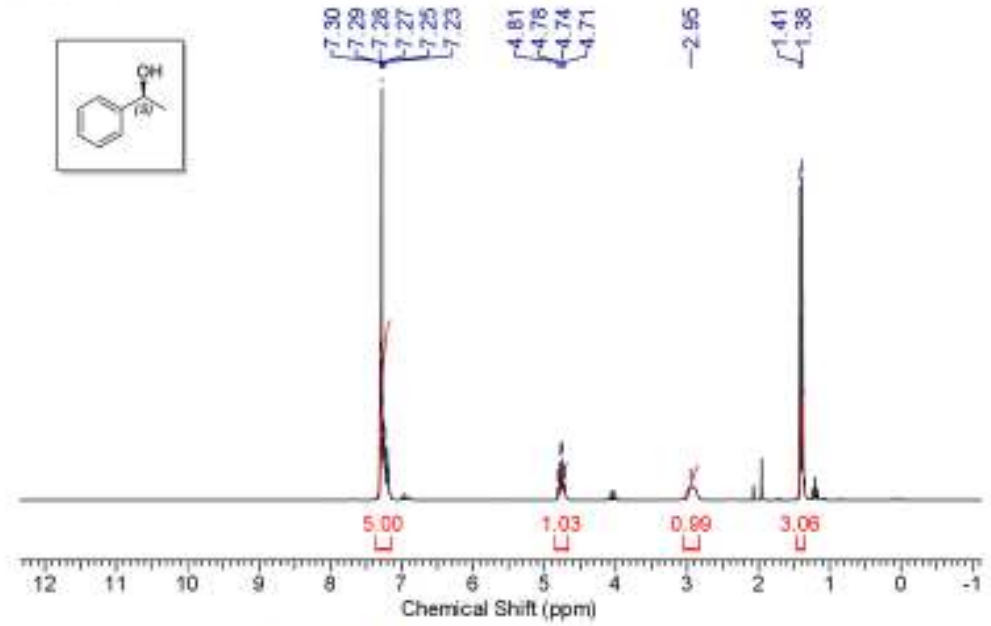
*4l. (R)-pentan-2-ol:*

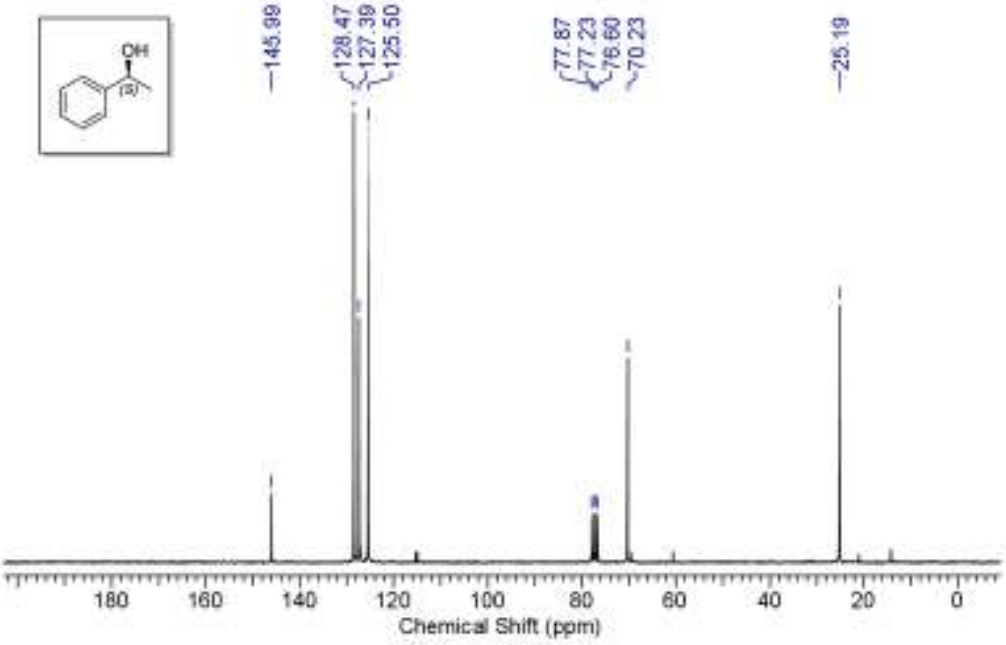



$^{1}$H NMR ($CDCl_3$ ,200MHz): δ = 3.65 - 3.96 (m, 1 H), 2.32 (br. s., 1 H), 1.30 - 1.57 (m, 4 H), 1.17 (d, *J*=6.2 Hz, 3 H), 0.79 - 1.06 ppm (m, 3 H); $^{13}$C NMR ($CDCl_3$ ,50MHz): δ ppm= 67.4, 41.3, 23.2, 18.8, 13.9; Enantiomeric excess is 88.16% [α] = +10.5, C= 1 in $CHCl_3$; Elemental analysis by HRMS (ESI) calculated mass 88.0888 and found 88.0985;

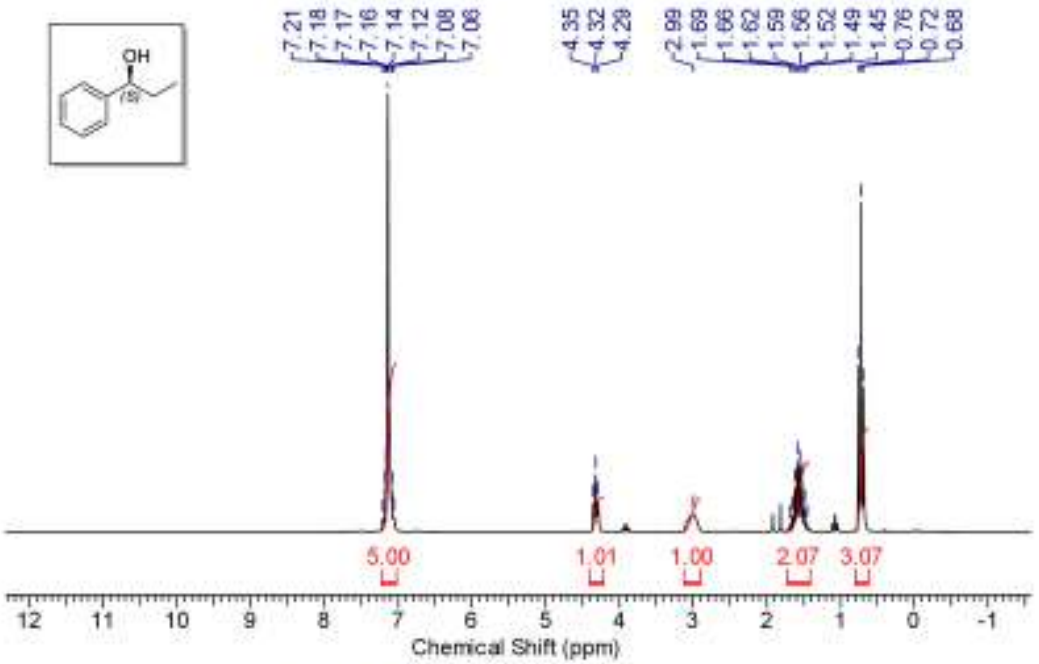
### 3.6.1 $^{1}H$ & $^{13}C$ NMR spectra

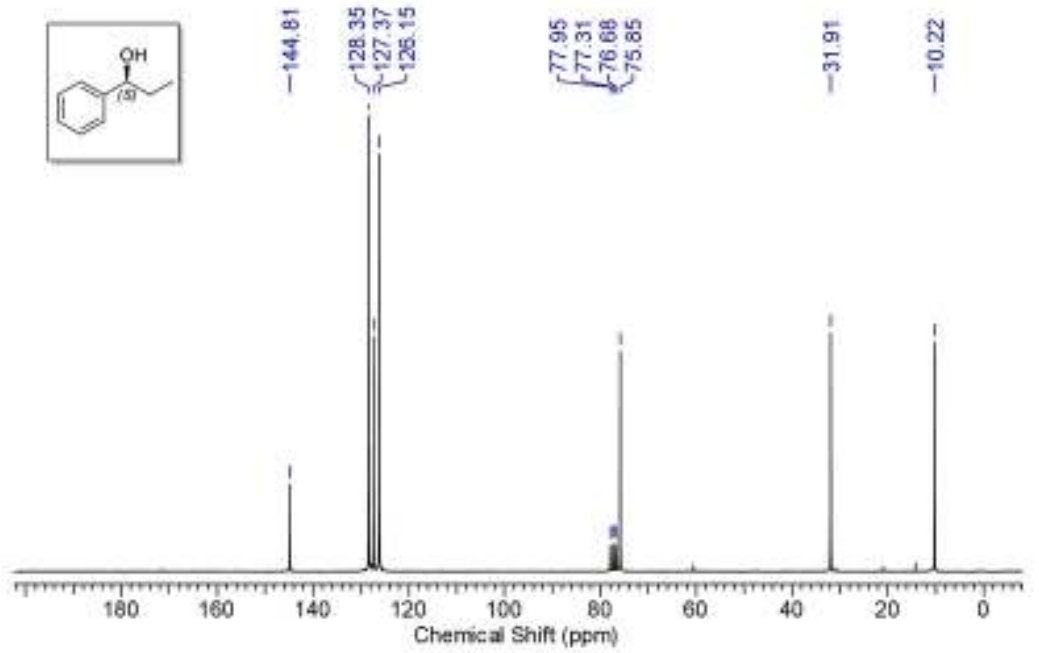
#### 2a. (S)-1-phenyl ethanol:



