Transition-Metal-Free Direct C(sp^3)-H Functionalization leading to Aza-γ-Carboline Alkaloid Analogues in Cascade Fashion

A project report submitted

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MASTER OF SCIENCE

By

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Under the supervision of

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To The

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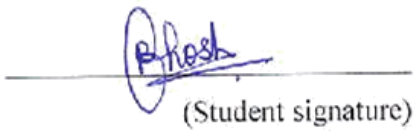
DECLARATION

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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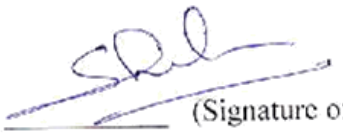

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APPROVAL SHEET

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Ruma Ghosh

Dedicated
To
My Parents and Sister

Abstract

Iodine promoted cascade reaction has been developed for the synthesis of unrivalled Aza-*γ*-carboline alkaloid analogues *via* C-H functionalization of 2*H*-indazoles. The construction of the product has been realized under metal-free condition *via* in situ formation of imine, transimination followed by cyclization. In this present method iodine played a triple role, in imine formation, transimination and imine activation. The key features of the present protocol are metal-free, peroxide-free, operational simplicity and wide substrates scope.

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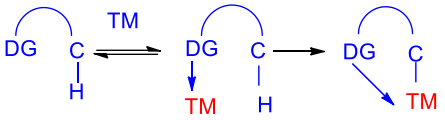
Introduction

Developing efficient environmentally benign routes for biologically important heterocycles is a constitute enterprise in organic chemistry.[1]Sustainability has emerged as a powerful approach in chemistry for the synthesis of diverse bio-active heterocyclic scaffolds.[2] For the construction of these heterocycles, transition metal-assisted C-C and C-Het (Heteroatom) bond forming reactions has become an integral part[3](figure 1). Among carbon heteroatom bond forming reactions, C-N bond formation have gained a lot of attention to construct heterocycles.[4] But an essential requirement of these conventional approaches include metal-based reagents either in stoichiometric or in catalytic amounts.[5] Among these methods, copper-catalysed C-N bond formation is the most noticeable.[6] Many biologically active molecules have been synthesised through C-N bond formation using Cu as catalyst by Buchwald,[6b] Hartwig,[6c] and Ma[6d] *et.al*. These methods have certain drawbacks like use of complex ligands, longer reaction times, harsh reaction conditions and pre-functionalised starting material.[7]

Fig. 1 Site selectivity controlled by transition metal catalyzed C-H activation.



Due to these shortcomings, focus has shifted to latent functional groups to activate C(sp^3)-H, C(sp^2)-H, C(sp)-H bonds in contrast to traditional methods which involved fully functionalized substrates.[8] They reduce the number of synthetic steps, improve atom economy and most prominently induce site selectivity.[9] Various functional groups that have been employed as directing groups for catalytic C-H bond functionalisation includes amide, anilide, imine, heterocycles, amine, carboxylic acid, ester, ketone, and hydroxyl groups.[9] Among them, Imines are versatile synthetic intermediates in a variety of organic transformations where imines are widely used in addition, reduction, aziridination, β-

lactamization, and cyclization reactions.[10] In contrast to previous reports, in our approach we have successfully demonstrated C(sp^3)-H functionalisation of benzylic carbon in benzyl amine via oxidative arylation leading to C-3 functionalised annulated indazoles. Even though there are various methods for the formation of imines,[11](figure 2) but very few reports have in situ generation of imine followed by cyclization leading to valuable heterocyclic scaffolds.[12](figure 3) Moreover in most of these methods, imine is inserted between two hetero nucleophiles but there are very few reports of insertion between a carbon and a hetero nucleophile.[13]. Aiming this, we have targeted the development of new heterocycles by choosing less explored substrate in the literature.

Fig. 2 Traditional and Modern method of Imine synthesis

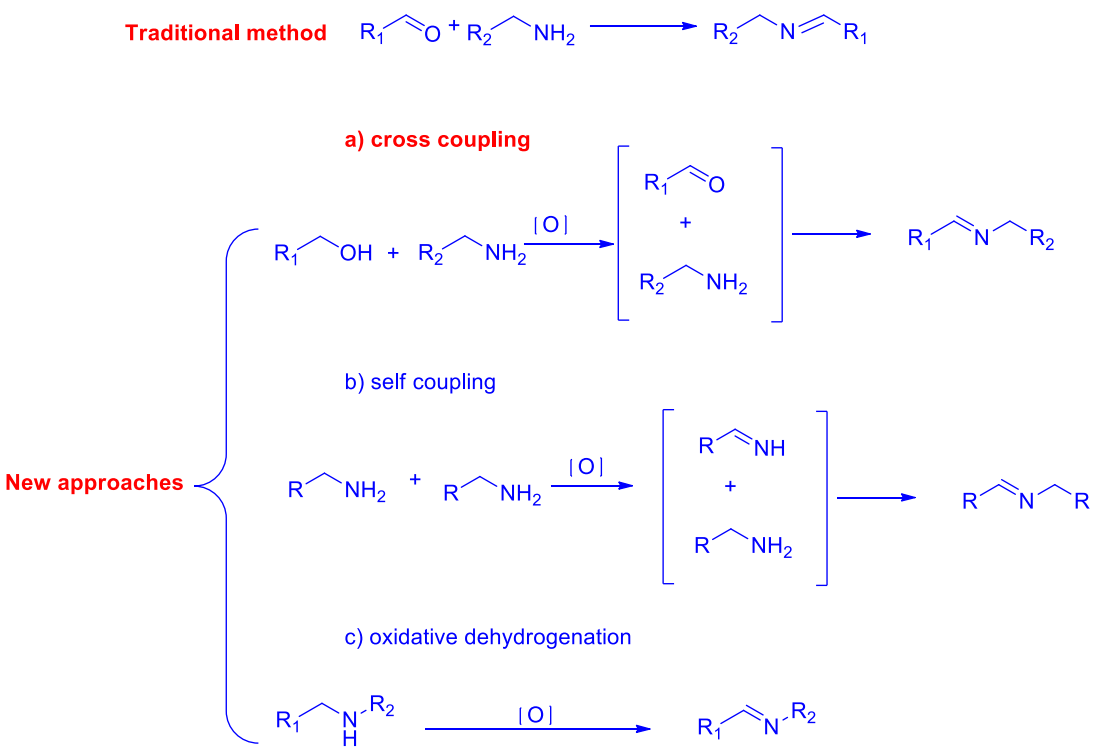
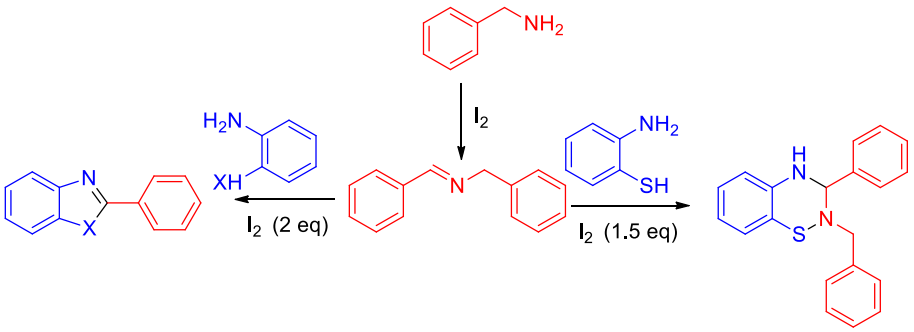
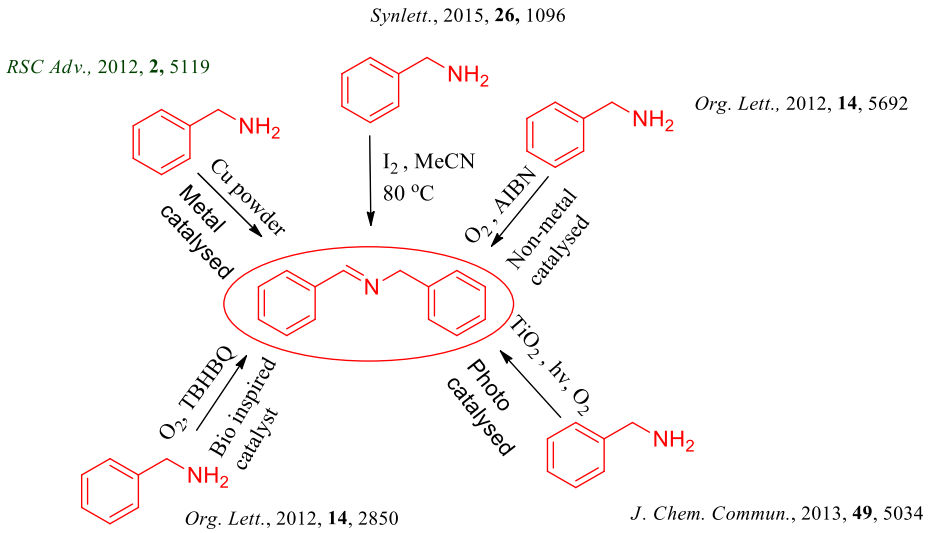


Figure 3: Application of Imine in heterocyclic synthesis



Conventionally, synthesis of imines involves the condensation of an amine with an aldehyde or ketone but alternative routes are appreciated.[14] (figure 2). The various new approaches of imine formation includes cross coupling between an alcohol and amine,[15] self-coupling between two amines[16] and oxidative dehydrogenation of secondary amines.[17] In our approach, we have focussed on the self-coupling of two amines to imine intermediates.

Fig 4. Previous methodologies for imine formation via self-coupling of primary amines



There are broadly four categories for Imine formation *via* cross-coupling of two primary amines.[16] They are metal-catalysed,[16b] non-metal-catalysed,[16a] photo-catalysed,[19] and Bio-inspired catalyst.[20] Out of them, I_2-mediated method is the most green and user-friendly.[21] Iodine is a non-metal under Group 17 of the periodic table. Although a relatively rare element, it is highly soluble in water which has contributed to its enrichment in the oceans.[22] It is the heaviest micronutrient element essential for all living organisms, with its deficiency known to cause severe health problems in animals and human beings.[23] Deficiency of this element in humans is known to cause goiter and even mental retardation.[24] The use of iodine as an inexpensive, non-toxic, readily available catalyst for various organic transformations

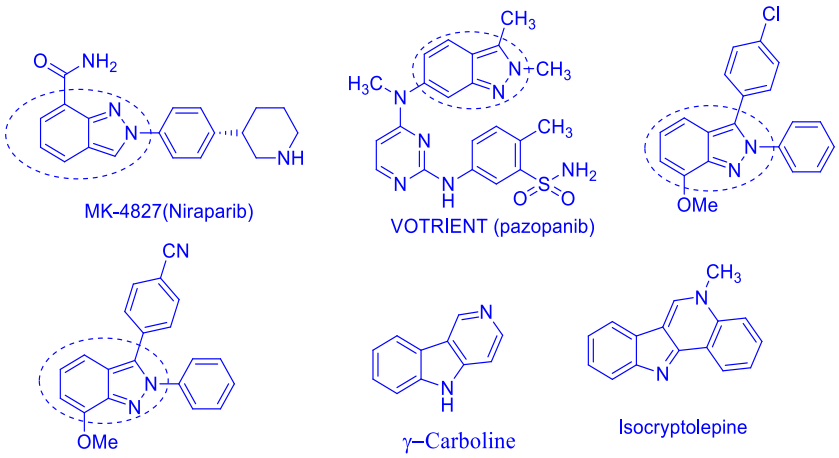
has recently been well reviewed.[25] Reviews have also appeared focusing on the role of iodine for Iodocyclization,[26] in the protection–deprotection of functional groups,[27] for electrophilic iodination of organiccompounds,[28] and for transformation of molecules containing oxygen functional groups.[29] Though acid catalysis remains the most widely used type of catalysis, the commonly used acid catalysts continue to pose serious health and safety problems. Moreover, the mild Lewis acidity of iodine has enhanced its utility for several organic transformations starting from minor catalytic amounts to higher stoichiometric levels.[30]

Biological and pharmaceutical importance of aza-*γ*-carboline alkaloid analogues.

Direct C-H bond activated reactions for the synthesis of nitrogen bearing poly heterocycles has emerged as a powerful tool for the synthesis of biologically active *N*-heterocycles.[31] These are the most abundant and integral scaffolds that occur ubiquitous in various fields like, bioactive natural products, synthetic drugs, pharmaceuticals, and agrochemicals. Among the *N*-heterocycles, 2*H*-indazoles occupy a special place in pharma sector than 1*H*-indazoles due to their potent bioactivities like anti-tumor,[32] anti-microbial,[33] anti-inflammatory,[34] HIV protease inhibition[35]*etc*. For example, drugs like MK-4827 (anticancer),[36] and pazopanib (tyrosine kinase inhibitor),[37]incorporate this basic scaffold (Figure 1). In recent years, there has been a rapid inflation in the development of fused heterocycles,[38] due to their amplified bioactivity[39]. Keeping this in mind, we wanted to synthesize indazole fused skeletons by using environmentally benign methods.

In continuation of our studies in the development of green and sustainable methods for the synthesis of indazole containing fused system,[40] herein, we wish to report "iodine-mediated" synthesis of indazoloquinoxalines through C-H functionalization of 2*H*-indazoles. This reaction operates through a sequential homo-coupling of two (aryl) methanamines via amine oxidation, transimination followed by cyclisation resulting in annulated indazoles.

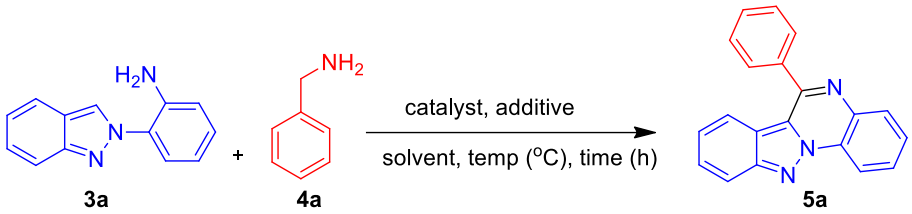
Figure 5: Representative examples of bio-active scaffolds.



Results and Discussion

Initially, to investigate the probability of approach and to optimize the reaction condition we have performed the bench mark reaction between 2-aminoindazole and benzyl amine in presence of DMSO solvent at 120 ^{o}C under oxygen atmosphere but we didn't observed the expected product (Table 1, entry 1). Then, on the basis of the previous methodologies for the synthesis of imines, we carried out the reaction with various catalysts, though we failed to get our expected product yet we have observed the formation of imine intermediate (Table 1, entry 3-7). By this, we were ascertained that activation of insitu generated imine is imperative for product formation. Accordingly, we used TFA as lewis acid additive for imine activation. Surprisingly, our desired cyclized product **5** was obtained, albeit in moderate yield (Table 1, entry 8).Continuing our zest, in order to increase the yield of the product we optimized the catalyst, solvent and temperature of our reaction but it didn't affect the yield much (Table 1, entry 10-15). In light of the aforestated advantages of using green catalyst, we incorporated molecular Iodine and gratifyingly, we observed the expected product with very good yield without additive (Table 1, entry 17). We tuned the reaction with various solvents, but we did not get any significant increase in yield (Table 1, entry 18-20). To make our protocol more environmentally benign, we have tried the reaction even in green solvents but our attempts went in vain (Table 1, entry 22-24). To validate the efficiency of iodine, we screened our reaction with its various equivalents and finally chose 1 equivalent of iodine, DMSO as solvent and 90 ^{o}C as reaction temperature, to further explore the protocol.

