Palladium Catalyzed Aerobic Oxidative Isocyanide Insertion Leading to 2-Amino Substituted 4(3H)-Quinazolinones

A Project Report Submitted

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Master of Science

by

CHAITRA C.

CY12M1008

Under the supervision of

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भारतीय प्रौद्योगिकी संस्थान हैदराबाद

Indian Institute of Technology Hyderabad

Department of Chemistry

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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I'm also thankful to all my friends and my parents for their encouragement, support and valuable suggestions throughout my M.Sc.

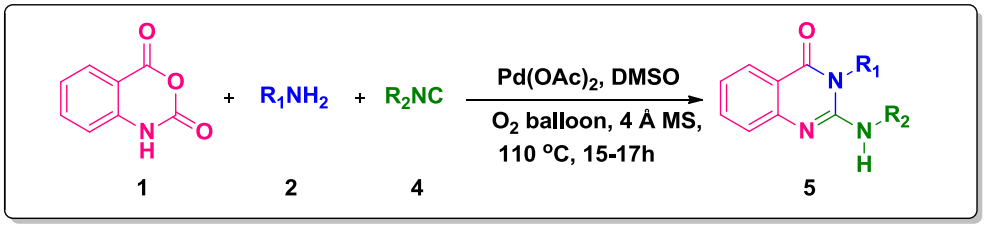
Dedicated

To

Lord Shri Krishna and my Beloved Parents

Abstract

An efficient one-pot cascade aerobic oxidative palladium-catalyzed multi-component reaction was developed through isocyanide insertion between less active amide NH and aromatic amine. This approach leads to an efficient synthesis of 2-amino-substituted 4(3H)-quinazolinones.



Contents:

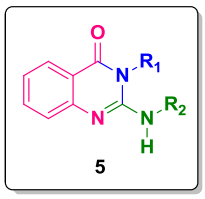
Palladium Catalyzed Aerobic Oxidative Isocyanide Insertion Leading to 2-Amino Substituted 4(3H)-Quinazolinones

1. Introduction:

Recently, the development of Multi-Component Reactions (MCRs) is in the wide employment of transition metals which catalyze various reactions to synthesize heterocyclic molecules.[1] MCR complies with several green principles, and is easier and less time consuming than the conventional synthesis. It offers several remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of steps, work up, extraction, purification thus minimizing the waste generated and rendering the transformation green.[2] Among the generally used transition metal catalysts like rhodium, ruthenium, palladium, iron and copper; palladium occupies a prominent position. Palladium catalyses variety of reactions and the one that is in boom presently among MCRs is the imidoylative reaction.

The very useful carbonylation (CO insertion) reaction in heterocyclic synthesis is now being replaced by imidoylation (isocyanide insertion). Even though isocyanides are known for its obnoxious odour, their synthetic utility is very huge in the field of heterocyclic synthesis.[3] Isocyanide undergoes nucleophilic attack, electrophilic addition, imidoylation, oxidation etc. The unique feature of isocyanide to act as a one carbon building block makes it important in drug design and discovery. The property of electrophilicity and nucleophilicity on same carbon is the cause for its utility in MCRs and subsequent combination reactions for the synthesis of nitrogen heterocycles.[3] This property is similar to that of CO which provides an opportunity for its replacement by isocyanide. Other advantages isocyanides have over CO are its easy handling and the property to bring about high diversity. Thus, having seen the scope of transition metal catalyzed MCRs it was inspiring for us to develop a transition metal catalyzed MCR in one pot for the synthesis of 2-amino-substituted 4(3H)-quinazolinone.

2. Biological and pharmaceutical importance:



5

2-amino-substituted 4(3H)-quinazolinone

Heterocyclic compounds are well noted for their wide presence among natural compounds and more importantly for its potent biological and medicinal properties. It is quite interesting to know that, among them, 4(3H)-quinazolinone group has a broad range of biological activities which includes antibacterial, antifungal, antiviral, antitumor, anticonvulsant[4a] etc. Apart from these, many alkaloids too incorporate this moiety. Its highly potent properties make it a very goodpharmacophore and it occupies a key role in drug design and discovery. For e.g. methaqualone[4a] (antimalarial), afloqualone[4a] (muscle relaxant). Guanidine moieties are other well known functionalities for their wide occurrence among natural products. They possess some unique properties with respect to their interaction with biological system which makes them important in medicinal chemistry. They are known to exhibit potent antibacterial, antiviral, antiparasitic, anticancer etc properties. For e.g. anagrelide[4b] (thrombocytosis), norastemizole[4c] (rhinitis).

It can be said that when two biologically potent functionalities are present within a same molecule, its bioactivity would be enhanced. One such molecule is 2-amino-substituted 4(3H)-quinazolinones. They have antibacterial, anti-inflammatory, antimalarial properties. These also act against plant pathogens like TMV, *Xanthomonas oryzae*, *Sclerotinia sclerotiorum*[4d] etc and thus useful agriculturally too. It is worth mentioning that, apart from these, 2-amino-substituted 4(3H)-quinazolinone moieties also have potent activity against Parkinson's and hypokinetic conditions which are now becoming common among people in the fast moving lifestyle.[4e] For e.g nolatrexed[4f] (anticancer), acyclovir[4g] (antiviral) (Fig. 1). Thus, the major role these molecules have was an impetus for us to work towards the synthesis of privileged 2-amino-substituted 4(3H)-quinazolinones, which are expected to be studied for their biological properties. Even though there are several strategies for its synthesis, exploring newer and efficient protocols would always be in demand.

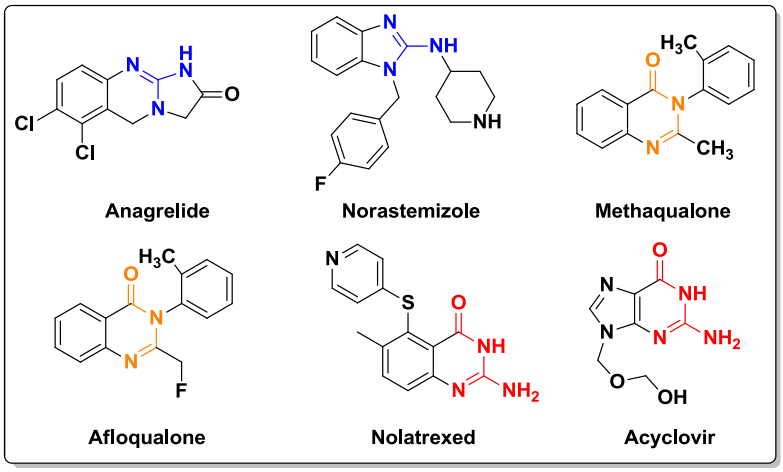
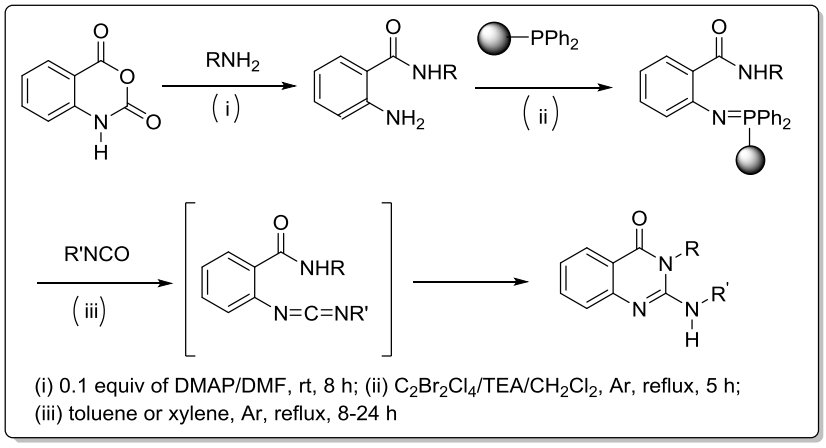


Fig. 1: Clinically useful quinazolinone and guanidine-containing heterocycles.

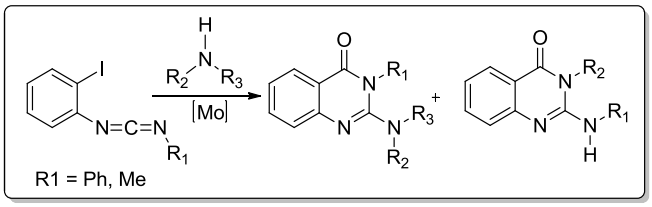
3. Previous Methodologies:

Since these molecules possess interesting and wide range of biological properties, its synthesis has drawn attention of many chemists. There are several reports regarding the synthesis of 2-amino-substituted 4(3H)-quinazolinones which employ quite different strategies. Herein, are presented some of the previous methods.

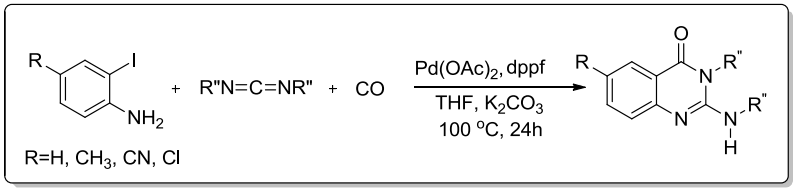
1. Solid-phase synthesis of 2-amino-substituted 4(3H)-quinazolinones.[5]



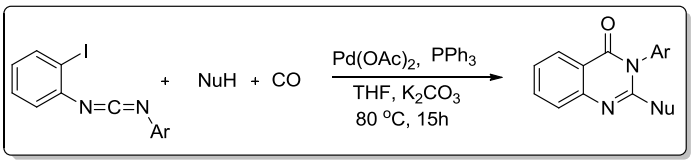
2. Molybdenum-mediated synthesis of quinazolin-4(3H)-ones.[6]



3. Palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with heterocumulenes.[7]



4. Tandem palladium-catalyzed addition/cyclocarbonylation.[8]



The highly useful 2-amino-substituted 4(3H)-quinazolinones has several reports for its synthesis, of which only a few relevant procedures are mentioned above. Few drawbacks the earlier methods possess are explained as follows.[9] Even though *combinatorial chemistry* has emerged as a powerful tool for the design and synthesis of pharmacologically relevant heterocyclic molecules, they have certain disadvantages like (a) one must take care that the functional groups of the components involved are compatible with the solid support used; (b) the desired properties of the target molecule must be retained after detaching from the support; (c) reaction conditions being heterogeneous do offer several shortcomings. Keeping this strategy apart, there are also other reports known for its synthesis in one-pot which employs transition metals, ligands, base and CO.

Thus, having gone through several available reports for the synthesis, we desired to employ one-pot MCR using the newly evolving strategy which involves aerobic oxidative isocyanide insertion catalysed by palladium. When compared with the already existing protocols that are catalysed by $Pd(OAc)_2$, we sought out to design a reaction that is ligand free, base free, use of readily available starting materials and replacement of highly toxic CO with isocyanide. Hence, this strategy reduces the amount of waste generated, makes work-up easier and better and newer than the existing protocols, thus making it eco-friendly. However, to the best of our knowledge there are no reports for the synthesis of 2-amino-substituted 4(3H)-quinazolinones in one pot without base and ligand, starting with isatoic anhydride.

4. Result and Discussion:

Currently, the number of transition metal catalysed reactions involving isocyanide insertion is increasing rapidly. There are several reports for the synthesis of biologically important heterocycles, for e.g. (a) Palladium catalysed multicomponent synthesis of oxazoline and benoxazole,[10] (b) Synthesis of pyridopyrimidines by palladium catalyzed isocyanide insertion,[11] (c) Synthesis of 4-aminophthalazine-1(2H)-ones by palladium catalyzed isocyanide insertion,[12] (d) Palladium catalysed synthesis of 2-aminobenzoxazinones by aerobic oxidative coupling,[13] (e) Palladium catalyzed reaction for the synthesis of isoquinolin-1(2H)-ones,[14] (f) Palladium catalyzed synthesis of isocoumarins and phthalides[15] etc. These reports on heterocyclic synthesis drove us to investigate an efficient method for the synthesis of 2-amino-substituted 4(3H)-quinazolinones catalyzed by palladium. We began to proceed with isatoic anhydride which opens with amine to give the desired dinucleophile under inert conditions (Scheme 1). To the same reaction mixture CyNC and catalyst were added, oxygen atmosphere which acts as oxidant in order to regenerate the catalyst was provided. The obtained dinucleophile serves as a substrate for isocyanide insertion, of which one is less active amide NH and the other being aromatic NH_2 (Scheme 1). For optimizing the reaction condition various bases, solvents and isocyanides of different equivalents were examined (Table 1 & 2). To our surprise, reaction went smoothly without any base and afforded very good yields with oxygen comparatively (Table 1). Most of the isocyanide insertion reactions reported so far exclusively used *tert*-butylisocyanide to get the desired results in very good yields. Moreover, reactions with primary and secondary isocyanides are reported to give low yields. But, in our case the observations was inverse to this. We obtained better results with secondary cyclohexylisocyanide while *tert*-butylisocyanide and various other isocyanides gave very low yields (Table 3). Thus, it is noteworthy to mention that reaction with *tert*-butylisocyanide failed to give expected results.

As shown, good yields were obtained with toluene and DMSO as solvent. In order to further expand the scope of reaction we chose DMSO as solvent with 1.5 equiv. of cyclohexylisocyanide, oxygen as oxidant at 110 ^{o}C as our optimum condition (Entry 11). We explored the generality of reaction with various amines like benzylic, aliphatic and aromatic amines. We observed that formation of

dinucleophile took 30 minutes with aliphatic and benzylic amines while 2h with aromatic amines, which was 100% completed. During the second step of the reaction we found that benzylic amines gave very good yields while aromatic and aliphatic amines gave low/no yields (Table 3). In the case of benzylic amines with electron donating group very good yields were obtained.

Scheme 1: Optimisation of reaction condition:

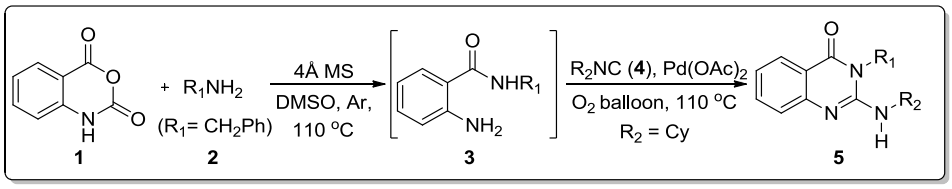


Table 1[a] Screening of solvents with various bases and oxygen.

