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Synthesis and cytotoxicity of azaheterocyclic compounds

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SYNTHESIS AND CYTOTOXICITY OF AZAHETEROCYCLIC COMPOUNDS

by

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A Thesis

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Dedications

I dedicate my dissertation work to my foster parents Shailesh Patel, Lata Patel, Dilip Kapadia and Geeta Kapadia who have been a constant source of support and encouragement during the challenges of graduate school life and I am truly thankful for having you in my life. A special feeling of gratitude to my loving parents Manhar Pandya and Jyotika Pandya who have always loved me unconditionally. My wife Neha Patel never left my side and is very special. I also dedicate this dissertation to my brother Chirag and sister Tami. I will always appreciate all they have done for me.

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Abstract

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SYNTHESIS AND CYTOTOXICITY OF AZAHETEROCYCLIC COMPOUNDS
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Multicomponent coupling reactions (MCRs) have been known for a long time and one such reaction that utilizes isocyanides is Passerini reaction. It is a powerful tool to synthesize libraries of different compounds. Azaheterocyclic compounds play an important role in medicinal chemistry. Motifs such as imidazoles, piperazines, pyrazoles, pyridines, triazoles, etc. are routinely observed in several compounds of pharmacological interest. Several natural products also contain these motifs in them. We have undertaken a library synthesis of heterocyclic molecules driven by our group's long-standing interest of synthesizing medicinally relevant small molecules employing green chemistry techniques.

This thesis details our efforts on the development of novel synthetic methodologies for the synthesis of functionalized azaheterocyclic compounds as potential anti-cancer agents. We initiated the synthesis of these compounds employing Passerini reaction as the key step. The biological evaluation of these synthetic derivatives showed some promise as anti-cancer agents.

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Chapter 1

Introduction

Multicomponent Coupling Reactions

The arrangement of specific sets of complicated molecules can be easily accomplished by utilizing diversity-oriented synthesis. A multi-component reaction (MCR) merges three or more structural motifs into one unique compound. With a limited number of reaction steps, MCRs provide easy access to large libraries of organic compounds with diverse functionalization.

History of Multicomponent Chemistry

The approach of MCR is not obscure in nature and it appears that adenine **1**, one of the key components of DNA and RNA, was prebiotically assembled by the arrangement of five fragments of hydrogen cyanide, in a process facilitated by ammonia under prebiotic pressure conditions (Figure 1). The additional nucleic bases have also been created under similar conditions involving HCN and water.[1]

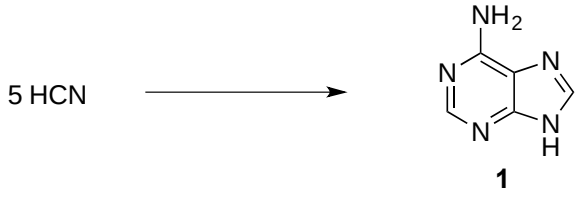

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Figure 1. Probiotic synthesis of adenine

Strecker's synthesis of α-amino nitriles **3** is one of the first examples of multicomponent reactions.[2] Strecker demonstrated an MCR of aldehydes **2** with

hydrogen cyanide and ammonia to generate α-amino nitriles **3**, which were further hydrolyzed to provide easy access to α-amino acids **4** (Figure 2).

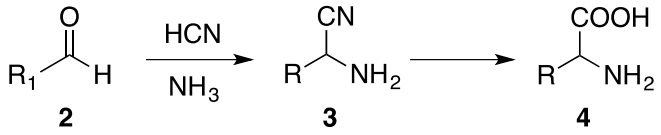


Figure 2. Strecker synthesis of α-aminoacids

Hantzsch described the synthesis of symmetrical dihydropyridines **6** by reacting aldehydes **2** with 2 moles of β-ketoesters **5** in the presence of ammonia (Figure 3).[3] Hantzsch also demonstrated the synthesis of pyrroles **9** by combining primary amines **7** with β-ketoesters **5**, and α-halogenated β-ketoesters **8**.[4]

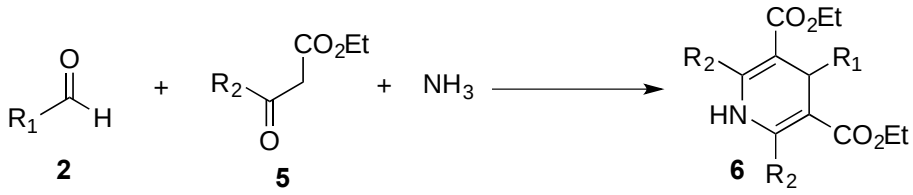


Figure 3. Hantzsch dihydropyridine synthesis

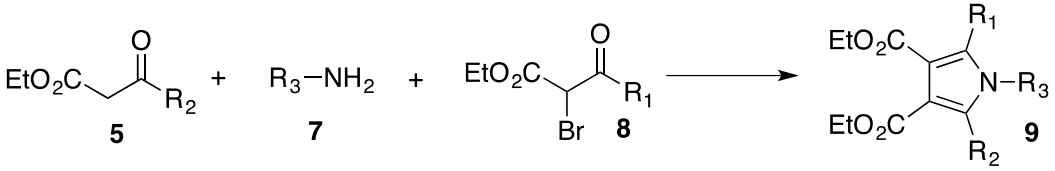


Figure 4. Hantzsch pyrrole synthesis

The Biginelli reaction first explained in 1893 is a multicomponent synthesis of dihydropyrimidines **13** via acid-catalyzed cyclocondensation of β-keto esters **10**, aromatic aldehydes **11**, and urea **12** (Figure 5).[5]

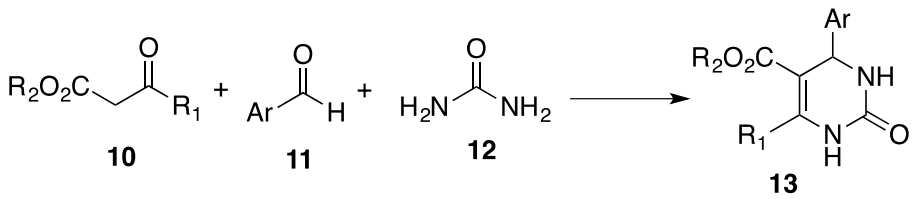


Figure 5. Biginelli synthesis of dihydropyrimidines

Sir Robert Robinson showed the first prominent use of MCRs in natural product chemistry via the synthesis of the alkaloid tropinone **18** starting from succinic dialdehyde **14**, methylamine **15**, and calcium salt of acetone dicarboxylic acid **16** (Figure 6).[6]

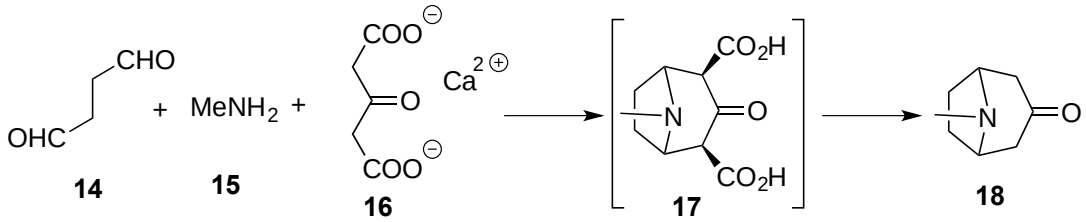


Figure 6. Robinson synthesis of tropinone

Passerini discovered the first MCR reaction involving isocyanides in 1921. In this reaction, carboxylic acids, carbonyl compounds, and isocyanides react with each other in a one-step transformation afforeding α-acyloxy carboxamides **22** (Figure 7).[7-10] While there have been multiple mechanisms proposed for this reaction, the most commonly invoked mechanism involves the attack of isocyanide in a concerted process.[11]

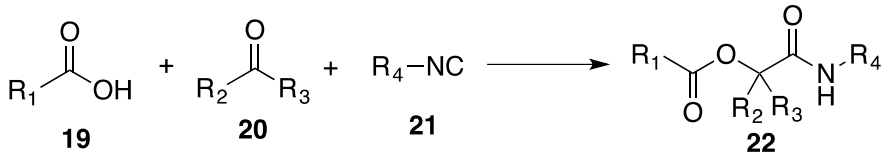


Figure 7. Passerini multicomponent coupling reaction

Bucherer and Bergs outlined a four-component coupling reaction in 1934 for the synthesis of hydantoins via a one-pot reaction of aldehyde **2** with HCN, NH_3 and CO_2. Hydantoins could be efficiently converted into α-amino acids through simple hydrolysis (Figure 8).[12]

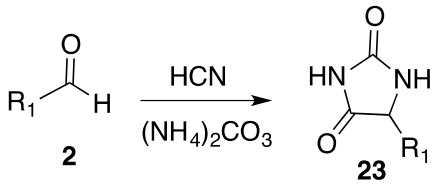


Figure 8. Bucherer-Bergs synthesis of hydantoin

Another illustration of MCR is the Asinger reaction disclosed in 1958. In this reaction, α-thiolocarbonyl compounds **25** when treated with ketones **24** in the presence of ammonia yielded thiazolines **26** (Figure 9).[13]

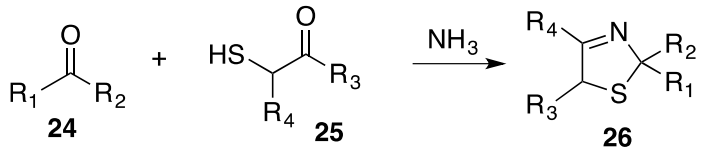


Figure 9. Asinger reaction

In 1959, Ugi et al. expanded the utility of Passerini reaction for the synthesis of α-acylamino amides **28** via the treatment of aldehydes **2** with primary amines **27**, carboxylic acids **19**, and isocyanides **21** (Figure 10).[14]

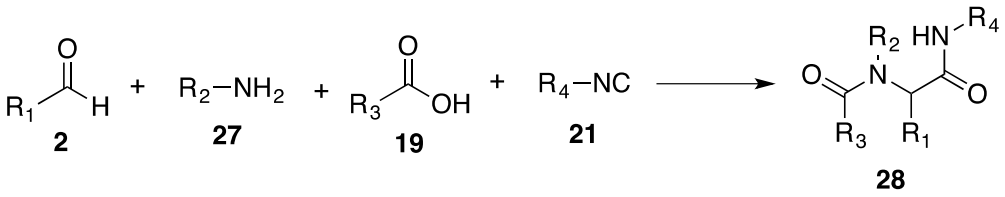


Figure 10. Ugi four component coupling reaction

Gewald *et al.* reported the synthesis of polysubstituted thiophenes **31** via the reaction of ketones **29** with active methylene compounds **30** in the presence of sulfur and tertiary amine base such as morpholine (Figure 11).[15]

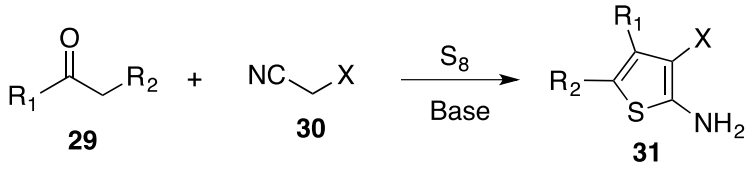


Figure 11. Gewald's reaction

Synthesis of Isocyanides

For a long time, isocyanides (isonitriles) have been described as a rare class of stable organic compounds with a divalent carbon. Most isocyanides have an unpleasant

smell, accordingly isocyanides have been examined as promising non-fatal weapons.[16] There have been several methods of synthesis reported for isocyanides.[17]

One of the first methods reported for the preparation of isocyanides **33** involves the reaction of silver cyanide with allyl iodide **32** (Figure 12).[18,19] The unpleasant odor associated with this reaction can be minimized via an *in situ* preparation of isocyanide, by reacting the corresponding bromides with silver and potassium cyanide in acetonitrile at 80ºC, in the presence of catalytic amount of TEBAC.[20]

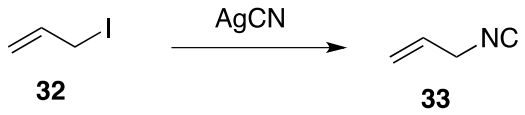


Figure 12. Lieke synthesis of isocyanides

Hofmann reported the synthesis of isocyanides **38** via condensation of the primary amine **36** with a dichlorocarbene **35**, produced *in situ* by heating chloroform **34** with potassium hydroxide (Figure 13).[21] However, this method suffers from the lack of reproducibility, small yield, and problems associated with the separation of isocyanides from amines. Ugi further upgraded this method by performing it in a biphasic medium - the combination of dichloromethane and water in the presence of a PTC (phase transfer catalyst).[22]

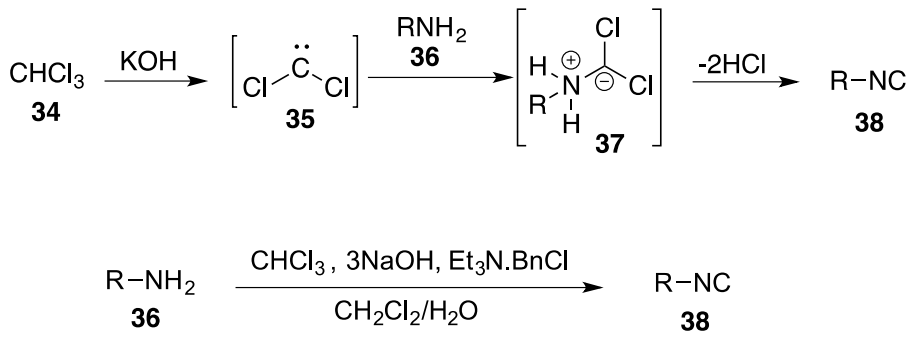


Figure 13. Hoffmann synthesis of isocyanides

Ugi also discovered a method for the formation of isocyanides using dehydration of *N*-monosubstituted formamides **40**, which in turn could be obtained from primary amines **36** and alkyl formate/formic acid **39** (Figure 14).[23] Miscellaneous dehydrating agents such as thionyl chloride, phosphorus tribromide, phosphorus pentoxide, phosphorus oxychloride, and oxalyl chloride have been employed in the presence of a base like triethylamine, pyridine, diisopropylethylamine for the conversion of formamide **40** to isocyanide **38**.[24]

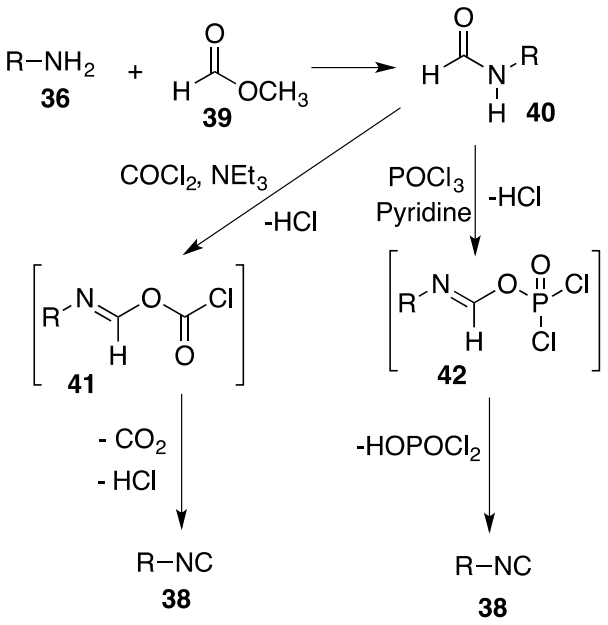


Figure 14. Synthesis of isocyanides via dehydration of formamide

Trifluoromethyl isocyanide **44** was synthesized via the treatment of magnesium with gem-dihalide **43** (Figure 15).[25]

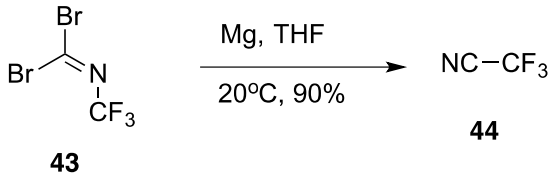


Figure 15. Synthesis of isocyanides from geminal dihalides

Another method for the preparation of isocyanides **48** involves the trapping of organolithium derivatives of oxazoles and benzoxazoles **45** with eletrophiles such as acid chloride (Figure 16).[26]

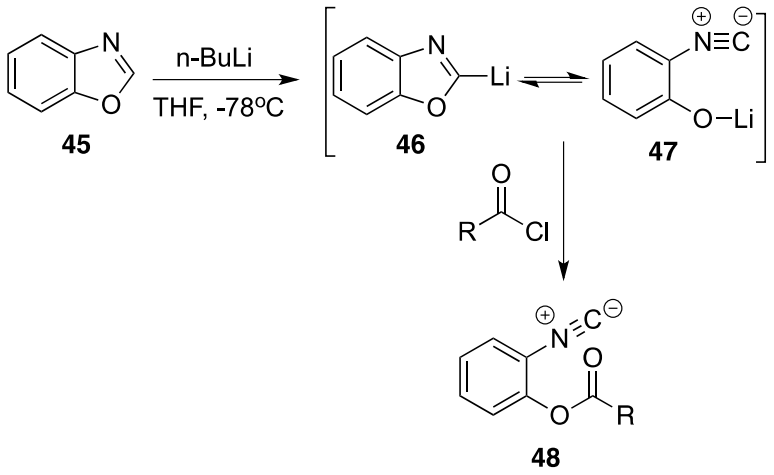


Figure 16. Synthesis of isocyanides from benzoxazole

Heterocyclic Motifs

In our present work we utilized chloroquinoline, chloropyridine, and pyrazole heterocyclic motifs for the diverse functionalization utilizing Passerini reaction. Quinoline moiety is the key building element in many naturally occurring compounds[27-28] and pharmacologically active substances.[29-32] Quinoline containing compounds are known to exhibit wide variety of biological activities such as anti-tuberculosis,[33] anti-malarial,[34] anti-bacterial,[35] anti-fungal,[36] anti-protozoic, antibiotic,[37] and anti-asthma.[38] Several quinolones based antimalarial drugs **49-54** are used in medicine and several others are in clinical trials (Figure 17).

