A Facile One-Pot Protocol for the Synthesis of Tetrazolyl Tetrahydroisoquinolines *via* novel Domino Intramolecular Cyclization/Azide-Ugi Sequence

A project report submitted

as a part of requirements for the degree of

MASTER OF SCIENCE

By

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INDIA

APRIL 2014

Declaration

I declare that this written submission represents my ideas in my own words, and where others ideas or words have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

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Approval Sheet

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I wish to express deep gratitude to my parents for their eternal love, support and encouragement.

Last but not the least I wish to thank the almighty for giving me this beautiful life so that I can enjoy his enchanting creation through the path of science.

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Dedicated

to

Bhagawan Sri Satya Sai Baba

Abstract

A facile one pot, four component domino reaction between 2-(2-bromoethyl)benzaldehyde, isocyanide, amine and sodium azide has been developed for the synthesis of novel tetrazolyl tetrahydroisoquinoline derivatives. The domino sequence involves intramolecular replacement of halide by iminium nitrogen followed by azide-ugi reaction. The developed reactions proceeded cleanly in a rapid manner to afford the corresponding tetrazolyl tetrahydroisoquinoline scaffolds with high to excellent yields.

Contents

A Facile One-Pot Protocol for the Synthesis of Tetrazolyl Tetrahydroisoquinolines *via* novel Domino Intramolecular Cyclization/Azide-Ugi Sequence

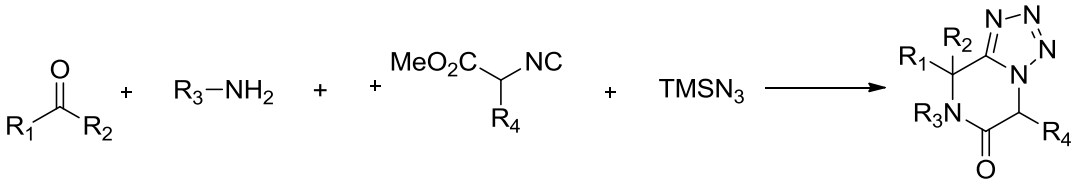
Introduction

The build/couple/pair strategy is particularly attractive for achieving scaffold diversification when ring-closing reactions are coupled with known MCRs.[1] Efficient construction of molecular complexity *via* domino or cascade, multicomponent reactions has recently drawn significant attention in the synthetic community due to its "green" nature. Moreover, improving already known MCRs also is of substantial interest in the domain of organic synthesis.[2] The use of relatively simple starting materials to drastically increase the levels of molecular complexity may be achieved in a single-pot operation by allowing reactive products to continue additional chemical transformations before workup.[1] MCRs allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of steps, work up, extraction and purification and hence minimize waste generation, rendering the transformation green. MCRs also allow considerable savings towards solvent, and waste disposal, as well as time consumed during work-ups and purifications.[1] MCRs play crucial role in diversity-oriented synthesis (DOS) and biology-oriented synthesis (BIOS) for effective synthesis of bio-relevant functional molecular libraries.

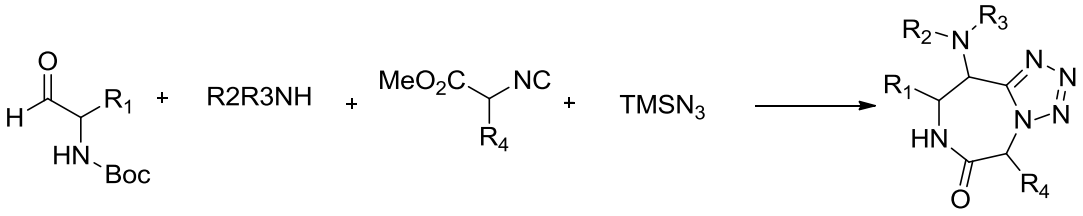
Today the majority of MCR chemistry performed with isocyanides, relates to the classical reactions of Passerini and Ugi. Indeed, the large number of different scaffolds now available mostly builds on these two MCRs and their combination with other types of reactions[3]. Isocyanides are considered as highly "unpleasant" compounds, due to their intensive odour. Unfortunately, this is true for most commercially available isocyanides. However, higher molecular weight isocyanides are often solid and odorless. Moreover, yielding to the common prejudice, only a few isocyanides are commercially available. Isocyanides can be easily prepared in one or two steps from their primary amine precursors.[3] They are highly reactive biphilic one carbon synthons. Till date Ugi MCR is the most versatile multicomponent reaction ever known. While most chemical reactions have their own scope and limitation, whereas the Ugi-4CR can convert almost all combinations of adducts into their products.[5] After the discovery of Ugi reaction various modifications of the same have been developed.[6] However,

the use of components other than carboxylic acids has been very less. One of the reasons why carboxylic acid is plays an important role in this reaction, mechanistically it involves itself in the activation of the imine followed by addition of an isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate to afford the final product by migration of the acyl group onto the nitrogen atom originating from the imine. Therefore, a carboxylic acid is necessary for the reaction of an isocyanide with an imine in the Ugi reaction, i.e., the use of a carboxylic acid limits application of this reaction to the construction of a broad range of molecules.[7,8]

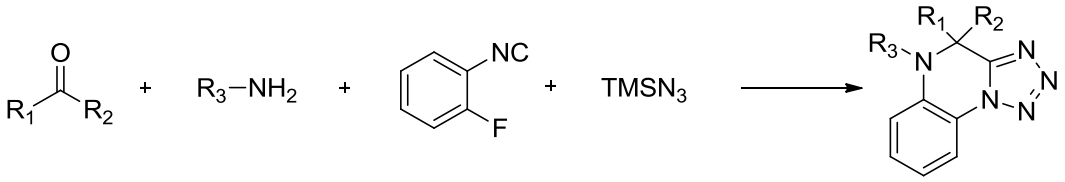
However, after considering these issues, an azide compound was chosen for the isocyanide based multicomponent reaction. Ugi first reported, the reaction of aldehyde with an isocyanide in the presence of hydrazoic acid instead of a carboxylic acid afforded 1*H*-tetrazoles *via* 1, 3-dipolar cycloaddition between a nitrilium intermediate and hydrazoic acid.[7,8] Several methods have been developed for the synthesis of 1, 5-disubstituted tetrazoles.[9] But till date the use of Ugi reaction can be claimed to be the best way to generate 1,5-disubstituted tetrazole moieties.



fused tetrazolo-ketopiperazines[10]



fused azepino-tetrazoles[11]



fused 4,5-dihydrotetrazolo[1,5-a]quinoxalines[12]

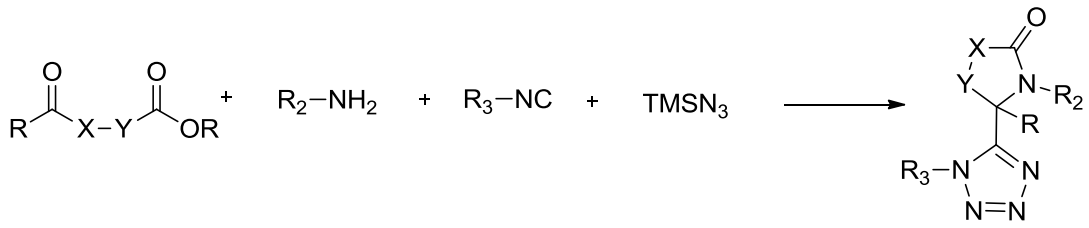


Figure 1: Ugi reactions which have yielded diverse tetrazole based scaffolds[13]

In the context of our MCR chemistry we aimed to construct structurally complex scaffolds by merging compatible reactions in a cascade manner, which may provide great opportunities for the development of novel synthetic routes to natural products and drug candidates with remarkable synthetic efficiency. To the best of our knowledge there are no reports for the synthesis of novel tetrahydroisoquinoline containing tetrazole moiety in one-pot fashion from easily available starting materials.

Biological and pharmaceutical importance

Figure 2: Tetrazole substituted with tetrahydroisoquinoline unit

The chemistry of heterocycles lies at the heart of drug discovery. Many known biological active compound contain heterocyclic core, which are indispensable element for bio-activity.[14] Among all aromatic heterocycles the chemistry of functionalized *N*-heterocycles in particular tetrazoles continues to be of interest because of the industrial and biological importance of these class of compounds. They can also act as a pharmacophore for the carboxylate group, increasing their utility. Tetrazole and its derivatives are used for biological activities such as antifungal, antibacterial, anti-inflammatory antiviral, antitubercolous, cyclooxygenase inhibitor; antinociceptive, hypoglycemic and anticancer activities.[15] Tetrazole analogues are reported to exhibit biological activity toward the cannabinoid-1 receptor (CB1), fatty acid amide hydrolase, melanin-concentrating hormone receptor 1, polo-like kinase 1, and to act as orally effective human growth hormone secretagogues. Cis-amide bonds have been shown to play key roles in protein secondary structures involved in several important biological systems.[15] In studies to

determine effective mimics of the cis-amide bond, the tetrazole ring and more specifically the 1,5-disubstituted tetrazole, has proven to be a valuable.[13]

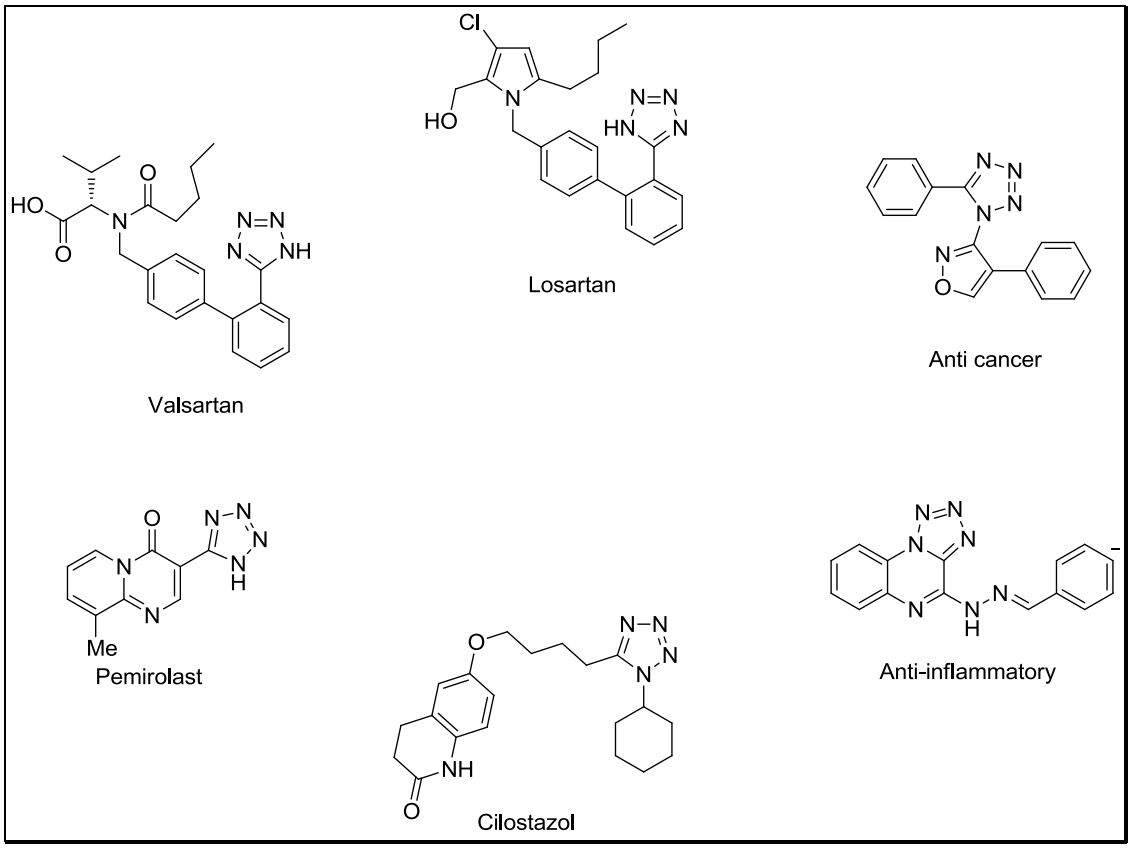


Figure 3: Some pharmaceutically important Tetrazoles[16]

Substituted 1,2,3,4-tetrahydroisoquinolines are substances of both natural and synthetic origin Isoquinoline alkaloids, especially 1,2,3,4-tetrahydroisoquinolines (THIQs), have long attracted significant attention due to their biological activity and also because they are important building blocks in natural product synthesis and drug discovery. In humans these chiral N-heterocyclic scaffolds affect many physiological and pathological processes, hence they have high medicinal value..[17]