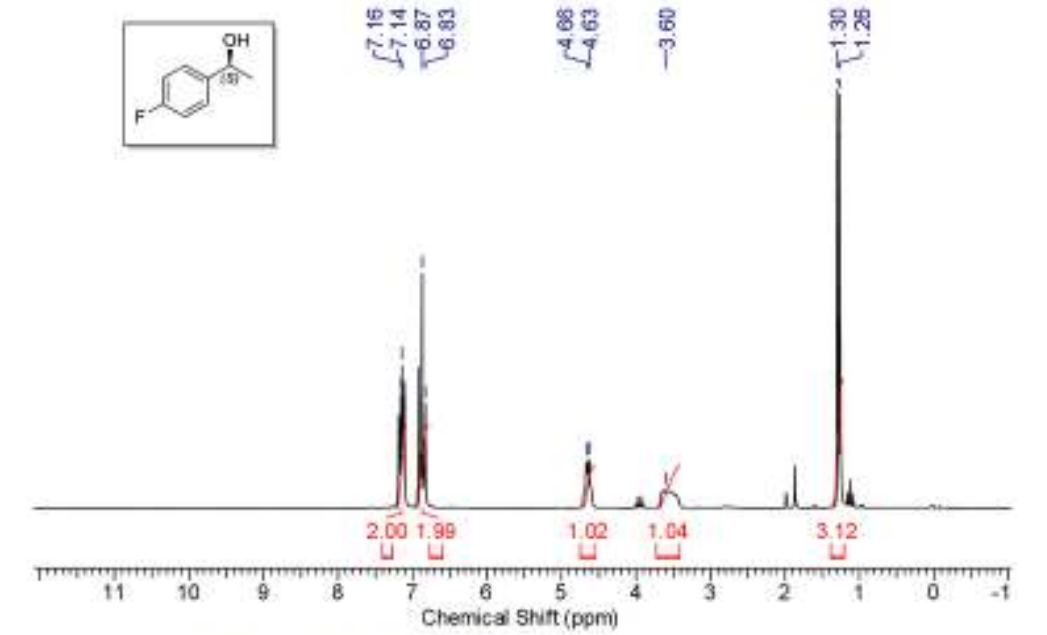



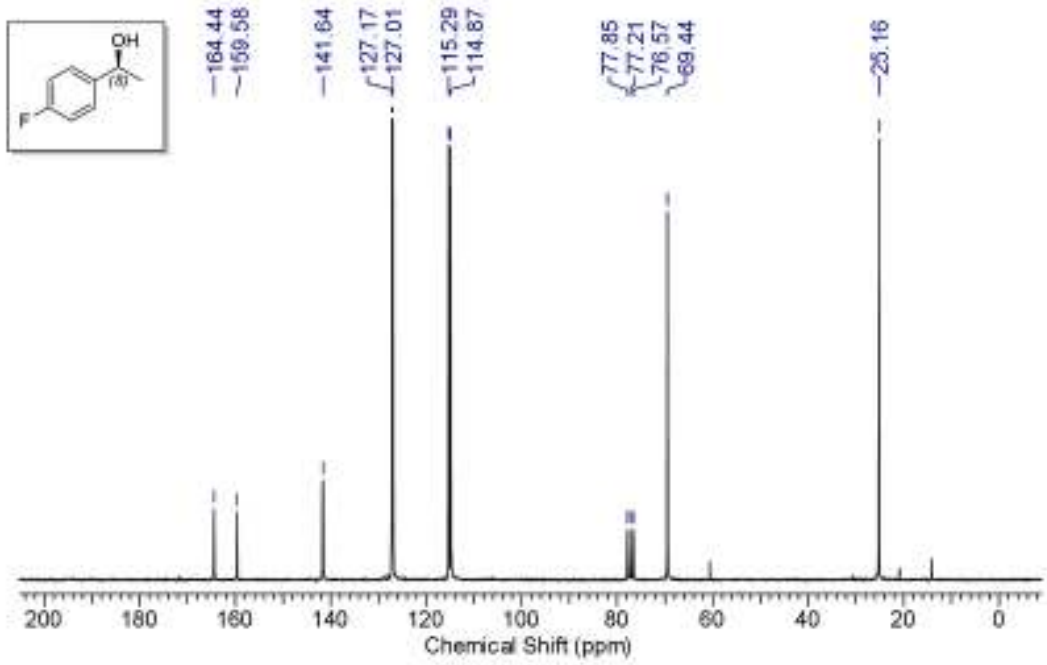
*2b. (S)-1-Phenyl propan-1-ol:*



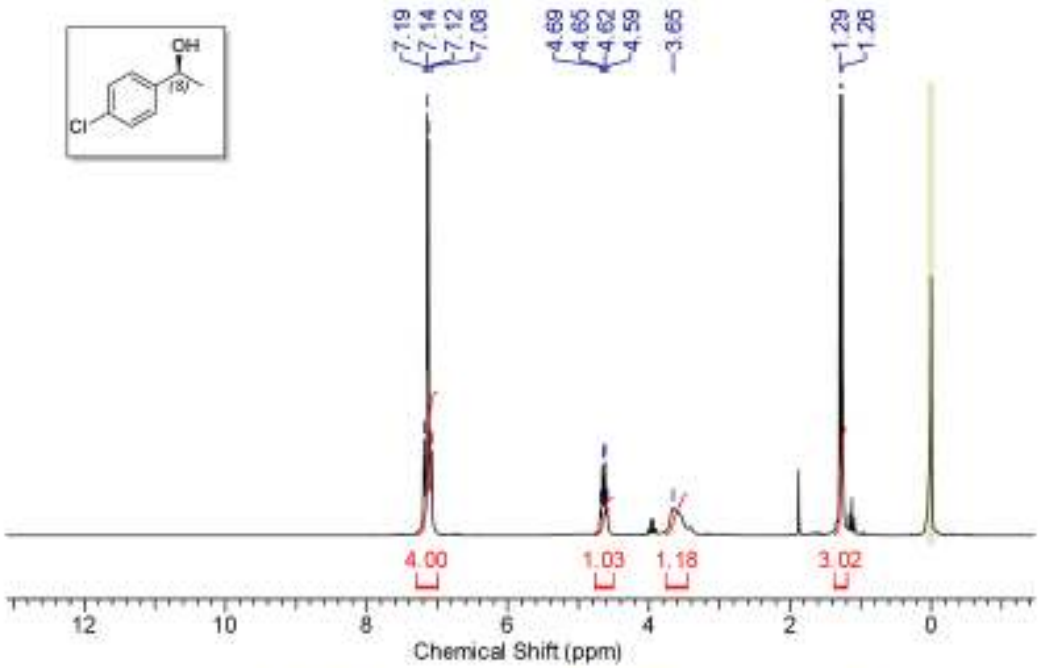



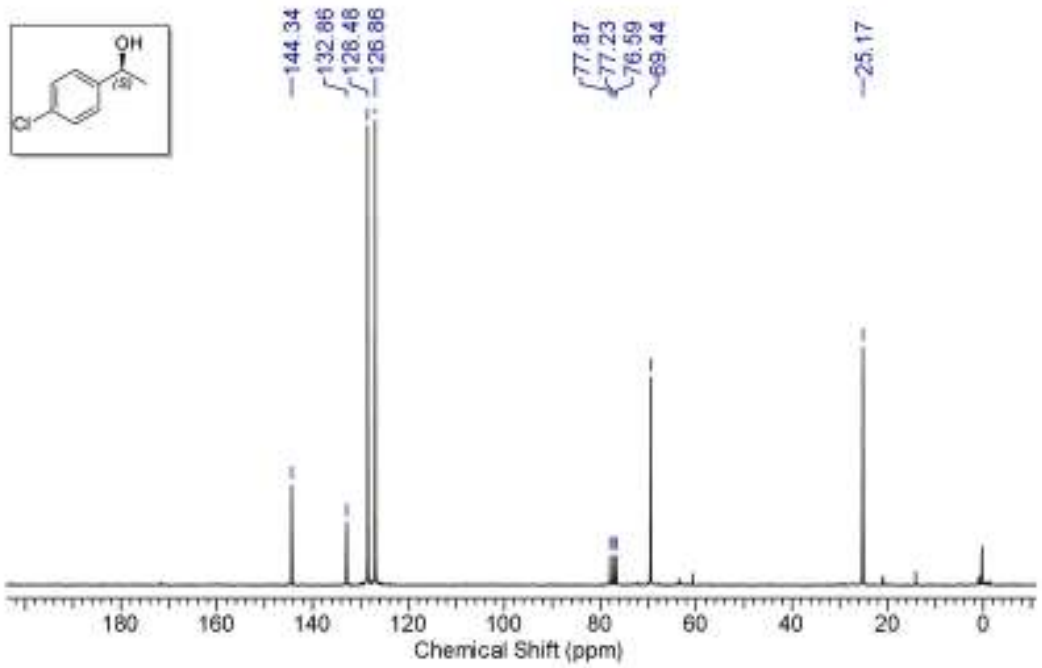
*2c. (S)-1-(-4-fluorophenyl) ethan-1-ol:*



