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SYNTHESIS AND CYTOTOXICITY OF AZAHETEROCYCLIC COMPOUNDS

by

Keyur Pandya

A Thesis

Submitted to the
Department of Chemistry & Biochemistry
College of Science & Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
May 19, 2017

Thesis Chair: Subash Jonnalagadda, Ph.D.

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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

Keyur Pandya

SYNTHESIS AND CYTOTOXICITY OF AZAHETEROCYCLIC COMPOUNDS

2017-2018

Subash Jonnalagadda, Ph.D.

Master of Science in Pharmaceutical Sciences

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.

Table of Contents

Abstract	v
List of Figures	viii
List of Tables	xii
Chapter 1: Introduction	1
Multicomponent Coupling Reactions	1
History of Multicomponent Chemistry	1
Synthesis of Isocyanides	5
Heterocyclic Motifs	9
Chapter 2: Azaheterocyclic Compounds via Passerini Reaction	14
Preparation of Chloroquinoline Conjugates.....	14
Preparation of Piperonal Conjugates	19
Preparation of Chloropyridine Conjugates	22
Preparation of Pyrazole Conjugates.....	26
Conclusions.....	31
Chapter 3: Experimental Procedures	32
Materials	32
Instrumentation	32
Procedures.....	32
Method for the Preparation of 2-Chloroquinoline-3-Carbaldehyde	32
Procedure for the Preparation of 4-(Bromomethyl)benzoic Acid.....	32
General Reaction Procedure for Preparation of Passerini Product	33

Table of Contents (Continued)

General Procedure for the Amination of Passerini Products	33
Preparation of N-Phenyl-N'-(1-Phenylethylidene)-Hydrazine	47
Preparation of 1, 3-Diphenyl-1H-Pyrazole-4-Carboxaldehyde	47
Preparation of the Aryl-1-Phenylpyrazole-4-Carboxylic Acid.....	48
Chapter 4: Spectral Characterization	51
References	65

List of Figures

Figure	Page
Figure 1. Probiotic synthesis of adenine	1
Figure 2. Strecker synthesis of α -aminoacids.....	2
Figure 3. Hantzsch dihydropyridine synthesis.....	2
Figure 4. Hantzsch pyrrole synthesis	2
Figure 5. Biginelli synthesis of dihydropyrimidines.....	3
Figure 6. Robinson synthesis of tropinone	3
Figure 7. Passerini multicomponent coupling reaction.....	4
Figure 8. Bucherer-Bergs synthesis of hydantoin.....	4
Figure 9. Asinger reaction.....	4
Figure 10. Ugi four component coupling reaction.....	5
Figure 11. Gewald's reaction.....	5
Figure 12. Lieke synthesis of isocyanides	6
Figure 13. Hoffmann synthesis of isocyanides	7
Figure 14. Synthesis of isocyanides via dehydration of formamide.....	8
Figure 15. Synthesis of isocyanides from geminal dihalides	8
Figure 16. Synthesis of isocyanides from benzoxazole	9

List of Figures (Continued)

Figure	Page
Figure 17. Quinoline-based antimalarial drugs.....	10
Figure 18. Pyridine-based drugs.	11
Figure 19. Pyrazole-based natural products.....	12
Figure 20. Pyrazole-based drugs.....	13
Figure 21. Preparation of chloroquinoline conjugates.....	14
Figure 22. Preparation of p-bromomethylbenzoic acid.	15
Figure 23. Preparation of 2-chloroquinoline aldehyde.	15
Figure 24. Passerini reaction with 2-chloroquinoline aldehyde.....	16
Figure 25. Preparation of 2-chloroquinoline-morpholine conjugate.	16
Figure 26. Preparation of 2-chloroquinoline-based amines.....	17
Figure 27. 2-Chloroquinoline-based amines.....	18
Figure 28. Preparation of piperonal-based amines.	20
Figure 29. Piperonal-based amines.	21
Figure 30. Preparation of 2-chloropyridine-based amines.....	23
Figure 31. 2-Chloropyridine-based amines.....	24
Figure 32. Preparation of quaternary ammonium salts.	26

List of Figures (Continued)

Figure	Page
Figure 33. Preparation of pyrazole derivatives.	27
Figure 34. Preparation of phenylhydrazone.	28
Figure 35. Preparation of pyrazole aldehyde.	28
Figure 36. Passerini reaction with pyrazole aldehyde.	29
Figure 37. Oxidation of pyrazole aldehyde.	29
Figure 38. Passerini reaction with pyrazole acid.	30
Figure 39. 400 MHz ^1H NMR of compound 74 in DMSO.	51
Figure 40. 100 MHz ^{13}C NMR of compound 74 in DMSO.	52
Figure 41. 400 MHz ^1H NMR of compound 75b in DMSO.	53
Figure 42. 100 MHz ^{13}C NMR of compound 75b in DMSO.	54
Figure 43. 400 MHz ^1H NMR of compound 80 in DMSO.	55
Figure 44. 100 MHz ^{13}C NMR of compound 80 in DMSO.	56
Figure 45. 400 MHz ^1H NMR of compound 81b in DMSO.	57
Figure 46. 100 MHz ^{13}C NMR of compound 81b in DMSO.	58
Figure 47. 400 MHz ^1H NMR of compound 83 in DMSO.	59
Figure 48. 100 MHz ^{13}C NMR of compound 83 in DMSO.	60

List of Figures (Continued)

Figure	Page
Figure 49. 400 MHz ^1H NMR of compound 84b in DMSO	61
Figure 50. 400 MHz ^1H NMR of compound 84b in DMSO	62
Figure 51. 400 MHz ^1H NMR of compound 95b in DMSO	63
Figure 52. 400 MHz ^1H NMR of compound 95b in DMSO	64

List of Tables

Table	Page
Table 1. In vitro Cytotoxicity of 2-Chloroquinoline Derivatives	19
Table 2. In vitro Cytotoxicity of Piperonal Derivatives	22
Table 3. In vitro Cytotoxicity of 2-Chloropyridine Derivatives	25

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

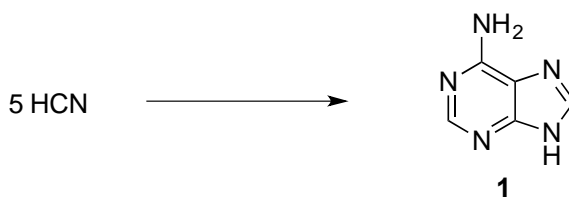


Figure 1. Probiotic synthesis of adenine

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).

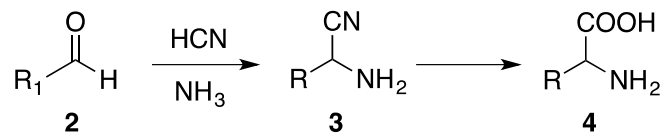


Figure 2. Strecker synthesis of α -aminoacids

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

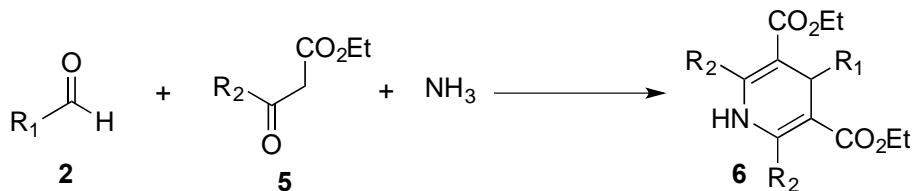


Figure 3. Hantzsch dihydropyridine synthesis

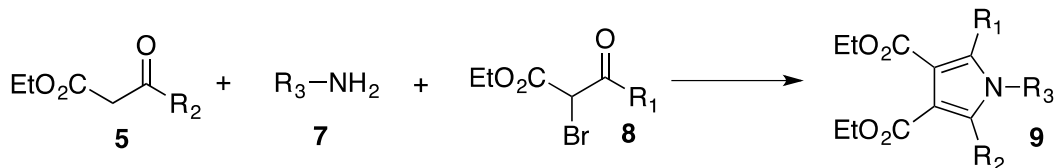


Figure 4. Hantzsch pyrrole synthesis

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

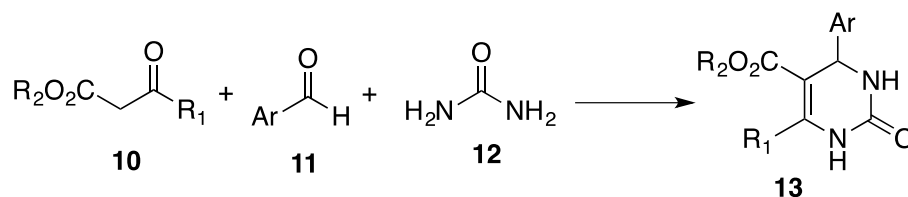


Figure 5. Biginelli synthesis of dihydropyrimidines

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

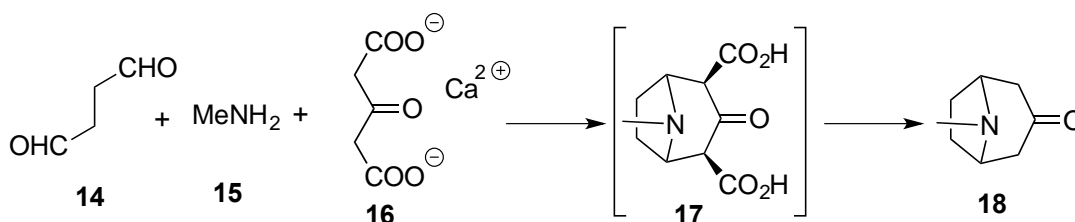


Figure 6. Robinson synthesis of tropinone

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 affording 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

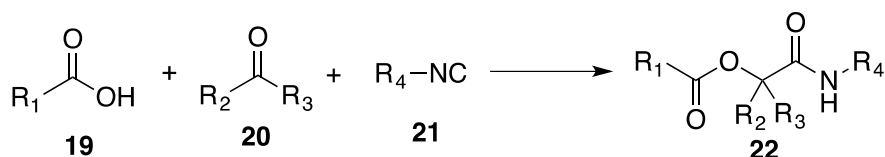


Figure 7. Passerini multicomponent coupling reaction

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, NH₃ and CO₂. Hydantoins could be efficiently converted into α-amino acids through simple hydrolysis (Figure 8).¹²

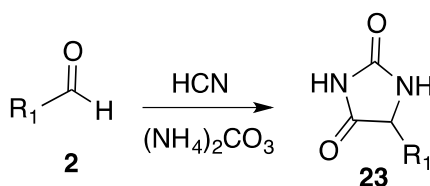


Figure 8. Bucherer-Bergs synthesis of hydantoin

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

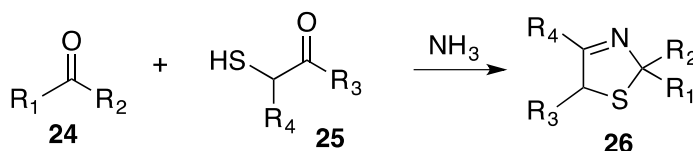


Figure 9. Asinger reaction

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

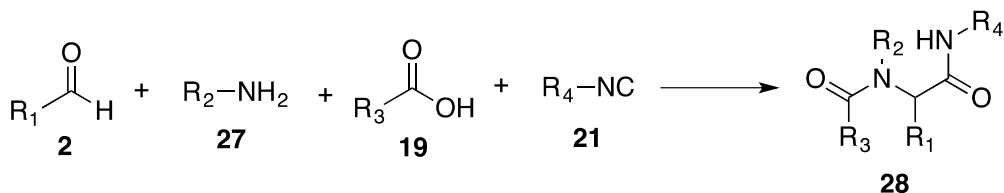


Figure 10. Ugi four component coupling reaction

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

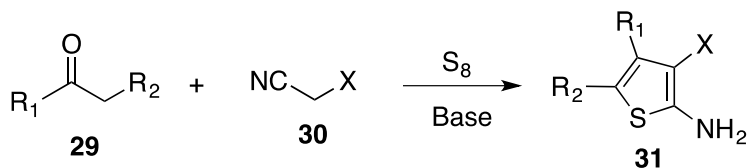


Figure 11. Gewald's reaction

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 80°C, in the presence of catalytic amount of TEBAC.²⁰

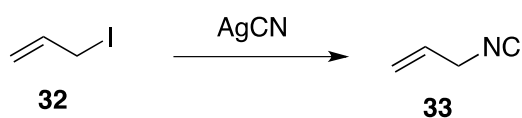


Figure 12. Lieke synthesis of isocyanides

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

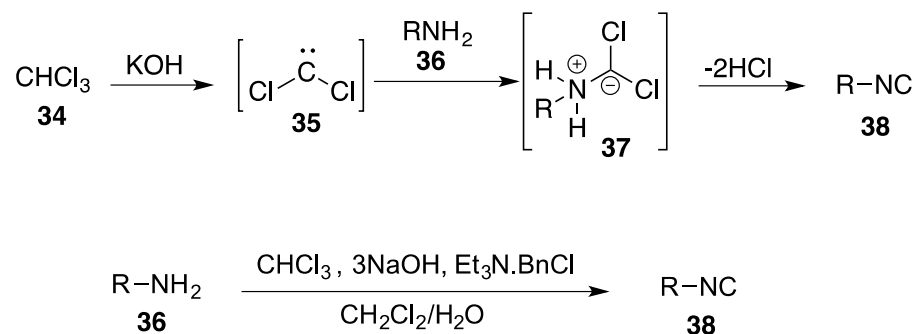


Figure 13. Hoffmann synthesis of isocyanides

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

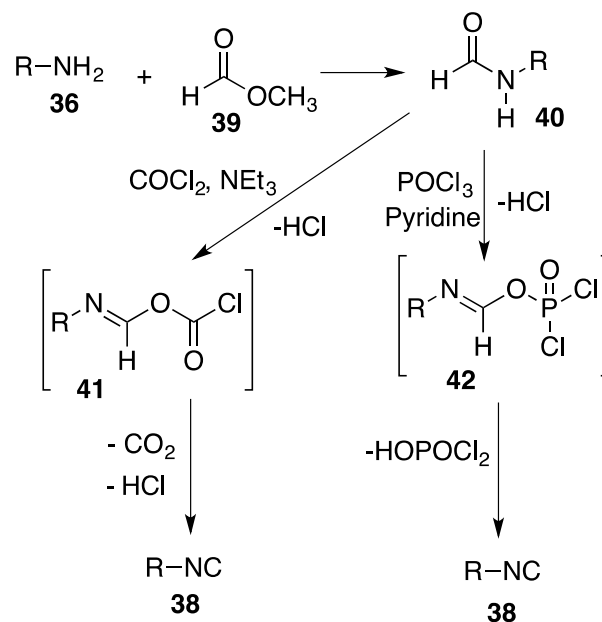


Figure 14. Synthesis of isocyanides via dehydration of formamide

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

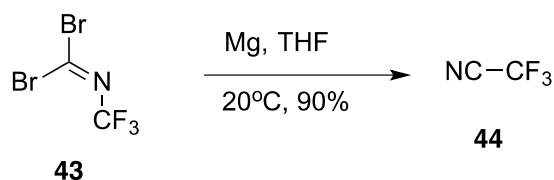


Figure 15. Synthesis of isocyanides from geminal dihalides

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

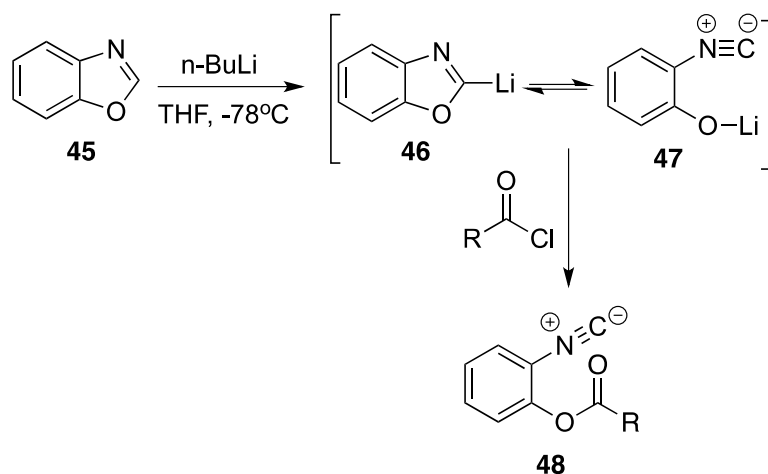


Figure 16. Synthesis of isocyanides from benzoxazole

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 compounds²⁷⁻²⁸ 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).