Table 1 Optimization conditions for the synthesis of **5a**[a,b]

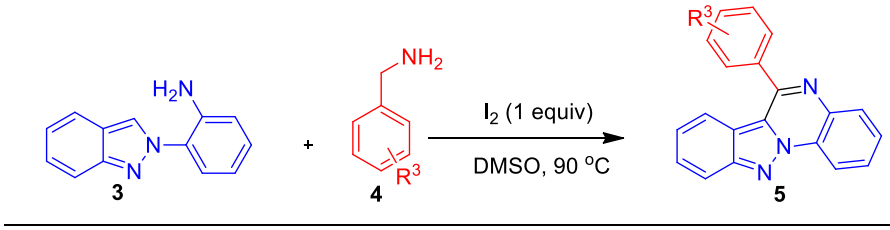


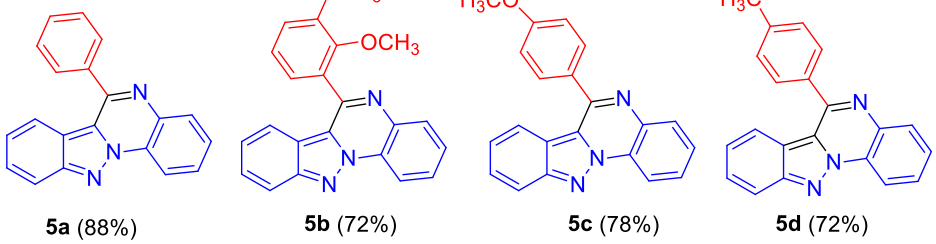
Entry	Catalyst (equiv)	Solvent	Additive	Temp (ºC)	Time (h)	Yield (%)
1[c]	—	DMSO	—	120	24	Nd
2[c]	—	Toluene	—	120	24	Nd
3	$CuCl_2.2H_2O$ (0.2)	DMSO	—	120	24	—[d]
4	CuBr (0.2)	DMSO	—	120	24	—[d]
5	$CuSO_4$ (0.2)	DMSO	—	120	24	—[d]
6	$CuBr_2$ (0.2)	DMSO	—	120	24	—[d]
7	$CuSO_4.5H_2O$ (0.2)	DMSO	—	120	24	—[d]
8	$CuSO_4.5H_2O$ (0.2)	DMSO	TFA(0.3)	90	24	48
9	CuBr (0.2)	DMSO	TFA(0.3)	90	24	50
10	$CuSO_4$ (0.2)	DMSO	TFA(0.3)	90	24	55
11	$CuCl_2.2H_2O$ (0.2)	DMF	TFA(0.3)	90	24	75
12	$CuSO_4.5H_2O$ (0.2)	ACN	TFA(0.3)	90	24	75
13	$CuSO_4.5H_2O$ (0.2)	1,4-Dioxane	TFA(0.3)	90	24	30
14	$CuSO_4.5H_2O$ (0.2)	Toluene	TFA(0.3)	90	24	Nd
15	$CuCl_2.2H_2O$ (0.2)	DMF	TFA(0.3)	110	24	65
16	I_2 (1)	DMSO	TFA (0.3)	100	24	70
17	**I_2 (1)**	**DMSO**	**—**	**90**	**24**	**88**
18	I_2 (1)	DMSO	—	110	24	85
19	I_2 (1)	DMF	—	90	24	50
20	I_2 (1)	ACN	—	90	24	85
21[c]	I_2 (1)	DMSO	—	90	24	88
22	I_2 (1)	H_2O	—	90	24	Nd
23	I_2 (1)	PEG-400	—	90	24	Nd
24	I_2 (1)	MeOH	—	90	24	Nd
25	I_2 (0.5)	DMSO	—	90	24	75
26	I_2 (1.5)	DMSO	—	90	24	85

[a]All reactions were carriedout on 1mmol scale of **3** and 1.5 mmol of **4** and entry 3-14 used 1 equiv base. [b]Isolated yields of chromatographically pure products. [c]O_2-balloon (1 atm) was used. Entry 1-9 and 19, 20 starting material was recovered. [d] amine self-coupling product was isolated.

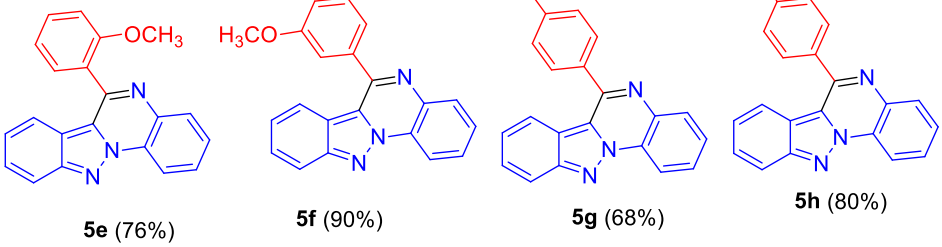
With the optimal conditions (Table 1, entry 16) in hand, we next probed the scope and generality of the protocol to various indazoles and amines. Firstly, we kept the indazole constant and modified the amine part. When we had electron donating groups at *ortho*- and *para* position of benzyl amines, they gave less yields (Table 2, **5b**, **5c**, **5d**, **5e**) but when electron donating groups (Table 2, **5f**) and electron withdrawing groups were at *meta*-position, they gave comparatively good yields (Table 2, **5j**,**5k**).

Table 3 Substrate scope of benzyl amine with respect to 2*H*-indazole (**5a-5k**)[a,b]

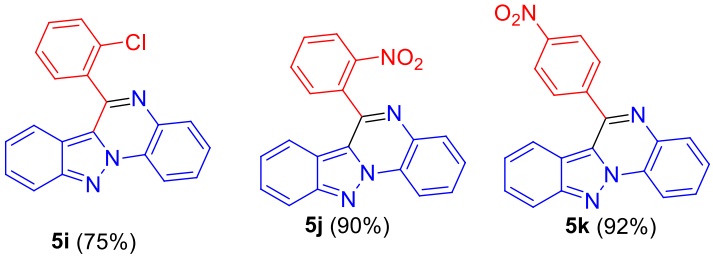




5a (88%) **5b** (72%) **5c** (78%) **5d** (72%)



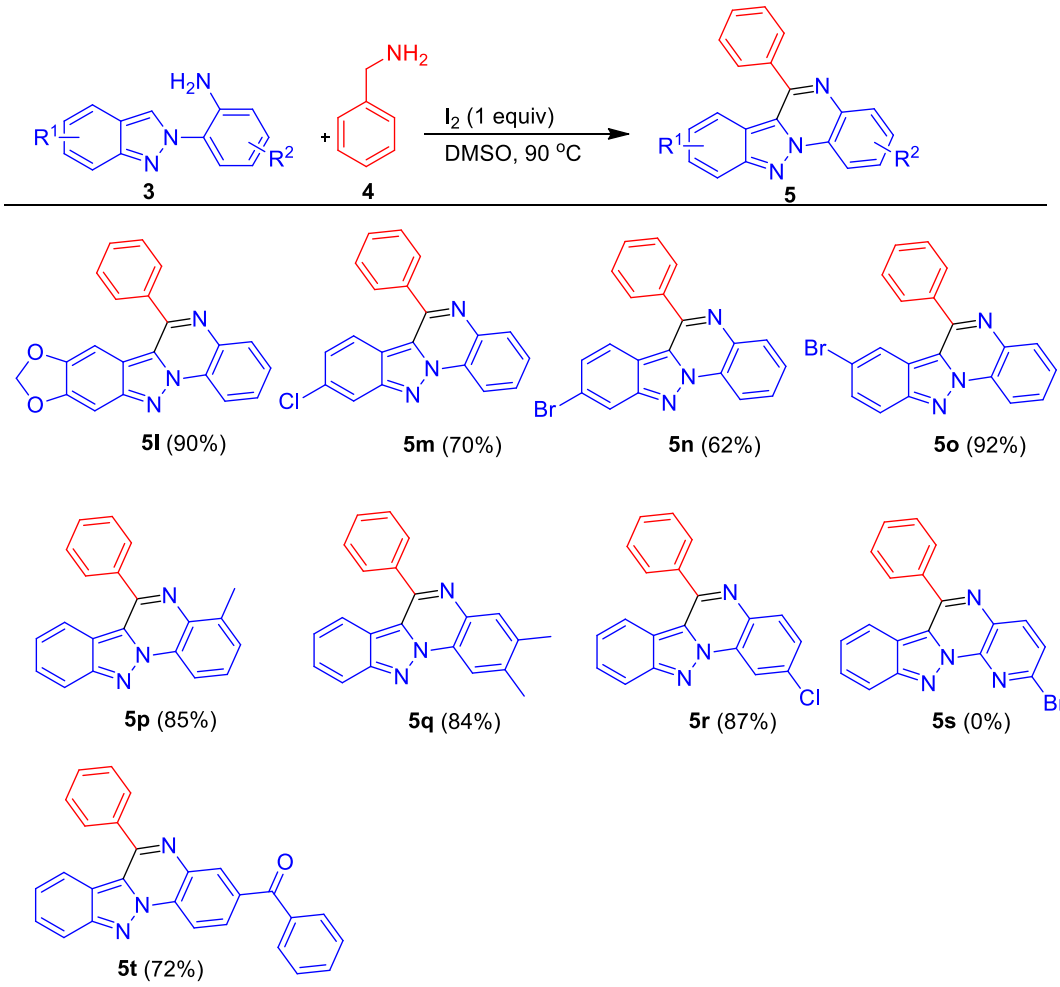
5e (76%) **5f** (90%) **5g** (68%) **5h** (80%)



5i (75%) **5j** (90%) **5k** (92%)

[a]Reaction conditions: **3** (1 mmol), **4** (1.5 equiv), I_2 (1 mmol) in 2 mL DMSO, at 90 ˚C for 15-20 h. [b]Yields in the parentheses are isolated yields of chromatographically pure products.

Table 2 Substrate scope of 2*H*-indazole with respect to benzylamines(**5l-5t**)

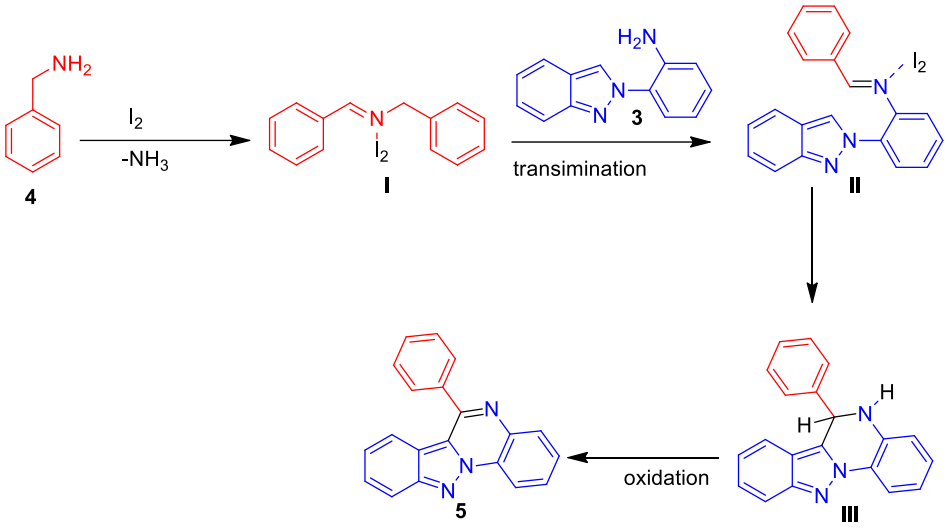


[a]Reaction conditions: **3** (1 mmol), **4**(1.5 equiv), I_2 (1mmol) in 2 mL DMSO, at 90 ˚C for 15-20h. [b]Yields in the parentheses are isolated yields of chromatographically pure products.

Next, we examined the indazoles by keeping amine component constant. When electron withdrawing and donating groups were at 5th and 6th position of azide partner of indazole, they didn't showed much difference in the yields (Table 3, **5l-5o**) whereas in the case of amine partner having electron donating groups, gave good yields (Table 3, **5p-5r**). Moreover, in the case of bromo substituted pyridine-amine, we failed to get our expected product (Table 3, **5s**).

Based on the literature reports for the formation of imine we proposed a plausible mechanism for the synthesis of Indazoloquinoxaline alkaloid analogues (**5**). At first, self-coupling of benzyl amine (**4**) takes place in presence of iodine to form corresponding imine, (**I**) which undergoes transimination to form imine intermediate (**II**). Intermediate (**II**) gets activated by iodine followed by cyclization, leads to formation of intermediate (**III**), which further undergoes aromatization to form indazoloquinoxaline (**5**)

Figure 5. Credible pathway for the synthesis of indazoloquinoxalines (**5**)



Conclusion

In summary we have successfully demonstrated C(sp^3)-H functionalisation under metal-free method in a tandem fashion using benzyl amine as C_1 synthon for C-3 functionalisation of indazoles resulting in interesting *N*-Heterocycles *i.e.* aza-γ-carboline alkaloid analogues. This reaction operates through a sequential homocoupling of two (aryl) methanamines via amine oxidation, transimination followed by cyclisation resulting in annulated indazoles. The key features of the present protocol are C(sp^3)-H functionalization, one carbon insertion, induced site selectivity, metal-free, free of harsh reagents, operational simplicity and wide substrates scope.

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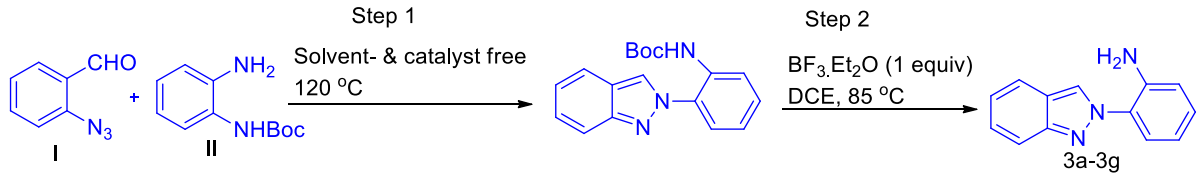
Experimental section

General information

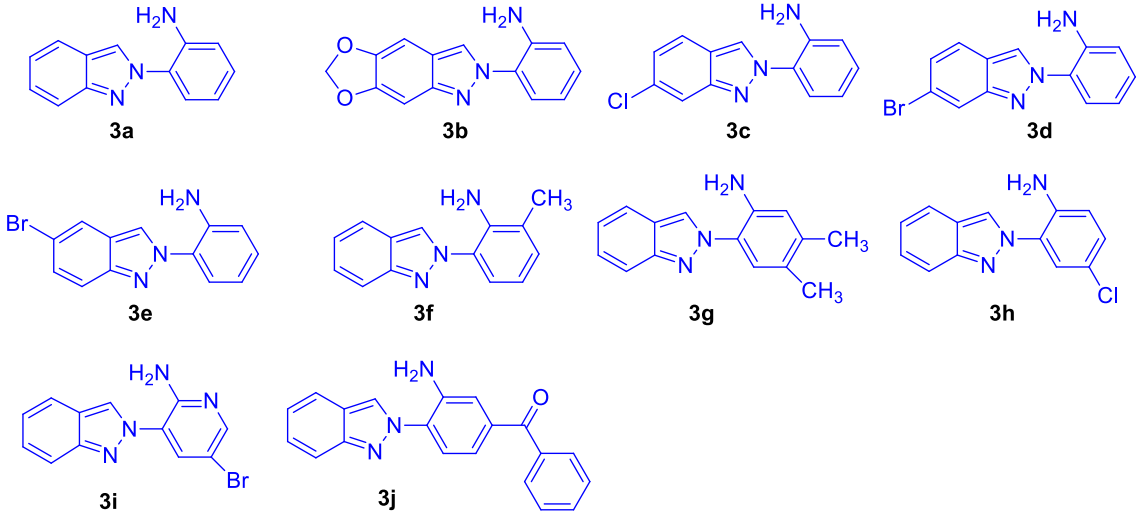
IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{1}HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. *O*-azido-benzaldehyde prepared by using literature known procedures,[1] 2-aminophenols all were commercial available. Pd-catalysts and all bases were purchased from Sigma Aldrich. All dry solvents were used, toluene and THF were dried over sodium metal and DMSO, CH_3CN and DMF were dried over calcium hydride and which are commercial available.

All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon, nitrogen and oxygen atmosphere wherever necessary. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ^{o}C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

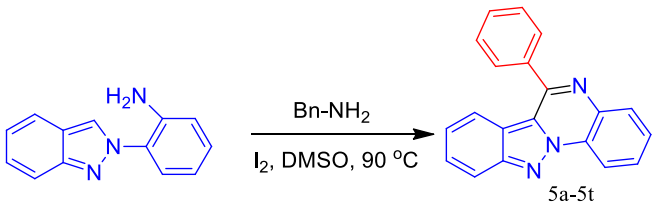
(I) General procedure (GP I) for the synthesis of 2-(2*H*-indazol-2-yl) aniline (3a-3g):



2-Azidobenzaldehyde **1** (1 mmol), Boc protected *o*-phenylenediamine**2** (1 mmol) were taken in a 10 mL round bottom flask and it was closed with stopper and placed in external heating oil bath at 120 °C (oil bath temperature) for 1-1:30h. After completion of the starting materials, the mixture was cooled to room temperature and DCE solvent was added followed by $BF_3.Et_2O$ and refluxed the reaction at 85 °C. Progress of the reaction was monitored by TLC until the reaction is completed. The reaction mixture was quenched by addition of aq. $NaHCO_3$ solution and extracted with ethyl acetate (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the product (**3a-3j)**.



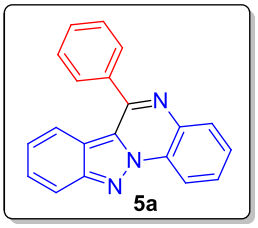
(V) General procedure (II) for the synthesis of aza-*γ*-carboline (5a-5t):



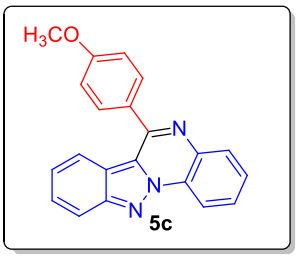
In an oven dried sealed tube, 2-(2*H*-indazol-2-yl)aniline **3a-3g** (1 mmol), benzyl amine **4a-4b** (2 mmol), molecular Iodine (1mmol) were added followed by addition of DMSO (2 mL). The resulting

reaction mixture was stirred at 90°C for 20-24 h. Progress of the reaction was monitored by TLC until the reaction is completed. The reaction mixture was quenched by addition of aq. $Na_4S_2O_3$solution and extracted with ethyl acetate (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the product aza-*γ*-carboline **5a-5t.** All the unknown compounds (**5a-5t**) were confirmed by FTIR, ^{1}H NMR, ^{13}CNMR and HR-MS Spectral analyses.