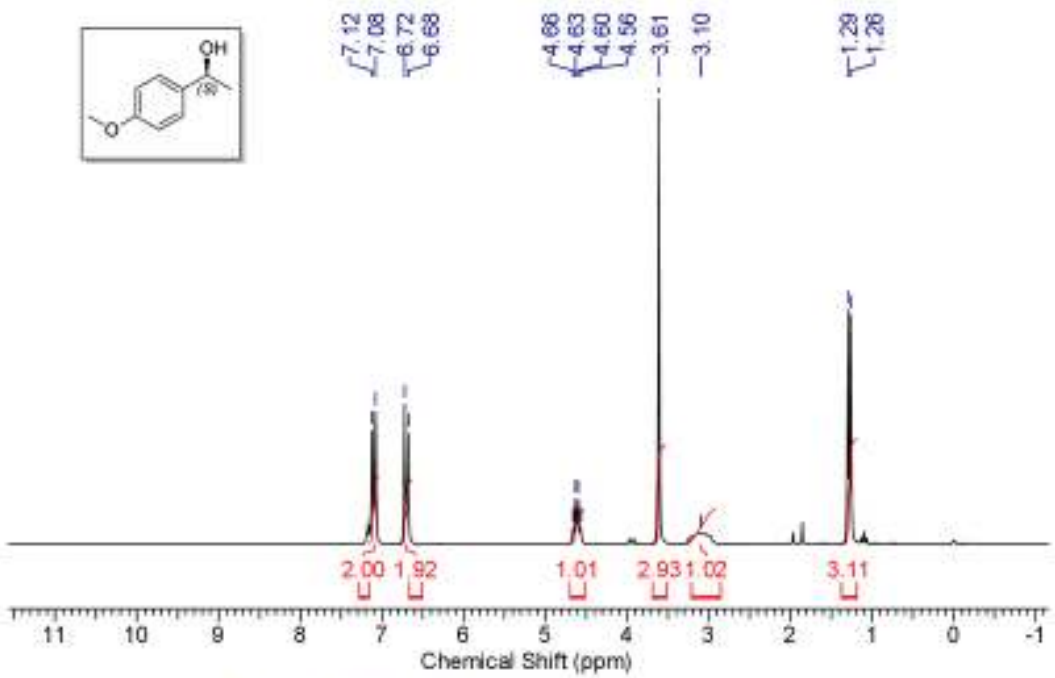



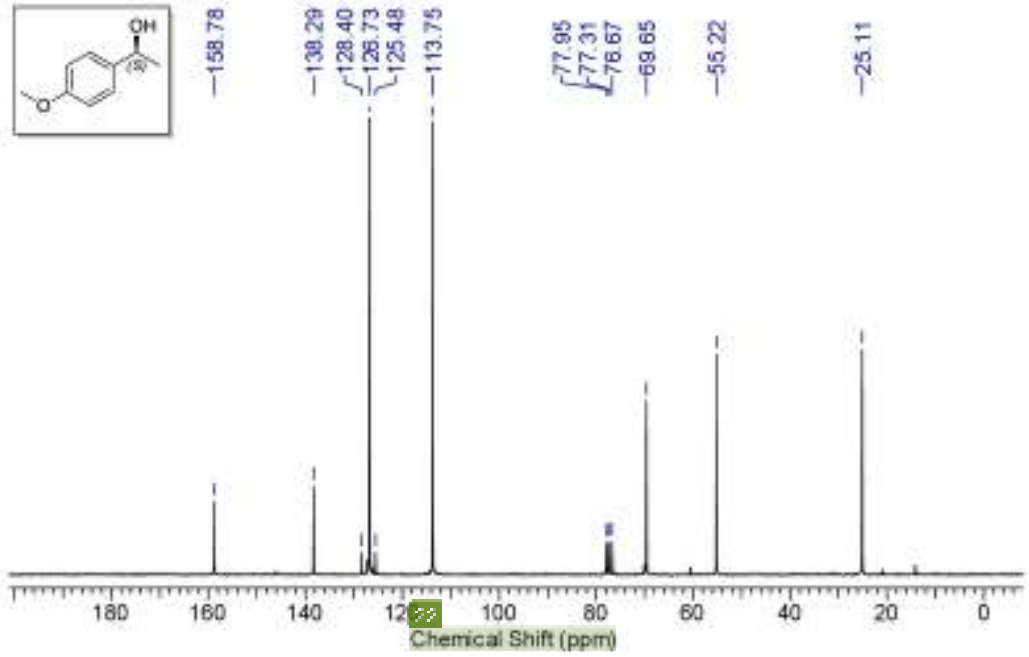
2e. (S)-1-(4-chlorophenyl) ethan-1-ol:



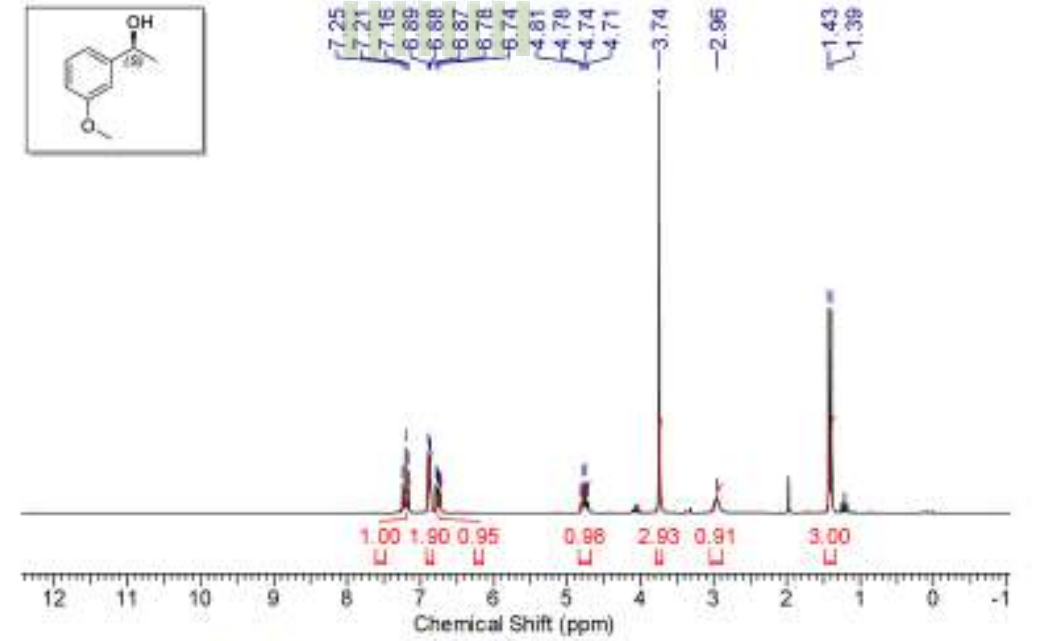



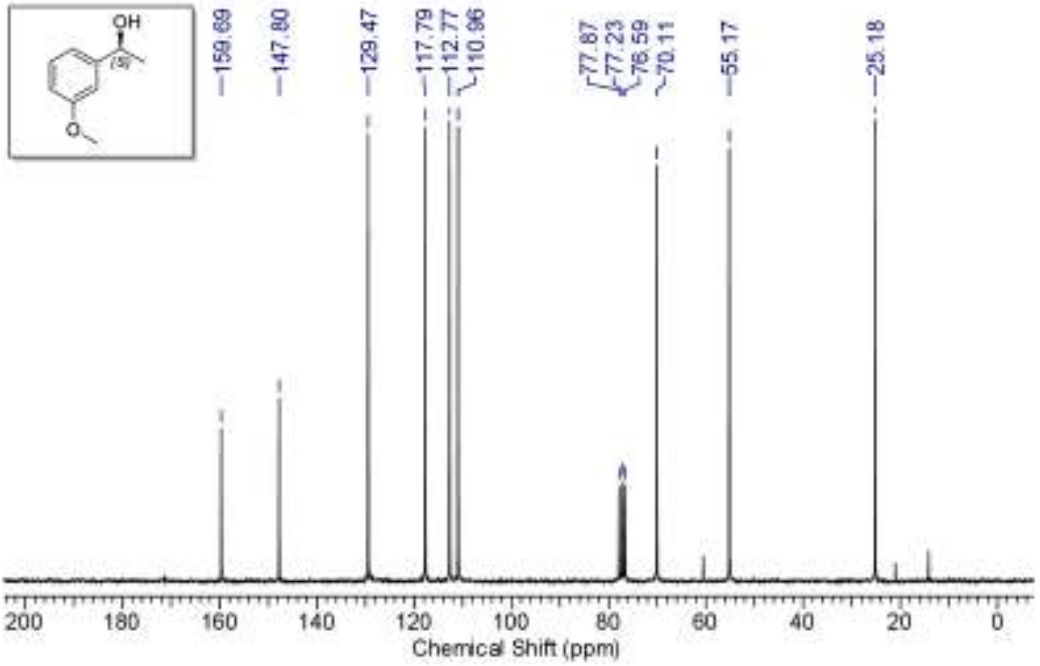
*2f. (S)-1-(4-methoxyphenyl) ethan-1-ol:*



