1-22-2021

Synthesis and cytotoxicity of trisubstituted imidazoles

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SYNTHESIS AND CYTOTOXICITY OF TRISUBSTITUTED IMIDAZOLES

by

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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
December 22, 2020

Thesis Chair: Kandalam Ramanujachary, Ph.D.

Dedication

I would like to dedicate this manuscript to my mother and my mentors who inspired and motivated me throughout my life.

Acknowledgments

I would like to express my deepest gratitude to my supervisors Profs. Kandalam Ramanuajchary and Subash Jonnalagadda for their constant encouragement, guidance and support without which this work would not have been possible. I would also like to thank Dr. Suman Pathi and all the colleagues at Rowan University for their kind support through this journey.

Abstract

Agasthya V. Kasibotla
SYNTHESIS AND CYTOTOXICITY OF TRISUBSTITUTED IMIDAZOLES
2017-2018
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Master of Science in Pharmaceutical Sciences

Aza heterocyclic compounds are an important class of organic compounds that play a major role in medicinal chemistry. Majority of the heterocyclic motifs such as imidazoles, triazoles, piperazines etc. act as building blocks for synthesizing active pharmaceutical ingredients. Several pharmaceutical drugs include these motifs due to their varying physicochemical properties, which enable them to exhibit wide range of pharmacological activities ranging from anti-fungal, anti-neoplastic, anti-helmintic, anti-microbial etc. Owing to their electron rich ring system, imidazole and piperazine based motifs have become an attractive target for design and development of novel chemical structures as new drugs. In the current study, we have synthesized a series of 2, 4, 5-trisubstituted imidazole-based compounds containing different pharmacophores using multicomponent coupling reactions such as Baylis-Hillman reaction and Debus-Radziszewski reaction. A preliminary report on the structural activity relationship of the synthetic compounds was also obtained based on an *in vitro* cytotoxicity evaluation against three cancer cell lines.

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Chapter 1

Introduction

Heterocyclic structures are an important motif found in majority of pharmacologically active compounds and natural products. The effectiveness of these ring systems as potent pharmaceuticals relates to their ability to manipulate lipophilicity, hydrogen bonding capacity of molecules and polarity thus improving the pharmacological, pharmacokinetic, and toxicological properties of the drug candidates.[1] Heterocyclic azoles, imidazoles in particular exhibit multitude of biological activities and are accordingly present in a variety of pharmaceutical drugs.

Multicomponent Coupling Reactions

Multi-component coupling reactions are particularly useful in pharmaceutical chemistry and are highly utilized in drug design and development.[1,2] Reactions such as Passerini reaction,[3-7] Ugi reaction,[8] Baylis-Hillman reaction,[9-16] click reaction, [17-20] etc. yield highly functionalized chemical structures and they are very highly employed in medicinal chemistry. For the past several years, our groups have been working on the development of novel small molecules using reactions such as Baylis-Hillman reaction, Passerini reaction, click reaction, aldol condensation, reductive amination, etc. for potential applications in drug discovery.[21-33]

Multicomponent coupling reactions (MCRs) are one pot synthesis reactions where two or more components react to form a final product of which all the atoms from each component contribute to the newly formed product.[34] MCRs are convenient and simple reactions with unique merit over traditional reactions.

Debus-Radziszewski Reaction

Debus-Radziszewski Reaction was first reported by Debus in 1858, fully developed by Radziszewski in 1882, and further modified by Weidenhagen in 1935. The Debus-Radziszewski synthesis is an organic reaction used for the synthesis of 2,4,5-trisubstituted imidazoles from a dicarbonyl, an aldehyde and ammonia in acetic acid (Figure 1). The dicarbonyl component is generally glyoxal, but may also include several 1,2-diketones and ketoaldehydes. The method is used commercially for producing several imidazoles and is an example of multi component reaction.[35]

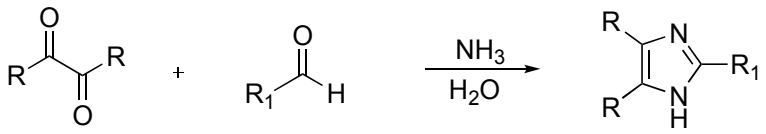


Figure 1. Debus-Radziszewski Reaction.

Baylis-Hillman Reaction

Another MCR that has been used immensely in the synthesis of heterocyclic compounds is the Baylis-Hillman Reaction (Figure 2). The Baylis–Hillman reaction is a carbon-carbon bond forming reaction between the α-position of an activated alkene and an aldehyde. This reaction offers a densely functionalized product (e.g., functionalized allyl alcohol in the case of aldehyde as the electrophile). This coupling of an activated alkene derivative with an aldehyde is catalyzed by a tertiary amine (e.g.: DABCO = 1,4-Diazabicyclo [2.2.2] octane). BH reaction has numerous advantages as a valuable synthetic method. It is an atom-economic coupling of multiple components and the reaction mechanism consists of 3 steps. (a) Michael addition of the base DABCO to an

activated alkene, (b) quenching the Zwitterion adduct with an electrophile, followed by (c) proton transfer and elimination of the catalyst.

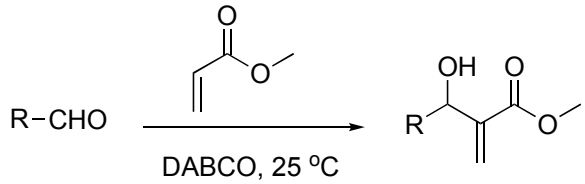


Figure 2. Baylis-Hillman Reaction.

This thesis will detail our efforts on the synthesis of novel azaheterocyclic motifs using these two reactions outlined above as the key steps. We envisaged the synthesis of novel 2,4,5-trisubstituted imidazoles as well as their corresponding quaternary ammonium salts in an effort to increase their efficacy and solubility. We also performed preliminary biological evaluations of the synthesized compounds to determine their cytotoxicity for potential applications in medicinal chemistry.

Chapter 2

Preparation of Azaheterocyclic Compounds

Owing to the importance of 2,4,5-trisubstituted imidazoles, as well as the diverse functionalization possibilities that are possible using Baylis-Hillman and Debus-Radziszewski reactions, we undertook a project involving the development of trisubstituted imidazoles as anticancer agents using these reactions as the key steps. We also planned to incorporate the groups such as *N*-methylpiperazine, *N,N,N'*-trimethylethylenediamine, morpholine etc. on this template to enhance water solubility. The Baylis-Hillman motif was chosen to enhance the efficacy as this template is a potent Michael acceptor and could potentially bind to a variety of biological targets (Figure 3).

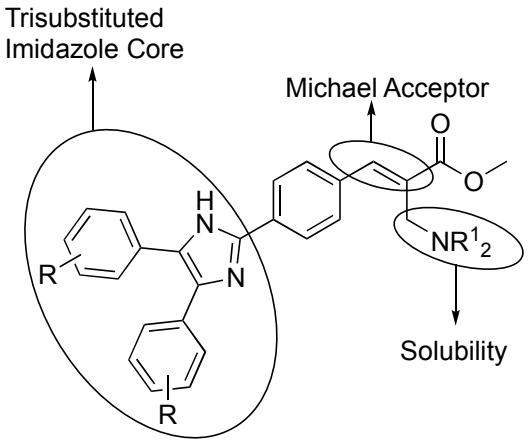


Figure 3. Proposed Conjugates via BH and Debus-Radziszewski reactions.

Synthesis of *p*-imidazolyl α-aminomethylcinnamates

In order to synthesize the corresponding final compounds, two different kinds of 1,2 diketone moieties were utilized. Initial reactions were optimized using benzil as the starting material. Once the conditions were optimized using benzil, we synthesized the corresponding para-fluoro substituted benzil derivative using a literature protocol. We chose the fluoro derivative because of the ubiquitous nature of fluorine and its vast applications in medicinal chemistry.

The 1,2-diketone required for the Debus-Radziszewski reaction was synthesized from its corresponding aldehyde by reacting it with KCN in ethanol to get an α-hydroxyketone which was further oxidized with copper (II) acetate, ammonium nitrate and 80% aqueous acetic acid to get the 1,2-diketone intermediate (Figure 4).

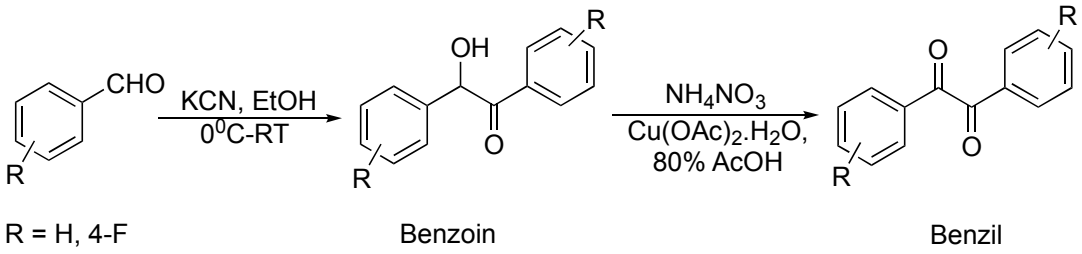


Figure 4. Preparation of Fluoro substituted Benzil.

During initial efforts, a variety of reaction conditions were screened in order to optimize the reaction conditions. In the first series of experiments, using the Debus-Radziszewski protocol, benzil (1,2-diketone) was coupled with terephthalaldehyde using sodium hydrogen phosphate and ammonium acetate under solvent free conditions to form

a trisubstituted imidazole aldehyde (Figure 5).

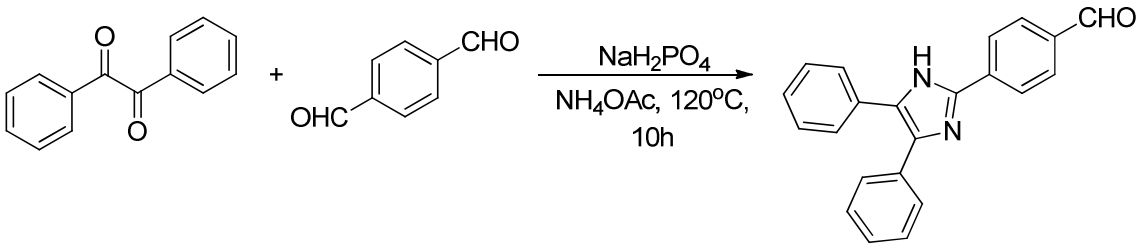


Figure 5. Synthesis of trisubstituted imidazole aldehyde.

The aldehyde adduct was then coupled with methyl acrylate using DABCO as catalyst in acetonitrile using the Baylis Hillman protocol. Acetonitrile was chosen as the solvent as it has been reported to accelerate the Baylis Hillman reaction, however, much to our dismay, the reaction did not materialize in the formation of the product (Figure 6). We attempted several other conditions including heating the reaction, changing solvents, etc. and none of our efforts were successful and we recovered the starting material in all of these conditions.

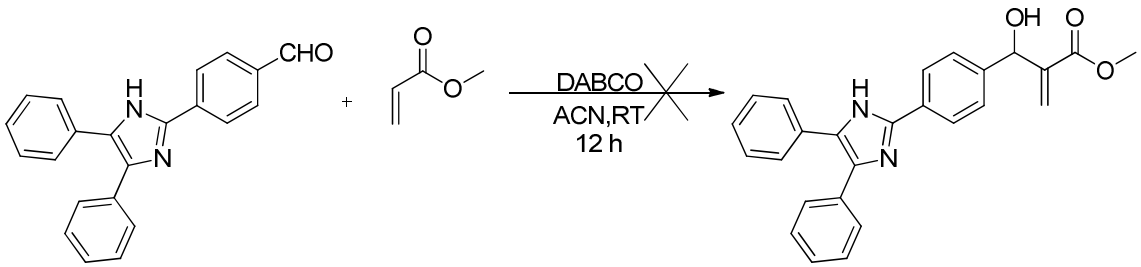


Figure 6. Attempted BH Reaction with trisubstituted imidazole aldehyde.

Following the unsuccessful efforts to synthesize the 2,4,5-trisubstituted imidazole analogs using the above figures 5 & 6, we envisioned the synthesis of these compounds by switching the order of Baylis-Hillman and Debus-Radziszewski reactions. Accordingly, terephthalaldehyde was initially coupled with methyl acrylate using DABCO as catalyst in acetonitrile (Figure 7). The coupling of the acrylate and aldehyde resulted in the formation of methyl 2-((4-formylphenyl) (hydroxy)methyl) acrylate and dimethyl 2,2'-(1,4-phenylenebis(hydroxymethylene))diacrylate as main products. In spite of our best efforts to optimize this reaction to form one adduct, we were unable to form one compound and a mixture of two products was invariably obtained (Figure 7).

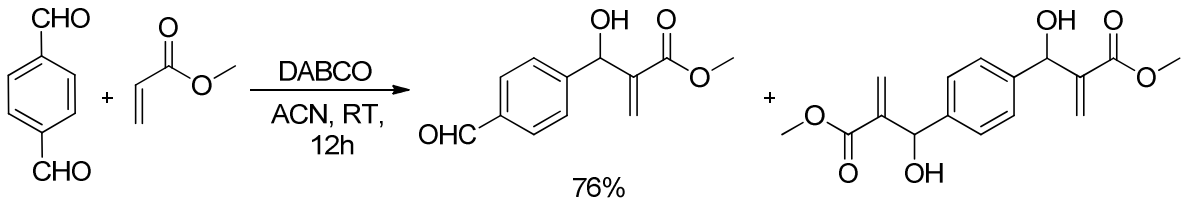


Figure 7. Baylis-Hillman reaction of terephthalaldehyde.

The mono-adduct, methyl 2-((4-formylphenyl) (hydroxy)methyl) acrylate **3** was purified using column chromatography and was used for further reactions. In an attempt to synthesize the target compounds, the alcohol group on BH adduct was acetylated by acetic anhydride and DMAP using methylene chloride as solvent. The obtained compound **4** was then reacted with corresponding secondary amine using K_2CO_3 as

catalyst in DMF to get the intermediate *p*-formyl α-aminomethylcinnamate **5** (Figure 8).

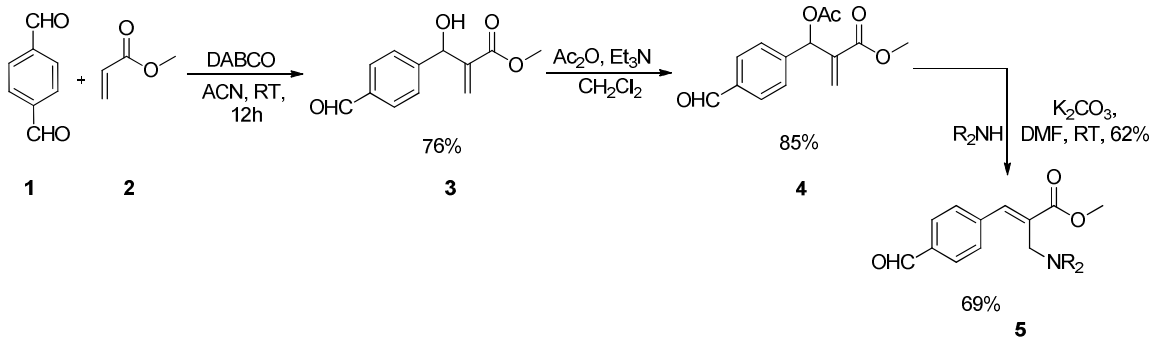


Figure 8. Synthesis of *p*-formyl α-aminomethylcinnamate.

The *p*-formyl α-aminomethylcinnamate **5** was coupled with benzil **6** using the Debus-Radziszewski protocol under two different conditions to obtain the final target trisubstituted imidazole product **9**. It was observed that the reaction of benzil and aldehyde **5** with ammonium acetate in the presence of acetic acid afforded better yields when compared to the reaction using sodium dihydrogen phosphate instead of acetic acid (Figure 9).