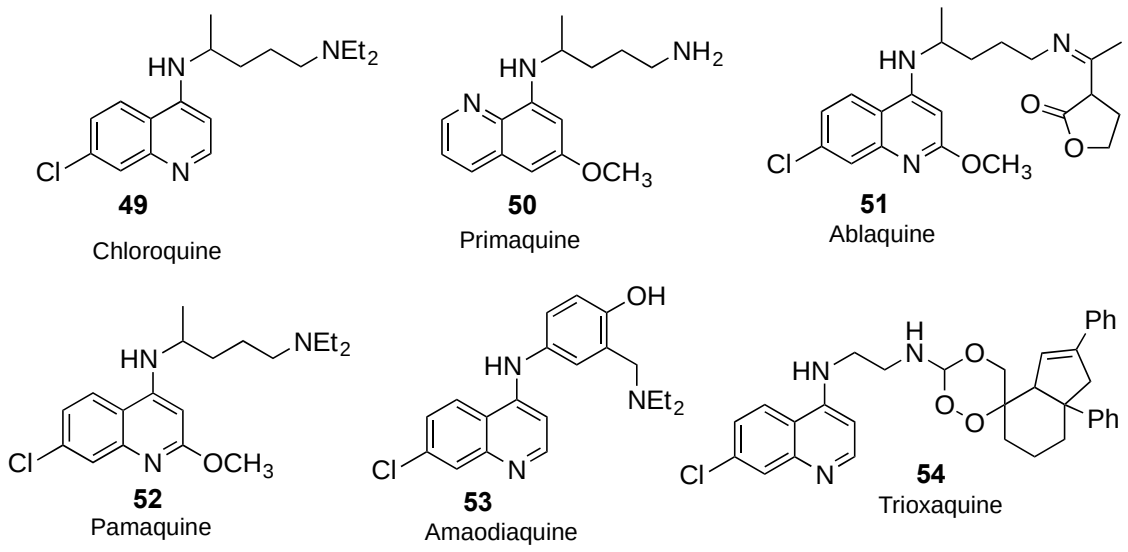


Figure 17. Quinoline-based antimalarial drugs[39]

Pyridine based compounds have also been widely utilized as drugs. Niflumic acid **55** is an analgesic and anti-inflammatory medication used for rheumatoid arthritis. Sulfapyridine **56** is used as antibacterial drug[40]. Mepyramine **58**, also known as pyrilamine is the first-generation antihistaminic drug.[41-43] Pinacidil **59** is a cyanoguanidine drug used for treating the symptoms of multiple sclerosis.[44] Picoxicam **60** is a nonsteroidal anti-inflammatory drug (Figure 18).

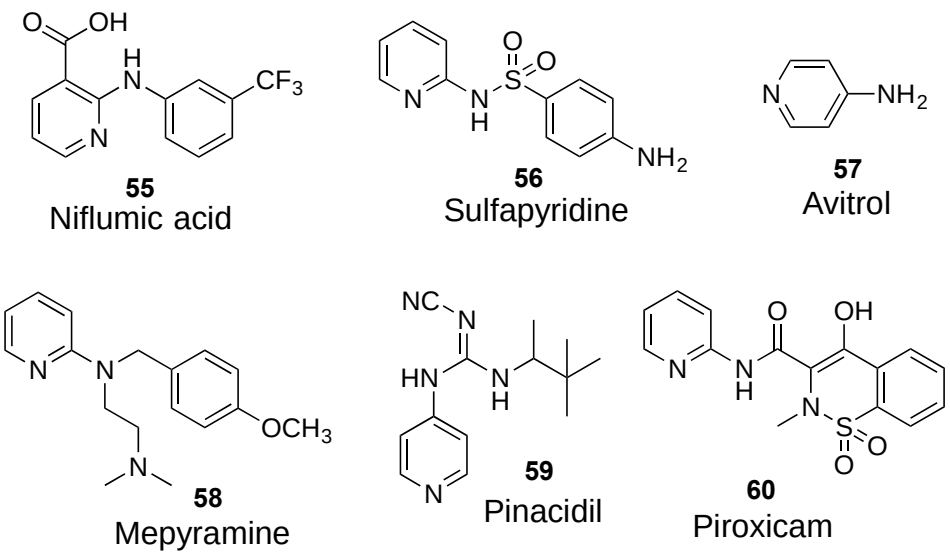


Figure 18. Pyridine-based drugs

Piperonal (heliotropin) is an aromatic aldehyde found in many essential oils,[45] vanilla and camphor[46,47] and has been shown to have antibacterial[48] and anxiolytic activities. Additionally, few piperonal derivatives display a promising anticancer activity,[49] antileishmanial effect[50] and other pharmacological activities.[51,52]

Pyrazoles play a significant role in natural product and medicinal chemistry. Knorr discovered the antipyretic action of pyrazole derivatives and named the compound antipyrine.[53] Kosuge and Okeda isolated 3-n-nonylpyrazole **61** from Houttuynia Cordata, a plant of the piperaceae group from tropical Asia, which displayed antimicrobial activity. They also isolated levo-β-(1-pyrazolyl) alanine **62** from watermelon seeds (Figure 19).[54]

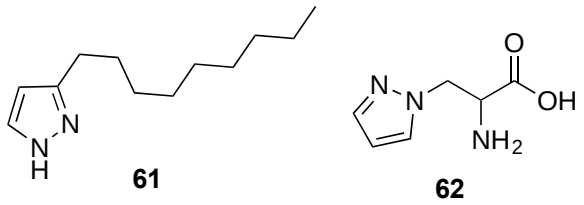


Figure 19. Pyrazole-based natural products

The pyrazole ring system is present in an array of drugs such as Celecoxib,[55] Ionazolac,[56] Pyrazofurin,[57] Fezolamin,[58] Rimonabant,[59] Ruxolitinib,[60] Crizotinib,[61] Tepoxalin[62] etc. (Figure 20).[63-65] Pyrazoles also play a role in agrochemicals and as bifunctional ligands in metal catalysis.[66]

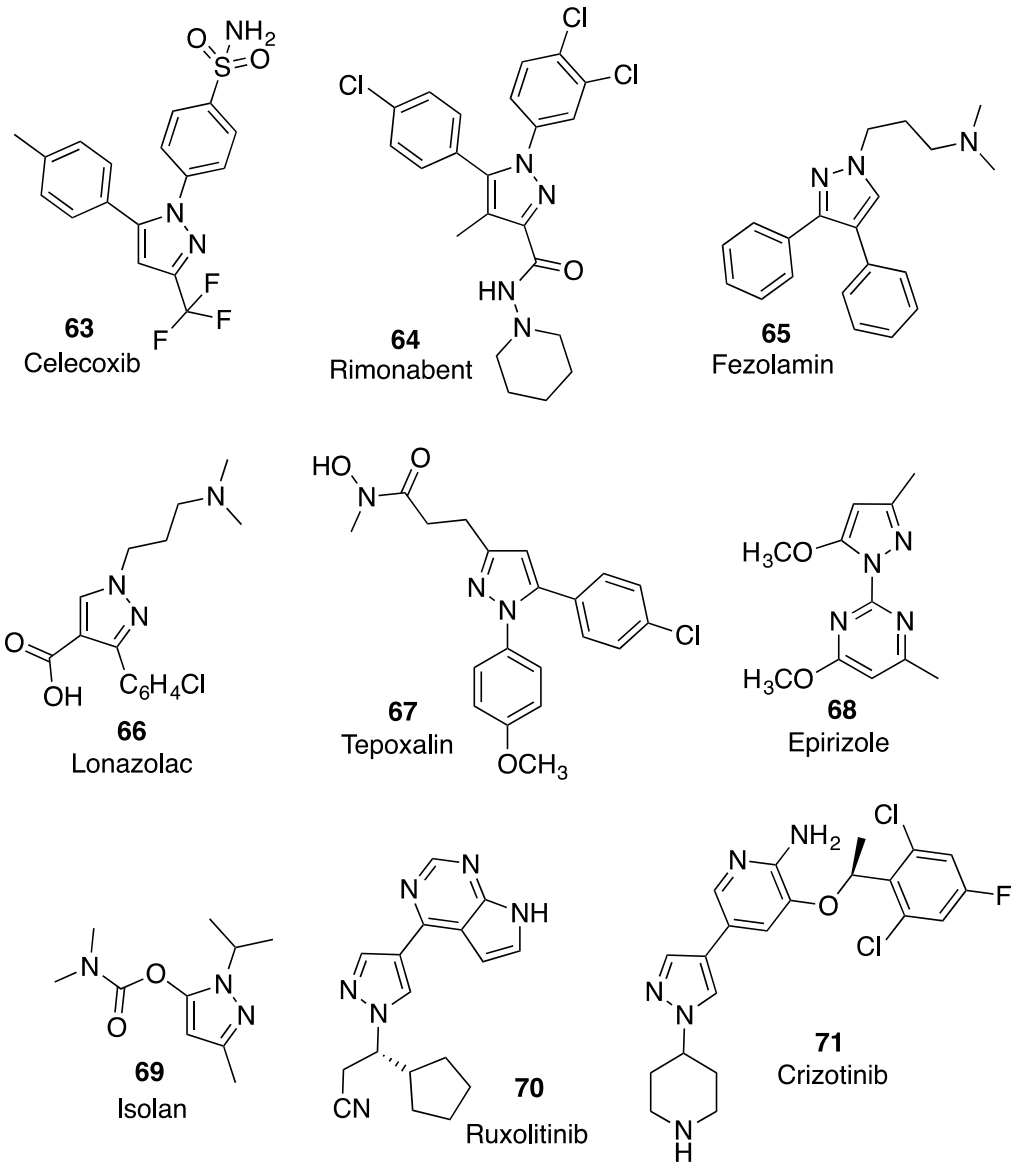


Figure 20. Pyrazole-based drugs

Chapter 2

Azaheterocyclic Compounds via Passerini Reaction

Preparation of Chloroquinoline Conjugates

We undertook the synthesis of azaheterocyclic compounds via Passerini reaction and the synthetic scheme is shown in Figure 21. The synthesis was initiated via a three-component coupling between *p*-bromomethylbenzoic acid **72**, chloroquinoline aldehyde **73**, and *t*-butylisocyanide. The resulting bromomethylbenzoate **74** was further treated with a variety of secondary amines to produce the target compounds **75** (Figure 21).

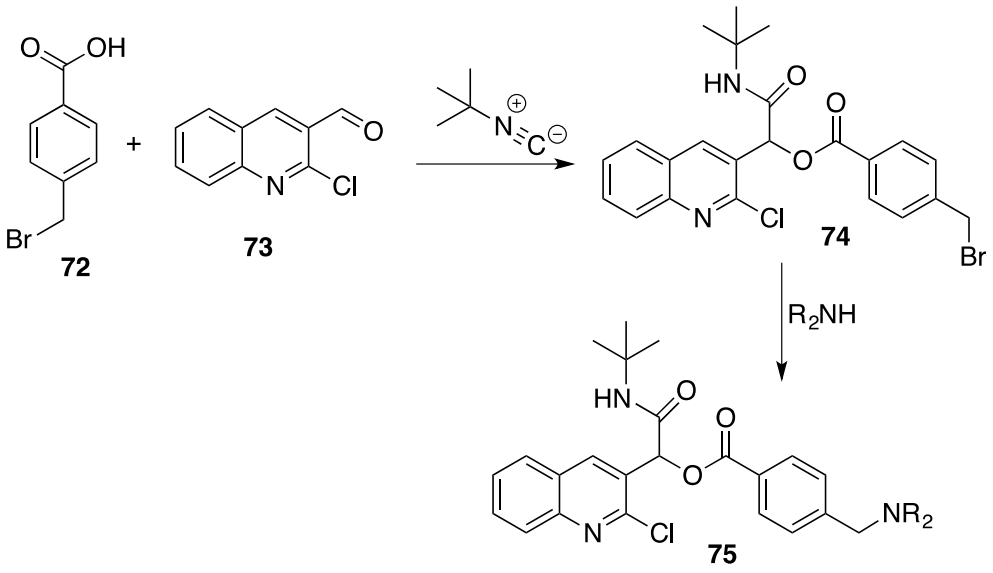


Figure 21. Preparation of chloroquinoline conjugates

p-Bromomethyl benzoic acid **72** was synthesized in 90% yield starting from *p*-toluic acid **76** using potassium bromate and sodium thiosulfate at room temperature via benzylic halogenation (Figure 22).[67] The compound **72** was confirmed by ^{1}H-NMR spectral analysis (signals at δ 4.7 (2H, benzylic methylene) and at δ 12.9 (1H, carboxylic acid).

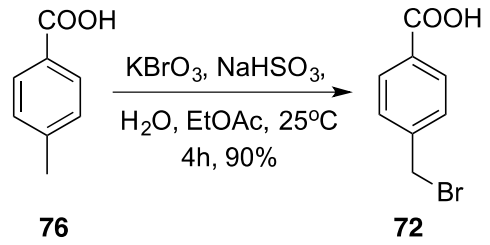


Figure 22. Preparation of *p*-bromomethylbenzoic acid

2-Chloroquinoline aldehyde **73** was synthesized from acetanilide **77** under Vilsmeier-Haack reaction conditions involving $POCl_3$ and DMF at 80°C in 89% yield.[68] The aldehyde **73** was confirmed by ^{1}H-NMR spectral analysis.

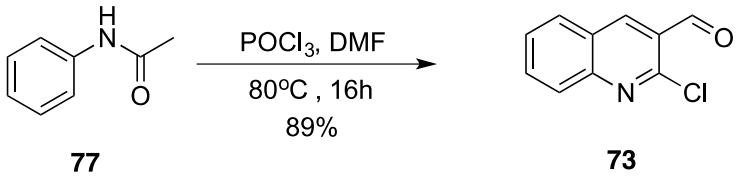


Figure 23. Preparation of 2-chloroquinoline aldehyde

p-Bromobenzoic acid **72** was subsequently reacted with chloroquinoline aldehyde **73** and *t*-butyl isocyanide in presence of a protic solvent (water) and stirred at room temperature for 12 hours to obtain the α-acyloxy amide **74** in 94% yield (Figure 24).

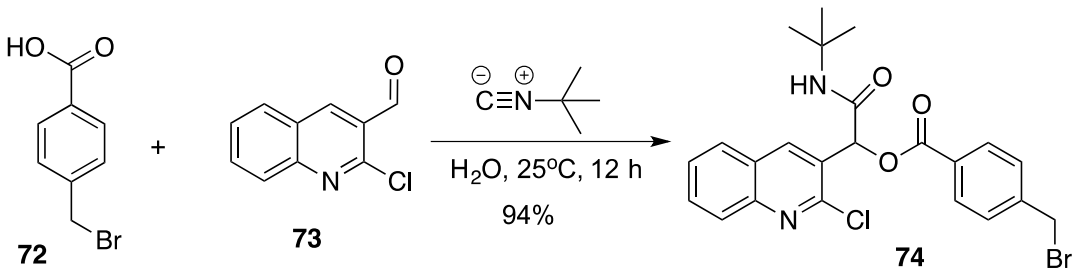


Figure 24. Passerini reaction with 2-chloroquinoline aldehyde

The benzylic bromide in **74** was substituted with morpholine **78a** in the presence of DMF and K_2CO_3 to yield the final target compound **75a** (Figure 25). The reaction was carried out at room temperature for 24 hours and the product was obtained in 90% yield.

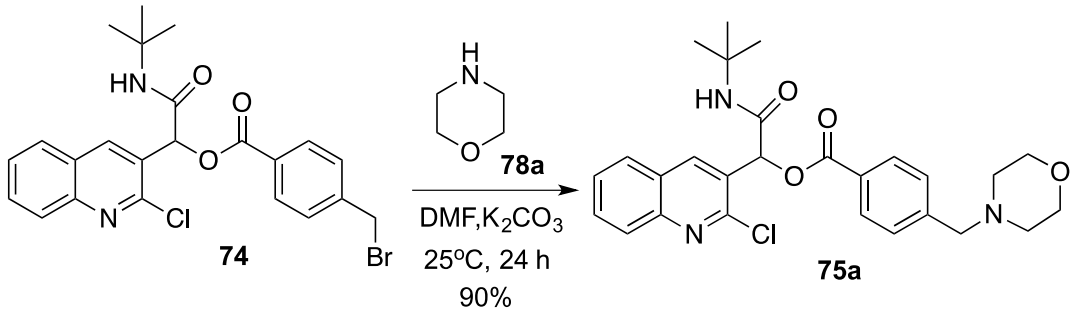


Figure 25. Preparation of 2-chloroquinoline-morpholine conjugate

After standardizing the above substitution, the bromide **74** was further treated with variety of amines such as *N*-methylpiperazine, imidazole, 4-aminopiperidine, triazole, pyrrolidine, 2-ethylimidazole, 2-methyl-5-methylimidazole, 4-nitroimidazole, and *N*-butoxycarbonylpiperazine to yield the target amine compounds **75b-j** respectively (Figures 26 and 27). All the synthesized compounds were tested for their biological activity against three cancer cell lines SK-MEL (melanoma), MCF-7 and MDA-MB-231 (breast cancer) (Table 1). None of these compounds showed significant cytotoxicity at ~20 μM concentration.