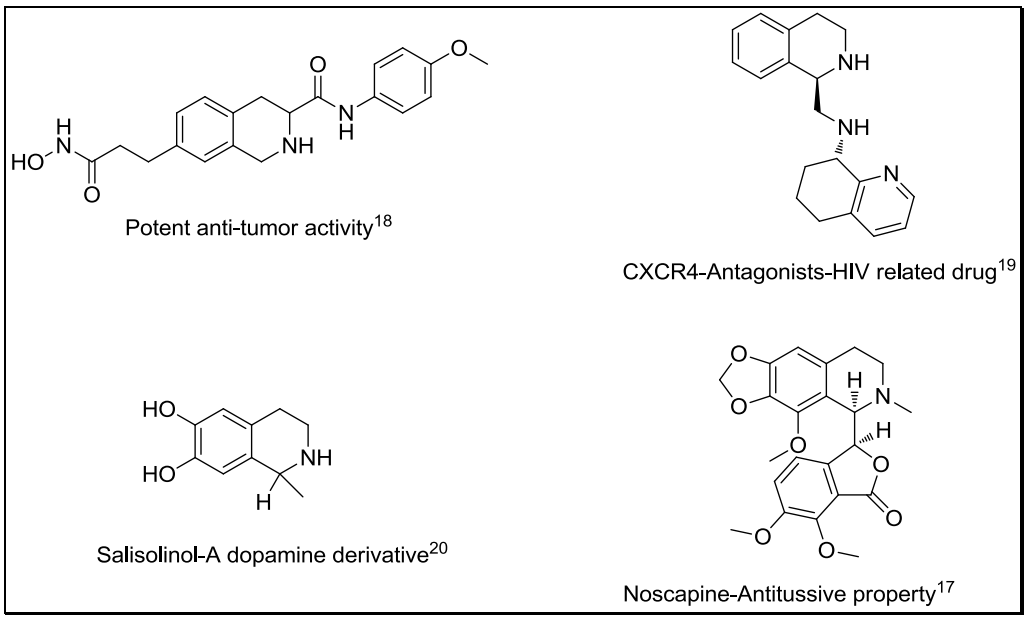


Figure 4: Some pharmaceutically important THIQs

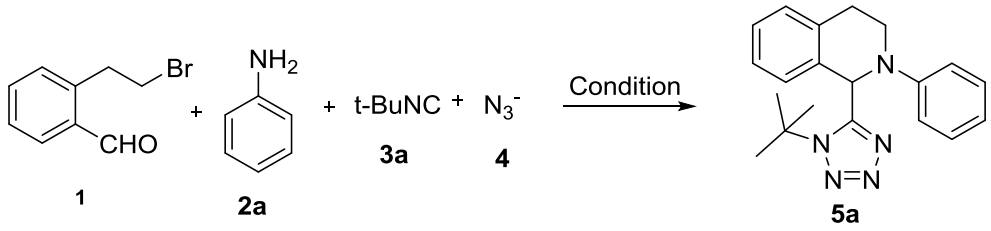
Survey of literature reveals that when one biodynamic heterocyclic system was coupled with another a molecule with enhanced biological activity was produced. The chemistry of these linked biheterocycles has been the fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile.[21] Keeping in view of high potential of 1,2,3,4-tetrahydroisoquinolines and tetrazoles as drug candidates the synthesis of some novel derivatives of tetrazole substituted 1,2,3,4-tetrahydroisoquinolines was undertaken which are expected to be studied later for their medicinal properties.

Results and Discussion

Initially, we have performed the reaction between 2-(2-bromoethyl)benzaldehyde **1**, aniline **2a**, t**-**butylisocyanide **3a** and azidotrimethylsilane **4** in methanol at room temperature, surprisingly, the first attempt provided the expected product (**5a**) in 20% yield (Table 1, entry 1). In order to optimize reaction conditions, we varied the equivalents of the azide component and the isocyanide components and saw only marginal increase in yields (entries 2 and 3). Higher concentration of reaction mixture also failed to improve the yield (entry 4). The attempt of solvent-free condition and heating with microwave/ultrasound was not useful. Surprisingly, by replacing azidotrimethylsilane with cheaper sodium azide drastically improved the yield and

gave the desired product in 86% yield within 10 min (entry 10). By increasing further concentration of reaction mixture, we achieved the higher yield of the product (96%) (entry 11), which also reduced the reaction time to 5 min. The study for optimizing conditions is depicted in Table 1.

Table 1: Optimization of reaction condition[a]



1 2a 3a 4 5a

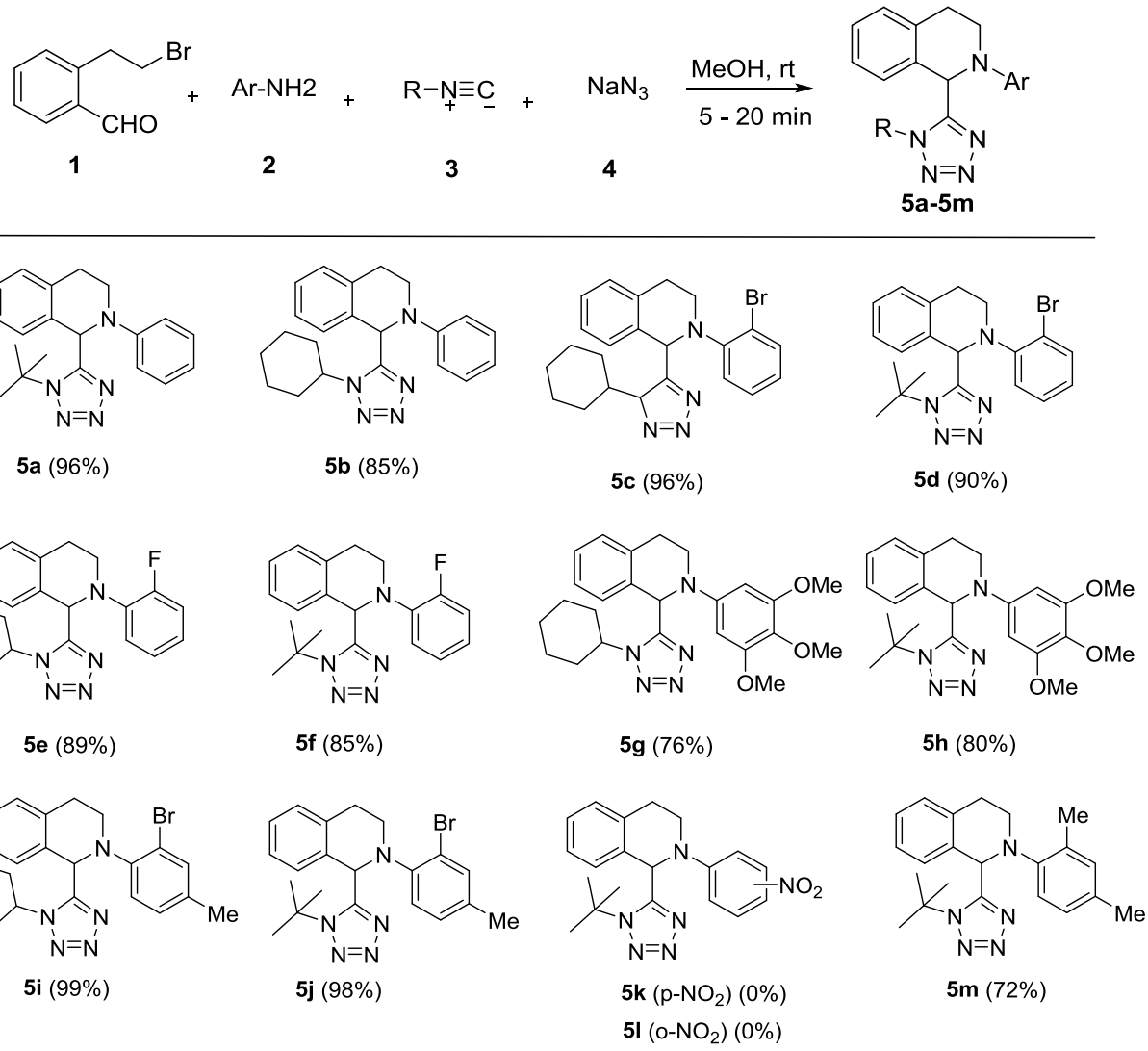
Entry	1a (Equiv.)	2a (Equiv.)	3a (Equiv.)	N^-_3 (Equiv.)	Condition	Time (Min)	Yield(%)[b] (5a)
1	1	1	1	1 ($TMSN_3$)	MeOH (5mL), rt	5	20
2	1	1	1.1	1.1 ($TMSN_3$)	MeOH (5mL), rt	15	25
3	1	1	1.5	1.5 ($TMSN_3$)	MeOH (5mL), rt	15	44
4	1	1	1.5	1.5($TMSN_3$)	MeOH (2mL), rt	15	50
5	1	1	1.5	1.5 ($TMSN_3$)	Neat reaction, rt	15	24
6	1	1	1.5	1.5 ($TMSN_3$)	Microwave, 50 °C (No Solvent)	10	-
7	1	1	1.5	1.5 ($TMSN_3$)	Sonication, rt (solvent-free)	25	32
8	1	1	1.5	1.5 ($TMSN_3$)	MeOH (5mL), 40 °C	25	33
9	1	1	1.5	1.5 ($TMSN_3$)	MeOH (5mL), reflux	30	-
10	1	1	1	1 (NaN_3)	MeOH (5mL)	10	86
11	**1**	**1**	**1**	**1 (NaN_3)**	**MeOH (2mL), rt**	**5**	**96**
12	1	1	1	1(NaN_3)	Neat reaction, rt	20	-

[a] All reactions were performed with 0.23 mmol of the aldehyde **1** as limiting reagent. [b] Isolated yield of chromatographically pure product.

With the optimal condition established, we explored the generality of the reaction by applying the methodology to the strong donating as well as withdrawing aromatic amines **3**, which gave

the corresponding products in high to excellent yield. In case of strong withdrawing nitro-amine, the reaction failed to give the desired product, which can be reasoned that, lack of lone pair availability for intramolecular amination reaction. The reaction proceeded in a facile manner with both *t*-butylisocyanide and cyclohexylisocyanide. The product formation was confirmed by FT-IR, NMR spectral analysis.

Table 2 The scope of the amines and isocyanides[a,b]



[a] All reactions were performed with 0.23 mmol of the aldehyde as limiting reagent. [b] Isolated yield of chromatographically pure product.

After successful accomplishment of this method we turned to the illustration of the reaction mechanism (Figure 5). Initially the aldehyde **1** and amine **2** react to give an imine **A** followed by intramolecular nucleophilic substitution with elimination of Br^- to form Mannich base **B** (isolated and characterised)**.** The electrophilic Mannich base **B** is then attacked by the isocyanide **3** to form intermediate **C,** which on neutralisation by the azide anion and further cycloaddition[7] can give product **5**.

In order to prove the proposed mechanism, we have did controlled experiment without adding isocyanide and sodium azide, which gave intermediate **B**, which on further treatment with isocyanide **3** and sodium azide **4** gave product in excellent yield, supports the proposed plausible mechanism.

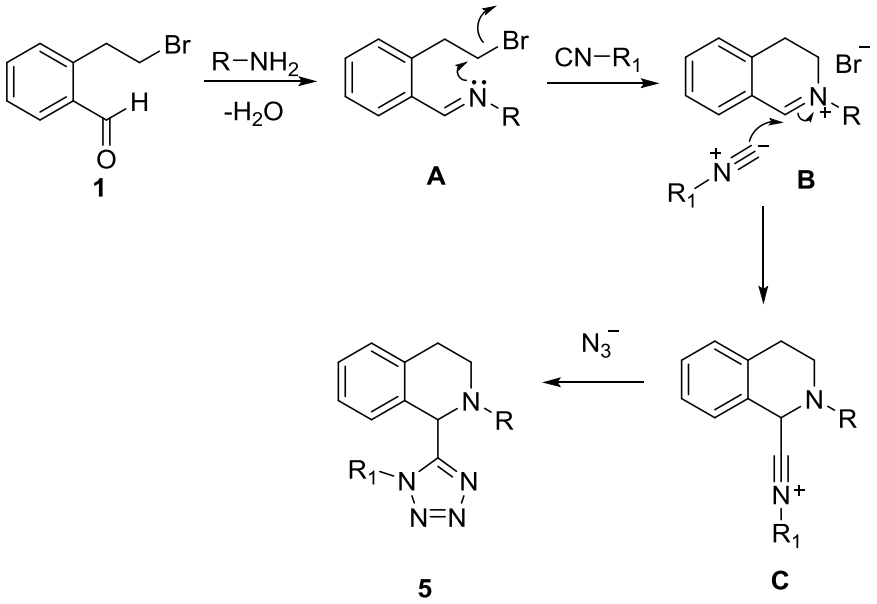


Figure 5: Plausible reaction mechanism.

Conclusion

In summary a very simple and efficient four component reaction for the synthesis of tetrazolo substituted tetrahydroisoquinoline has been achieved *via* intramolecular cyclization/azide-Ugi sequence. Present methodology shows wide substrate scope with high to excellent yield. The salient features of this method is excellent yields, short reaction time, cleaner reaction profile, high bond forming index (BFI), and the use of inexpensive and readily available starting material. We believe that, this method could be very useful for biology-oriented combinatorial synthesis (BIOS).

Experimental section

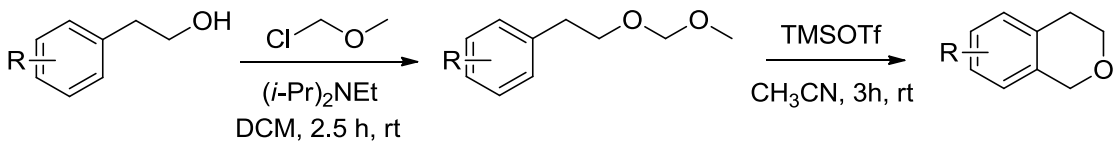
General information

In this section the preparations of all the compounds that have been made in the course of thesynthesis of tetrazolyl tetrahydroisoquinolines have been discussed. For the experiments, all starting material and reagents are purchased from standard commercial sources or were prepared in the laboratory. All the glasswares were cleaned with soap water followed by acetone and dried in hot air oven at 100 ˚C for 2h. Solvents were distilled prior to use; petroleum ether with a boiling point range 40-60 ˚C was used.

IR spectra were recorded on the Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295K in $CDCl_3$; chemical shifts value (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either tetramethylsilane (TMS) (δ-H = 0.00 ppm) or $CHCl_3$ (δ-H = 7.26ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at 298K in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [(δ-C=77.00ppm) central line of triplet]. In ^{13}C NMR the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT- 135 spectra. In ^{1}H NMR, the following abbreviations were used throughout the thesis; s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br.s = broad singlet. The assignment of the signals was confirmed by ^{1}H, ^{13}C and DEPT spectra. Reactions were monitored by TLC on silica gel (254 mesh) using a combination of petroleum ether and ethyl acetate as eluents.