Spectral data of all compounds (5a-5t):

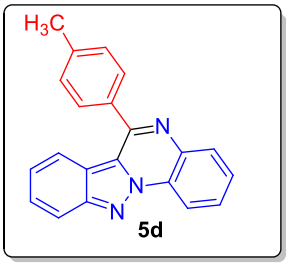


6-phenylindazolo[2,3-*a*]quinoxaline (5a): Light yellow solid (88 %); mp 220-222 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3740, 2945, 2882, 1517, 1476, 1340, 1237, 1194, 1127, 1090, 966, 896, 745, 707, 678; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.89 (dd, 1H, J_a = 8.1 and J_b = 1.2Hz), 8.27 (dd, 2H, J_a = 8.1 and J_b = 1.2Hz), 8.07-8.06 (m, 2H), 7.76-7.78 (m, 2H), 7.61-7.63 (m, 5H), 7.23-7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.4, 149.6, 138.4, 138.1, 130.5, 130.3, 129.4, 129.2, 129.1, 128.5, 128.4, 123.4, 121.6, 117.7, 117.5, 116.8; HR-MS (ESI+) m/z calculated for $[C_{20}H_{13}N_3]^+$ = $[M+H]^+$: 296.1188; found: 296.1183.

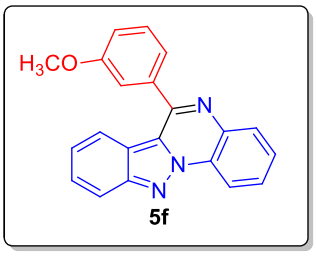


6-(4-methoxyphenyl)indazolo[2,3-*a*]quinoxalines (5c): Yellow solid (78%); mp 210-230 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3740, 2944, 2892, 1553, 1502, 1459, 1339, 1296, 1174, 1129,

1029, 920, 827, 786, 751; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.90-8.87 (m, 1H), 8.25 (d, 1H, J = 2Hz), 8.08 (d, 1H, J = 8.8Hz), 7.7-7.77 (m, 2H), 7.77-7.75 (m, 3H), 7.59 (ddd, 1H, J_a = 8.8 and J_b = 8Hz, J_c = 1Hz), 7.27-7.19 (m, 1H), 7.19-7.18 (m, 2H), 3.99 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): 161.3, 138.1, 130.4.1, 129.8, 128.8 , 128.1, 128.0, 123.0, 121.4, 117.5, 116.4, 114.3; HR-MS (ESI+) m/z calculated for $[C_{21}H_{15}N_3O]^+ = [M+H]^+$: 326.1293; found: 326.1295.

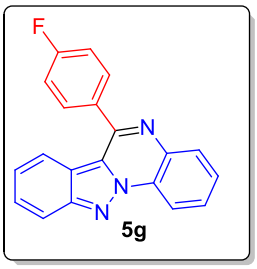


6-(*p*-tolyl)indazolo[2,3-*a*]quinoxaline (5d): Yellow solid (82%); mp 222−224˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3740, 3391, 3360, 3009, 1639, 1517, 1475, 1422, 1341, 1193, 1126, 966, 787, 723; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.87 (dd, 1H, J_a = 8.1 and J_b = 1.2Hz), 8.25 (dd, 1H, J_a = 8.1 and J_b = 1.2Hz), 8.06 (d, 1H, J = 8.3Hz), 7.83 (d, 2H, J = 7.8Hz), 7.82-7.78 (m, 3H), 7.56 (d,1H, J = 7.8Hz), 7.46(d,2H, J = 7.8Hz), 7.24(dd, 1H, J_a = 15.9 and J_b = 8.6Hz), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.5, 149.6, 140.6, 138.4, 135.3, 130.2, 129.8, 129.2, 129.1, 128.4, 123.3, 121.7, 117.7, 117.5, 116, 123.0, 121.4, 117.4, 117.2, 116.4, 21.6; HR-MS (ESI+) m/z calculated for $[C_{21}H_{15}N_3]^+ = [M+H]^+$: 310.1344; found: 310.1344.

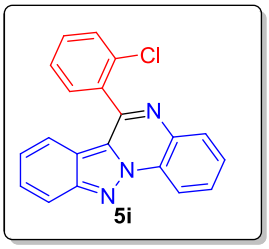


6-(4-methoxyphenyl)indazolo[2,3-*a*]quinoxaline(5f):Yellow solid (90%); mp 146−150˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3791, 3686, 3002, 2934, 2834, 1785, 1625, 1578, 1508, 1359,

1285, 1151, 970, 931, 872, 836, 743, 691; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.89-8.87 (m, 1H) , 8.27 (dd, 1H, J_a = 7.8 and J_b = 1 Hz), 8.06(d, 1H, J = 8.8Hz), 7.75-7.65 (m, 2H), 7.66(d, 1H, J = 8.8Hz), 7.57-7.55 (m, 2H), 7.51-7.49 (m, 2H), 7.27-7.24 (m, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 159.9, 153.9, 149.3, 139.0, 138.0, 130.0, 130.0, 129.1, 128.2, 128.1, 127.9, 125.7, 123.1, 121.3, 121.4, 120.6, 117.4, 117.2, 116.5, 113.7, 55.4; HR-MS (ESI+) m/z calculated for $[C_{21}H_{15}N_3O]^+$ = $[M+H]^+$: 326.1293; found: 326.1285.

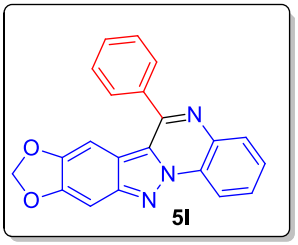


6-(4-fluorophenyl)indazolo[2,3-*a*]quinoxalines (5g): White solid(68%); mp 180−190 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3740, 3391, 3360, 3009, 1639, 1517, 1475, 1422, 1341, 1193, 1126, 966, 787, 723 ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.9 (dd, 1H, J_a = 8.3 and J_b = 1.5 Hz), 8.26 (dd, 1H, J_a = 8.1 and J_b = 1.2 Hz), 8.09 (d, 2H ,J = 8.8Hz), 7.95 (dd, 2H, J_a = 8.8 and J_b = 5.4 Hz), 7.95-7.83 (m, 2H), 7.65-7.60 (m, 2H), 7.38-7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 165.3, 153.0, 149.3, 138.0, 134.0, 131.0, 130.9, 129.9, 129.2, 128.3, 128.2, 127.8, 125.6, 123.3, 121.0, 117.6, 117.1, 116.5, 116.2, 115.9; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}FN_3]^+$ = $[M+H]^+$: 314.1094 ; found: 314.1091.



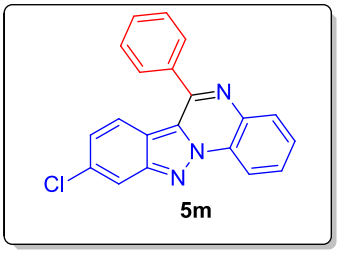
6-(2-Chlorophenyl)indazolo[2,3-*a*]quinoxalines (5i): Yellow solid (75%); mp 144−160 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 3440, 3332, 3061, 1621, 1512, 1476, 1432, 1385, 1358, 1325, 1229, 1196, 1128, 953, 786, 710; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.93 (dd, 1H, J_a = 8.3 and

J_b = 1 Hz), 8.31 (dd, 1H, J_a = 7.8 and J_b = 1 Hz), 8.08 (d,1H, J = 8.8Hz), 7.68-7.65 (m, 1H), 7.64-7.62 (m, 1H), 7.61-7.58 (m, 5H), 7.27-7.25 (m, 1H), 7.09 (d, 1H, J = 8.3Hz) ;^{13}C NMR ($CDCl_3$, 100 MHz): 151.7, 149.2, 137.9, 136.5, 133.2, 131.2, 130.6, 130.2, 130.1, 129.6, 128.3, 128.2, 128.1, 127.6, 126.1, 123.6, 120.4, 117.4, 117.3, 116.5; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}ClN_3]^+$ = $[M+H]^+$: 330.098; found: 330.0796.



5l

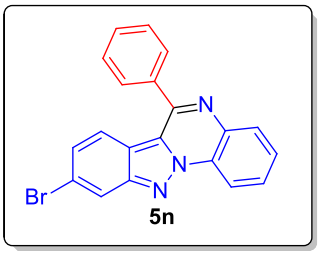
6-phenyl-[1,3]dioxolo[4',5':5,6]indazolo[2,3-*a*]quinoxaline (5l): Yellow solid (90 %); mp 208-210 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 2992, 2894, 1504, 1469, 1326, 1243, 1195, 1120, 1033, 954, 824, 759, 706, 574; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.72 (dd, 1H, J_a = 8.3 and J_b = 1Hz), 8.3 (dd, 1H, J_a = 8.3 and J_b = 1.5Hz), 7.85-7.84 (m, 2H), 7.67-7.65 (m, 1H), 7.65-7.64 (m, 4H), 7.30 (s, 1H), 7.58 (s, 1H), 6.75(s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8, 150.5, 147.3, 146.5, 137.7, 137.2, 130.2, 129.9, 129.0, 128.9, 128.7, 128.1, 127.6, 127.0, 125.7, 115.7, 112.7, 112.0, 101.8, 97.3, 94.7;HR-MS (ESI+) m/z calculated for $[C_{21}H_{13}N_3O_2]^+$ = $[M+H]^+$: 340.1086; found: 340.1075.



5m

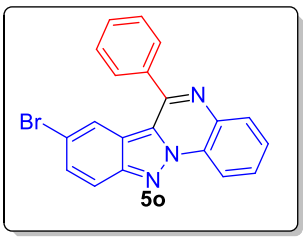
9-chloro-6-phenylindazolo[2,3-*a*]quinoxalines (5m): Light yellow solid(70 %); mp 228-234 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 3608, 3121, 2991, 2882, 1760, 1649, 1639, 1552, 1518, 1391, 1282, 1193, 966, 937, 865, 812, 744, 678; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.86 (dd, 1H, J_a

= 8.1 and J_b = 1.7Hz), 8.28 (dd, 1H, J_a = 8.1 and J_b = 1.2Hz), 7.91-7.93 (m, 3H), 7.83 (d, 3H,J = 7.8Hz), 7.80-7.82 (m, 3H), 7.65-7.67 (m,4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.0, 147.7, 138.2, 137.4, 131.8, 130.6, 130.1, 129.4, 129.1, 128.7, 128.6, 125.1, 124.9, 124.5, 124.0, 123.6, 119.1, 118.4, 116.6, 116.5; HR-MS (ESI+) m/z calculated for $[C_{21}H_{15}ClN_3]^+$ = 329.0720; found: 329.0718.



5n

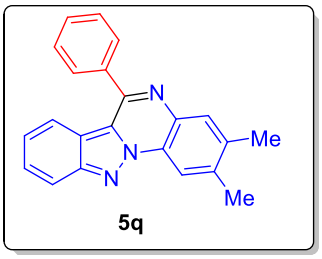
9-bromo-6-phenylindazolo[2,3-*a*]quinoxalines (5n): Yellow solid (62 %); mp ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 2992, 2882, 1518, 1472, 1341, 1241, 1192, 1127, 1079, 965, 840, 746, 707, 678; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.85 (dd, 1H, J_a = 8.1 and J_b = 1.2Hz), 8.27 (dd, 1H, J_a = 8.1 and J_b = 1.7Hz), 7.91-7.93 (m, 3H), 7.82-7.84 (m, 3H), 7.68-7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.3, 148.0, 138.5, 137.7, 132.0, 130.9, 130.4, 129.7, 129.4, 129.0, 128.9, 128.0, 123.8, 119.4, 118.7, 116.9, 116.8; HR-MS (ESI+) m/z calculated for $[C_{21}H_{15}ClN_3]^+$ = 373.0215; found: 373.0214.



5o

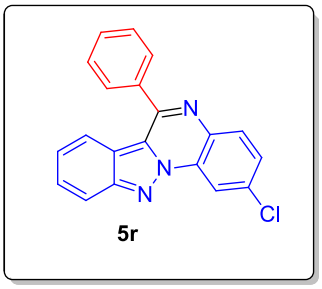
8-bromo-6-phenylindazolo[2,3-*a*]quinoxalines (5o): Yellow solid (92 %); mp 200-210 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 3524, 3391, 3106, 1640, 1519, 1476, 1422, 1392, 1367, 1341, 1271, 1195, 1126, 967, 788, 745; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.84 (m, 1H), 8.27 (dd, 1H, J_a = 8.1 and J_b = 1.7Hz), 7.8-8.0 (m, 1H), 7.8 (ddd, 2H, J_a = 10.4, J_b = 8.2 and J_c = 2Hz), 7.7-7.6 (m, 2H), 7.5-7.8 (m, 3H), 7.3-7.5 (m, 1H), 7.2-7.4 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.5, 149.6, 137.8, 137.2, 130.1, 129.7, 129.1, 128.7, 128.4, 128.2, 127.3, 126.3, 125.6, 122.2, 121.9,

119.5, 116.2, 115.4; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}BrN_3]^+ = [M+H]^+$: 374.0293; found: 374.0291.



5q

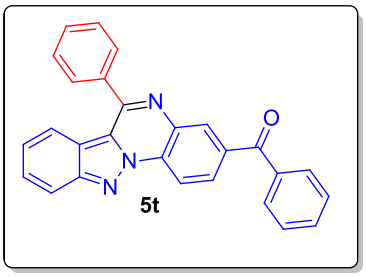
2,3-dimethyl-6-phenylindazolo[2,3-*a*]quinoxaline (5q): Yellow solid (84 %); mp 200-210 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3732, 3668, 3211, 2918, 2854, 1766, 1642, 1629, 1533, 1512, 1361, 1228, 1193, 914, 873, 805, 757, 650; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.64 (s, 1H), 7.91-7.90 (m, 2H), 7.90-7.89 (m, 2H), 7.64-7.63 (m, 4H), 7.63-7.62 (m, 1H), 7.56-7.26 (m, 1H), 2.59 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8, 150.0, 138.2, 137.5, 130.4, 130.0, 129.4, 129.0, 128.8, 128.5, 127.7, 126.7, 125.9, 122.6, 122.2, 119.9, 116.5, 115.8; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}BrN_3]^+ = [M+H]^+$: 323.1422; found: 323.1420.



5r

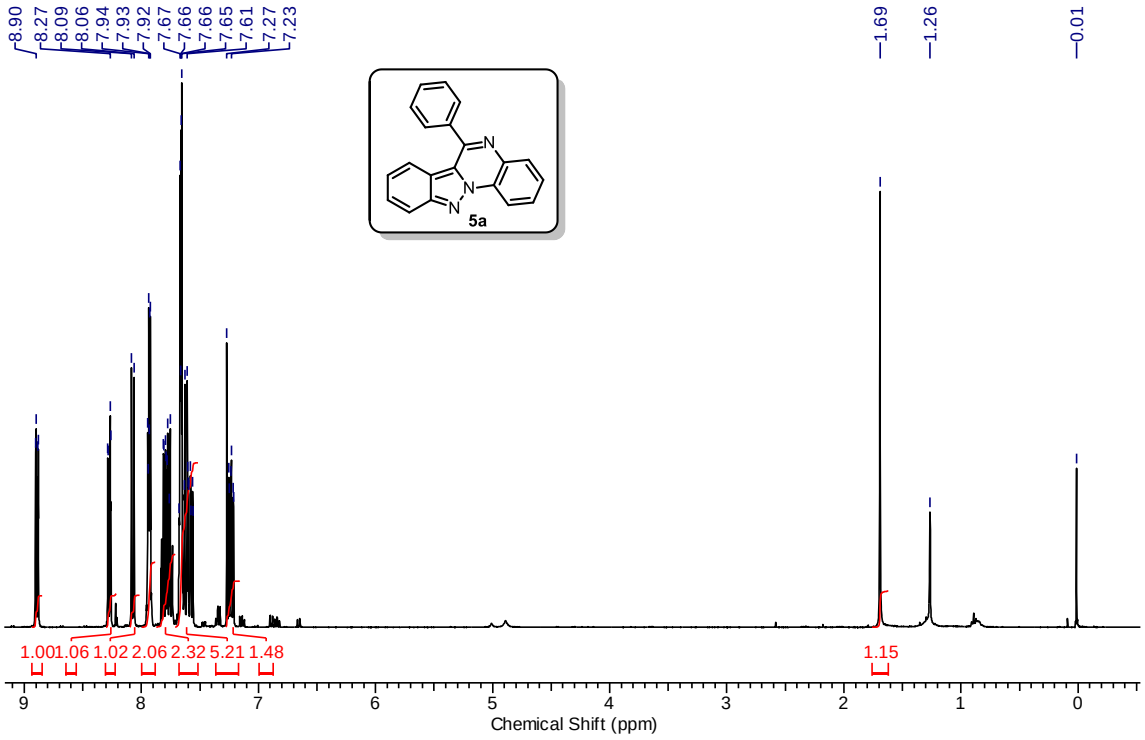
2-chloro-6-phenylindazolo[2,3-*a*]quinoxaline (5r):Yellow solid (78%); mp 200-210 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3725, 3628, 3032, 2924, 2852, 1750, 1641, 1624, 1549, 1508, 1360, 951, 872, 824, 759, 700; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.88 (d, 1H, J = 2.4 Hz), 8.17 (d, 1H,J = 8.8 Hz), 8.03 (s, 1H), 7.91 (dd, 2H, J_a = 3.9 and J_b = 2.9Hz), 7.67-7.65 (m, 6H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8, 150.0, 138.2, 137.5, 130.4, 130.0, 129.4, 129.0, 128.8, 128.5,

127.7, 126.7, 125.9, 122.6, 122.2, 119.9, 116.5, 115.8; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}BrN_3]^+ = [M+H]^+$: 329.0720; found: 329.0717.