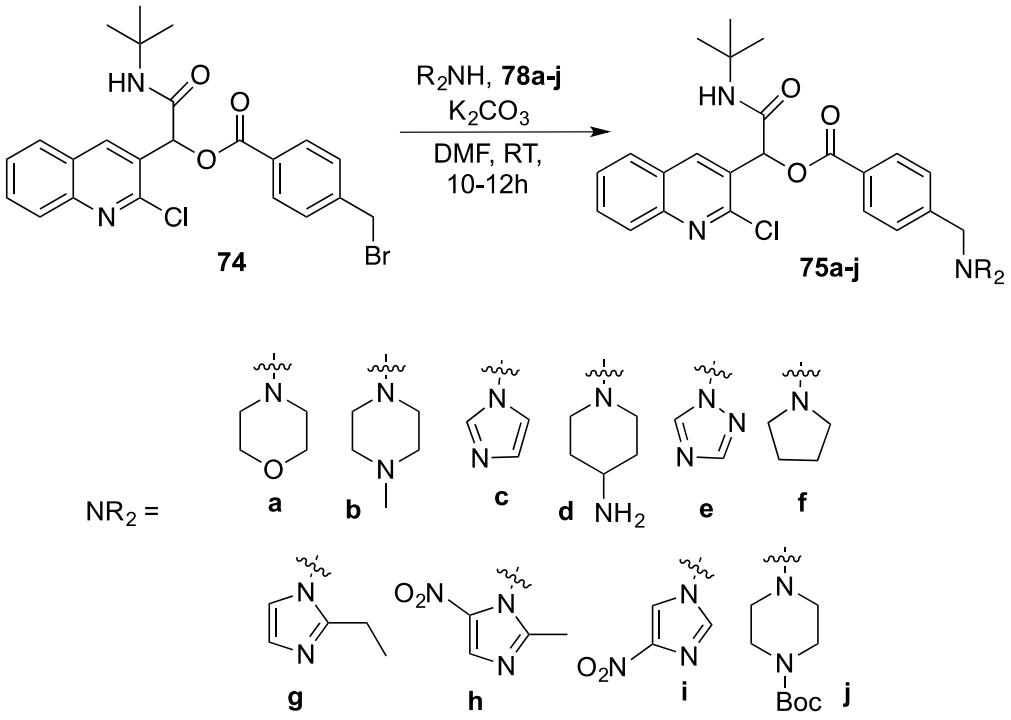


Figure 26. Preparation of 2-chloroquinoline-based amines

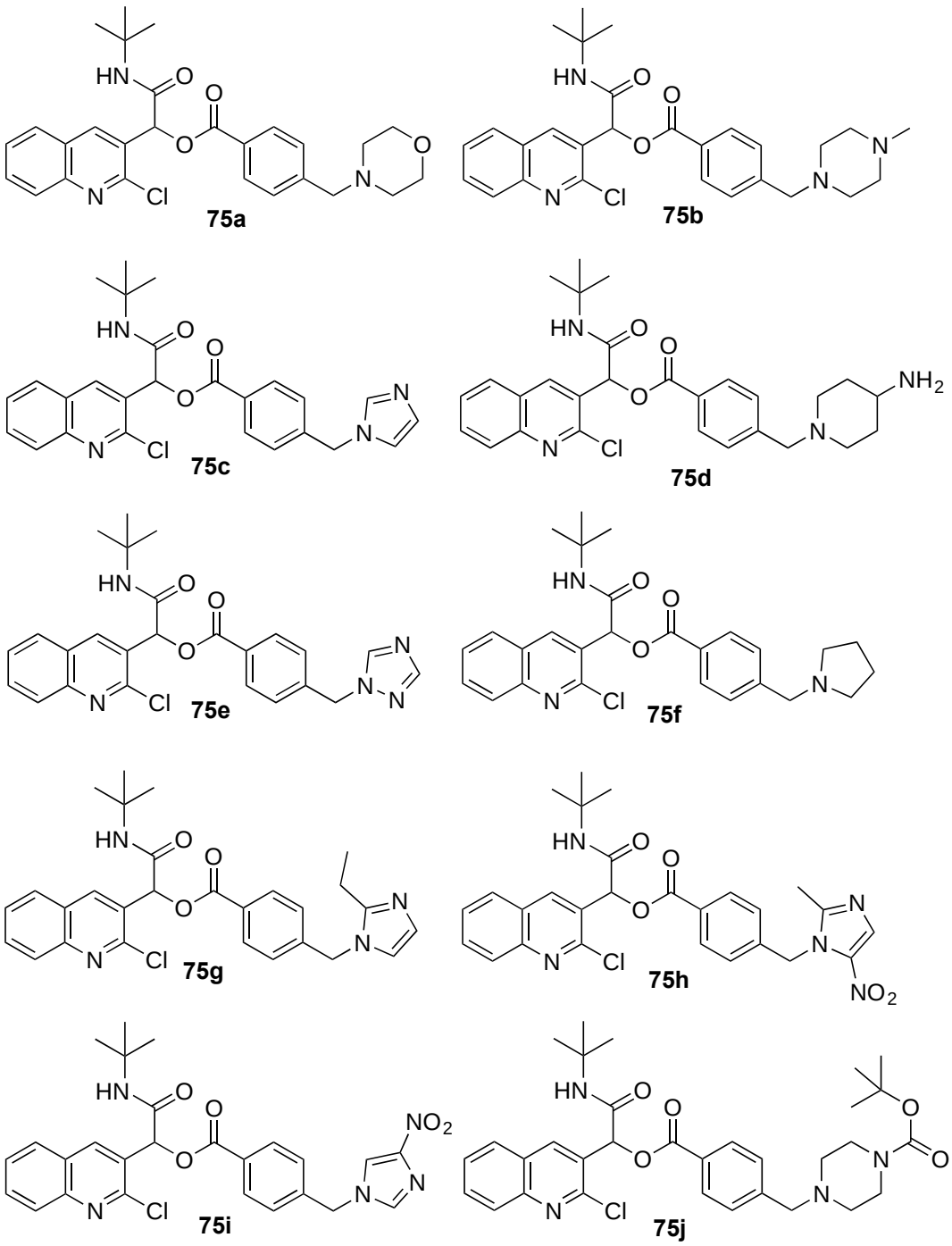


Figure 27. 2-Chloroquinoline-based amines

Table 1

In Vitro Cytotoxicity of 2-Chloroquinoline Derivatives.

#	Product	Yield (%)	M.P. (°C)	Cytotoxicity (IC_{50} μM)			CLogP
				SKMEL5	MCF-7	MDA-MB-231	
1.	**74**	96	142-143	>20	>20	>20	5.2202
2.	**75a**	55	119-120	>20	>20	>20	4.1852
3.	**75b**	89	140-145	>20	>20	>20	4.7462
4.	**75c**	51	113-116	19.0	>20	>20	3.4782
5.	**75d**	51	98-99	>20	>20	>20	3.8012
6.	**75e**	70	104-106	>20	>20	>20	3.5113
7.	**75f**	68	103-108	>20	>20	>20	4.9062
8.	**75g**	82	109-111	>20	>20	14.55	4.5992
10.	**75h**	87	143-144	>20	>20	>20	4.1873
9.	**75i**	88	130-131	>20	>20	>20	3.6783
11.	**75j**	89	105-107	>20	>20	>20	6.1582

Preparation of Piperonal Conjugates

We then shifted our focus toward the synthesis of piperonal based Passerini adduct **80**. The reaction of p-bromomethylbenzoic acid **72** with piperonal **79** and *t*-butylisocyanide yielded the benzylic bromide **80**, which was further treated with variety of secondary amines to yield the target amine compounds **81a-e** (Figures 28 and 29). All the synthesized compounds were tested for their biological activity against three cancer cell lines SK-MEL (melanoma), MCF-7 and MDA-MB-231 (breast cancer) (Table 2). None of these compounds showed significant cytotoxicity at ~20 μM concentration.

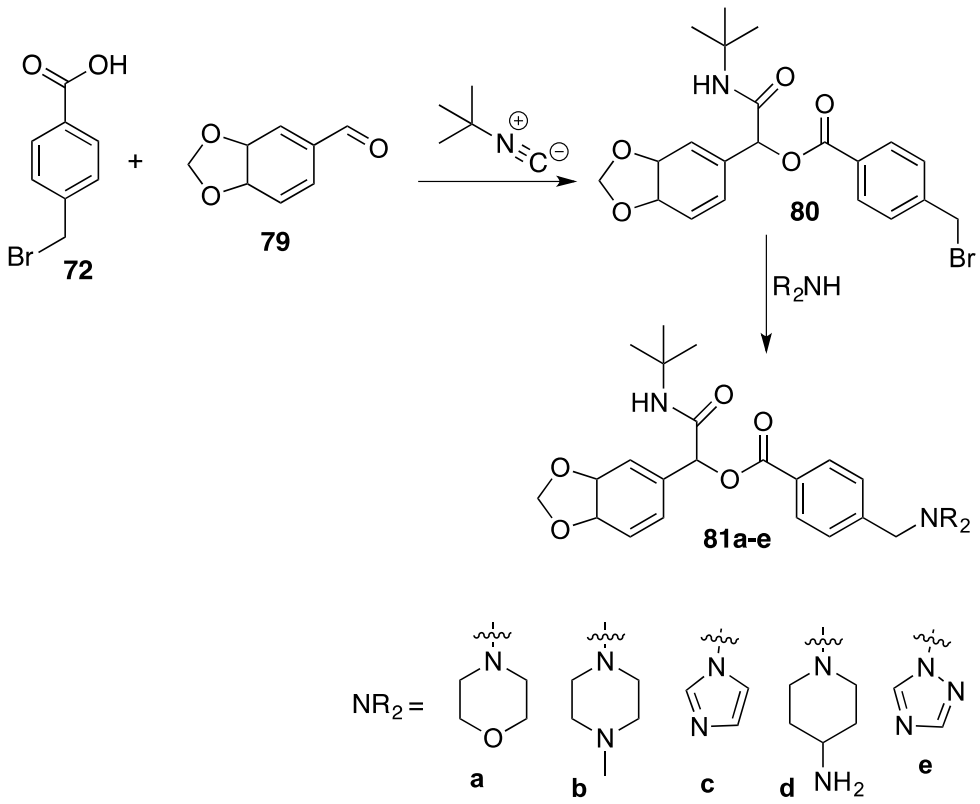


Figure 28. Preparation of piperonal-based amines

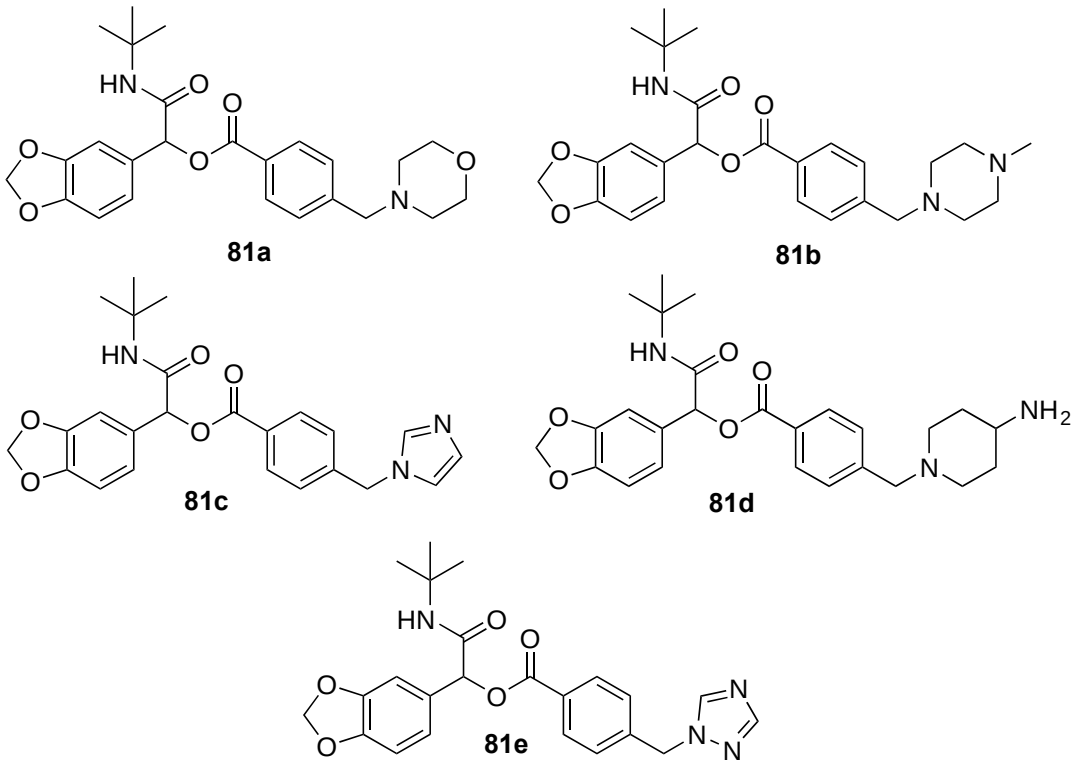


Figure 29. Piperonal-based amines

Table 2

In Vitro Cytotoxicity of Piperonal Derivatives.

#	Product	Yield (%)	M.P. (°C)	Cytotoxicity (IC_{50} μM)			CLogP
				SKMEL5	MCF-7	MDA-MB-231	
1.	**80**	98	153-155	>20	>20	>20	4.5012
2.	**81a**	92	178-180	>20	>20	>20	3.4662
3.	**81b**	78	92-93	>20	>20	>20	4.0272
4.	**81c**	67	83-84	>20	>20	>20	3.0822
5.	**81d**	54	92-94	>20	>20	~20	2.7592
6.	**81e**	50	120-121	>20	>20	>20	2.7923

Preparation of Chloropyridine Conjugates

Finally, we synthesized the chloropyridine based Passerini adducts **83** and **84**. The reaction of p-bromomethylbenzoic acid **72** with chloropyridine aldehyde **82** and *t*-butylisocyanide yielded the benzylic bromide **83**, which was further treated with variety of secondary amines to yield the target amine compounds **84a-e** (Figures 30 and 31). All the synthesized compounds were tested for their biological activity against three cancer cell lines SK-MEL (melanoma), MCF-7 and MDA-MB-231 (breast cancer) (Table 3). Most of these compounds did not show significant cytotoxicity at ~20 μM concentration. The benzylic bromide **83** exhibited toxicity against SK-MEL and MDA-MB-231 cell lines with IC_{50} values ranging between ~4-6 μM (Table 3).

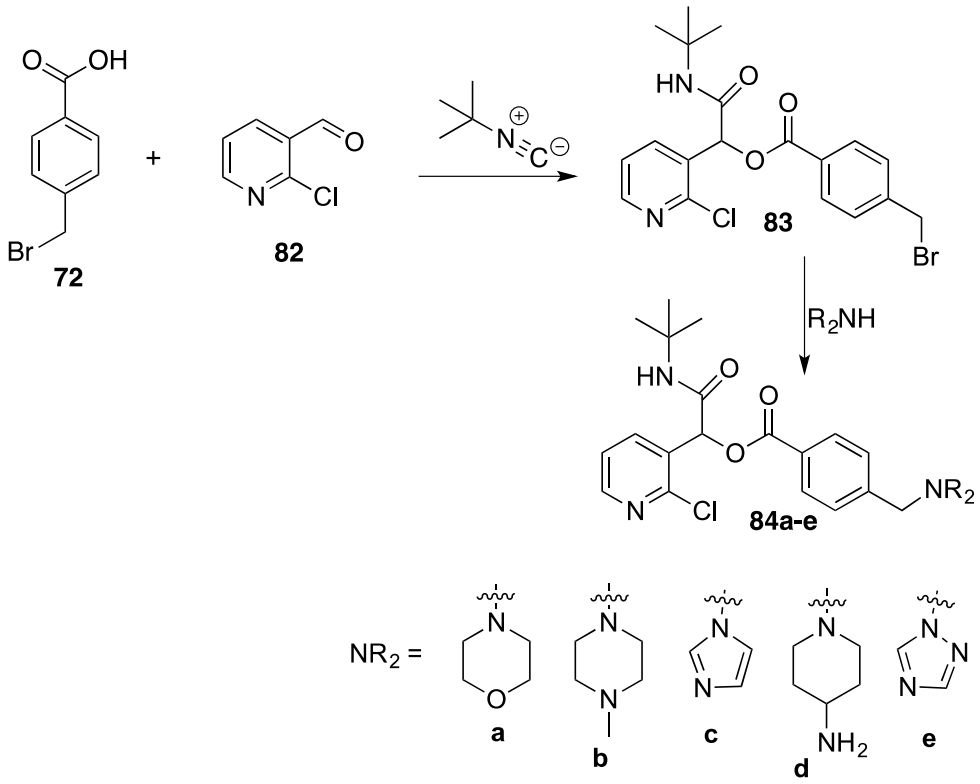


Figure 30. Preparation of 2-chloropyridine-based amines

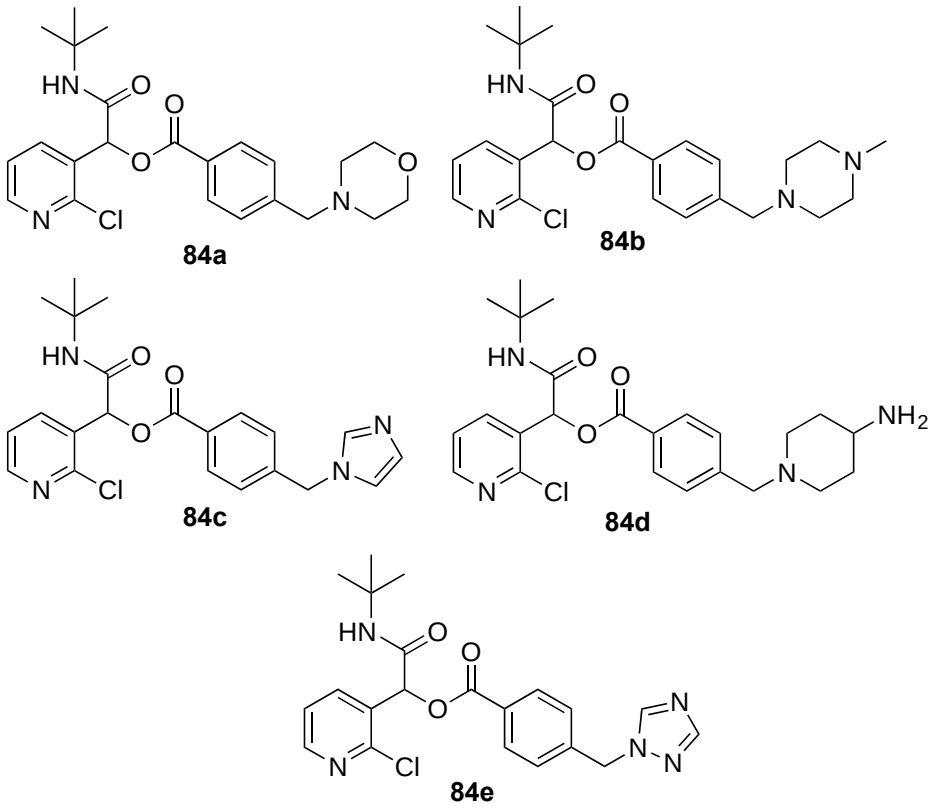


Figure 31. 2-Chloropyridine-based amines

Table 3

In Vitro Cytotoxicity of 2-Chloropyridine Derivatives.

#	Product	Yield (%)	M.P. (°C)	Cytotoxicity (IC_{50} µM)			CLogP
				SKMEL5	MCF-7	MDA-MB-231	
1.	**83**	92	128-129	4.05	16.16	6.39	3.8362
2.	**84a**	80	78-80	>20	>20	>20	2.8012
3.	**84b**	71	99-100	>20	>20	>20	3.3622
4.	**84c**	77	103-104	>20	>20	>20	2.4172
5.	**84d**	59	113-115	>20	>20	>20	2.0942
6.	**84e**	76	95-97	>20	>20	>20	2.1273

In an effort to increase the solubility and efficacy of the target compounds, the *N*-methylpiperazine adducts **75b**, **81b**, and **84b** were converted to the corresponding quaternary ammonium salts **85-87** respectively upon treatment with methyl iodide in acetonitrile (Figure 32).