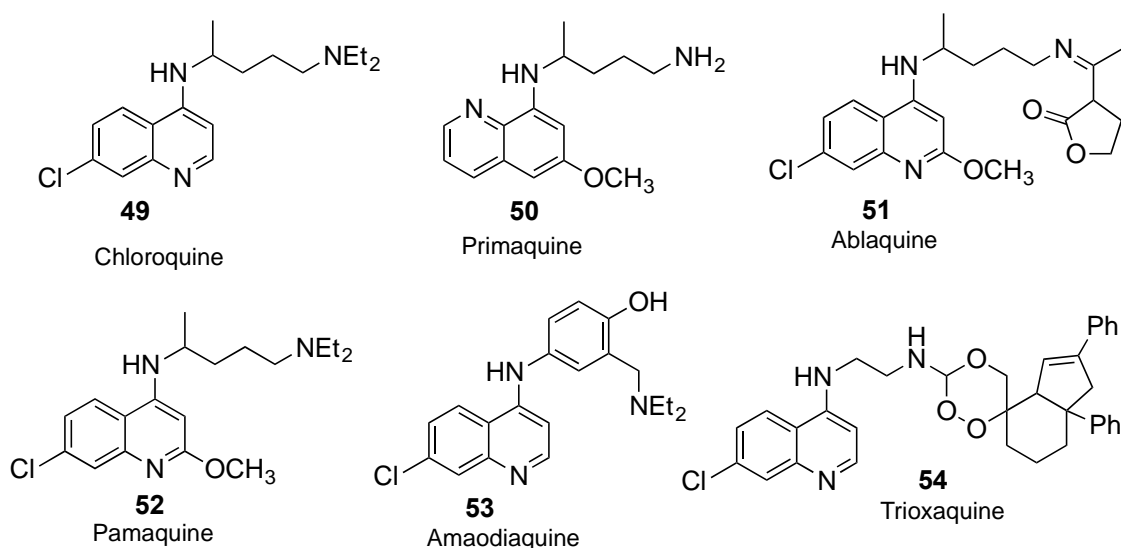


Figure 17. Quinoline-based antimalarial drugs³⁹

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 drug⁴⁰. 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).

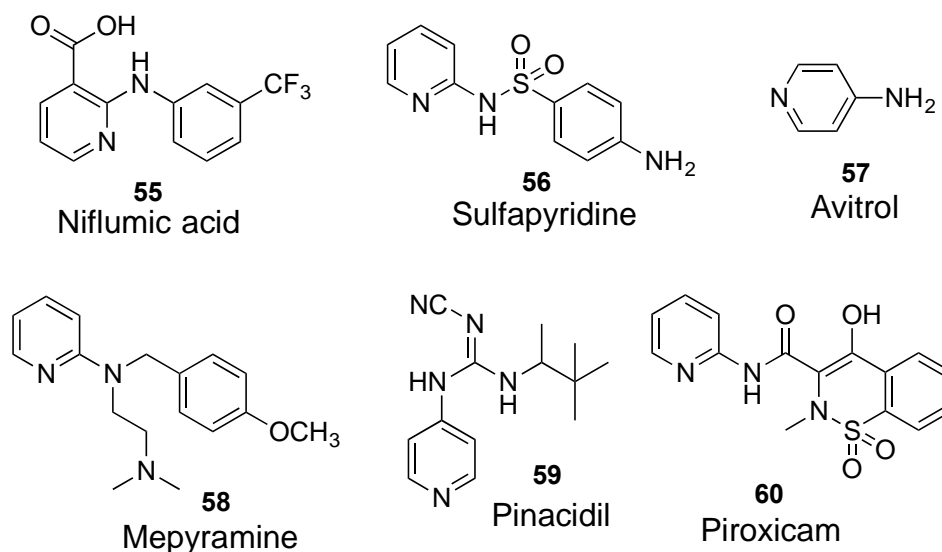


Figure 18. Pyridine-based drugs

Piperonal (heliotropin) is an aromatic aldehyde found in many essential oils,⁴⁵ vanilla and camphor^{46,47} and has been shown to have antibacterial⁴⁸ and anxiolytic activities. Additionally, few piperonal derivatives display a promising anticancer activity,⁴⁹ antileishmanial effect⁵⁰ 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

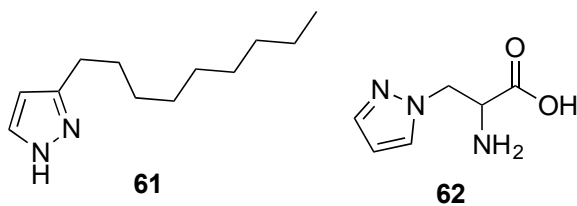


Figure 19. Pyrazole-based natural products

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 Tepoxalin⁶² etc. (Figure 20).⁶³⁻⁶⁵ Pyrazoles also play a role in agrochemicals and as bifunctional ligands in metal catalysis.⁶⁶

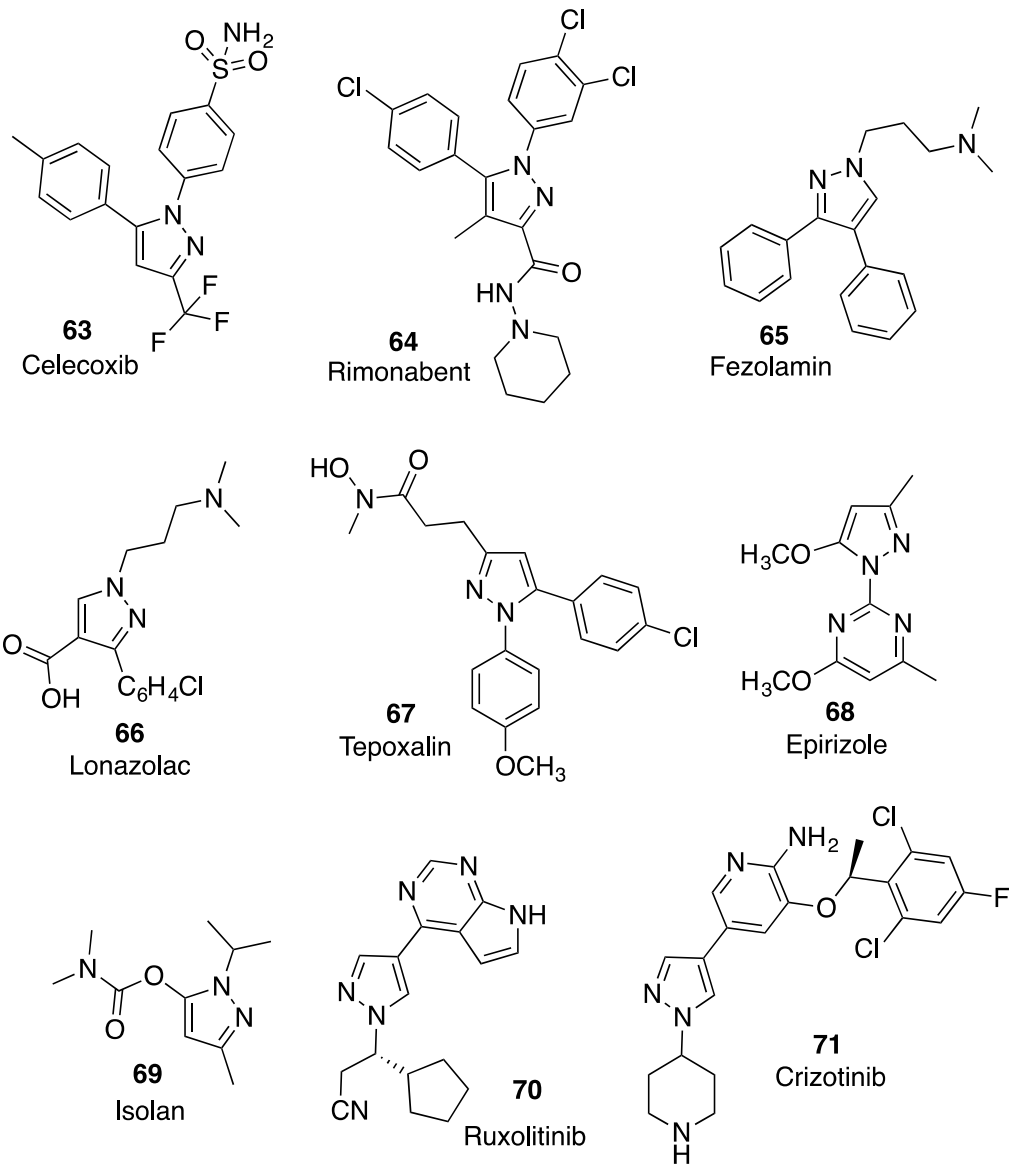


Figure 20. Pyrazole-based drugs

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).

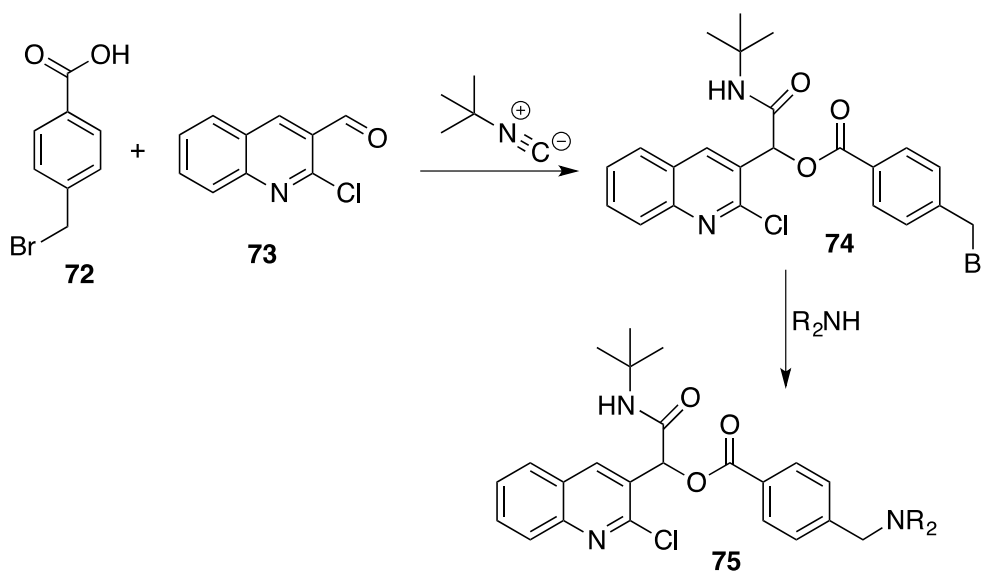


Figure 21. Preparation of chloroquinoline conjugates

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 ¹H-NMR spectral analysis (signals at δ 4.7 (2H, benzylic methylene) and at δ 12.9 (1H, carboxylic acid)).

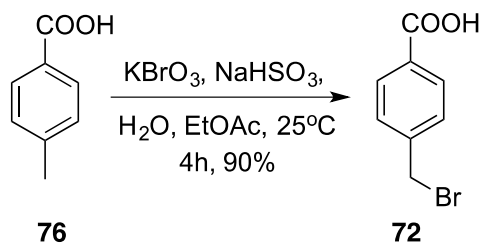


Figure 22. Preparation of *p*-bromomethylbenzoic acid

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 $^1\text{H-NMR}$ spectral analysis.

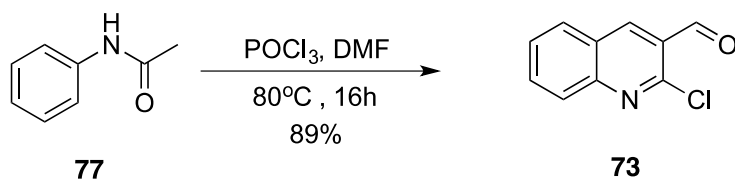


Figure 23. Preparation of 2-chloroquinoline aldehyde

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).

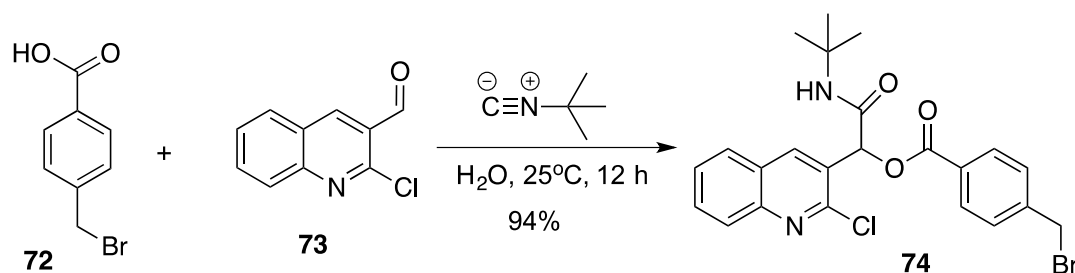


Figure 24. Passerini reaction with 2-chloroquinoline aldehyde

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.