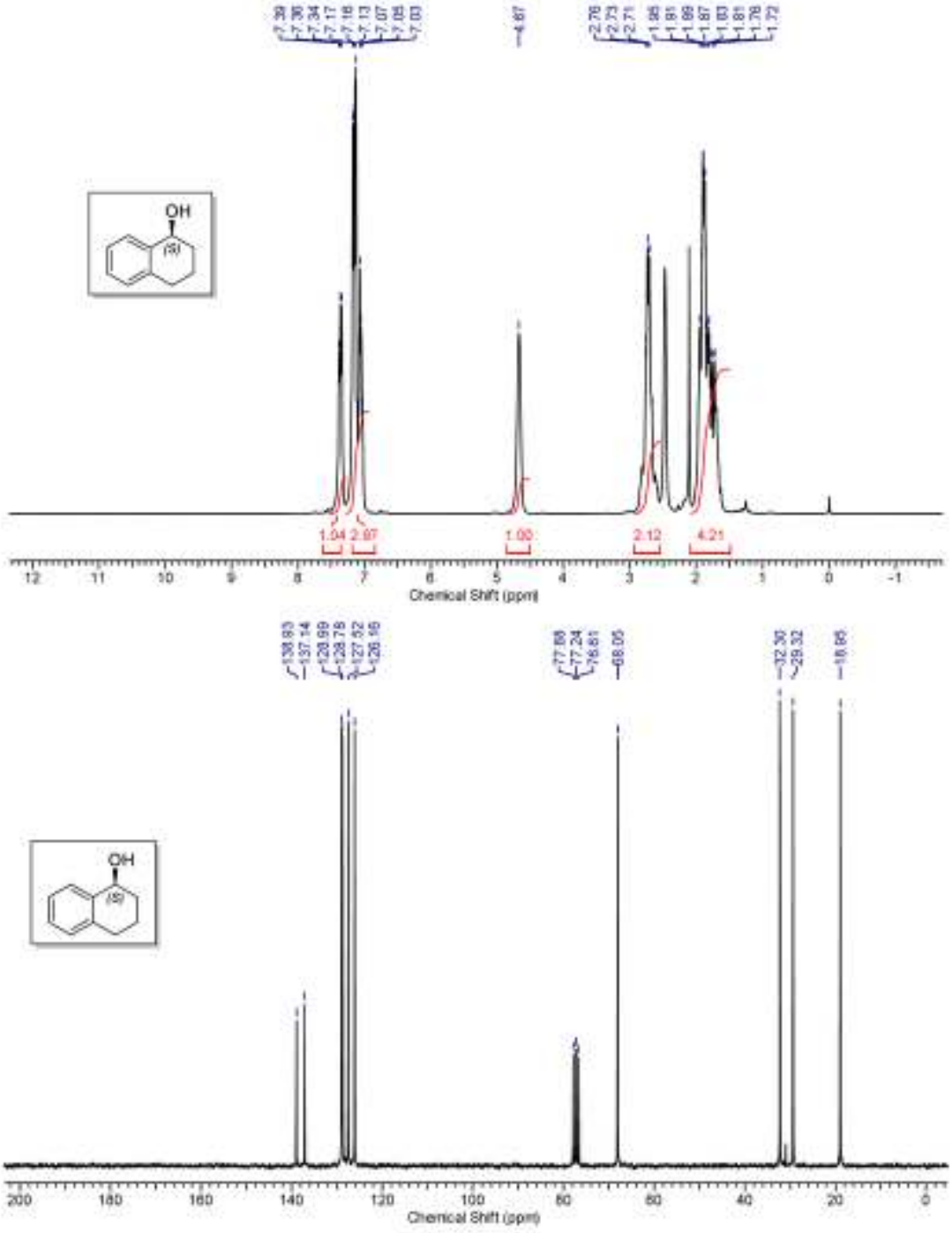



*2g. (S)-1-(3-methoxyphenyl) ethan-1-ol:*

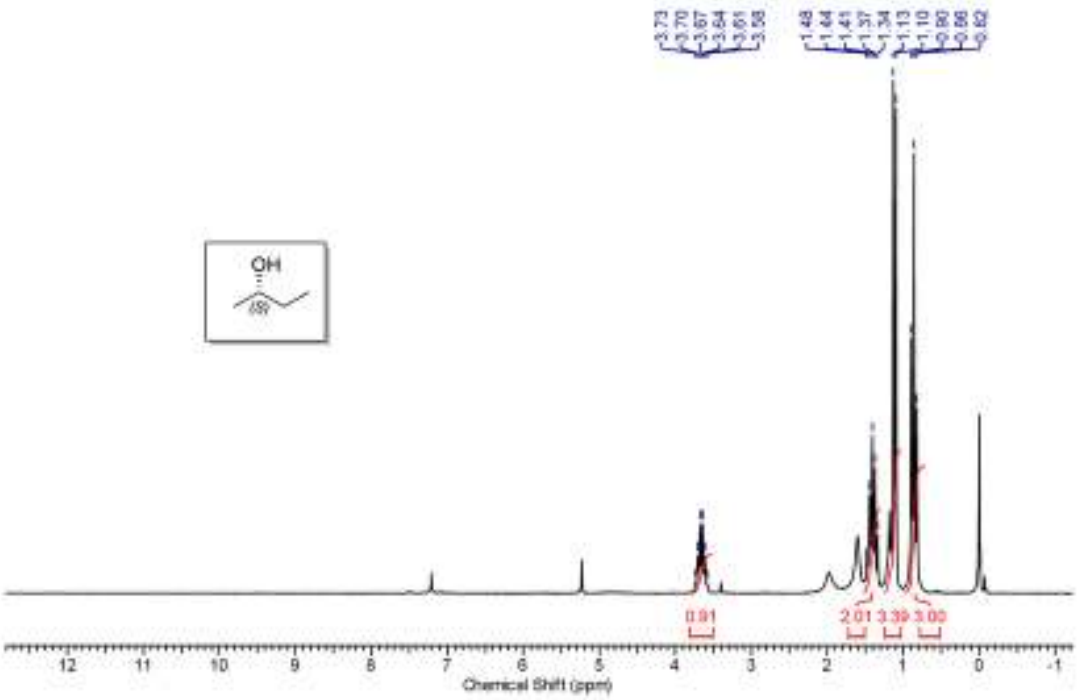


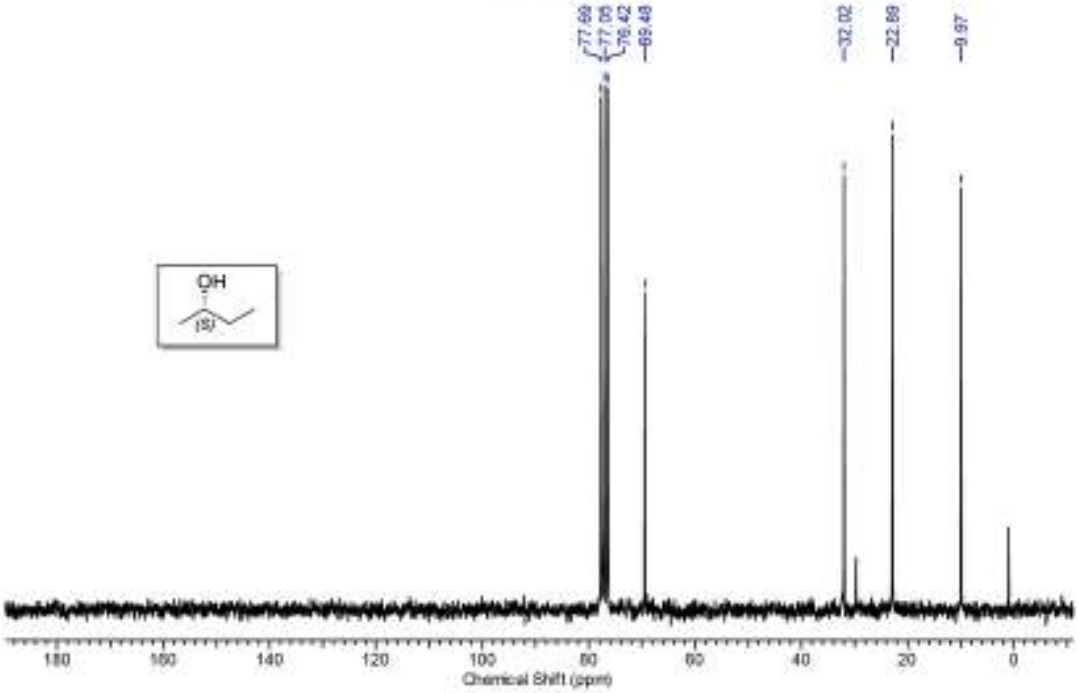



*2i. (S)-1,2,3.4-tetrahydronapthalen-1-ol:*

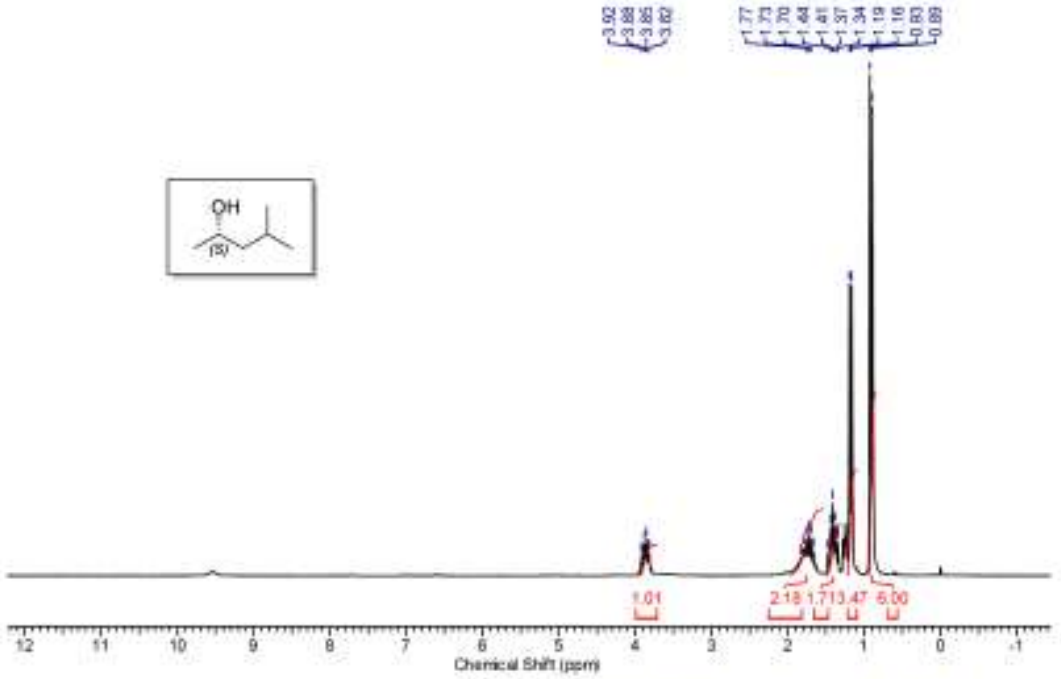


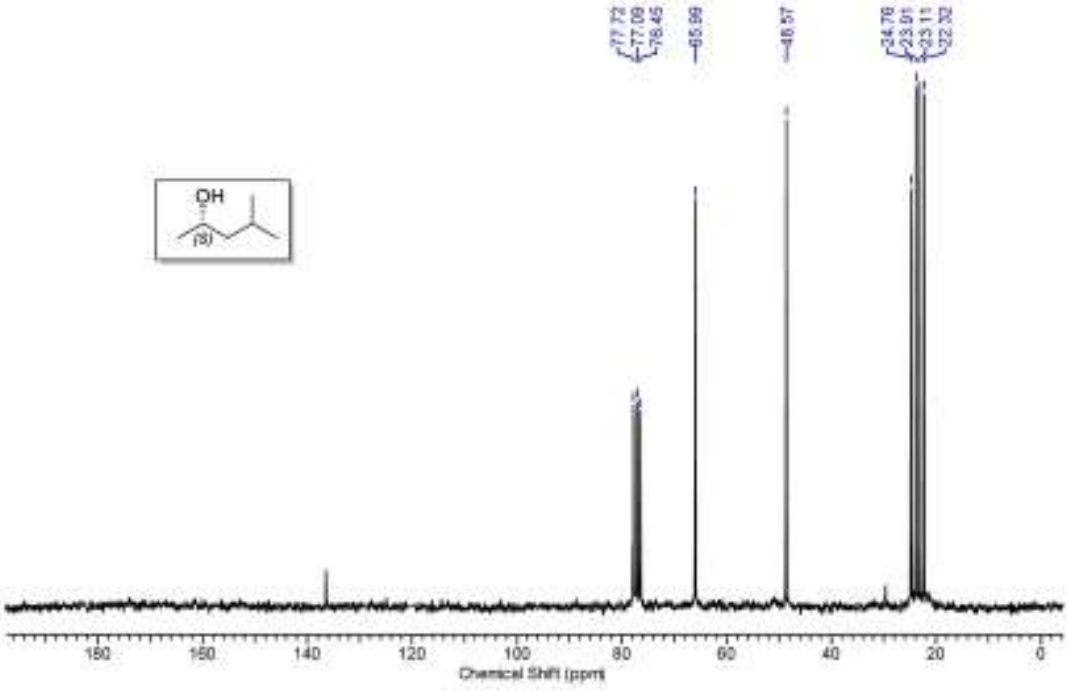