Preparation of starting material

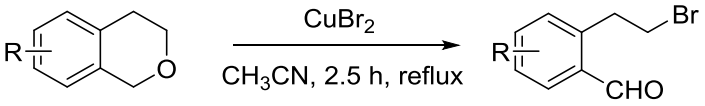
1) General Procedure for preparation of isochromans.[22]



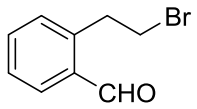
A mixture of the substituted phenylethyl alcohol (4.97 mmol), chloromethyl methyl ether (7.046 mmol) and N,N-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 ml) was stirred under nitrogen atmosphere for 2.5 h at rt. The reaction mixture was then washed with water, dried (Na_2SO_4) and the solvent was removed in vaccuo. The crude MOM acetal was dissolved in dried acetonitrile and added to cooled (0 ^{o}C) solution of trimethylsilyl

trifluoromethanesulfonate (TMSOTf). The reaction was carried out under nitrogen atmosphere for 3h. Then the mixture was quenched by the addition of l M $NaHCO_3$. The organic phase was washed with brine, dried with sodium sulphate and evaporated under reduced pressure. Purification by column chromatography afforded corresponding substituted isochromans.

2) General procedure for the preparation of benzaldehydes: [22]



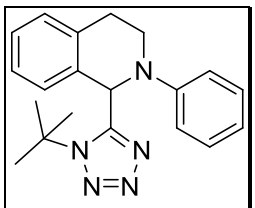
To a solution of the substituted isochroman (7.46 mmol) derivatives in acetonitrile (15 ml), $CuBr_2$ (8.95 mmol) was added under nitrogen atmosphere. The solution was refluxed for about 2hr and then cooled to room temperature. The reaction mixture was added water, extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with Na_2SO_4, filtered and concentrated and then purified by silica gel column chromatography to afford the product.



1 (68%)

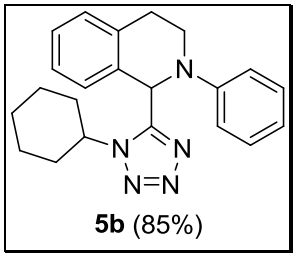
Representative experimental procedure for the synthesis of 1-(1-tert-butyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-phenylisoquinoline 5a : 2-(2-bromoethyl)benzaldehyde **1a** (50 mg, 0.232 mmol) and **2a** aniline (21.6 mg, 0.232 mmol) were taken in an 5 mL round bottom flask and then stirred for 2 min to form the solid mannich base, then 2 mL of methanol was added to dissolve the solid. Then sodium azide (15.11 mg, 0.232 mmol) and t-butyl isocyanide **3a** (19 mg, 0.232 mmol) were added in succession to the reaction mixture and monitored the completion reaction by TLC. After completion of the reaction, the methanol solvent was completely evaporated under reduced pressure. Then the reaction mixture was extracted with ethyl acetate (2 X 20 ml). The extracted layer was washed with brine solution and allowed to dry over Na_2SO_4. The crude extract was purified by filtration through a silica gel (100-200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **5a** as a white solid (74.3 mg, 96% yield).

Spectral data



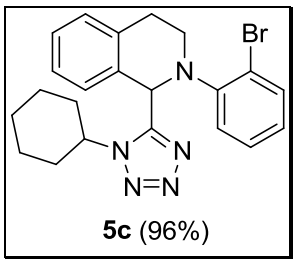
5a (96%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-phenylisoquinoline (5a) : white solid; mp 260-262 °C; 74.3 mg; 96% yield; IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3062, 2978, 2925, 2154, 1494, 758, 740, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 1.71 (s, 9H), 2.61 - 2.70 (m, 1H), 2.83 (ddd, *J* = 17.1, 11.0 and 6.6 Hz, 1H), 3.52 - 3.72 (m, 2H), 6.15 (s, 1H), 6.92 - 7.01 (m, 3 H), 7.01 - 7.08 (m, 1H), 7.15 (d, *J* = 6.8 Hz, 1H), 7.18 - 7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.5, 29.8, 45.4,53.8, 62.2, 76.7, 77.0, 77.4, 119.8, 121.8, 126.4, 127.7, 127.8, 128.1, 129.1, 129.5, 129.7, 132.3, 135.3, 149.0, 155.4.



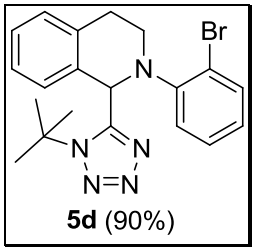
5b (85%)

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-phenylisoquinoline (5b) : white solid; mp 174-176 ºC; 70.8 mg; 85% yield; IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3061, 3026, 2934, 2858, 1597, 1495, 750, 733, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm = 0.85 - 1.04 (m, 3H), 1.12 - 1.35 (m, 3H), 1.53 - 1.77 (m, 5H), 1.82 - 1.93 (m, 2H), 3.02 (dt, *J* = 16.5 and 4.9 Hz, 1H), 3.20 (ddd, *J* = 16.1, 7.8 and 4.9 Hz, 1H), 3.45 (ddd, *J* = 12.6, 7.9 and 4.4 Hz, 1H), 3.68 - 3.77 (m, 1H), 4.41 (tt, *J* = 11.74 and 3.9 Hz, 1H), 6.22 (s, 1H), 6.88 - 6.98 (m, 2H), 7.05 - 7.10 (m, 2H), 7.11 - 7.18 (m, 1H), 7.21 - 7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 14.4, 22.2, 25.0, 25.0, 25.9, 29.2, 31.9, 32.6, 32.9, 49.4, 55.2, 58.5, 77.3, 77.6, 120.7, 123.0, 126.9, 127.9, 128.0, 129.5, 129.6, 132.5, 134.9, 149.61, 154.8.



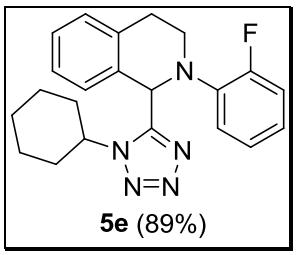
5c (96%)

2-(2-Bromophenyl)-1-(5-cyclohexyl-5H-1,2,3-triazol-4-yl)-1,2,3,4-tetrahydroisoquinoline (5c) : white solid; mp 224-226 ºC; 97.4 mg; 96% yield; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3060,2934, 2857,1452, 1027, 812, 793, 733, 702, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.51 - 0.60 (m, 1H), 0.79 - 0.96 (m, 1H), 1.05 - 1.18 (m, 1H), 1.20 - 1.47 (m, 2H), 1.49 - 1.64 (m, 2H), 1.67 - 1.77 (m, 1H), 1.78 - 1.92 (m, 2H), 2.97 (dt, *J* = 16.1 and 3.2 Hz, 1H), 3.08 (ddd, *J* = 12.2, 10.3 and 3.4 Hz, 1H), 3.55 (ddd, *J* = 15.8, 10.4 and 5.1 Hz, 1H), 3.75 - 3.88 (m, 1H), 4.53 (tt, *J* = 11.7 and 3.7 Hz, 1H), 6.43 (s, 1H) 6.74 (d, *J* = 8.3 Hz, 1H), 6.91 (td, *J* = 7.7 and 1.7 Hz, 1H), 7.06 - 7.14 (m, 2H), 7.19 - 7.26 (m, 1H), 7.29 (s, 1H) 7.36 (d, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 7.8 and 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.8, 25.4, 25.5, 29.6 ,32.1, 32.4, 51.0, 54.9, 57.9, 76.8, 77.1, 77.4, 120.7,123.2, 125.9, 126.54, 127.7, 128.4, 129.3, 132.5,133.9, 134.6, 146.8, 153.8.



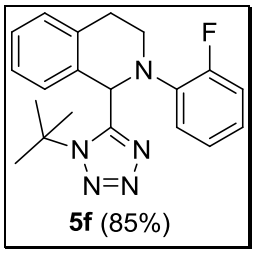
5d (90%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-2-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinoline (5d) : pale yellow solid; mp 200-202 °C; 85.1 mg; 90% yield; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3062, 2982, 2939, 2831, 1474, 758, 738, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.64 (br s., 9H), 2.81 - 2.91 (m, 2H), 3.50 (br. s, 1H), 3.91 (br s, 1H), 6.03 (br. s, 1H), 6.96 (t, *J* = 7.6 Hz, 3H), 7.10 - 7.19 (m, 3H), 7.21 - 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.7, 55.1, 62.3, 76.7, 77.3, 116.3, 116.5, 122.4, 124.4, 124.4, 124.6, 126.5, 127.3, 127.8, 129.7, 132.6, 135.1, 137.1, 137.2, 155.0.



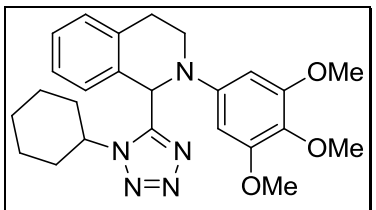
5e (89%)

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (5e) : Pale yellow solid; mp 230–232 ºC; 79.9 mg; 89% yield; IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3065, 2935, 2858, 1500, 749, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 0.69 (d, *J* = 12.7 Hz, 1H), 0.76 - 0.94 (m, 1H), 1.07 (qt, *J* = 12.8 and 3.0 Hz, 1H), 1.16 - 1.32 (m, 3H), 1.32 - 1.45 (m, 2H), 1.50 - 1.61 (m, 1H), 1.67 - 1.82 (m, 2H), 2.90 (dt, *J* = 16.0 and 3.5 Hz, 1H), 3.14 - 3.33 (m, 1H), 3.61 (dt, *J* = 11.6 and 4.5 Hz, 1H), 4.45 (tt, *J* = 11.7 and 3.7 Hz, 1H), 6.24 (s, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.87 - 6.93 (m, 3H), 6.93 - 6.98 (m, 1H), 7.02 - 7.07 (m, 1H), 7.08 - 7.15 (m, 1H), 7.15 - 7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 24.8, 25.4, 29.3, 32.1, 32.5, 49.5, 54.5, 58.1, 76.7, 77.3, 116.0, 116.2, 122.6, 124.5, 124.9, 125.0, 126.6, 127.4, 127.6, 129.2, 132.2, 134.3, 136.7, 136.8, 153.9, 155.6, 158.1.



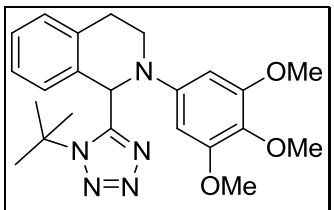
5f (85%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-2-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (5f) : Pale yellow solid; mp 222-224 °C; 69.3 mg; 85% yield; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3063, 2983, 2939, 1499, 1228, 753, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 1.66 (s, 9H), 2.69 - 2.90 (m, 2H), 3.34 - 3.54 (m, 1H), 3.54 - 3.76 (m, 1H), 6.05 (br. s, 1H), 6.85 - 7.10 (m, 4H), 7.17 - 7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 29.7, 55.1, 62.3, 76.7, 77.3, 116.3, 116.5, 122.4, 124.4, 124.4, 124.6, 126.5, 127.3, 127.8, 129.7, 132.6, 135.1, 137.1, 137.2, 155.0.



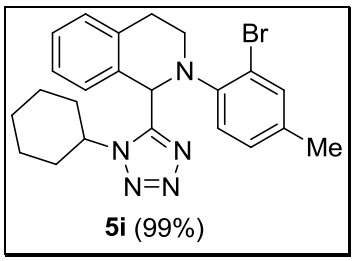
5g (76%)

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-(3,4,5 trimethoxyphenyl)isoquinoline (5g) : Yellow solid; mp 150-152 ºC, 79.2 mg; 76% yield, IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 2934, 2857, 1586, 1507, 1451, 1236, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.81 - 1.06 (m, 2H), 1.12 - 1.39 (m, 2H), 1.51 - 1.77 (m, 3H), 1.79 - 1.96 (m, 3H), 1.99 - 2.20 (m, 2H), 3.00 - 3.15 (m, 1H), 3.24 - 3.43 (m, 2H), 3.75 - 3.96 (m, 9H), 4.44 (tt, *J* = 11.7 and 3.7 Hz, 1H), 6.16 (s, 1H), 6.28 (s, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.01 - 7.18 (m, 2H), 7.22 - 7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 14.1, 20.2, 24.7, 25.3, 25.3, 29.5, 32.0, 32.3, 51.1, 54.9 , 57.7, 60.3, 76.7, 77.3, 120.3, 122.6, 126.3, 127.2, 127.5, 128.8, 129.2, 132.5, 134.1, 134.5, 135.9, 144.0, 153.7.



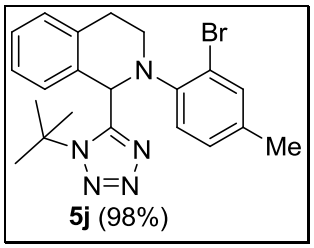
5h (80%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-(3,4,5-trimethoxyphenyl)isoquinoline (5h) : White solid; mp 218-220 ºC; 78.5 mg; 80% yield, IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3059, 2980, 2931, 1493, 758, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 1.26 (d, *J* = 2.45 Hz, 9H), 2.26 (s, 9H), 3.32 (t, *J* = 5.38 Hz, 1H), 4.74 (br. s, 1H), 5.43 (s, 1H), 7.35 - 7.42 (m, 1H), 7.75 - 7.91 (m, 1H), 8.19 (d, *J* = 9.29 Hz, 1H), 8.61 (d, *J* = 2.45 Hz, 2H), 9.31 (d, *J* = 7.34 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): ppm = 24.8, 31.0, 40.3, 47.2, 49.8, 56.4, 61.8, 124.3, 128.3, 130.5, 133.3, 134.1, 136.8, 138.7, 140.3, 149.3, 152.2, 158.1, 168.8, 171.3, 175.8, 180.2.