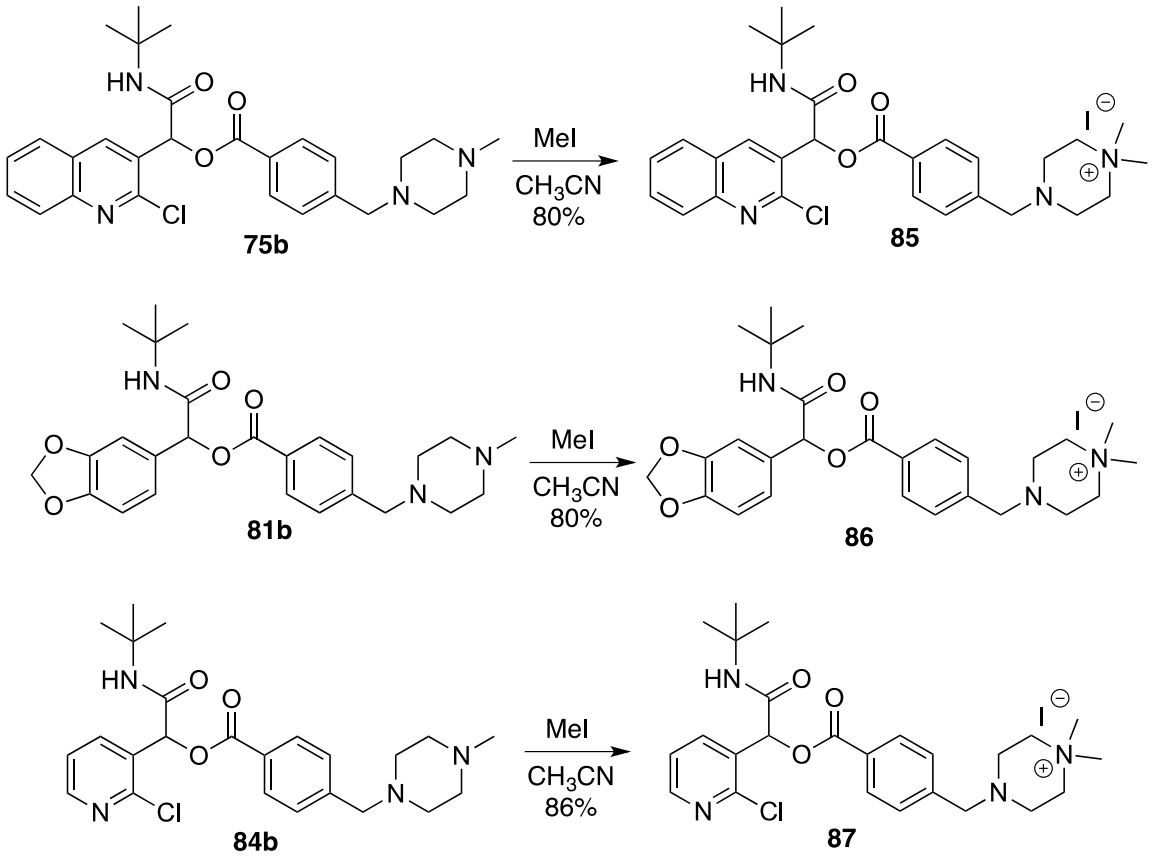


Figure 32. Preparation of quaternary ammonium salts

Preparation of Pyrazole Conjugates

The outline for the synthesis of pyrazole based Passerini adducts is shown in Figure 33. The synthesis was initiated with the condenstaion of acetophenone **88** with phenyl hydrazine **89** to yield the hydrazone **90**. Hydrazone **90** upon Vilsmeier-Haack formylation yielded the aldehyde **91** which upon oxidation with $KMnO_4$ furnished the carboxylic acid **92**. The reaction of acid **92** with benzaldehyde **93** benzyl isocyanide **94** resulted in the formation of the target Passerini adduct **95** (Figure 33).

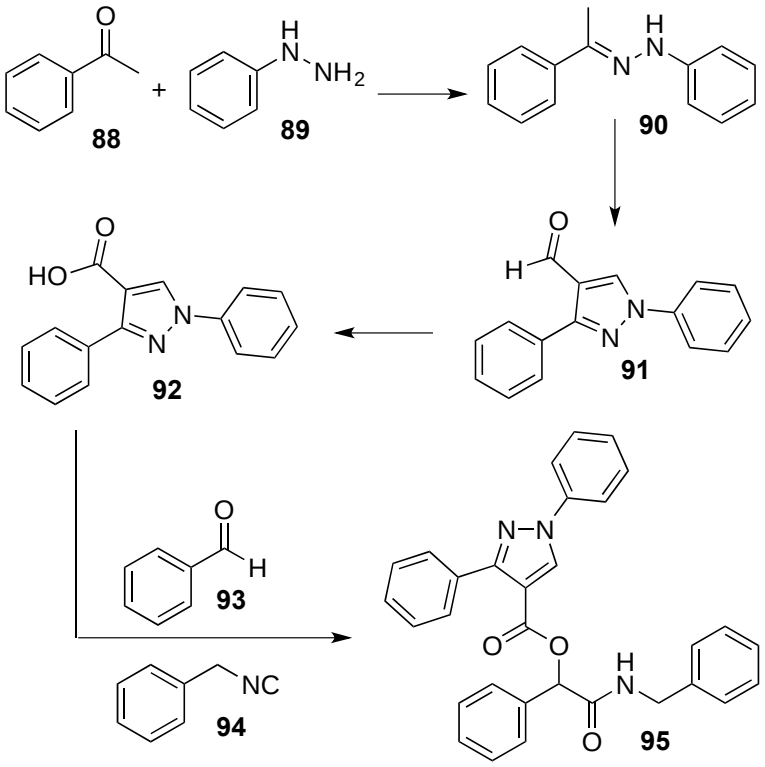


Figure 33. Preparation of pyrazole derivatives

Hydrazine hydrochloride **89** and acetophenone **88** were refluxed in anhydrous ethanol in the presence of catalytic acetic acid for 7 hours and the completion of reaction was monitored by TLC using10% EtOAc/Hexane. The reaction mixture was cooled to room temperature, when the product precipitated out of the reaction mixture. The product was filtered, washed with cold ethanol and dried under vaccum to obtaine pure acetophenone phenylhydrazone as a yellow solid in 93% yield (Figure 34).

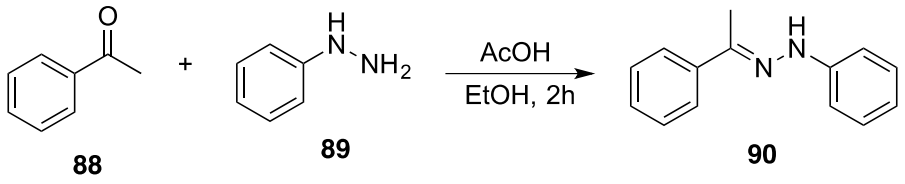


Figure 34. Preparation of phenylhydrazone

Phosphoryl chloride was added to DMF and the mixture stirred for 1hr at 0°C. The mixture was then slowly added to a solution of acetophenone phenylhydrazone **90** in DMF and the reaction mixture was allowed to stir for 10 min at 0°C and gradually heated to 60°C for 4hr. The reaction was monitored by TLC using 30% EtOAc/Hexane as the eluant. The reaction mixture was cooled to room temperature and basified with cold and saturated aqueous sodium hydroxide solution to effect precipitation. The precipitate was filtered and washed with cold water to obtain the product aldehyde **91** as a off white solid in 92% yield (Figure 35).

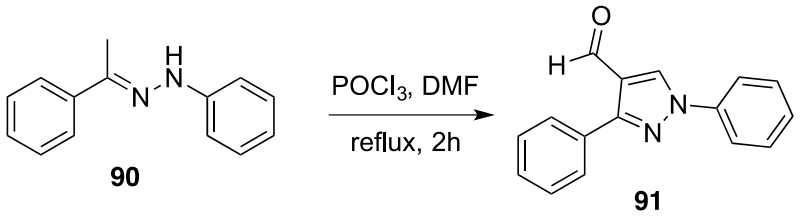


Figure 35. Preparation of pyrazole aldehyde

Initially Passerini coupling was attempted with pyrazole aldehyde **91**, benzoic acid **96** and benzyl isocyanide **94** in water at room temperature However, this reaction did not materialize and no product formation was obtained even upon heating for an extended

period of time (Figure 36). Accordingly, we shifted our focus to converting the pyrazole aldehyde **91** to the corresponding acid **92** as it was presumed that the electrophilicity of the pyrazole aldehyde was drastically reduced because of the pyrazole ring system.

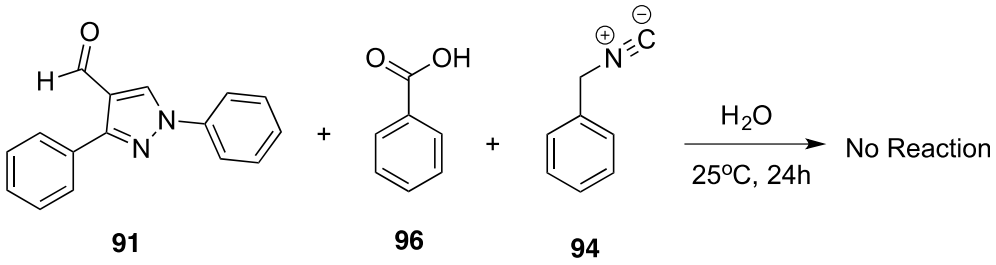


Figure 36. Passerini reaction with pyrazole aldehyde

Aldehyde **91** was dissolved in pyridine: water (1:1) and $KMnO_4$ was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was monitored by TLC using 30% EtOAc/Hexane. Upon completion, ice cold water was added to the reaction mixture followed by the addition of aq. NaOH to effect precipitation. The mixture was filtered and the filtrate was acidified with conc. HCl which resulted in the precipitation. The solid was filtered and recrystallized in hexane to yield the carboxylic acid **92** (Figure 37).[69]

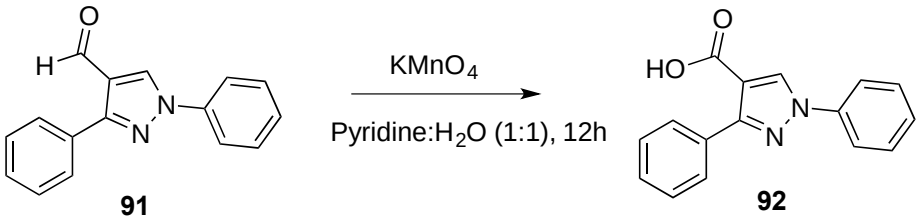


Figure 37. Oxidation of pyrazole aldehyde

As expected, the Passerini reaction was fruitful by converting pyrazole aldehyde to pyrazole acid. The reaction of acid **92** with benzaldehyde **93** and benzyl isocyanide **94** under aqueous conditions resulted in the formation of a-acetoxyamide **95a** (Figure 38). Similarly, compounds **95b**, and **95c** were obtained by replacing acetophenone with dichloroacetophenone and benzaldehyde with p-chlorobenzaldehyde respectively (Figure 38).

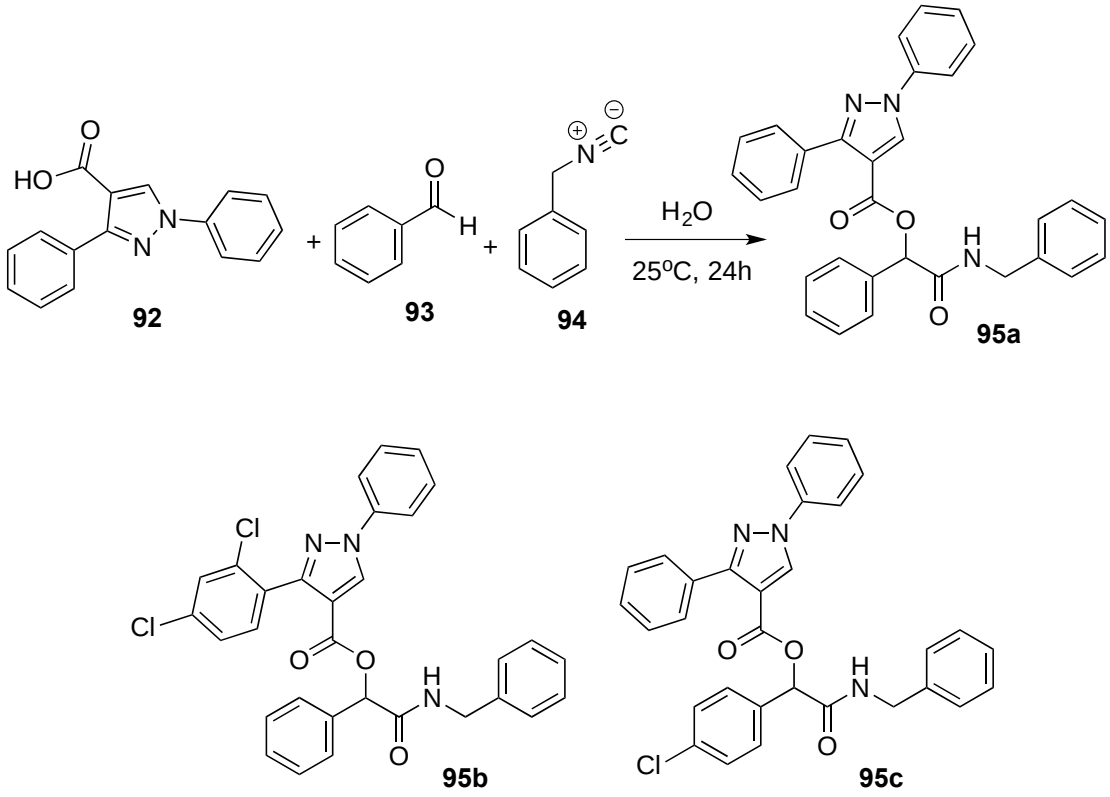


Figure 38. Passerini reaction with pyrazole acid

Conclusions

In conclusion, we have prepared a series of azaheterocyclic compounds using Passerini reaction as a key step in the synthesis. The heterocyclic motifs synthesized include quinoline, pyridine, and pyrazole. The synthesized compounds were tested for their biological efficacy against melanoma and breast cancer cells. While most of the compounds tested did not show promising cytotoxicity, these assays gave us valuable insights for further development of these conjugates towards drug discovery.

Chapter 3

Experimental Procedures

Materials

All the reactants were of reagent grade, and purchased from Acros Organics, Alfa Aesar or Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific.

Instrumentation

Nuclear Magnetic Spectroscopy (NMR) spectra were produced using the Varian 400 MHz spectrophotometer. The instrument was maintained at 25° C operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures

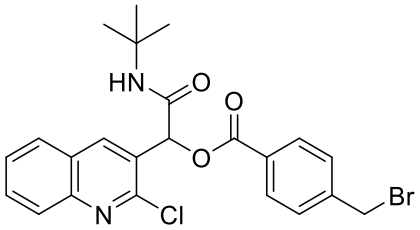
Method for the preparation of 2-chloroquinoline-3-carbaldehyde.[70] Phosphorus oxychloride (6.5 mL, 70.0 mmol) was slowly added to *N*,*N*-dimethylformamide (2.3 mL, 30.0 mmol) at 0°C and this solution was slowly added to acetanilide (1.3 g, 10.0 mmol) and heated at 80°C for 16h. The reaction mixture was then poured on ice, and the white product was filtered and dried. The compound was purified by recrystallization from a petroleum ether/ ethyl acetate mixture.

Procedure for the preparation of 4-(bromomethyl)benzoic acid. *p*-Toluic acid (4.0 g) was dissolved in 60.0 mL of EtOAc and treated with KBrO3 (14.7 g) in 50.0 mL of water. A solution of NaHSO3 (9.2 g) in 50.0 mL water was added dropwise over 20 minutes. The reaction mixture turned brown upon addition and it was further stirred for

4.5-5 hrs and quenched with 100.0 mL of 1M $Na_2S_2O_3$ solution. The two layers were separated and the aqueous layer was extracted twice using ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and recrystallized in methanol to yield the acid.

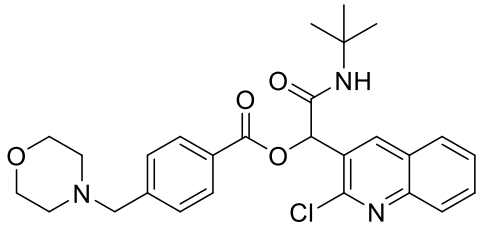
General reaction procedure for preparation of Passerini product.[71,71,73] To a suspension of the aldehyde (1 mmol) and acid (1 mmol) in 10.0 mL water was added isocyanide (1.02 mmol). The reaction mixture was sonicated and vortex stirred repeatedly for 30 minutes and then stirred overnight. The reaction mixture was filtered and washed with saturated solution of $NaHCO_3$ followed by hexane to obtain the pure product.

General procedure for the amination of Passerini products. To a solution of the Passerini adduct (1 mmol) in DMF (6 mL), K_2CO_3 (20 mmol), and amine (1.2 mmol) were added and stirred overnight at room temperature. Ice cold water was added to the reaction mixture and stirred for 5 minutes. The precipitate was filtered, washed with cold water (2 x 10.0 mL), and dried under vaccum to obtain the pure product.

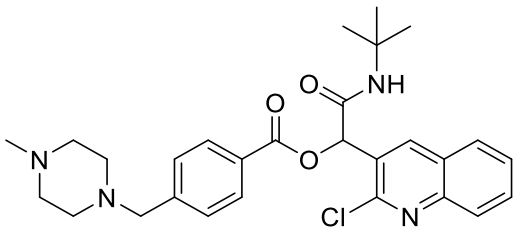


2-(tert-Butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl4-(bromomethyl)benzoate():

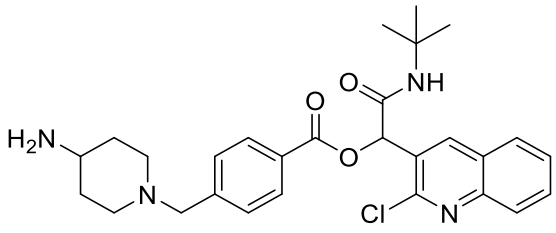
Yield: 96 %; color less solid, mp 142 – 143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.42 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.96 – 7.99 (m, 3H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 4.74 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 165.1, 150.3, 147.3, 144.6, 139.4, 132.3, 130.6, 130.4, 129.3, 129.2, 128.9, 128.5, 128.2, 127.3, 7.3.4, 51.6, 33.7, 29.0 ESIMS: m/z calculated for $C_{23}H_{22}BrClN_2O_3$ $(M+H)^+$ 489.06 found 488.50.