Entry	Solvent	Catalyst[b]	Temp.(°C)	Additive[c]	Time (h)	Yield[d] (%)
1.	Toluene	$Pd(OAc)_2$	110	K_2CO_3/4ÅMS	30	35
2.	Dioxane	$Pd(OAc)_2$	90	K_2CO_3/4ÅMS	24	0
3.	Toluene	$Pd(OAc)_2$	110	Cs_2CO_3/4ÅMS	20	40
4.	Toluene	$Pd(OAc)_2$	110	Na^{t}OBu/4ÅMS	30	40
5.	Toluene	$Pd(OAc)_2$	110	K^{t}OBu/4ÅMS	30	45
6.	Toluene	$Pd(OAc)_2$	110	NaOMe/4ÅMS	30	10
7.	Toluene	$Pd(OAc)_2$	120	O_2	24	30
8.	MeTHF	$Pd(OAc)_2$	77	O_2	30	10
9.	Toluene	$Pd(OAc)_2$	110	O_2/4ÅMS	17	72
10.	CH_3CN	$Pd(OAc)_2$	85	O_2/4ÅMS	17	0
11.	**DMSO**	**$Pd(OAc)_2$**	**110**	**O_2/4ÅMS**	**17**	**75**

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **4** (1.5 mmol), [b] 5 mol% of $Pd(OAc)_2$, [c] 1.5 equiv. base., [d] isolated yield after column chromatography.

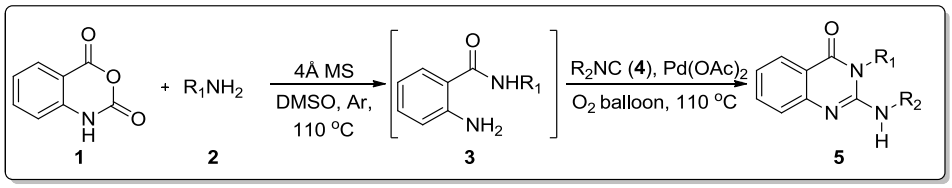
Table 2[a] Screening of isocyanide equivalents and additive.

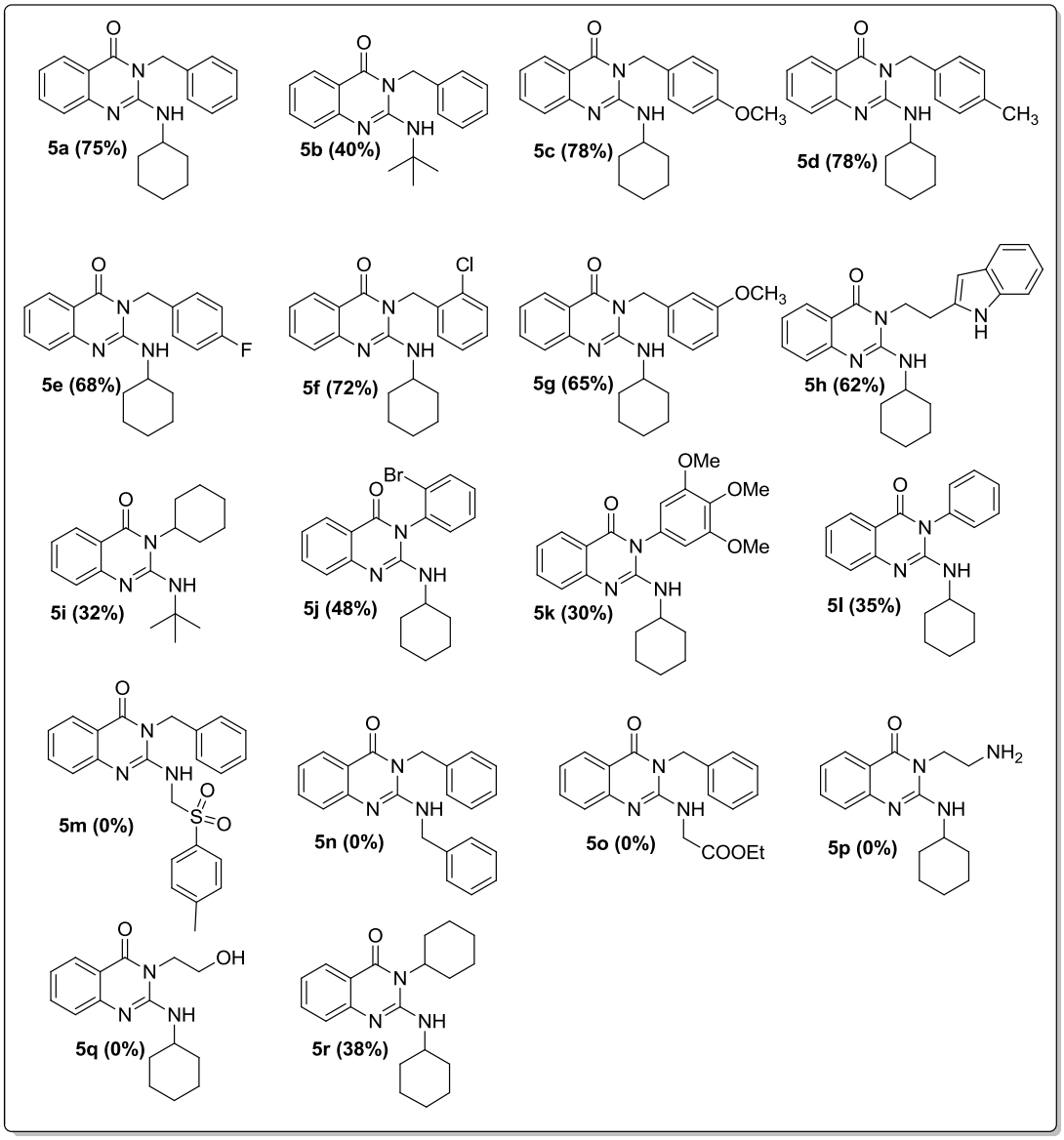
Entry	Solvent	CyNC (equiv.)	Additive[c]	Time (h)	Yield[d] (%)
1.	DMSO	1.0	K^{t}OBu/4ÅMS	20	35
2.	DMSO	1.2	K^{t}OBu/4ÅMS	30	40
3.	DMSO	1.5	K^{t}OBu/4ÅMS	24	40
4.	DMSO	1.2	O_2/4ÅMS	24	30
5.	**DMSO**	**1.5**	**O_2/4ÅMS**	**17**	**75**

6.	Toluene	1.5	O_2/4ÅMS	17	72
7.	Toluene	2.0	O_2/4ÅMS	17	72

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), 5 mol% of $Pd(OAc)_2$, [c] 1.5 equiv., [d] isolated yield after column chromatography.

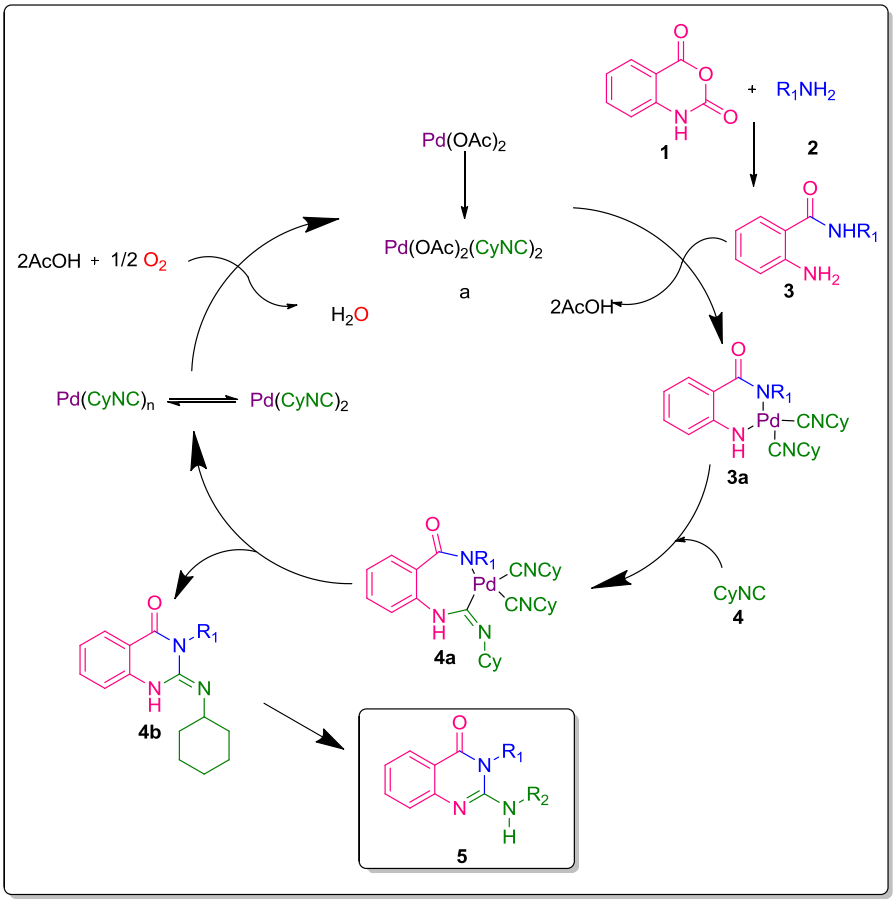
Table 3: Scope of various amines and isocyanides for the synthesis of 2-amino-substituted 4(3H)-quinazolinones (**5a-r**). [a]





[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **4** (1.5 mmol), 5 mol% of $Pd(OAc)_2$, isolated yield after column chromatography.

5. Mechanism:



Plausible mechanism involves the formation of dinucleophile (3) from isatoic anhydride **1** and amine **2**. Catalyst **a** reacts with the dinucleophile to form **3a**, which is followed by isocyanide insertion giving rise to intermediate **4a.** This eventually undergoes reductive elimination to afford Pd^0 which is stabilized by coordination of multiple isocyanides and oxidized by molecular oxygen to regenerate the catalyst.

6. Conclusion

In conclusion, we were successful in developing a novel and facile one-pot palladium catalysed isocyanide insertion by aerobic oxidation for the synthesis of biologically important 2-amino-substituted 4(3H)-quinazolinones. The procedure is operationally simple, employs $Pd(OAc)_2$ which is of low cost relatively, eliminates the use of additional ligand or base.

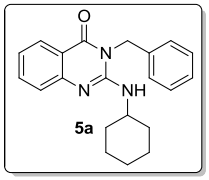
7. Experimental Section

General: IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ in ppm) and coupling constants (J in 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 Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ in ppm) are reported relative to $CHCl_3$ (δ_C = 77.00 ppm). In the ^{1}H-NMR, the following abbreviations are used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s = broad singlet, sept = septet. The assignment of signals were confirmed by ^{1}H and ^{13}C spectral data. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. Melting points were determined using melting point apparatus manufactured by GUNA enterprises, India and are uncorrected. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Solvents were distilled prior to use.

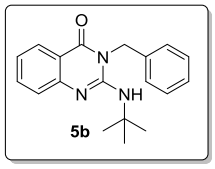
General Procedure:

In an oven dried Schlenk tube under nitrogen atmosphere, were added isatoic anhydride (1 equiv., 0.609 mmol), amine (1 equiv., 0.609 mmol) and activated 4Å molecular sieves (150 mg) followed by addition of dry DMSO (2 mL). The reaction mixture was stirred at 110 ^{o}C for 30 minutes to 2 h. The completion of first step was monitored by TLC. Once dinucleophile was formed $Pd(OAc)_2$ (5mol%), CyNC (1.5 equiv., 0.913 mmol) were added under nitrogen atmosphere. It was evacuated and filled with O_2 using balloon. The resulting reaction mixture was stirred at 110 ^{o}C. Progress of the reaction was monitored by TLC. The reaction mixture was then quenched with water and the product was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product (**5a-r)** was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent, which afforded the desired product.

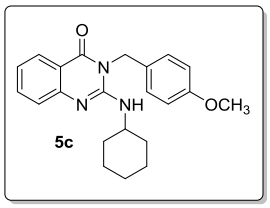
Spectral Data



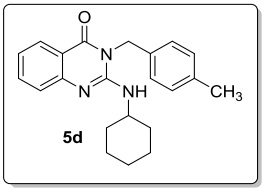
3-Benzyl-2-(cyclohexylamino)quinazolin-4(3H)-one (5a): White solid (75%), Mp 106-108 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3324, 3059, 2921, 1627, 1584, 1517, 1487, 1384, 1230, 1198, 1029, 951, 751, 640. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.18 (dd, 1H, J_a = 8.1 and J_b = 1.2 Hz), 7.60-7.56 (m, 1H), 7.38-7.30 (m, 4H), 7.29-7.26 (m, 1H), 7.17 (t, 1H, J = 7.6 Hz), 5.32 (s, 2H), 4.36 (d, 1H, J = 6.8 Hz), 3.99-3.91 (m, 1H), 1.83 (dd, 2H, J_a = 8.6 and J_b = 3.7 Hz), 1.53-1.46 (m, 3H), 1.40-1.29 (m, 2H), 1.18-0.98 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.2, 149.5, 149.2, 135.3, 134.4, 129.4, 128.2, 127.4, 126.6, 124.9, 122.4, 116.9, 49.7, 44.6, 42.5, 25.6, 24.2. HR-MS (ESI+) m/z calculated for $[C_{21}H_{24}N_3O]^+$ = $[M+H]^+$: 334.1914; found: 334.1901..



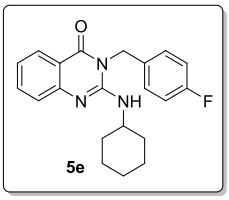
3-Benzyl-2-(tert-butylamino)quinazolin-4(3H)-one (5b): White solid (40%), Mp 110–112 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3435, 3032, 2961, 2925, 1672, 1584, 1567, 1477, 1362, 1208, 1148, 976, 766, 695. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.18 (dd, 1H, J_a = 8.1 and J_b = 1.2 Hz), 7.58-7.56 (m, 1H), 7.38-7.31 (m, 4H), 7.26 (d, 2H, J = 7.3 Hz), 7.19-7.15 (m, 1H), 5.3 (s, 2H), 4.32 (s, 1H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.3, 149.1, 148.4, 135.5, 134.2, 129.3, 128.2, 127.3, 126.7, 125.3, 122.4, 116.9, 52.6, 44.9, 28.8.



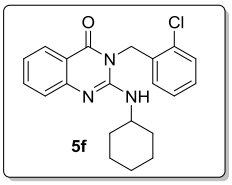
2-(Cyclohexylamino)-3-(4-methoxybenzyl)quinazolin-4(3H)-one (5c): White solid (78%), Mp 130-132 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3421, 2999, 2928, 2852, 1662, 1610, 1578, 1561, 1475, 1450, 1346, 1247, 1176, 1033, 982, 765, 693. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.18 (dd, 1H, *J*a = 7.8 and J_b = 1 Hz), 7.60-7.56 (m, 1H), 7.37 (d, 1H, *J* = 8.3 Hz), 7.21 (d, 2H, *J* = 8.8 Hz), 7.17 (m, 1H), 6.88 (d, 2H, *J* = 8.3 Hz), 5.26 (s, 2H), 4.44 (d, 1H, *J* = 6.8 Hz), 3.99-3.93 (m, 1H), 3.79 (s, 3H), 1.88-1.86 (dd, 2H, J_a = 8.1 and J_b = 3.7 Hz), 1.54-1.52 (m, 3H), 1.41-1.32 (m, 2H), 1.20-1.15 (m, 1H), 1.10-1.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.4, 159.7, 149.4, 149.3, 134.3, 127.9, 127.3, 127.2, 124.9, 122.3, 116.9, 114.7, 55.3, 49.7, 44.1, 32.6, 25.6, 24.3.