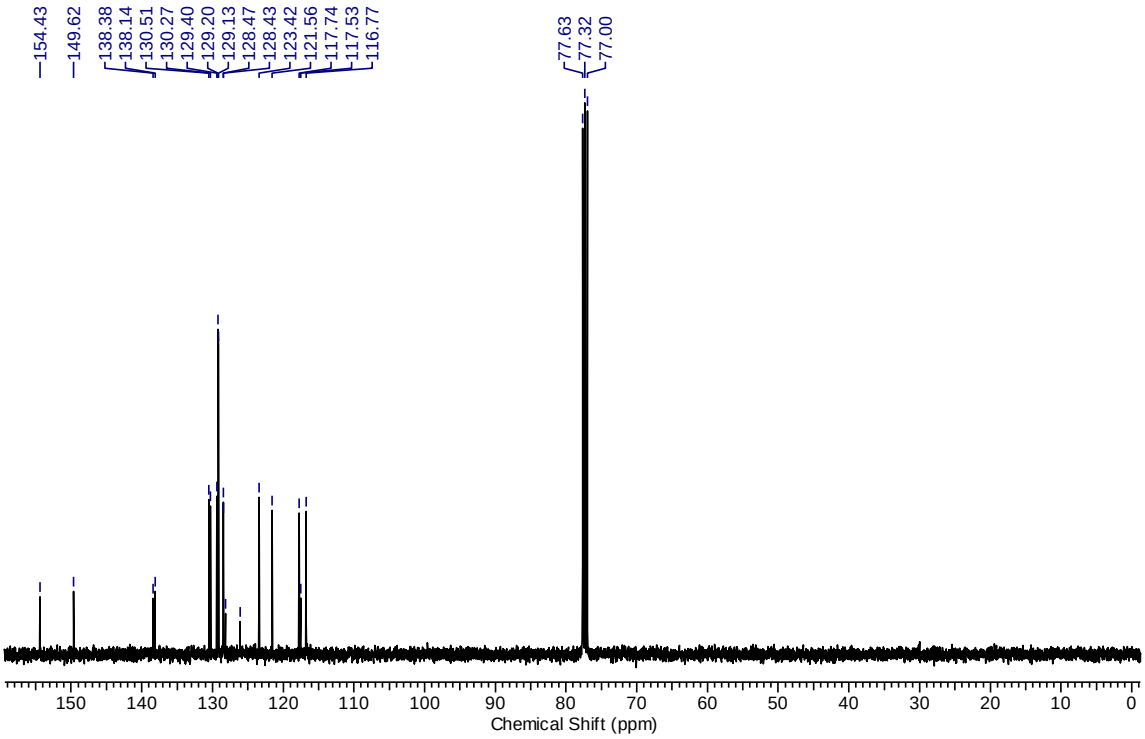


phenyl(6-phenylindazolo[2,3-*a*]quinoxalin-3-yl)methanone (5t): Yellow solid (72 %); mp 200-210 ˚C; IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3739, 2991, 2880, 1517, 1475, 1366, 1276, 1127, 1091, 967, 936, 865, 787, 745, 678; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.62 (d, 1H, J = 8.3Hz), 8.28 (d, 1H, J = 1.5Hz), 7.96 (dd, 1H, J_a = 8.8 and J_b = 2Hz), 7.72 (d, H, J = 8.8Hz), 7.58-7.53 (m, 2H), 7.30-7.29 (m, 4H), 7.26-7.24 (m,1H), 7.19-7.15 (m, 2H), 6.92-6.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 195.5, 155.2, 149.8, 137.4, 137.2, 137.2, 136.9, 132.8, 132.8, 130.5, 130.2, 130.1, 129.8, 129.0, 128.8, 128.7, 128.5, 126.2, 123.8, 121.3, 117.7, 117.3, 117.0, 29.7; HR-MS (ESI+) m/z calculated for $[C_{20}H_{12}BrN_3]^+ = [M+H]^+$: 399.1372 ; found: 399.1370.

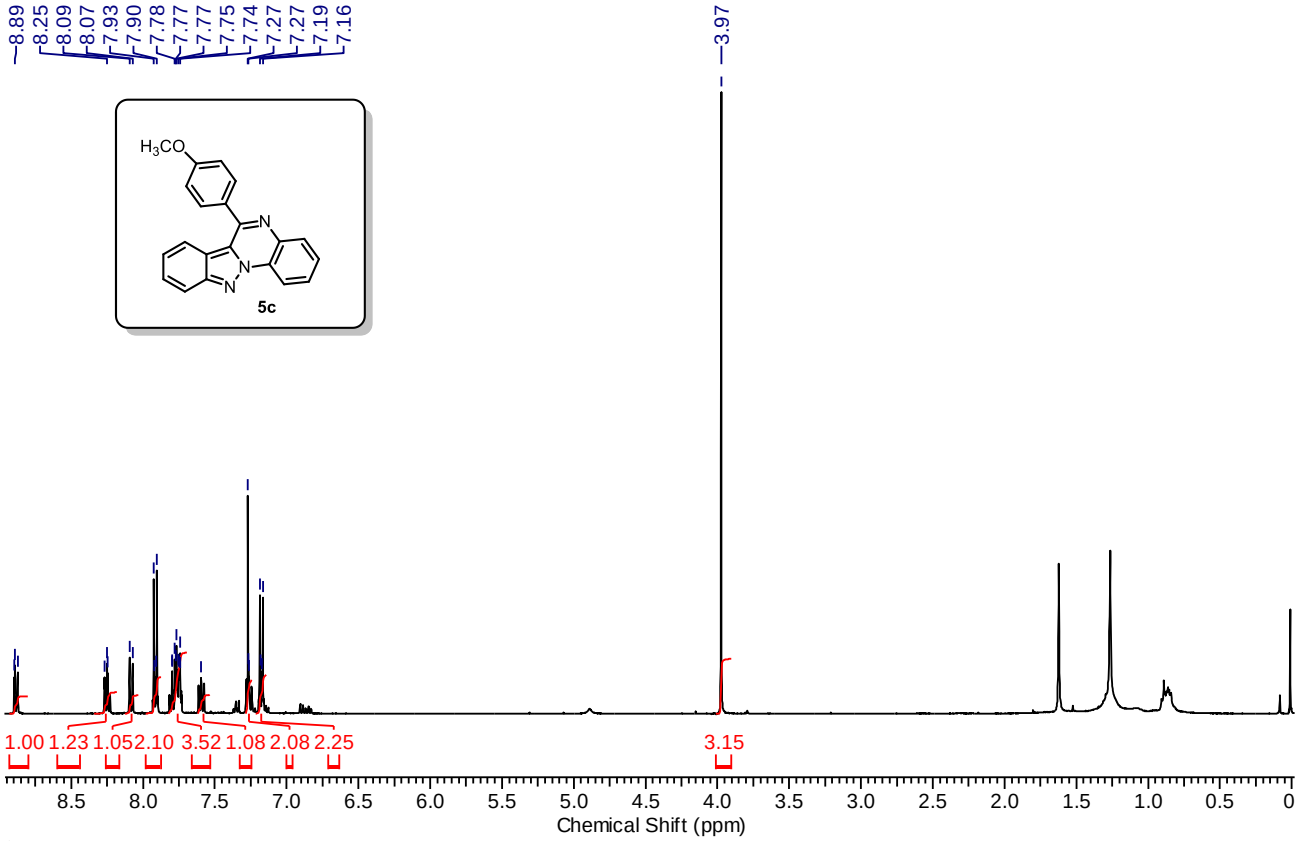
Copies of 1H, 13C NMR Spectra of all Compounds (S3, S4, 3a-w, 5 and 6a-i):



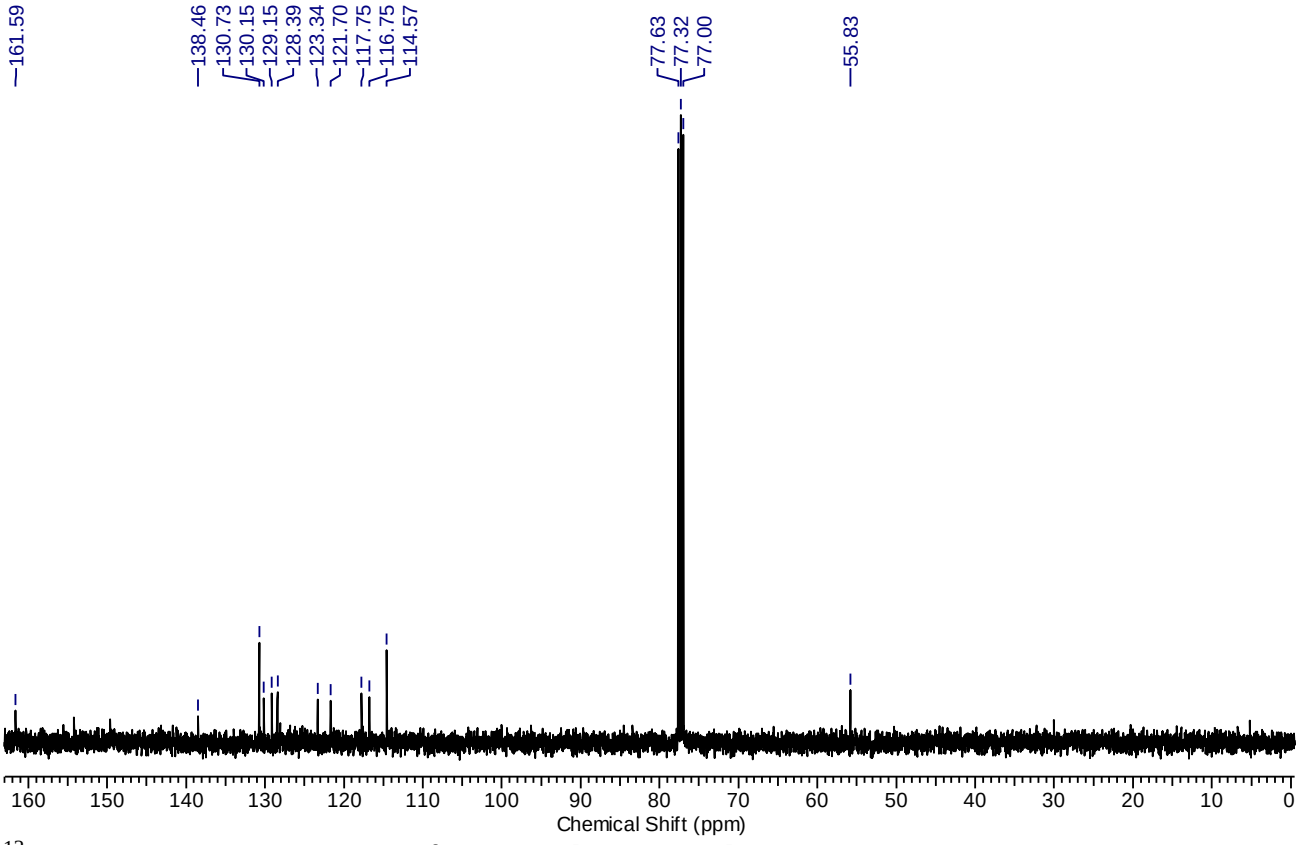
^{1}H NMR (400 MHz) spectrum of compound **5a** in $CDCl_3$



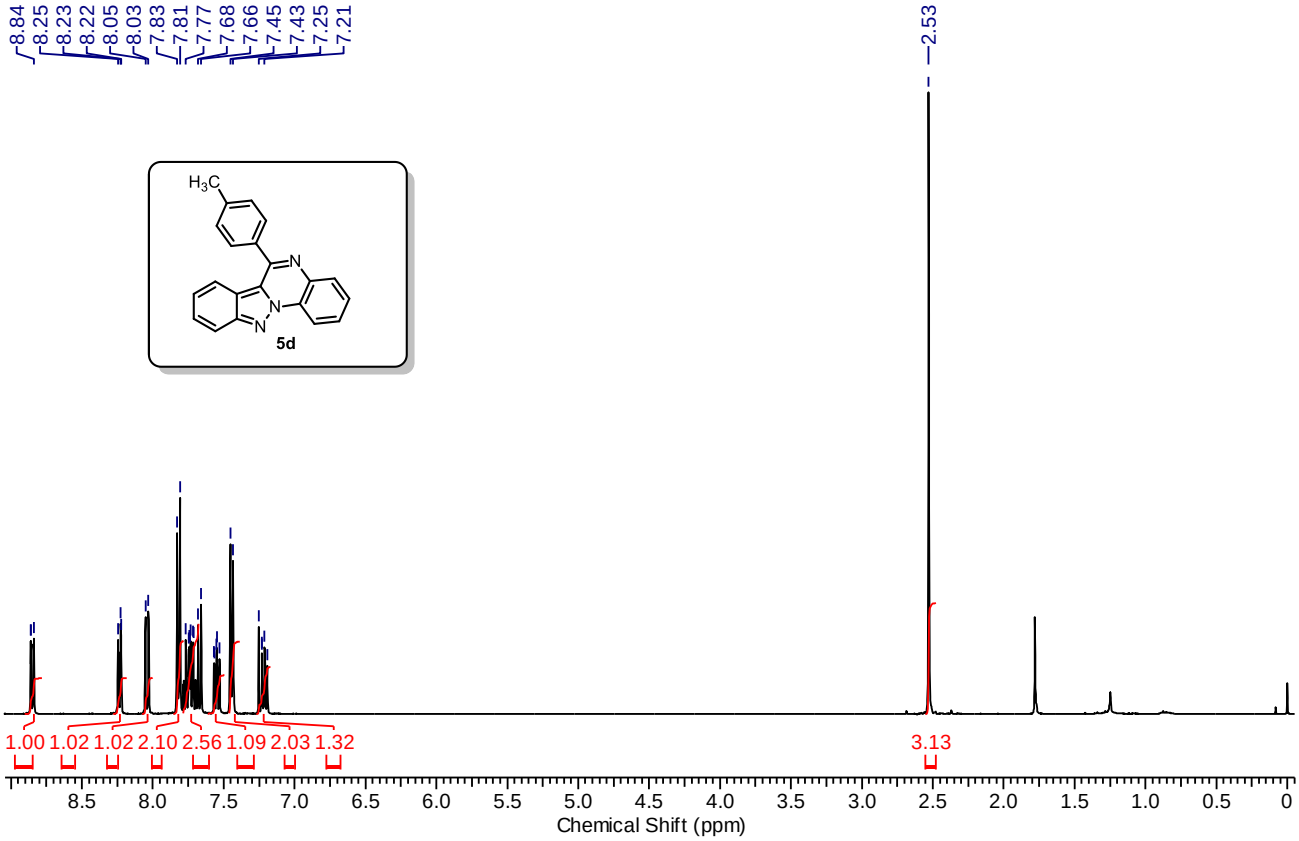
^{13}C NMR (100 MHz) spectrum of compound **5a** in $CDCl_3$