2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl-4-(morpholinomethyl) benzoate():Yield: 55%; color less solid; mp 119 – 120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.39 – 8.42 (m, 1H), 8.17 – 8.21 (m, 1H), 8.10 – 8.14 (m, 1H), 7.96 – 8.01 (m, 1H), 7.91 – 7.96 (m, 2H), 7.83 – 7.89 (m, 1H), 7.64 – 7.71 (m, 1H), 7.42 – 7.48 (m, 2H), 6.44 – 6.46 (m, 1H), 3.52 (s, 4H), 3.50 (s, 2H), 2.32 (s, 4H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 165.4, 150.3, 147.3, 145.0, 139.3, 132.3, 130.2, 129.8, 129.2, 129.1, 128.5, 128.3, 128.2, 127.3, 73.2, 66.8, 62.6, 53.8, 51.6, 29.0; ESIMS: m/z calculated for $C_{27}H_{30}ClN_3O_4$ $(M+H)^+$ 496.20 found 496.00.

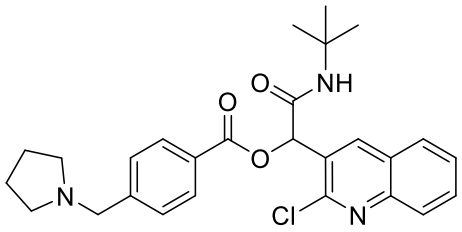


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((4-methylpiperazin-1-yl)methyl)benzoate(): Yield: 89%; color less solid; mp.140 – 145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.41 (s, 1H), 8.19 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.84 – 7.88 (m, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 6.46 (s, 1H), 3.47 (s, 2H), 2.20 – 2.45 (m, 8H), 2.11 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 165.4, 150.3, 147.3, 145.5, 139.3, 132.2, 130.5, 130.2, 129.9, 129.7, 129.2, 129.1, 128.4, 128.2, 127.3, 73.2, 62.2, 55.3, 53.2, 51.6, 46.4, 29.0; ESIMS: m/z calculated for $C_{28}H_{33}ClN_4O_3$ $(M+H)^+$ 509.23 found 509.00.

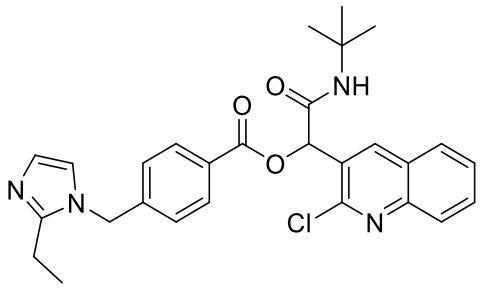


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl4-((4-aminopiperidin-1-yl)methyl)benzoate(): Yield: 51%; color less solid; mp 98 – 99 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.41 (s, 1H), 8.19 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 7.7 Hz, 2H), 7.86 (t, J = 7.7 Hz, 1H), 7.68 (dd, J = 8.1, 7.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 6.46 (s, 1H), 3.47 (s, 2H), 3.23 (br s, 2H), 2.62 – 2.71 (m, 2H),

1.92 (t, *J* = 10.8 Hz, 2H), 1.66-1.56 (m, 2H), 1.29 (s, 9H), 1.13 – 1.24 (m, 3H); ESIMS: m/z calculated for $C_{28}H_{33}ClN_4O_3$ $(M+H)^+$ 509.23 found 509.00.

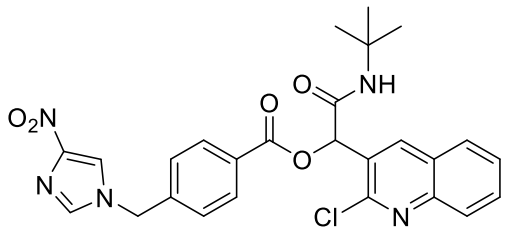


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-(pyrrolidin-1-ylmethyl) benzoate():Yield: 68%; color less solid; mp 103 – 108 °C; ^{1}H NMR (400 MHz, Acetone-d_6): δ (ppm) 8.47 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.77 (m, 1H), 7.57 – 7.62 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 6.49 (s, 1H), 3.58 (s, 2H), 1.95 (m, 4H), 1.61 – 1.67 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.9, 165.4, 150.3, 147.3, 139.3, 132.3, 130.2, 129.5, 129.1, 129.0, 128.5, 128.2, 128.1, 127.2, 73.2, 59.7, 54.1, 51.6, 28.9, 23.8; ESIMS: m/z calculated for $C_{27}H_{30}ClN_3O_3$ $(M+H)^+$ 480.21 found 480.00

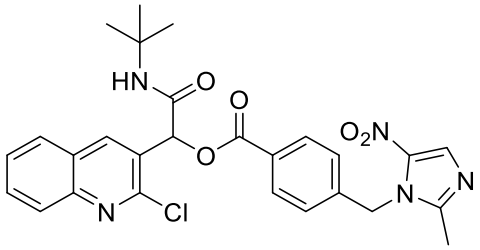


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl4-((2-ethyl-1H-imidazol-1-yl)methyl)benzoate(): Yield: 82%; color less solid; mp 109 – 111 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.40 (s, 1H), 8.20 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.95 – 7.99

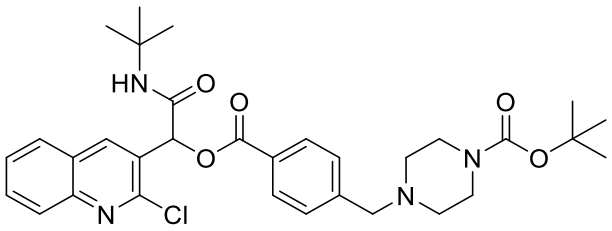
(m, 2H), 7.85 (dd, *J* = 1.4, 7.0 Hz, 1H), 7.67 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 1.2 Hz, 1H), 6.79 (d, *J* = 1.2 Hz, 1H), 6.45 (s, 1H), 5.24 (s, 2H), 1.28 (s, 9H), 1.03 – 1.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.9, 165.2, 150.3, 149.2, 147.3, 144.4, 139.3, 132.3, 130.7, 129.2, 128.9, 128.7, 128.5, 128.2, 127.8, 127.3, 121.0, 51.6, 48.6, 28.9, 20.0, 12.7; ESIMS: m/z calculated for $C_{28}H_{29}ClN_4O_3$ $(M+H)^+$ 505.20 found 504.60.



2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl4-((4-nitro-1H-imidazol-1-yl)methyl)benzoate(): Yield: 88%; color less solid; mp 130 – 131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.49 (d, *J* = 1.4 Hz, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.96 – 8.03 (m, 4H), 7.86 (ddd, *J* = 1.4, 7.0, 8.5 Hz, 1H), 7.68 (ddd, *J* = 1.2, 7.0, 8.1 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 5.40 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.8, 165.1, 150.3, 147.9, 147.3, 142.6, 139.3, 138.2, 132.3, 130.8, 129.4, 129.1, 128.9, 128.9, 128.5, 128.2, 127.3, 122.3, 73.3, 51.6, 50.9, 28.9; ESIMS: m/z calculated for $C_{26}H_{24}ClN_5O_5$ $(M+H)^+$ 522.16 found 521.90.

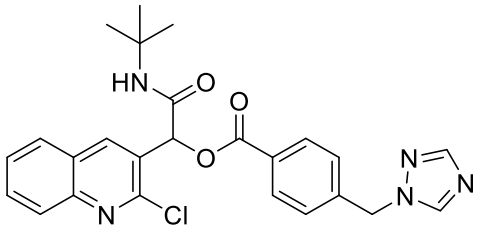


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl4-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)benzoate(): Yield: 87%; color less solid; mp 143 – 144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.44 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.99 (m, 3H), 7.85 (t, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.48 (s, 1H), 5.40 (s, 2H), 2.23 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.9, 165.2, 150.3, 147.3, 146.2, 145.9, 142.2, 139.4, 132.3, 130.9, 129.2, 129.2, 128.9, 128.5, 128.4, 128.2, 127.3, 123.4, 73.3, 51.6, 50.0, 28.9, 13.4; ESIMS: m/z calculated for $C_{27}H_{26}ClN_5O_5$ $(M+H)^+$ 536.17 found 535.80.

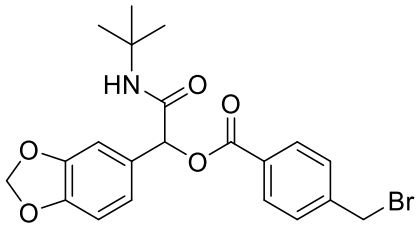


tert-Butyl 4-(4-((2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethoxy) carbonyl) benzyl) piperazine-1-carboxylate ( ): Yield: 89%; color less solid; mp 105 – 107 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.40 (s, 1H), 8.19 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 6.46 (s, 1H), 3.52 (s, 2H), 3.27 (m, 4H), 2.28 (m, 4H), 1.35 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.9, 165.4, 154.4,

150.3, 147.3, 145.1, 139.4, 132.3, 130.2, 129.8, 129.2, 129.1, 128.5, 128.3, 128.2, 127.3, 79.4, 73.2, 62.1, 53.0, 51.6, 29.0, 28.7; IR (KBr): 2950, 1725, 1710, 1450 cm^{-1}; ESIMS: m/z calculated for $C_{32}H_{39}ClN_4O_5$ $(M+H)^+$ 595.27 found 595.10.

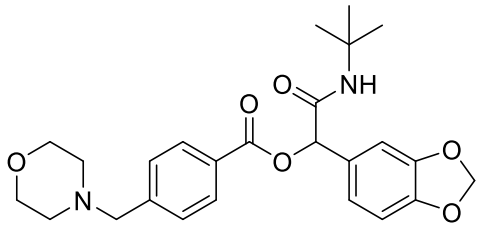


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((1H-1,2,4-triazol-1-yl)methyl)benzoate(): Yield: 70%; color less solid; mp 104 – 106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.68 (d, *J* = 1.2 Hz, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.98 (m, 3H), 7.85 (d, *J* = 1.5 Hz, 1H), 7.67 (d, *J* = 1.2 Hz, 1H), 7.40 – 7.36 (m, 2H), 6.45 (s, 1H), 5.51 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 165.9, 165.2, 152.6, 150.3, 147.3, 145.2, 142.8, 139.3, 132.3, 130.6, 129.2, 128.9, 128.8, 128.5, 128.2, 127.3, 73.3, 52.3, 51.6, 28.9; ESIMS: m/z calculated for $C_{25}H_{24}ClN_5O_3$ $(M+H)^+$ 478.17 found 477.40.

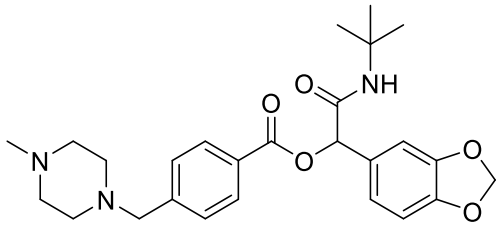


1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4(bromomethyl)benzoate(): Yield: 98 %; color less solid; mp 153 – 155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.98 (s, 1H), 7.96 (s, 1H), 7.87 (s, 391H), 7.57 – 7.61 (m, 2H), 7.09 (d, *J* = 1.7

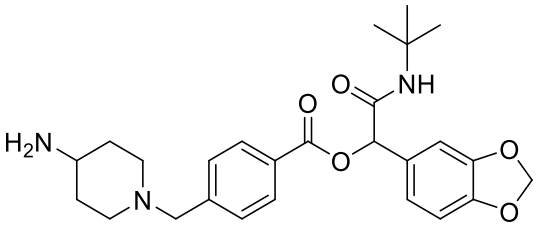
Hz, 1H), 7.04 (dd, *J* = 1.8, 8.0 Hz, 1H), 6.94 (s, 1H), 6.03 (d, *J* = 1.3 Hz, 2H), 5.92 (s, 1H), 4.75 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 167.8, 165.2, 148.1, 147.9, 144.3, 130.5, 130.4, 130.4, 130.3, 129.7, 121.9, 108.8, 108.3, 101.9, 76.0, 51.2, 51.1, 33.8, 29.0; ESIMS: m/z calculated for $C_{21}H_{22}BrNO_5$ $(M+H)^+$ 448.08 found 470.10.



1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4-(morpholinomethyl)benzoate (): Yield: 92%; color less solid; mp 178 – 180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.94 (d, *J* = 8.2 Hz, 2H), 7.87 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 1H), 7.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 5.92 (s, 1H), 3.53 – 3.58 (m, 4H), 3.52 (s, 2H), 2.35 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.8, 165.5, 148.1, 147.9, 144.7, 130.6, 130.0, 129.7, 128.8, 121.9, 108.8, 108.2, 101.9, 75.8, 66.8, 62.6, 53.8, 51.0, 29.0; ESIMS: m/z calculated for $C_{25}H_{30}N_2O_6$ $(M+H)^+$ 455.22 found 455.20.



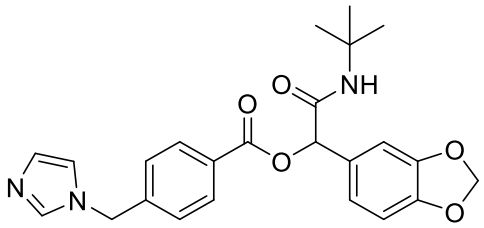
1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl4-((4-methylpiperazin-1-yl)methyl)benzoate(): Yield: 78%; color less solid; mp 92 – 93 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.93 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H), 5.92 (s, 1H), 3.50 (s, 2H), 2.17 – 2.43 (m, 8H), 2.12 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.8, 165.5, 148.0, 147.9, 145.2, 130.5, 130.0, 129.6, 128.7, 121.9, 108.8, 108.2, 101.9, 75.8, 62.2, 55.3, 53.2, 51.1, 46.4, 29.0; ESIMS: m/z calculated for $C_{26}H_{33}N_3O_5$ $(M+H)^+$ 468.25 found 468.20.



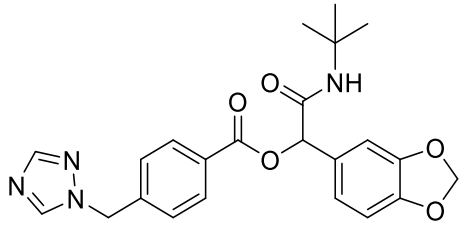
1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl4-((4-aminopiperidin-1-yl)methyl)benzoate(): Yield: 54%; color less solid; mp 92 – 94 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.02 (d, *J* = 5.8 Hz, 1H), 7.83 – 7.97 (m, 2H), 7.42 (t, *J* = 6.7 Hz, 1H), 7.00 – 7.12 (m, 2H), 6.89 – 6.95 (m, 1H), 6.02 (d, *J* = 5.2 Hz, 1H), 5.91 (d, *J* = 5.6 Hz, 1H), 5.42 (d, *J* = 5.8 Hz, 0H), 3.76 (s, 0H), 3.48 (d, *J* = 5.2 Hz, 1H), 2.67 (d, *J* = 11.2 Hz, 1H), 1.92 (s, 1H), 1.62 (d, *J* = 13.1 Hz, 2H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.8, 165.5, 148.1, 147.9,

145.7, 130.6, 130.0, 129.5, 128.6, 121.9,

108.8, 108.2, 101.9, 75.8, 62.4, 52.7, 51.1, 35.9, 29.0; ESIMS: m/z calculated for $C_{26}H_{33}N_3O_5$ $(M+H)^+$ 468.25 found 468.20.

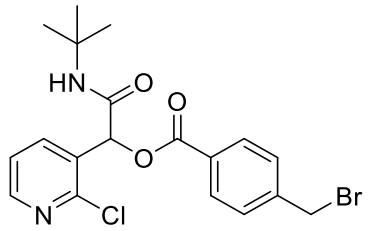


1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl4-((1H-imidazol-1-yl)methyl)benzoate(): Yield: 67%; color less solid; mp 83 – 84 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.96 (d, J = 7.2 Hz, 2H), 7.85 (s, 1H), 7.75 (s, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.16 (s, 1H), 7.08 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.89 – 6.93 (m, 2H), 6.02 (s, 2H), 5.91 (s, 1H), 5.29 (s, 2H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.8, 165.3, 148.1, 147.9, 144.1, 138.3, 130.5, 130.4, 129.6, 129.3, 128.3, 121.9, 120.3, 108.8, 108.2, 101.9, 75.9, 51.1, 49.7, 29.0; ESIMS: m/z calculated for $C_{24}H_{25}N_3O_5$ $(M+H)^+$ 436.19 found 435.70.



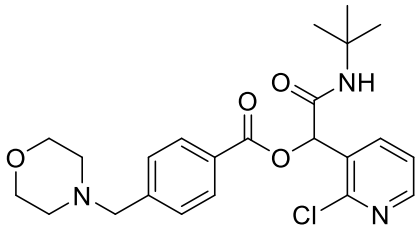
1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl4-((1H-1,2,4-triazol-1-yl)methyl)benzoate(): Yield: 50%; color less solid; mp 120 – 121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.68 (d, J = 1.9 Hz, 1H), 7.95 – 8.01 (m, 2H), 7.86 (d, J = 5.2 Hz, 1H), 7.57 – 7.63 (m, 1H), 7.35 – 7.39 (m, 1H),$_{42}$7.09 (dd, J = 1.6, 4.2 Hz, 1H), 7.04 (ddd, J

= 1.7, 4.4, 8.0 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.02 (d, *J* = 1.2 Hz, 2H), 5.92 (d, *J* = 5.4 Hz, 1H), 5.52 (s, 1H), 5.43 (d, *J* = 5.4 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.8, 152.6, 148.1, 147.9, 145.2, 142.5, 130.4, 129.5, 128.7, 121.9, 108.8, 108.2, 108.2, 101.9, 75.9, 52.3, 51.1, 29.0; ESIMS: m/z calculated for $C_{23}H_{24}N_4O_5$ $(M+H)^+$ 437.18 found 436.10.