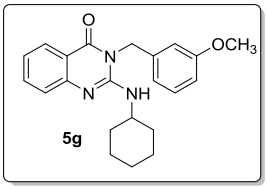
2-(Cyclohexylamino)-3-(4-methylbenzyl)quinazolin-4(3H)-one (5d): White solid (78%), Mp 138–140 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3422, 2926, 2853, 1659, 1562, 1475, 1346, 1224, 1147, 1069, 986, 765, 695. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.18 (dd, 1H, *J* = 7.8 Hz), 7.59-7.55 (m, 1H), 7.37 (d, 1H, *J* = 8.3 Hz), 7.18-7.16 (m, 5H), 5.28 (s, 2H), 4.4 (d, 1H, *J* = 6.8 Hz), 3.90-3.99 (m, 1H), 2.33 (s, 3H), 1.80-1.87 (m, 2H), 1.50 (d, 3H, *J* = 10.3 Hz), 1.30-1.41 (m, 2H), 1.12-1.19 (m, 1H), 0.99-1.08 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.2, 149.5, 149.3, 138.0, 134.3, 132.21, 130.0, 127.3, 126.6, 124.9, 122.4, 116.9, 49.8, 44.4, 32.5, 25.6, 24.2, 21.1.



2-(Cyclohexylamino)-3-(4-fluorobenzyl)quinazolin-4(3H)-one (5e): White solid (68%), Mp 118-120 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.17 (dd, 1H, J_a= 8.1 and J_b = 1.2 Hz), 7.61-7.57 (m, 1H), 7.38 (d, 1H, J = 7.38 Hz), 7.20-7.16 (m, 1H), 7.06 (t, 2H, J = 8.6 Hz), 5.29 (s, 2H), 4.27 (d, 1H, J = 7.3 Hz), 4.00-3.94 (m, 1H), 1.90-1.86 (m, 2H), 1.52 (d, 3H, J = 10.3 Hz), 1.42-1.33 (m, 2H), 1.18-1.14 (m, 1H), 1.08-1.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.7, 163.1, 161.3, 149.4, 148.9, 134.5, 131.1, 131.0, 128.4, 128.3, 127.3, 125.0, 122.5, 116.8, 116.4, 116.2, 49.8, 43.9, 32.6, 25.6, 24.3.

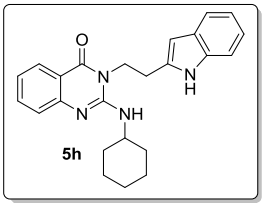


3-(2-Chlorobenzyl)-2-(cyclohexylamino)quinazolin-4(3H)-one (5f): White solid (72%), Mp 108-110 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.08-8.06 (m, 1H), 7.51-7.47 (m, 1H), 7.30 (dd, 2H, J_a= 16.9 and J_b = 8.1 Hz), 7.16-7.11 (m, 1H), 7.09-7.04 (m, 3H), 5.34 (s, 2H), 4.28 (d, 1H, J = 7.3 Hz), 3.89 (dtd, 1H, J_a = 10.1, J_b = 6.7 and J_c = 3.9 Hz), 1.82-1.78 (m, 2H), 1.47 (d, 3H, J = 8.8 Hz), 1.31-1.22 (m, 2H), 1.08-1.00 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.2, 149.5, 148.5, 134.5, 132.6, 132.4, 129.6, 129.4, 128.2, 127.9, 127.3, 125.0, 122.4, 116.7, 50.1, 41.1, 32.7, 25.6, 24.5.

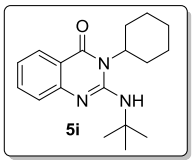


2-(Cyclohexylamino)-3-(3-methoxybenzyl)quinazolin-4(3H)-one (5g): White solid (65%), Mp 108–110 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3423, 2969, 2853,

1662, 1579, 1563, 1476, 1347, 1261, 1147, 1049, 985, 766, 694. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.19 (dd, 1H, J_a = 7.8 and J_b = 1.0 Hz), 7.62-7.57 (m, 1H), 7.38 (d, 1H, J = 8.3 Hz), 7.31-7.27 (m, 1H), 7.18 (t, 1H, J = 7.1 Hz), 6.86 (dd, 2H, J_a = 7.1 and J_b = 4.2 Hz), 6.82 (s, 1H), 5.30 (s, 2H), 4.41 (d, 1H, J = 6.8 Hz), 3.97 (dd, 1H, J_a = 7.6 and J_b = 4.2 Hz), 3.78 (s, 3H), 1.86 (dd, 2H, J_a = 8.3 and J_b = 3.9 Hz), 1.55-1.49 (m, 3H), 1.42-1.33 (m, 2H), 1.21-1.15 (m, 1H), 1.10-1.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.1, 160.5, 149.4, 149.2, 136.9, 134.3, 130.4, 127.3, 124.9, 122.4, 118.9, 116.8, 113.78, 112.2, 55.3, 49.7, 44.6, 32.5, 25.5, 24.2.

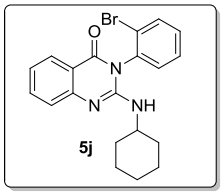


3-(2-(1H-indol-2-yl)ethyl)-2-(cyclohexylamino)quinazolin-4(3H)-one (5h): Yellow solid (62%), Mp 108-110 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.40 (br s, 1H), 8.02 (d, 1H, J = 8.3 Hz), 7.54 (d, 1H, J = 7.3 Hz), 7.43-7.39 (m, 1H), 7.26 (d, 1H, J = 7.8 Hz), 7.18 (d, 1H, J = 8.3 Hz), 7.13-7.09 (m, 1H), 7.07-6.99 (m, 2H), 6.77 (s, 1H), 4.17 (t, 2H, J = 6.1 Hz), 3.61 (d, 1H, J = 7.3 Hz), 3.44-3.41 (m, 1H), 3.15 (t, 2H, J = 6.1 Hz), 1.44-1.33 (m, 6H), 1.16-0.99 (m, 3H), 0.80-0.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.3, 149.6, 149.3, 136.7, 134.2, 126.8, 126.6, 124.8, 123.2, 122.8, 120.2, 118.0, 117.1, 111.9, 111.8, 49.7, 43.5, 31.9, 25.5, 24.8, 24.1.

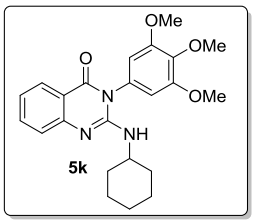


2-(Tert-butylamino)-3-cyclohexylquinazolin-4(3H)-one (5i): White solid (32%), Mp 82–84 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3496, 2930, 2856, 1669, 1568, 1519, 1478, 1361, 1205, 1137, 953, 764, 697. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.07 (dd, 1H, J_a = 8.2 and J_b = 1.2Hz), 7.54-7.50 (m, 1H), 7.34-7.26 (m, 1H), 7.12-7.08 (m, 1H), 5.14 (br s, 1H), 4.6 (br s, 1H), 2.16-2.04 (m, 2H), 1.94-1.70 (m, 6H), 1.60-

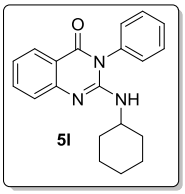
1.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 163.5, 148.7, 148.3, 133.9, 127.1, 124.8, 122.1, 52.6, 30.4, 29.3, 26.6, 25.7.



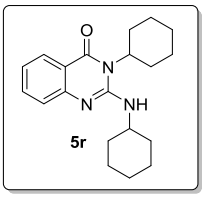
3-(2-Bromophenyl)-2-(cyclohexylamino)quinazolin-4(3H)-one (5j): White solid (48%), Mp 162-164 ^{o}C. IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3288, 2920, 2851, 1735, 1631, 1602, 1567, 1474, 1329, 1231, 1119, 1020, 957, 758, 648. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.13 (dd, 1H, J_a = 7.8 and J_b =1 Hz), 7.82 (dd, 1H, J_a = 8.1 and J_b = 1.2 Hz), 7.63-7.59 (m, 1H), 7.56-7.52 (m, 1H), 7.44-7.37 (m, 3H), 7.18-7.14 (m, 1H), 4.07-4.02 (m, 1H), 3.71 (d, 1H, J = 7.3Hz), 2.04-1.92 (m, 2H), 1.70-1.57 (m, 3H), 1.45-1.31 (m, 3H), 1.18-1.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 162.0, 149.8, 147.9, 134.7, 134.5, 134.3, 131.4, 130.9, 129.5, 127.3, 125.0, 123.6, 122.4, 117.4, 49.8, 32.9, 32.8, 29.7, 28.8, 26.4, 25.6, 24.6, 24.5. HR-MS (ESI+) m/z calculated for $[C_{20}H_{21}BrN_3O]^+$ = $[M+H]^+$: 398.0863; found: 398.0879.



2-(Cyclohexylamino)-3-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (5k): White solid (30%), Mp 162–164 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.02-8.00 (m, 1H), 7.63-7.59 (m, 1H), 7.26-7.23 (m, 3H), 7.17-7.13 (t, 1H, J = 7.6 Hz), 4.76 (br s, 1H), 3.86-3.80 (m, 1H), 2.07-2.04 (m, 2H), 1.78-1.73 (dt, 2H, J_a= 13.4 and J_b = 3.8 Hz), 1.67-1.63 (m, 4H), 1.48-1.38 (m, 3H), 1.30-1.18 (m, 9H).

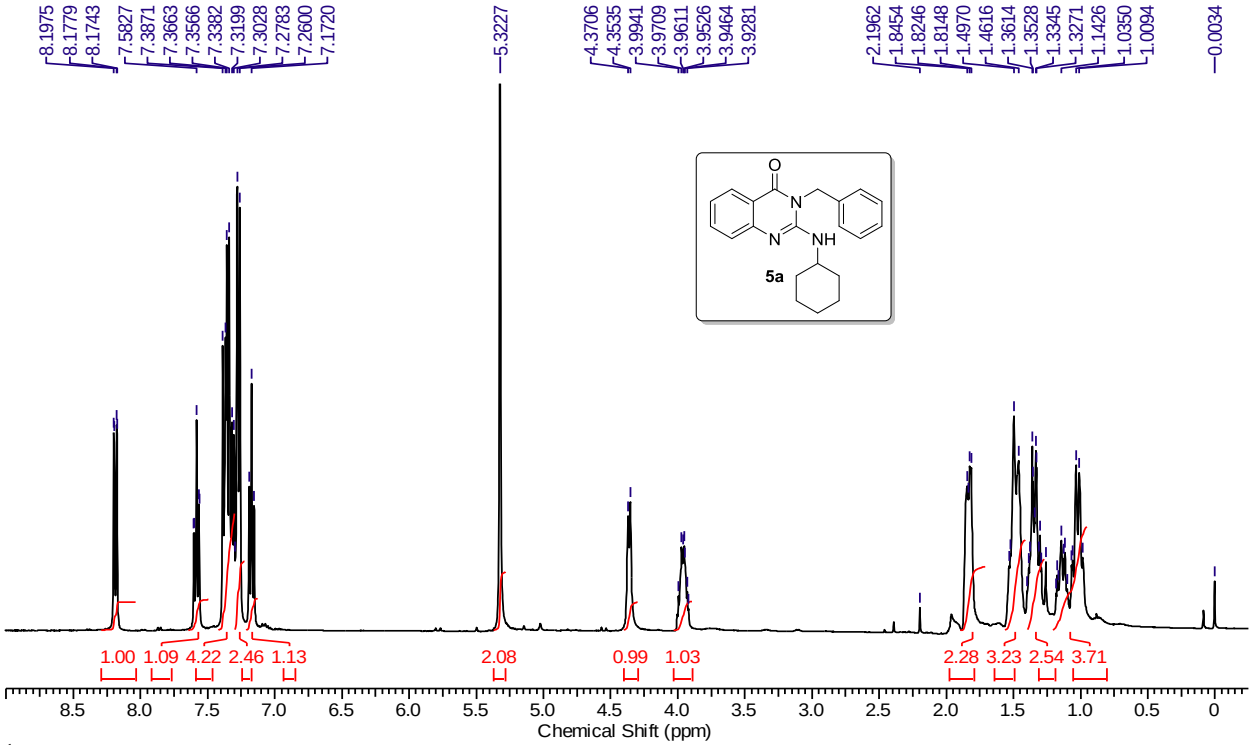


2-(Cyclohexylamino)-3-phenylquinazolin-4(3H)-one (5l): White solid (35%), Mp 158–160 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.01 (dd, 1H, J_a = 8.1 and J_b =1.2 Hz), 7.69-7.58 (m, 2H), 7.42-7.23 (m, 2H), 7.14 (m, 1H), 4.90 (br s, 1H), 3.81 (m, 1H), 2.06 (dd, 1H, J_a = 12.2 and J_b = 2.9 Hz), 1.77-1.72 (m, 3H), 1.65-1.61 (m, 1H), 1.48-1.37 (m, 2H), 1.30-1.18 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 160.1, 150.6, 136.6, 128.7, 124.2, 123.4, 119.9, 113.2, 50.2, 32.9, 25.4, 24.6.