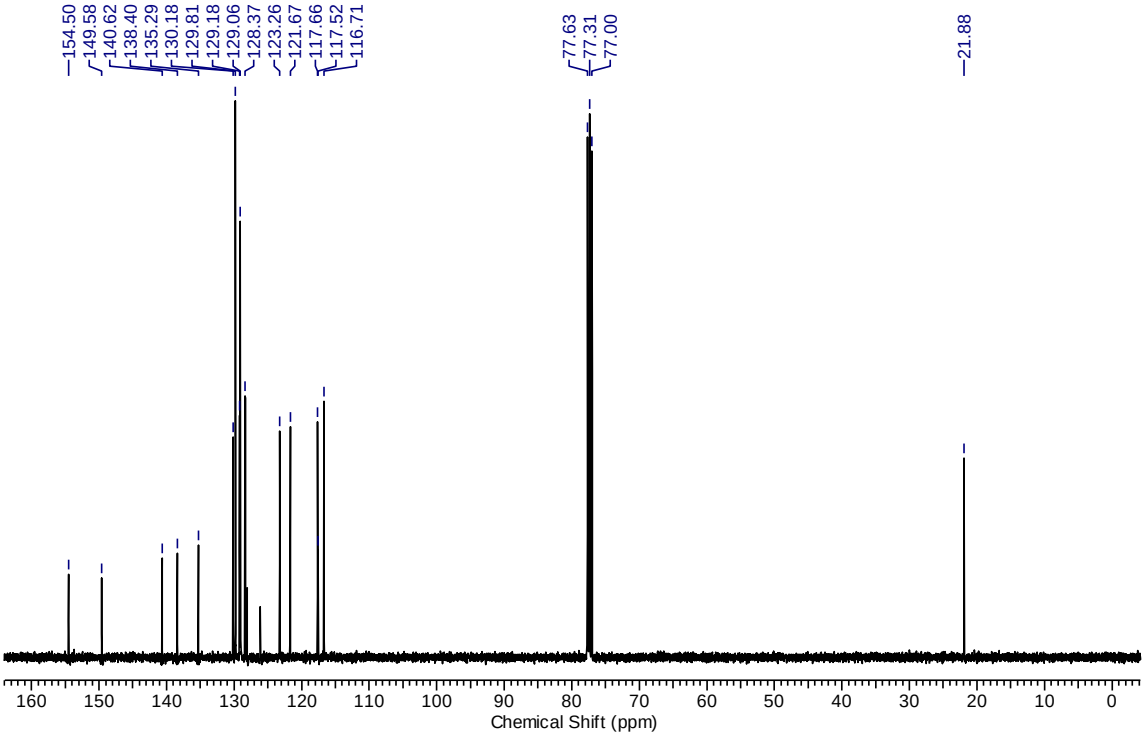
^{1}H NMR (400 MHz) spectrum of compound **5c** in $CDCl_3$



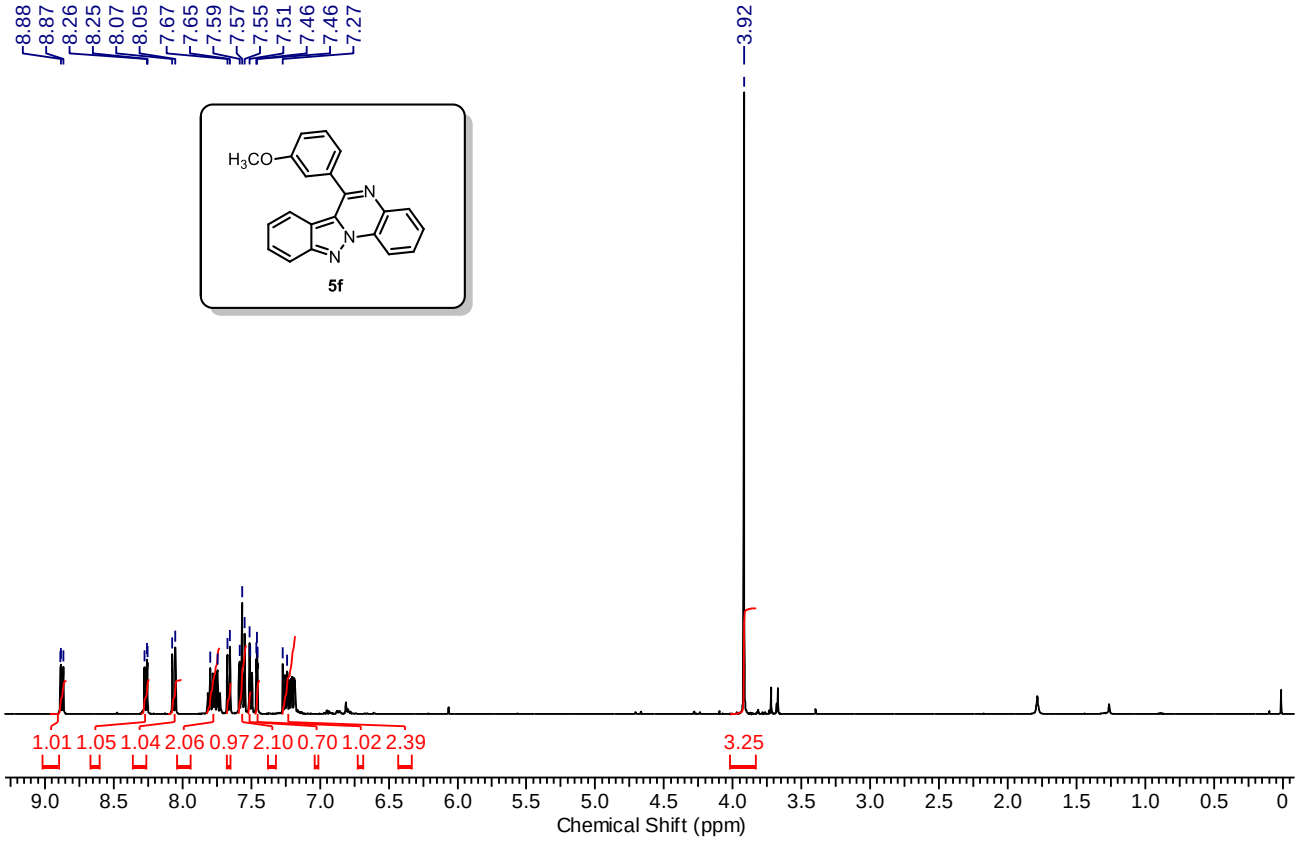
^{13}C NMR (100 MHz) spectrum of compound **5c** in $CDCl_3$



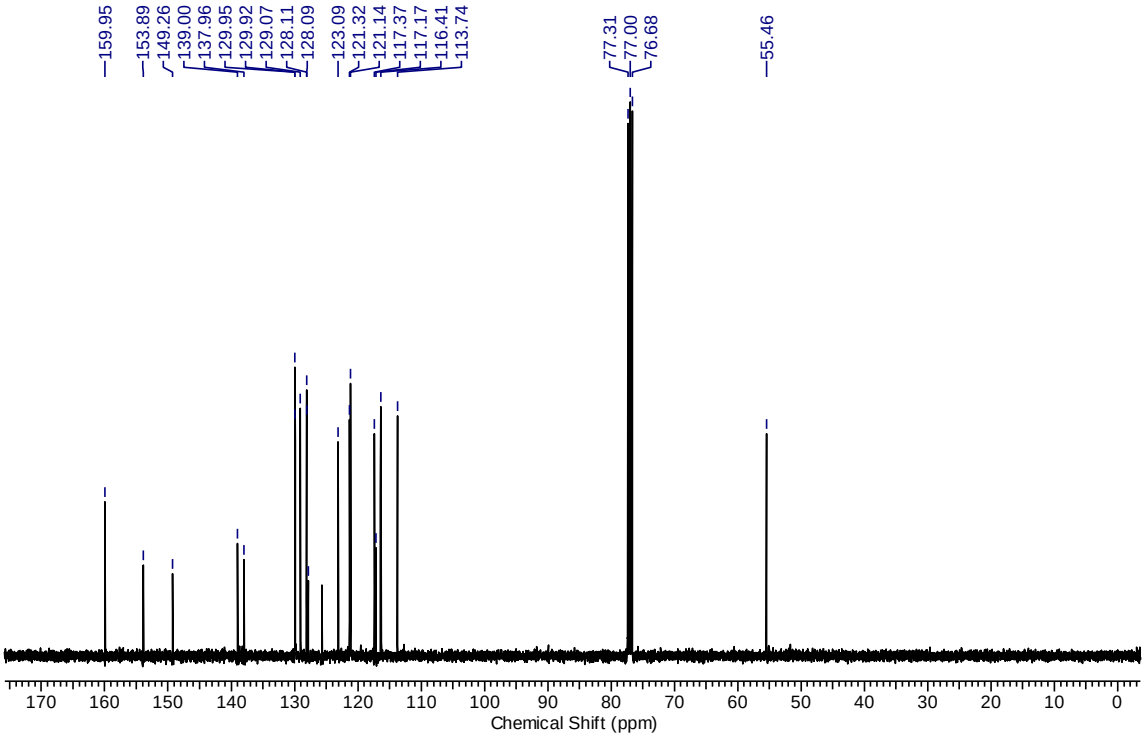
^{1}H NMR (400 MHz) spectrum of compound **5d** in $CDCl_3$



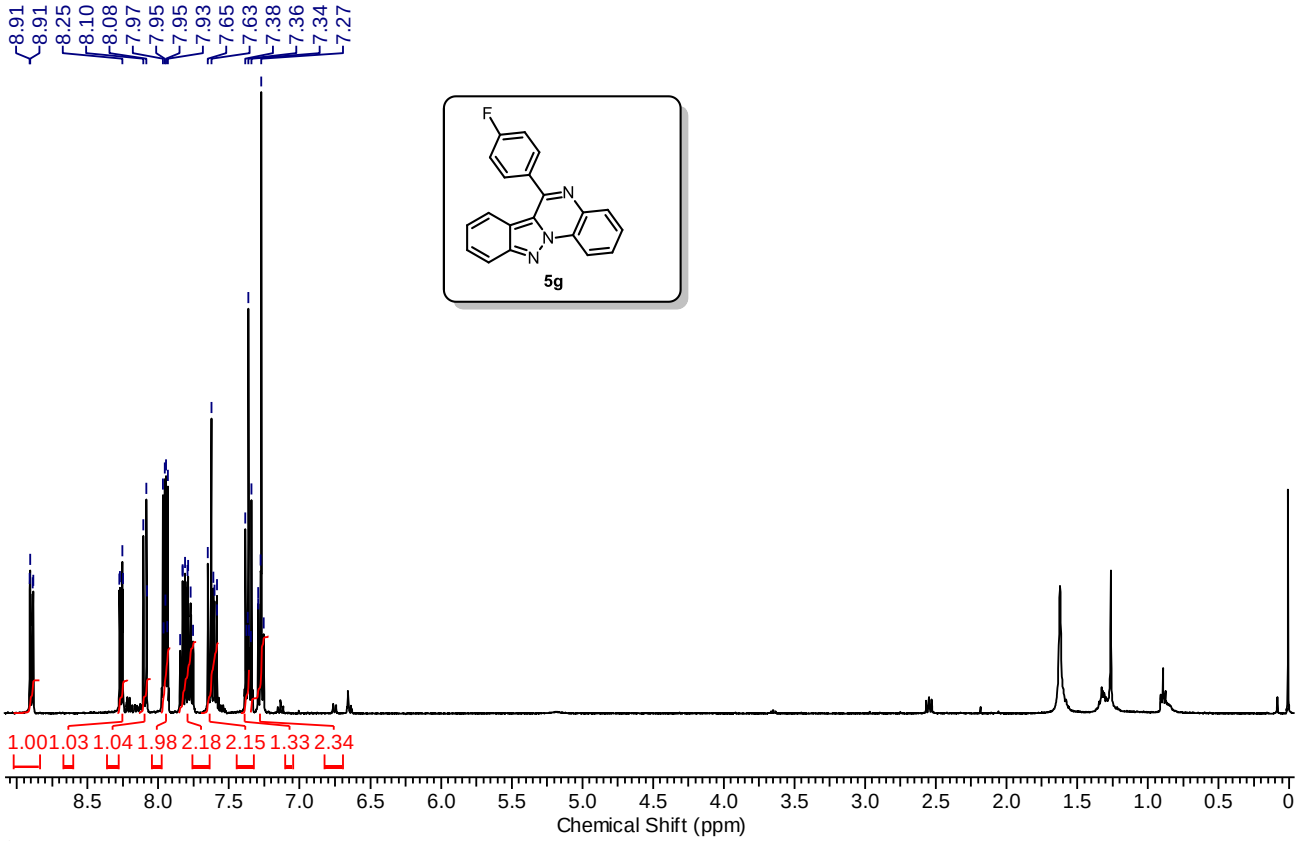
^{13}C NMR (100 MHz) spectrum of compound **5d** in $CDCl_3$



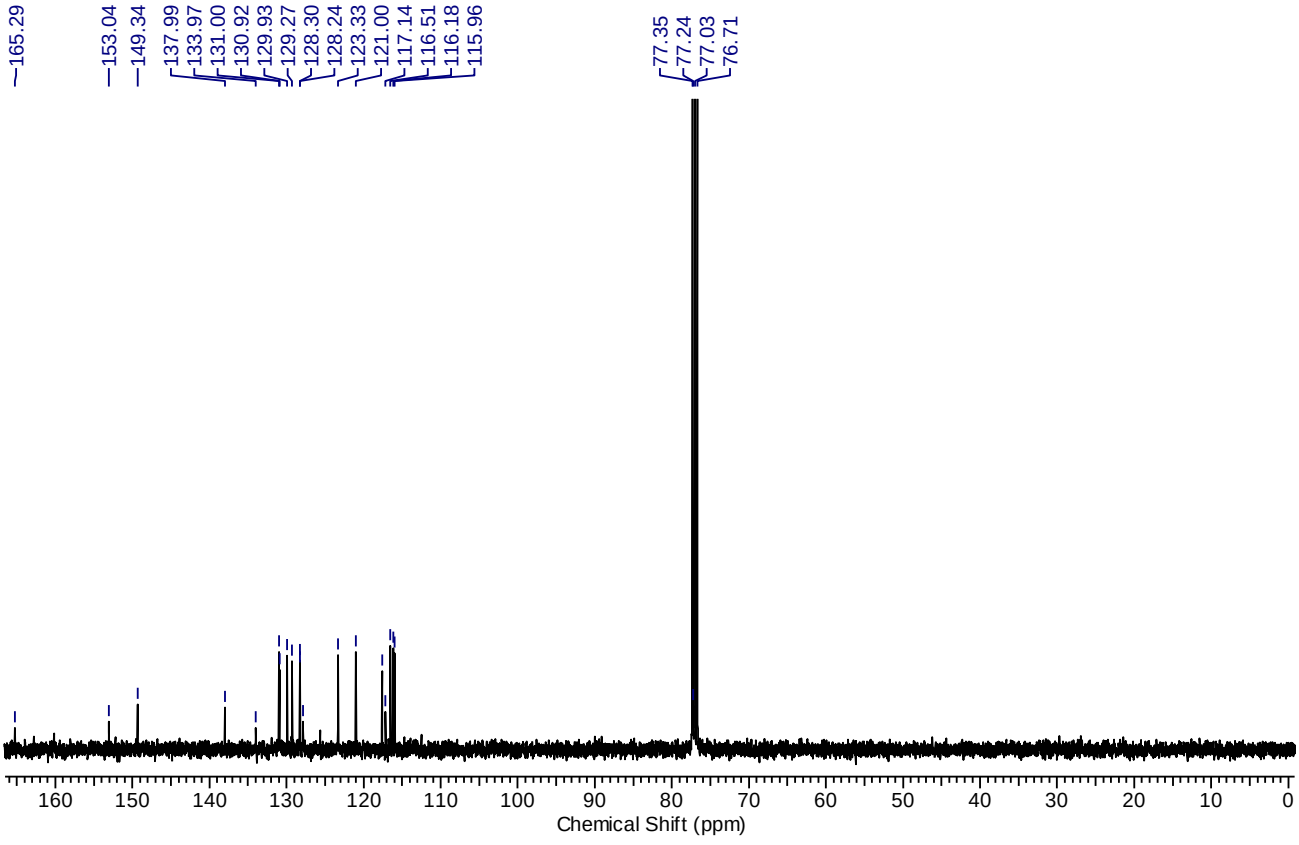
^{1}H NMR (400 MHz) spectrum of compound **5f** in $CDCl_3$