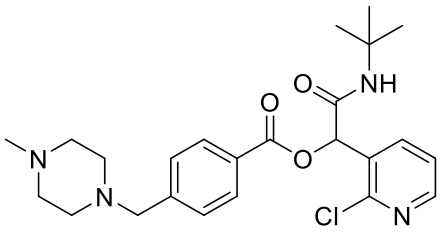


2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-(bromomethyl)benzoate:

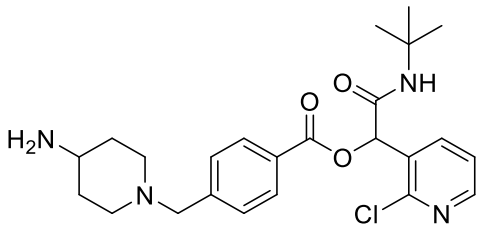
Yield: 92 %, color less solid, mp 138 – 140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.44 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.16 (s, 1H), 7.93 – 7.96 (m, 2H), 7.86 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.57 – 7.61 (m, 2H), 7.51 (dd, *J* = 4.8, 7.7 Hz, 1H), 6.31 (s, 1H), 4.75 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.7, 165.0, 151.0, 150.5, 144.6, 139.2, 131.4, 130.6, 130.4, 129.2, 124.2, 73.2, 51.6, 33.7, 28.9; ESIMS: m/z calculated for $C_{19}H_{20}BrClN_2O_3$ $(M+H)^+$ 439.04, found 439.00



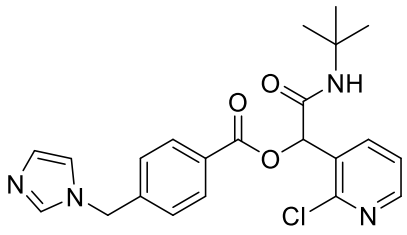
2-(tert-Butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl 4-(morpholinomethyl)benzoate: Yield: 80 %; color less solid; mp 78 – 80 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.43 (dq, *J* = 2.4, 4.4 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.91 (dt, *J* = 2.1, 8.8 Hz, 2H), 7.86 (dt, *J* = 1.8, 7.7 Hz, 1H), 7.50 (ddd, *J* = 2.0, 4.6, 7.5 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.31 (d, *J* = 1.2 Hz, 1H), 3.53 (dd, *J* = 6.3, 11.0 Hz, 6H), 2.33 (d, *J* = 4.7 Hz, 4H), 1.27 (d, *J* = 2.2 Hz, 10H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 167.8, 165.5, 148.1, 147.9, 144.7, 130.5, 130.1, 129.7, 128.8, 121.9, 108.8, 108.2, 101.9, 75.8, 66.8, 62.6, 53.8, 51.1, 29.0; ESIMS: m/z calculated for $C_{23}H_{28}ClN_3O_4$ $(M+H)^+$ 446.19 found 446.20.



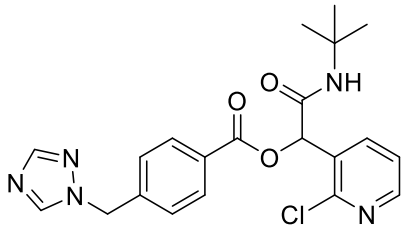
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((4-methylpiperazin-1-yl)methyl)benzoate: Yield: 71 %; color less solid; mp 99 – 100 °C; ^{13}C NMR (101 MHz, DMSO-d_6): *δ* (ppm) 165.9, 165.4, 150.9, 150.5, 145.3, 139.2, 131.4, 130.1, 129.9, 128.0, 124.3, 72.9, 62.1, 54.9, 52.8, 51.6, 46.0, 28.9; ESIMS: m/z calculated for $C_{24}H_{31}ClN_4O_3(M+H)^+$ 459.22 found 459.20



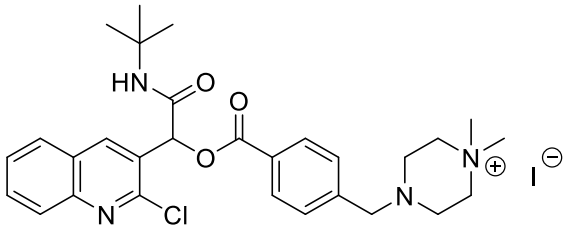
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((4-aminopiperidin-1-yl)methyl)benzoate: Yield: 59%; color less solid, mp 113 – 115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.43 (dd, *J* = 1.9, 4.8 Hz, 1H), 8.15 (s, 1H), 7.88 – 7.92 (m, 1H), 7.85 (dd, *J* = 1.9, 7.8 Hz, 1H), 7.50 (dd, *J* = 4.7, 7.7 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 6.30 (s, 1H), 3.48 (s, 1H), 2.69 (d, *J* = 11.4 Hz, 1H), 1.89 – 1.97 (m, 1H), 1.67 (d, *J* = 12.5 Hz, 2H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6): *δ* (ppm) 165.9, 165.4, 150.9, 150.5, 145.3, 139.2, 131.4, 130.1, 129.9, 128.0, 124.3, 72.9, 62.1, 55.0, 52.8, 51.6, 46.0, 28.9. ESIMS: m/z calculated for $C_{24}H_{31}ClN_4O_3(M+H)^+$ 459.22 found 459.20



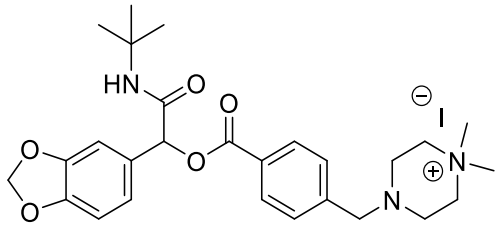
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((1H-imidazol-1-yl)methyl)benzoate (): Yield: 77%; color less solid; mp 103 – 104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.41 (d, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.99 – 8.04 (m, 2H), 7.86 (dt, *J* = 5.5, 8.4 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.34 (td, *J* = 6.3, 5.8, 2.8 Hz, 1H), 6.47 (s, 1H), 5.42 (d, *J* = 6.0 Hz, 2H), 1.29 (s, 8H). ESIMS: m/z calculated for $C_{22}H_{23}ClN_4O_3$ $(M+H)^+$ 427.16 found 427.20



2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((1H-1,2,4-triazol-1-yl)methyl)benzoate (): Yield: 76 %; color less solid; mp 95 – 97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.67 (s, 1H), 8.43 (dd, *J* = 1.8, 4.7 Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.85 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.50 (dd, *J* = 4.8, 7.6 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 5.51 (s, 2H), 1.26 (s, 9H). ESIMS: m/z calculated for $C_{21}H_{22}ClN_5O_3$ $(M+H)^+$ 428.15 found 427.20



4-(4-((2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethoxy)carbonyl)benzyl)-1,1-dimethylpiperazin-1-ium iodide(): Yield: 80%; color less solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.45 (s, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 8.02 – 7.94 (m, 0H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.56 (q, *J* = 9.8, 8.6 Hz, 1H), 7.47 – 7.40 (m, 2H), 6.57 (s, 1H), 6.35 (s, 1H), 3.71 (d, *J* = 19.0 Hz, 5H), 3.51 (s, 5H), 2.84 (s, 3H), 1.39 (s, 9H).



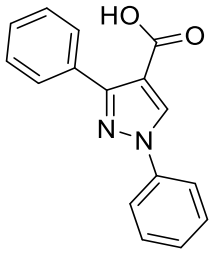
4-(4-((1-(Benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethoxy)carbonyl)benzyl)-1,1-dimethylpiperazin-1-ium iodide: Yield: 80%; color less solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (d, *J* = 7.0 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 6.95 – 7.01 (m, 2H), 6.80 (dd, *J* = 1.5, 8.4 Hz, 1H), 6.08 (s, 1H), 5.95 (s, 2H), 3.75 (s, 2H), 3.71 (m, 4H), 3.54 (s, 6H), 2.85 (m, 4H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.7, 165.0, 148.3, 148.1, 143.0, 130.2, 129.7, 129.3, 128.8, 121.9, 108.6, 107.9, 101.7, 75.9, 68.1, 62.5, 60.9, 51.9, 46.5, 28.9; ESIMS: m/z calculated for $C_{27}H_{36}IN_3O_5$ $(M+H)^+$ 610.18 found 482.30.

Preparation of *N*-phenyl-*N*'-(1-phenylethylidene)-hydrazine.[74] Phenyl hydrazine hydrochloride (2.0 g, 13.8 mmol) was added to a solution of acetophenone (1.8 g, 15.2 mmol) in 50.0 mL of ethanol at 0°C followed by the slow addition of glacial acetic acid (1.5 mL). The reaction mixture was then refluxed for 2hr. The completion of the reaction mixture was checked by TLC using 10% EtOAc/hexane. The reaction mixture was cooled to room temperature to effect precipitation. The product was filtered, washed with cold ethanol (2 x 10.0 mL) and dried under vaccum to obtain pure acetophenone phenylhydrazone as a yellow solid (2.8 g, 90% yield).

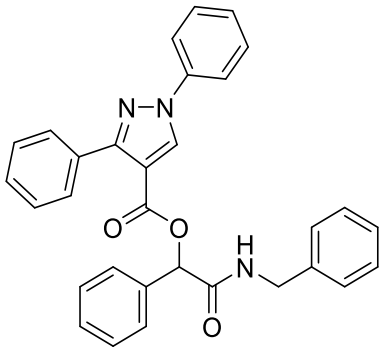
Preparation of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde.[75] Phosphoryl chloride (1.0 mL, 11.4 mmol) was added to *N*,*N*-dimethylformamide (0.8 mL, 11.4 mmol) at 0°C and the mixture stirred for 1h. This mixture was then slowly added to a solution of

acetophenone phenylhydrazone (2.0 g, 9.5 mmol) in DMF (5.0 mL) and the reaction mixture was allowed to stir for 10 minutes and gradually heated to 60°C for 4hr. The reaction was monitored by TLC using 30% EtOAc/hexane. The reaction mixture was cooled to room temperature and basified with cold and saturated aqueous sodium hydroxide solution (pH ~8.0) to cause precipitation. The solid was filtered and washed with cold water (2 x 20.0 mL) to obtain the crude product as a off white solid (2.2 g, 92% yield)

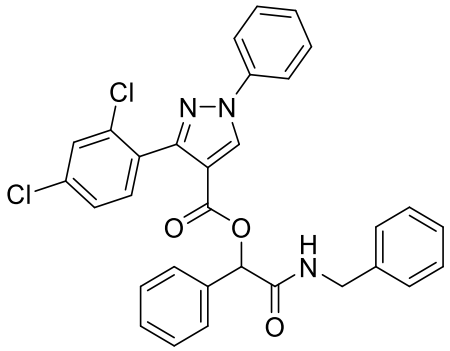
Preparation of the aryl-1-phenylpyrazole-4-carboxylic acid. Aldehyde (1 mmol) was dissolved in 50 mL (pyridine: water =1:1) and $KMnO_4$ (1 mmol) was added. The reaction was stirred overnight at room temperature. The completion of reaction was monitored by TLC using 30% EtOAc/hexane. Upon completion, ice cold water was added to the reaction mixture followed by the addition of aq. NaOH to effect precipitation. The mixture was filtered and the filtrate was acidified with conc. HCl which resulted in the precipitation. The solid was filtered and recrystallized in hexane to yield the carboxylic acid



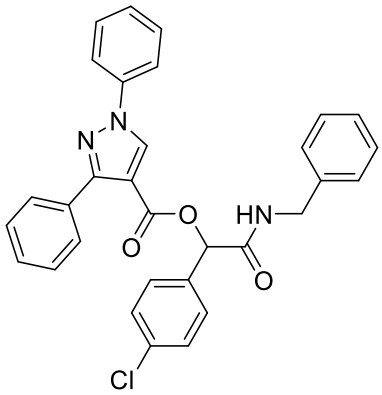
1,3-diphenyl-1H-pyrazole-4-carboxylic acid: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.55 (s, 1H), 9.06 (d, *J* = 2.1 Hz, 1H), 7.93 – 7.98 (m, 3H), 7.80 (dt, *J* = 2.1, 7.71 Hz, 2H), 7.48 – 7.56 (m, 3H), 7.40 – 7.44 (m, 3H).



2-(benzylamino)-2-oxo-1-phenylethyl 1,3-diphenyl-1H-pyrazole-4-carboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.28 (s, 1H), 8.76 – 8.85 (m, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 3.9 Hz, 2H), 7.49 – 7.58 (m, 5H), 7.39 (dd, *J* = 9.9, 18.5 Hz, 9H), 7.11 – 7.26 (m, 6H), 6.07 (s, 1H), 4.29 (d, *J* = 13.2 Hz, 2H).



2-(benzylamino)-2-oxo-1-phenylethyl 3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazole-4-carboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.32 (s, 1H), 8.98 (t, *J* = 5.9 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.74 – 7.81 (m, 2H), 7.68 (d, *J* = 1.0 Hz, 1H), 7.50 – 7.58 (m, 3H), 7.34 – 7.47 (m, 6H), 7.19 – 7.31 (m, 6H), 6.46 (s, 1H), 6.46 (s, 1H), 4.36 (dd, *J* = 3.0, 5.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.2, 161.5, 153.7, 139.4, 139.1, 134.8, 134.7, 134.7, 133.4, 132.0, 131.2, 130.1, 129.5, 129.4, 129.1, 128.7, 128.3, 128.1, 127.5, 127.3, 119.8, 112.2, 71.8, 42.7.



2-(benzylamino)-1-(4-chlorophenyl)-2-oxoethyl 1,3-diphenyl-1H-pyrazole-4-carboxylate: Yield: 49%; color less solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.55 (d, *J* = 1.5 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.64 (dd, *J* = 5.3, 2.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 1.5 Hz, 0H), 7.36 – 7.28 (m, 11H), 7.26 (d, *J* = 1.4 Hz, 1H), 6.21 (s, 1H), 5.95 (d, *J* = 6.2 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 168.07, 161.09, 154.05, 139.14, 137.88, 135.17, 134.60, 133.23, 132.85, 129.89, 129.83, 129.65, 129.27, 129.16, 129.09, 129.06, 128.88, 128.46, 128.16, 127.80, 127.78, 119.91, 113.37, 75.14, 43.37.