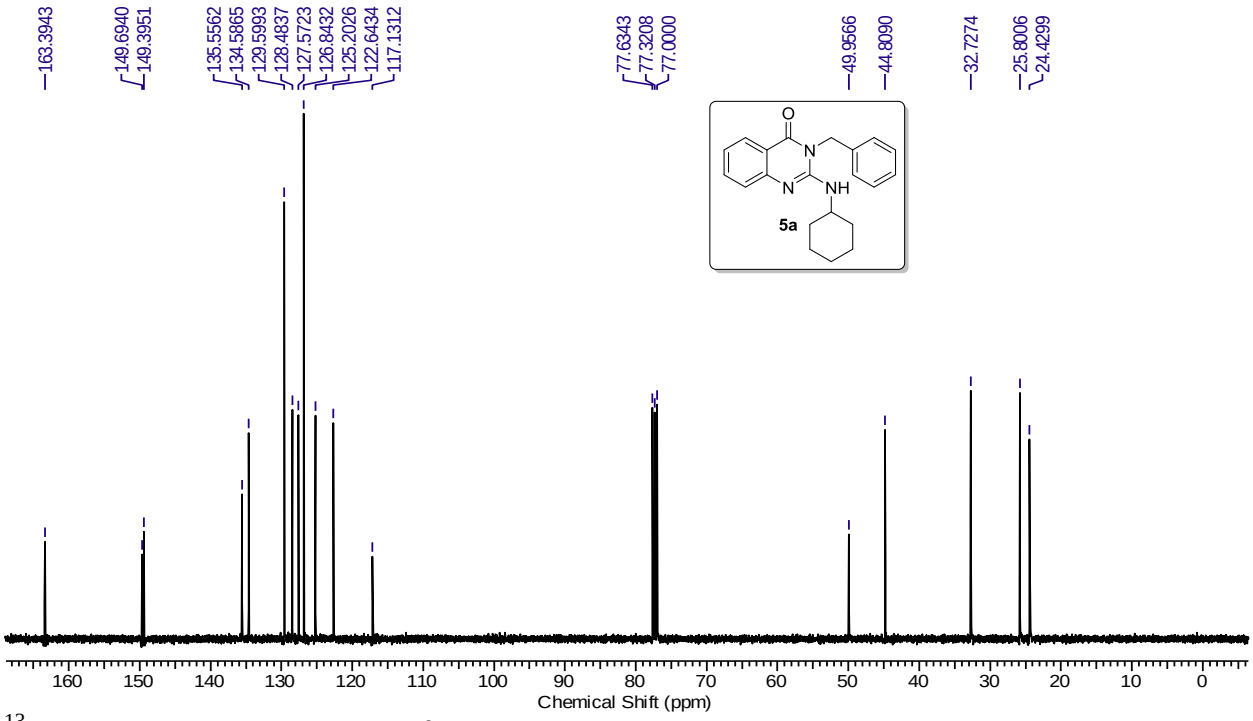


3-Cyclohexyl-2-(cyclohexylamino)quinazolin-4(3H)-one (5r): White solid (38%), Mp 162–164 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.02 (dd, 1H, J_a = 8.1 and J_b =1.2 Hz), 7.64-7.66 (m, 1H), 7.27-7.25 (m, 1H), 7.16 (t, 1H,J = 7.6 Hz), 4.82 (br s, 1H), 4.15-4.07 (m, 1H), 3.86-3.79 (m, 1H), 2.07 (dd, 3H, J_a = 13.0 and J_b = 3.7 Hz), 1.79-1.63 (m, 8H), 1.49-1.39 (m, 4H), 1.31-1.19 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 160.1, 150.6, 136.7, 128.7, 124.2, 123.4, 50.2, 32.9, 25.4, 24.6.

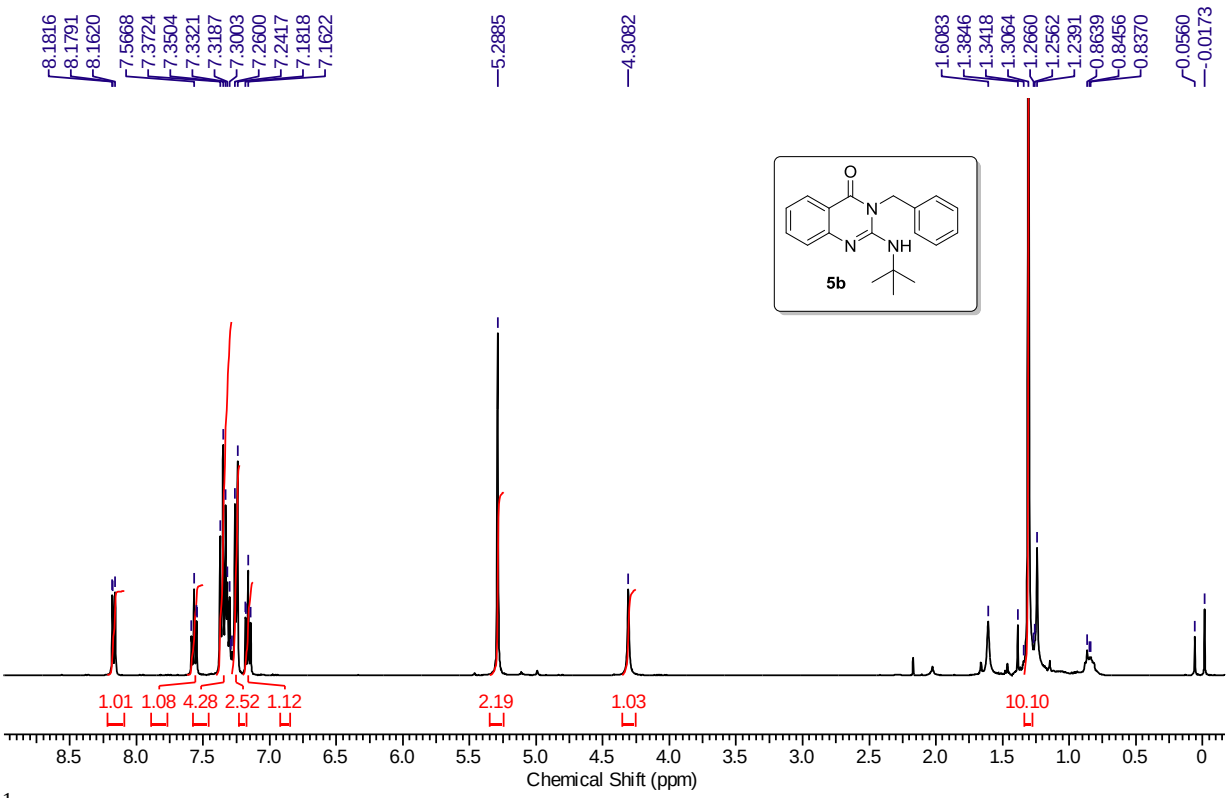
Copies of ^{1}H, ^{13}C NMR Spectral Data



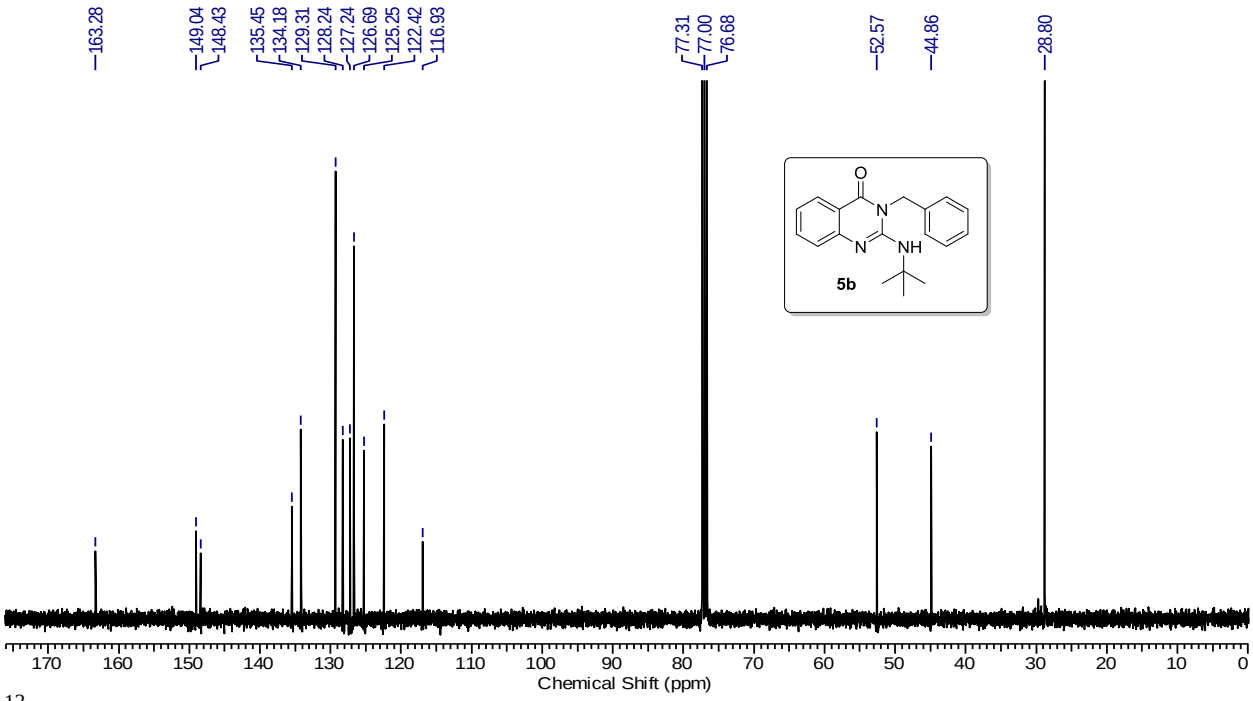
^{1}H NMR (400MHz) spectrum of compound **5a** in $CDCl_3$.



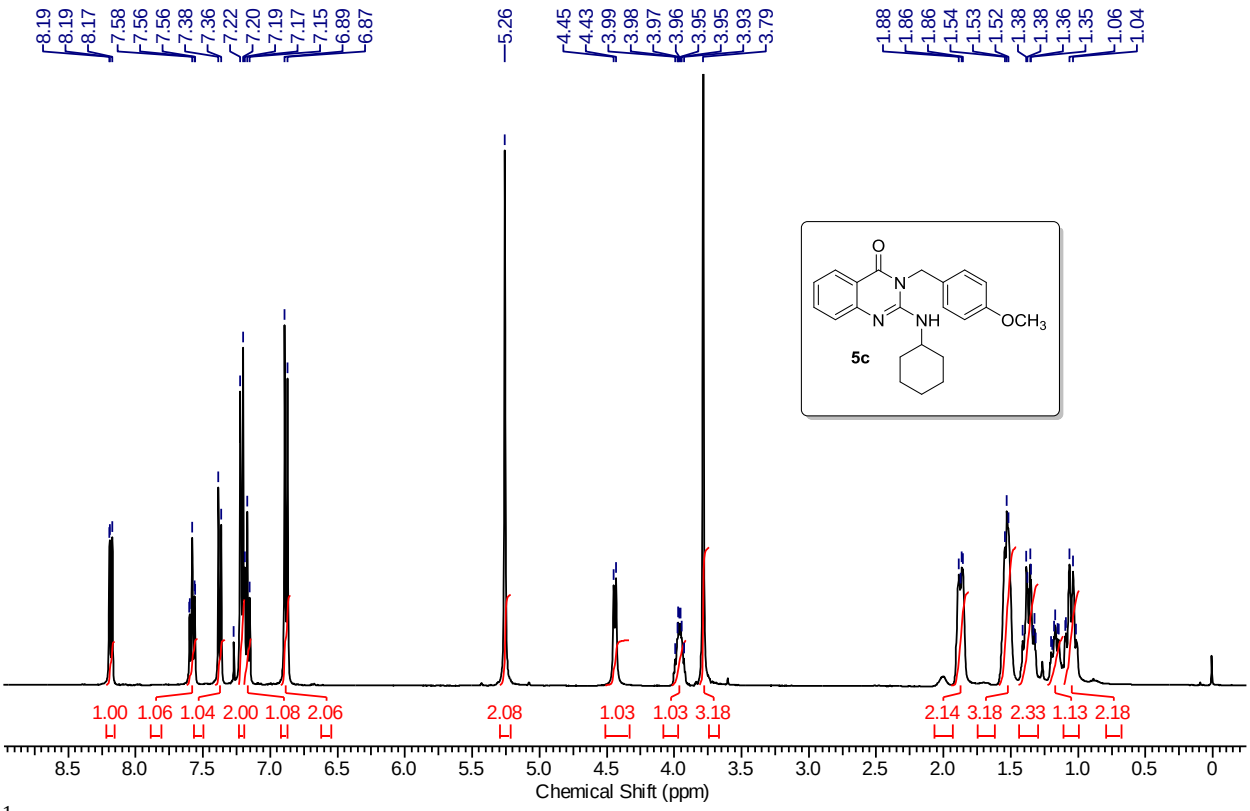
^{13}C NMR (100MHz) spectrum of compound **5a** in $CDCl_3$.



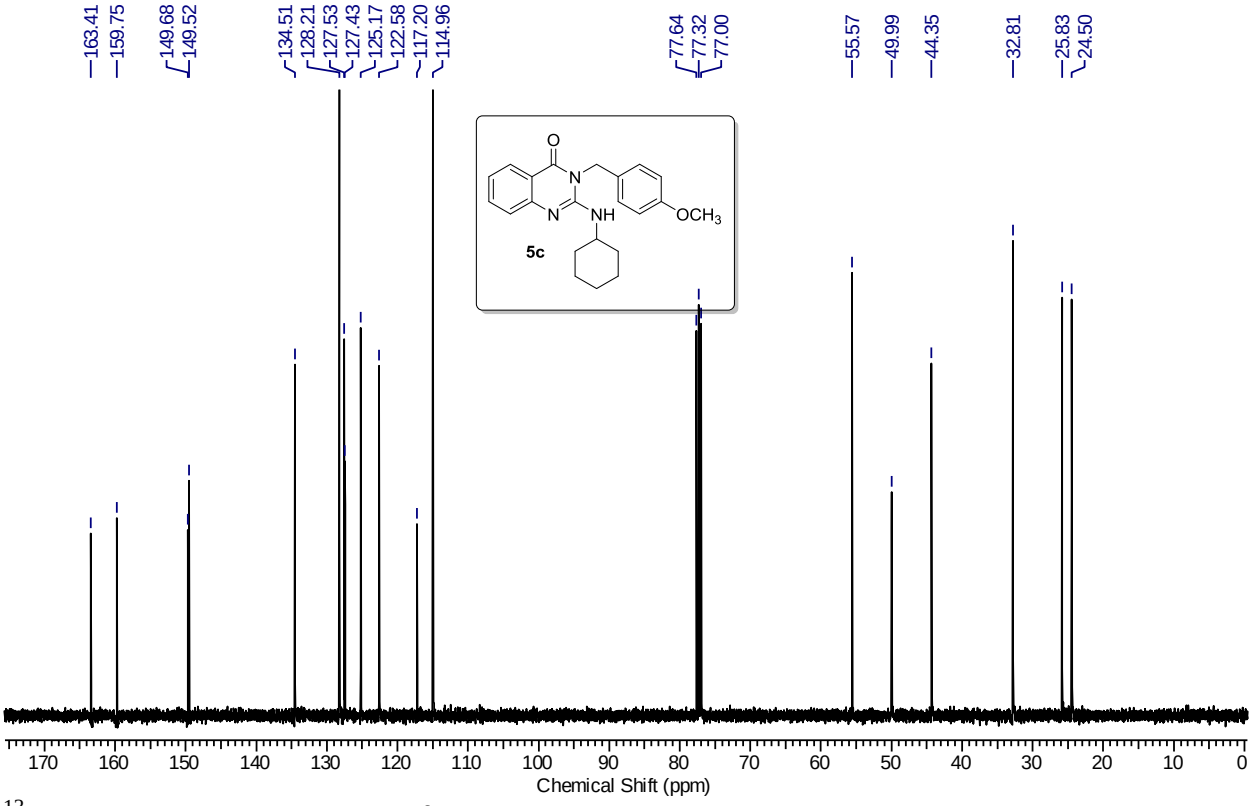
^{1}H NMR (400MHz) spectrum of compound **5b** in $CDCl_3$.