*2j. (S)-butan-2-ol:*



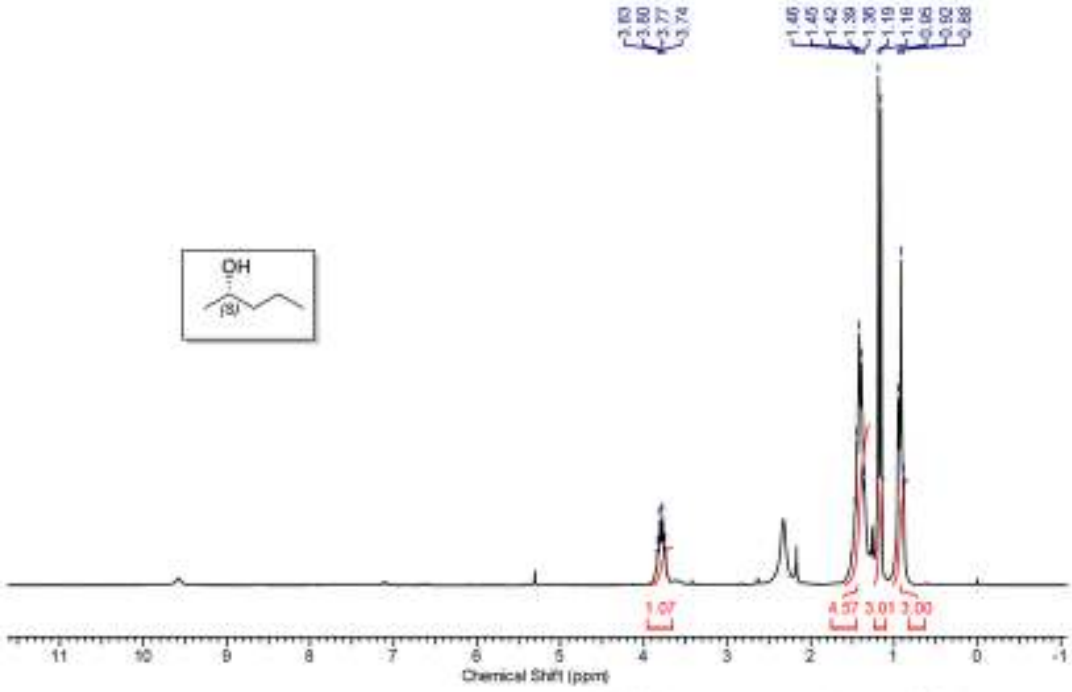



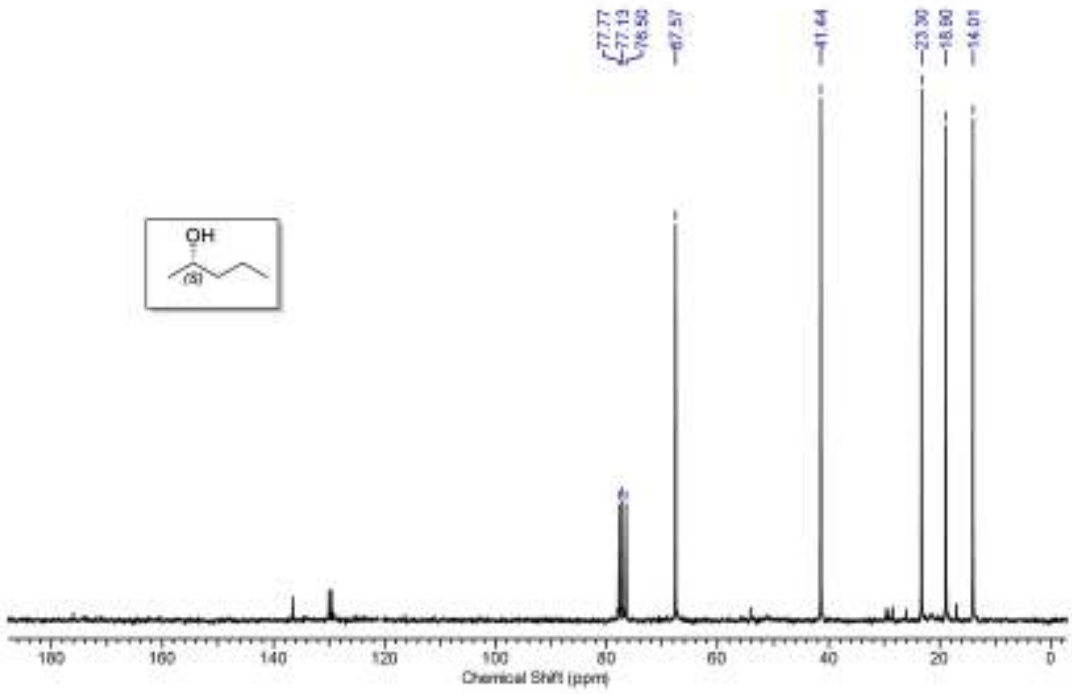
*2k. (S)-4-methylpentan-2-ol:*



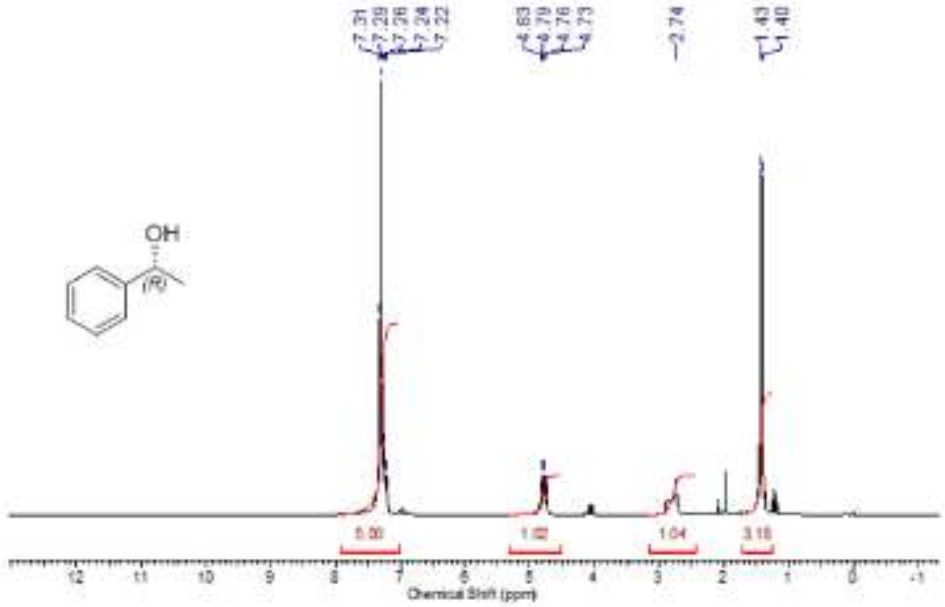



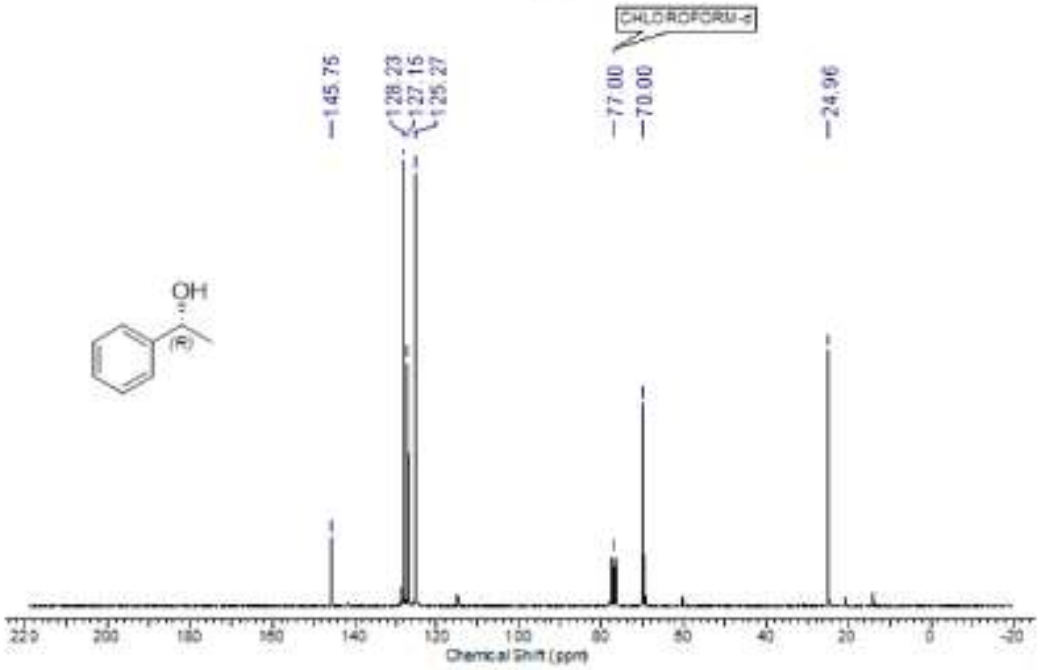
*2l. (S)-pentan-2-ol:*



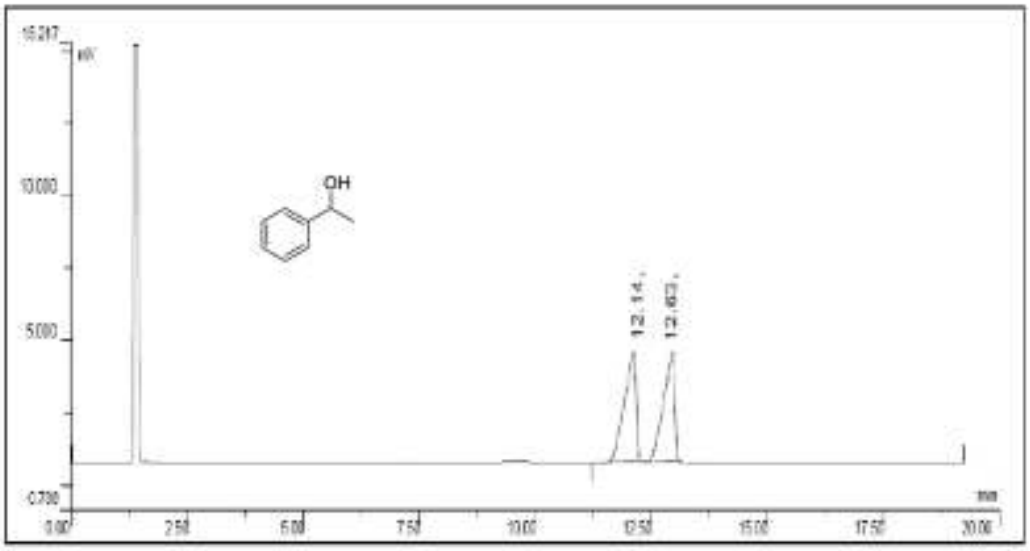