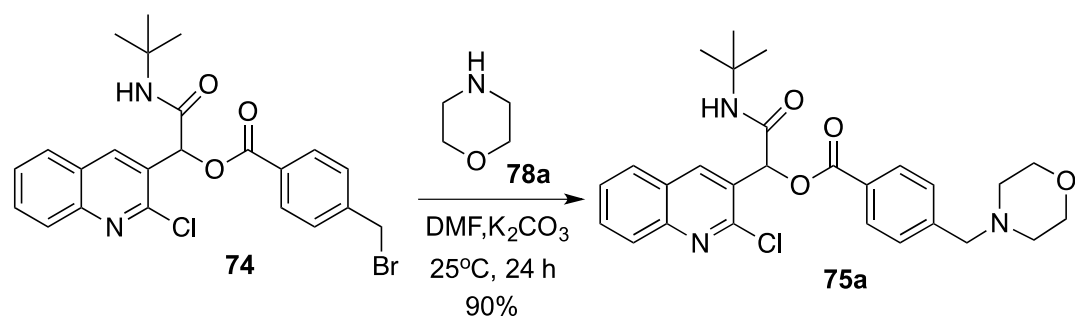


Figure 25. Preparation of 2-chloroquinoline-morpholine conjugate

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 $\sim 20 \mu M$ concentration.

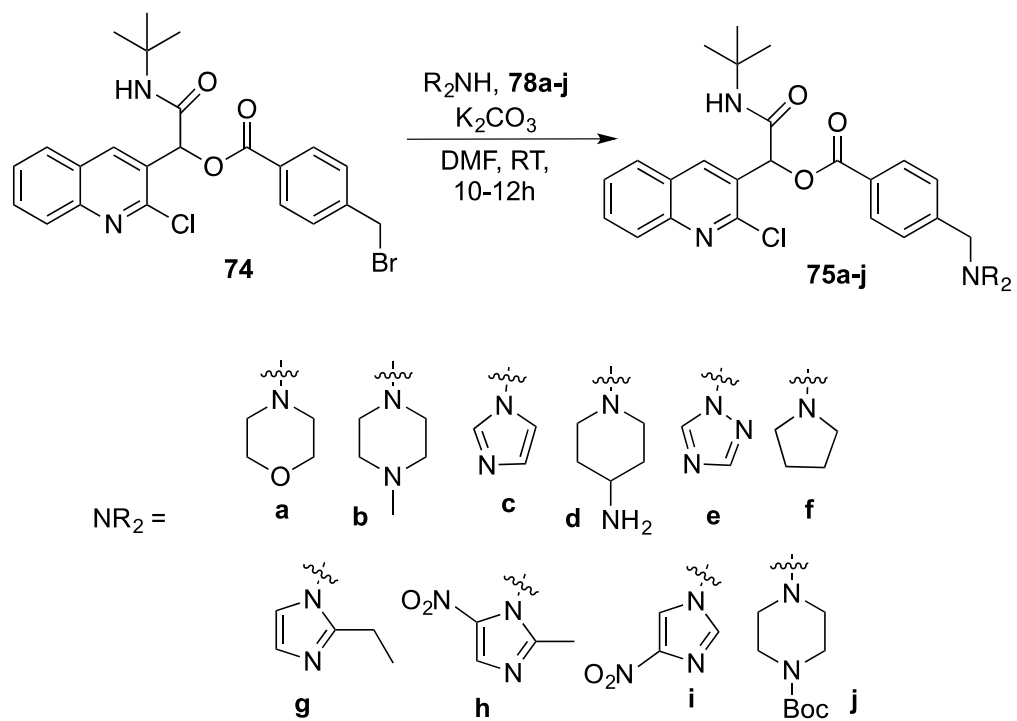


Figure 26. Preparation of 2-chloroquinoline-based amines

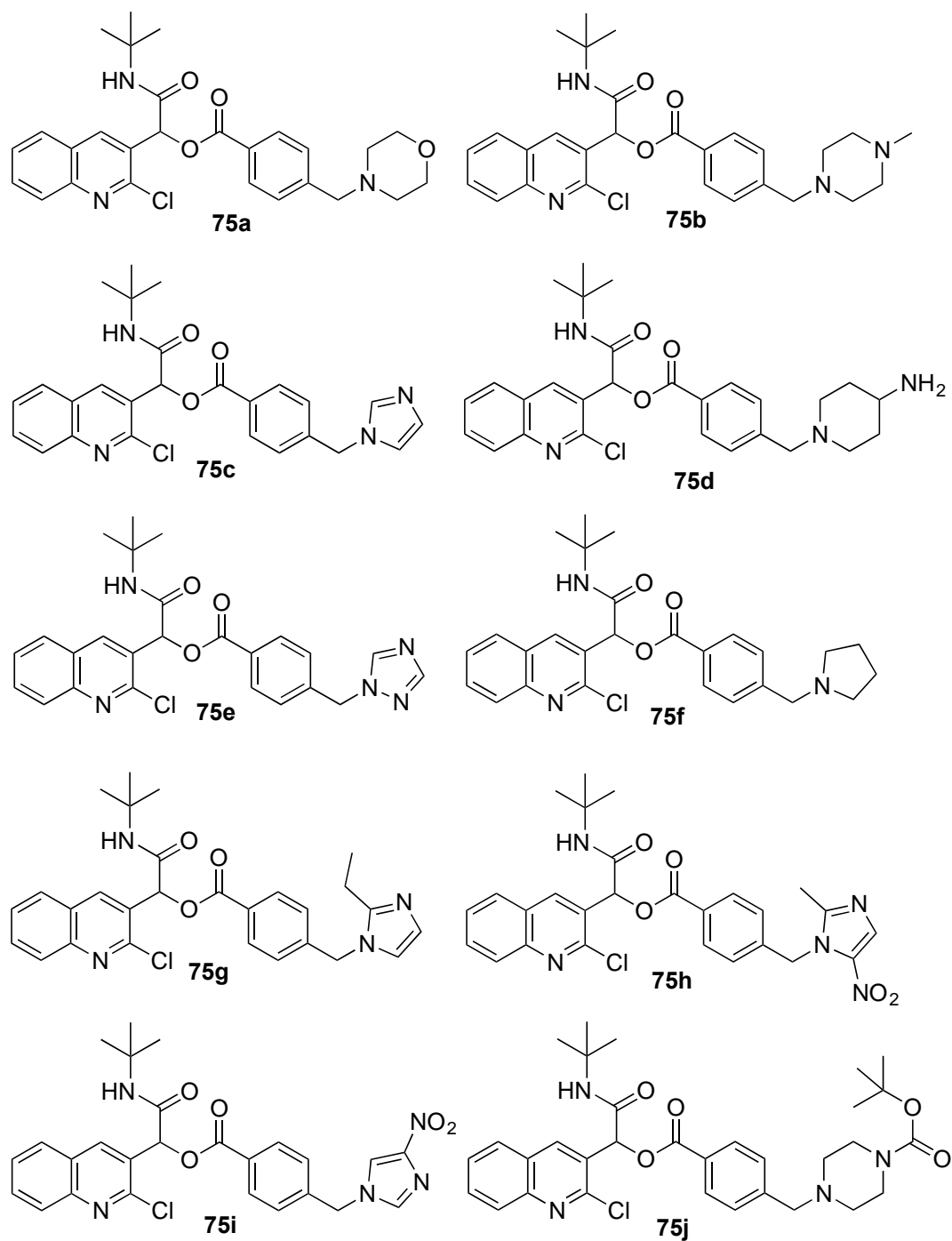


Figure 27. 2-Chloroquinoline-based amines

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.

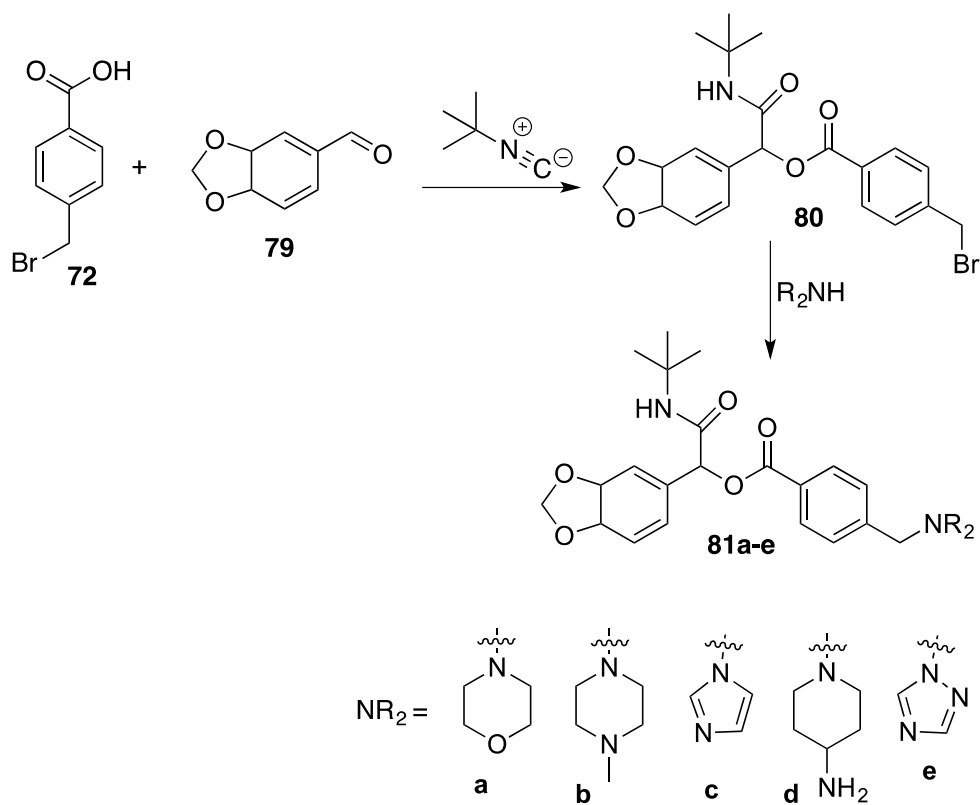


Figure 28. Preparation of piperonal-based amines

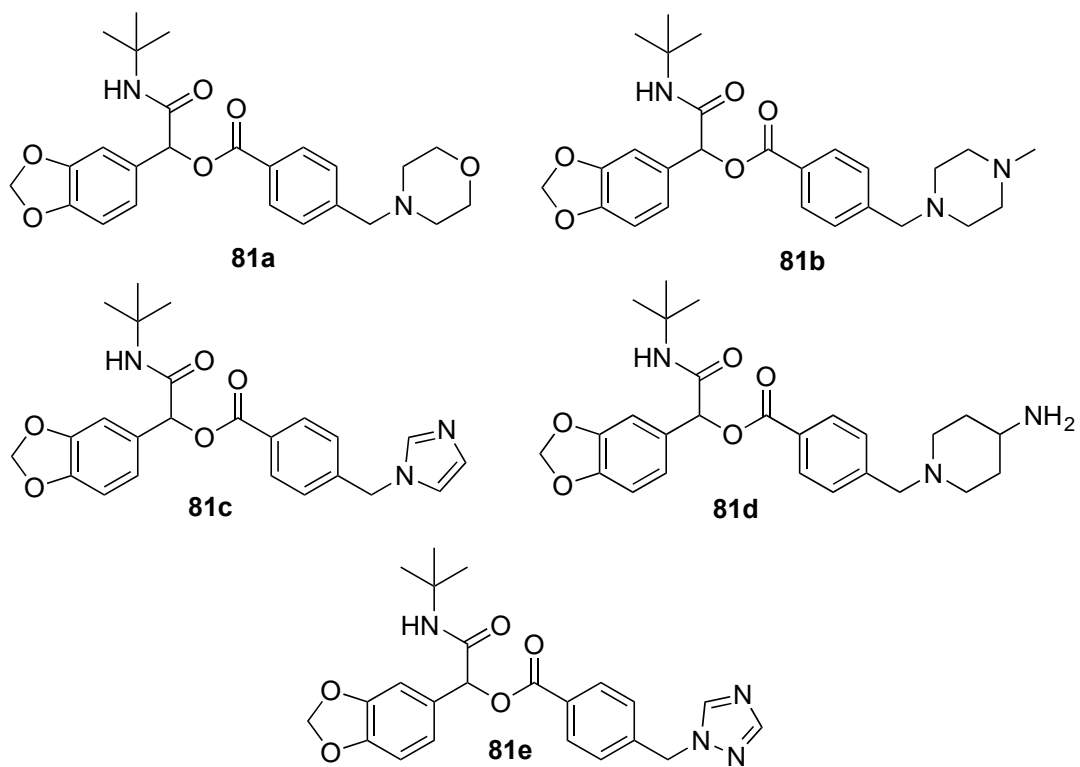


Figure 29. Piperonal-based amines

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 IC₅₀ values ranging between ~4-6 μM (Table 3).