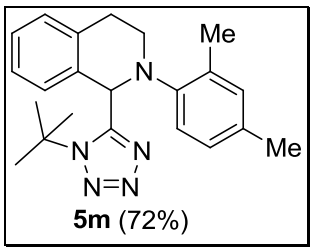
5i (99%)

2-(2-Bromo-4-methylphenyl)-1-(1-cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-isoquinoline (5i) : White solid; mp 180-182 °C, 103.9 mg; 99% yield, IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 3028, 2933, 2857, 1491, 1451, 745, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.56 (d, *J* = 12.2 Hz, 1H), 0.81 - 0.93 (m, 1H), 1.06 - 1.18 (m, 1H), 1.23 - 1.44 (m, 2H), 1.49 - 1.62 (m, 2H), 1.70 - 1.77 (m, 3H), 1.78 - 1.91 (m, 2H), 2.04 (m, 3H), 2.21 (s, 3 H), 2.91 - 3.08 (m, 2H), 3.54 (ddd, *J* = 15.77, 10.39 and 4.65 Hz, 1H), 3.72 - 3.78 (m, 1H), 4.50 - 4.60 (m, 1H), 6.39 (s, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.99 (dd, *J* = 8.5 and 1.7 Hz, 1H), 7.09 (t, *J* = 7.34 Hz, 1H), 7.19 - 7.25 (m, 2H), 7.28 (s, 1H), 7.36 (d, *J* = 1Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 14.1, 20.2, 24.7, 25.3, 25.3, 29.5, 32.0, 32.3, 51.1, 54.9, 57.7, 60.7, 76.7, 77.3, 120.3, 122.6, 126.4, 127.2, 127.5, 128.8, 129.2, 132.5, 134.1, 134.5, 135.9, 144.1, 153.7.



5j (98%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-2-(2-bromo-4-methylphenyl)-1,2,3,4-tetrahydro-isoquinoline (5j) : Pale brown solid, 96.9 mg; mp 260-262 ºC; 98% yield; IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 2980, 2924, 1491, 1239, 772, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.66 (br. s, 9H), 2.25 (s, 3H), 2.74 (br. s, 1H), 2.78 - 2.91 (m, 1H), 3.45 (br. s, 1H), 3.86 (br. s, 1H), 5.98 (br. s, 1H), 6.70 (br. s, 1H), 6.92 (d, *J* = 7.3 Hz, 2H), 7.12 - 7.25 (m, 2H), 7.27 (br. s, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 20.2, 30.2, 43.1, 55.4, 76.7, 77.3, 120.5, 123.8, 126.3, 126.8, 127.5, 129.0, 134.3, 135.8, 145.2, 154.9.



5m (72%)

1-(1-Tert-butyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-2-(2,4-dimethylphenyl)isoquinoline (5m) : White solid; mp 196-198 °C; 60.4 mg; 72% yield; IR (MIR-ATR, 4000-600 cm^{-1}): ν_{max} = 2298, 2938, 1500, 1374, 1208, 1110, 942, 816, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 1.54 (br. s, 9H), 2.14 (s, 3H), 2.17 (s, 3H) 2.65 - 2.81(m, 1H), 3.02 (m, 1H), 2.99 (m, 1H), 3.80 (br. s, 1H), 5.87 (br. s, 1H), 6.57 (br. s, 1H), 6.73 (d, *J* = 7.8 Hz, 2H) 6.93 (s, 1H), 7.05 - 7.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 17.7, 20.7, 30.1, 47.6, 55.7, 76.7, 77.3, 126.2, 126.7, 127.2, 127.4, 128.50, 129.7, 132.0, 133.8, 133.9, 135.8, 136.3, 138.7, 145.9.

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Spectra

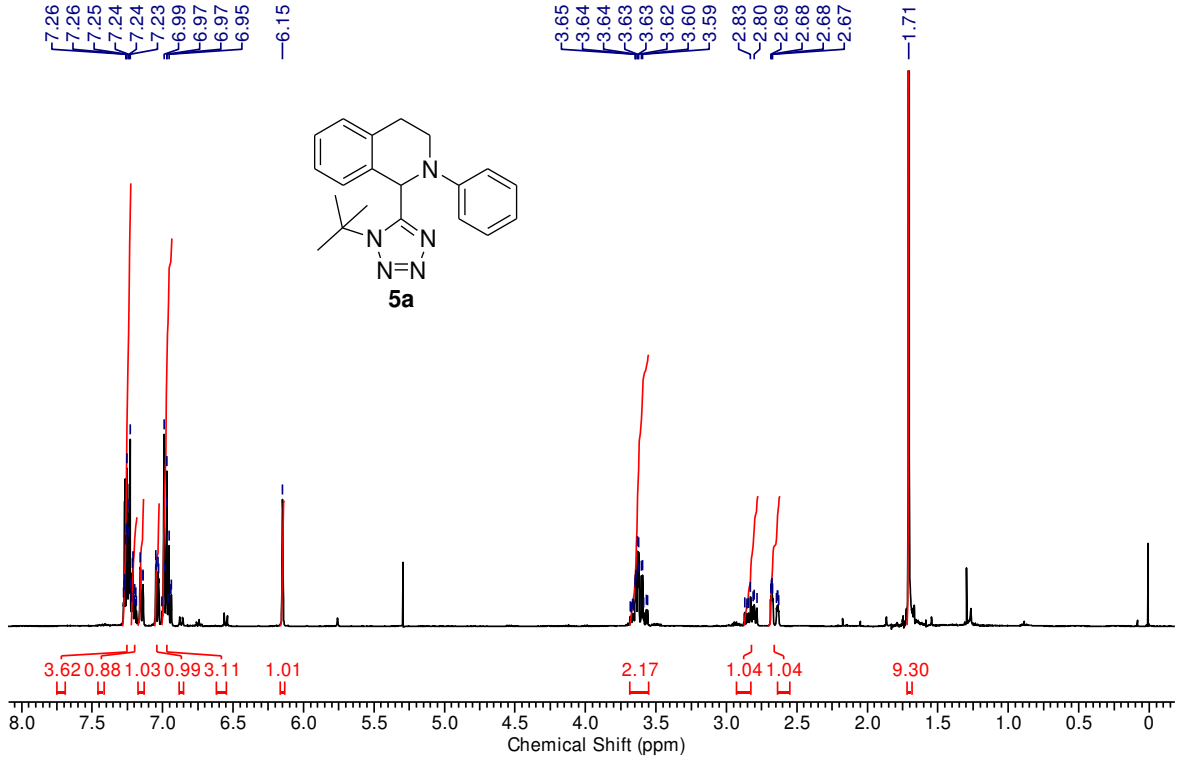

Figure 6. ^{1}H NMR (400 MHz) spectrum of compound **5a** in $CDCl_3$.

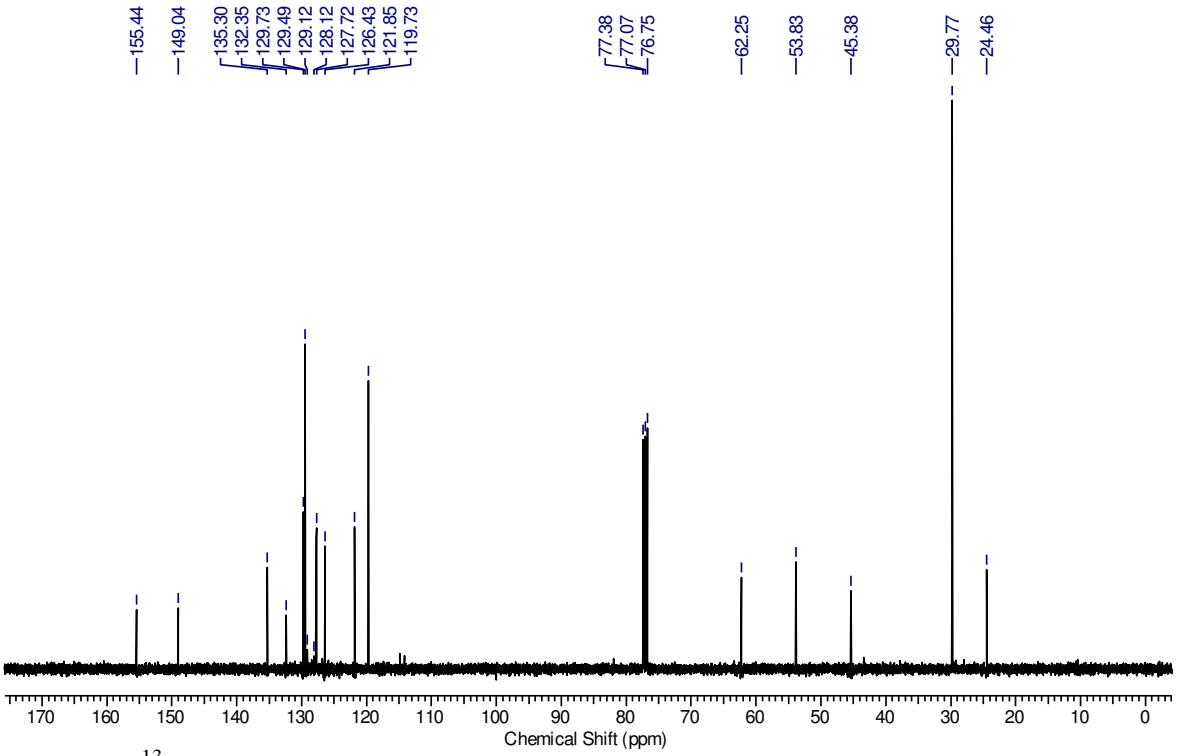

Figure 7. ^{13}C NMR (400 MHz) spectrum of compound **5a** in $CDCl_3$.

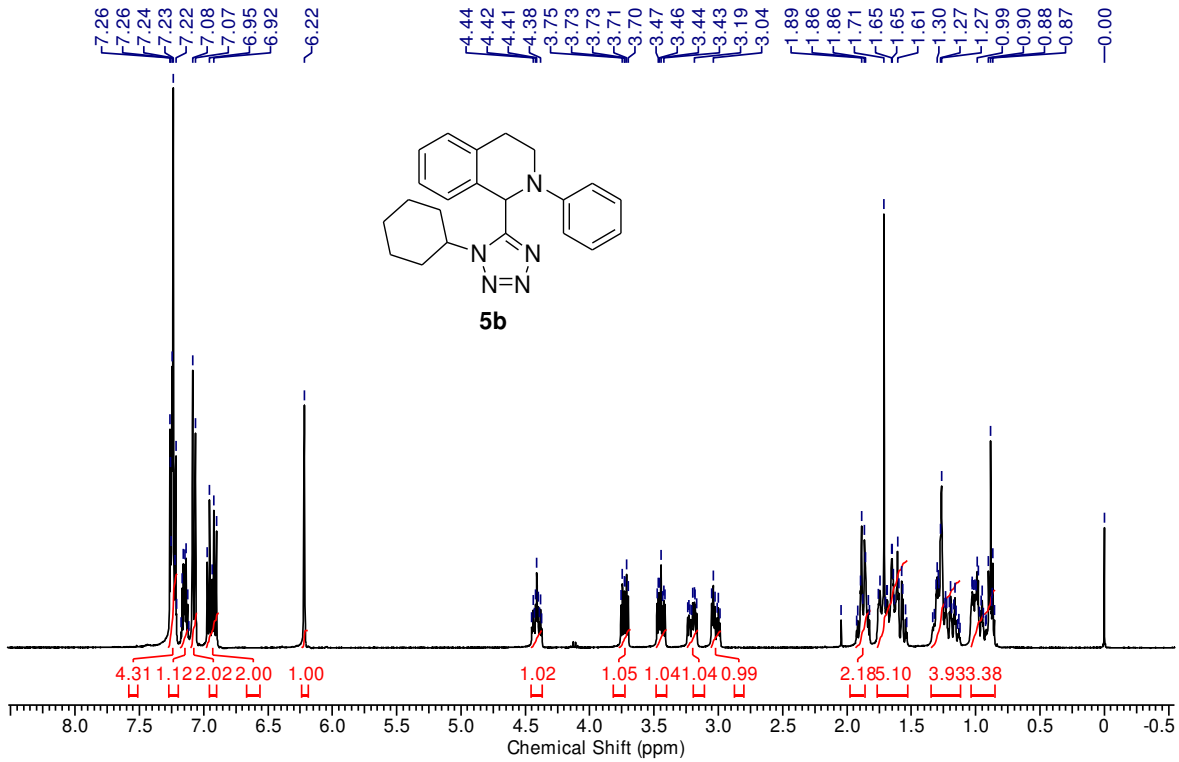

Figure 8. ^{1}H NMR (400 MHz) spectrum of compound **5b** in $CDCl_3$.