*4a. (R) 1-Phenyl ethanol:*



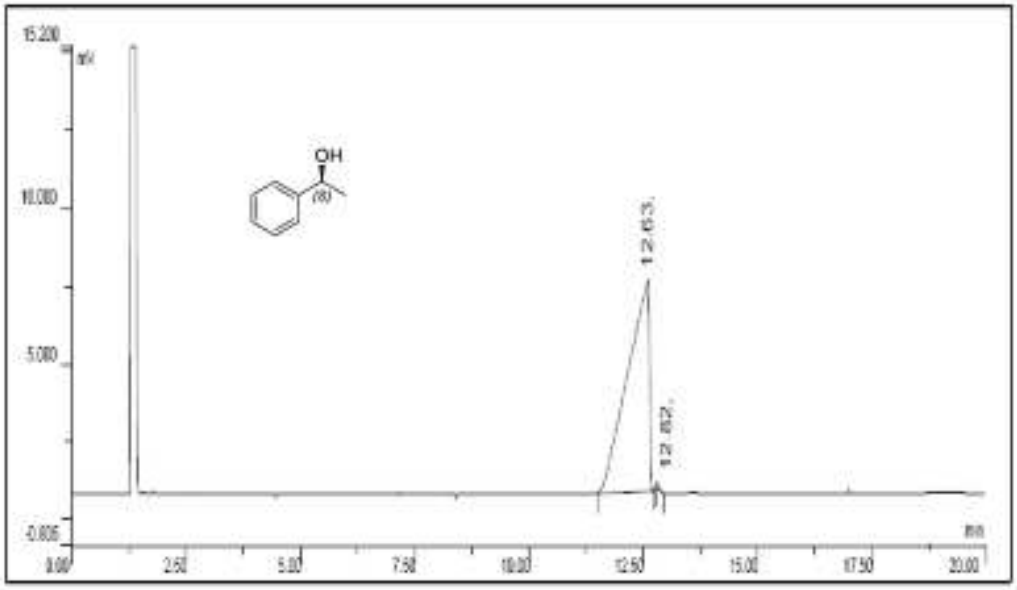



### 3.6.2 GC spectra of acteophenone

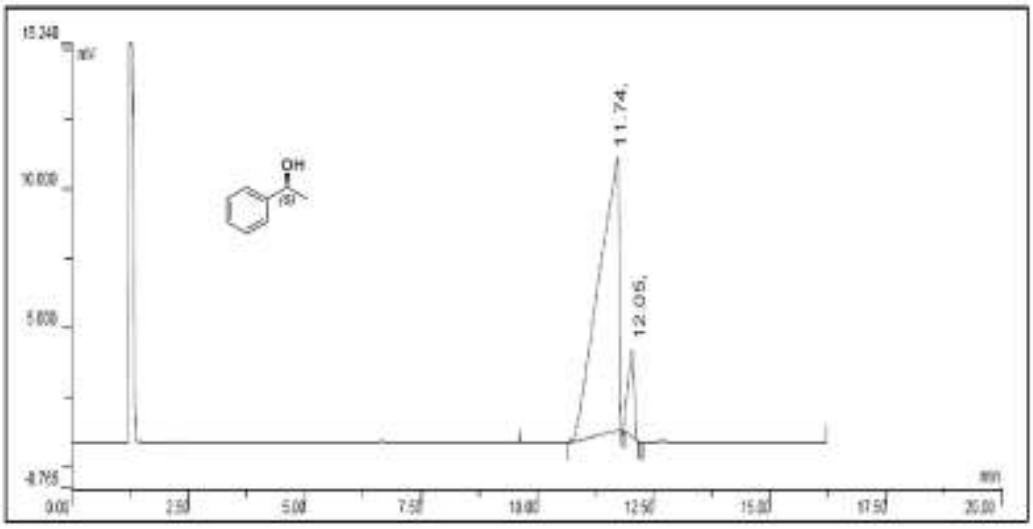
*GC spectra of racemic mixture (Table 3, entry no. 1):*



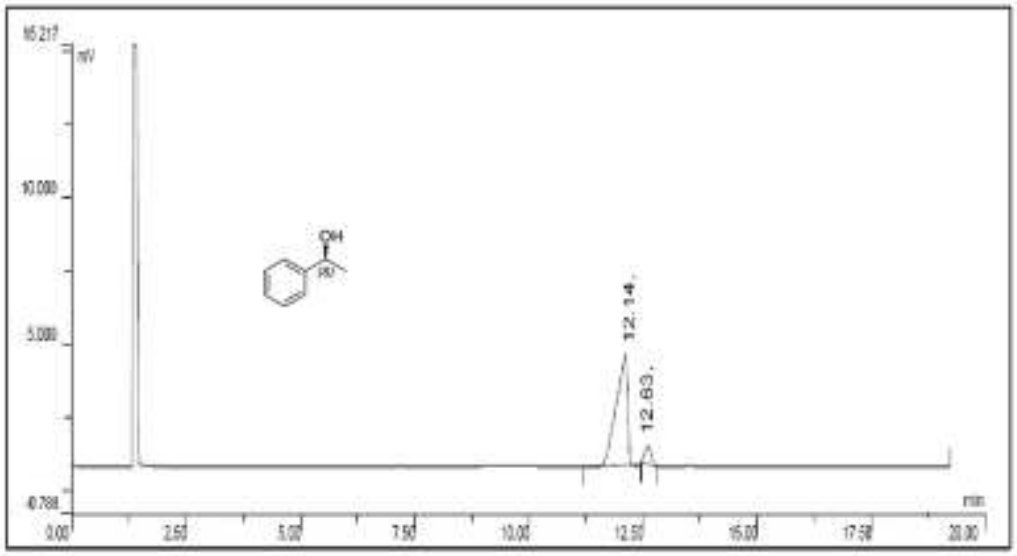

*GC spectra of (S)-1-phenyl ethanol (Table 3, entry 2):*