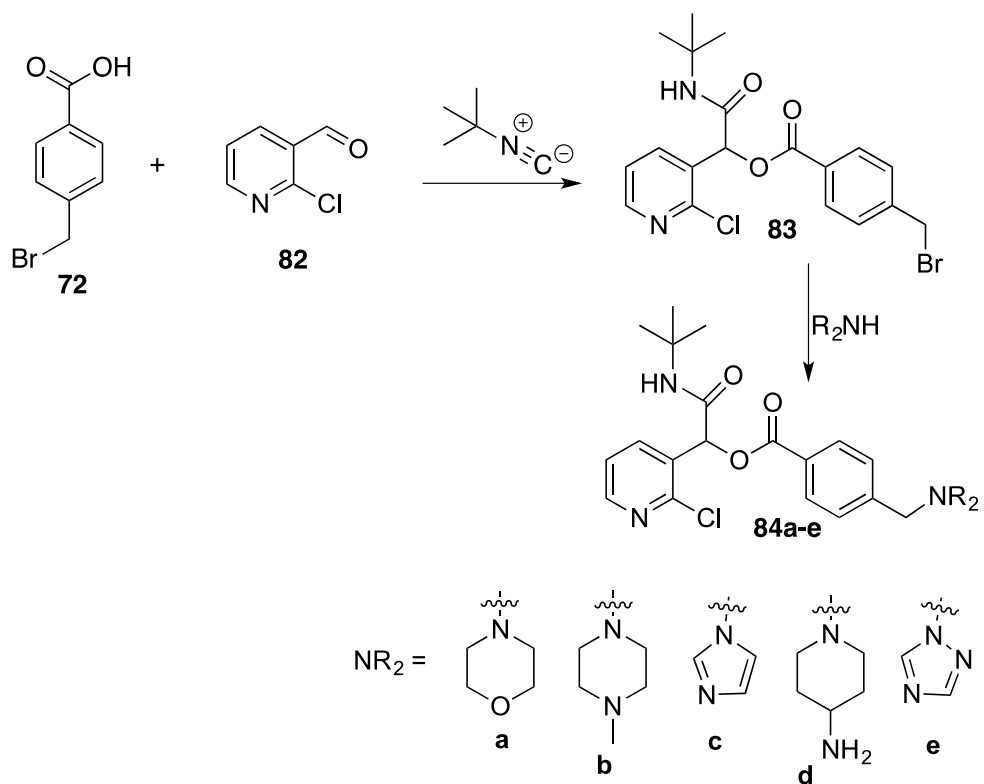


Figure 30. Preparation of 2-chloropyridine-based amines

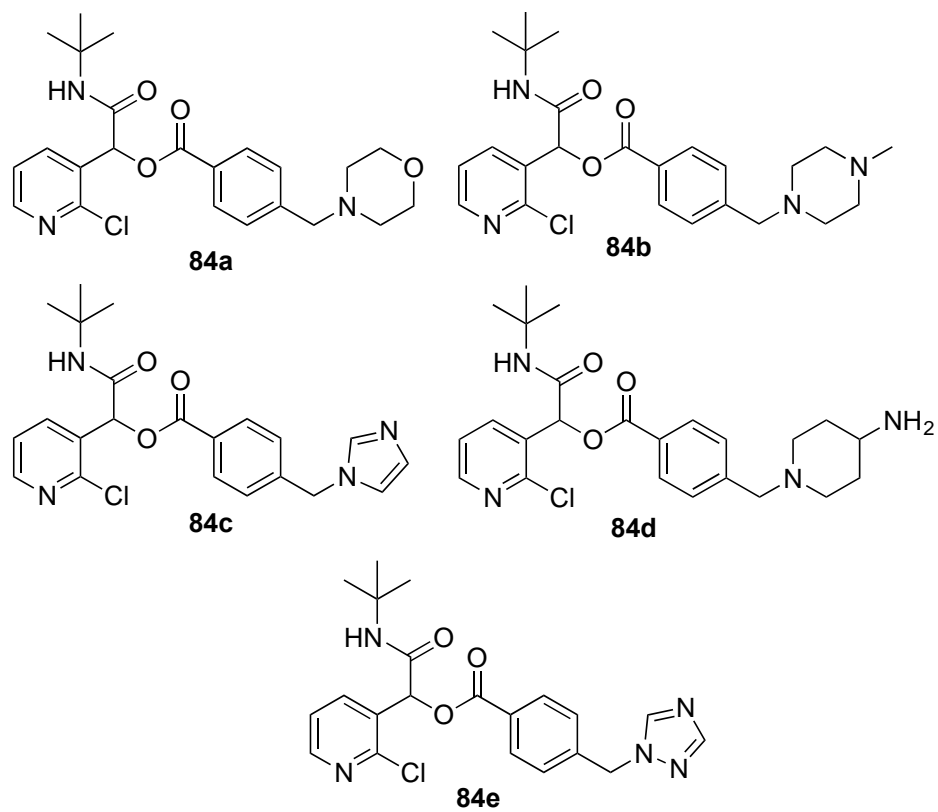


Figure 31. 2-Chloropyridine-based amines

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).

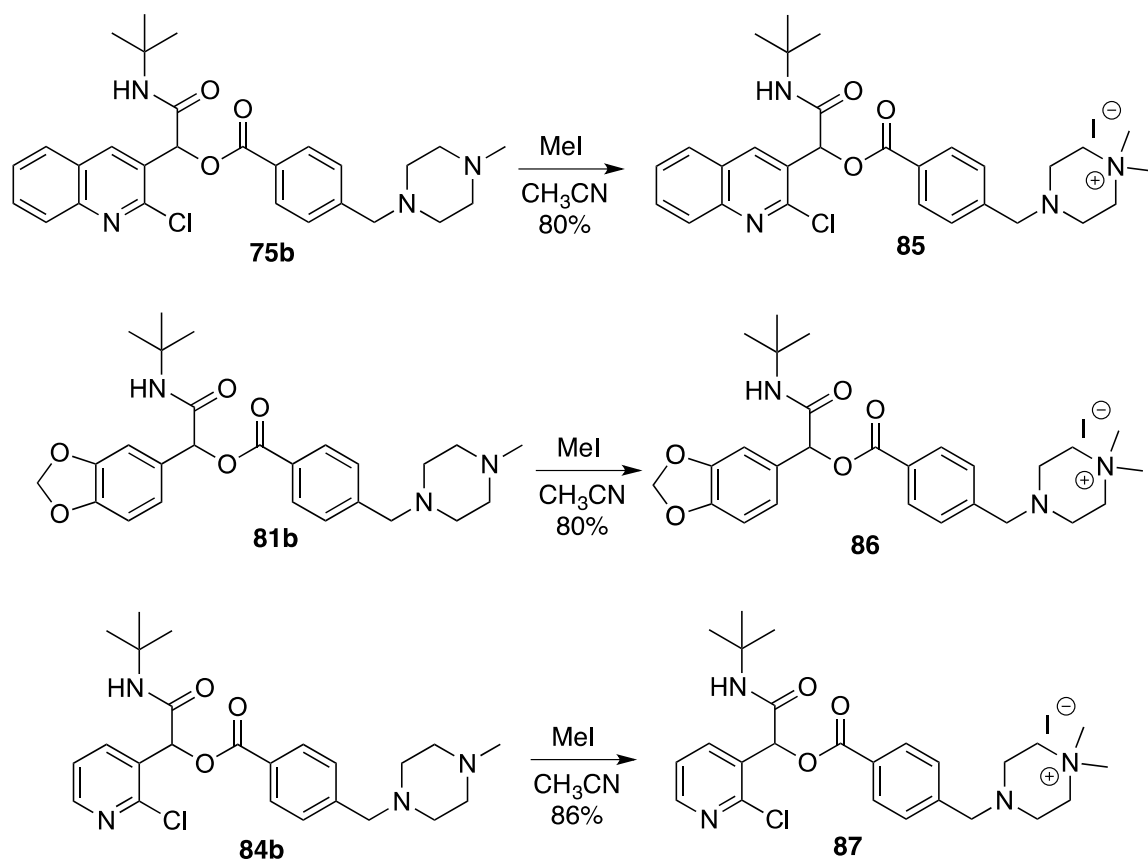


Figure 32. Preparation of quaternary ammonium salts

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 condensation 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).

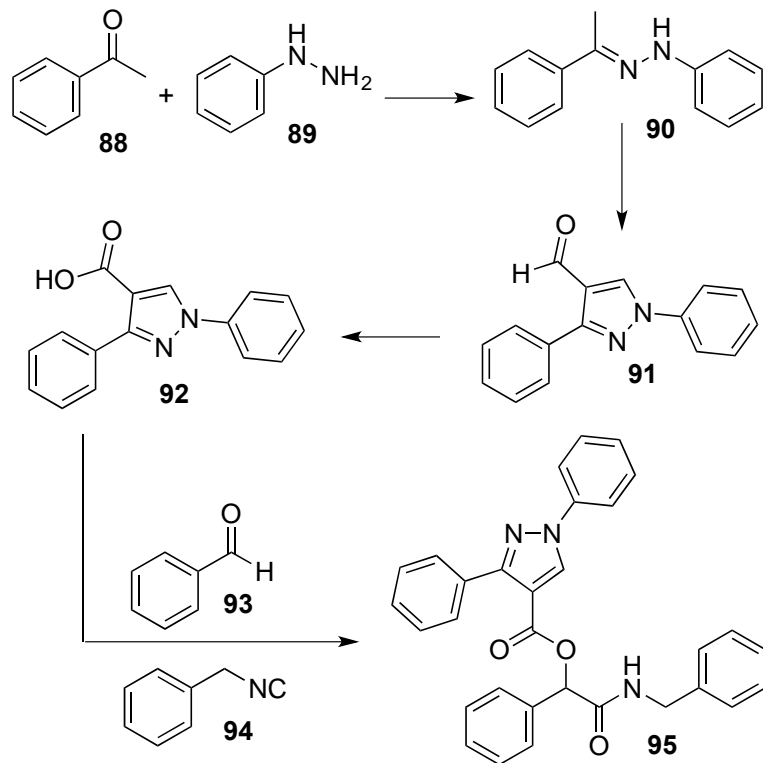


Figure 33. Preparation of pyrazole derivatives

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 using 10% 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 vacuum to obtain pure acetophenone phenylhydrazone as a yellow solid in 93% yield (Figure 34).

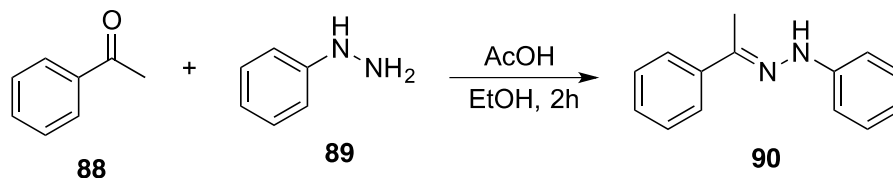


Figure 34. Preparation of phenylhydrazone

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).

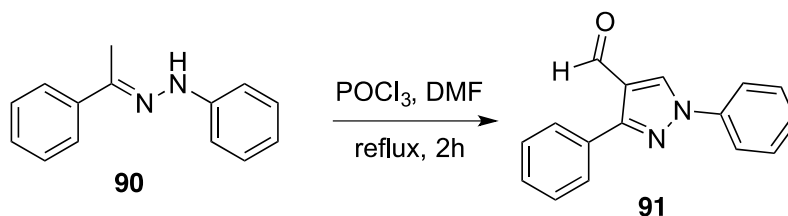


Figure 35. Preparation of pyrazole aldehyde

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.

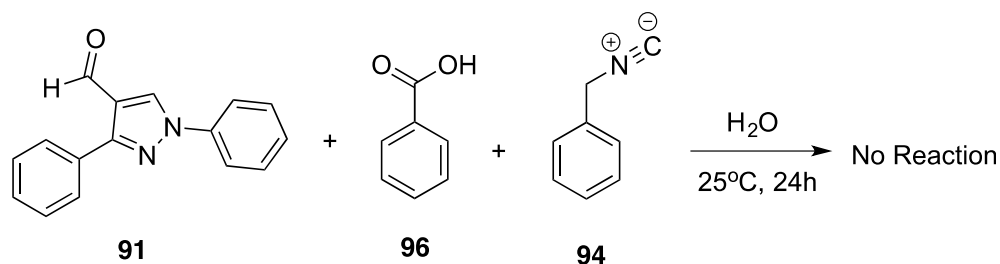


Figure 36. Passerini reaction with pyrazole aldehyde

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

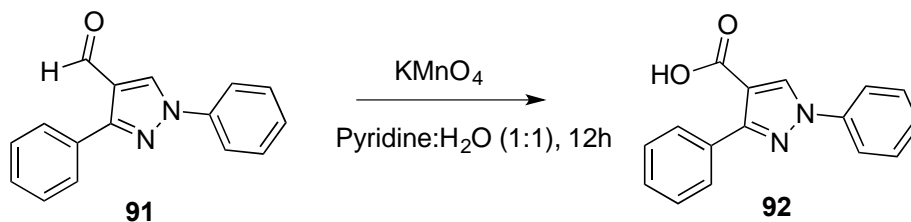


Figure 37. Oxidation of pyrazole aldehyde

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 α -acetoxyamide **95a** (Figure 38). Similarly, compounds **95b**, and **95c** were obtained by replacing acetophenone with dichloroacetophenone and benzaldehyde with p-chlorobenzaldehyde respectively (Figure 38).

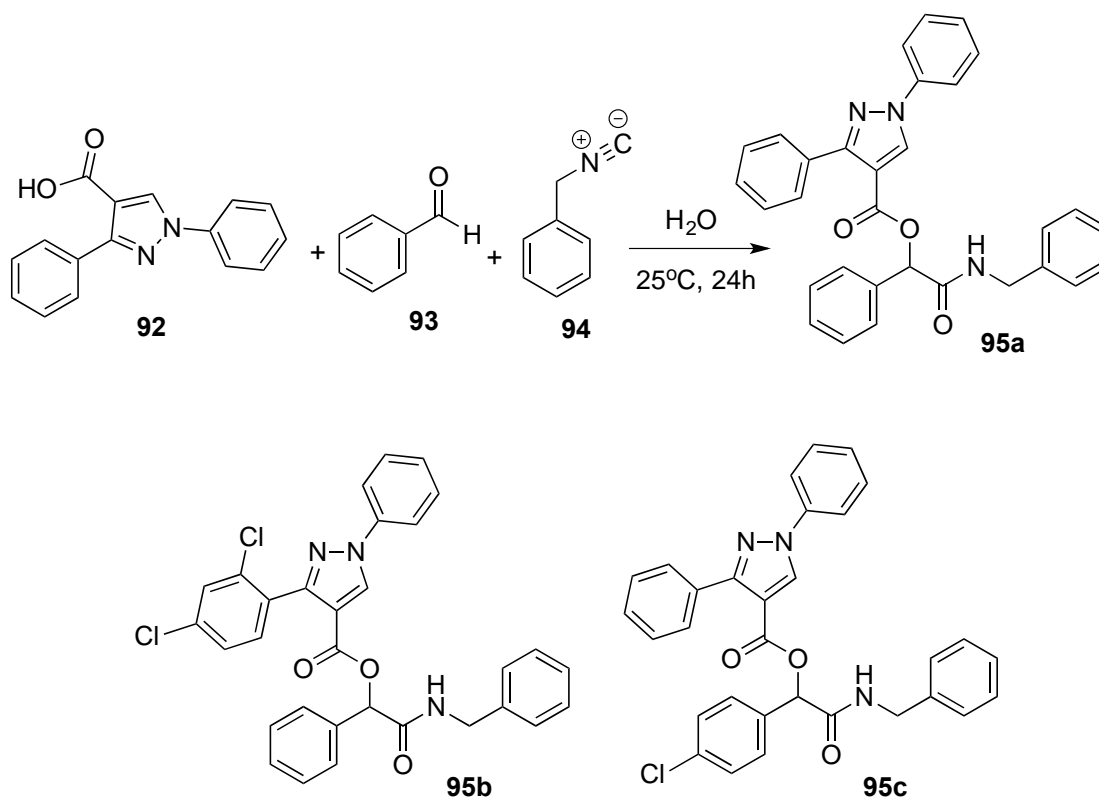


Figure 38. Passerini reaction with pyrazole acid

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 ¹H NMR, and 100 MHz for ¹³C NMR. The deuterated solvent (CDCl₃, DMSO-d₆) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures

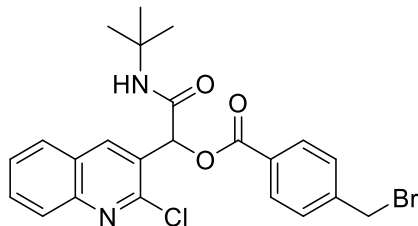
Method for the preparation of 2-chloroquinoline-3-carbaldehyde.⁷⁰ Phosphorus oxychloride (6.5 mL, 70.0 mmol) was slowly added to *N,N*-dimethylformamide (2.3 mL, 30.0 mmol) at 0°C and this solution was slowly added to acetanilide (1.3 g, 10.0 mmol) and heated at 80°C for 16h. The reaction mixture was 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 Na₂S₂O₃ solution. The two layers were separated and the aqueous layer was extracted twice using ethyl acetate. The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo* and recrystallized in methanol to yield the acid.