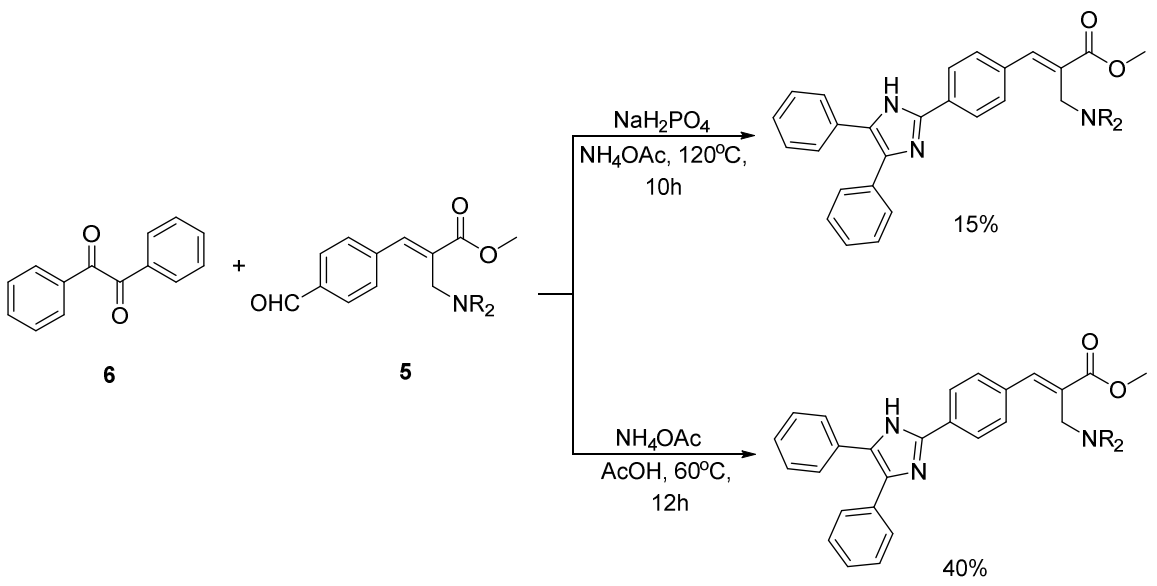


Figure 9. Preparation of *p*-imidazolyl α-aminomethylcinnamates.

In spite of our best efforts, we were not able to increase the yield of these reactions any further. Accordingly, a second strategy was developed to further increase the yield of the final products. This involved the BH reaction of terephthalaldehyde and coupling the adduct **3** with 1,2-diketone to form trisubstituted imidazolyl-Baylis Hillman conjugates **7a-b**. The conjugate was then acetylated and reacted with different secondary amines in the presence of K_2CO_3 and DMF to yield the final products **9a-p**. The overall reaction scheme is presented below (Figure 10). We employed amines such as imidazole, triazole, nitroimidazole, nitromethylimidazole, morpholine, pyrazine, and trimethylethylene diamine and the compounds prepared in this methodology are shown in Figures 11-12.

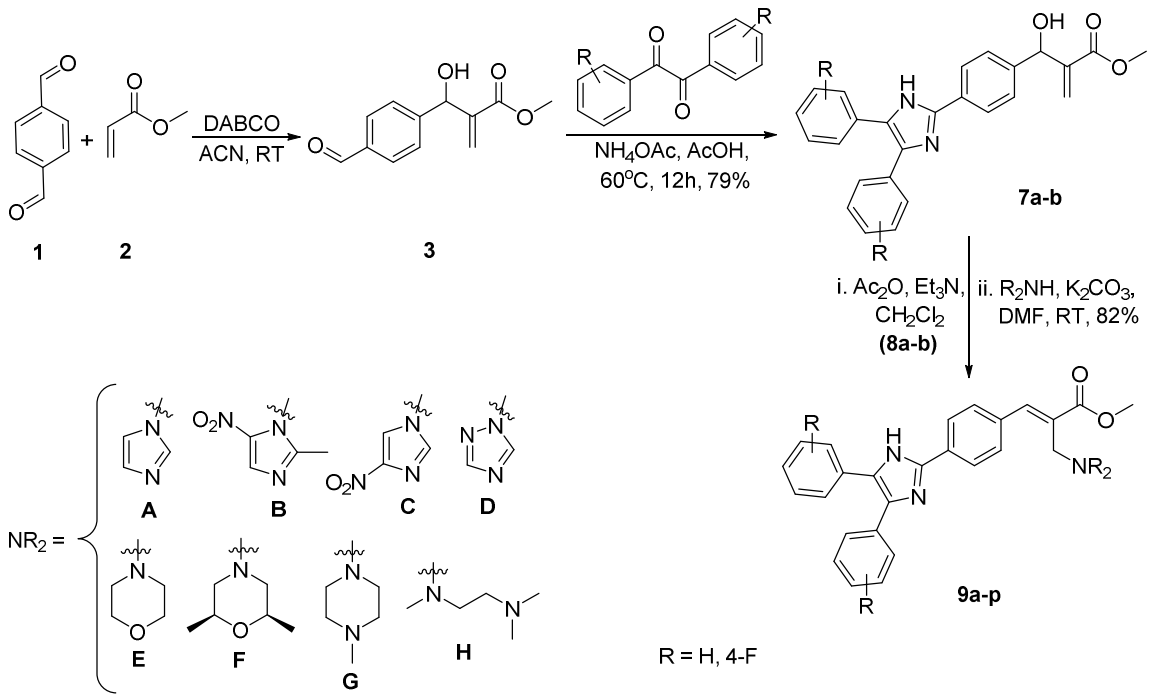


Figure 10. Optimized synthesis of *p*-imidazolyl α-aminomethylcinnamates.

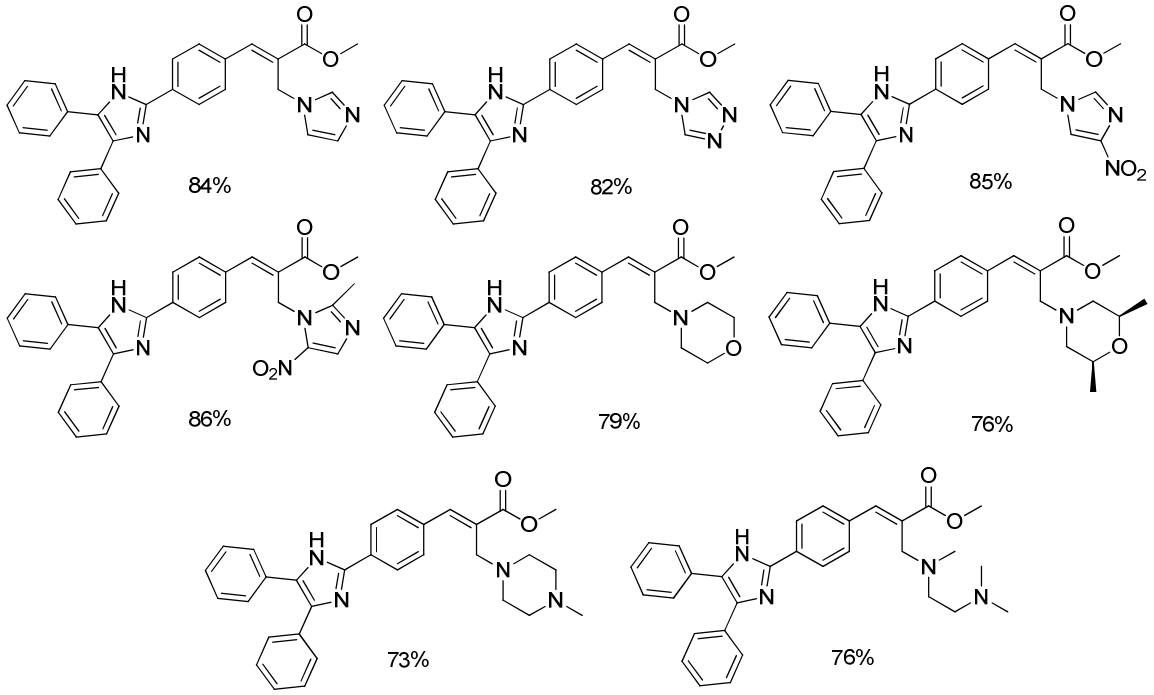


Figure 11. *p*-imidazolyl α-aminomethylcinnamates.

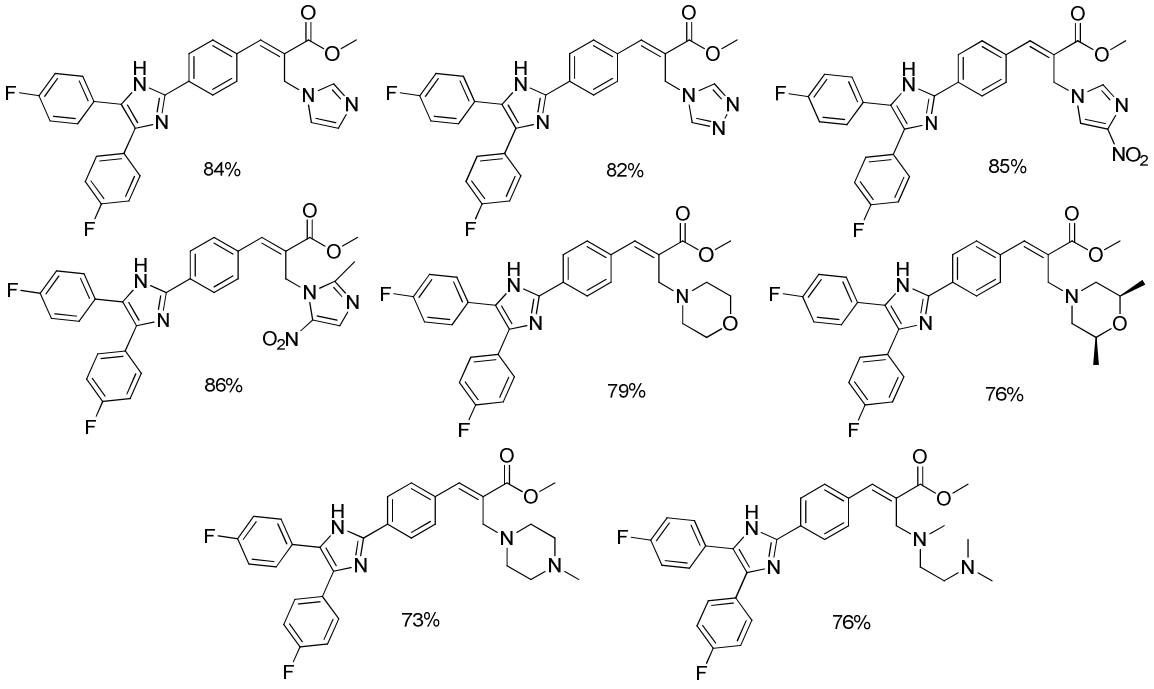


Figure 12. Fluoro analogs of *p*-imidazolyl α-aminomethylcinnamates.

Synthesis of Quaternary Ammonium Salts

Considering the vast applications of quaternary ammonium salts in medicinal chemistry, we synthesized quaternary salts of select few target imidazoles by reacting them with methyl iodide, allyl bromide and methyl 2-(bromomethyl)acrylate. Quaternization was achieved by reacting the appropriate tertiary amine with the corresponding alkyl halide at room temperature (Figure 13). The reaction was successful under multiple solvent systems; however, the best results were obtained with tetrahydrofuran as the solvent. The salts synthesized in this protocol are shown in Figure 14 **(10a-l)**.

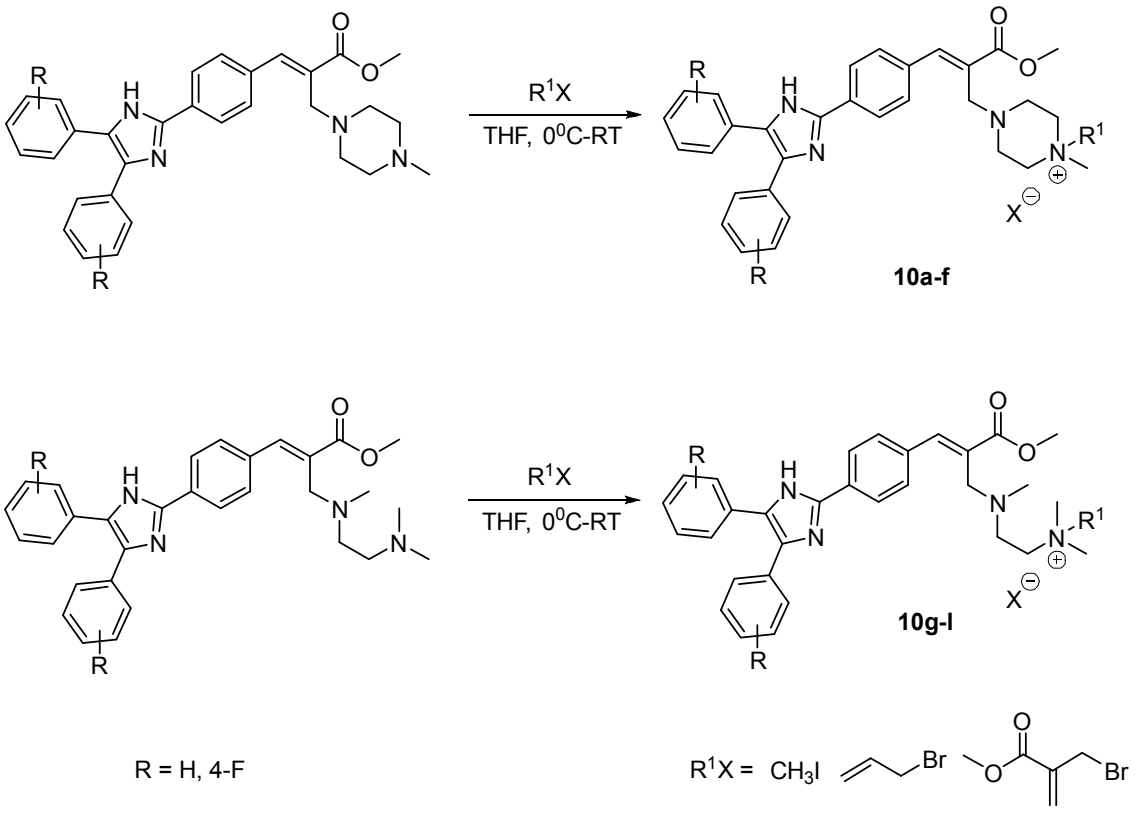


Figure 13. Preparation of quaternary ammonium salts.

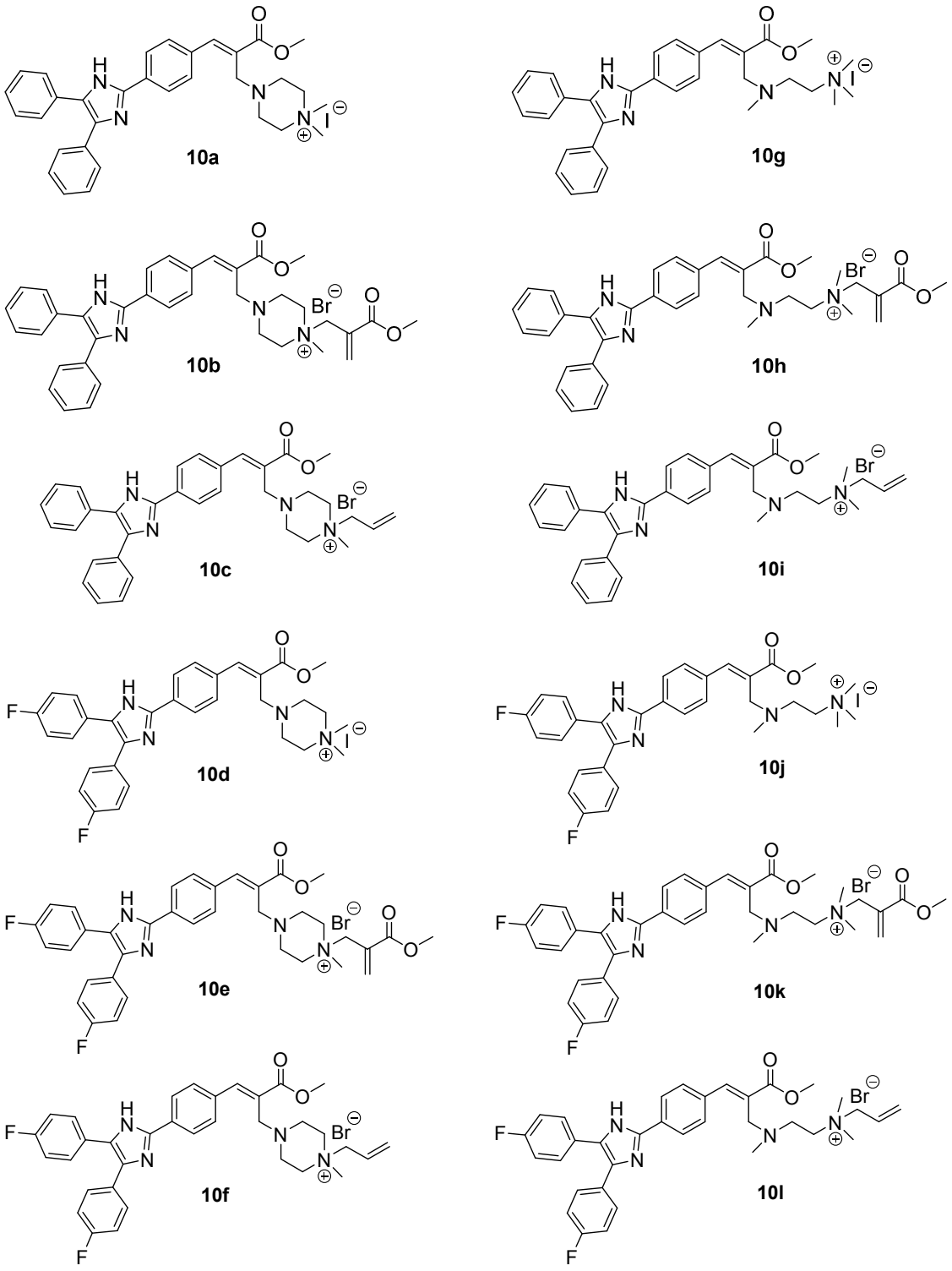


Figure 14. Quaternary ammonium salts.