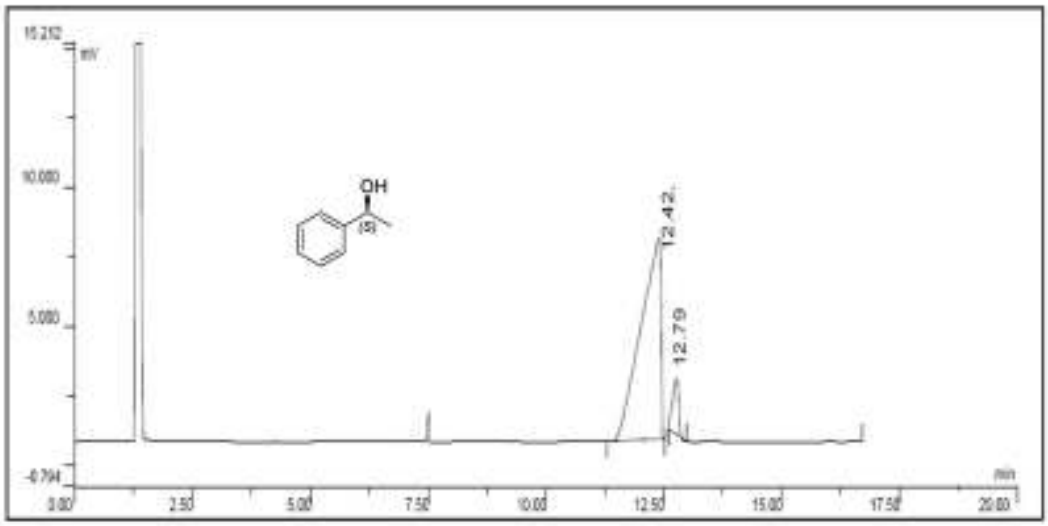
*GC spectra of (S)-1-phenyl ethanol (Table 3 entry 3):*



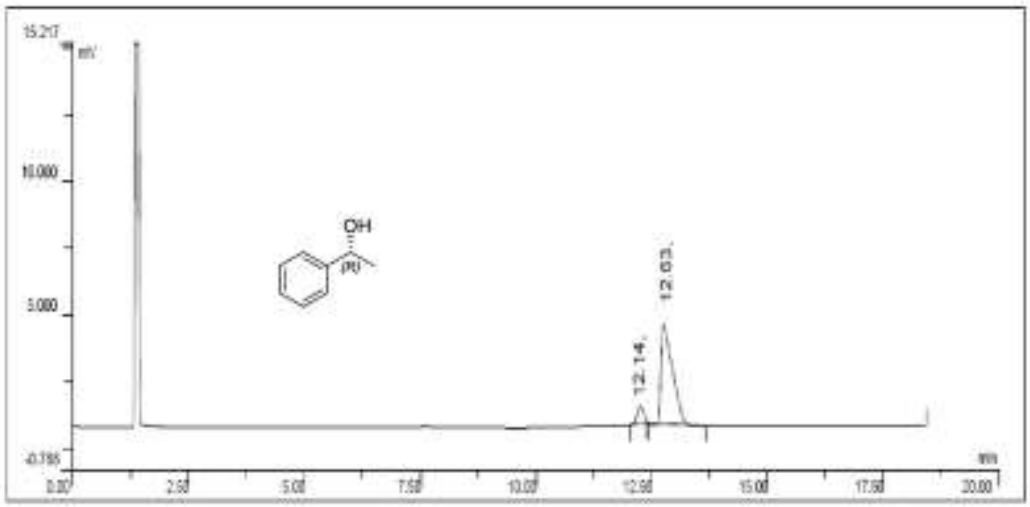

*GC spectra of (S)-1-phenyl ethanol (Table 3, entry 4):*



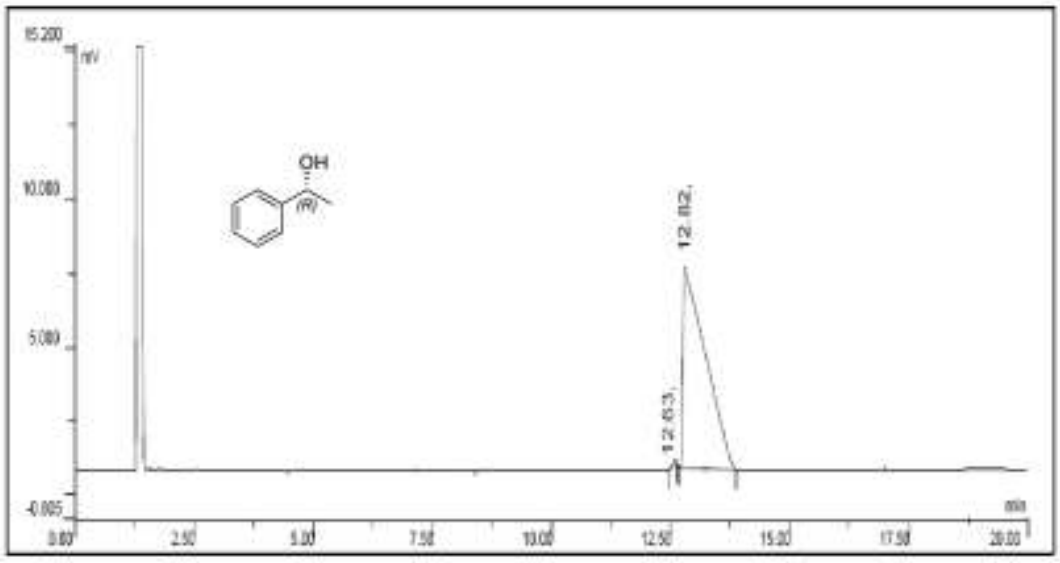
*GC spectra of (S)-1-phenyl ethanol (Table 3, entry 5):*