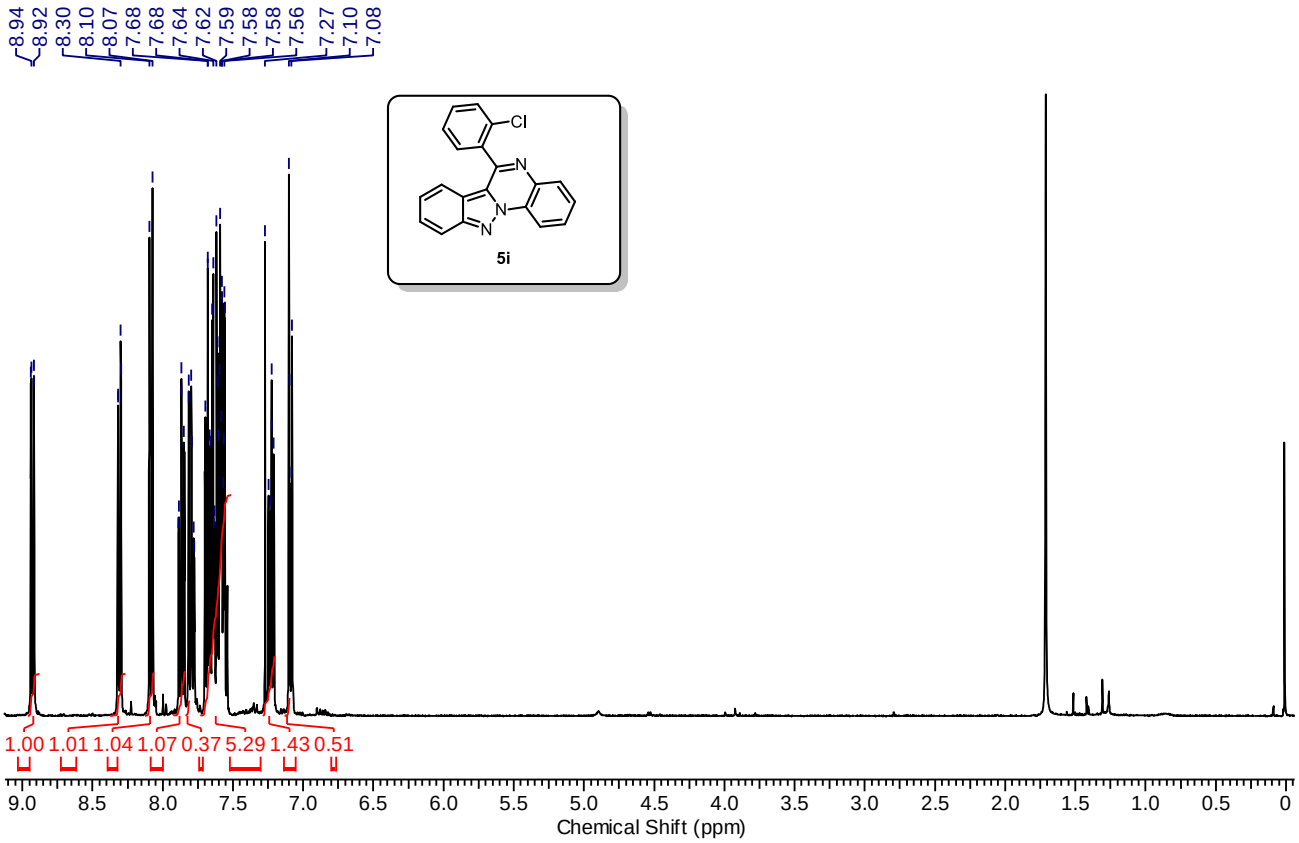
^{13}C NMR (100 MHz) spectrum of compound **5f** in $CDCl_3$



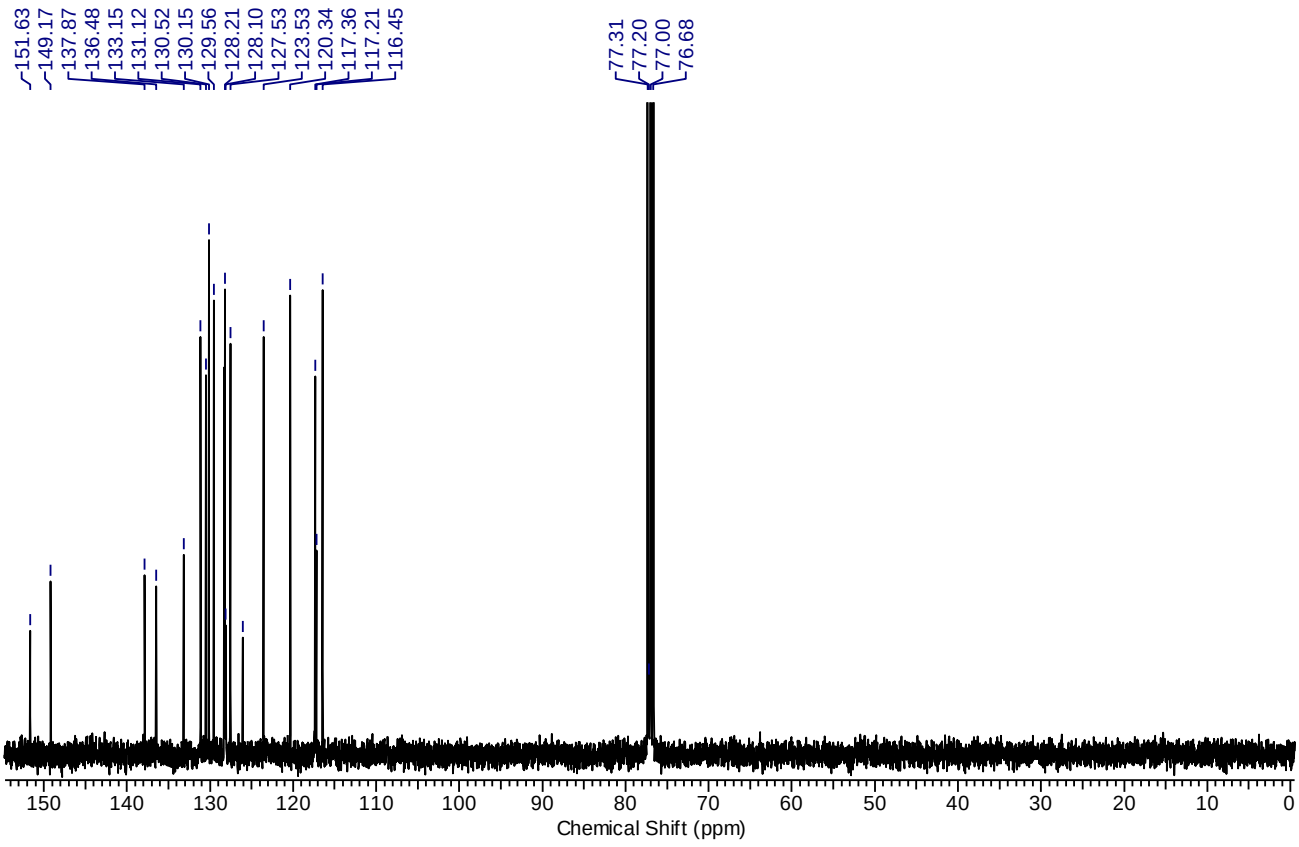
^{1}H NMR (400 MHz) spectrum of compound **5g** in $CDCl_3$



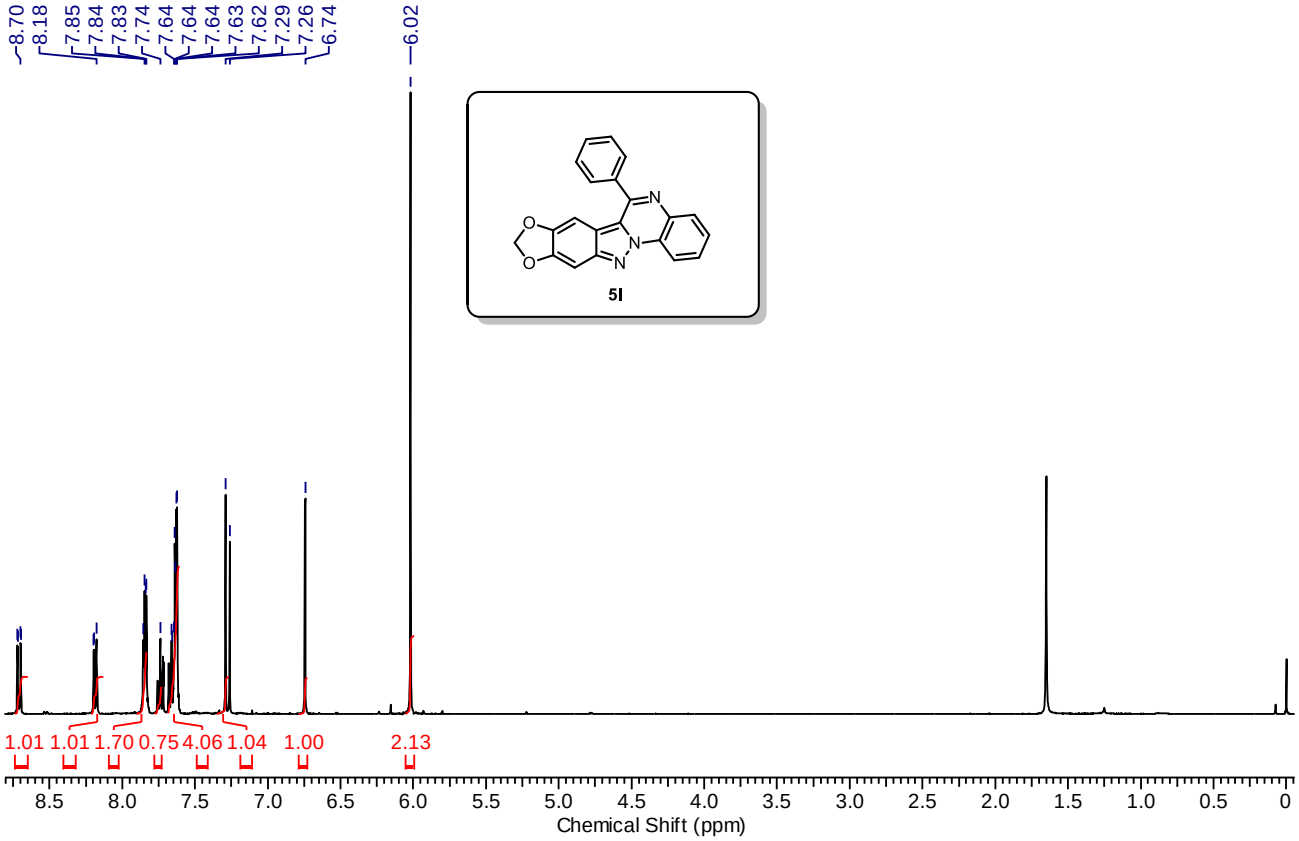
^{13}C NMR (100 MHz) spectrum of compound **5g** in $CDCl_3$



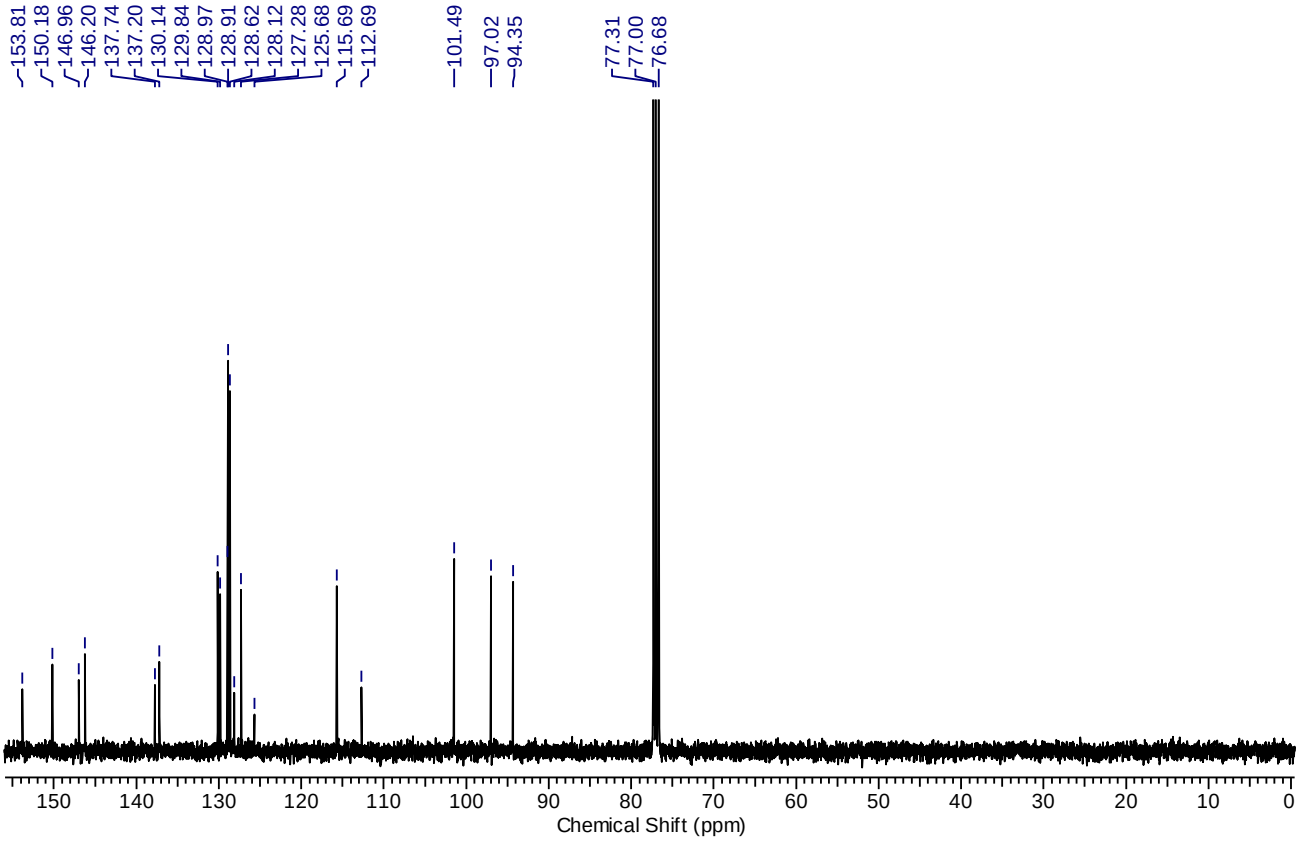
^{1}H NMR (400 MHz) spectrum of compound **5i** in $CDCl_3$



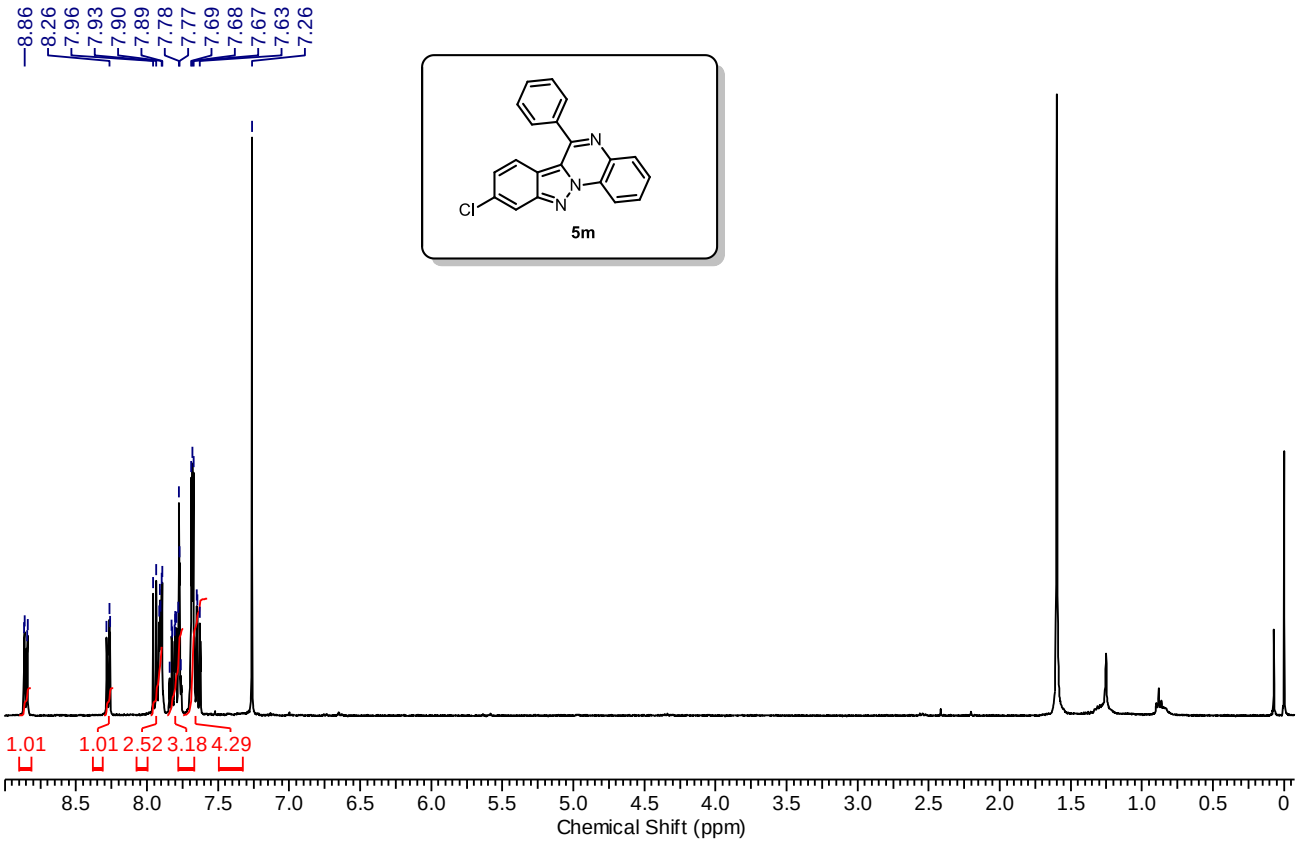
^{13}C NMR (100 MHz) spectrum of compound **5i** in $CDCl_3$