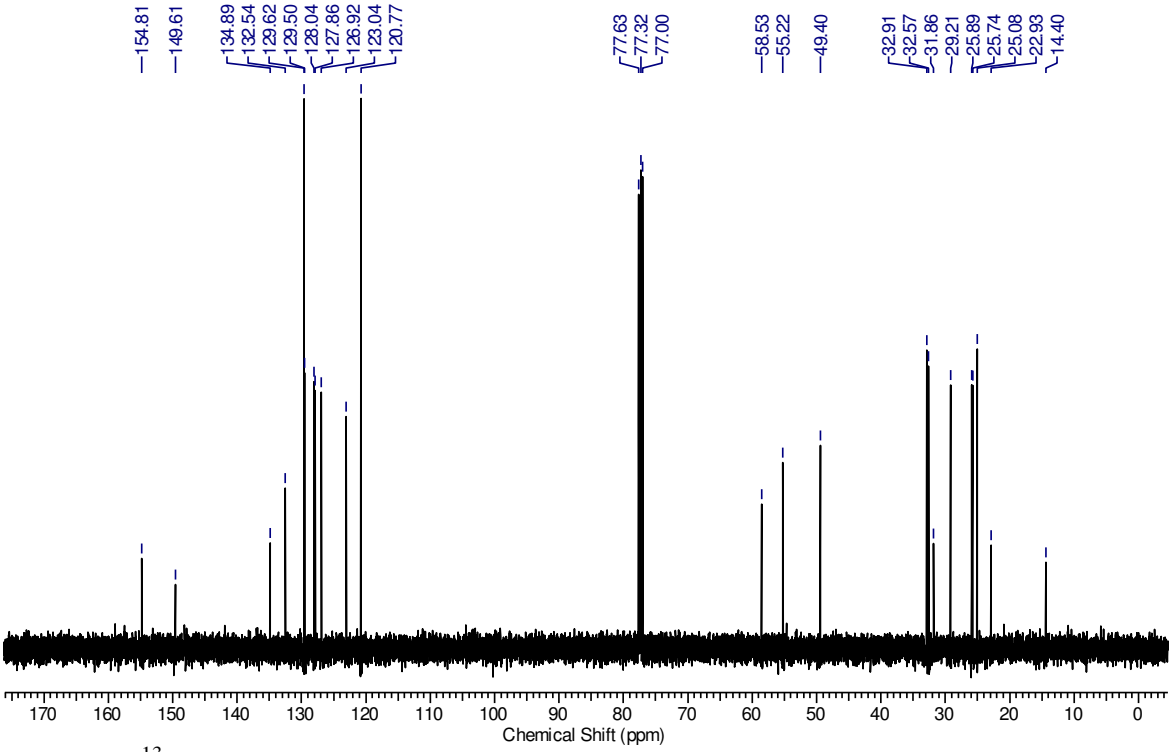

Figure 9. ^{13}C NMR (100 MHz) spectrum of compound **5b** in $CDCl_3$

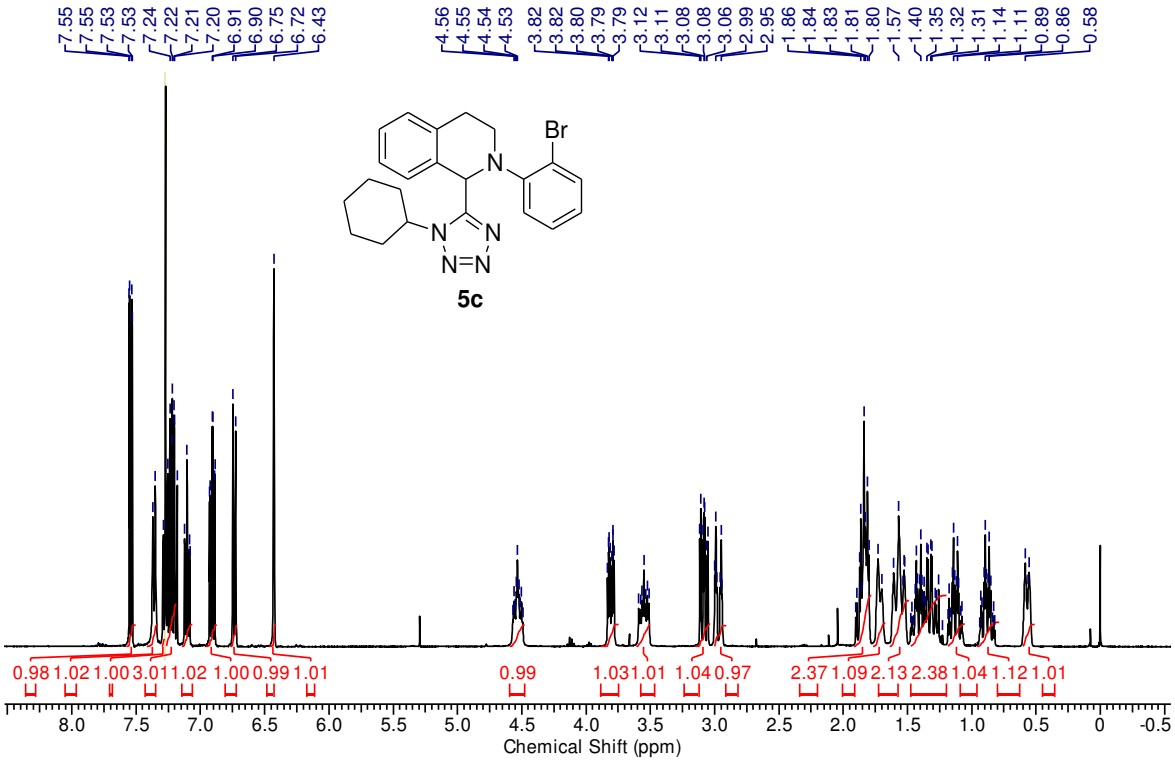

Figure 10. ^{1}H NMR (400 MHz) spectrum of compound **5c** in $CDCl_3$.

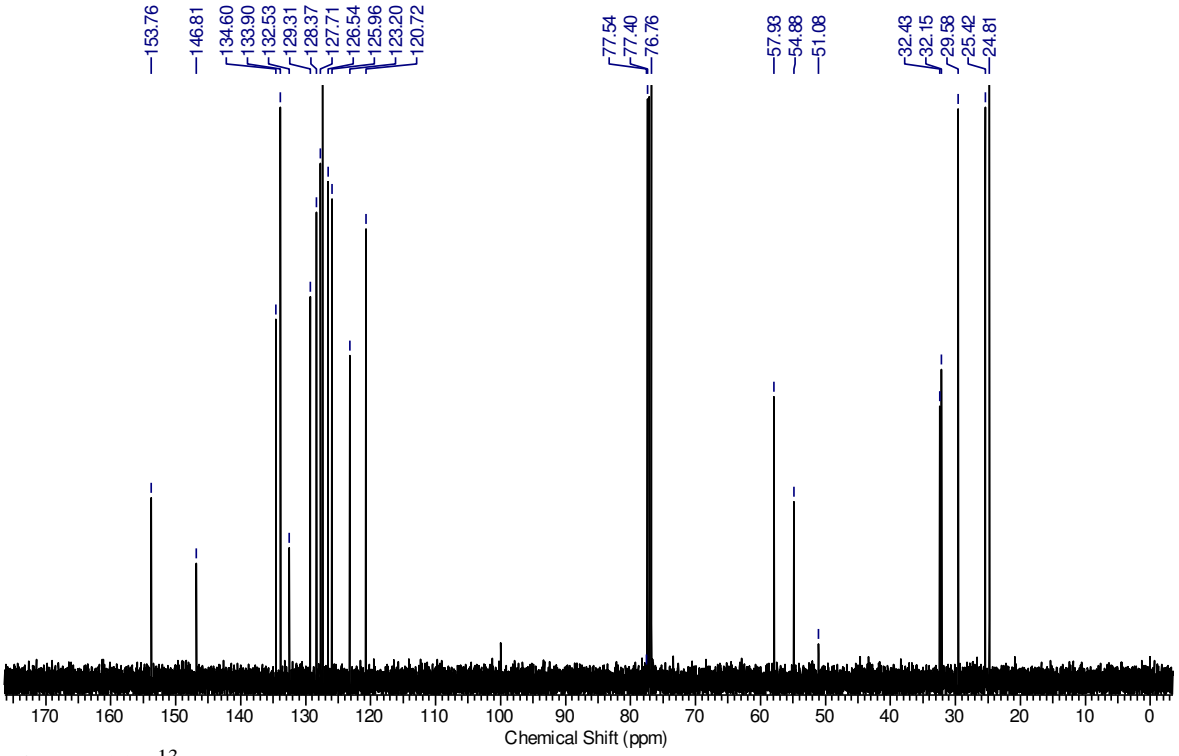

Figure 11. ^{13}C NMR (100MHz) spectrum of compound **5c** in $CDCl_3$.

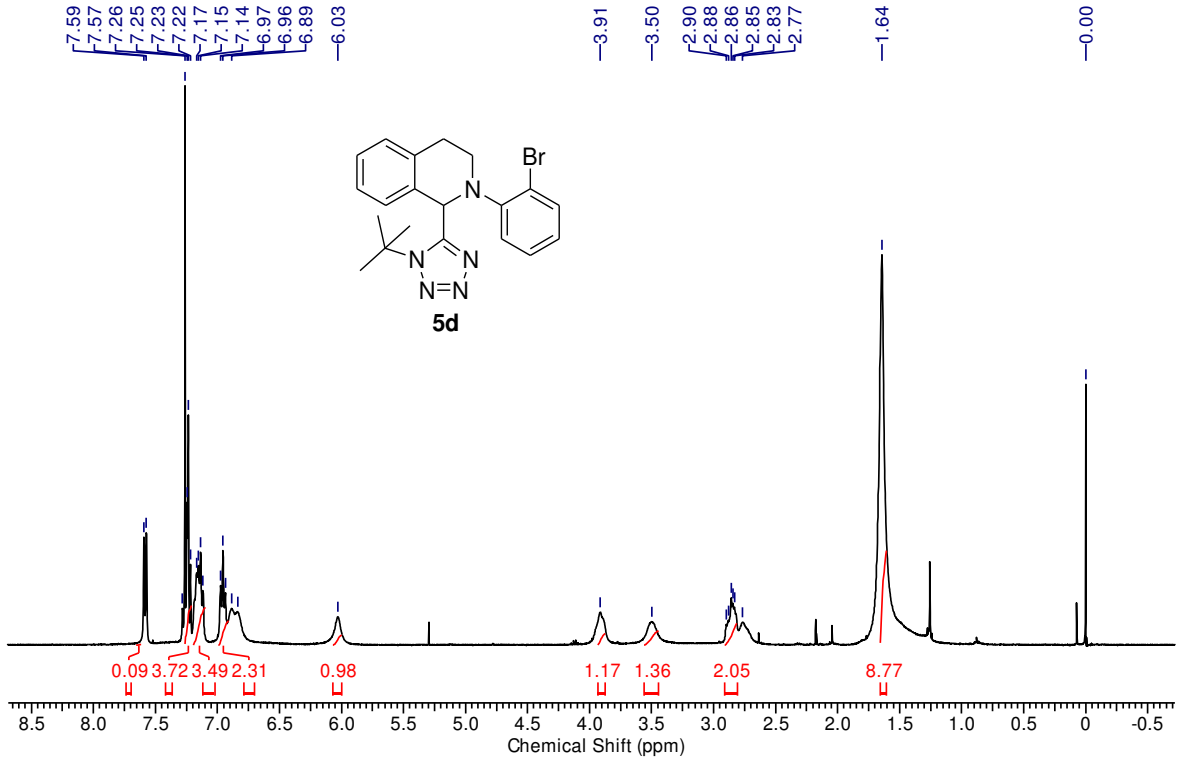

Figure 12. ^{1}H NMR (400 MHz) spectrum of compound **5d** in $CDCl_3$.