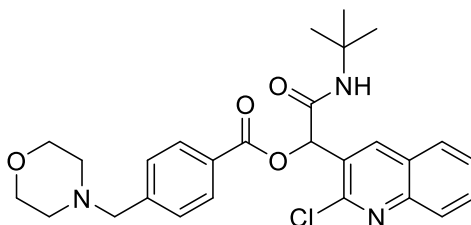
General reaction procedure for preparation of Passerini product.^{71,71,73} To a suspension of the aldehyde (1 mmol) and acid (1 mmol) in 10.0 mL water was added isocyanide (1.02 mmol). The reaction mixture was sonicated and vortex stirred repeatedly for 30 minutes and then stirred overnight. The reaction mixture was filtered and washed with saturated solution of NaHCO₃ 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), K₂CO₃ (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 vacuum to obtain the pure product.



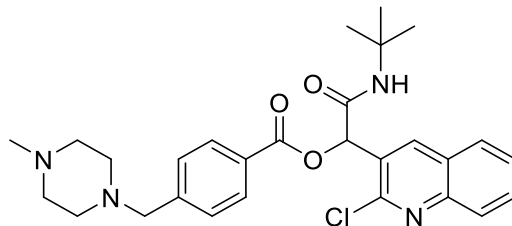
2-(tert-Butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-(bromomethyl)benzoate():

Yield: 96 %; color less solid, mp 142 – 143 °C; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (101 MHz, DMSO-d₆) 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 C₂₃H₂₂BrClN₂O₃ (M+H)⁺ 489.06 found 488.50.

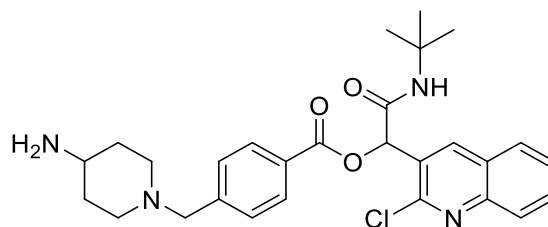


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-(morpholinomethyl)benzoate():

Yield: 55%; color less solid; mp 119 – 120 °C; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (101 MHz, DMSO-d₆) 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 C₂₇H₃₀ClN₃O₄ (M+H)⁺ 496.20 found 496.00.

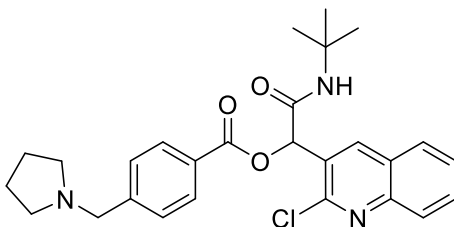


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((4-methylpiperazin-1-yl)methyl)benzoate(): Yield: 89%; color less solid; mp.140 – 145 °C; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 8.41 (s, 1H), 8.19 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.84 – 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); ¹³C NMR (101 MHz, DMSO-d₆) 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 C₂₈H₃₃ClN₄O₃ (M+H)⁺ 509.23 found 509.00.



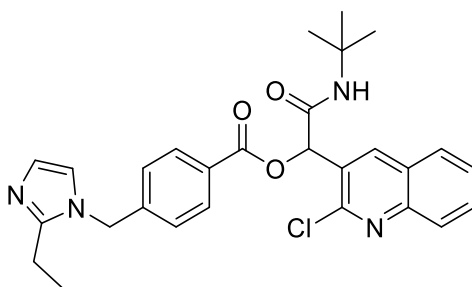
2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((4-aminopiperidin-1-yl)methyl)benzoate(): Yield: 51%; color less solid; mp 98 – 99 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.41 (s, 1H), 8.19 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.86 (t, *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)

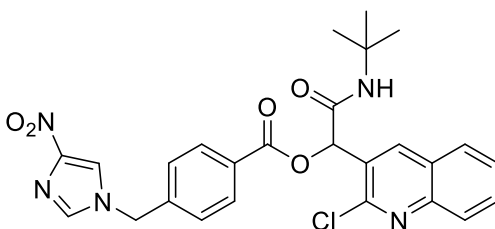
benzoate(): Yield: 68%; color less solid; mp 103 – 108 °C; ¹H NMR (400 MHz, Acetone-d₆): δ (ppm) 8.47 (s, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 7.89 (d, $J = 8.2$ Hz, 1H), 7.77 (m, 1H), 7.57 – 7.62 (m, 1H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.32 (s, 1H), 6.49 (s, 1H), 3.58 (s, 2H), 1.95 (m, 4H), 1.61 – 1.67 (m, 4H), 1.30 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): 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



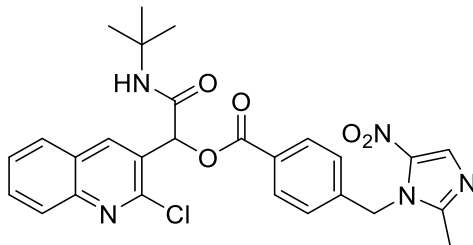
2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((2-ethyl-1H-imidazol-1-

yl)methyl)benzoate(): Yield: 82%; color less solid; mp 109 – 111 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.40 (s, 1H), 8.20 (s, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 7.95 – 7.99

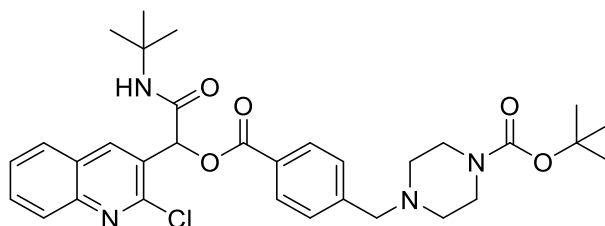
(m, 2H), 7.85 (dd, $J = 1.4, 7.0$ Hz, 1H), 7.67 (dd, $J = 1.1, 8.1$ Hz, 1H), 7.21 (d, $J = 8.2$ Hz, 1H), 7.11 (d, $J = 1.2$ Hz, 1H), 6.79 (d, $J = 1.2$ Hz, 1H), 6.45 (s, 1H), 5.24 (s, 2H), 1.28 (s, 9H), 1.03 – 1.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6): δ (ppm) 165.9, 165.2, 150.3, 149.2, 147.3, 144.4, 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 $\text{C}_{28}\text{H}_{29}\text{ClN}_4\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 505.20 found 504.60.



2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((4-nitro-1H-imidazol-1-yl)methyl)benzoate: Yield: 88%; color less solid; mp 130 – 131 °C; ^1H 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 $\text{C}_{26}\text{H}_{24}\text{ClN}_5\text{O}_5$ ($\text{M}+\text{H}$) $^+$ 522.16 found 521.90.

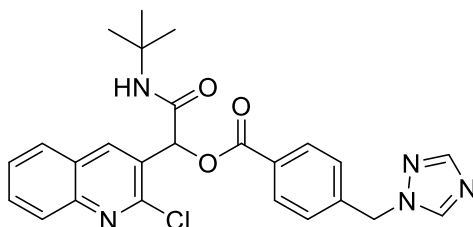


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)benzoate: Yield: 87%; color less solid; mp 143 – 144 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.44 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.99 (m, 3H), 7.85 (t, *J* = 8.2 Hz, 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); ¹³C NMR (101 MHz, DMSO-d₆): 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 C₂₇H₂₆ClN₅O₅ (M+H)⁺ 536.17 found 535.80.

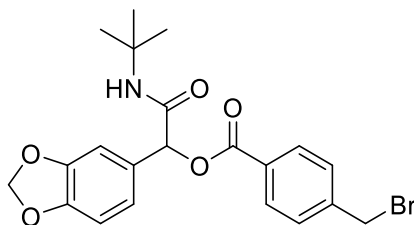


tert-Butyl 4-((2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethoxy) carbonyl) benzyl piperazine-1-carboxylate (): Yield: 89%; color less solid; mp 105 – 107 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.40 (s, 1H), 8.19 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 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); ¹³C NMR (101 MHz, DMSO-d₆): 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 $\text{C}_{32}\text{H}_{39}\text{ClN}_4\text{O}_5$ ($\text{M}+\text{H}$)⁺ 595.27 found 595.10.

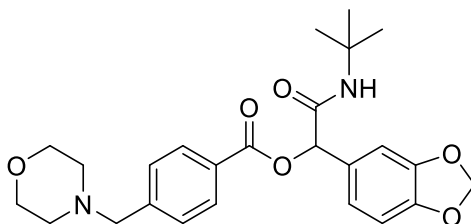


2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl 4-((1H-1,2,4-triazol-1-yl)methyl)benzoate(): Yield: 70%; color less solid; mp 104 – 106 °C; ¹H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.68 (d, $J = 1.2$ Hz, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 1H), 7.90 – 7.98 (m, 3H), 7.85 (d, $J = 1.5$ 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); ¹³C 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 $\text{C}_{25}\text{H}_{24}\text{ClN}_5\text{O}_3$ ($\text{M}+\text{H}$)⁺ 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; ¹H 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, $J = 1.7$

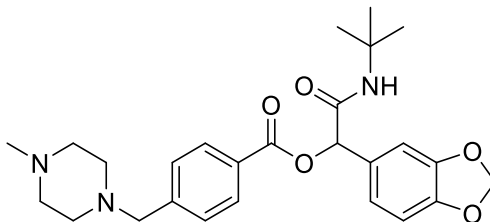
Hz, 1H), 7.04 (dd, $J = 1.8, 8.0$ Hz, 1H), 6.94 (s, 1H), 6.03 (d, $J = 1.3$ Hz, 2H), 5.92 (s, 1H), 4.75 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm) 167.8, 165.2, 148.1, 147.9, 144.3, 130.5, 130.4, 130.4, 130.3, 129.7, 121.9, 108.8, 108.3, 101.9, 76.0, 51.2, 51.1, 33.8, 29.0; ESIMS: m/z calculated for $\text{C}_{21}\text{H}_{22}\text{BrNO}_5$ ($\text{M}+\text{H}$) $^+$ 448.08 found 470.10.



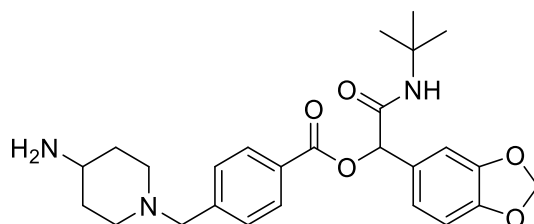
1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl

4-

(morpholinomethyl)benzoate ($\text{}$): Yield: 92%; color less solid; mp 178 – 180 °C; ^1H 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 $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 455.22 found 455.20.

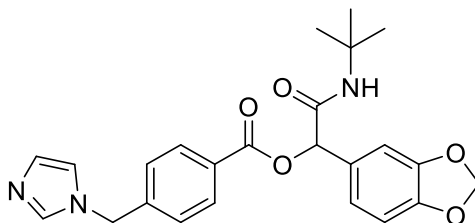


1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4-((4-methylpiperazin-1-yl)methyl)benzoate(): Yield: 78%; color less solid; mp 92 – 93 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.93 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.92 (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); ¹³C NMR (101 MHz, DMSO-d₆): 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 C₂₆H₃₃N₃O₅ (M+H)⁺ 468.25 found 468.20.

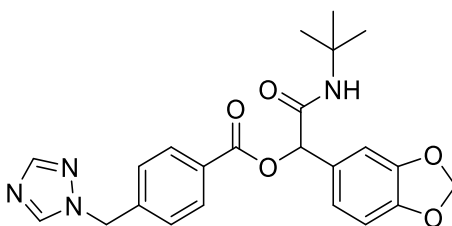


1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4-((4-aminopiperidin-1-yl)methyl)benzoate(): Yield: 54%; color less solid; mp 92 – 94 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.02 (d, *J* = 5.8 Hz, 1H), 7.83 – 7.97 (m, 2H), 7.42 (t, *J* = 6.7 Hz, 1H), 7.00 – 7.12 (m, 2H), 6.89 – 6.95 (m, 1H), 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); ¹³C NMR (101 MHz, DMSO-d₆): 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.

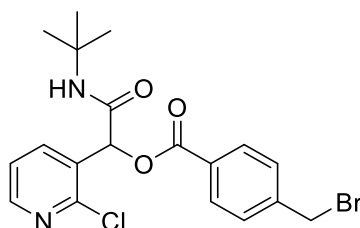


1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4-(1H-imidazol-1-yl)methylbenzoate(): Yield: 67%; color less solid; mp 83 – 84 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.96 (d, *J* = 7.2 Hz, 2H), 7.85 (s, 1H), 7.75 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.16 (s, 1H), 7.08 (s, 1H), 7.03 (d, *J* = 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); ¹³C NMR (101 MHz, DMSO-d₆): 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.



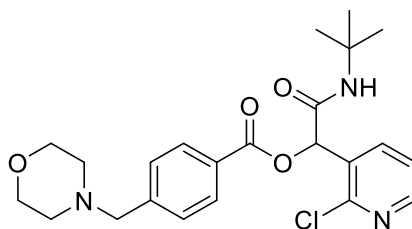
1-(benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethyl 4-(1H-1,2,4-triazol-1-yl)methylbenzoate(): Yield: 50%; color less solid; mp 120 – 121 °C; ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 8.68 (d, *J* = 1.9 Hz, 1H), 7.95 – 8.01 (m, 2H), 7.86 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.63 (m, 1H), 7.35 – 7.39 (m, 1H), 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 $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_5$ ($\text{M}+\text{H}$) $^+$ 437.18 found 436.10.

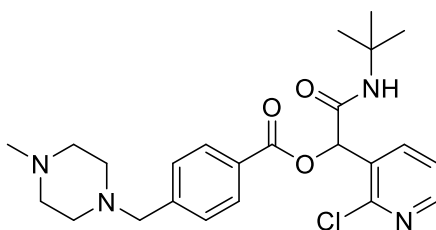


2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl 4-(bromomethyl)benzoate:

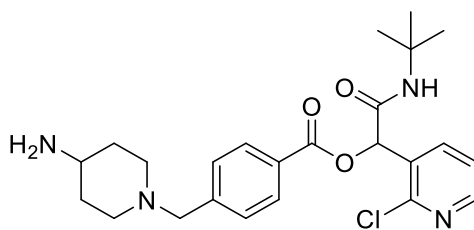
Yield: 92 %, color less solid, mp 138 – 140 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.44 (dd, $J = 4.8, 1.9$ Hz, 1H), 8.16 (s, 1H), 7.93 – 7.96 (m, 2H), 7.86 (dd, $J = 1.9, 7.7$ Hz, 1H), 7.57 – 7.61 (m, 2H), 7.51 (dd, $J = 4.8, 7.7$ Hz, 1H), 6.31 (s, 1H), 4.75 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (101 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 $\text{C}_{19}\text{H}_{20}\text{BrClN}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 439.04, found 439.00



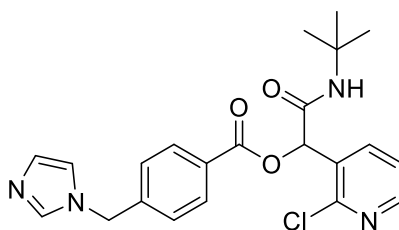
2-(tert-Butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl 4-(morpholinomethyl)benzoate: Yield: 80 %; color less solid; mp 78 – 80 °C; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 8.43 (dq, *J* = 2.4, 4.4 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.91 (dt, *J* = 2.1, 8.8 Hz, 2H), 7.86 (dt, *J* = 1.8, 7.7 Hz, 1H), 7.50 (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); ¹³C NMR (101 MHz, DMSO-d₆) 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 C₂₃H₂₈ClN₃O₄ (M+H)⁺ 446.19 found 446.20.