In order to identify the optimal conditions for the ammonium salt formation, different solvents were used and the results are shown in Table 1. The reactions were carried out in three different solvents acetonitrile, ether, and tetrahydrofuran at different reaction time intervals. All the reactions were carried out at room temperature. When the reaction was carried out in the presence of acetonitrile for 6 hours and 18 hours, the percentage yield of the product was ~10% and ~20% respectively. Similar result was found when the reaction was carried out in the presence of ether for 7 hours, however an increase in the percentage yield of the product was observed when the reaction time was increased to 18 hours. The percentage yield was found to be doubled (40%) at 18 hours with ether. The best yields of the product were obtained when the reaction was carried out in the presence of tetrahydrofuran. The product yield was found to be 50% when the reaction was carried out for 5 hours and 95% after stirring for 16 hours. Based on the optimization, all the remaining salts were synthesized using tetrahydrofuran as solvent and the reaction was carried out for 16 hours. The product was precipitated out and was filtered. All the quaternary salts were further purified by triturating with diethyl ether and were analyzed using NMR and mass spectrometry.

Table 1

Effect of the solvent on alkylation of tertiary amines with alkyl halides.

#	Alkyl Halide	Solvent	Time (h)	Conditions	Conversion
1	CH_3I	CH_3CN	6	RT	~ 10%
2	CH_3I	CH_3CN	18	RT	~ 20%
3	CH_3I	Ether	7	RT	~20%
4	CH_3I	Ether	18	RT	~ 40%
5	CH_3I	THF	5	RT	~ 50%
6	CH_3I	THF	16	RT	~ 95%

Biological Evaluation

The synthesized compounds 2,4,5 trisubstituted imidazoles **9a-p** and their quaternary salts **10a-l** were screened for in vitro cytotoxicity against skin cancer (SK-MEL-5), breast cancer (MCF-7) and triple negative breast cancer (MDA-MB-231) cell lines. A protocol of 48 h continuous drug exposure was used, and a MTT cell proliferation assay was employed to estimate cell viability. The cell lines were grown in their respective media containing 10% fetal bovine serum and were seeded into 96-well microtiter plates in 200 µL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 ºC, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs. Aliquots of 2 µL of the test compounds were added to the wells already containing 198 µL of cells, resulting in the required final concentrations of test compounds. For each compound, four concentrations (2.5, 5, 10 and 20 µM) were evaluated, and each was done in triplicate wells. Plates were incubated further for 48 h, and the experiment was terminated by the addition of 10 µL of 5% MTT and incubated further for 60 min at 37 ºC. Later, the plates1were washed and air-dried and bound stain was subsequently dissolved using 100 µL of DMSO. The absorbance was monitored on a multimode plate reader at a wavelength of 570 nm. Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells.

The IC_{50} (µM) values for the 2,4,5 trisubstituted imidazoles are shown in Tables 2-3 and IC_{50} (µM) values of the quaternary salts are shown in tables 4-6.

Table 2

Cytotoxicity Evaluation (IC_{50}) of Benzil Derivatives.

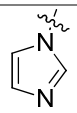
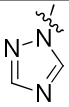
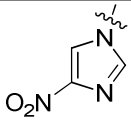
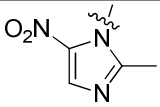
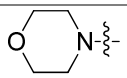
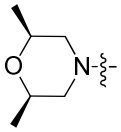
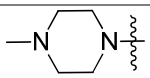
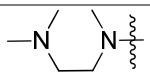
#	NR_2	SK-MEL-5 (μM)	MCF-7 (μM)	MDA-MB-231 (μM)
1		>20	17.99	19.78
2		>20	19.84	>20
3		>20	16.50	19.45
4		>20	9.66	5.86
5		7.97	9.07	5.21
6		13.50	>20	>20
7		12.36	9.44	**5.68**
8		7.04	**3.02**	**2.66**

Table 3

Cytotoxicity Evaluation (IC_{50}) of Fluorobenzil Derivatives.

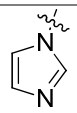
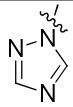
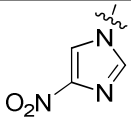
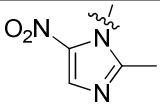
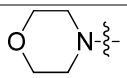
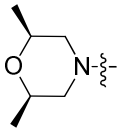
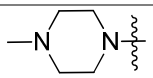
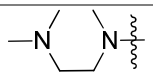
#	NR_2	SK-MEL-5 (μM)	MCF-7 (μM)	MDA-MB-231 (μM)
1		>20	19.00	19.76
2		>20	>20	>20
3		>20	>20	>20
4		>20	>20	>20
5		19.43	>20	>20
6		>20	6.50	2.99
7		5.80	**2.74**	**2.17**
8		6.41	**2.46**	**2.34**

Table 4

Cytotoxicity Evaluation (IC_{50}) of Benzil-piperazine Salts.

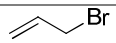
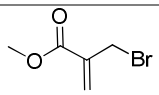
#	NR_2	SK-MEL-5 (μM)	MCF-7 (μM)	MDA-MB-231 (μM)
1	CH_3I	>20	9.40	8.41
2		>20	9.58	14.30
3		13.50	6.94	6.16

Table 5

Cytotoxicity Evaluation (IC_{50}) of Fluorobenzil-piperazine Salts.

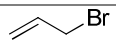
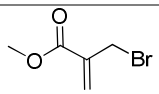
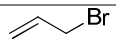
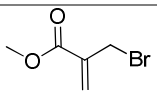
#	NR_2	SK-MEL-5 (μM)	MCF-7 (μM)	MDA-MB-231 (μM)
1	CH_3I	>20	15.58	15.09
2		>20	>20	>20
3		7.13	4.83	3.45

Table 6

Cytotoxicity Evaluation (IC_{50}) of Benzil-trimethylethylenediamine Salts.

#	NR_2	SK-MEL-5 (μM)	MCF-7 (μM)	MDA-MB-231 (μM)
1	CH_3I	>20	>20	>20
2		>20	>20	>20
3		2.67	**1.43**	**0.54**

Based on the IC_{50} values for the various derivatives tested, we were able to identify some lead derivatives, for further development as potential anticancer agents (Figure 15).

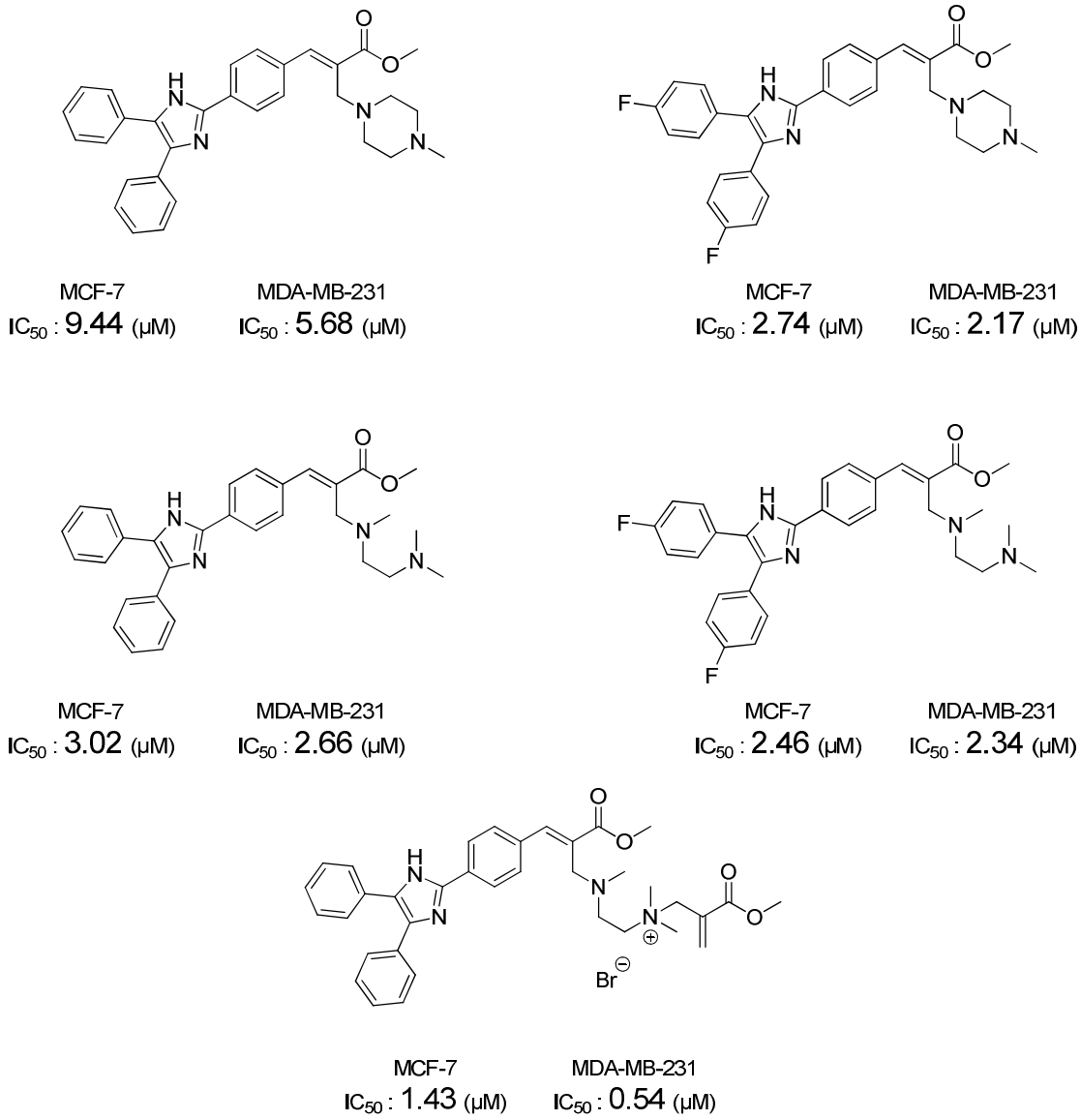


Figure 15. Lead Derivatives

Conclusions

In conclusion, we have been able to optimize the synthesis of trisubstituted imidazoles employing Baylis-Hillman and Debus-Radziszewski reactions as the key steps. We were also able to obtain quaternary salts of these trisubstituted imidazoles using different alkyl halides. The synthesized compounds were evaluated for

their biological activity through cell viability assay. All the synthesized trisubstituted imidazole derivatives as well as some of the intermediates were evaluated for their general cytotoxicity against human skin (SK-MEL-5), and human breast cancer (MCF-7 & MDA-MB-231) cell lines. The preliminary biological evaluation of these molecules has shown some promise and we have been able to identify few leads for future development as anti-cancer agents.

Chapter 3

Experimental Procedures

Materials and Methods

All the reactants were of reagent grade, 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. All operations were carried out under an inert atmosphere of nitrogen. Glassware for all reactions was oven dried at 125 °C and cooled under nitrogen prior to use. Liquid reagents and solvents were introduced by oven-dried syringes or cannulas through septa sealed flasks under a nitrogen atmosphere.

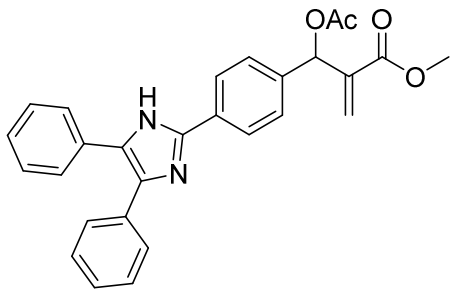
Instrumentation

Nuclear Magnetic Spectroscopy (NMR) spectra were produced using a Varian 400 MHz spectrophotometer. The instrument was maintained at 25° C operating at 400 MHz for ^{1}H NMR, and 101 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.

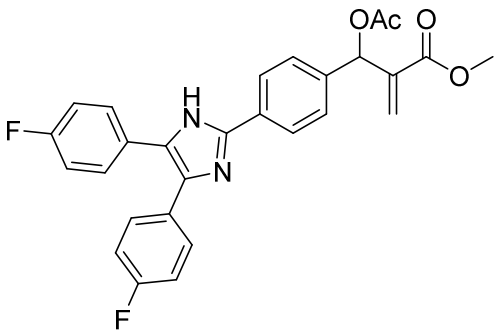
Procedures

General procedure for Debus-Radziszewski Reaction. To a stirred solution of methyl 2-((4-formylphenyl)(hydroxy)methyl)acrylate (1 mmol) in acetic acid (10 mL), was added substituted benzil (0.8 mmol), followed by addition of NH_4OAc (25 mmol) and refluxed for 10 h. Upon completion (TLC), then the pH was adjusted to 8 with saturated $NaHCO_3$ to affect precipitation. The resulting solid was filtered and dried under vacuum to obtain pure methyl 2-((4-(4,5-diaryl-1*H*-imidazol-2-yl) phenyl) (hydroxy) methyl) acrylate in good yields. The obtained compound (1 mmol) was dissolved in

dichloromethane (10 mL) at 0 °C, was added acetic anhydride (1.5 mmol), followed by addition of triethylamine (1.5 mmol) and DMAP (0.1 mmol). Upon completion (monitored by TLC), diluted with water and extracted with ethyl acetate (2 X 15 mL), the combined extracts were washed saturated NH_4Cl, brine and dried over anhydrous Na_2SO_4. Concentrated the organic layer under vacuum and purified by silica gel column chromatography (hexanes: ethyl acetate) to obtain pure 2-(acetoxy(4-(4,5-diaryl-1*H*-imidazol-2-yl)phenyl)methyl)acrylate (8a) as solids in 73-79% yield (over two steps). Same procedure was followed for the synthesis of methyl 2-(acetoxy(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)methyl)acrylate (8b).

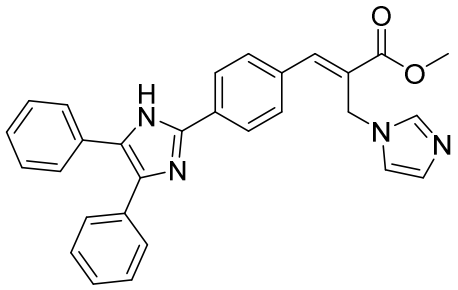


Methyl 2-(acetoxy(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)methyl)acrylate (8a): Pale yellow solid; mp: °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 2H), 7.53 – 7.37 (m, 4), 7.31 (d, J = 8.2 Hz, 2H), 7.28 – 7.16 (m, 6H), 6.66 (s, 1H), 6.38 (s, 1H), 5.83 (s, 1H), 3.64 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 165.5, 145.8, 139.2, 137.7, 130.2, 128.4, 127.9, 127.3, 126.4, 125.6, 72.9, 52.1, 21.0;

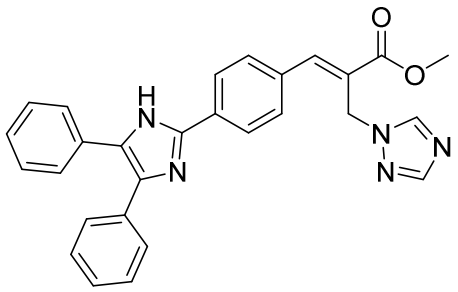


Methyl 2-(acetoxy(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl) methyl)acrylate (8b): Yield: 81%; pale yellow solid; mp: °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, J = 8.0 Hz, 2H), 7.53 – 7.37 (m, 4), 7.31 (d, J = 8.2 Hz, 2H), 7.28 – 7.16 (m, 6H), 6.66 (s, 1H), 6.38 (s, 1H), 5.83 (s, 1H), 3.64 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 165.5, 145.8, 139.2, 137.7, 130.2, 128.4, 127.9, 127.3, 126.4, 125.6, 72.9, 52.1, 21.0;

General procedure for nucleophilic substitution. To a stirred solution of methyl 2-(acetoxy(4-(4,5-diaryl-1*H*-imidazol-2-yl)phenyl)methyl)acrylate (1 mmol), was added appropriate secondary amine (1.2 mmol), followed by addition of K_2CO_3 (1.5 mmol) at room temperature, and stirred for 10-12 h. Upon completion via thin layer chromatography, diluted with cold water to affect precipitation, filtered off solid and dried under vacuum. Then purified by triturating with diethyl ether to obtain pure cinnamate derivatives.