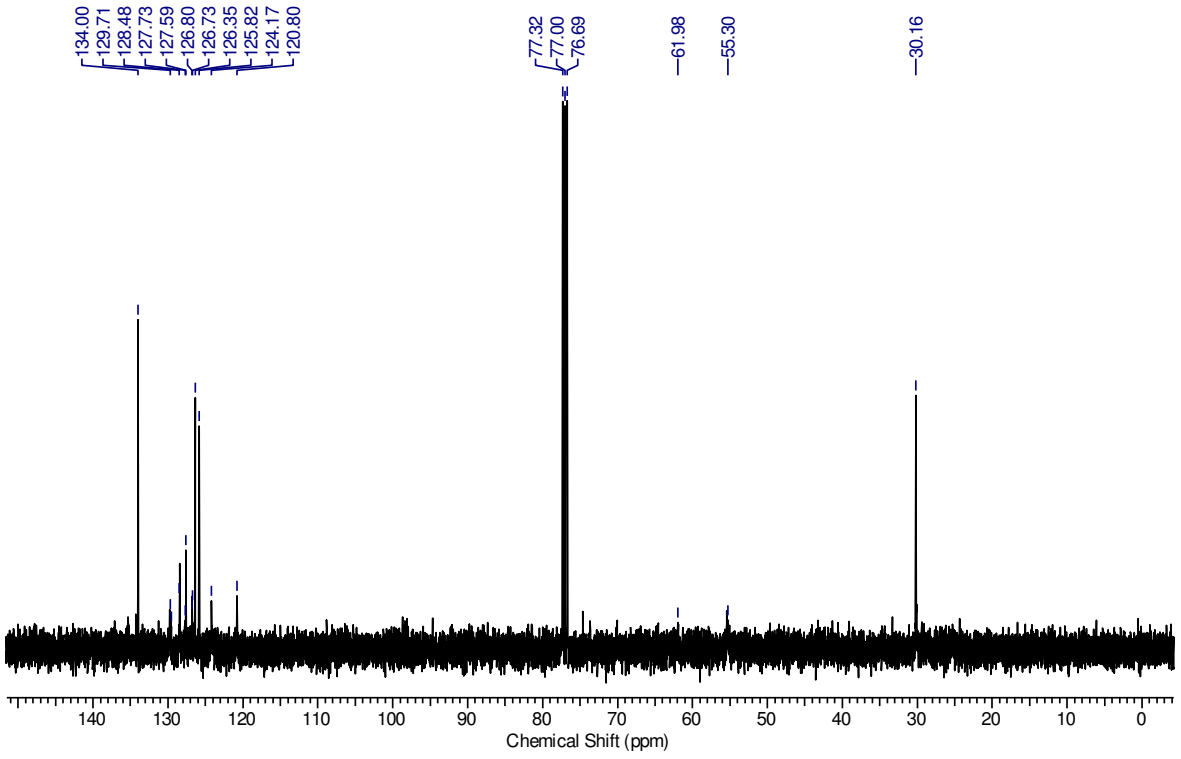

Figure 13. ^{13}C NMR (100 MHz) spectrum of compound **5d** in $CDCl_3$

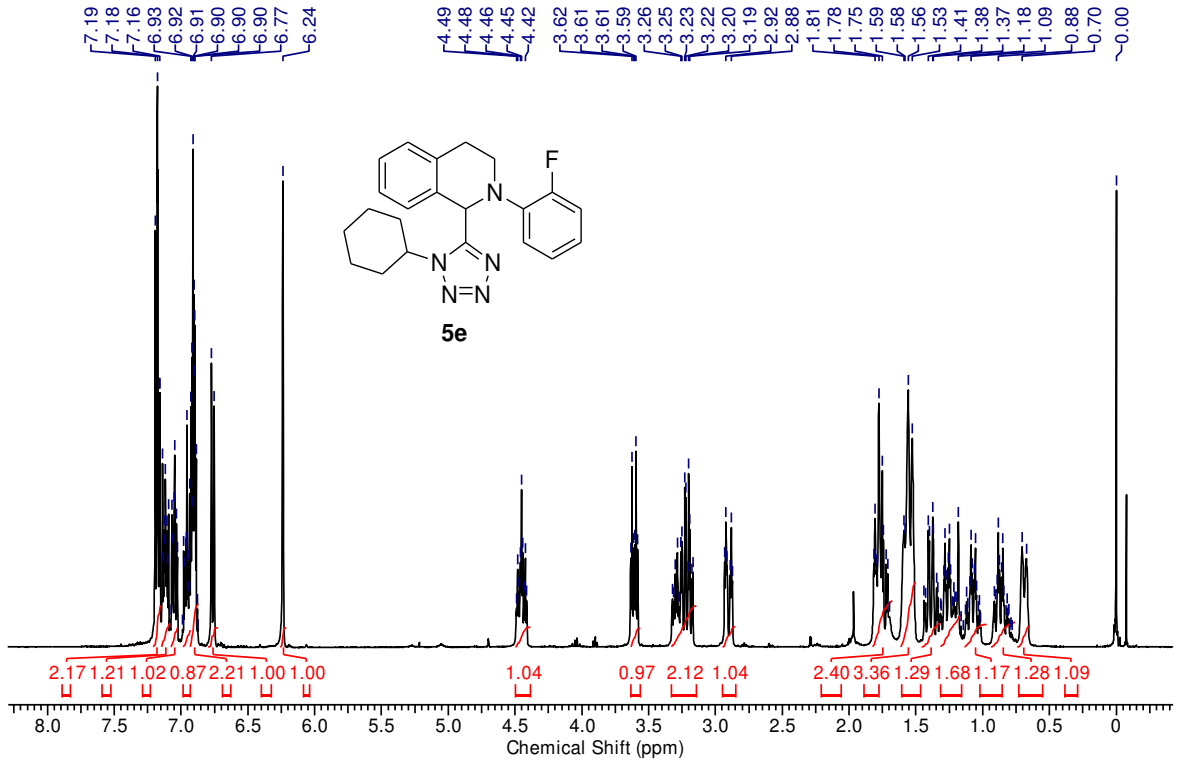

Figure 14. ^{1}H NMR (400 MHz) spectrum of compound **5e** in $CDCl_3$.

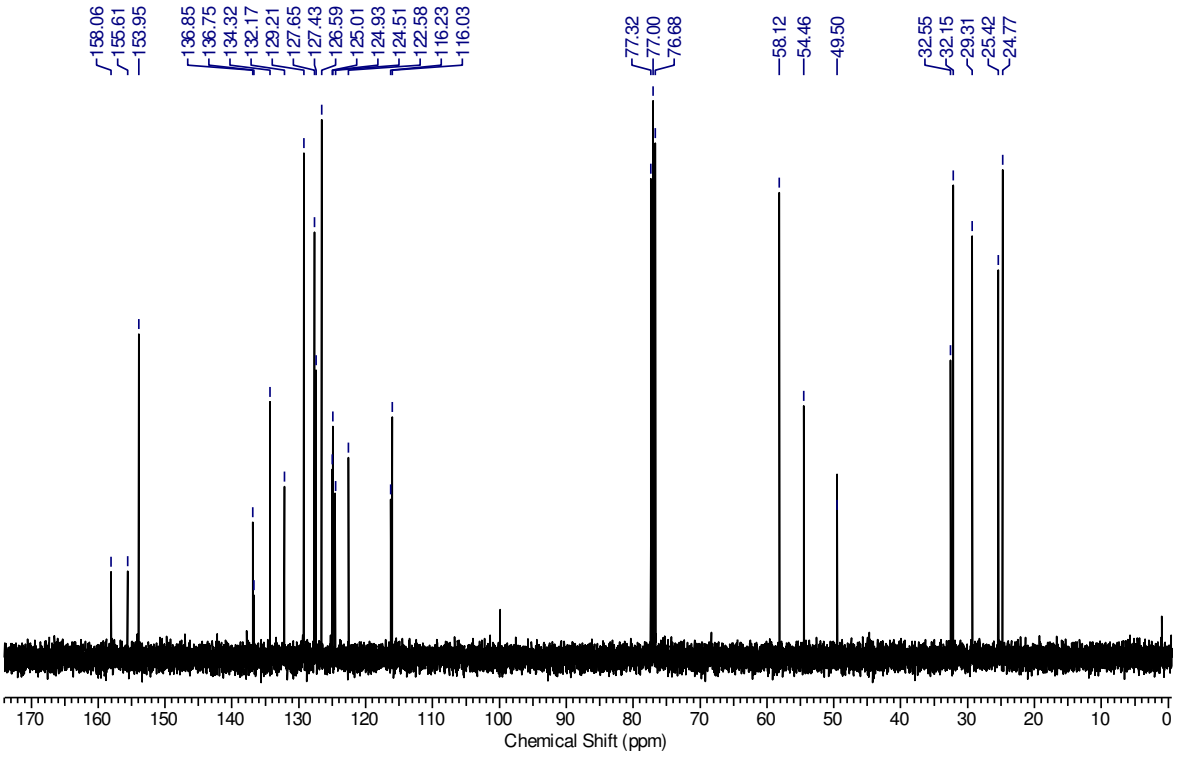

Figure 15. ^{13}C NMR (100 MHz) spectrum of compound **5e** in $CDCl_3$.

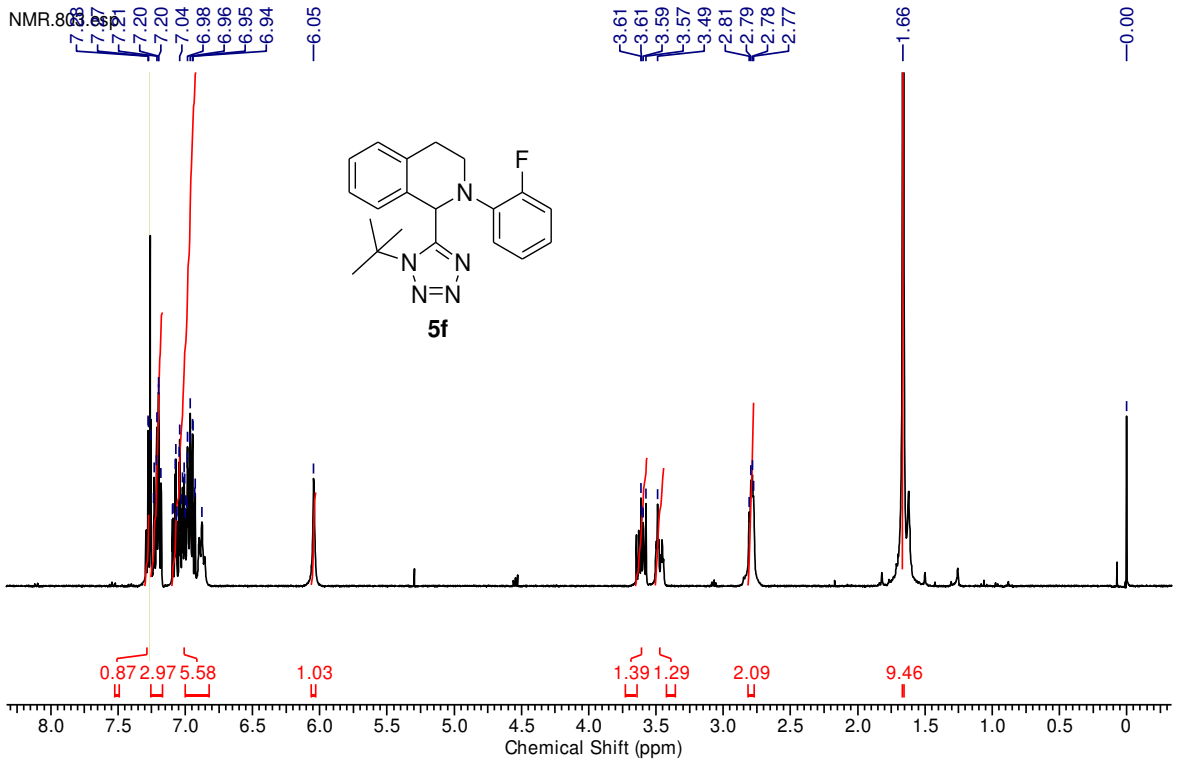

Figure 16. ^{1}H NMR (400 MHz) spectrum of compound **5f** in $CDCl_3$.

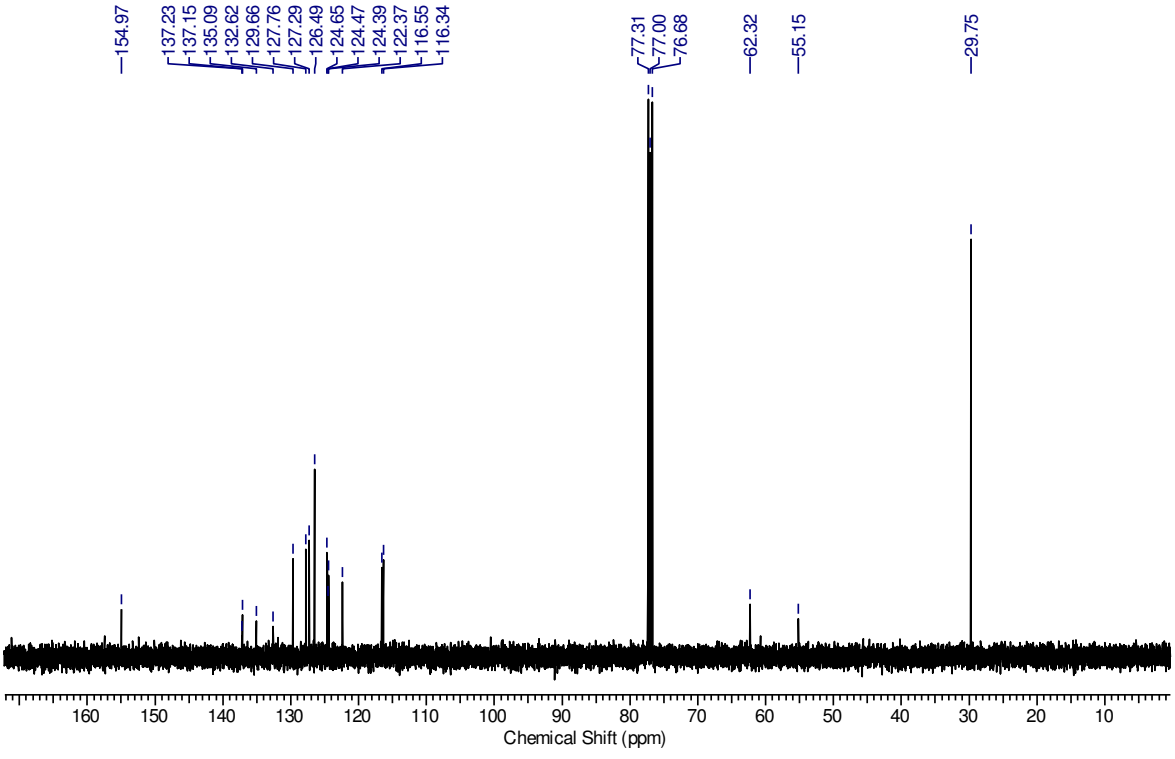

Figure 17. ^{13}C NMR (100 MHz) spectrum of compound **5f** in $CDCl_3$.

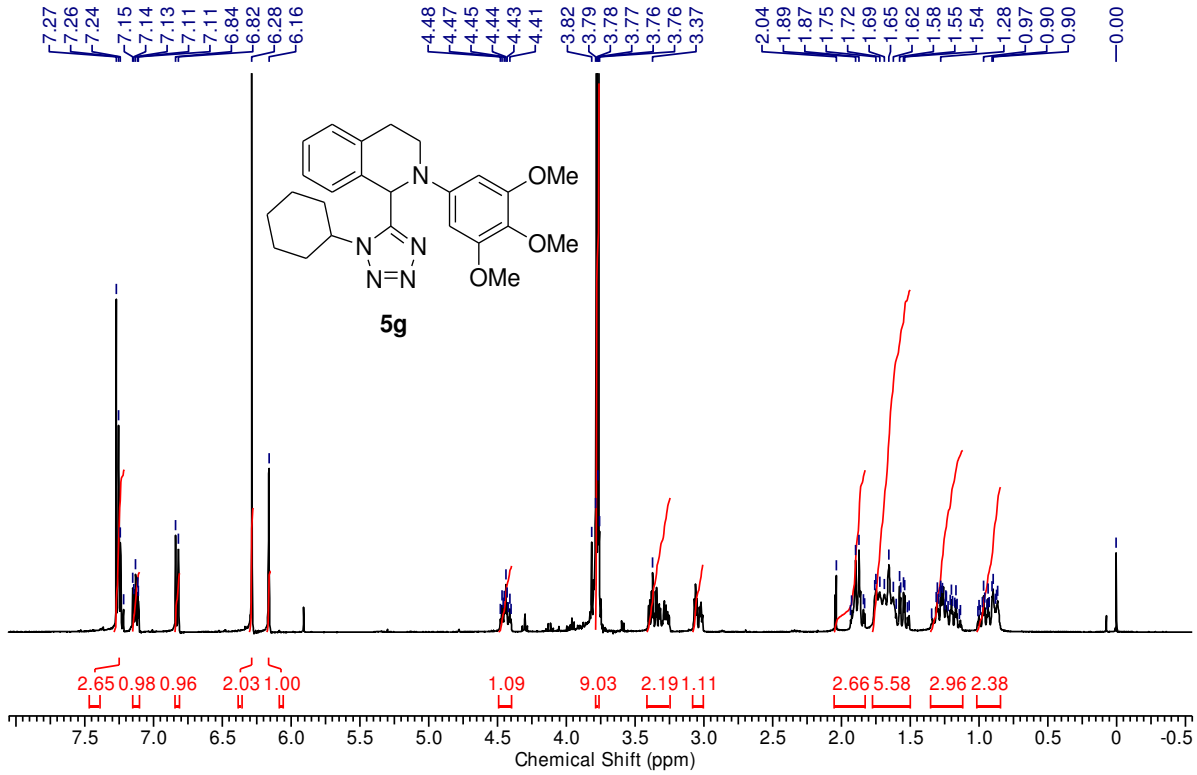

Figure 18. ^{1}H NMR (400 MHz) spectrum of compound **5g** in $CDCl_3$.