Chapter 4

Spectral Characterization

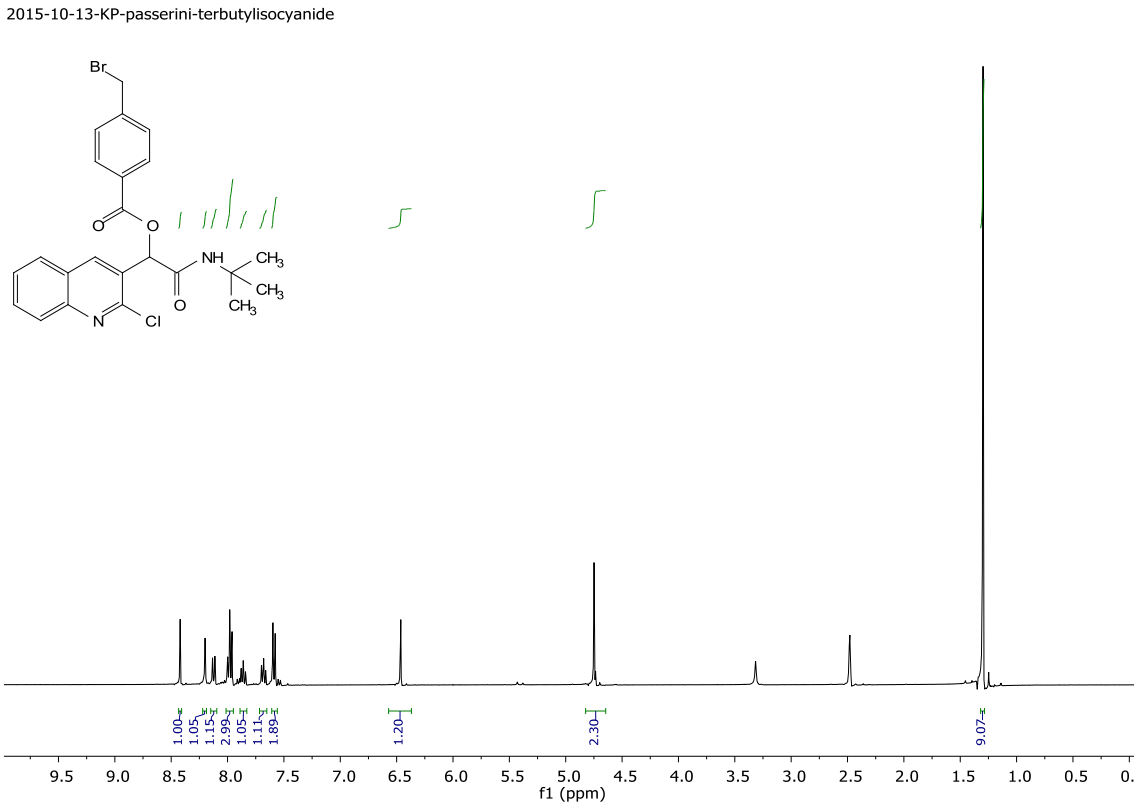


Figure 39. 400 MHz ^{1}H NMR of compound **74** in DMSO

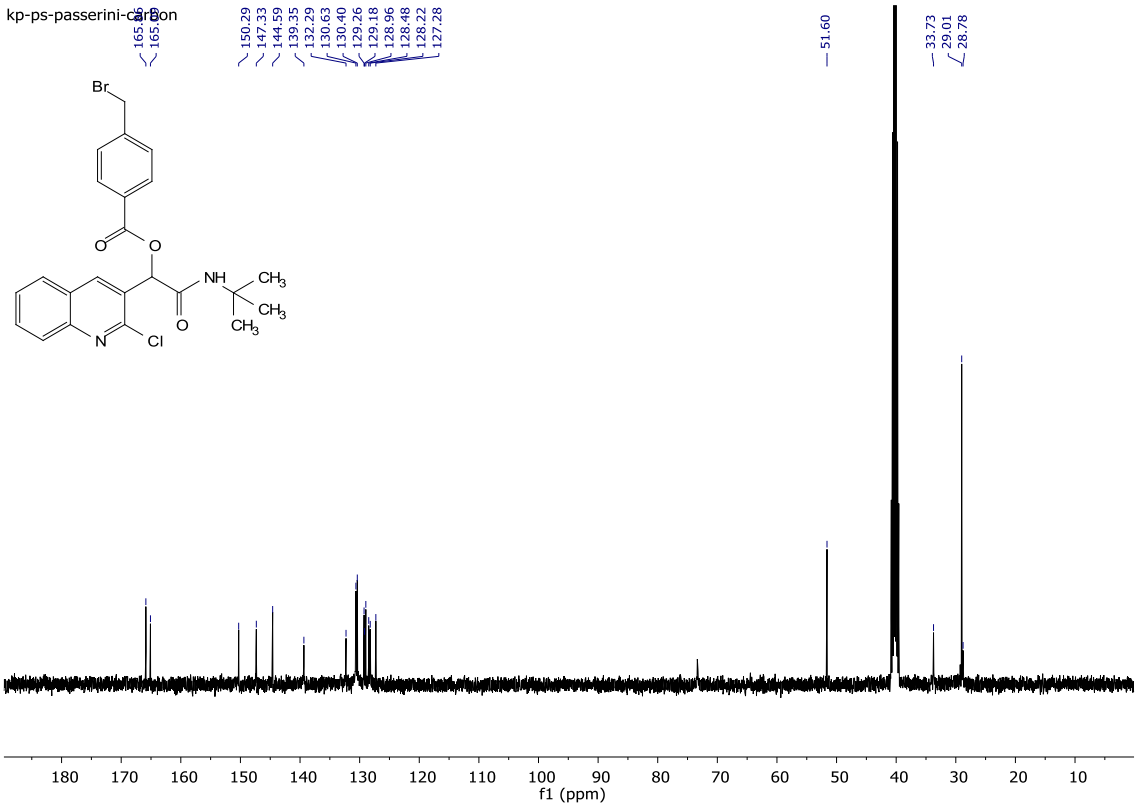


Figure 40. 100 MHz ^{13}C NMR of compound **74** in DMSO

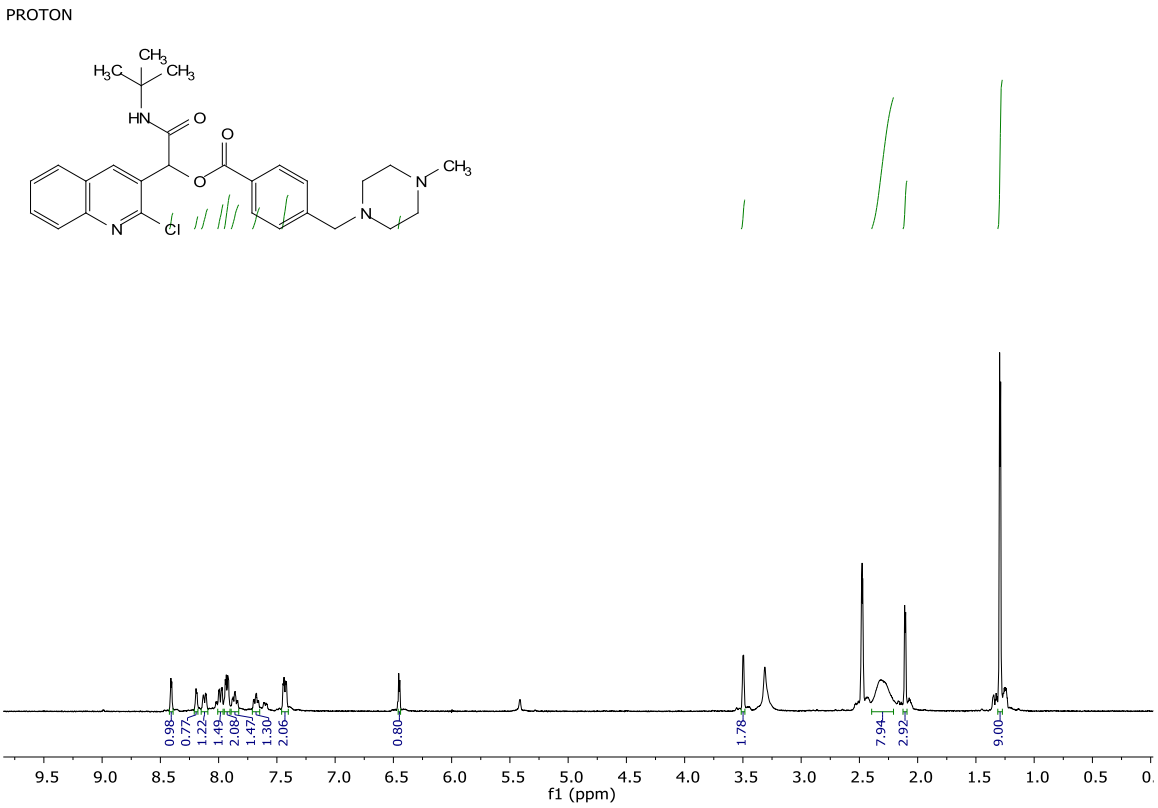


Figure 41. 400 MHz ^{1}H NMR of compound **75b** in DMSO

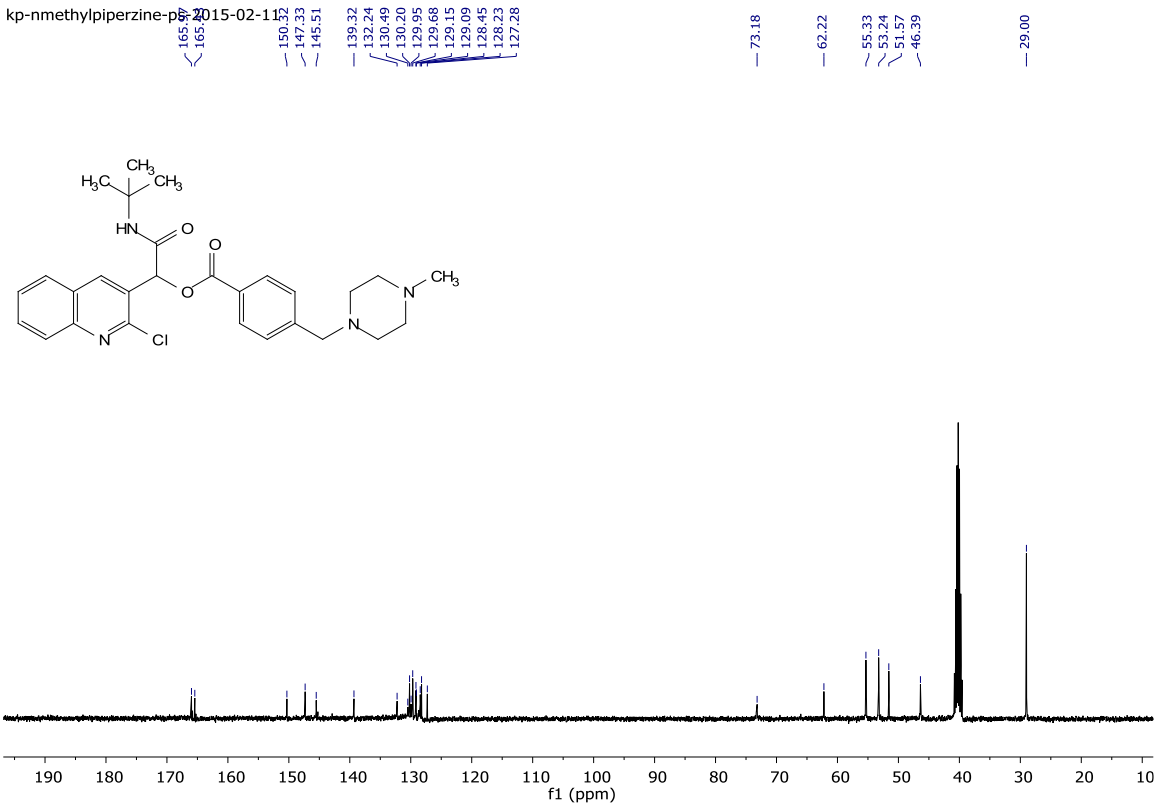


Figure 42. 100 MHz ^{13}C NMR of compound **75b** in DMSO

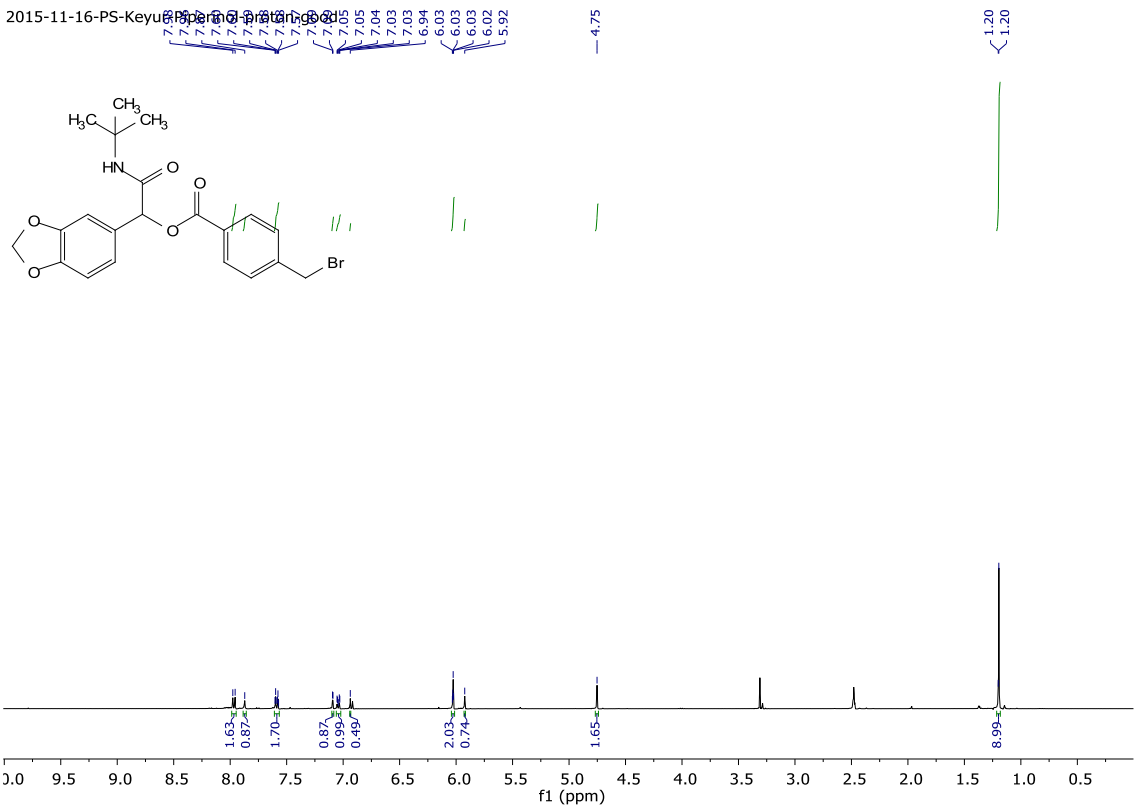


Figure 43. 400 MHz ^{1}H NMR of compound **80** in DMSO

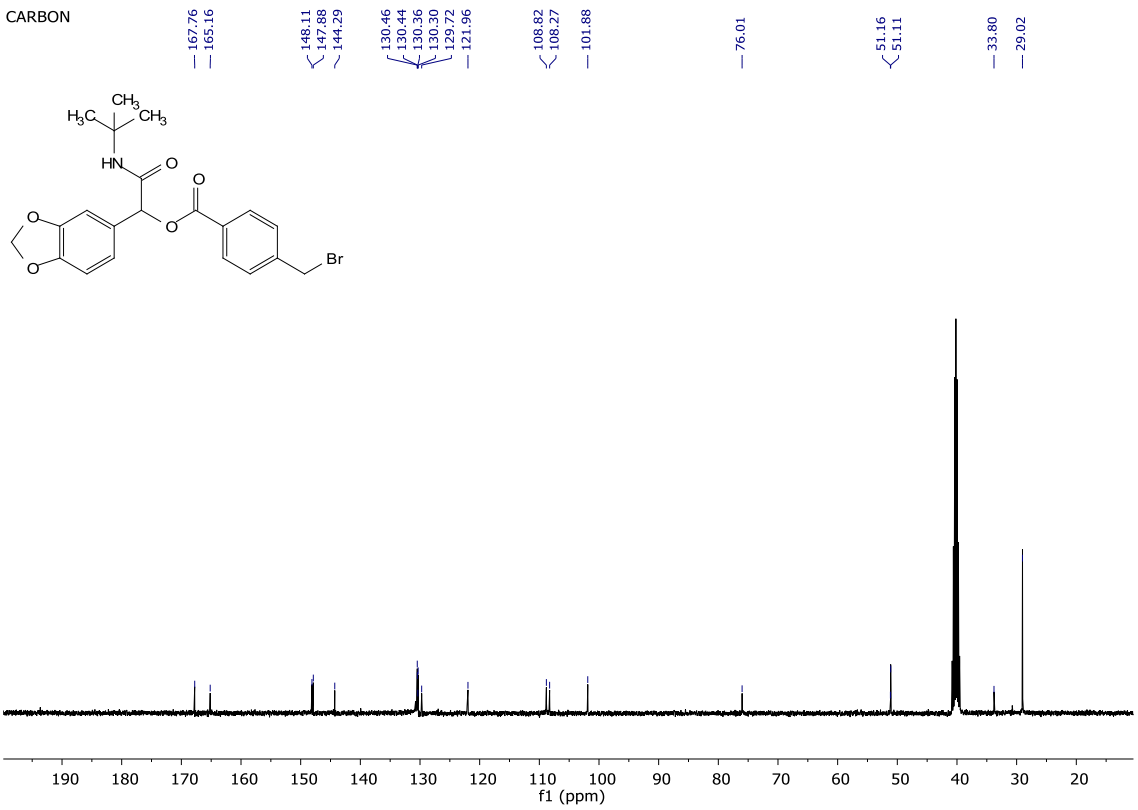


Figure 44. 100 MHz ^{13}C NMR of compound **80** in DMSO

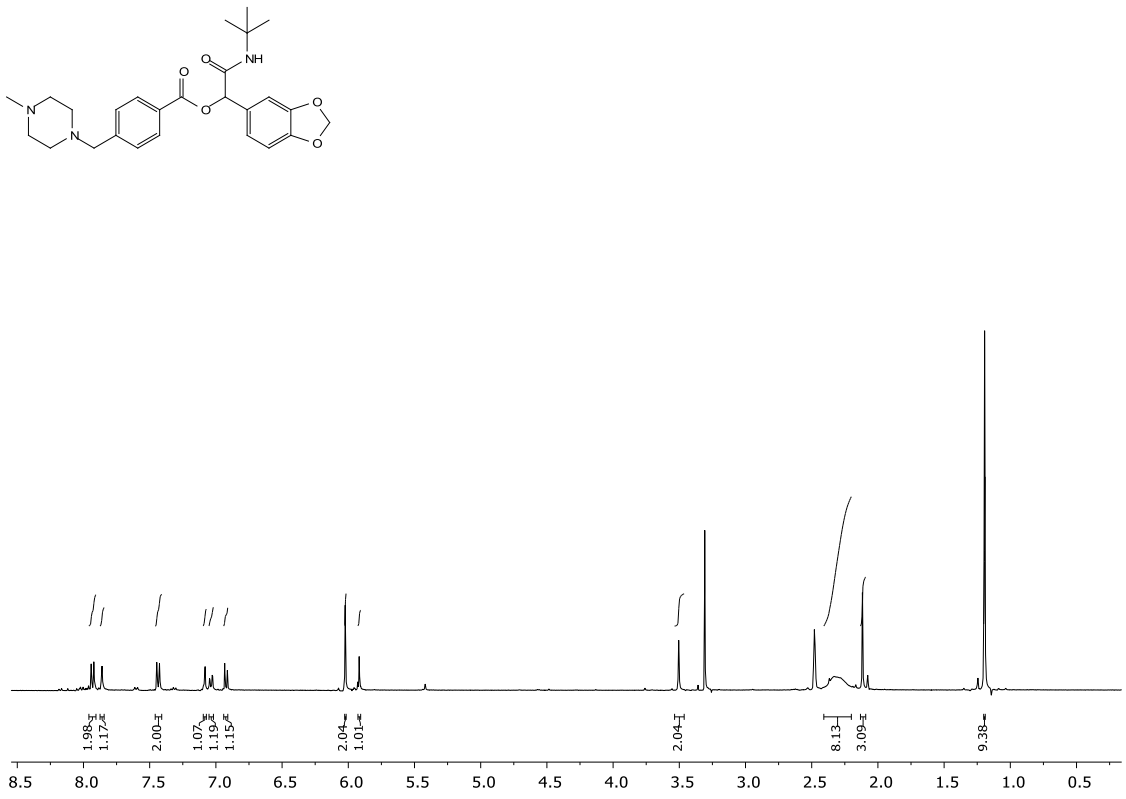


Figure 45. 400 MHz ^{1}H NMR of compound **81b** in DMSO