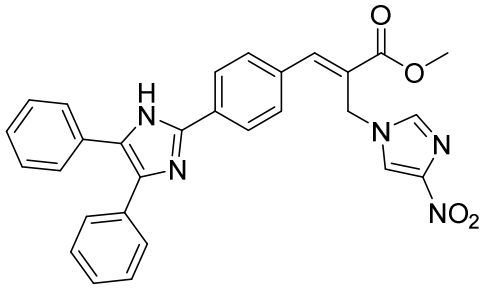


Methyl (E)-2-((1H-imidazol-1-yl)methyl)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)acrylate (9a): Yield: 84%; pale yellow solid; mp: 223 – 225 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.14 (d, J = 7.6 Hz, 2H), 7.96 (s, 1H), 7.70 – 7.33 (m, 10H), 7.34 – 7.15 (m, 3H), 7.02 (s, 1H), 6.87 (s, 1H), 5.05 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.5, 145.3, 143.9, 138.3, 135.6, 133.8, 131.9, 131.5, 130.7, 129.6, 129.4, 129.1, 128.9, 128.6, 127.8, 127.3, 127.2, 126.1, 53.1, 43.3. HRMS (ESI): *m/z*, calcd. for $C_{29}H_{25}N_4O_2$ $[M+H]^+$ 461.1972, found 461.1961.

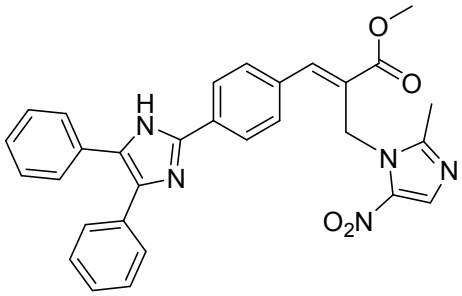


Methyl (E)-2-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl) acrylate (9b): Yield: 82%; yellow solid; mp: 109 – 111 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.80 (s, 1H), 8.58 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.99 (d, J = 7.7 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.1 Hz, 2H), 7.38 (t, J = 6.4 Hz, 1H), 7.29 (t, J = 7.2 Hz, 2H), 7.22 (d, J = 6.8 Hz, 1H), 5.23 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.6, 156.7,

149.9, 148.6, 142.8, 140.2, 138.4, 136.6, 136.1, 135.4, 134.0, 133.9, 133.6, 133.4, 133.1, 132.3, 131.8, 130.6, 130.5, 57.4, 50.8; HRMS (ESI): *m/z*, calcd. for $C_{28}H_{24}N_5O_2$ $[M+H]^+$ 461.1925, found 461.1901.

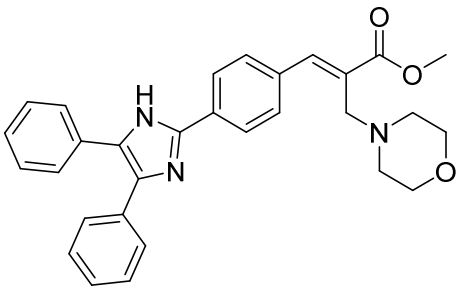


Methyl (E)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-((4-nitro-1H-imidazol-1-yl)methyl) acrylate (9c): Yield: 85%; yellow solid; mp: 235 – 237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.83 (s, 1H), 8.27 (s, 1H), 8.15 (d, J = 8.0 Hz, 2H), 8.03 (s, 1H), 7.84 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.56 – 7.24 (m, 10H), 5.20 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.1, 147.6, 145.3, 145.2, 137.9, 133.5, 132.0, 130.9, 129.1, 128.5, 128.0, 126.1, 125.4, 121.8, 53.1, 44.9; HRMS (ESI): *m/z*, calcd. for $C_{29}H_{23}N_5NaO_4$ $[M+Na]^+$ 528.1642, found 528.1610.

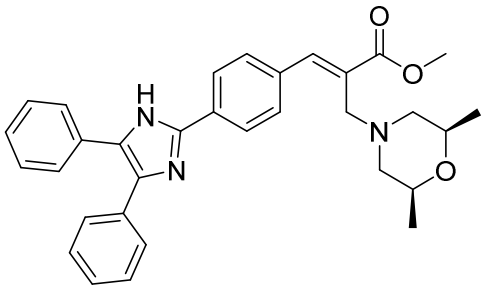


Methyl (E)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylate (9d): Yield: 86%; yellow solid; mp: 258 – 260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.83 (s, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.06 (s, 1H),

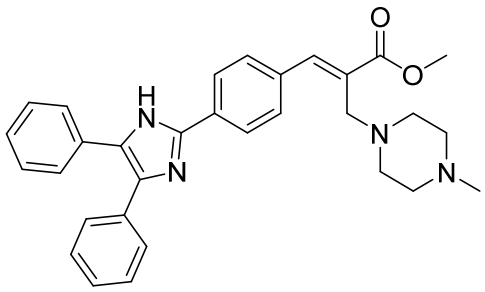
8.03 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.1 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.21 7.24 – 7.17(m, 1H), 5.11 (s, 2H), 3.72 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.9, 146.1, 145.9, 145.3, 144.7, 138.3, 135.5, 133.6, 131.9, 131.4, 130.7, 129.6, 129.4, 129.1, 128.9, 128.7, 127.8, 127.4, 126.0, 125.8, 122.1, 53.1, 43.8, 13.4. HRMS (ESI): *m/z*, calcd. for $C_{30}H_{25}N_5NaO_4$ $[M+Na]^+$ 542.1799, found 528.1771.



Methyl (E)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-(morpholinomethyl)acrylate (9e): Yield: 79%; pale yellow solid; mp: 210 – 212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.54 (d, J = 7.3 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 3.75 (s, 3H), 3.56 (m, 4H), 3.32 (s, 2H), 2.40 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.8, 145.6, 143.1, 138.3, 135.7, 135.1, 131.8, 131.6, 131.5, 129.4, 129.3, 129.1, 129.1, 128.9, 128.5, 127.8, 127.3, 125.7, 66.9, 54.2, 53.6, 52.8. HRMS (ESI): *m/z*, calcd. for $C_{30}H_{30}N_3O_3$ $[M+H]^+$ 480.2282, found 480.2267.

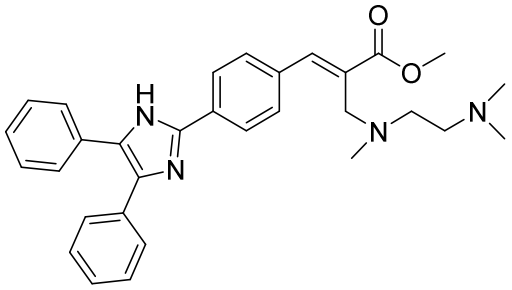


Methyl (E)-2-(((2S,6R)-2,6-dimethylmorpholino) methyl)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)acrylate (9f): Yield: 76%; pale yellow solid; mp: 168 – 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.89 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 6.4 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.43-7.28 (m, 6H), 3.84 (s, 3H), 3.69-3.60 (m, 2H), 3.34 (s, 2H), 2.68 (d, J = 10.7 Hz, 2H), 1.87 (t, J = 10.8 Hz, 2H), 1.15 (s, 3H), 1.14 (s, 3H); HRMS (ESI): *m/z*, calcd. for $C_{32}H_{34}N_3O_3$ $[M+H]^+$ 508.2595, found 508.2574.

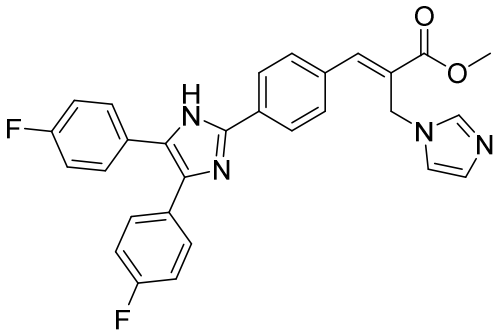


Methyl (E)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-((4-methylpiperazin-1-yl)methyl) acrylate (9g): Yield: 73%; pale yellow solid; mp: 184 – 186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.87 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 7.3 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.41 – 7.27 (m, 6H), 3.82 (s, 3H), 3.36 (s, 2H), 2.63 – 2.31 (m, 8H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 145.6, 143.0, 138.3, 135.7, 135.1, 131.9, 131.5, 130.3, 130.2, 129.7, 129.3,

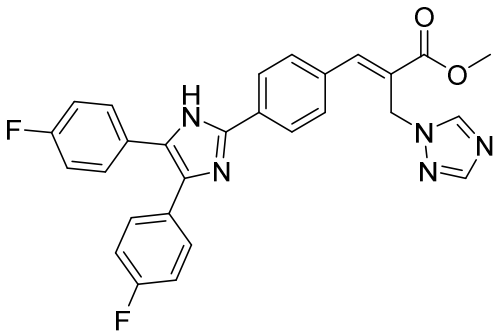
129.1, 129.1, 128.9, 128.9, 127.8, 127.8, 127.3, 125.7, 55.4, 53.7, 52.8, 52.7, 46.3; HRMS (ESI): *m/z*, calcd. for $C_{31}H_{33}N_4O_2$ $[M+H]^+$ 493.2598, found 493.2584.



Methyl (E)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)-3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)acrylate (9h): Yield: 76%; pale yellow solid; mp: 161 – 163 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.75 (s, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.44 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 3.74 (s, 3H), 3.36 (s, 2H), 2.46 – 2.41 (m, 2H), 2.33 (t, J = 6.7 Hz, 2H), 2.12 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.1, 145.6, 142.1, 138.2, 135.7, 135.1, 131.8, 131.6, 131.4, 130.7, 129.4, 129.4, 129.2, 128.9, 128.6, 127.8, 127.3, 125.7, 57.4, 55.6, 53.7, 52.7, 46.1, 42.2;

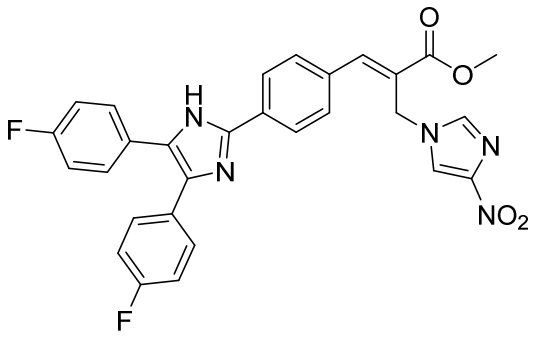


Methyl(E)-2-((1H-imidazol-1-yl)methyl)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl) phenyl)acrylate (9i): Yield: 85%; pale yellow solid; mp: 225 – 227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (s, 1H), 8.12 (d, J = 7.8 Hz, 2H), 7.96 (s, 1H), 7.60 – 7.56 (m, 3H), 7.51 (dd, J = 7.8, 5.7 Hz, 4H), 7.34 – 7.09 (m, 4H), 7.01 (s, 1H), 6.87 (s, 1H), 5.05 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 167.45, 162.14 (d, J = 243.9 Hz), 145.35, 143.87, 137.71, 133.91, 131.82, 130.66, 129.23, 127.16, 126.06, 119.49, 116.15 (d, J = 21.3 Hz), 53.04, 43.27; HRMS (ESI): *m/z*, calcd. for $C_{29}H_{23}F_2N_4O_2$ $[M+H]^+$ 497.1784, found 497.1755.

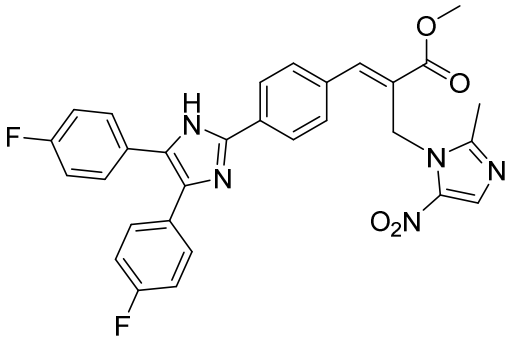


Methyl (E)-2-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl) phenyl)acrylate (9j): Yield: 83%; pale yellow solid; mp: 229 – 231 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.84 (s, 1H), 8.58 (s, 1H), 8.13 (d, J = 7.9 Hz, 2H), 8.00 (s, 1H), 7.97 (s, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.59 – 7.44 (m, 4H), 7.38-7.06 (m,

4H), 5.23 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.10, 163.34 (d, J = 242.5 Hz), 161.23, 152.18, 145.64, 145.39, 144.08, 137.41, 133.97, 131.89, 131.31 (d, J = 7.0 Hz), 130.89, 129.59 (d, J = 7.6 Hz), 128.36 (d, J = 2.6 Hz), 127.83 (d, J = 3.9 Hz), 126.07, 125.93, 116.45 (d, J = 21.3 Hz), 115.86 (d, J = 21.3 Hz), 52.92, 46.25; HRMS (ESI): *m/z*, calcd. for $C_{28}H_{21}F_2N_5NaO_2$ $[M+Na]^+$ 520.1556, found 520.1535.

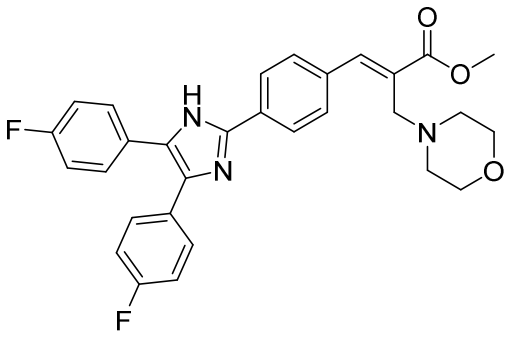


Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-((4-nitro-1H-imidazol-1-yl)methyl)acrylate (9k): Yield: 87%; pale yellow solid; mp: 225 – 227 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.87 (s, 1H), 8.26 (s, 1H), 8.12 (d, J = 8.0 Hz, 2H), 8.03 (s, 1H), 7.84 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.34 – 7.25 (m, 2H), 7.18 – 7.10 (m, 2H), 5.20 (s, 2H), 3.74 (s, 3H);

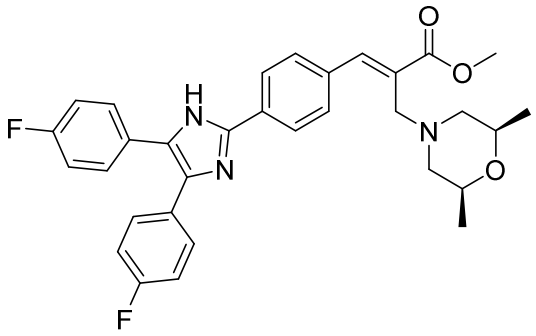


Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-((2-methyl-5-nitro-1H-imidazol-1-yl)methyl)acrylate (9l): Yield: 82%; yellow solid; mp: 254 –

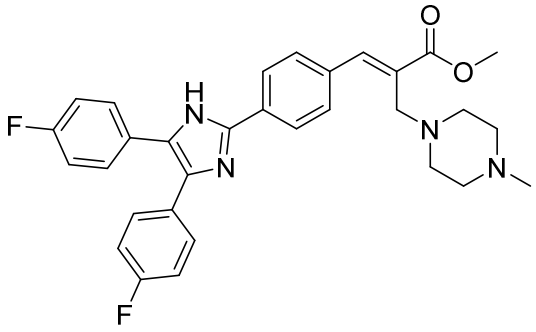
256 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.86 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 8.06 (s, 1H), 8.02 (s, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.57 – 7.47 (m, 4H), 7.30 (t, J = 8.8 Hz, 2H), 7.14 (t, J = 8.7 Hz, 2H), 5.11 (s, 2H), 3.72 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 166.85, 162.34 (d, J = 242.2 Hz), 161.32, 145.99, 145.30, 144.63, 137.46, 133.73, 131.91, 131.34 (d, J = 8.9 Hz), 130.78, 129.57 (d, J = 5.2 Hz), 125.99, 125.85, 122.14, 116.46 (d, J = 17.6 Hz), 115.86 (d, J = 21.3 Hz), 53.05, 43.88, 13.45.



Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(morpholinomethyl) acrylate (9m): Yield: 74%; pale yellow solid; mp: 224 – 226 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.81 (s, 1H), 8.12 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.82 (s, 1H), 7.56 – 7.48 (m, 4H), 7.29 (t, J = 8.7 Hz, 2H), 7.14 (t, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.56 (m, 4H), 3.31 (s, 2H), 2.42-2.36 (m, 4H); HRMS (ESI): *m/z*, calcd. for $C_{30}H_{27}F_2N_3NaO_3$ $[M+Na]^+$ 538.1913, found 538.1894. ^{13}C NMR (101 MHz, DMSO): δ 168.6, 162.14 (d, J = 246.5 Hz), 161.57 (d, J = 248.2 Hz), 145.4, 142.8, 134.9, 131.6, 131.1, 130.96 (d, J = 7.6 Hz), 129.36 (d, J = 8.0 Hz), 129.1, 125.5, 116.14 (d, J = 24.6 Hz), 115.59 (d, J = 24.0 Hz), 66.7, 53.9, 53.3, 52.5;

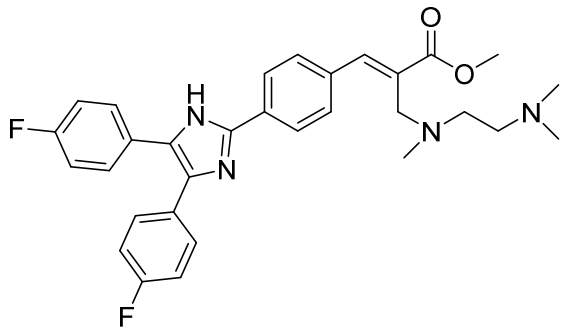


Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(((2S,6R)-2,6-dimethyl morpholino)methyl)acrylate (9n): Yield: 75%; pale yellow solid; mp: 118 – 120 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.80 (s, 1H), 8.11 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.82 (s, 1H), 7.57-7.44 (m, 4H), 7.29 (t, J = 8.5 Hz, 2H), 7.14 (t, J = 8.2 Hz, 2H), 3.74 (s, 3H), 3.58 – 3.44 (m, 2H), 3.28 (s, 1H), 2.68-2.60 (m, 2H), 1.71 (t, J = 10.3 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H); HRMS (ESI): *m/z*, calcd. for $C_{32}H_{31}F_2N_3NaO_3$ $[M+Na]^+$ 566.2226, found 566.2210.



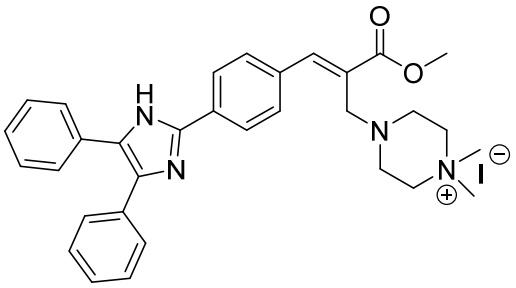
Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-((4-methylpiperazin-1-yl) methyl)acrylate (9o): Yield: 72%; yellow solid; mp: 204 – 206 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.81 (s, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.80 (s, 1H), 7.59 – 7.46 (M, 4H), 7.36 – 7.25 (m, 2H), 7.19 – 7.10 (m, 2H), 3.74 (s, 3H), 3.29 (s, 2H), 2.45 – 2.22 (m, 8H), 2.12 (s, 3H); HRMS (ESI): *m/z*, calcd.

for $C_{31}H_{30}F_2N_4NaO_2$ $[M+Na]^+$ 551.2229, found 551.2204.

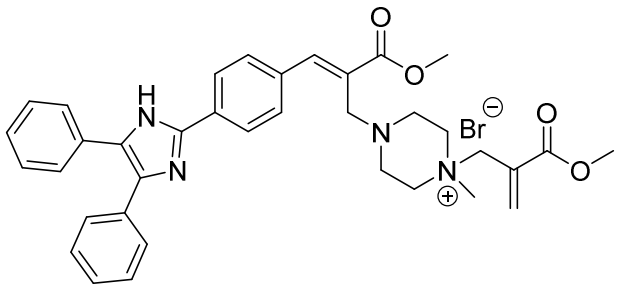


Methyl (E)-3-(4-(4,5-bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(((2-(dimethylamino) ethyl)(methyl)amino)methyl)acrylate (9p): Yield: 76%; pale yellow solid; mp: 81 – 83 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.09 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 7.7 Hz, 2H), 7.75 (s, 1H), 7.56 – 7.48 (m, 4H), 7.33 – 7.10 (m, 4H), 3.74 (s, 3H), 3.34 (s, 2H), 2.43 (t, J = 6.3 Hz, 2H), 2.33 (t, J = 6.6 Hz, 2H), 2.12 (s, 3H), 2.11 (s, 6H).

General procedure for the synthesis of quaternary ammonium salts. To a stirred solution of appropriate tertiary amine (1 mmol), was added alkyl halide (1.3 mmol) in tetrahydrofuran (5 mL), and stirred for overnight to affect the precipitation. Then filtered the solid and the resulting the solid was purified by triturating with diethyl ether to obtain pure quaternary ammonium salts in good yields.

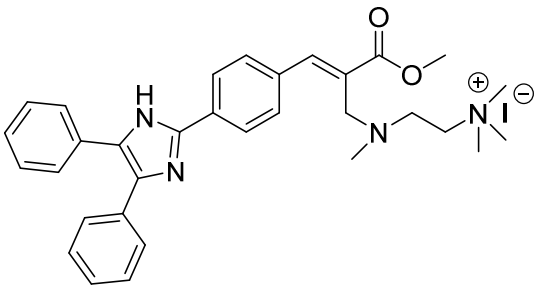


(E)-4-(3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl)-1,1-dimethyl piperazin-1-ium iodide (10a): Yield: 89%; pale cream solid; mp: 205 – 207 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.81 (s, 1H), 8.17 (d, J = 8.3 Hz, 2H), 7.88 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 7.3 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 3.77 (s, 3H), 3.47 (s, 2H), 3.41 (s, 4H), 3.11 (s, 6H), 2.78 (s, 4H); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 168.7, 145.5, 143.7, 138.2, 135.7, 134.8, 131.9, 131.6, 131.5, 129.5, 129.4, 129.1, 128.9, 128.8, 127.7, 127.3, 125.9, 61.4, 52.9, 52.6, 46.3.

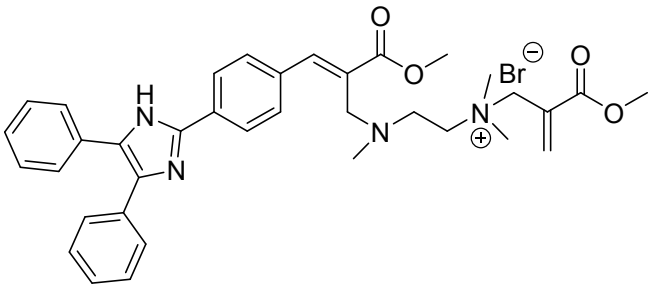


(E)-4-(3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl)-1-(2-(methoxy carbonyl)allyl)-1-methylpiperazin-1-ium bromide (10b): Yield: 81%; yellow solid; mp: 140 – 142 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.22 (d, J = 8.5 Hz, 2H), 7.93 – 7.86 (m, 3H), 7.56 – 7.50 (m, 4H), 7.49 – 7.39 (m, 6H), 6.81 (s, 1H), 6.47 (s, 1H), 4.35 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.53 (s, 2H), 3.47 – 3.36 (m, 4H), 2.98 (s, 3H),

2.92 – 2.73 (m, 4H);

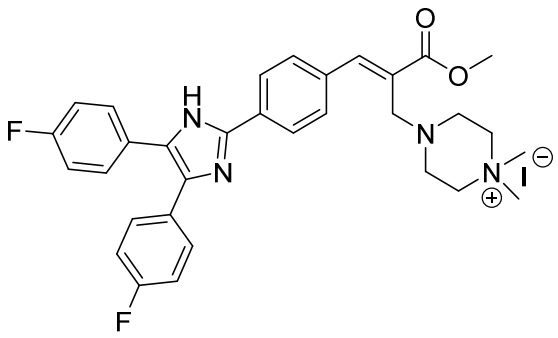


(E)-2-((3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl)(methyl) amino)-N,N,N-trimethylethan-1-aminium iodide (10g): Yield: 86%; pale yellow solid; mp: 203 – 205 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.79 (s, 1H), 8.14 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 7.4 Hz, 2H), 7.49 (d, J = 7.1 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 3.76 (s, 3H), 3.49 (s, 2H), 3.44 (t, J = 5.8 Hz, 2H), 3.03 (s, 9H), 2.76 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 145.5, 141.9, 138.2, 135.7, 134.8, 131.5, 131.4, 131.3, 130.3, 129.5, 129.4, 129.1, 128.9, 128.6, 127.8, 127.3, 125.8, 61.9, 53.6, 53.2, 52.9, 51.6, 41.2;

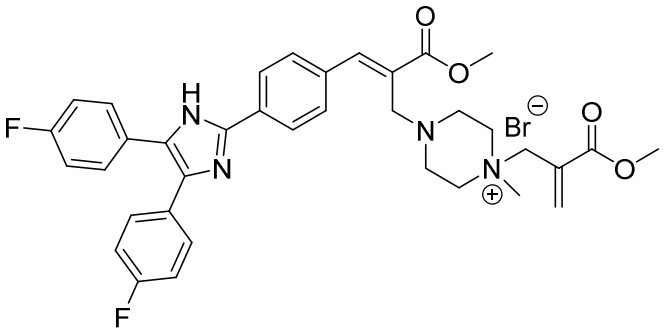


(E)-N-(2-((3-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)-2-

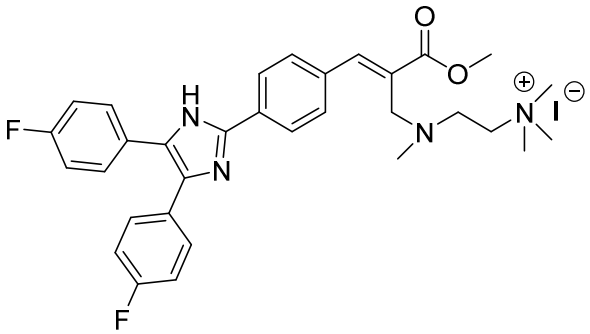
(methoxycarbonyl)allyl)(methyl) amino)ethyl)-2-(methoxycarbonyl)-N,N-dimethylprop-2-en-1-aminium bromide (10h): Yield: 79%; pale yellow solid; mp: 87 – 89 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, J = 8.5 Hz, 2H), 7.92 – 7.84 (m, 3H), 7.53 (d, J = 6.7 Hz, 4H), 7.49 – 7.38 (m, 6H), 6.81 (s, 1H), 6.47 (s, 1H), 4.35 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.57 – 3.36 (m, 10H), 2.98 (s, 3H), 2.82 – 2.74 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 145.5, 142.0, 138.2, 135.7, 134.8, 131.4, 131.3, 130.3, 129.5, 129.4, 129.2, 129.1, 128.9, 128.6, 128.0, 127.8, 127.3, 126.7, 125.9, 66.4, 60.1, 53.6, 52.9, 51.2, 50.5, 41.5;



(E)-4-(3-(4-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl)-1,1-dimethylpiperazin-1-ium iodide (10d): Yield: 86%; pale yellow solid; mp: 256 – 258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.84 (s, 1H), 8.15 (d, J = 6.5 Hz, 2H), 7.87 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 6.6 Hz, 2H), 7.56 – 7.48 (m, 4H), 7.31 (t, J = 8.8 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.46 (s, 2H), 3.41 (m, 4H), 3.11 (s, 6H), 2.77 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ. ^{13}C NMR (101 MHz, DMSO) δ 168.72, 162.39 (d, J = 253.0 Hz), 145.57, 143.65, 137.35, 134.91, 131.88, 131.41, 131.27 (d, J = 6.3 Hz), 129.60, 129.58 (d, J = 11.0 Hz), 128.82, 128.34 (d, J = 6.7 Hz), 127.79 (d, J = 5.1 Hz), 125.90, 61.40, 52.93, 52.60, 46.28.

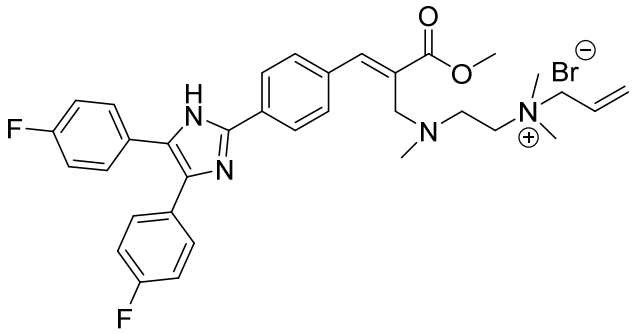


(E)-4-(3-(4-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl)-1-(2-(methoxycarbonyl)allyl)-1-methylpiperazin-1-ium bromide (10e): Yield: 82%; pale yellow solid; mp: 130 – 132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.16 (d, J = 7.3 Hz, 2H), 7.87 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.57 – 7.47 (m, 4H), 7.36 – 7.10 (m, 4H), 6.80 (s, 1H), 6.47 (s, 1H), 4.34 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.47 (s, 2H), 3.45 – 3.36 (m, 4H), 2.98 (s, 3H), 2.91 – 2.70 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 168.69, 166.32, 162.15 (d, J = 244.1 Hz), 145.53, 143.65, 141.72, 134.96, 131.88, 131.32, 130.70 (d, J = 7.8 Hz), 130.52 (d, J = 14.0 Hz), 129.03, 128.83, 125.95, 116.17 (d, J = 21.0 Hz), 67.68, 60.21, 53.36, 52.89, 52.58, 46.15, 25.79.



(E)-2-((3-(4-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl)allyl) (methyl)amino)- N,N,N-trimethylethan-1-aminium iodide

(10j): Yield: 82%; yellow solid; mp: 138 – 140 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.82 (s, 1H), 8.11 (d, J = 8.2 Hz, 2H), 7.77 (s, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.30 (t, J = 8.7 Hz, 2H), 7.15 (t, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.48 (s, 2H), 3.44 (t, J = 5.8 Hz, 2H), 3.03 (s, 9H), 2.79 – 2.71 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 168.90, 161.79 (d, J = 242.4 Hz), 145.51, 141.91, 137.35, 134.87, 131.98, 131.95, 131.35, 131.29, 129.58 (d, J = 7.2 Hz), 127.81 (d, J = 2.5 Hz), 125.83, 116.48 (d, J = 22.0 Hz), 115.88 (d, J = 20.8 Hz), 61.95, 53.63, 53.26, 52.89, 51.61, 41.21;



(E)-N-(2-((3-(4-(4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl)phenyl)-2-(methoxycarbonyl) allyl) (methyl)amino)ethyl)-N,N-dimethylprop-2-en-1-aminium bromide (10l): Yield: 77%; yellow solid; Mp: 128 – 130 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.84 (s, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.77 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.56 – 7.46 (m, 4H), 7.30 (t, J = 8.5 Hz, 2H), 7.15 (t, J = 8.2 Hz, 2H), 6.08 – 5.93 (m, 1H), 5.63 – 5.50 (m, 2H), 3.94 (d, J = 6.4 Hz, 2H), 3.75 (s, 3H), 3.48 (s, 2H), 3.43 – 3.36 (m, 2H), 2.98 (s, 6H), 2.82 – 2.72 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, DMSO): δ 168.90, 145.52, 141.96, 137.34, 134.85, 132.01, 131.37, 131.30, 130.35, 129.60 (d, J = 8.1 Hz), 128.30 (d, J = 2.1 Hz), 128.03 (d, J = 2.1 Hz), 126.69, 125.87, 116.44 (d, J = 20.8 Hz), 115.88 (d, J = 21.7 Hz), 66.45, 60.09, 53.60, 52.88, 51.19, 50.53, 41.44.