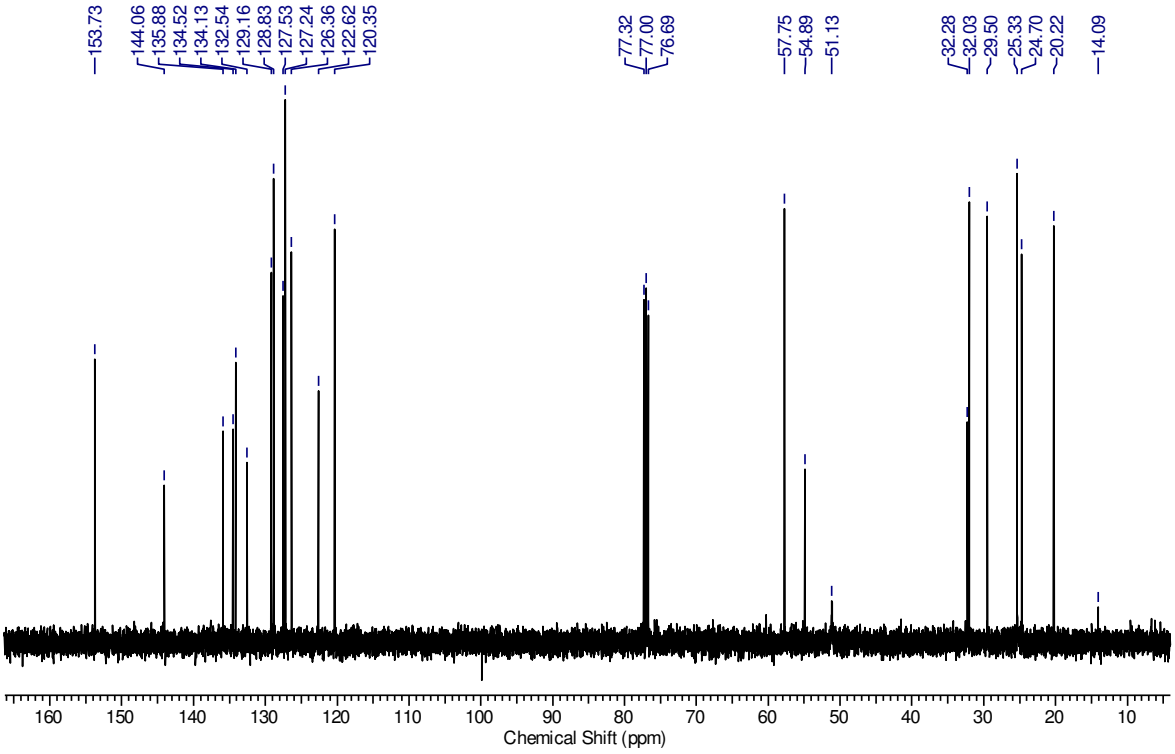

Figure 19. ^{13}C NMR (100 MHz) spectrum of compound **5g** in $CDCl_3$

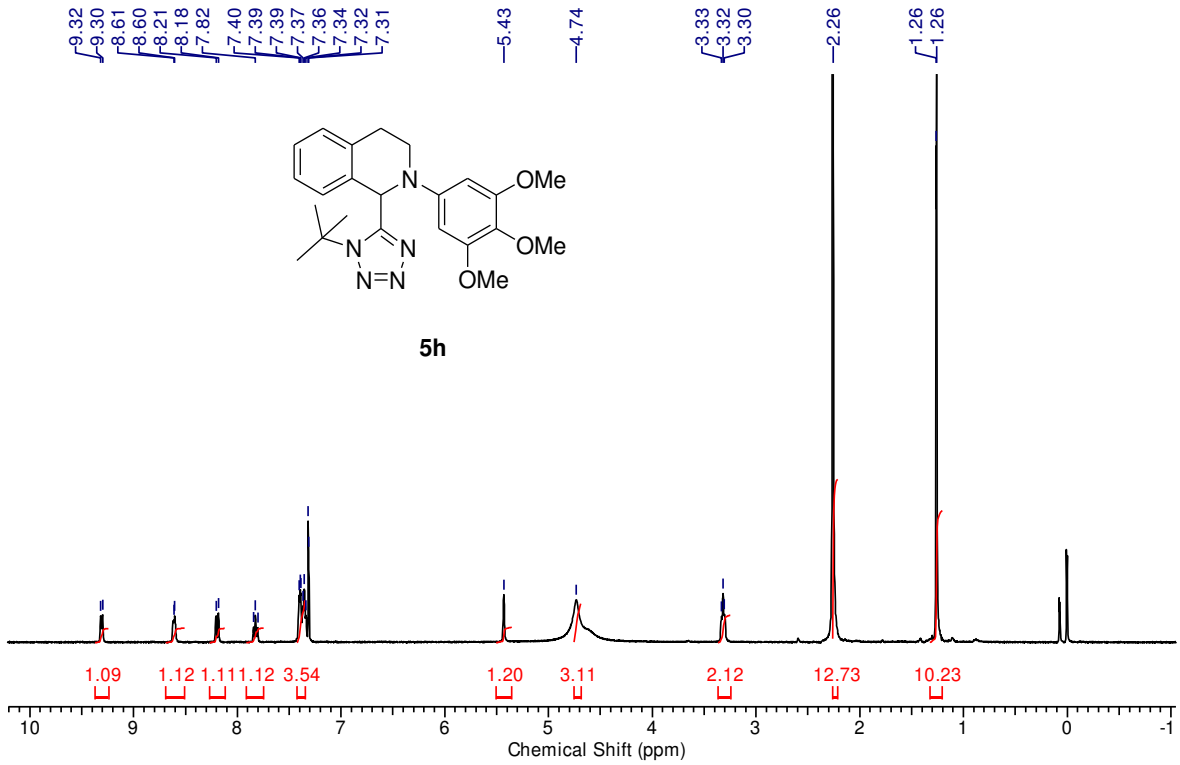

Figure 20. ^{1}H NMR (400 MHz) spectrum of compound **5h** in $CDCl_3$

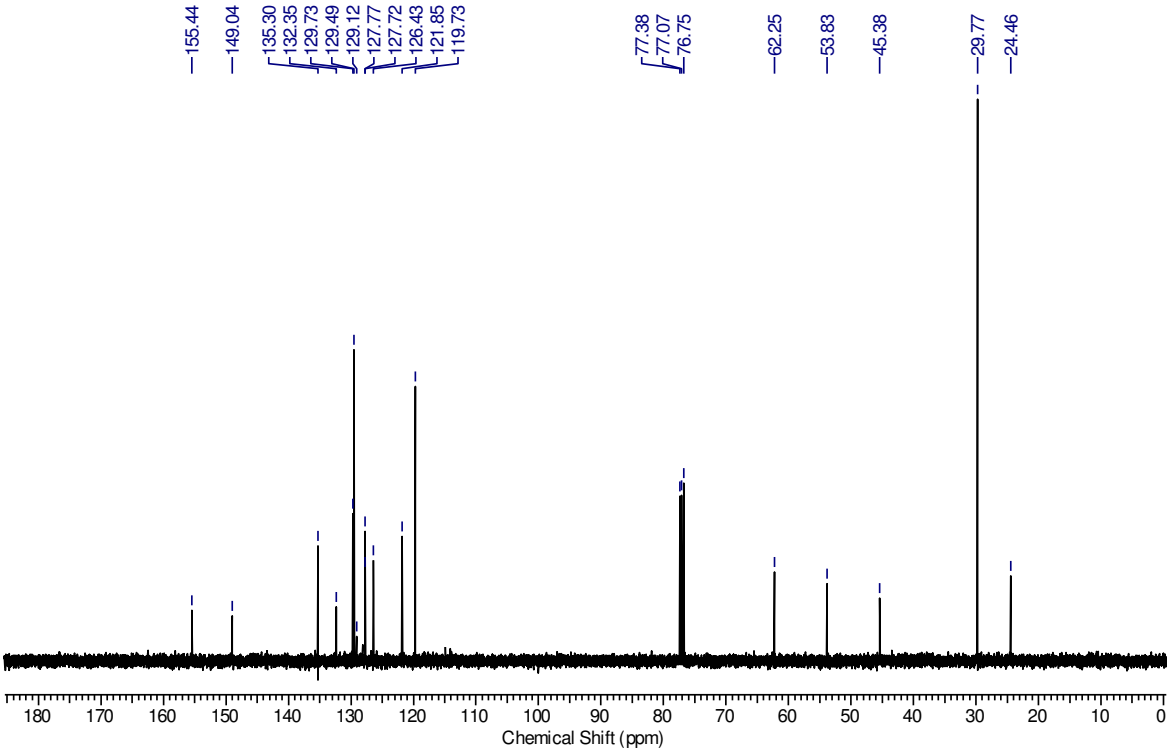

Figure 21. ^{13}C NMR (100 MHz) spectrum of compound **5h** in $CDCl_3$

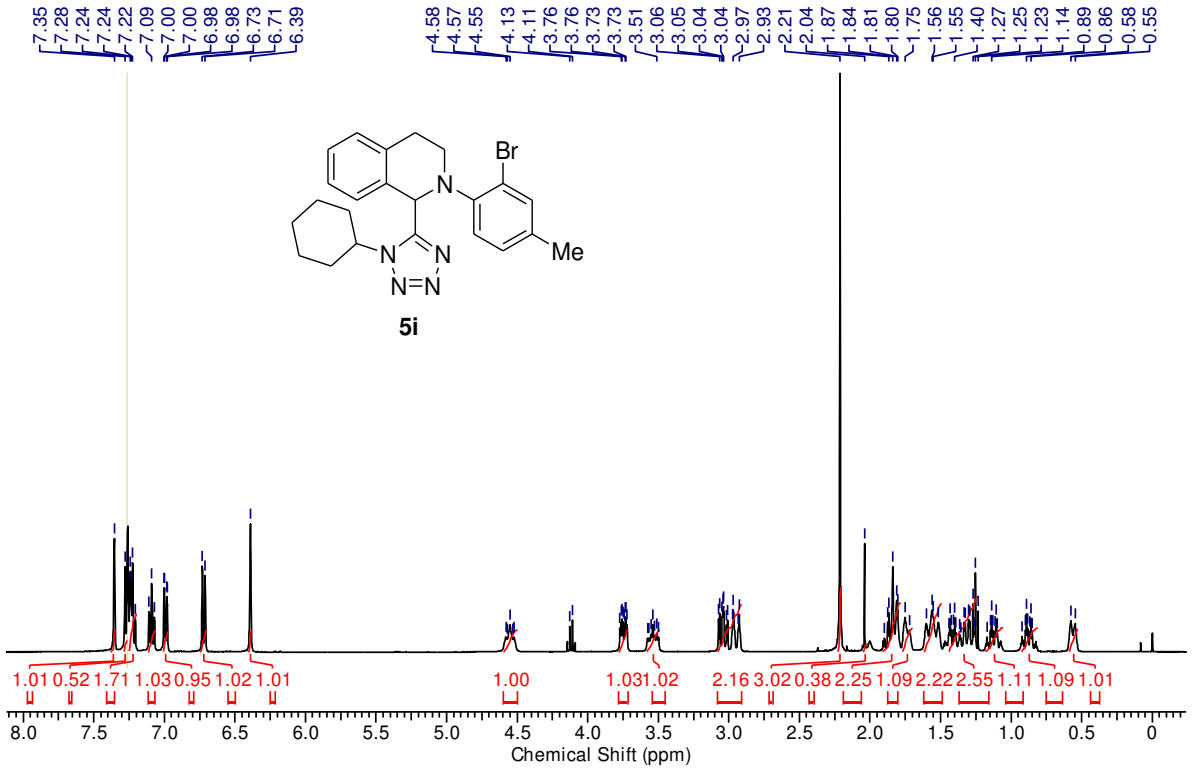

Figure 22. ^{1}H NMR (400 MHz) spectrum of compound **5i** in $CDCl_3$

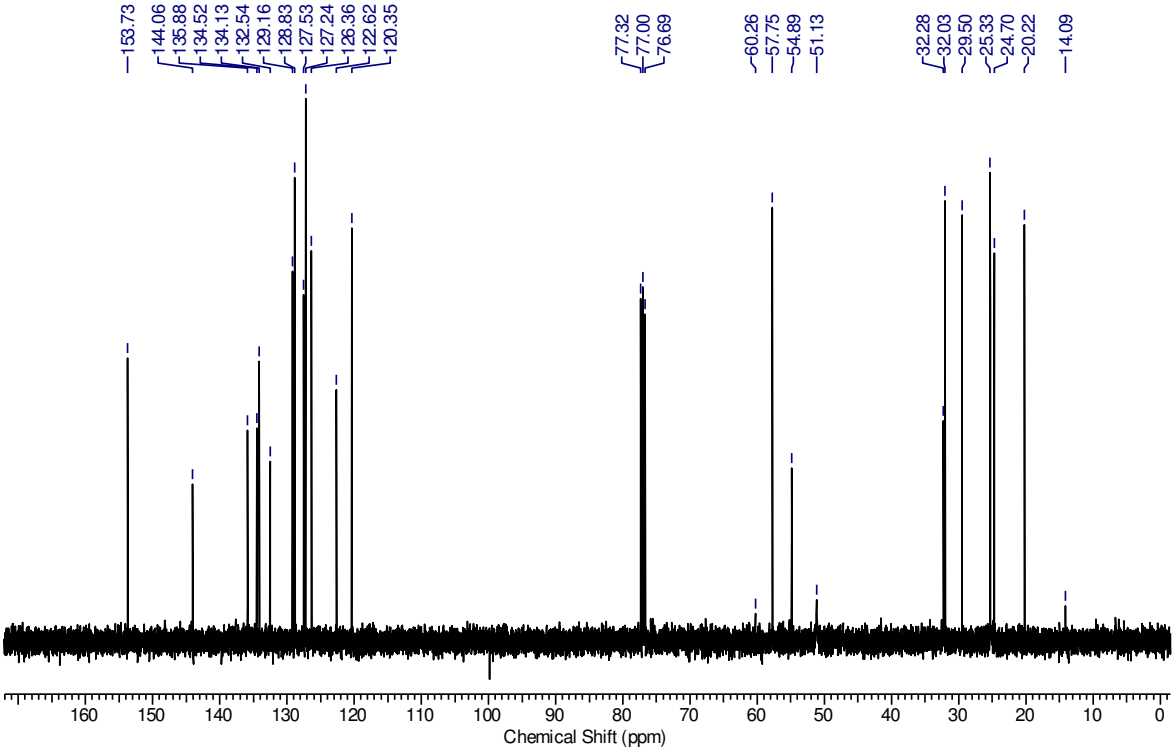