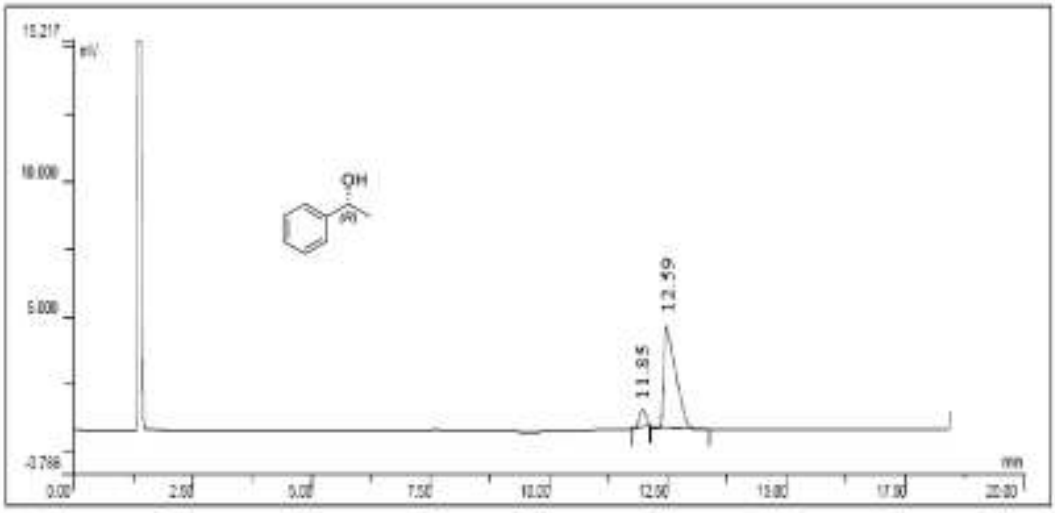

*GC spectra of (R)-1-phenyl ethanol (Table 4, entry 1):*



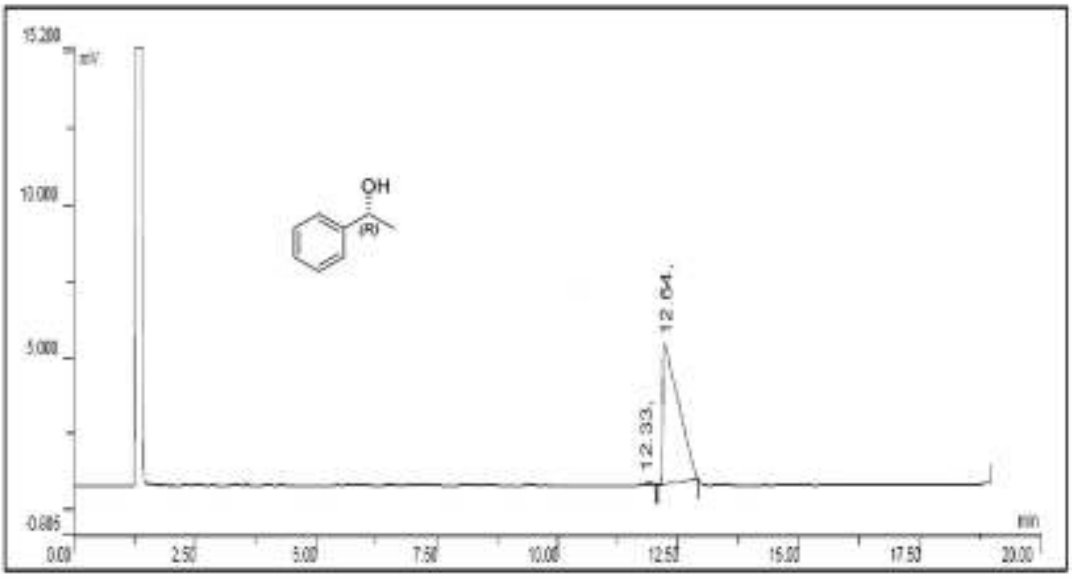
*GC spectra of (R)-1-phenyl ethanol (Table 4, entry 2):*




*GC spectra of (R)-1-phenyl ethanol (Table 4, entry 3):*



*GC spectra of (R)-1-phenyl ethanol (Table 4, entry 4):*



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## Overall Summery & Outlook of Thesis

In the overall summery of thesis entitle "Synthesis of amino acid amide based ionic liquids: Their utilization in asymmetric transfer hydrogenation". Initially in chapter I we started one step synthesis of *N* aryl *R* and *S* amino acid amides from aliphatic natural amino acids and weakly nucleophilic aryl amines. The moderate to excellent yield was obtained. By using this synthetic method we have also synthesized *R* and *S* Tocainide (Active Pharmaceutical Ingredient) from unprotected *D* & *L* alanine and 2,6-dimethyl aniline using dichlorodimethyl silane as simultaneous protecting and activating agent with good to excellent yield. This method can be easily scalable for synthesis of Tocainide. The one step synthetic method used here reduces multi-steps of amidation reaction and minimizes the toxic and hazardous by-products formation.

In second chapter we have successfully synthesized amino acid amide based CILs by protonation of amino acid amide with HCl, $HNO_3$, $H_2SO_4$, and $HClO_4$. Protonation of *N* aryl amino acid amide using $HClO_4$ as protonating agent is not hydroscopic compare to other protonating acids because $HClO_4$ is strong acid and counter anion of $HClO_4$ is weakly nucleophilic and due to this it is not susceptible to hydrolysis of coordinating anion. Therefore, ssing $HClO_4$ as protonating agent we have successfully synthesized *N* aryl *R* and *S* amino acid amide based CILs with excellent yields. This synthetic method of CILs does not epimerize the stereogenic centre of amino acid amide, which was confirmed by CD Spectro-photometer.

In third chapter amino acid amide based CILs are successfully used as stereo-selective organo catalyst in ATH of ketones with excellent yield and excellent enatio-selectivity. This is the first example to use metal free catalyst in ATH of ketones. These CILs of amino acid amide may provide the attractive alternative to conventional asymmetric metal catalyst for ATH of ketones. The catalyst is an easy to recycle and reuse without losing its activity and enantio-selectivity.

## List of Publications and Petants

### Publications:

1. Chiral Amino Acid Amide Based Ionic Liquids as Stereoselective Organocatalyst In Asymmteric Transfer Hydrogenation of Acetophenone at Room Temperature.
   **Balasaheb R Javle**, Anil K. Kinage, *ChemistrySelect* 2018, 3, 2623 – 2625

2. Continuous synthesis of Tocainide and their derivatives using unprotected amino acid **Balasaheb R Javle**, Anil K. Kinage 'Manuscript under communication'

3. One Pot Synthesis of Chiral N-Aryl Amino Acid Amides from Weakly Nucleophilic Aryl Amines and Unprotected Aliphatic Amino Acids
   Balasaheb R Javle and Dr Anil K Kinage 'Manuscript under communication'

4. Synthesis, Antioxidant, Anti-Inflammatory, and Antimicrobial Screening of Newer Thiophene-Fused Arylpyrazolyl 1,3,4-Oxadiazoles.
   Pravin Mahajan, Vrushali Patil, **Balasaheb Javale**, C. H. Gill, *Journal of Phospharous, sulfer and silicon and the related elements*, vol 190, 2015, issue 11, 1803-1813

5. Solvent-free Knoevenagel Condensation over Amino Acid Amide based Ionic Liquid as an Efficient and Eco-friendly catalyst
   Pralhad Burate, **Balasaheb Javle**, Anil K Kinage 'Manuscript under communication'

### Patents:

6. Chiral siliceous composition useful as chiral heterogeneous catalyst and a process for the preparation thereof.
   Anil K Kinage, **Balasaheb Javale**, Pralhad Burate, '**US 2016251287 A1'**

7. Chiral siliceous composition useful as chiral heterogeneous catalyst and a process for the preparation thereof.
   Anil K Kinage, **Balasaheb Javale**, Pralhad Burate, '**WO 2015063800 A2'**

**Erratum**

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