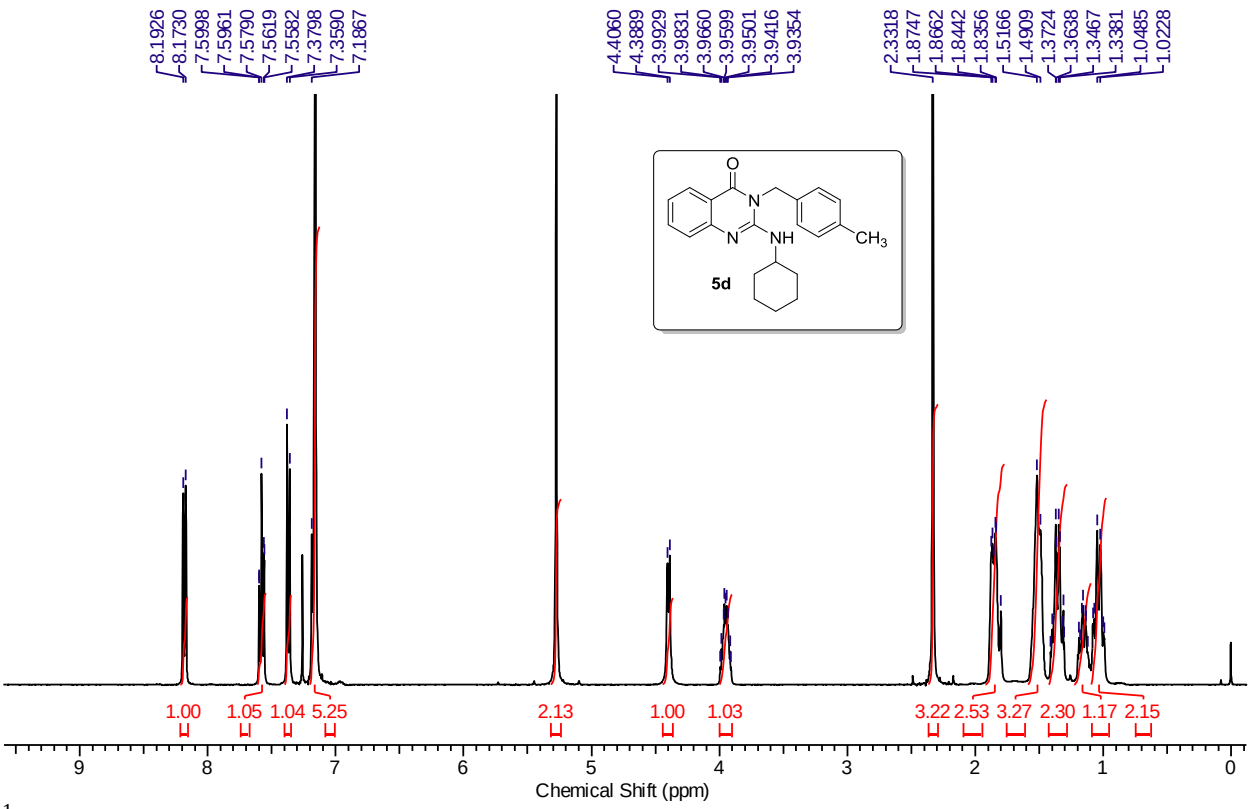
^{13}C NMR (100MHz) spectrum of compound **5b** in $CDCl_3$.



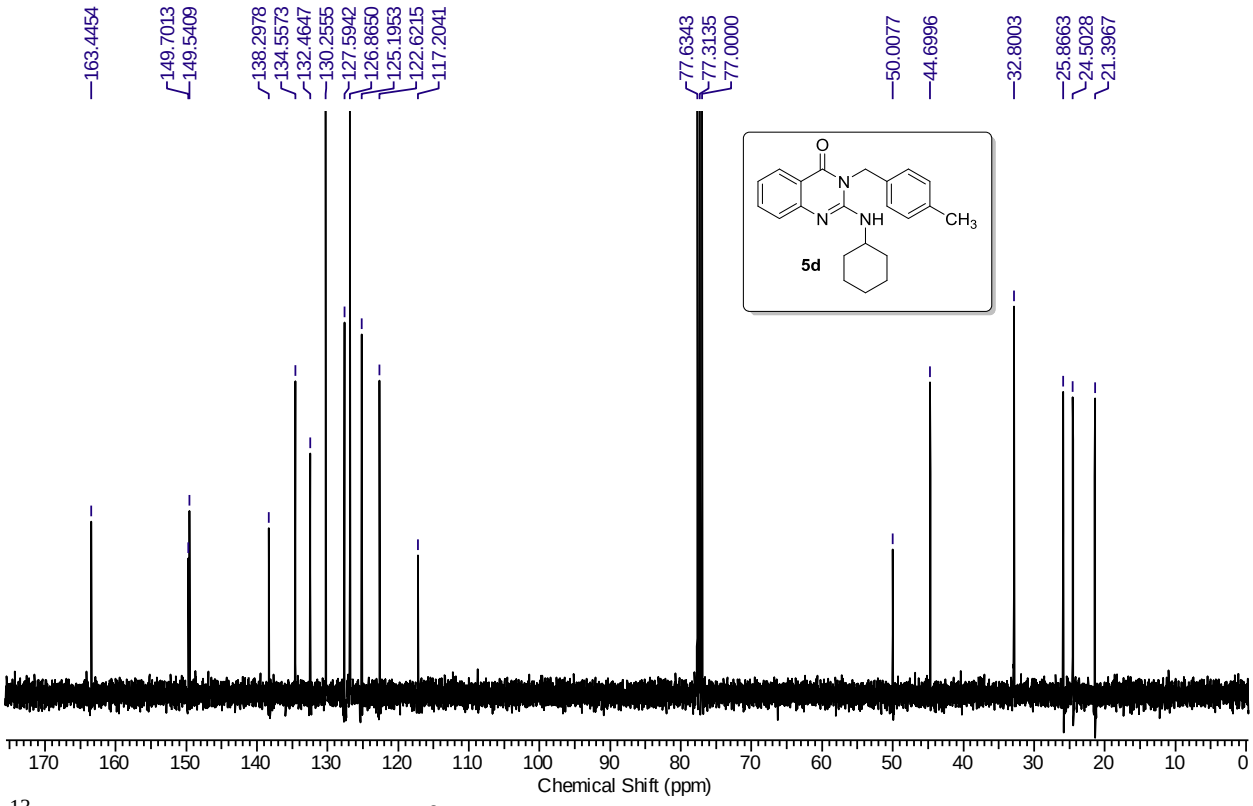
^{1}H NMR (400MHz) spectrum of compound **5c** in $CDCl_3$.



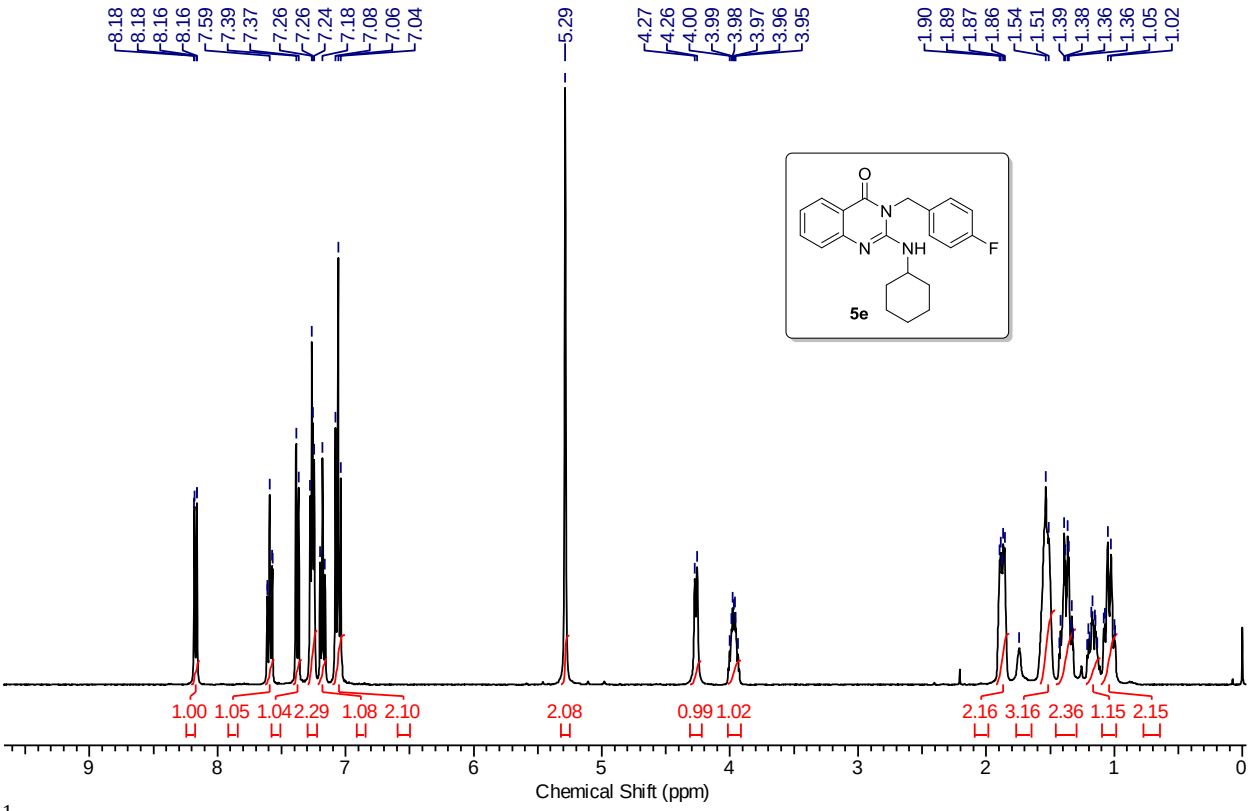
^{13}C NMR (100MHz) spectrum of compound **5c** in $CDCl_3$.



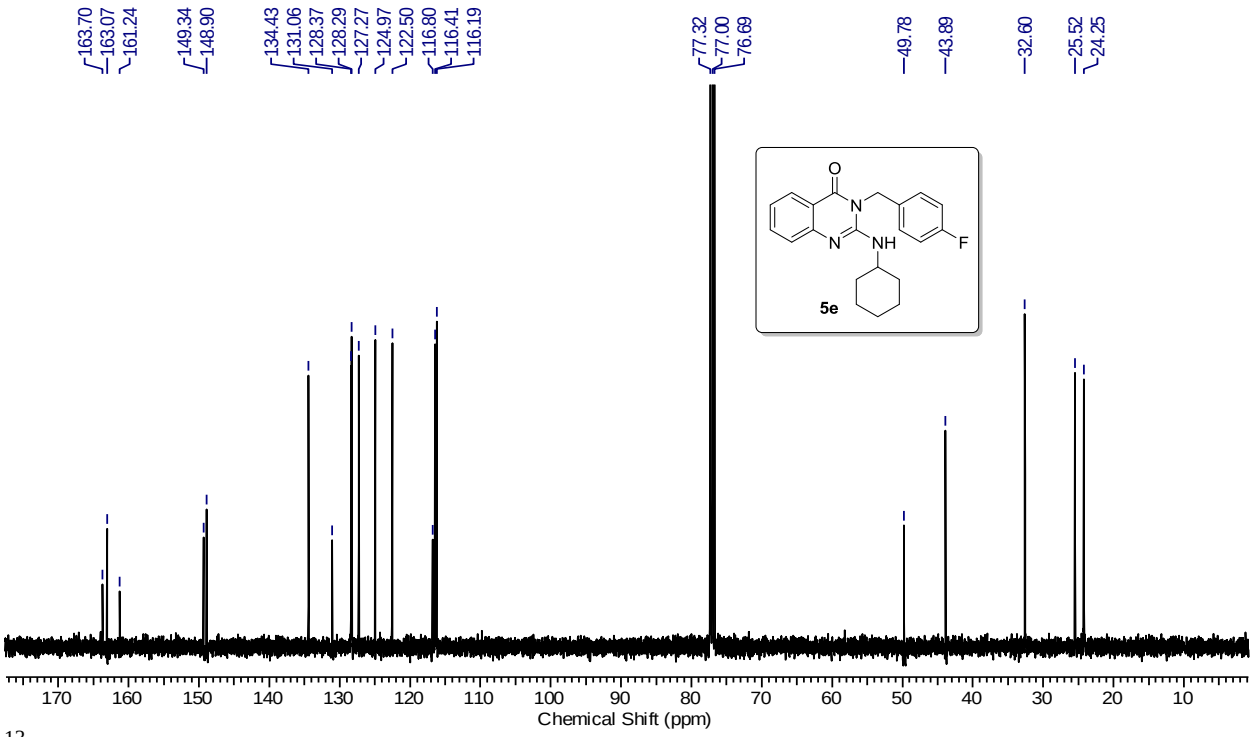
^{1}H NMR (400MHz) spectrum of compound **5d** in $CDCl_3$.



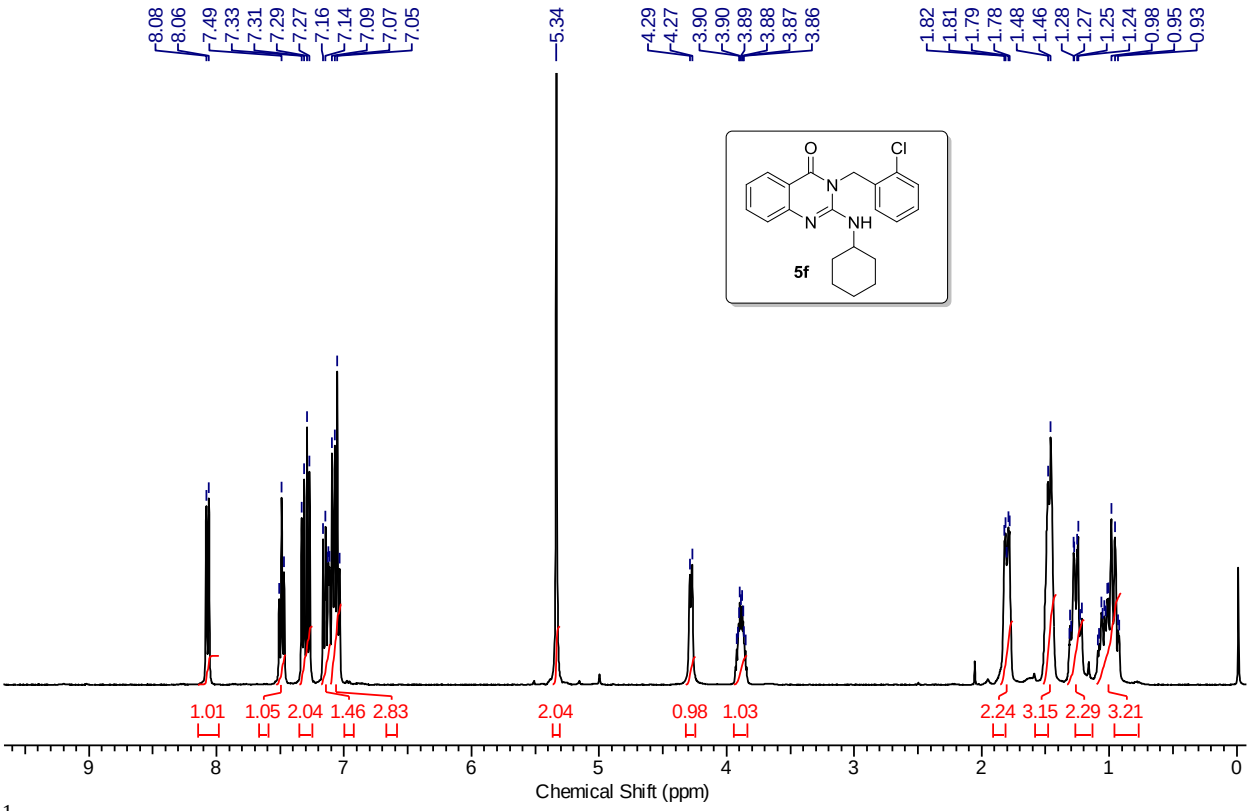
^{13}C NMR (100MHz) spectrum of compound **5d** in $CDCl_3$.