Figure 23. ^{13}C NMR (100 MHz) spectrum of compound **5i** in $CDCl_3$

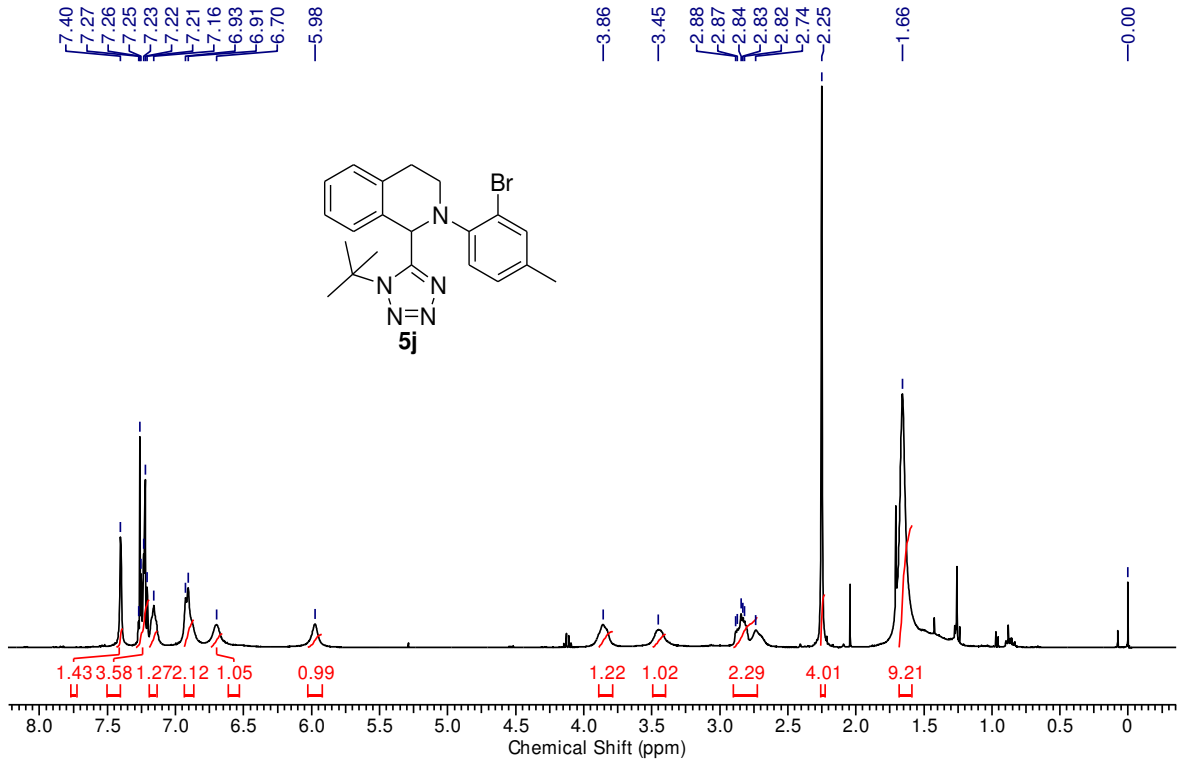

Figure 24. ^{1}H NMR (400 MHz) spectrum of compound **5j** in $CDCl_3$

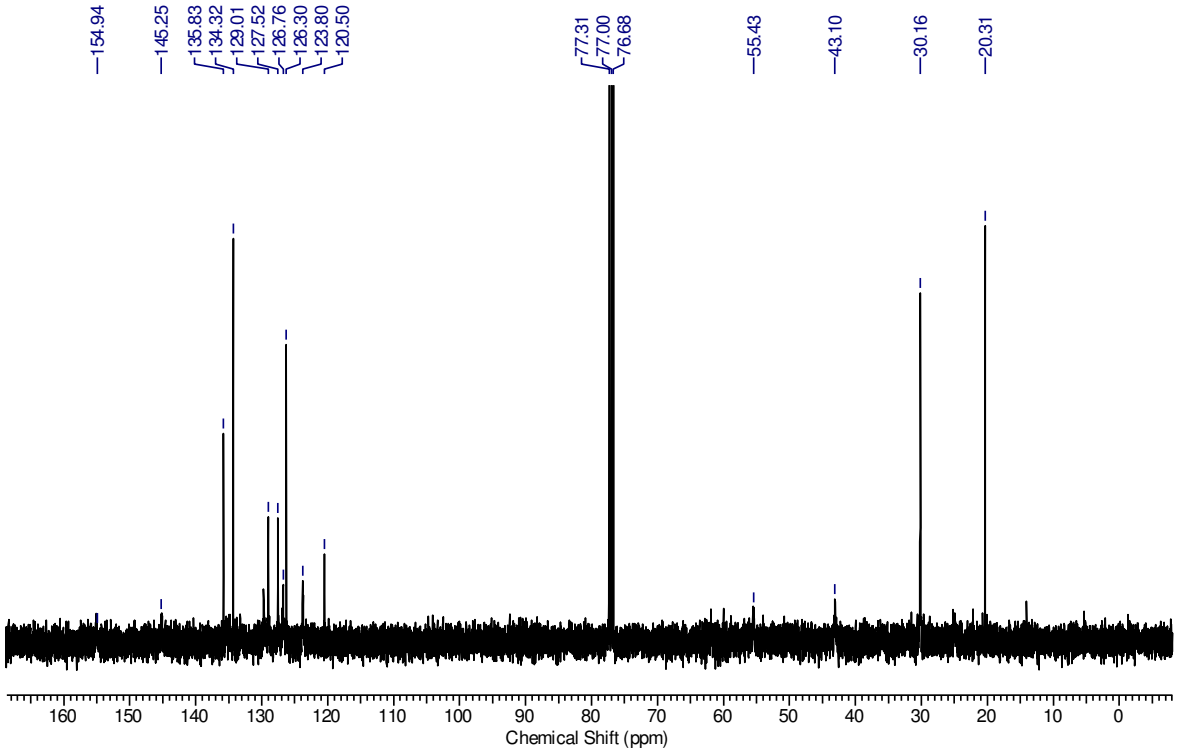

Figure 25. ^{13}C NMR (100 MHz) spectrum of compound **5j** in $CDCl_3$

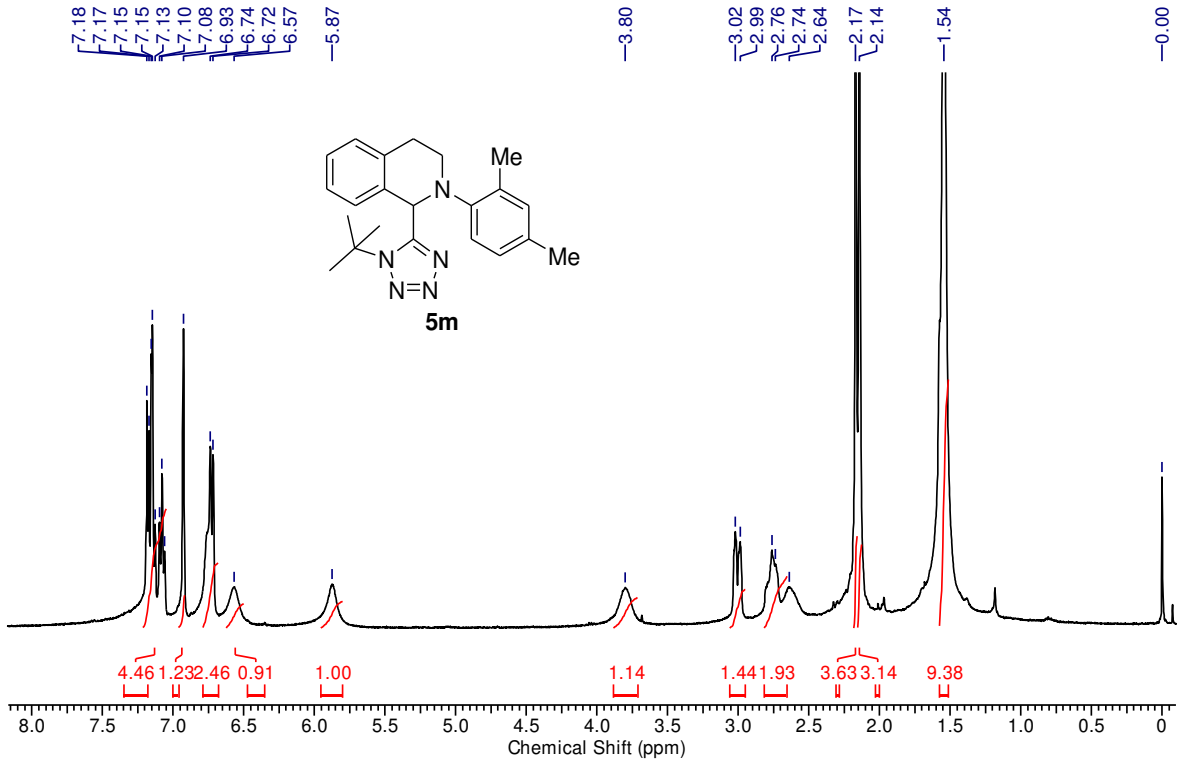

Figure 26. ^{1}H NMR (400 MHz) spectrum of compound **5m** in $CDCl_3$

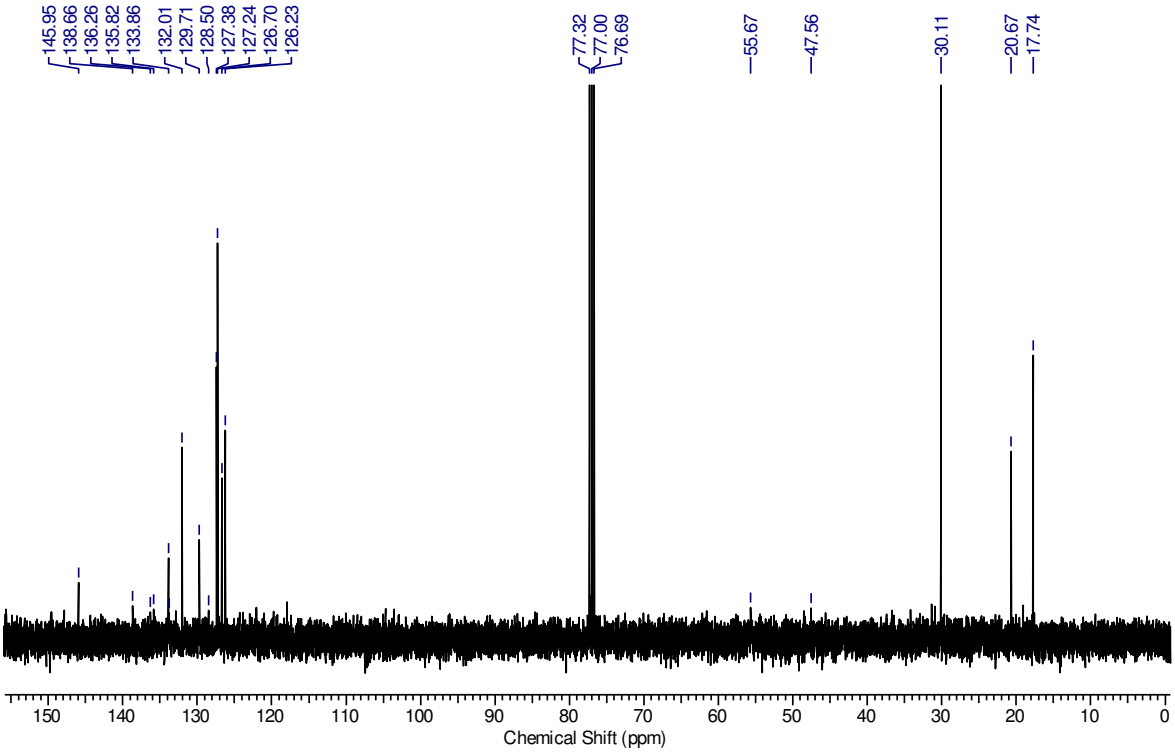

Figure 27. ^{13}C NMR (100 MHz) spectrum of compound **5m** in $CDCl_3$.