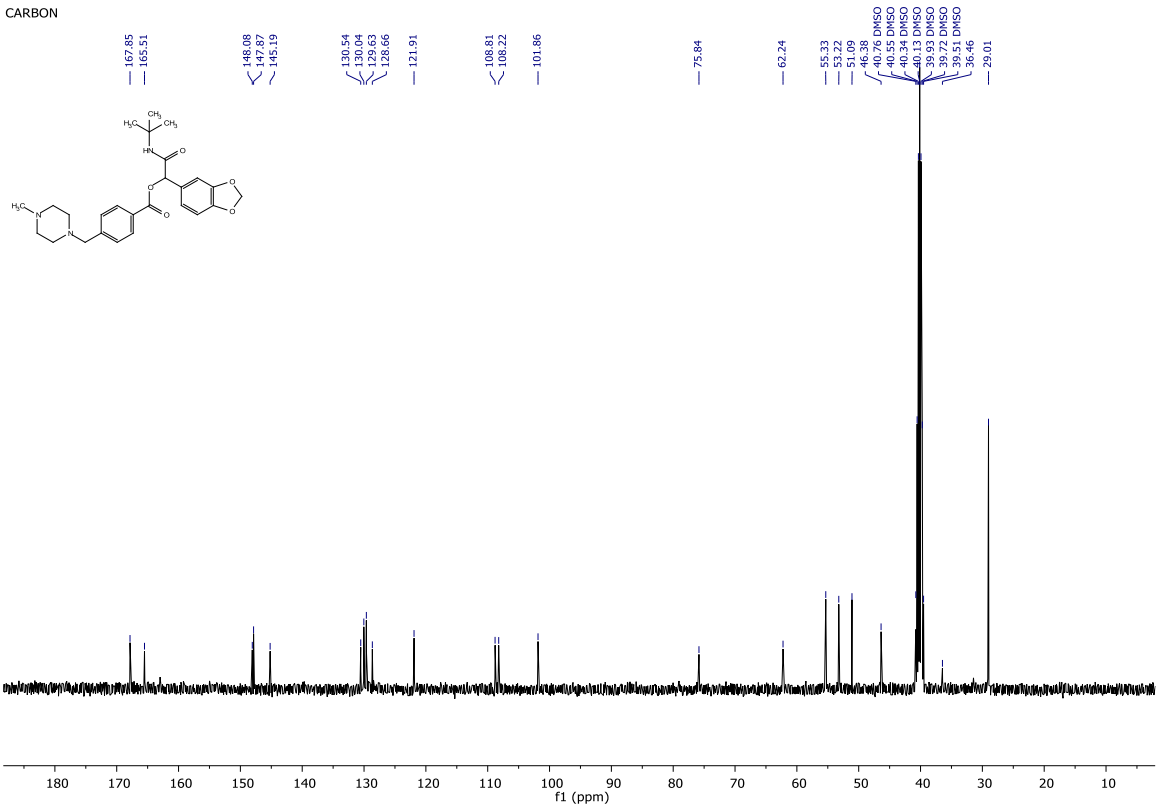


Figure 46. 100 MHz ^{13}C NMR of compound **81b** in DMSO

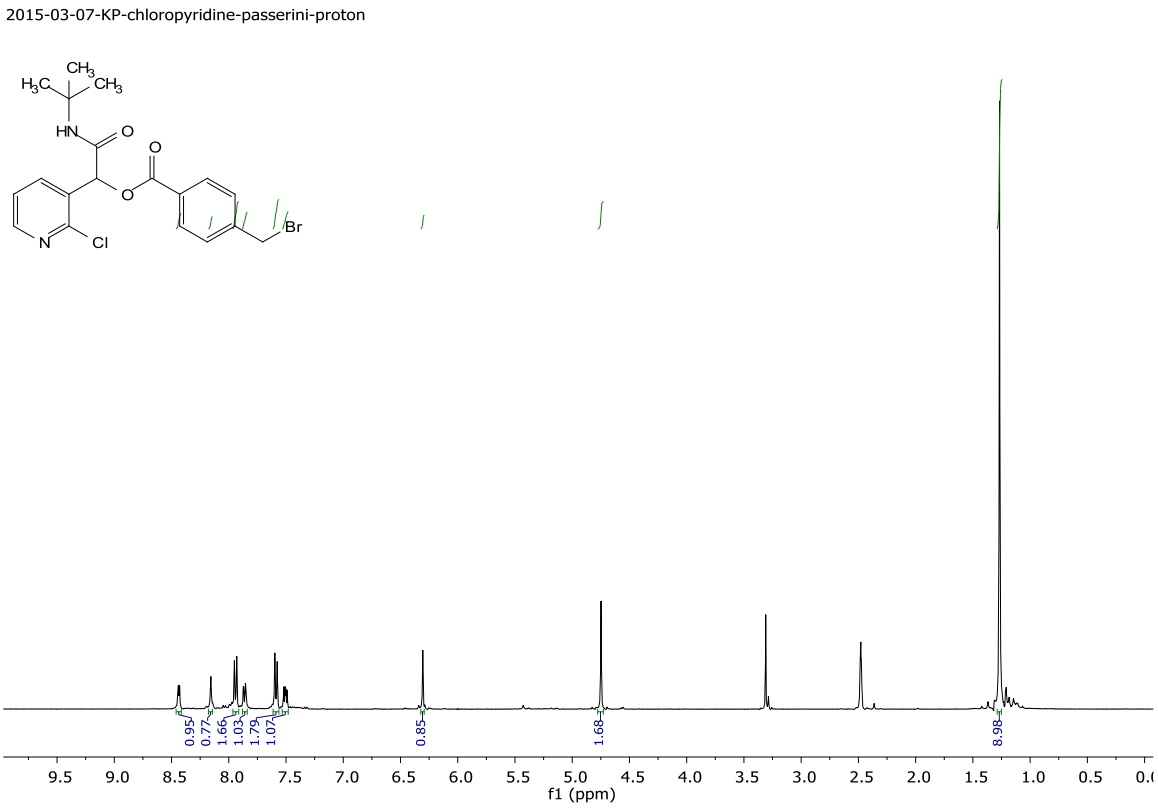


Figure 47. 400 MHz ^{1}H NMR of compound **83** in DMSO

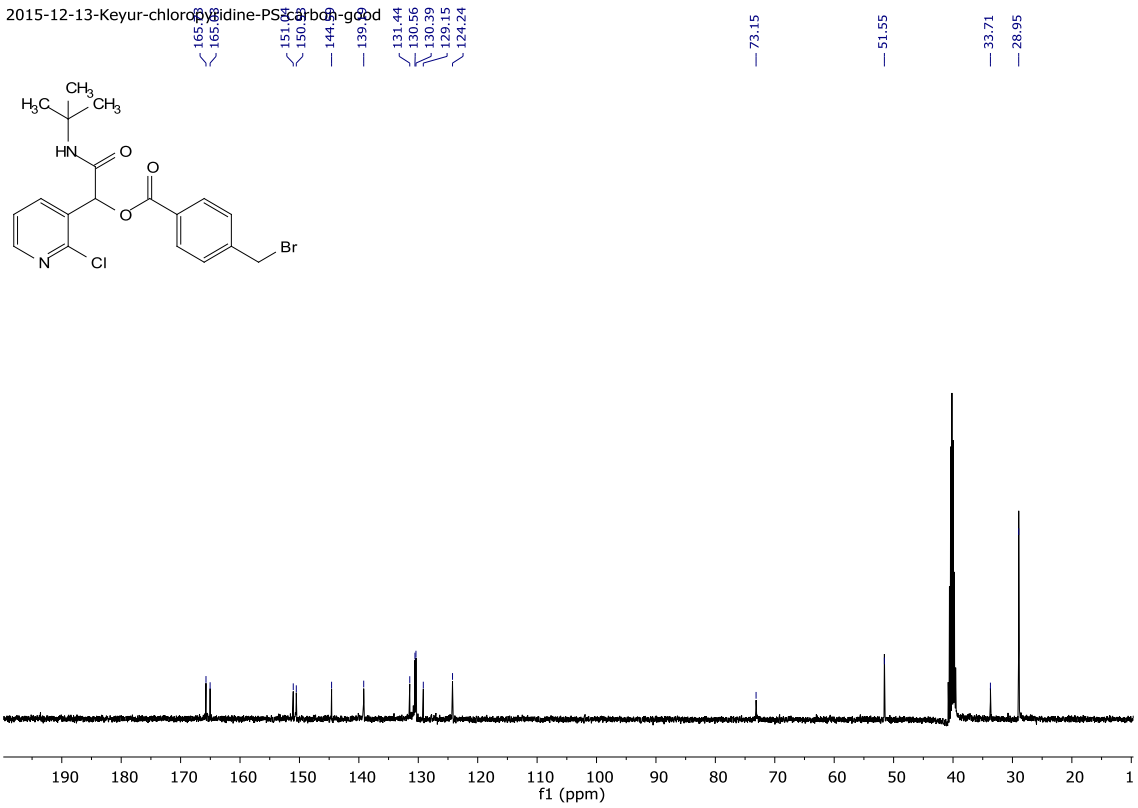


Figure 48. 100 MHz ^{13}C NMR of compound **83** in DMSO

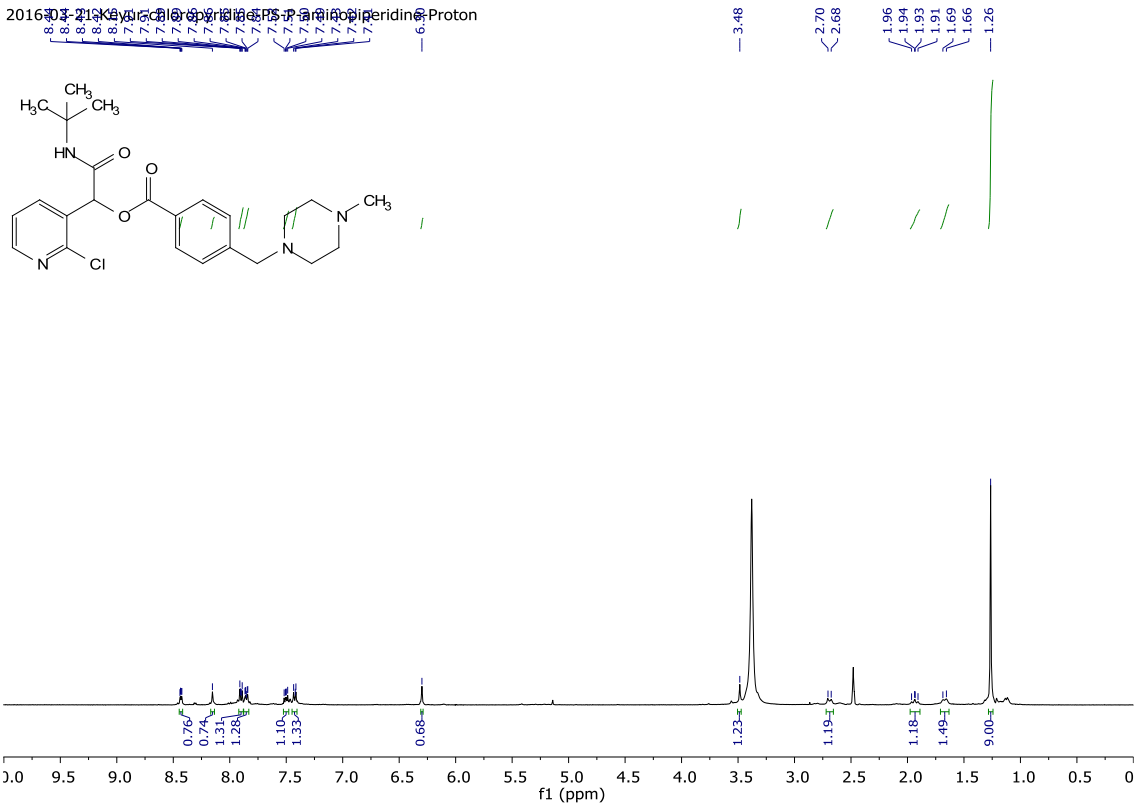


Figure 49. 400 MHz ^{1}H NMR of compound **84b** in DMSO

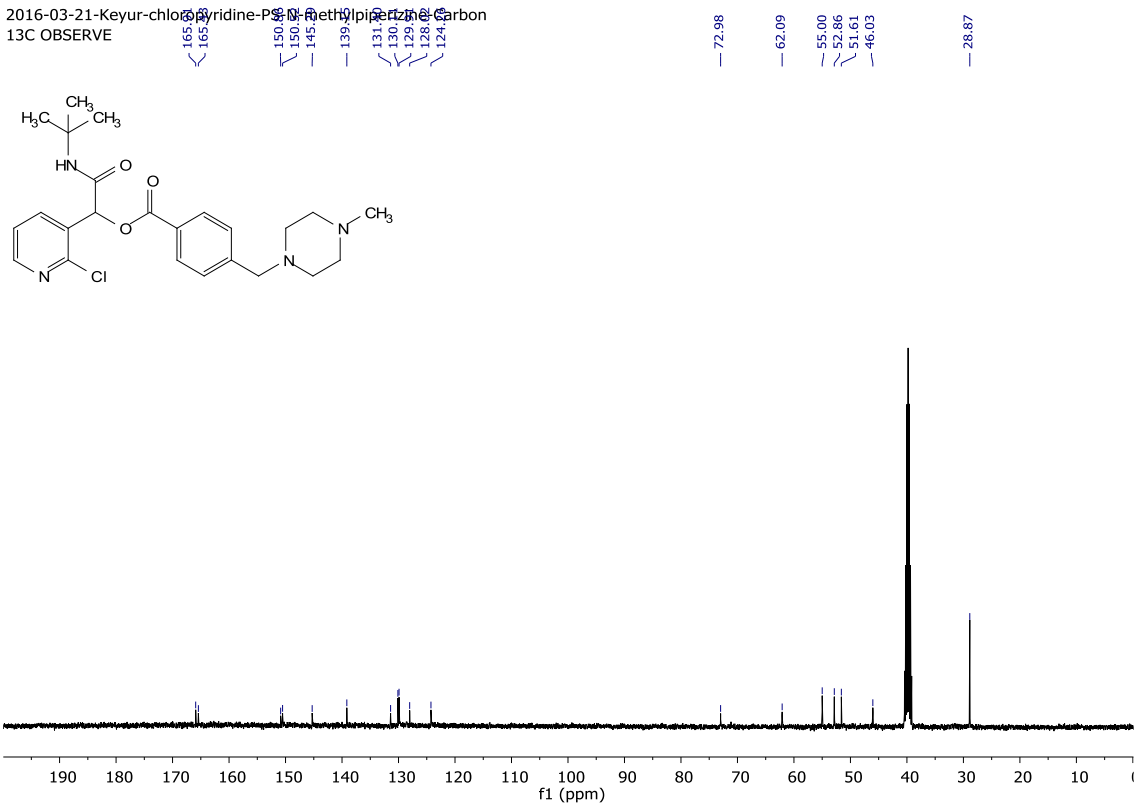


Figure 50. 100 MHz ^{13}C NMR of compound **84b** in DMSO

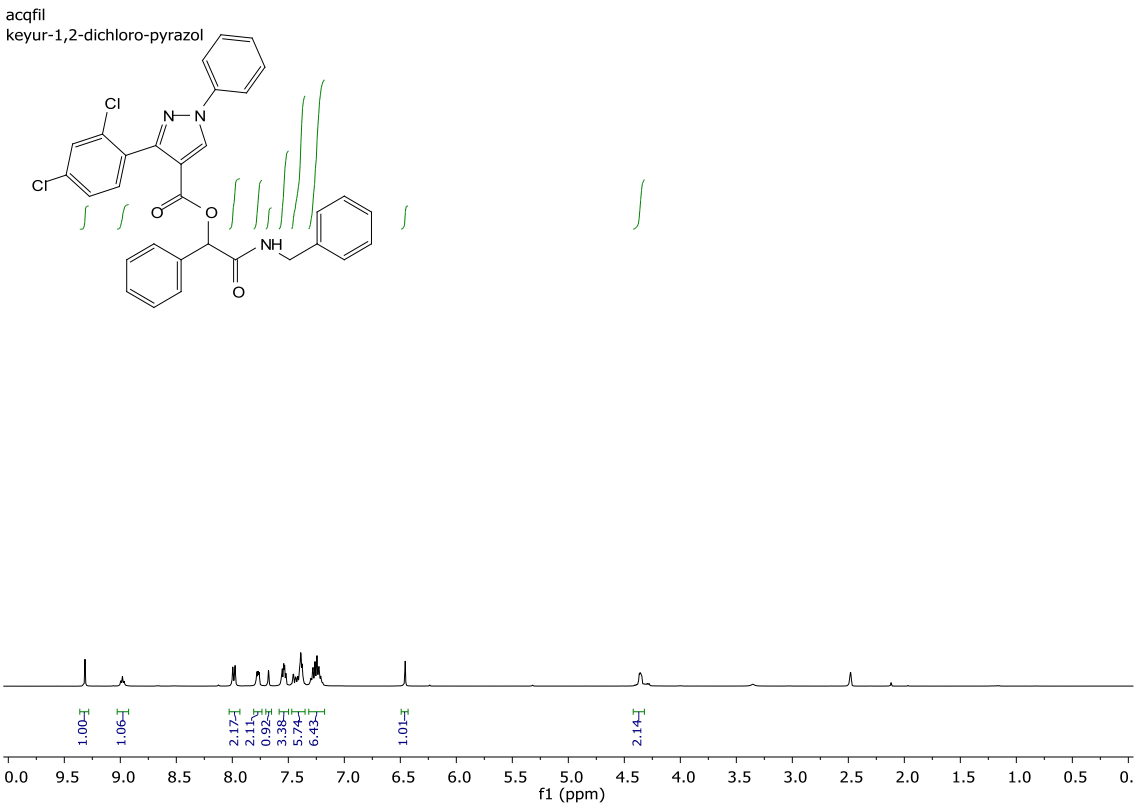


Figure 51. 400 MHz ^{1}H NMR of compound **95b** in DMSO

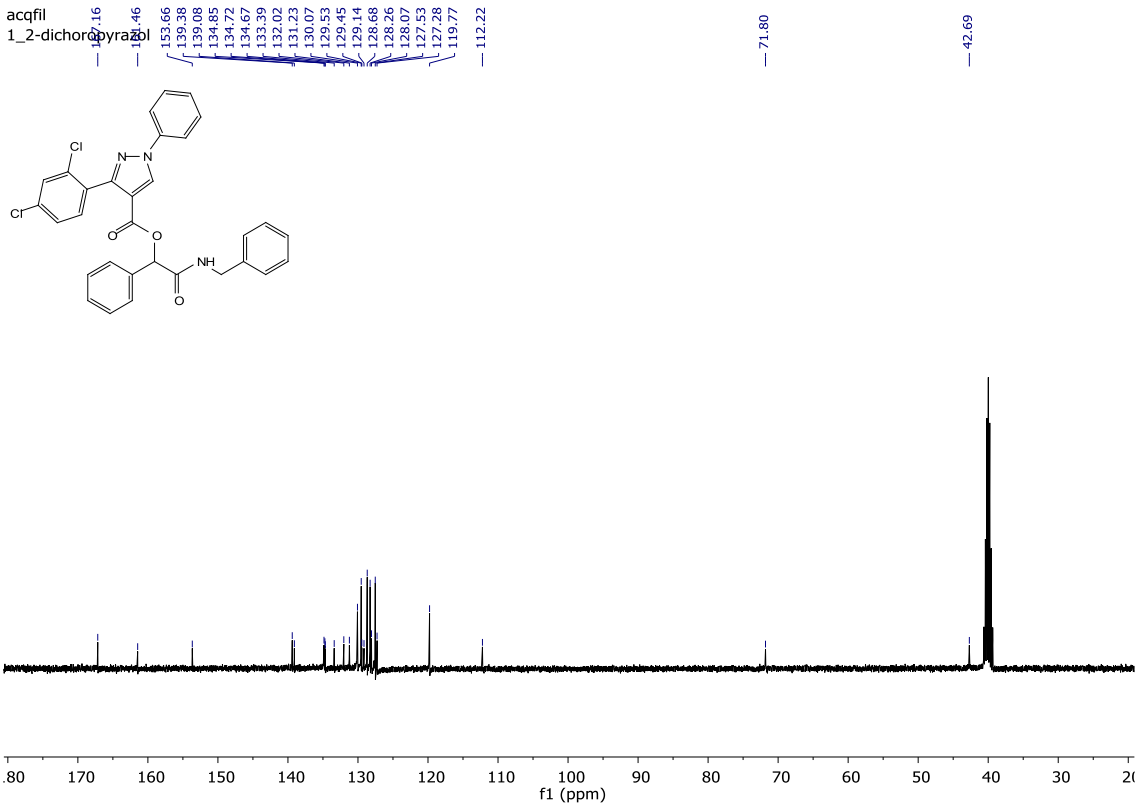


Figure 52. 100 MHz ^{13}C NMR of compound **95b** in DMSO

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