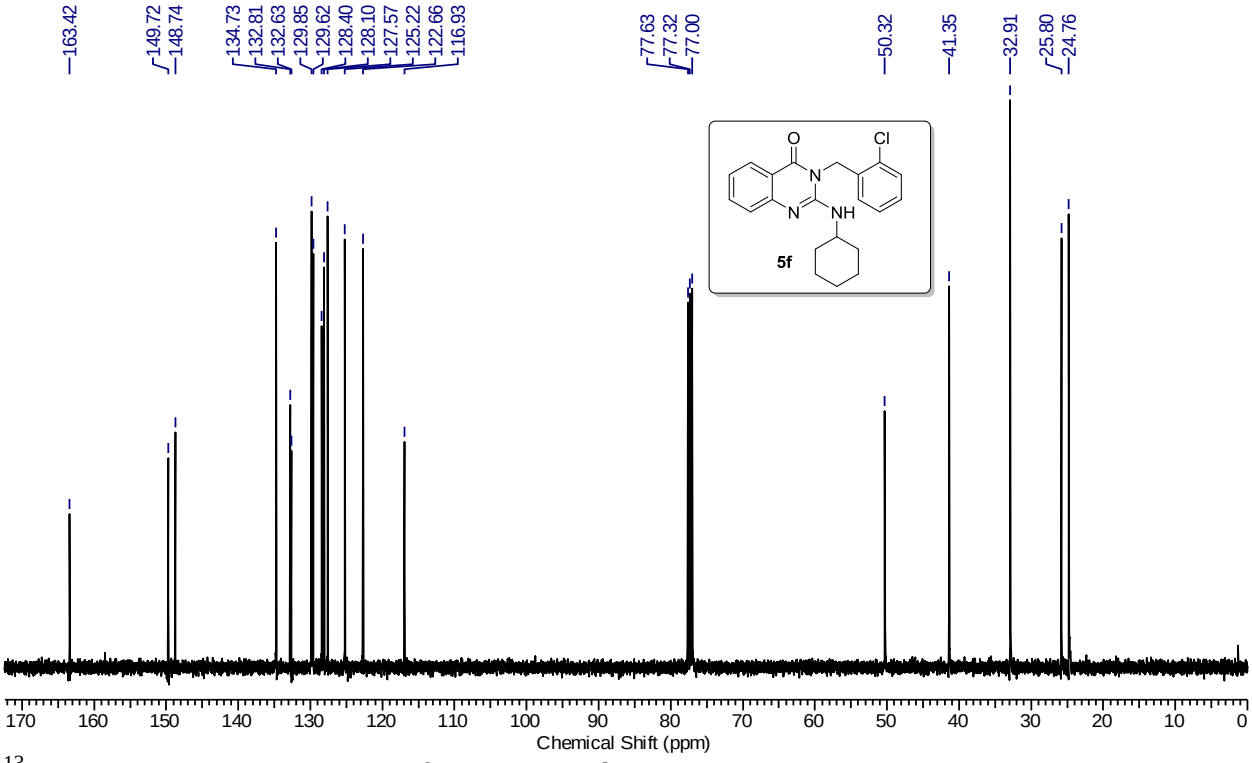
^{1}H NMR (400MHz) spectrum of compound **5e** in $CDCl_3$.



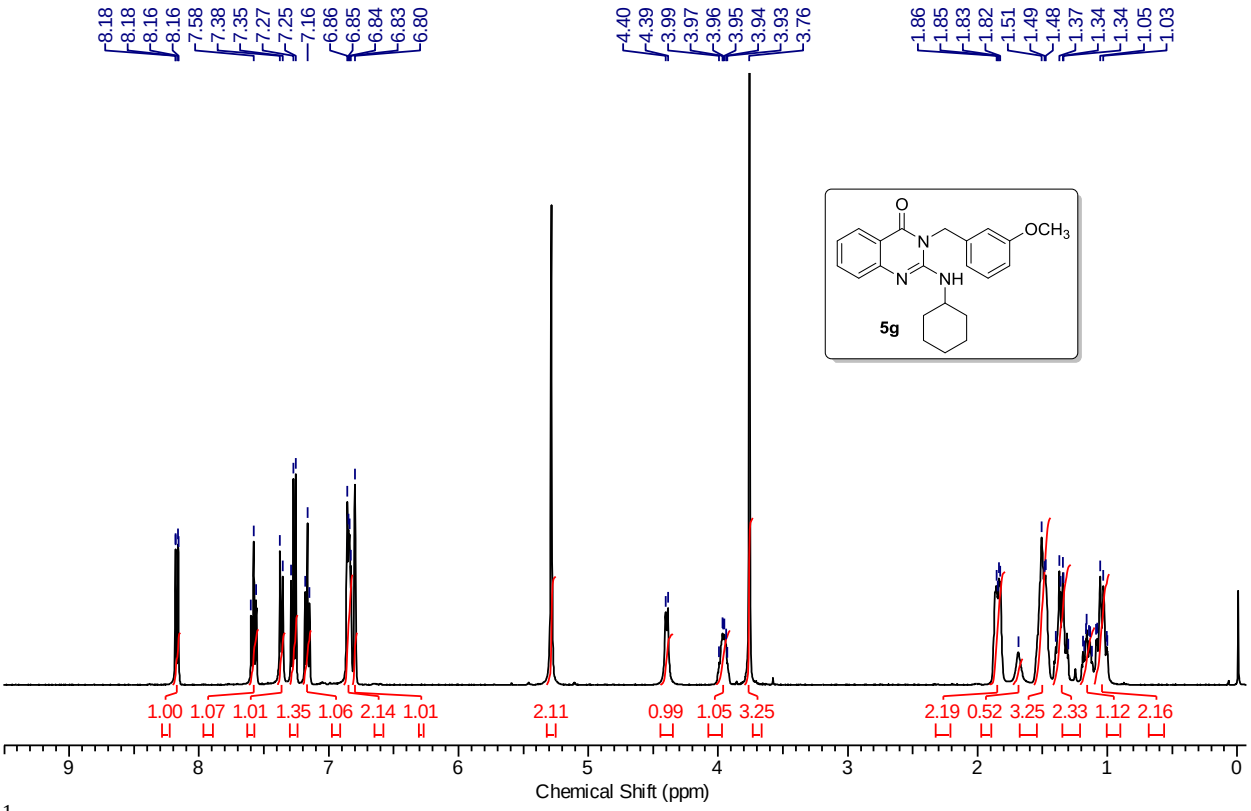
^{13}C NMR (100MHz) spectrum of compound **5e** in $CDCl_3$.



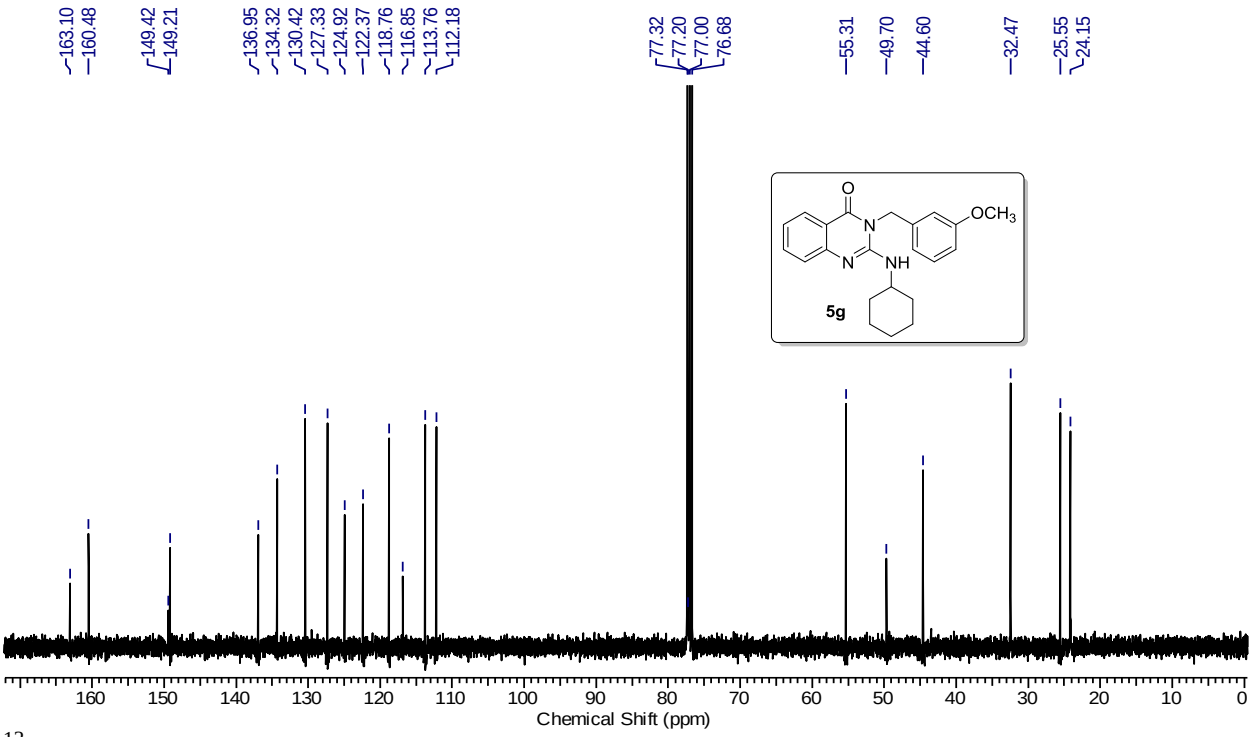
^{1}H NMR (400MHz) spectrum of compound **5f** in $CDCl_3$.



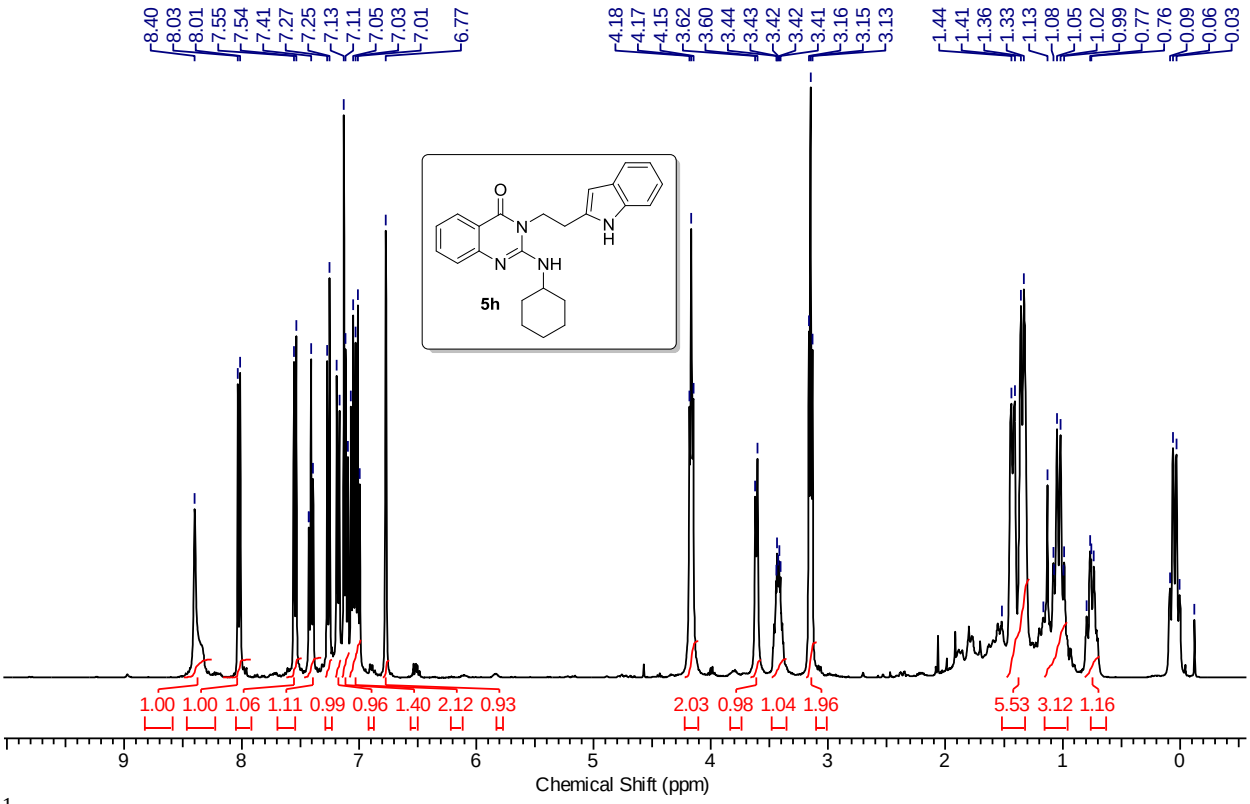
^{13}C NMR (100MHz) spectrum of compound **5f** in $CDCl_3$



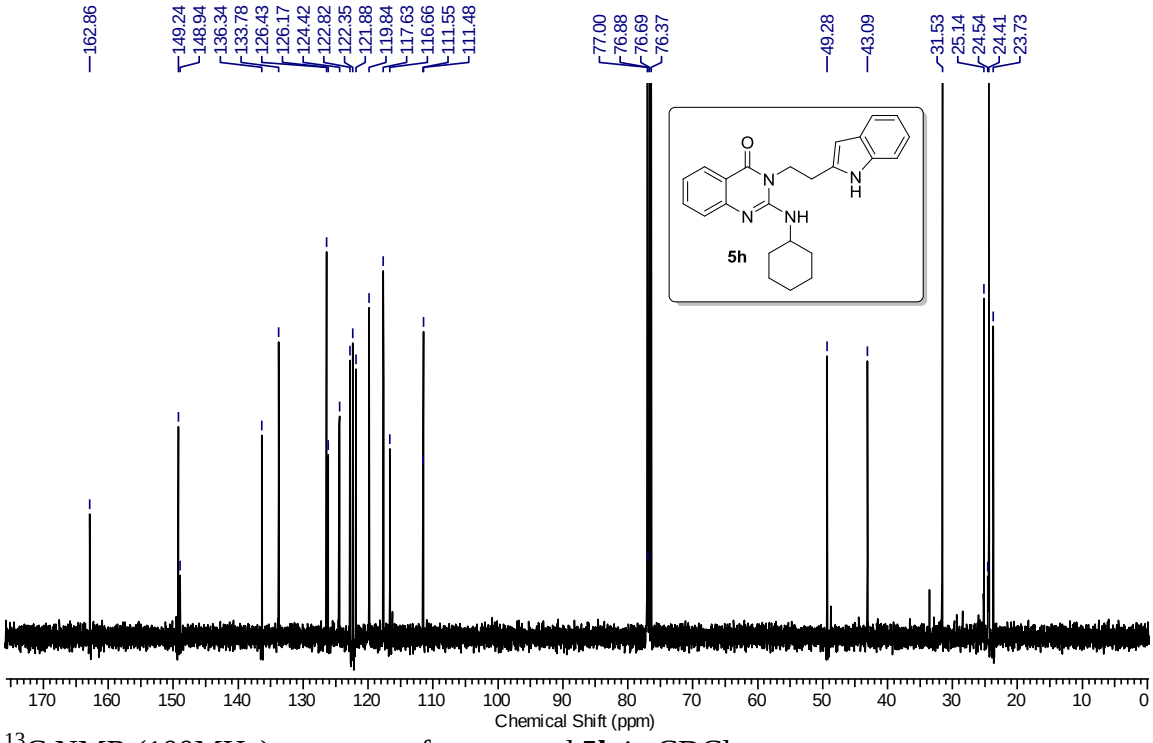
^{1}H NMR (400MHz) spectrum of compound **5g** in $CDCl_3$.