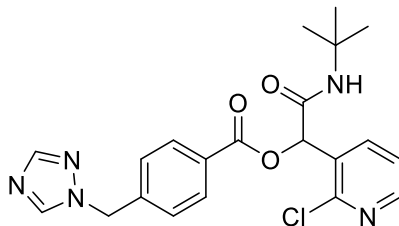
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl-((4-methylpiperazin-1-yl)methyl)benzoate: Yield: 71 %; color less solid; mp 99 – 100 °C; ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 165.9, 165.4, 150.9, 150.5, 145.3, 139.2, 131.4, 130.1, 129.9, 128.0, 124.3, 72.9, 62.1, 54.9, 52.8, 51.6, 46.0, 28.9; ESIMS: *m/z* calculated for C₂₄H₃₁ClN₄O₃(M+H)⁺ 459.22 found 459.20



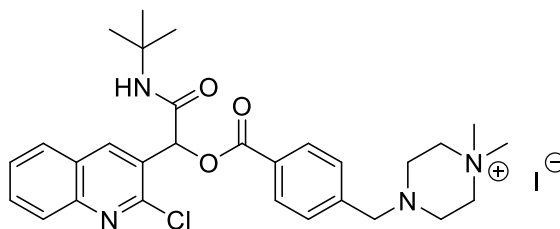
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((4-aminopiperidin-1-yl)methyl)benzoate: Yield: 59%; color less solid, mp 113 – 115 °C; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 8.43 (dd, *J* = 1.9, 4.8 Hz, 1H), 8.15 (s, 1H), 7.88 – 7.92 (m, 1H), 7.85 (dd, *J* = 1.9, 7.8 Hz, 1H), 7.50 (dd, *J* = 4.7, 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); ¹³C NMR (101 MHz, DMSO-d₆): 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 C₂₄H₃₁ClN₄O₃(M+H)⁺ 459.22 found 459.20



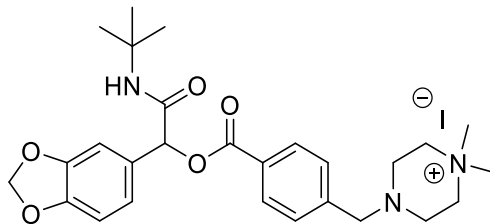
2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl4-((1H-imidazol-1-yl)methyl)benzoate (): Yield: 77%; color less solid; mp 103 – 104 °C; ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 8.41 (d, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.99 – 8.04 (m, 2H), 7.86 (dt, *J* = 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 C₂₂H₂₃ClN₄O₃(M+H)⁺ 427.16 found 427.20



2-(tert-butylamino)-1-(2-chloropyridin-3-yl)-2-oxoethyl 4-((1H-1,2,4-triazol-1-yl)methyl)benzoate (): Yield: 76 %; color less solid; mp 95 – 97 °C; ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₁H₂₂ClN₅O₃ (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; ¹H 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).



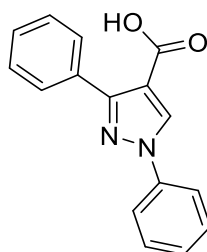
4-(4-((1-(Benzo[d][1,3]dioxol-5-yl)-2-(tert-butylamino)-2-oxoethoxy)carbonyl)benzyl)-1,1-dimethylpiperazin-1-ium iodide: Yield: 80%; color less solid; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.01 (d, $J = 7.0$ Hz, 2H), 7.43 (d, $J = 7.3$ Hz, 2H), 6.95 – 7.01 (m, 2H), 6.80 (dd, $J = 1.5, 8.4$ Hz, 1H), 6.08 (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 $\text{C}_{27}\text{H}_{36}\text{IN}_3\text{O}_5$ ($\text{M}+\text{H}$) $^+$ 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 vacuum to obtain pure acetophenone phenylhydrazone as a yellow solid (2.8 g, 90% yield).

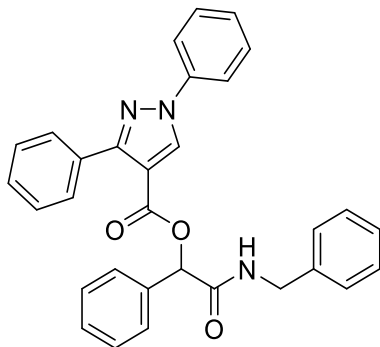
Preparation of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde.⁷⁵ Phosphoryl chloride (1.0 mL, 11.4 mmol) was added to *N,N*-dimethylformamide (0.8 mL, 11.4 mmol) at 0°C and the mixture stirred for 1h. This mixture was then slowly added to a solution of

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)

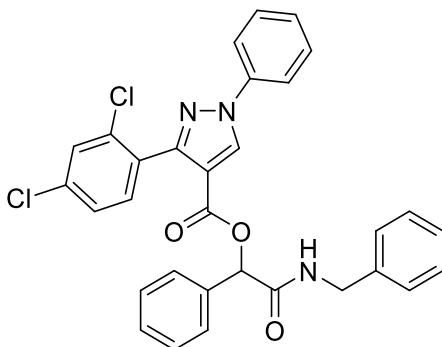
Preparation of the aryl-1-phenylpyrazole-4-carboxylic acid. Aldehyde (1 mmol) was dissolved in 50 mL (pyridine: water =1:1) and KMnO₄ (1 mmol) was added. The reaction was stirred overnight at room temperature. The completion of reaction was monitored by TLC using 30% EtOAc/hexane. Upon completion, ice 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



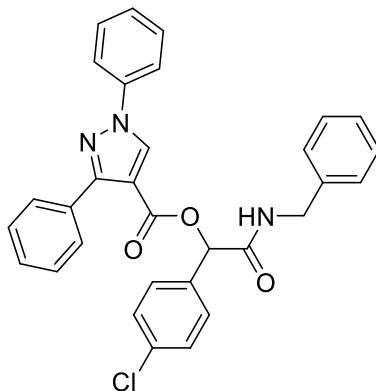
1,3-diphenyl-1H-pyrazole-4-carboxylic acid: ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 12.55 (s, 1H), 9.06 (d, *J* = 2.1 Hz, 1H), 7.93 – 7.98 (m, 3H), 7.80 (dt, *J* = 2.1, 7.71 Hz, 2H), 7.48 – 7.56 (m, 3H), 7.40 – 7.44 (m, 3H).



2-(benzylamino)-2-oxo-1-phenylethyl 1,3-diphenyl-1H-pyrazole-4-carboxylate: ^1H 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: ^1H 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; ^1H 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