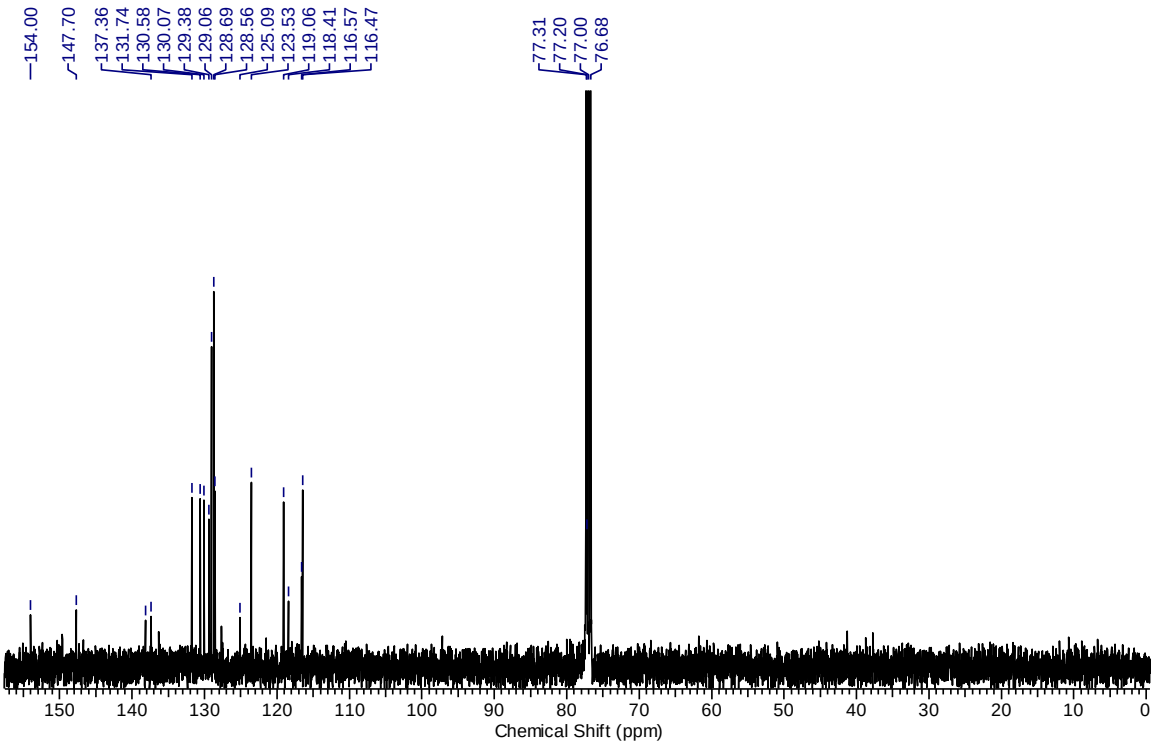
^{1}H NMR (400 MHz) spectrum of compound **5l** in $CDCl_3$



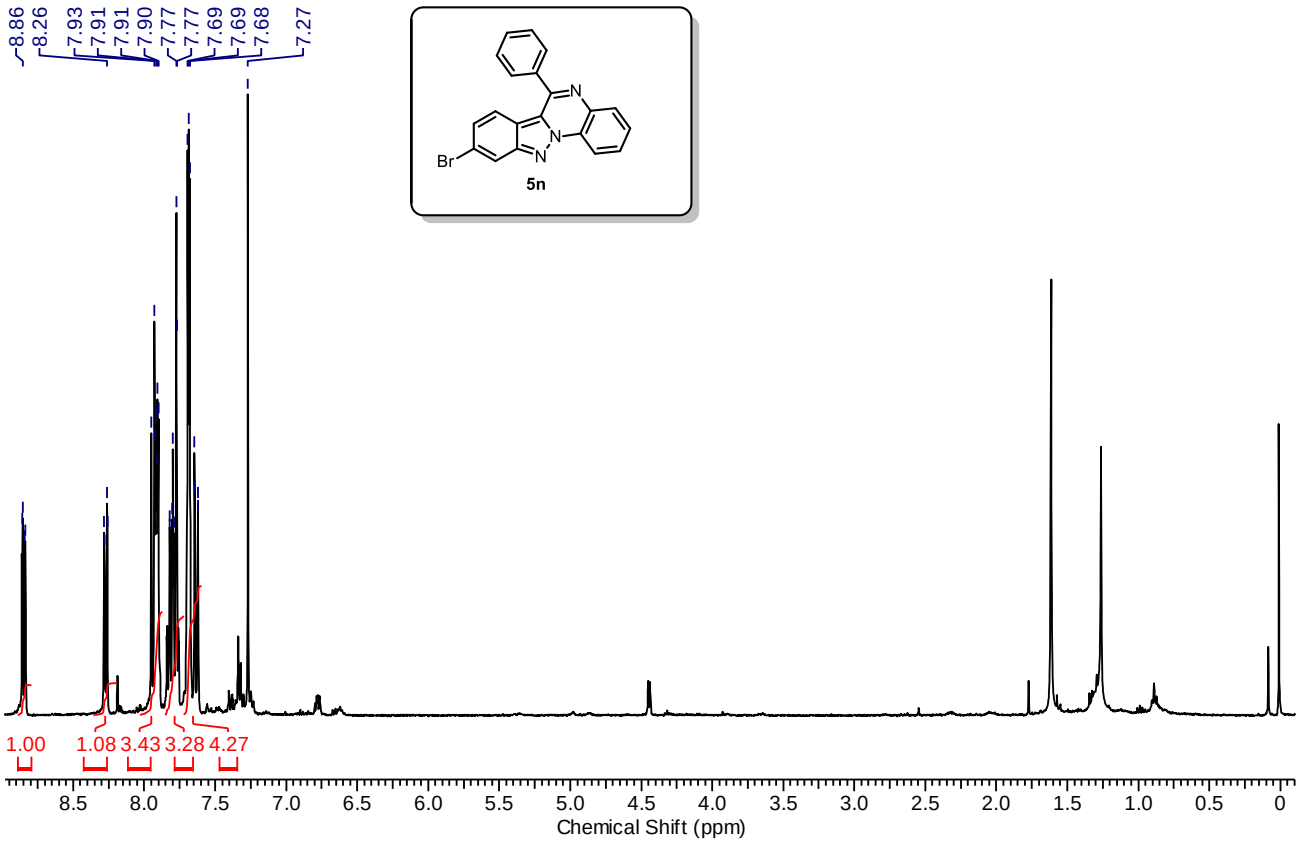
^{13}C NMR (100 MHz) spectrum of compound **5l** in $CDCl_3$



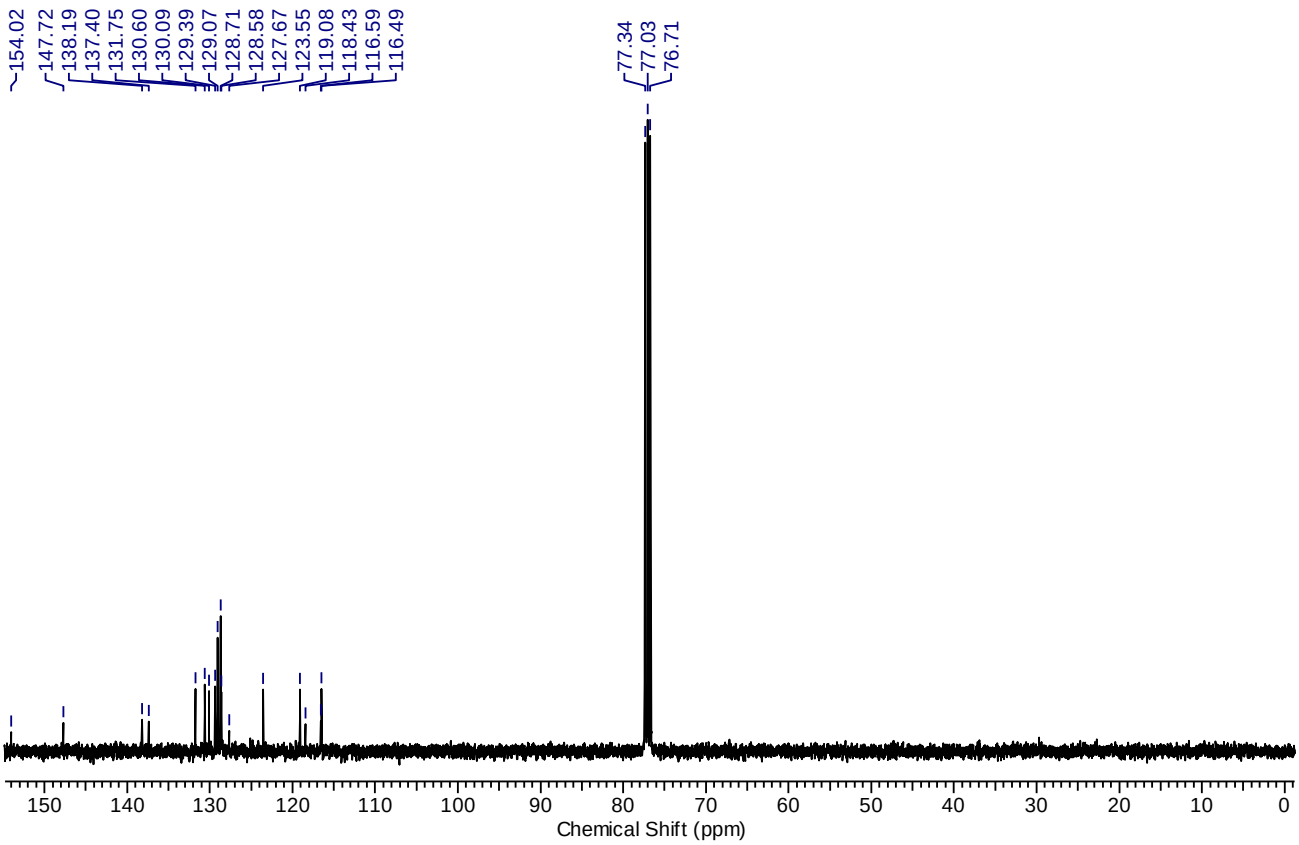
^{1}HNMR (400 MHz) spectrum of compound **5m** in $CDCl_3$



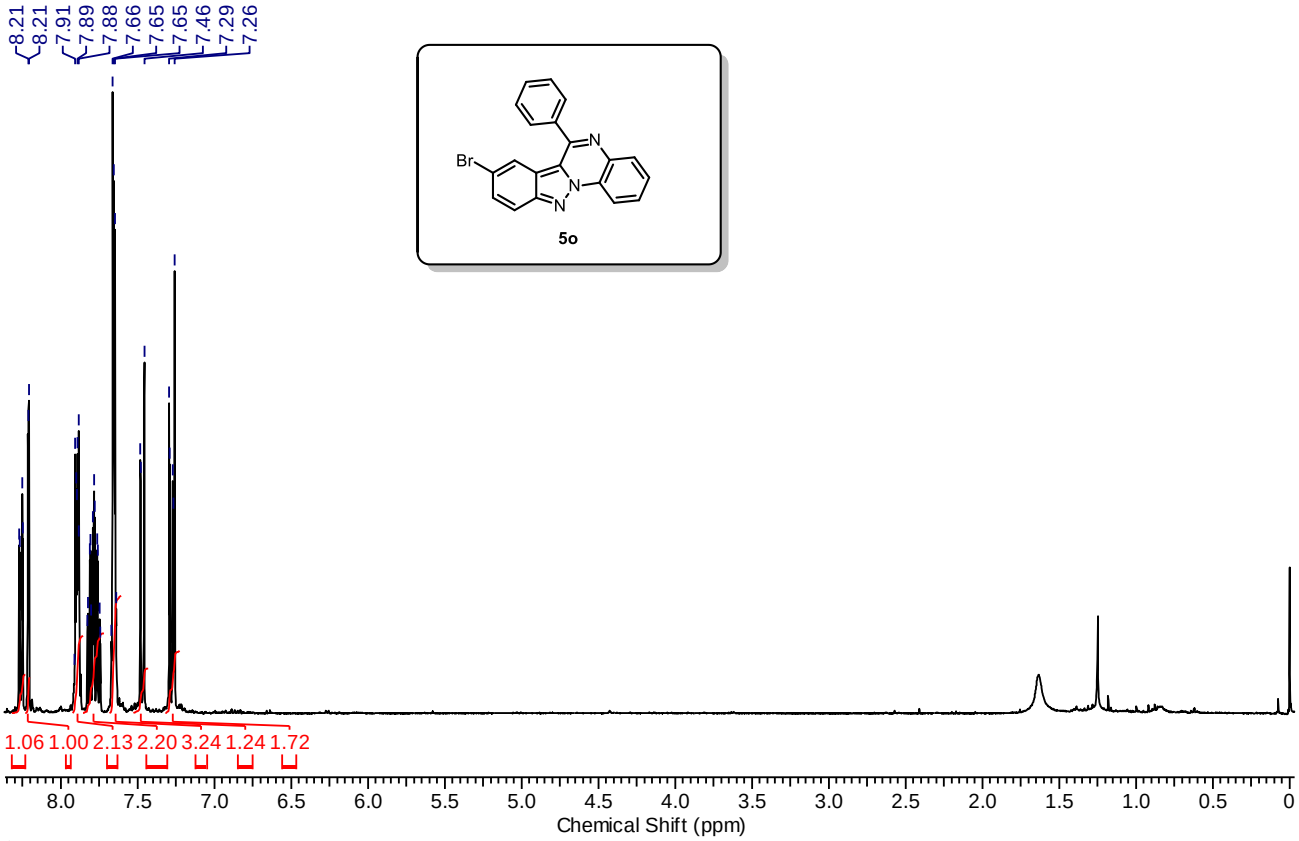
^{13}CNMR (100 MHz) spectrum of compound **5m** in $CDCl_3$



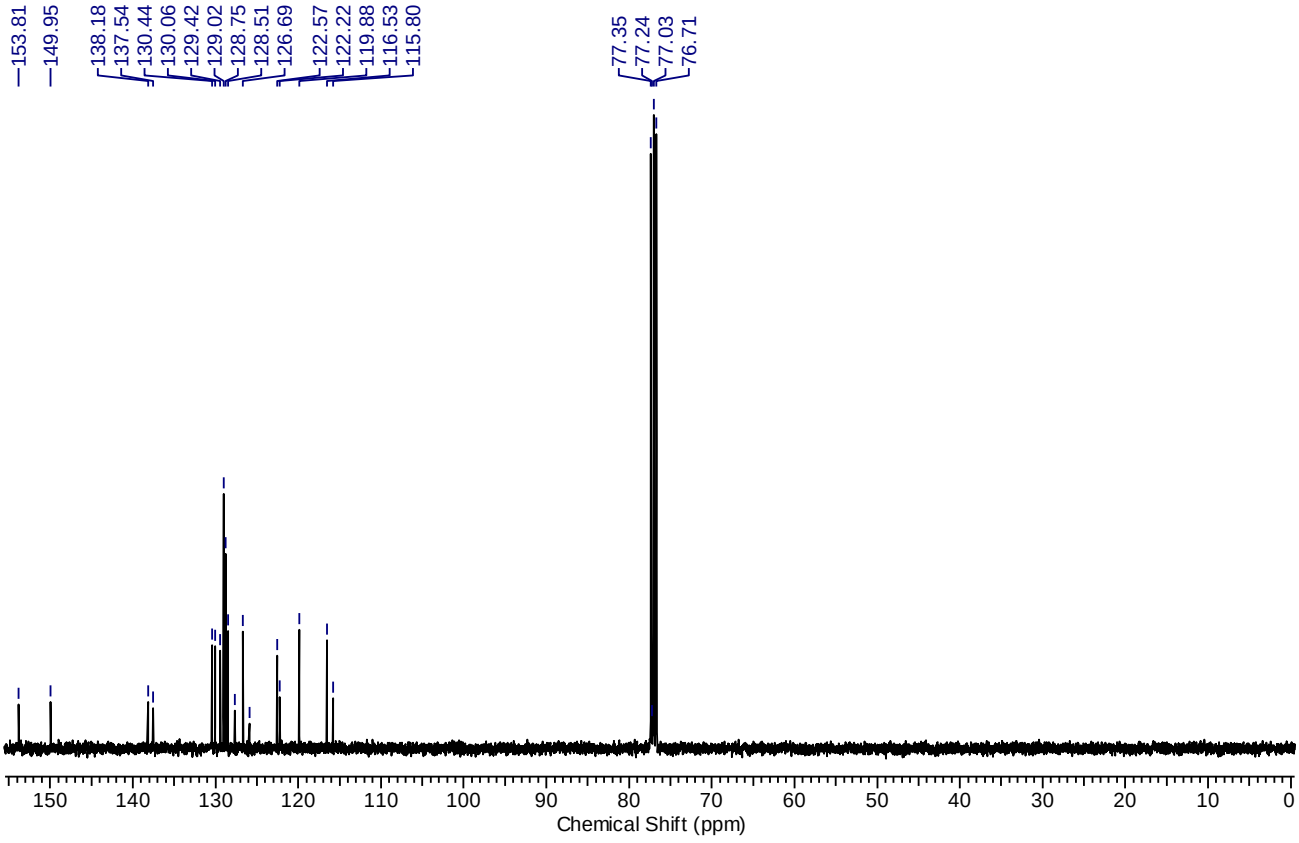
^{1}HNMR (400 MHz) spectrum of compound **5n** in $CDCl_3$