Chapter 4

Spectral Characterization

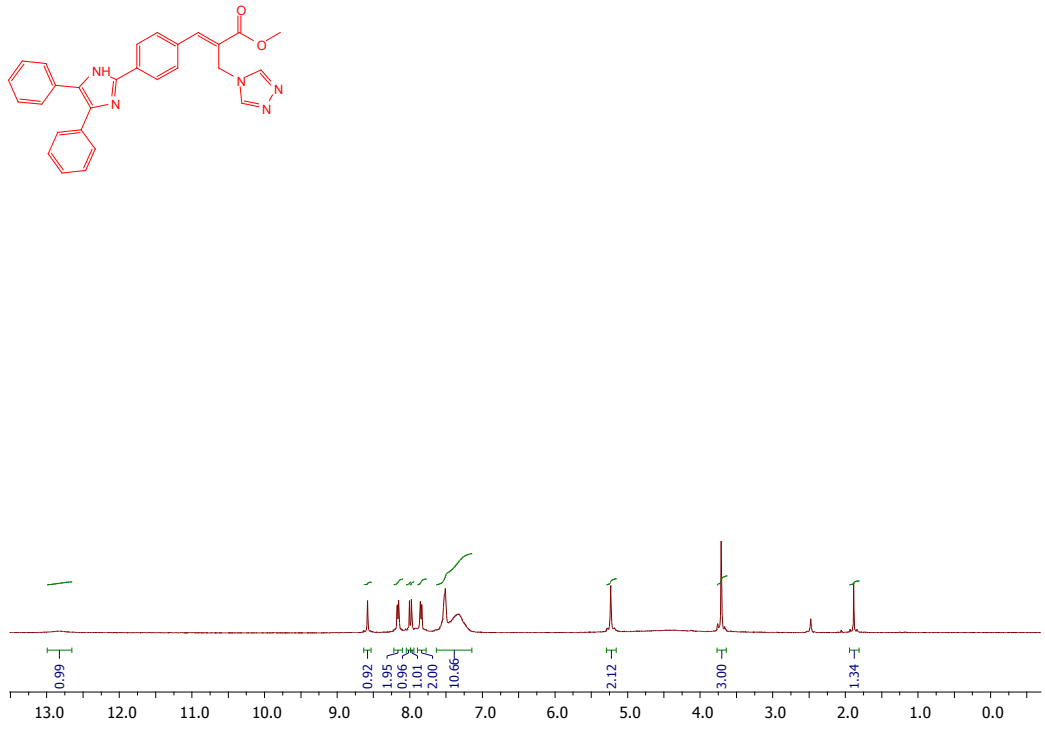


Figure 16. 400 MHz ^{1}H NMR of Compound **9b** in $CDCl_3$

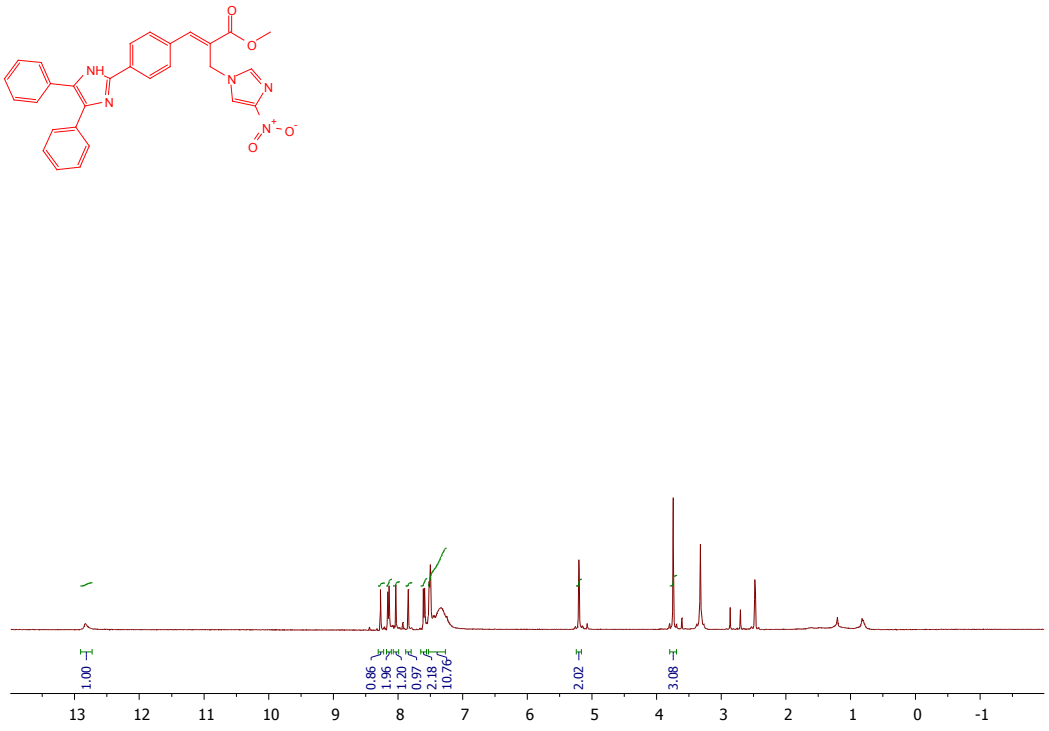


Figure 17. 400 MHz ^{1}H NMR of Compound **9c** in $CDCl_3$

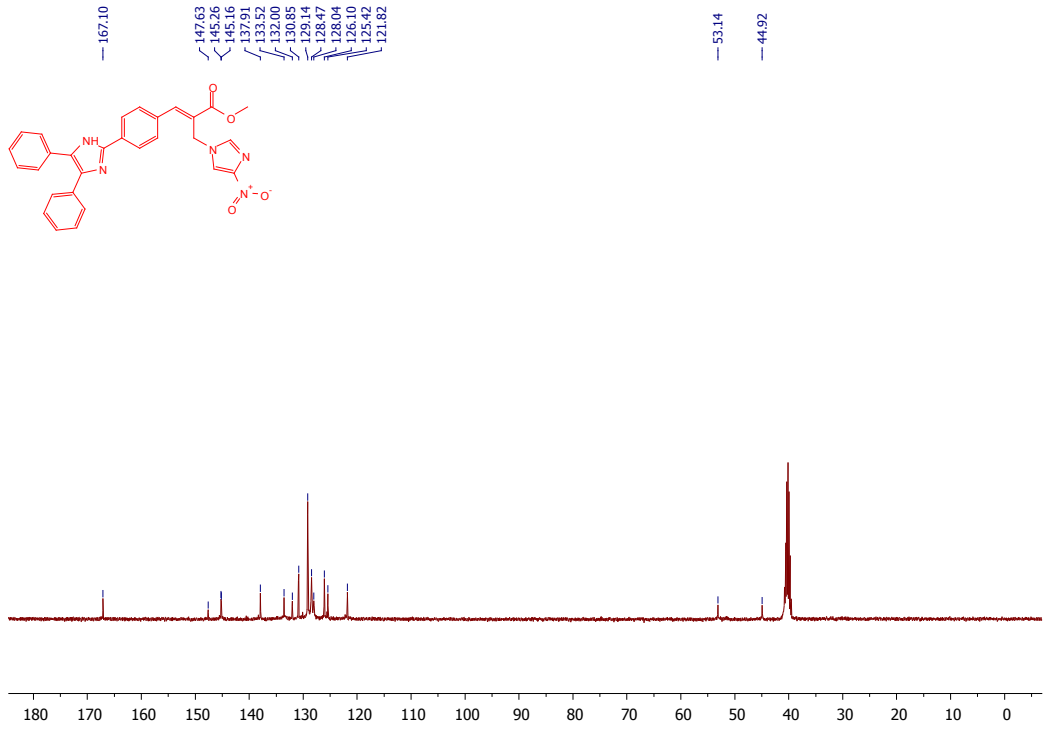


Figure 18. 101 MHz ^{13}C NMR of Compound **9c** in $CDCl_3$

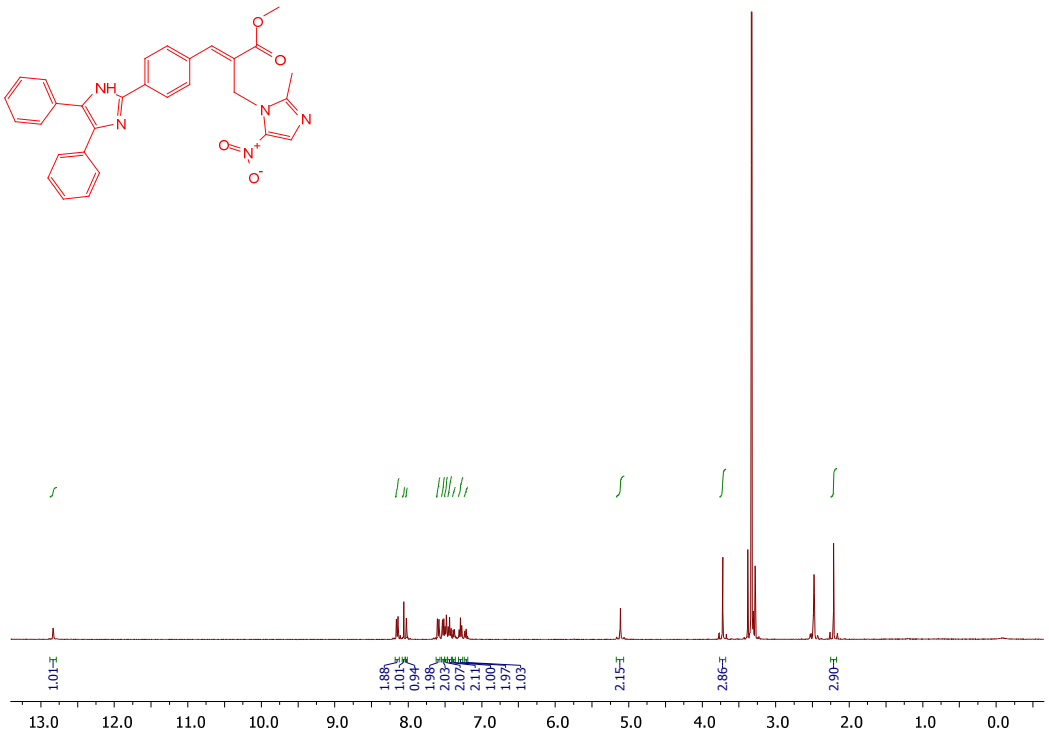


Figure 19. 400 MHz ^{1}H NMR of Compound **9d** in $CDCl_3$

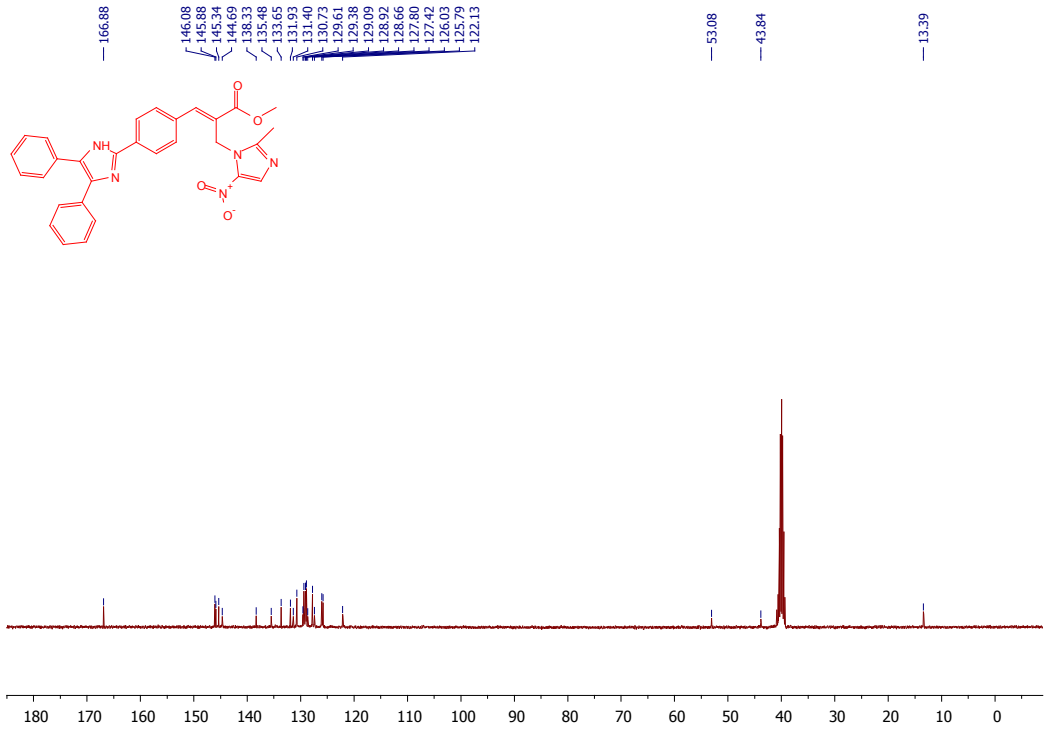


Figure 20. 101 MHz ^{13}C NMR of Compound **9d** in $CDCl_3$

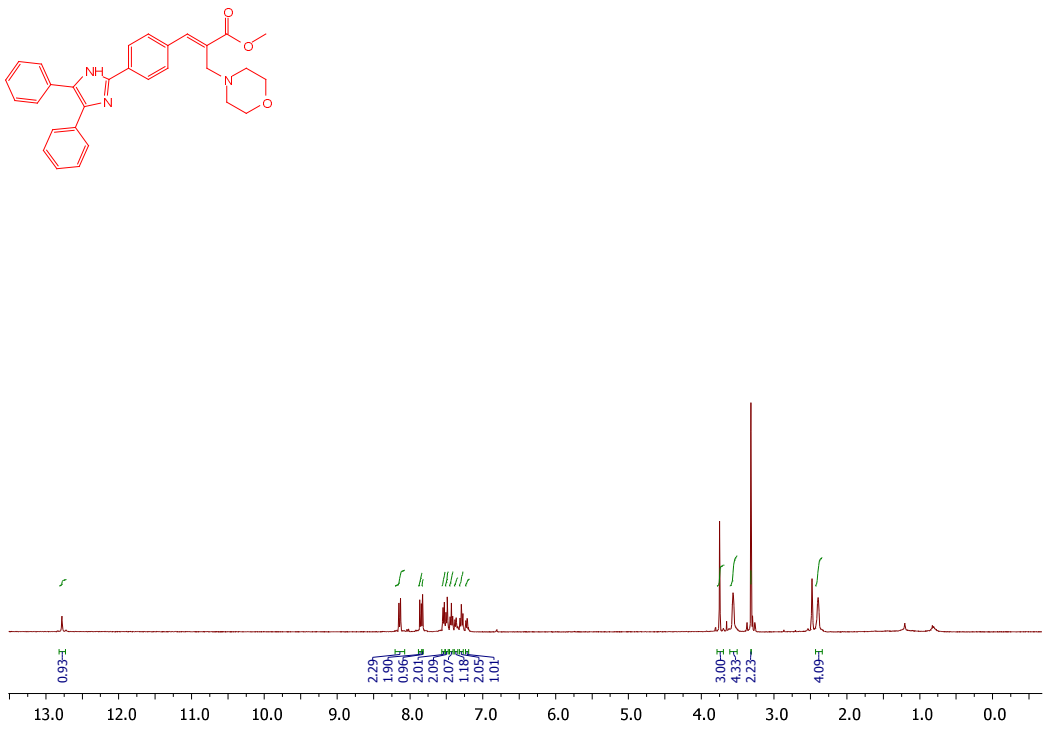


Figure 21. 400 MHz ^{1}H NMR of Compound **9e** in $CDCl_3$