2015-10-13-KP-passerini-terbutylisocyanide

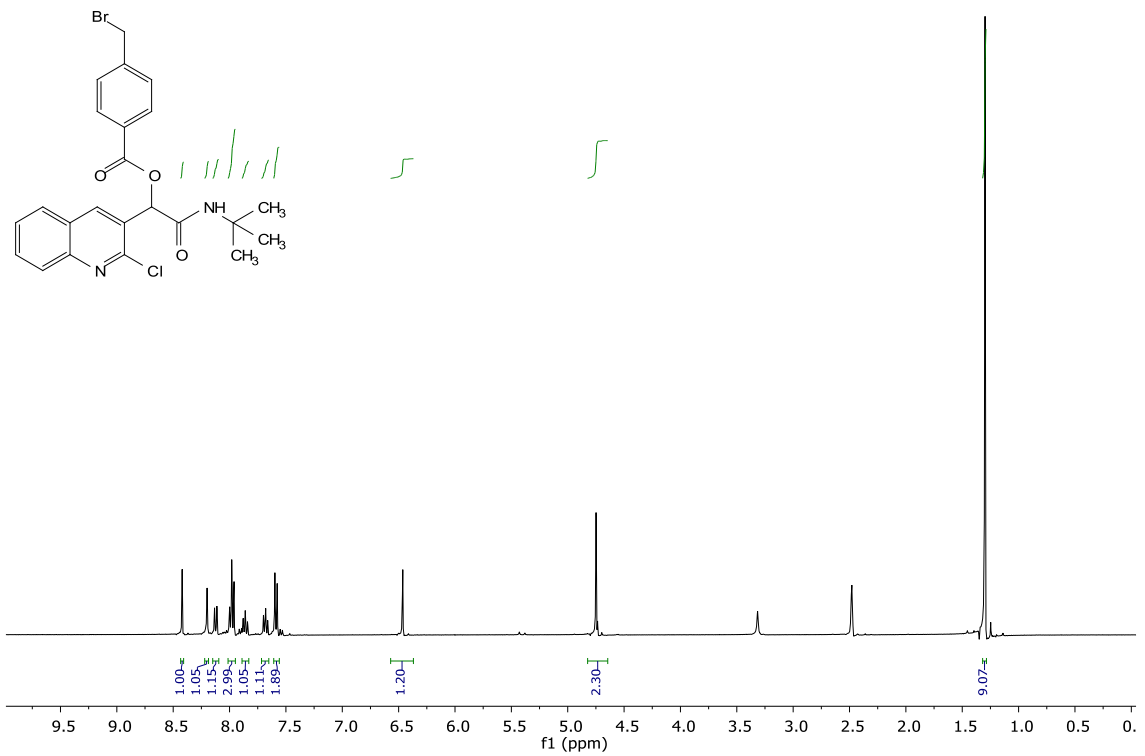


Figure 39. 400 MHz ^1H NMR of compound **74** in DMSO

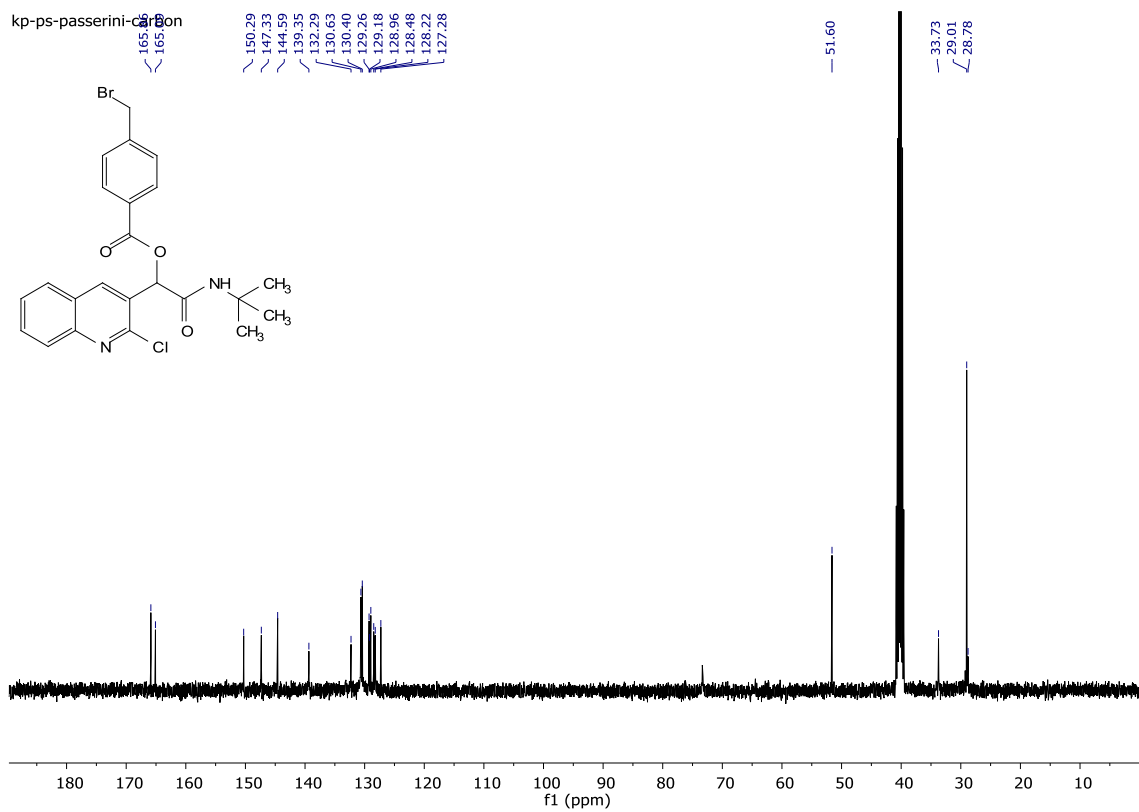


Figure 40. 100 MHz ^{13}C NMR of compound **74** in DMSO

PROTON

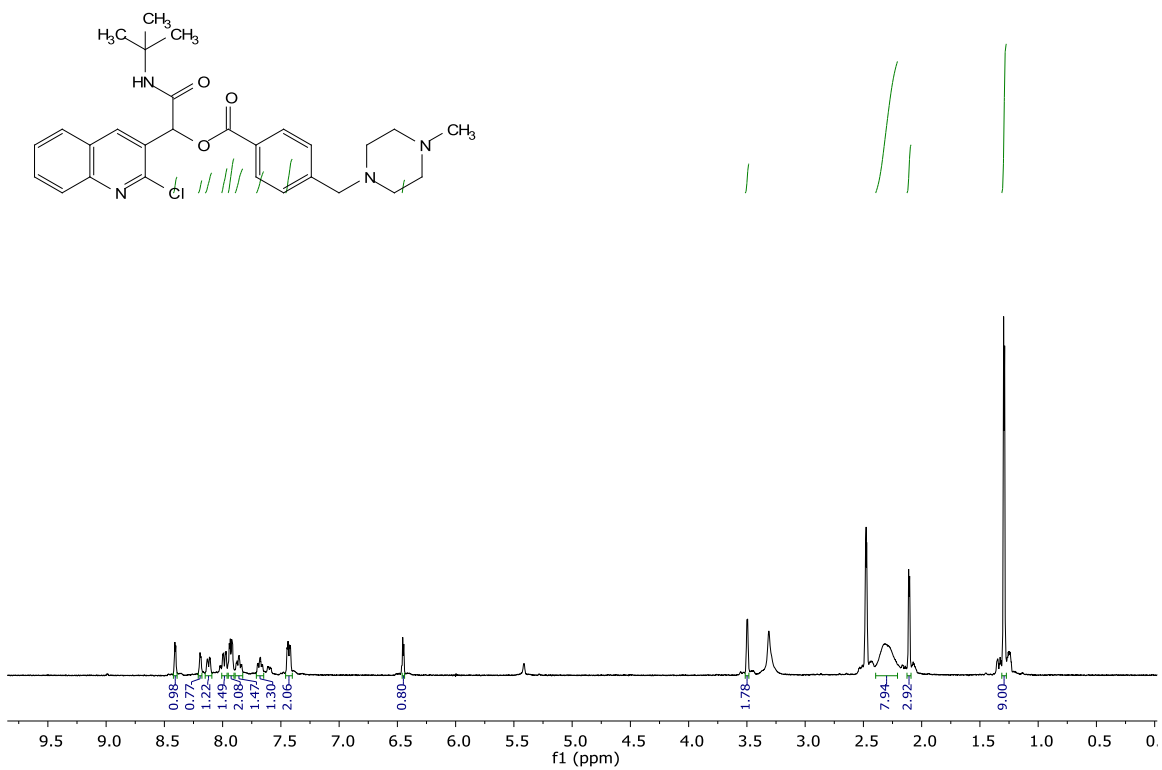


Figure 41. 400 MHz ¹H NMR of compound **75b** in DMSO

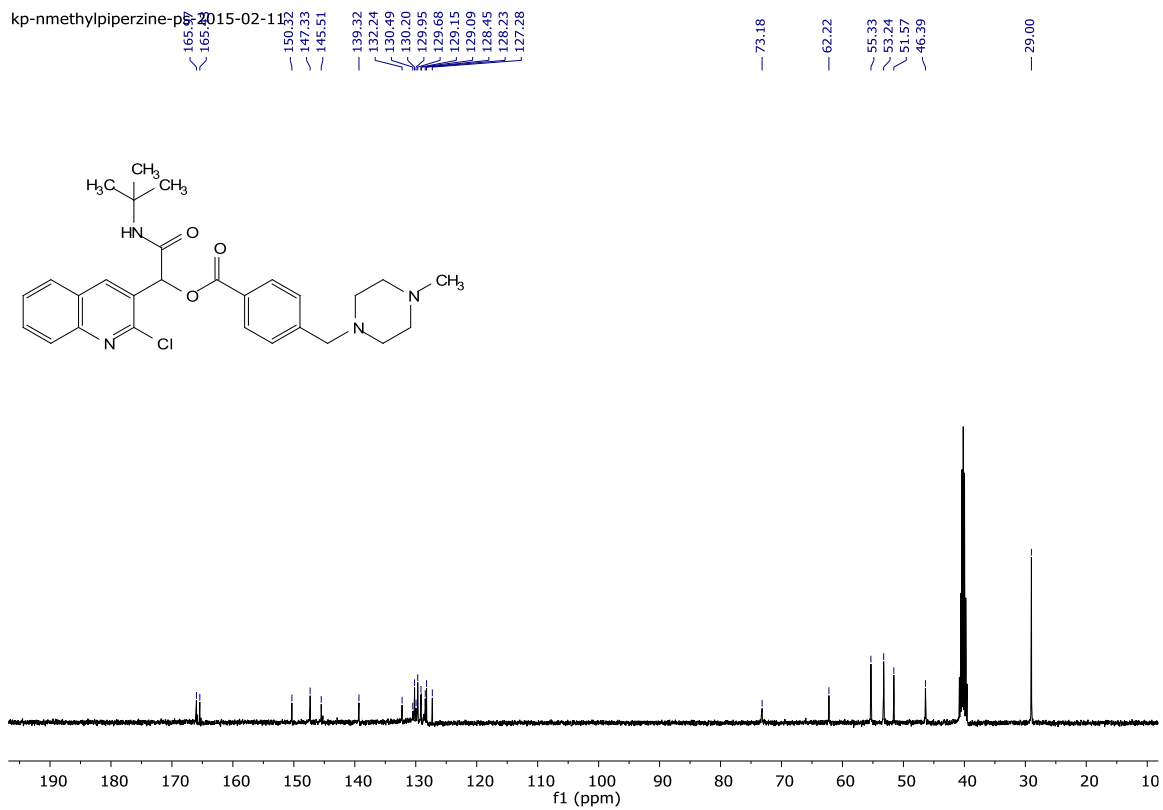


Figure 42. 100 MHz ^{13}C NMR of compound **75b** in DMSO

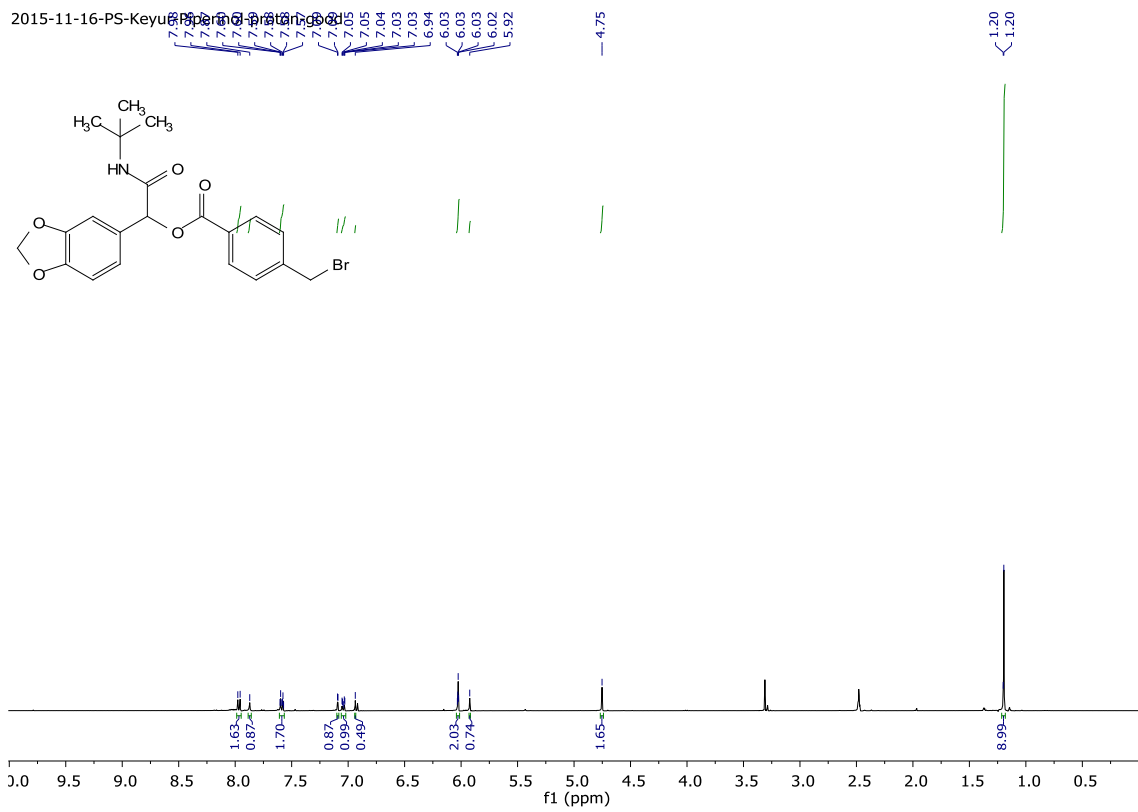


Figure 43. 400 MHz ^1H NMR of compound **80** in DMSO

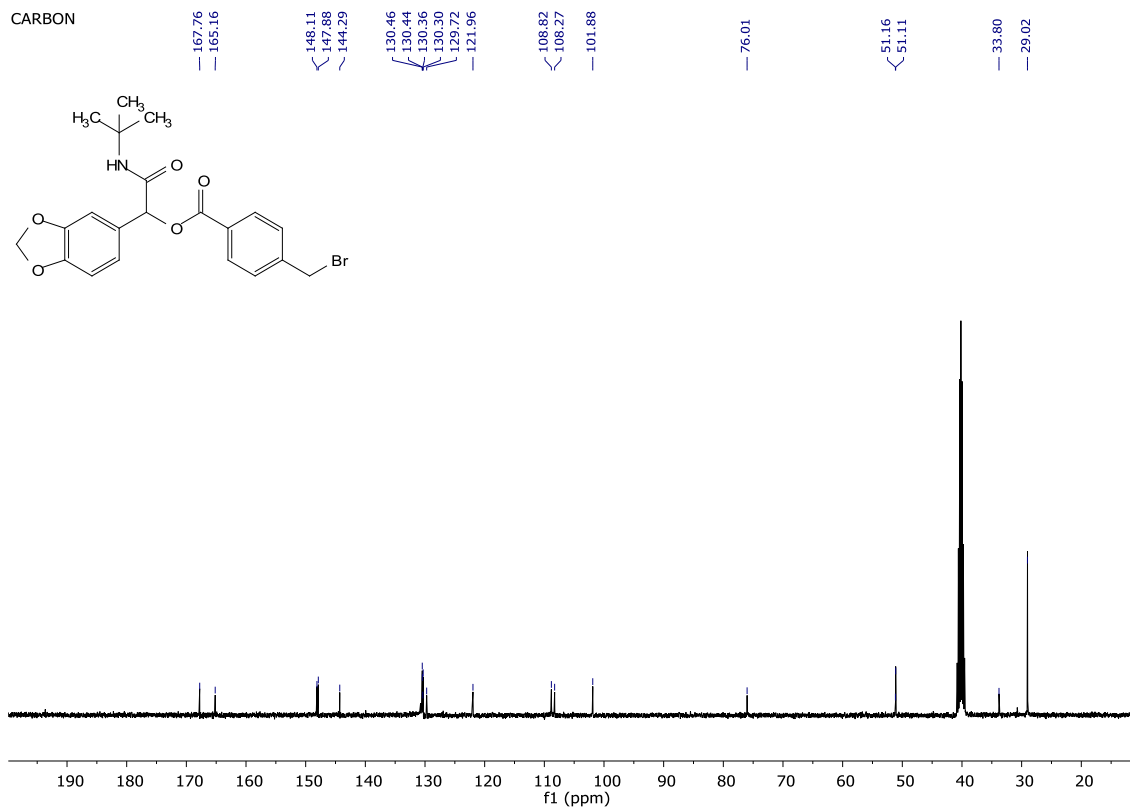


Figure 44. 100 MHz ^{13}C NMR of compound **80** in DMSO

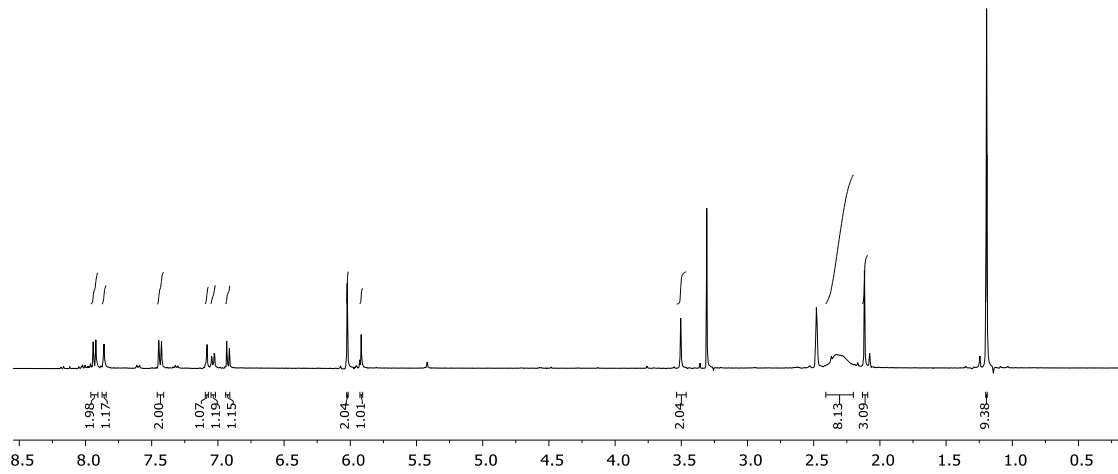
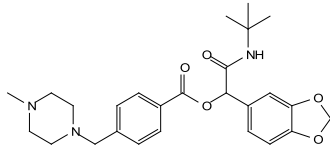