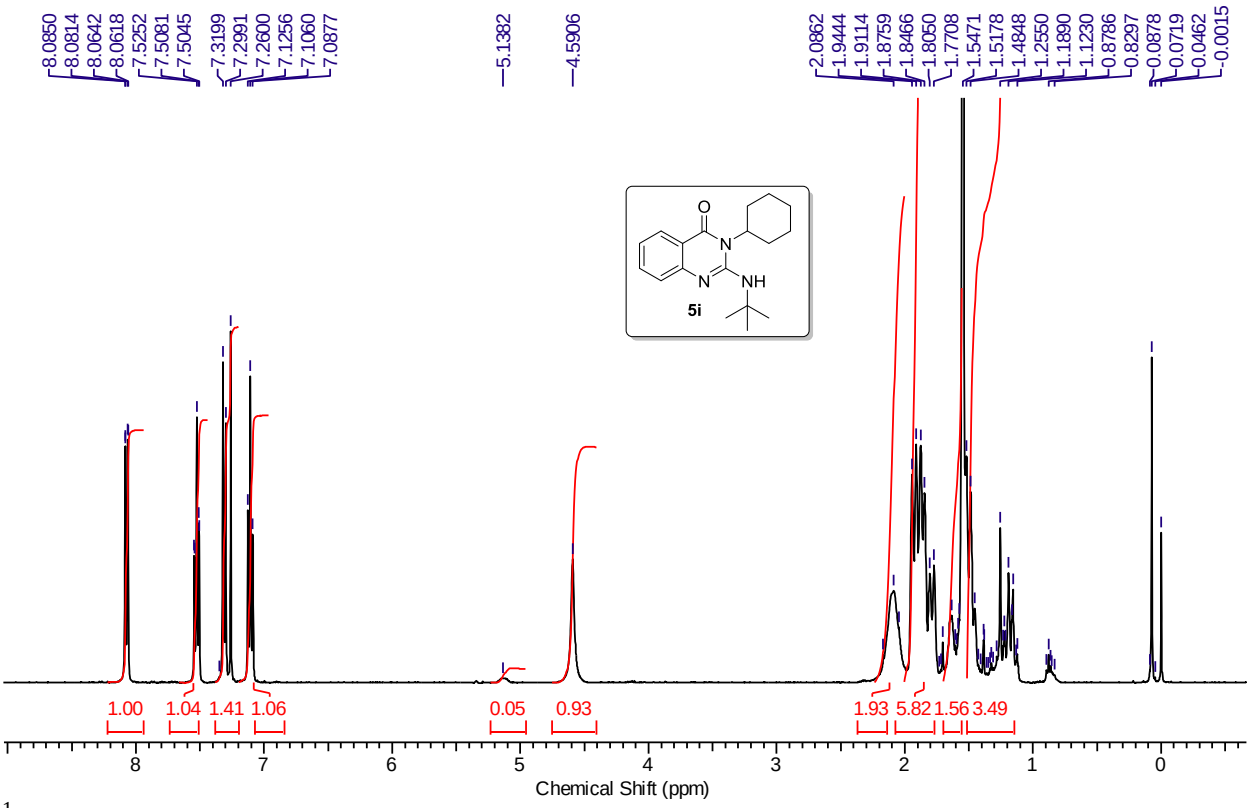
^{13}C NMR (100MHz) spectrum of compound **5g** in $CDCl_3$.



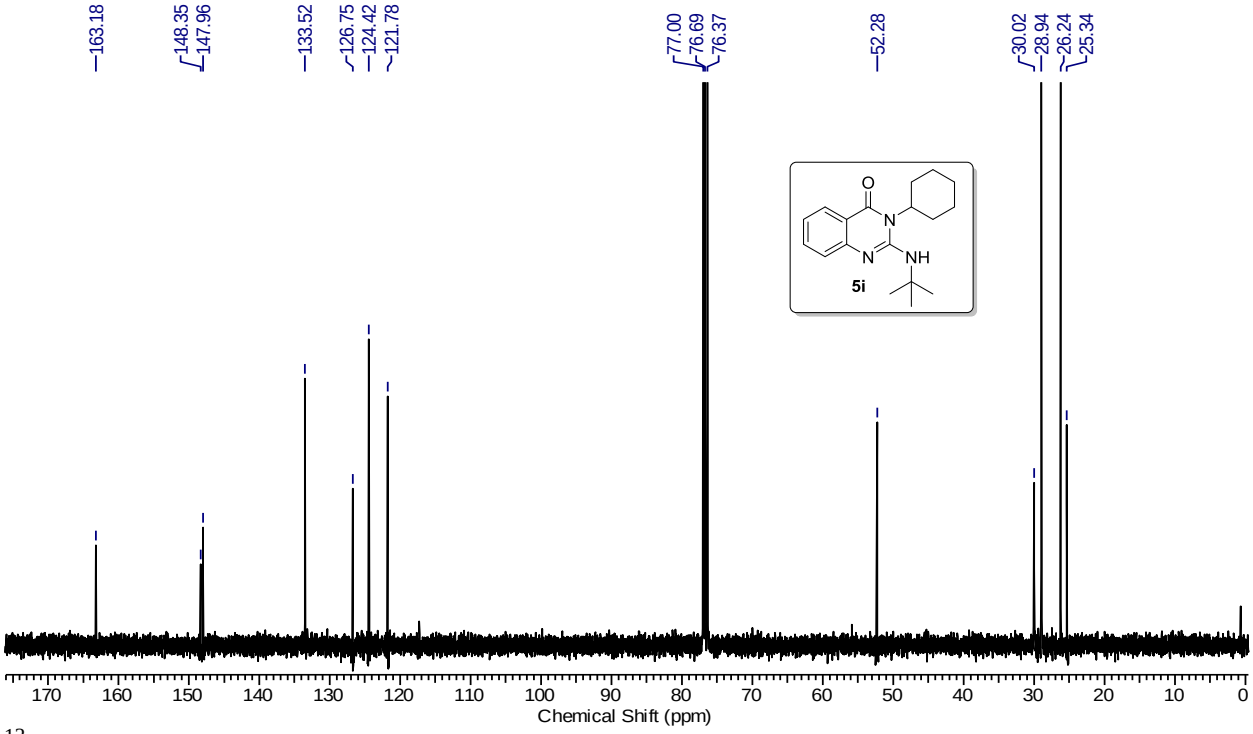
^{1}H NMR (400MHz) spectrum of compound **5h** in $CDCl_3$.



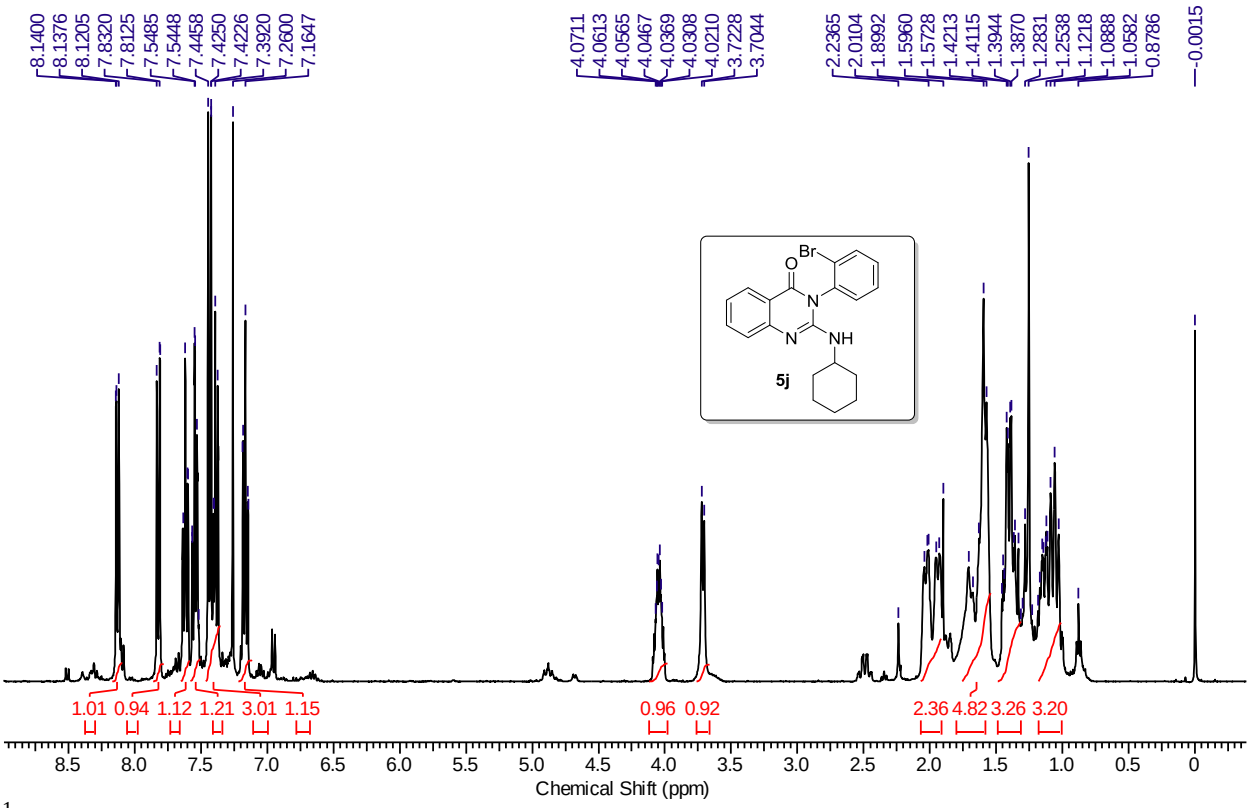
^{13}C NMR (100MHz) spectrum of compound **5h** in $CDCl_3$.



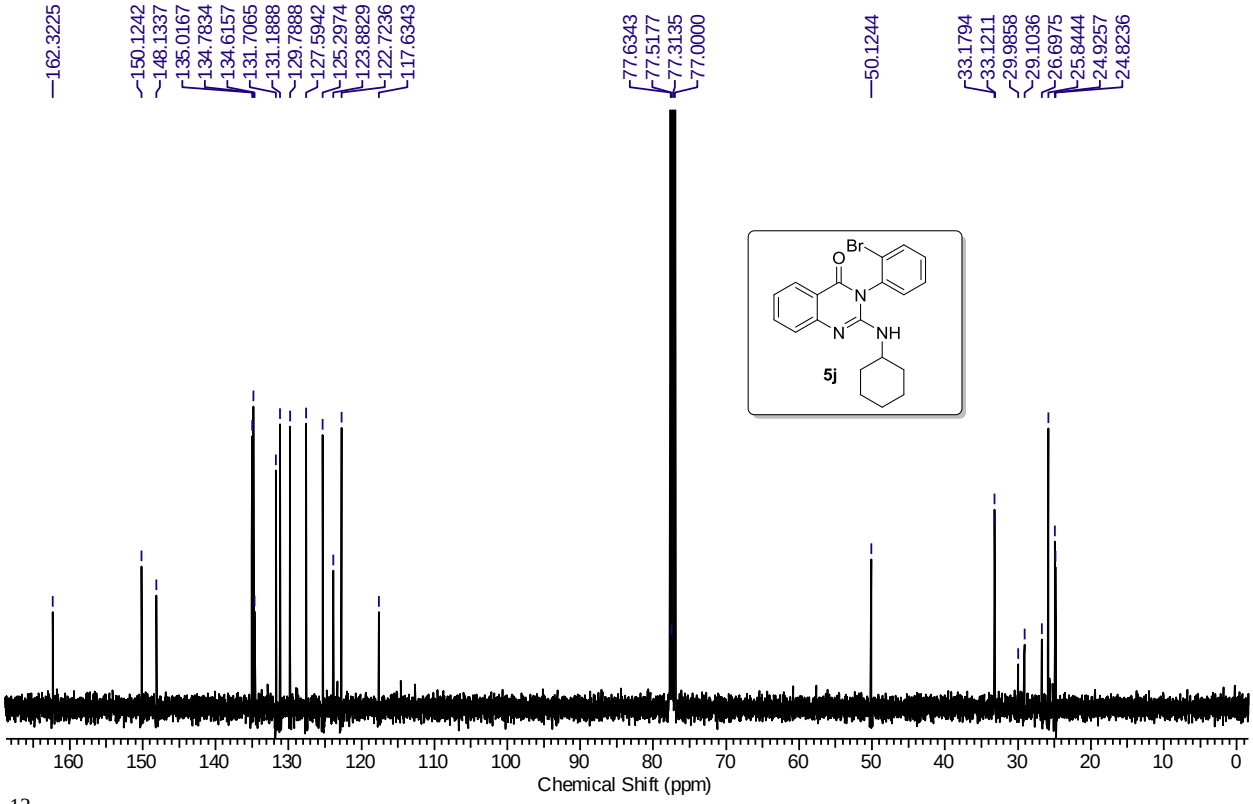
^{1}H NMR (400MHz) spectrum of compound **5i** in $CDCl_3$.