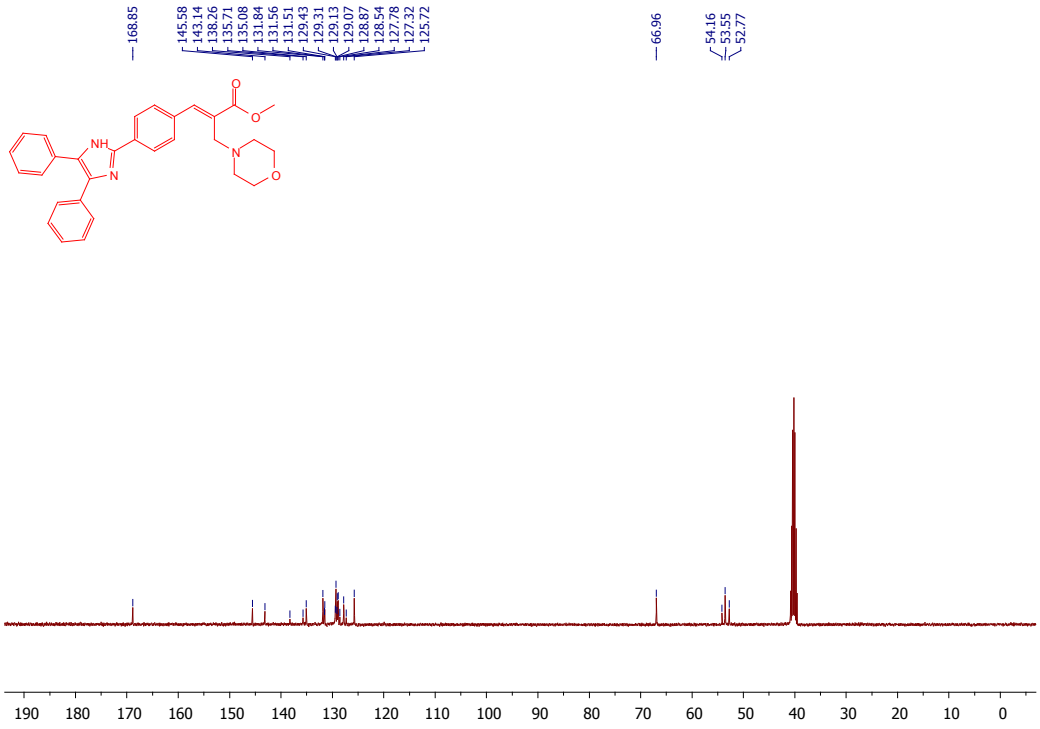


Figure 22. 101 MHz ^{13}C NMR of Compound **9e** in $CDCl_3$

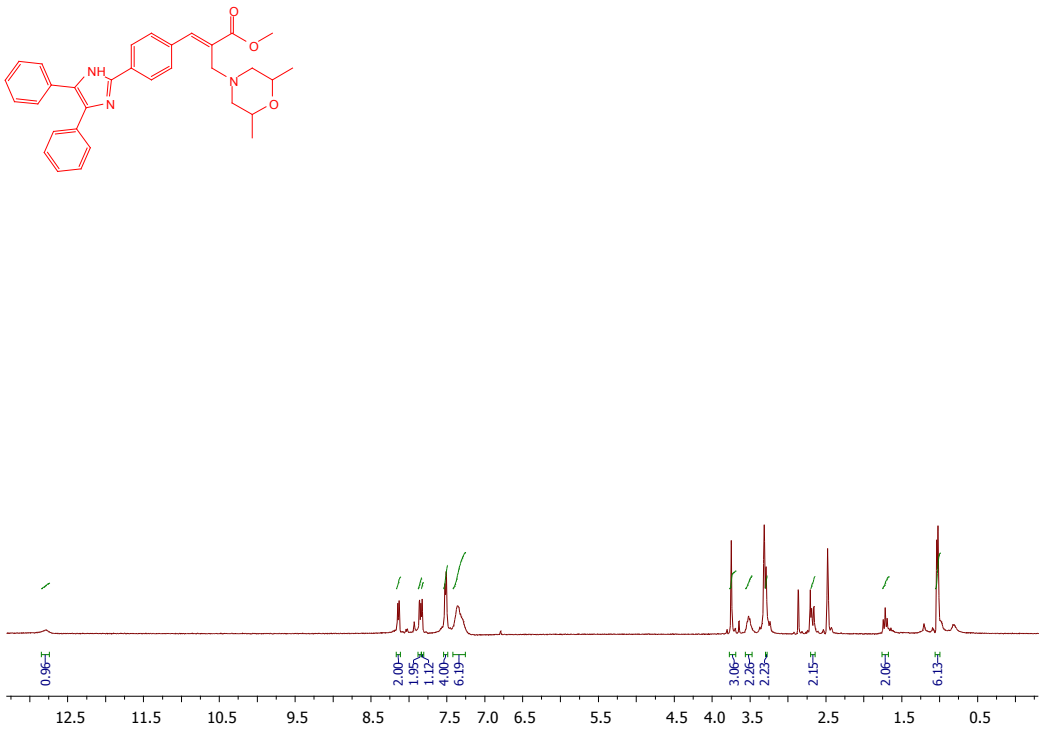


Figure 23. 400 MHz ^{1}H NMR of Compound **9f** in $CDCl_3$

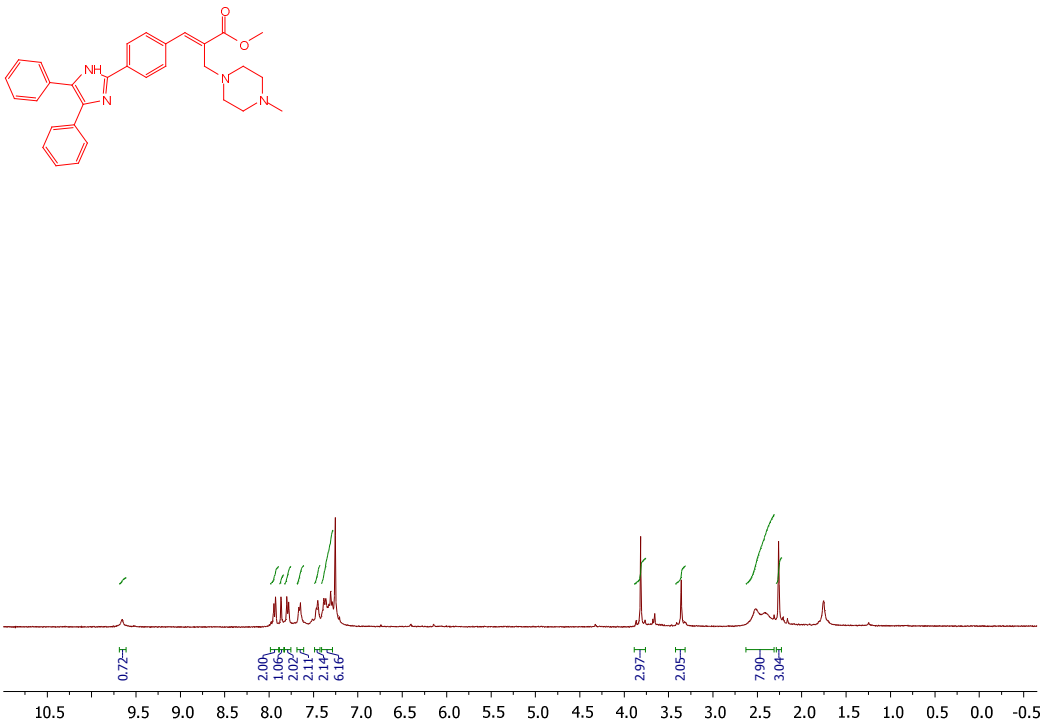


Figure 24. 400 MHz ^{1}H NMR of Compound **9g** in $CDCl_3$

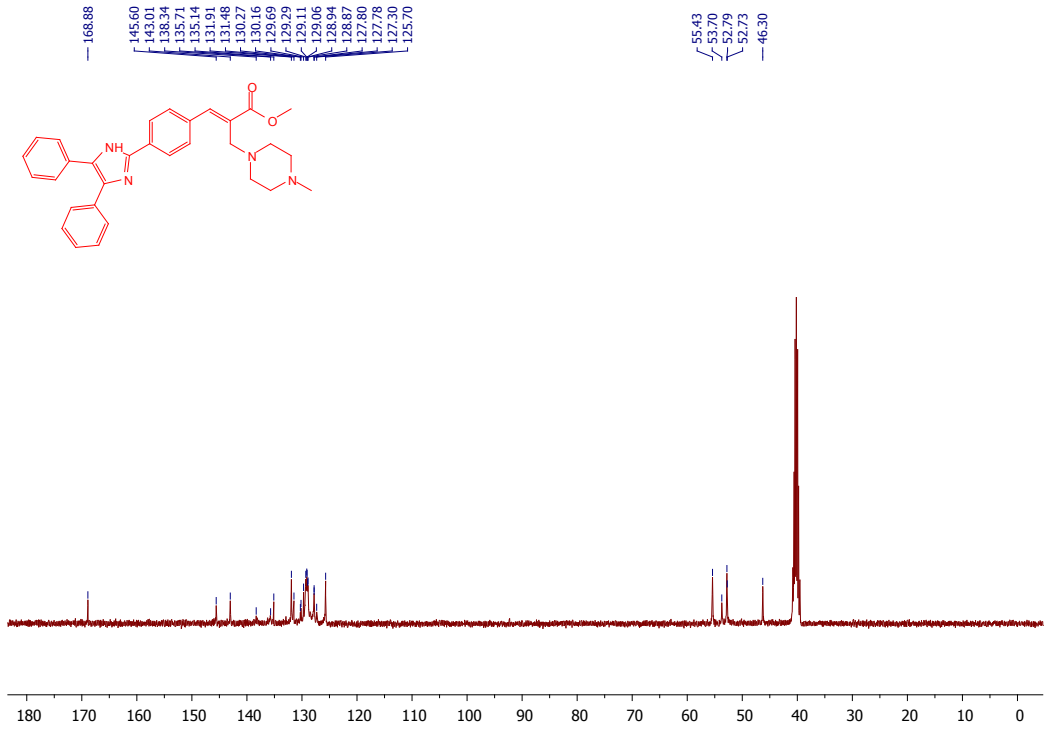


Figure 25. 101 MHz ^{13}C NMR of Compound **9g** in $CDCl_3$

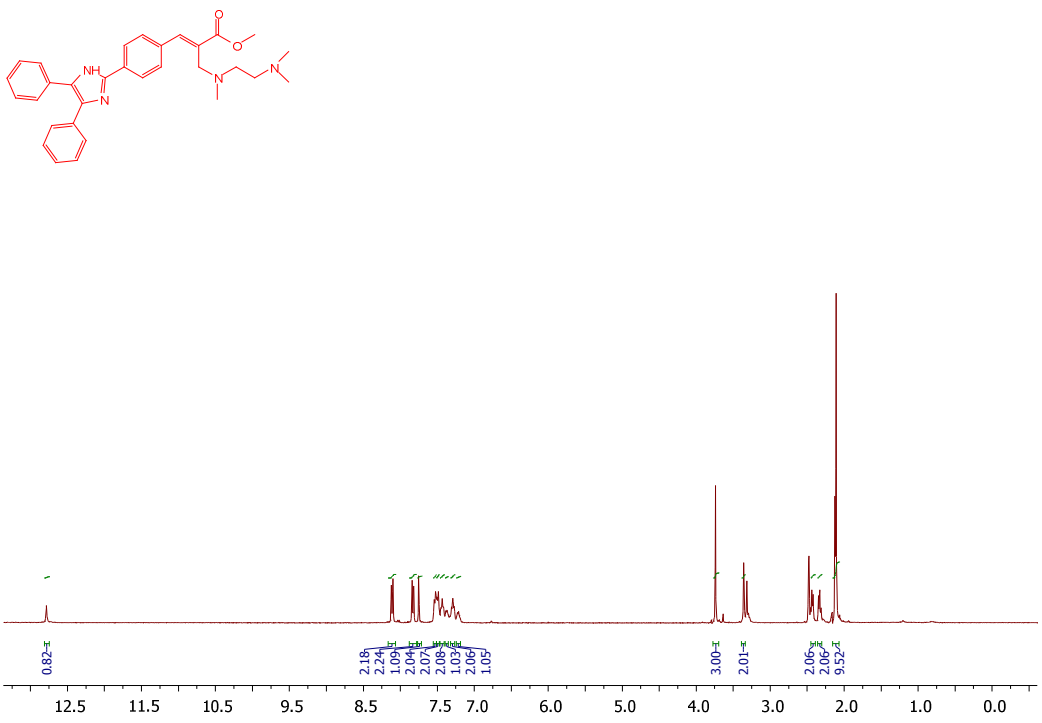


Figure 26. 400 MHz ^{1}H NMR of Compound **9h** in $CDCl_3$

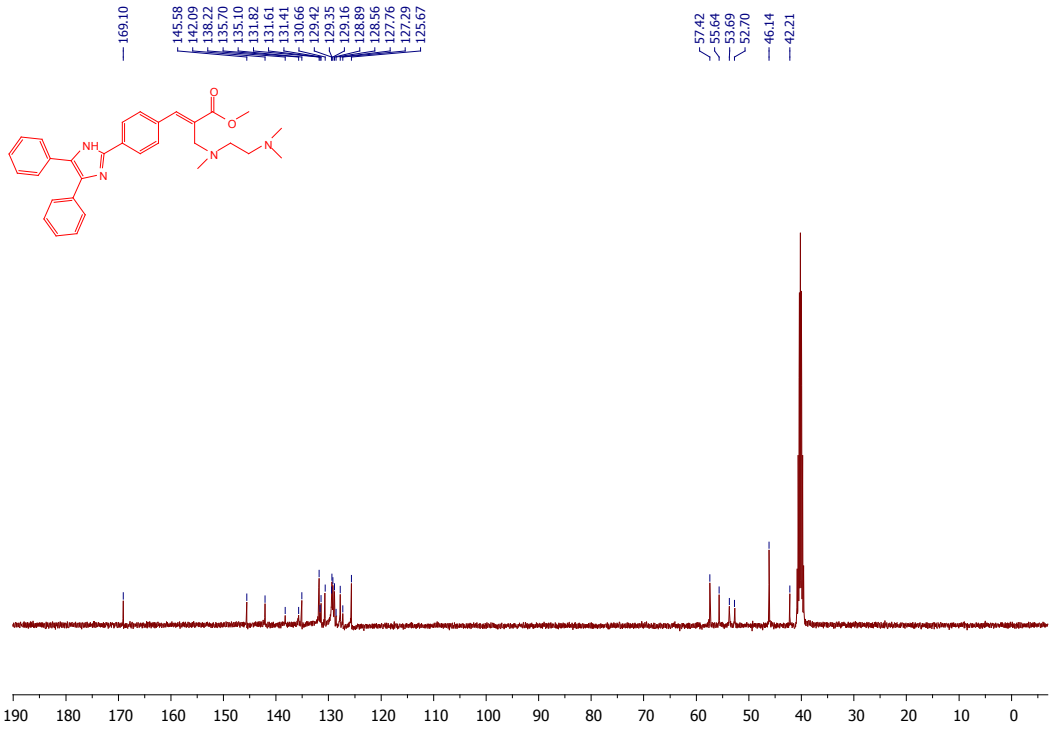


Figure 27. 101 MHz ^{13}C NMR of Compound **9h** in $CDCl_3$

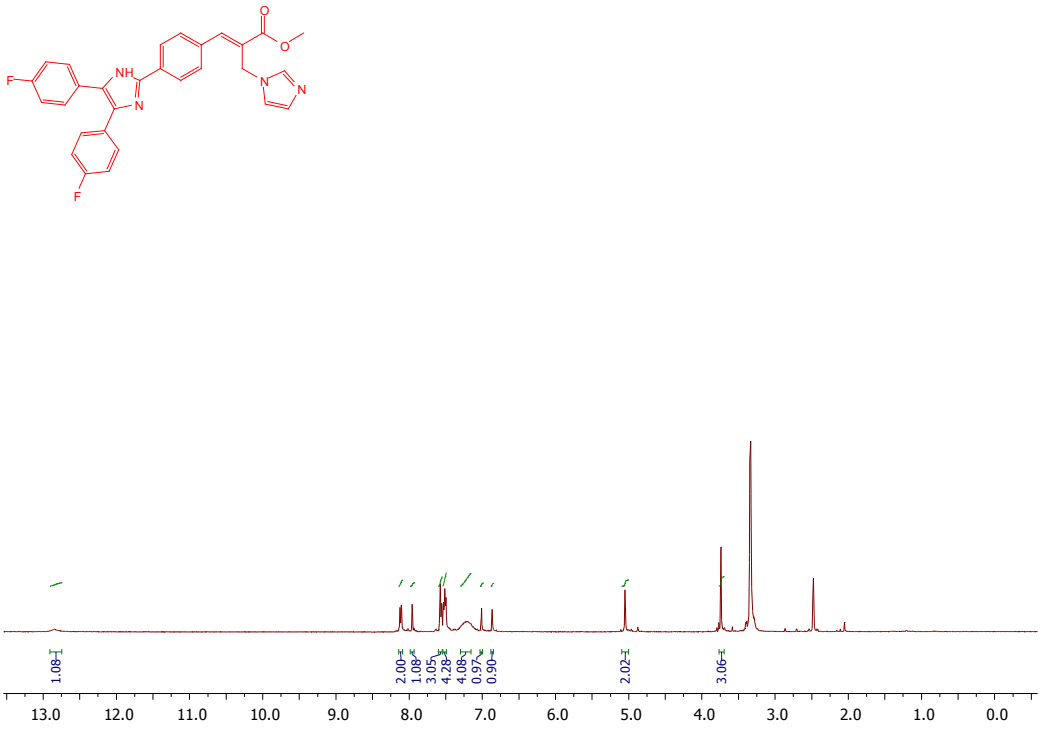