Figure 45. 400 MHz ^1H NMR of compound **81b** in DMSO

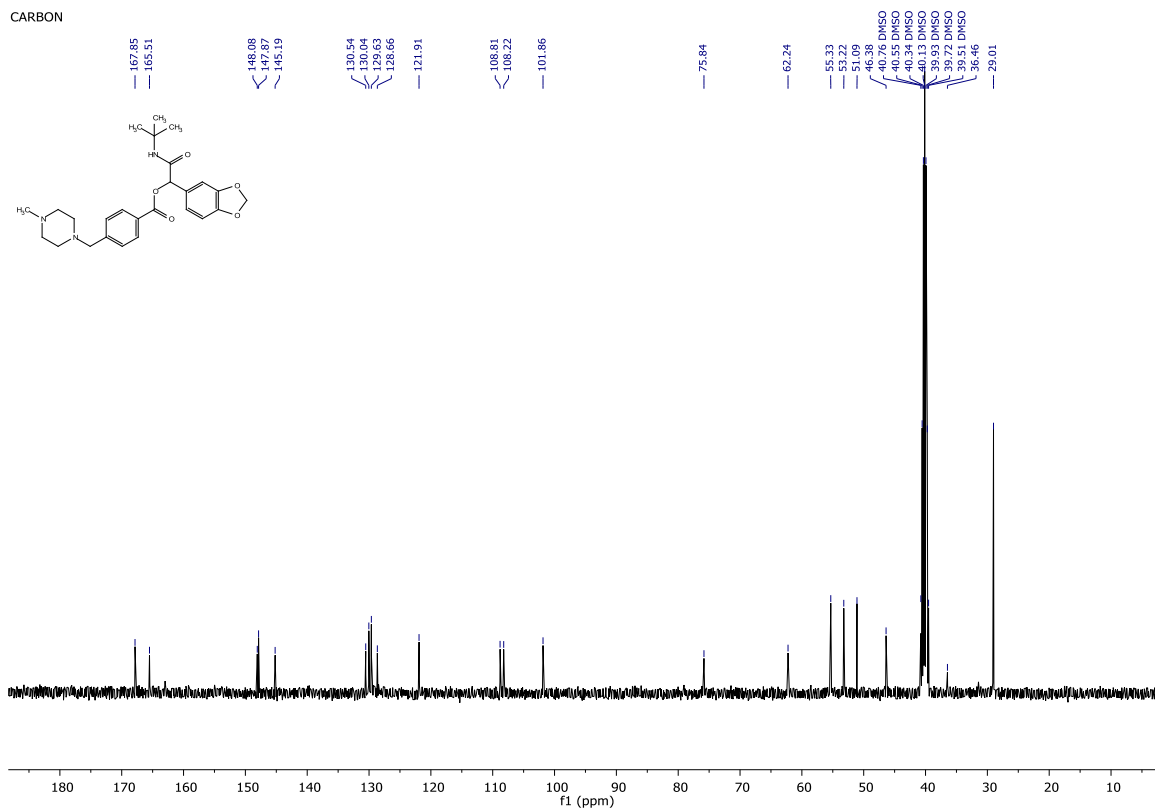


Figure 46. 100 MHz ^{13}C NMR of compound **81b** in DMSO

2015-03-07-KP-chloropyridine-passerini-proton

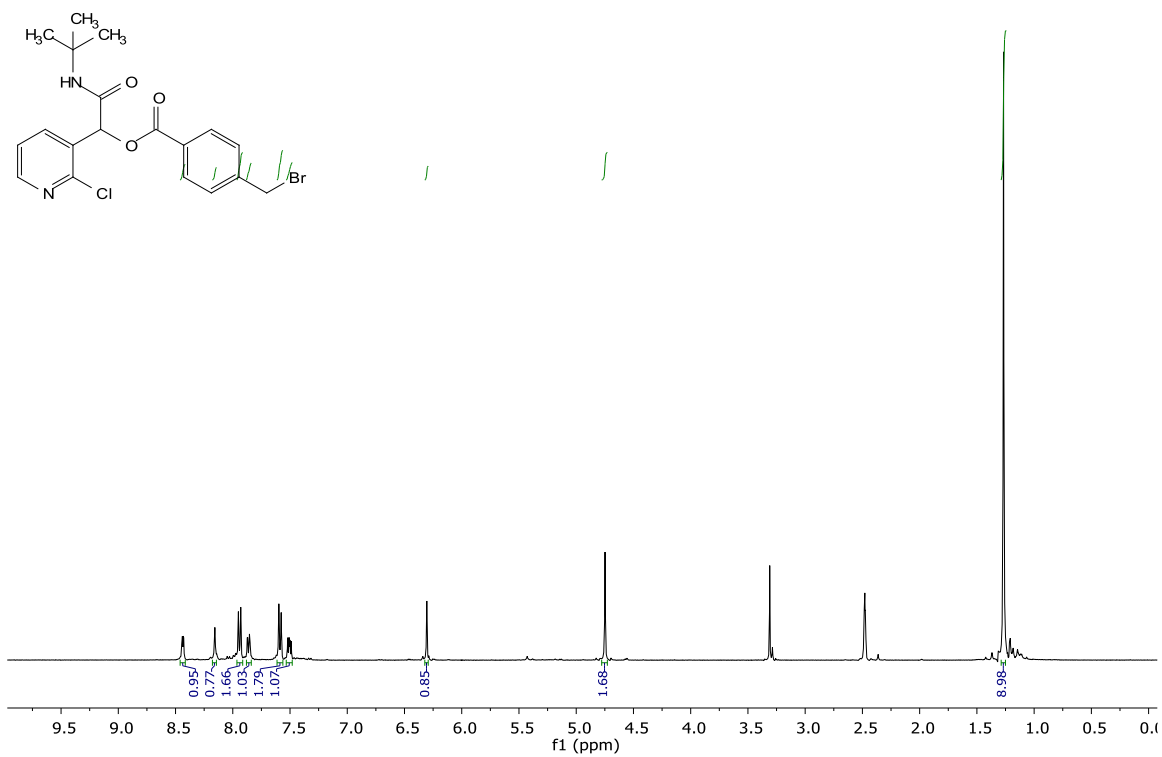


Figure 47. 400 MHz ¹H NMR of compound **83** in DMSO

2015-12-13-Keyur-chloropyridine-PS carbon good

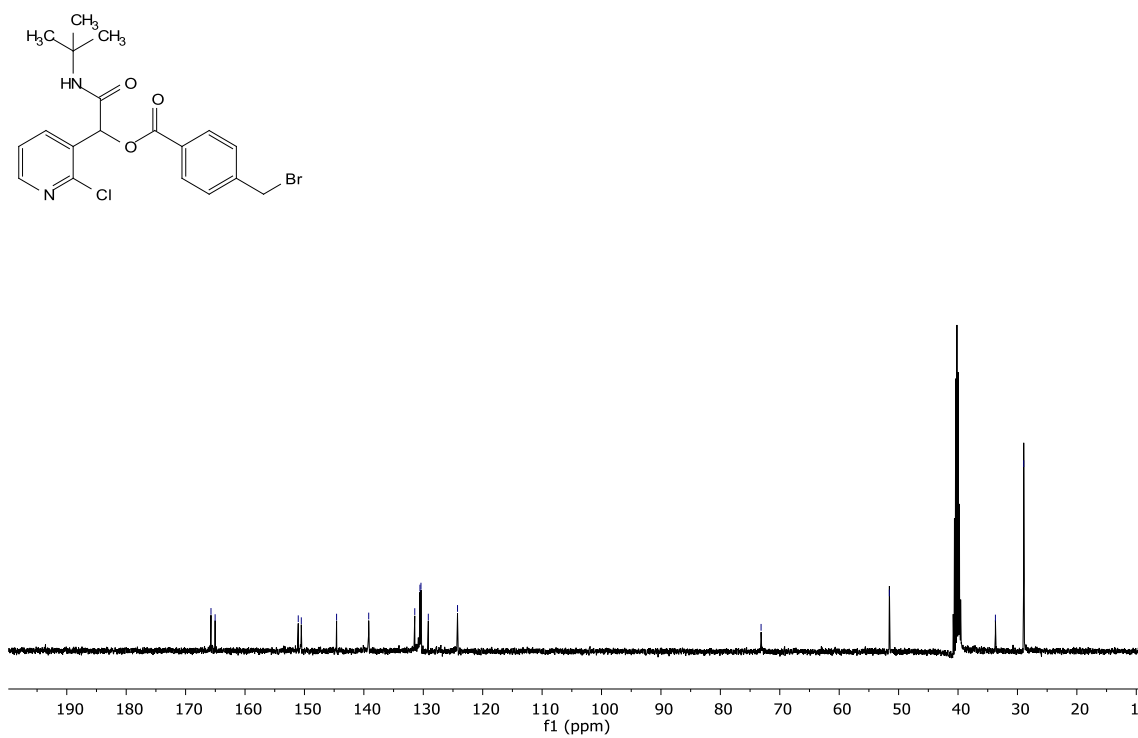


Figure 48. 100 MHz ^{13}C NMR of compound **83** in DMSO

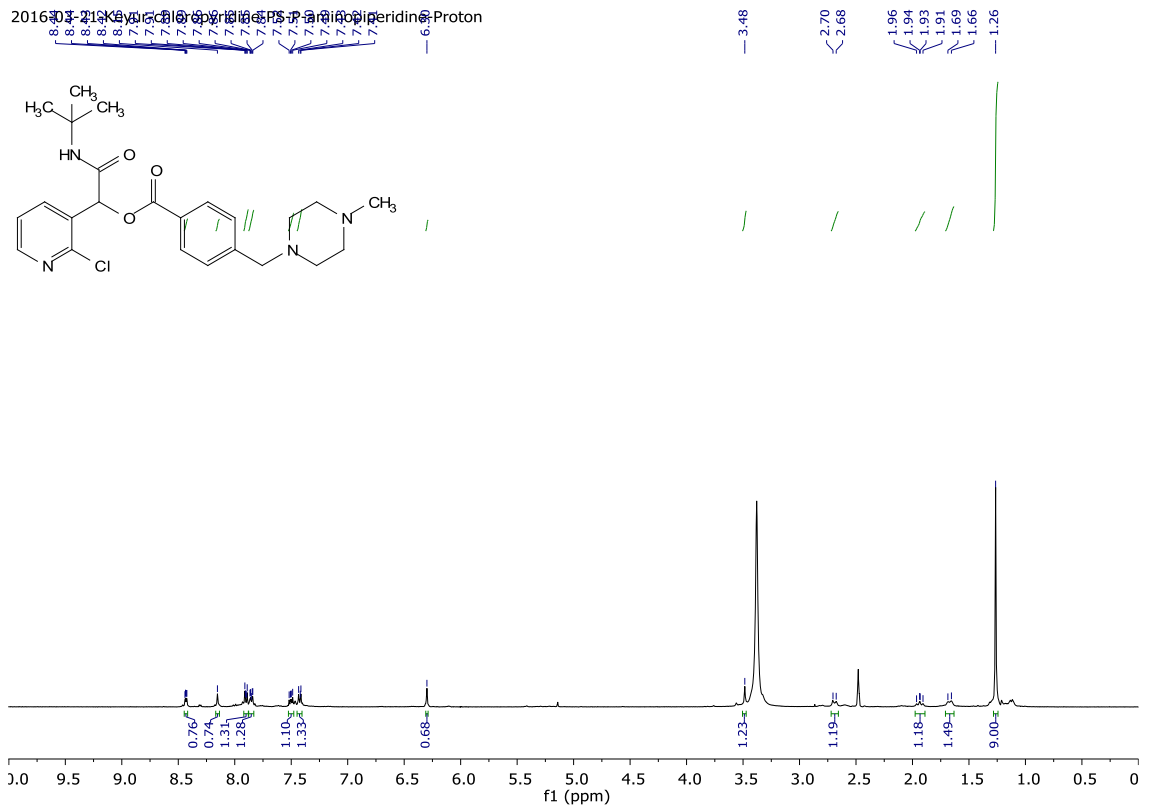


Figure 49. 400 MHz ^1H NMR of compound **84b** in DMSO

2016-03-21-Keyur-chloropyridine-PS-1-Methylpiperazine-Carbon
13C OBSERVE

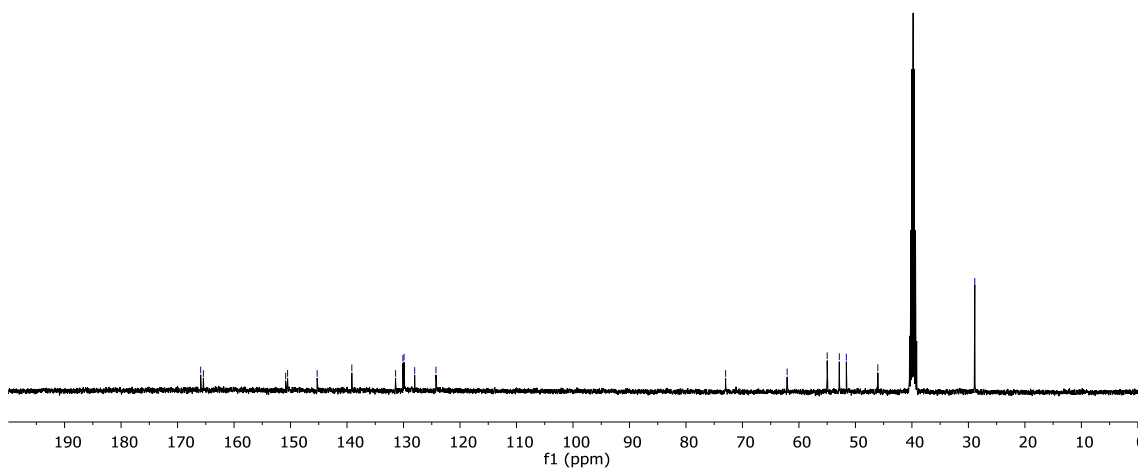
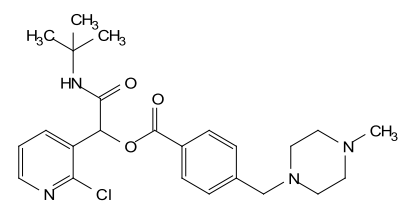


Figure 50. 100 MHz ^{13}C NMR of compound **84b** in DMSO

acqfil

keyur-1,2-dichloro-pyrazol

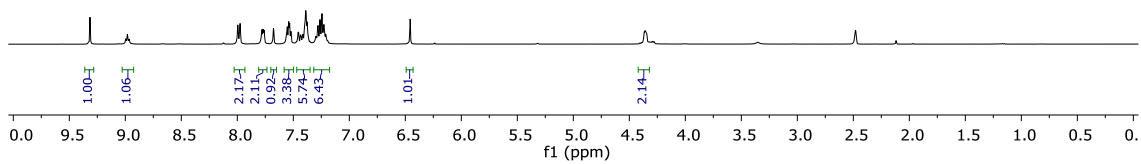
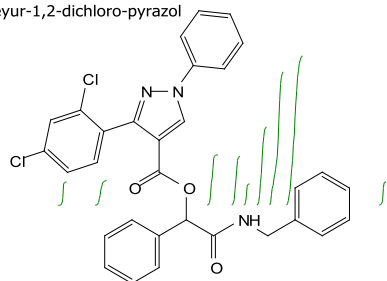


Figure 51. 400 MHz ¹H NMR of compound **95b** in DMSO

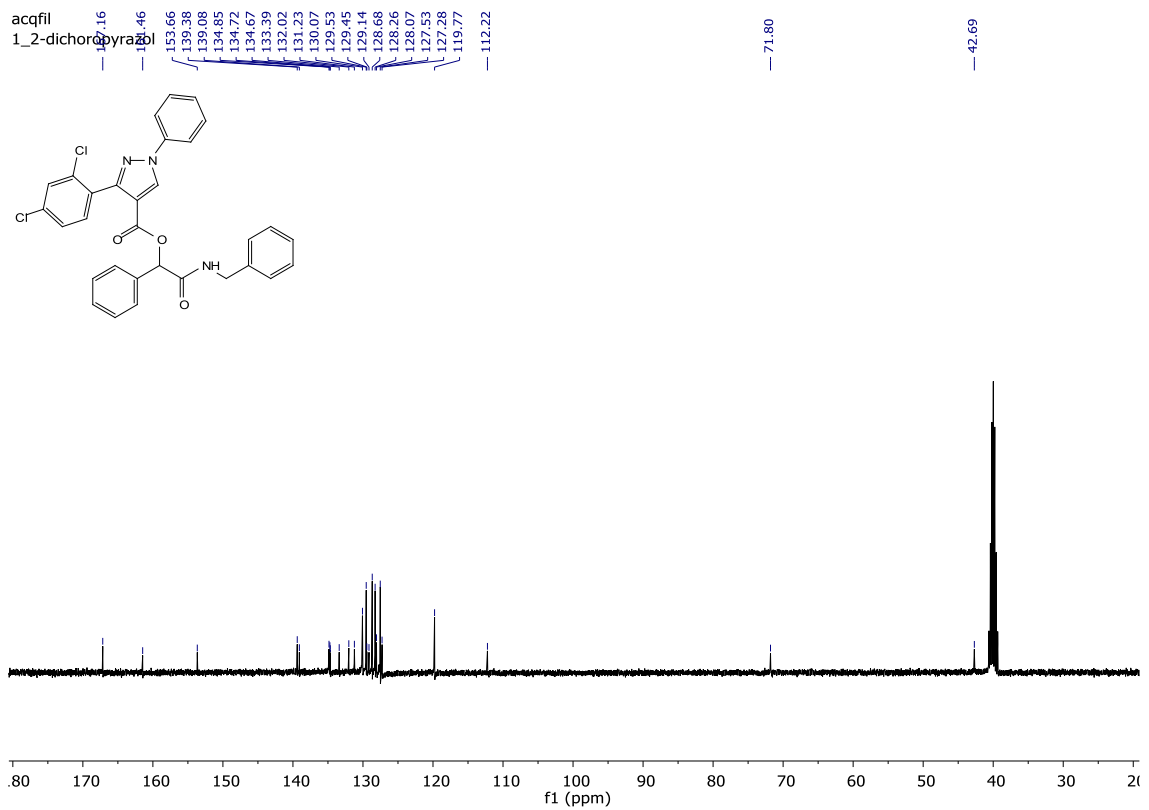


Figure 52. 100 MHz ^{13}C NMR of compound **95b** in DMSO

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