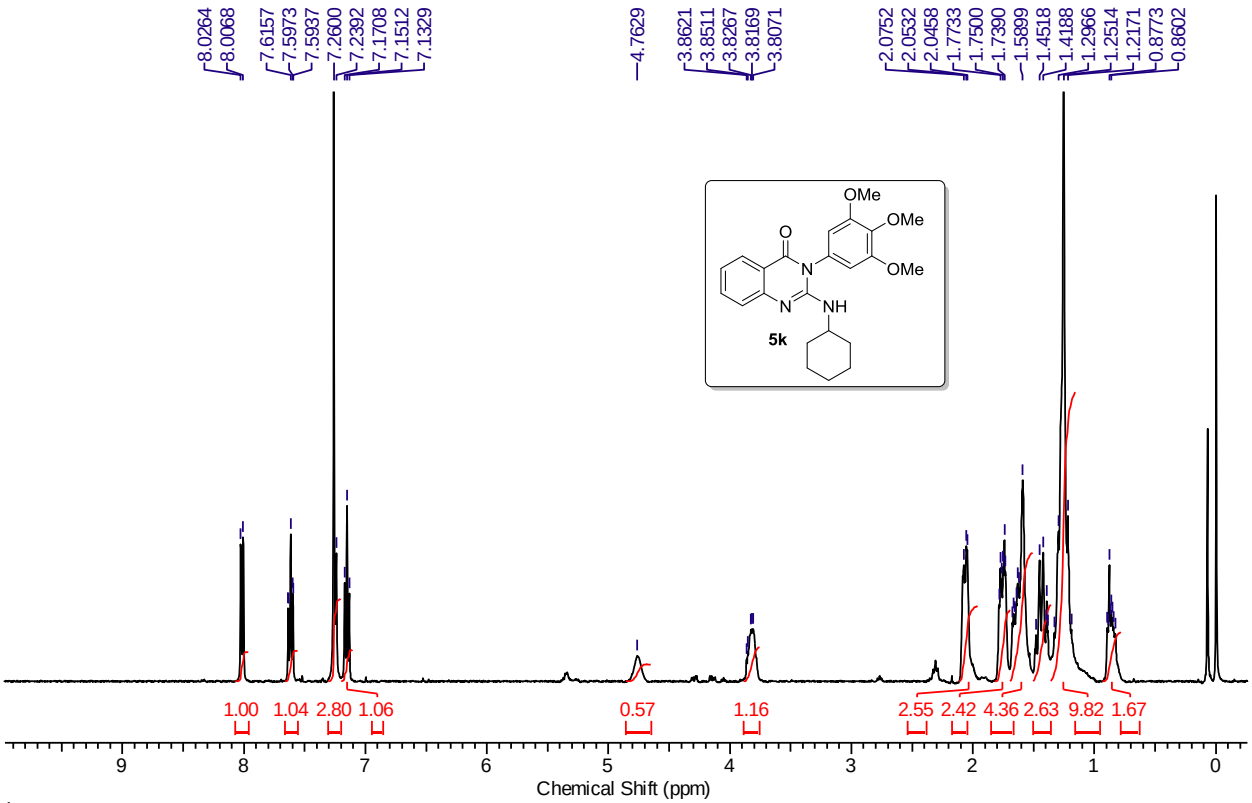
^{13}C NMR (100MHz) spectrum of compound **5i** in $CDCl_3$.



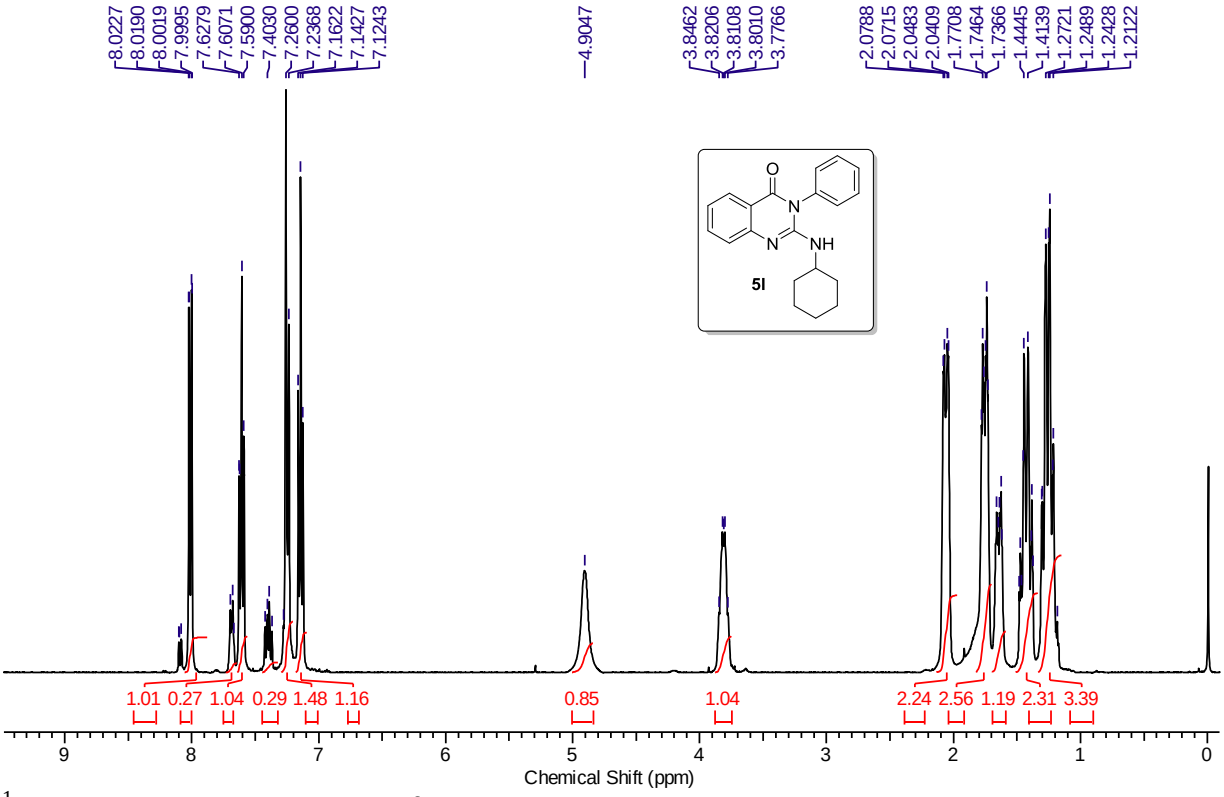
^{1}H NMR (400MHz) spectrum of compound **5j** in $CDCl_3$.



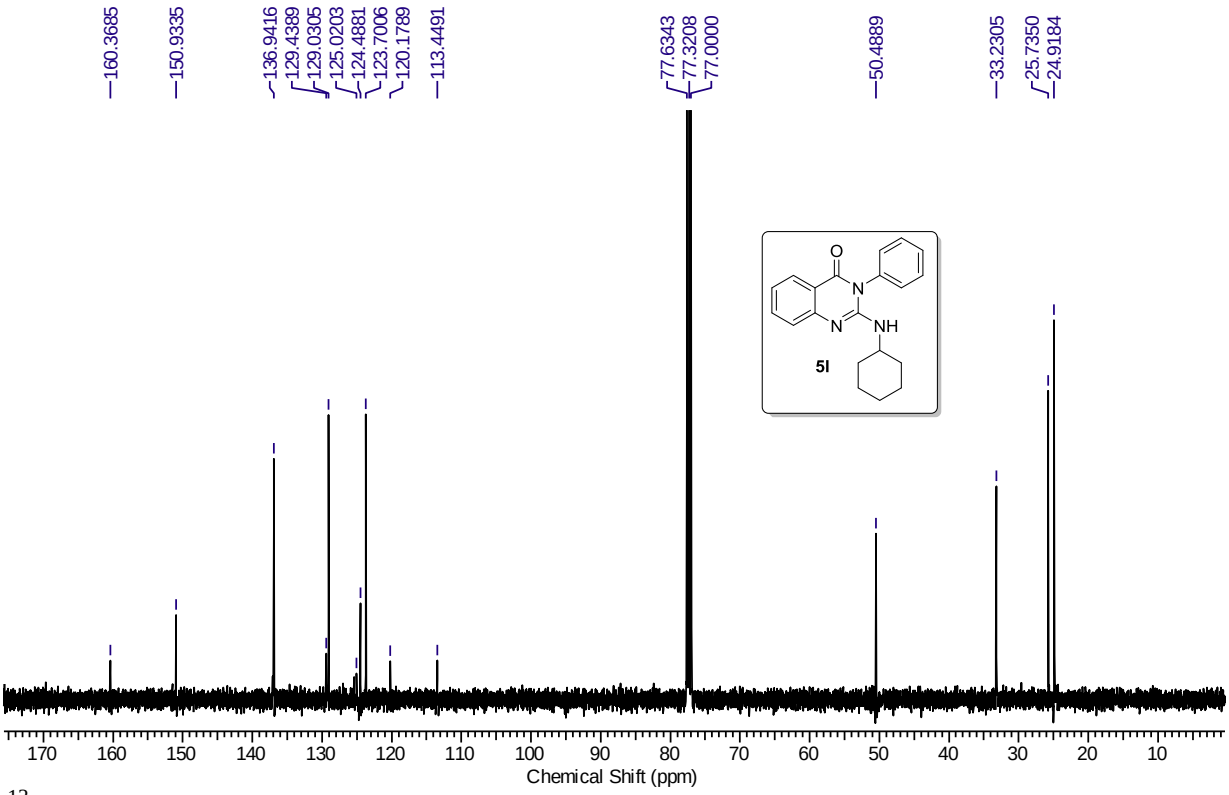
^{13}C NMR (100MHz) spectrum of compound **5j** in $CDCl_3$.



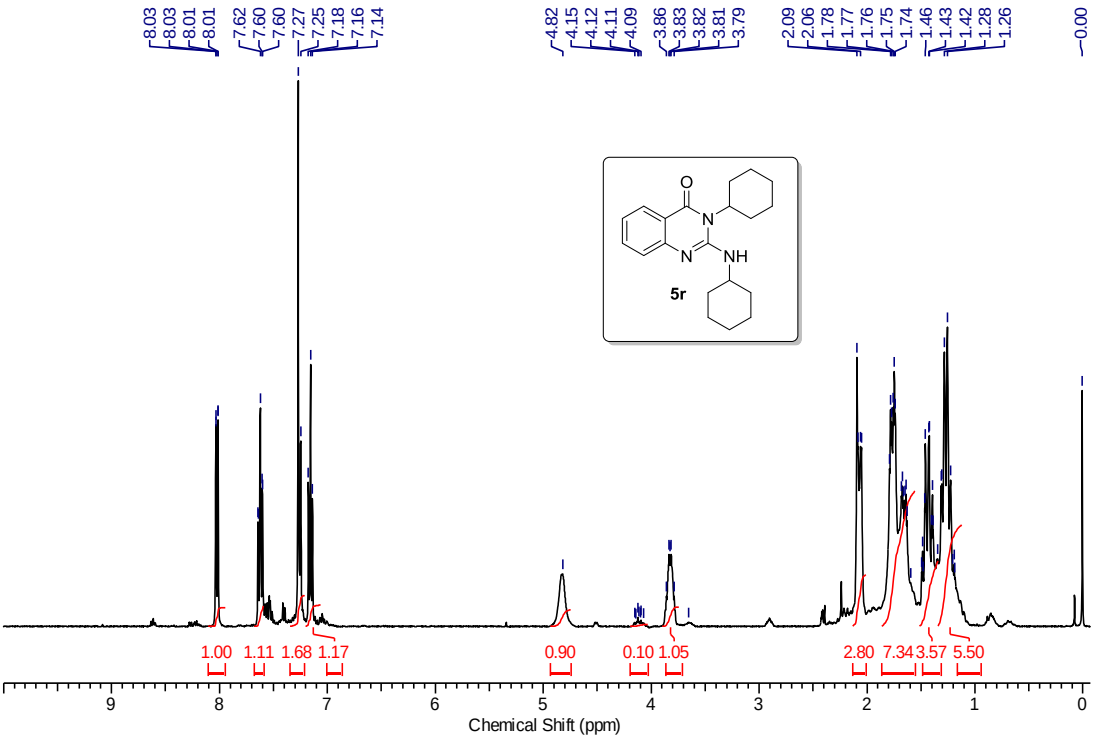
^{1}H NMR (400MHz) spectrum of compound **5k** in $CDCl_3$.



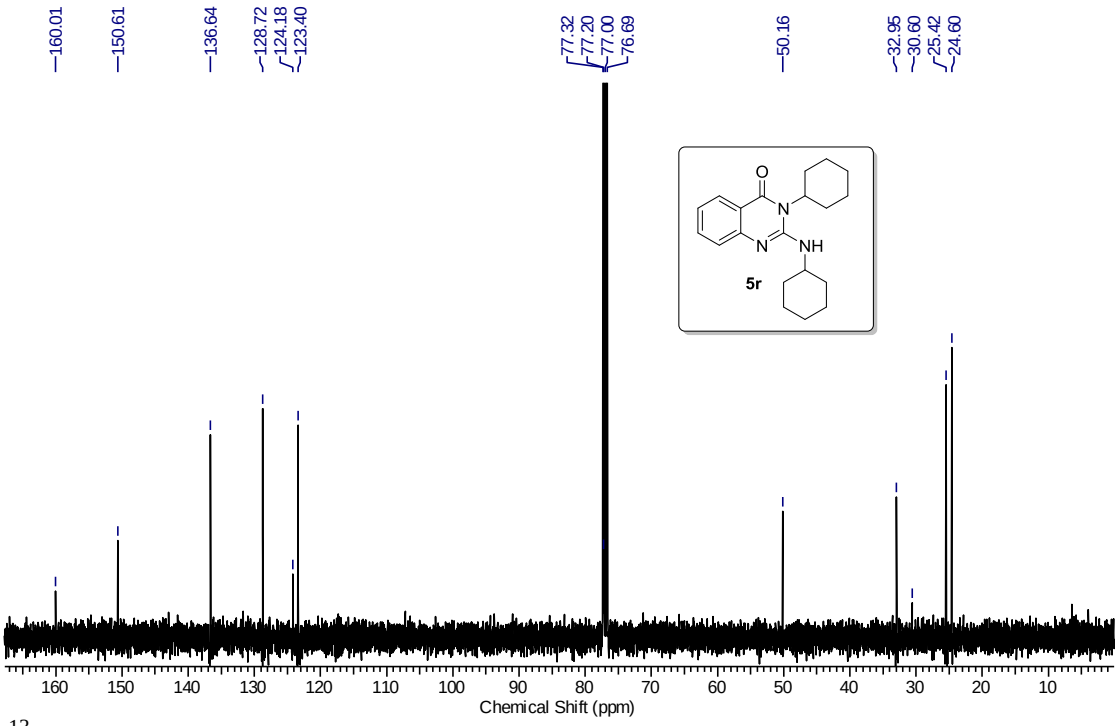
^{1}H NMR (400MHz) spectrum of compound **5l** in $CDCl_3$



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



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



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

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