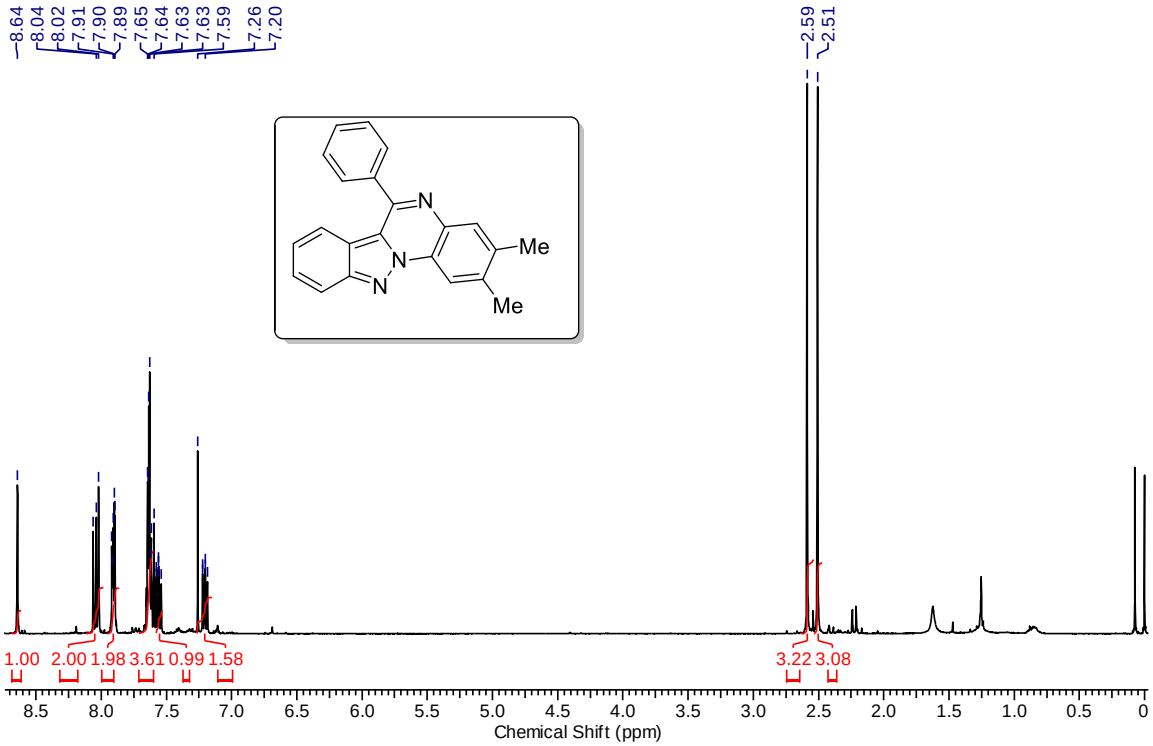
^{13}C NMR (100 MHz) spectrum of compound **5n** in $CDCl_3$



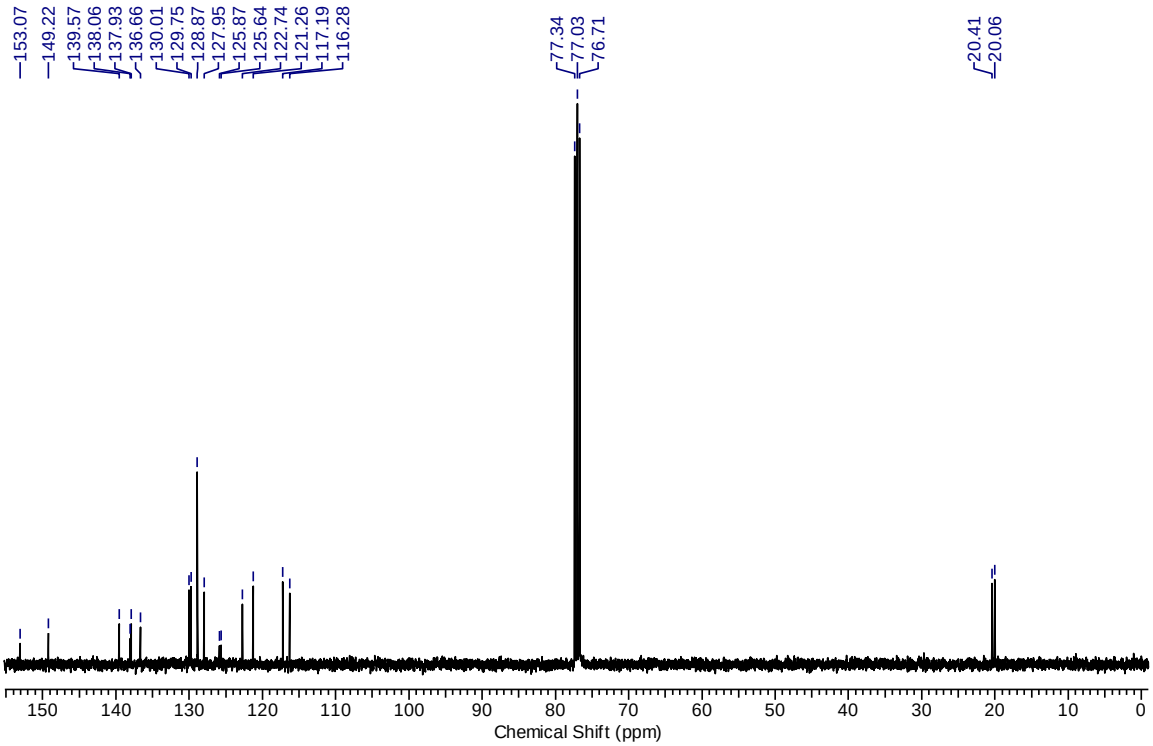
^{1}H NMR (400 MHz) spectrum of compound **5o** in $CDCl_3$



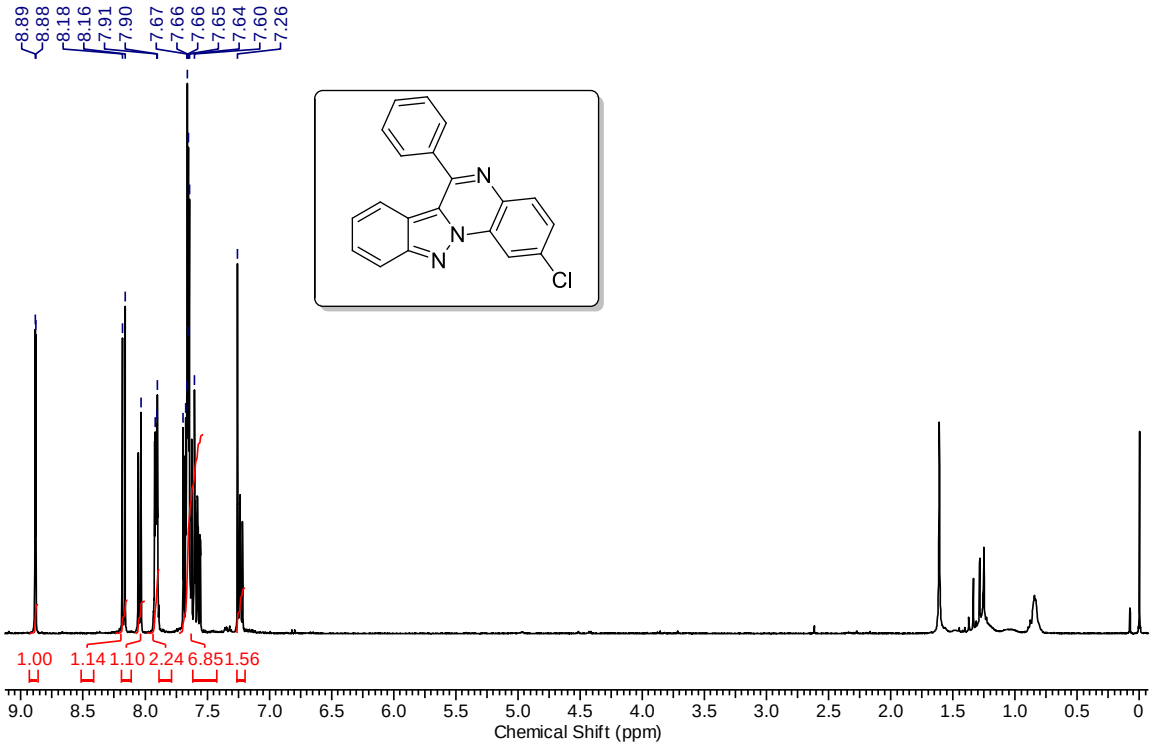
^{13}C NMR (100 MHz) spectrum of compound **5o** in $CDCl_3$



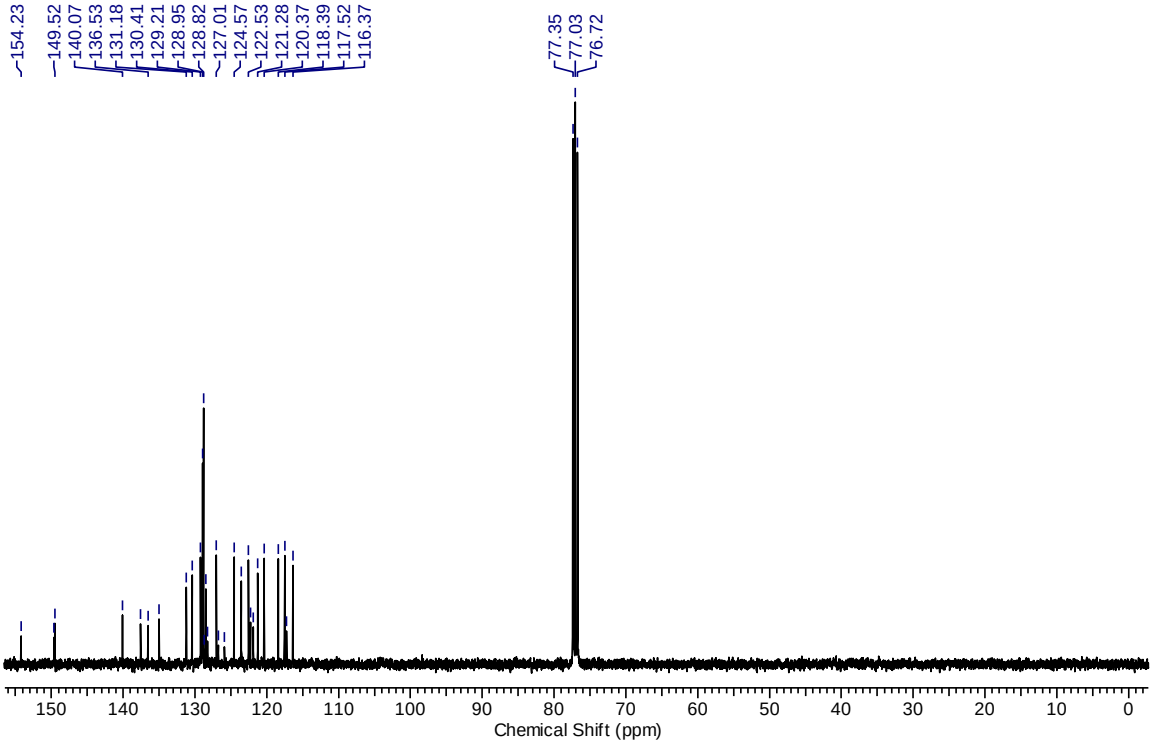
^{1}H NMR (400 MHz) spectrum of compound **5q** in $CDCl_3$



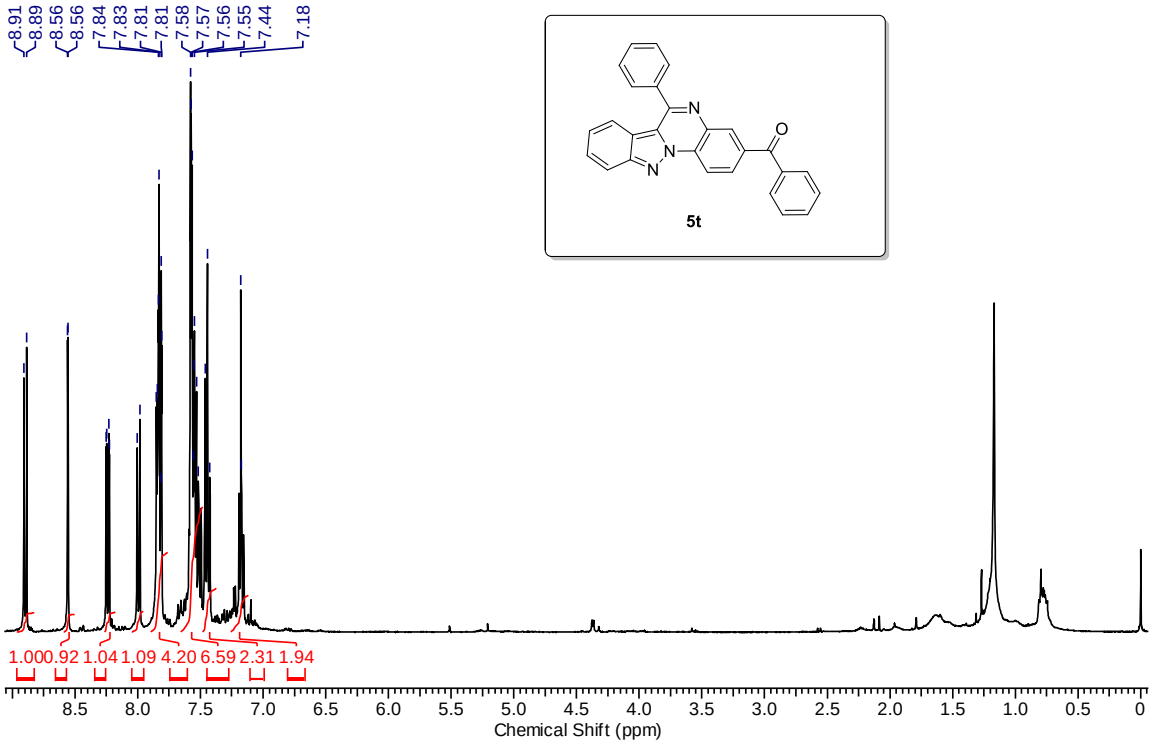
^{13}C NMR (100 MHz) spectrum of compound **5q** in $CDCl_3$



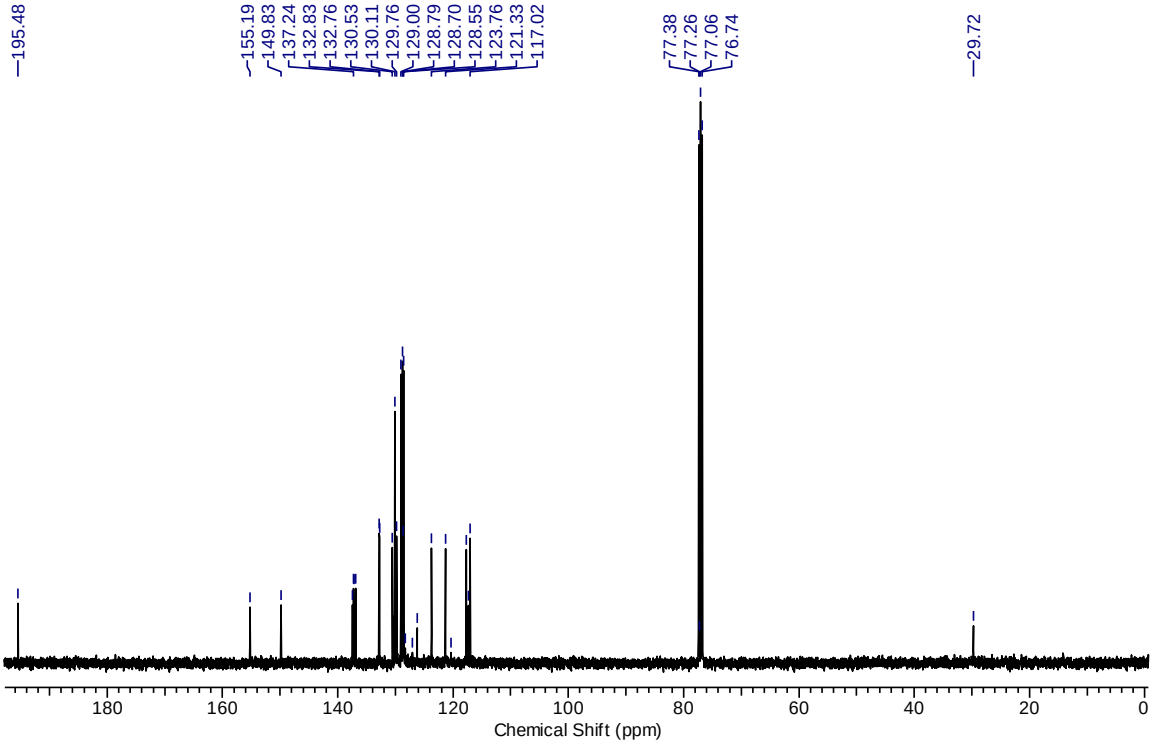
^{1}H NMR (400 MHz) spectrum of compound **5r** in $CDCl_3$



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



^{1}H NMR (400 MHz) spectrum of compound **5t** in $CDCl_3$



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