Figure 28. 400 MHz ^{1}H NMR of Compound **9i** in DMSO-d_6

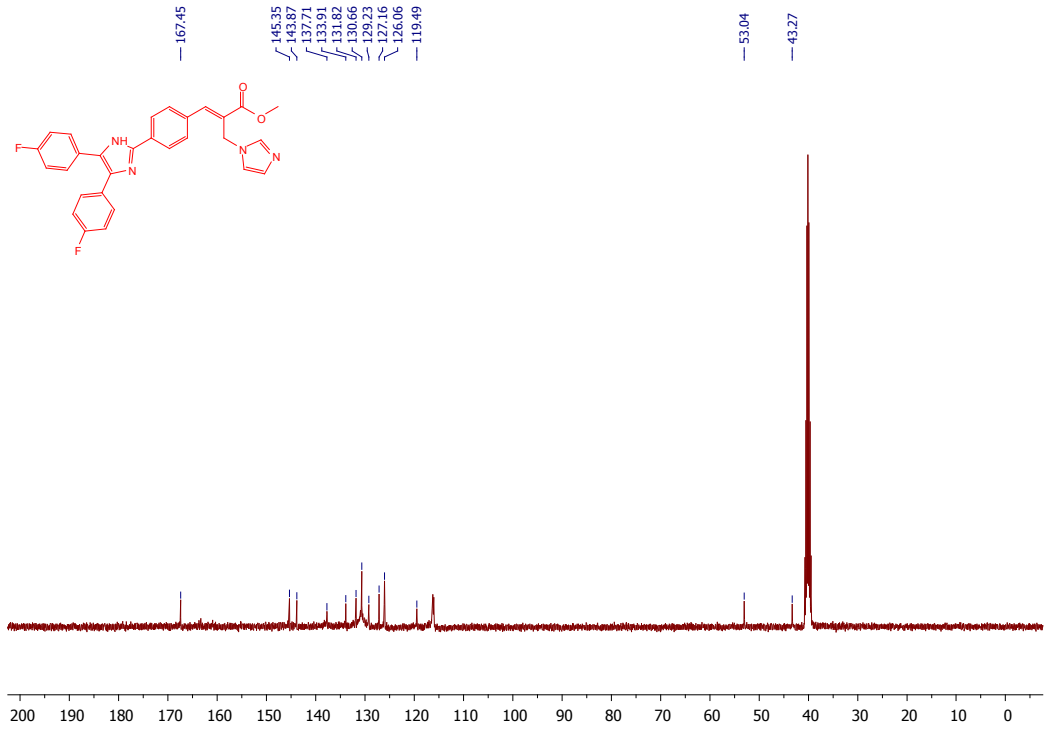


Figure 29. 101 MHz ^{13}C NMR of Compound **9i** in DMSO-d_6

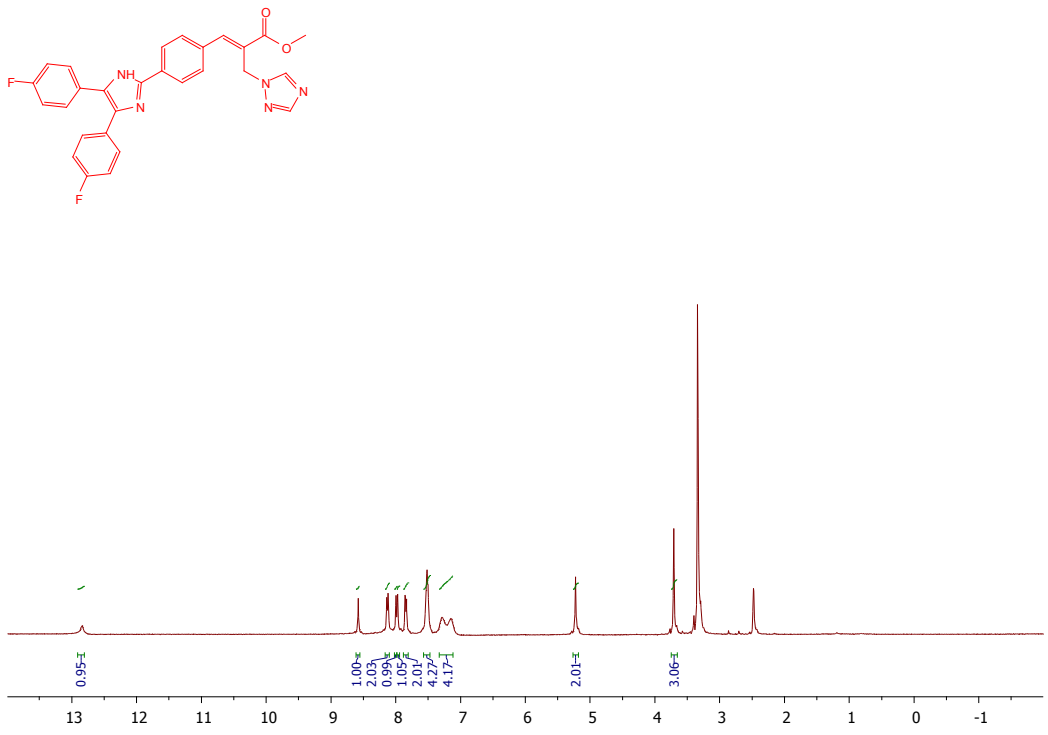


Figure 30. 400 MHz ^{1}H NMR of Compound **9j** in $CDCl_3$

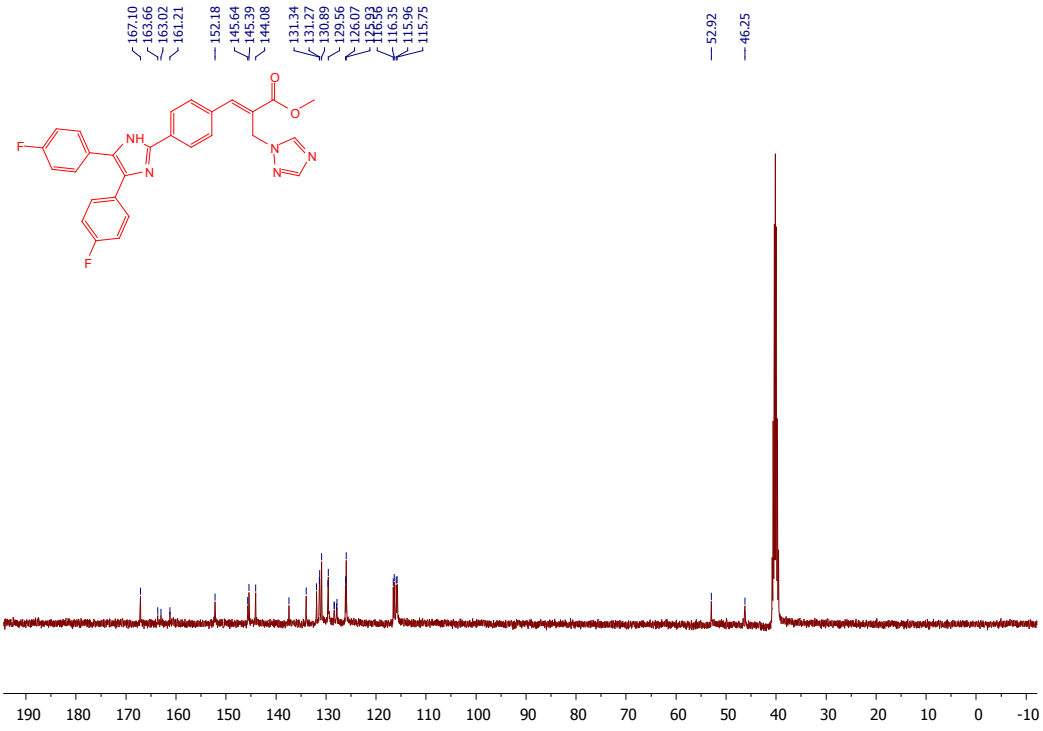


Figure 31. 101 MHz ^{13}C NMR of Compound **9j** in $CDCl_3$

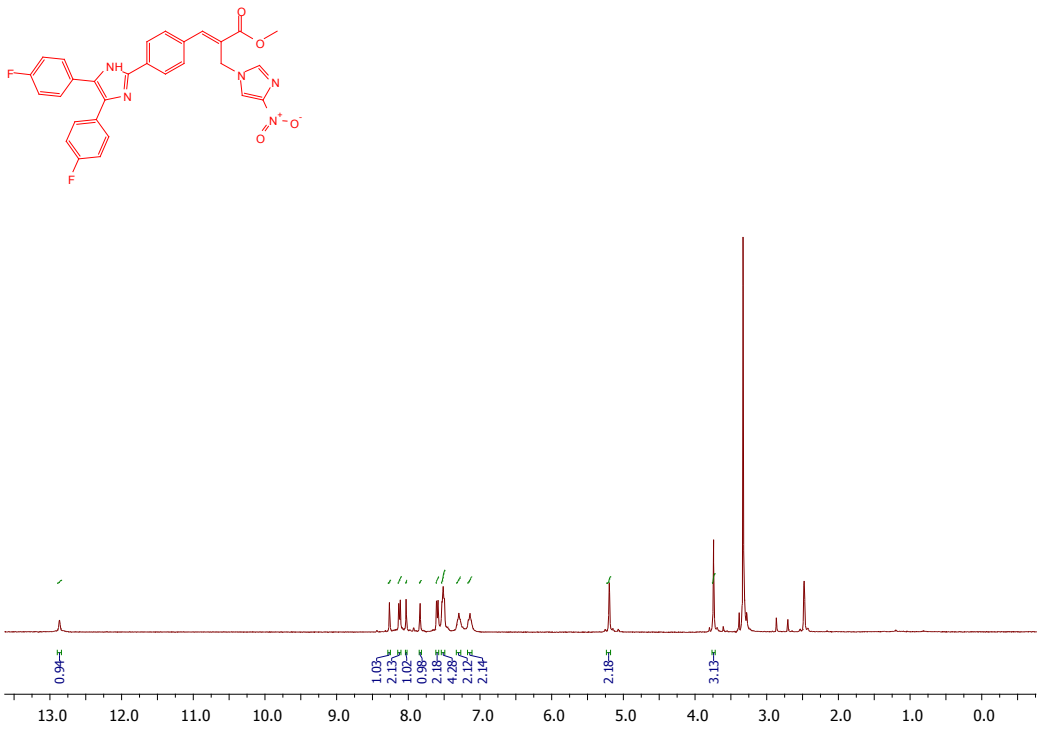


Figure 32. 400 MHz ^{1}H NMR of Compound **9k** in $CDCl_3$

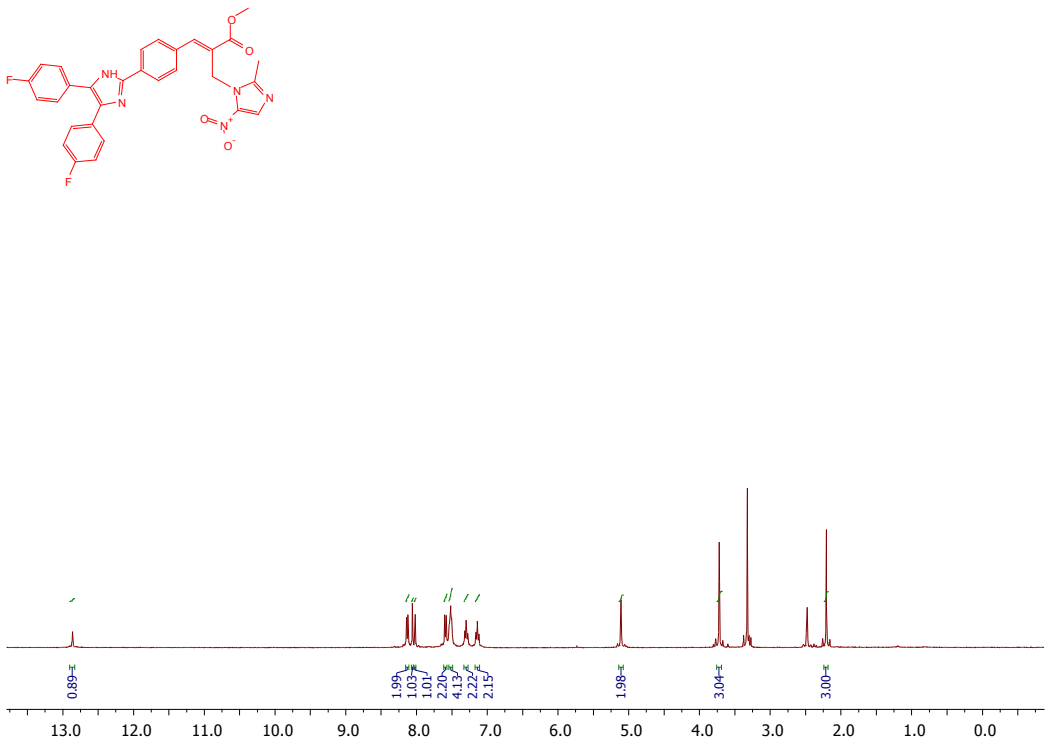


Figure 33. 400 MHz ^{1}H NMR of Compound **9l** in $CDCl_3$

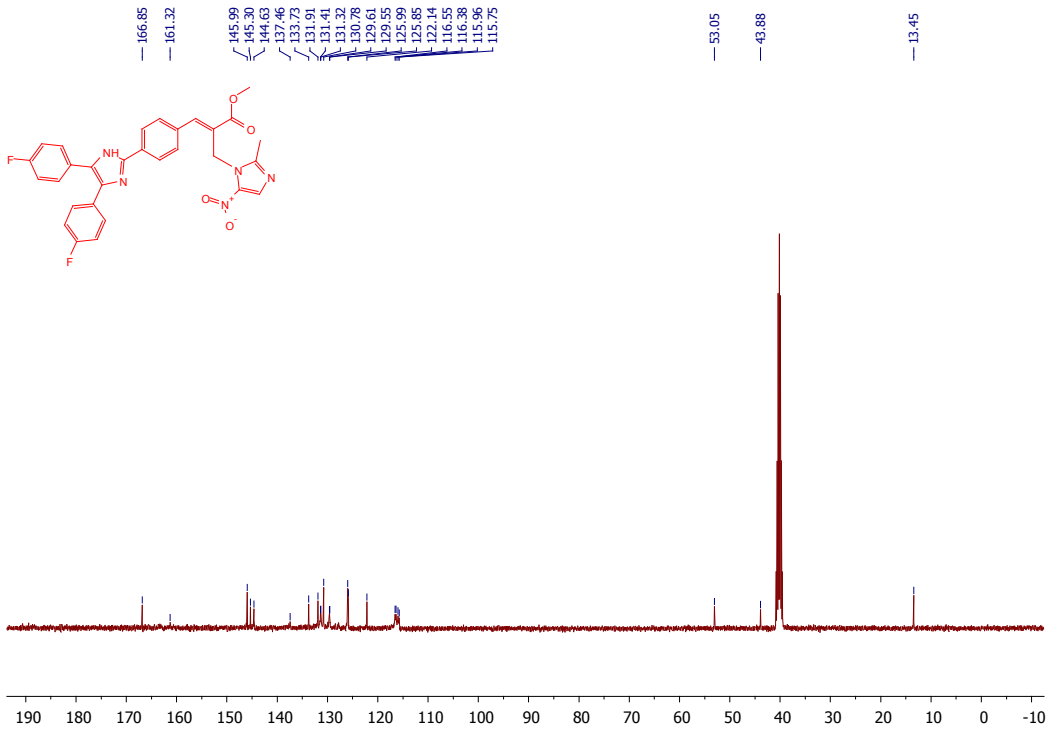


Figure 34. 101 MHz ^{13}C NMR of Compound **9l** in $CDCl_3$

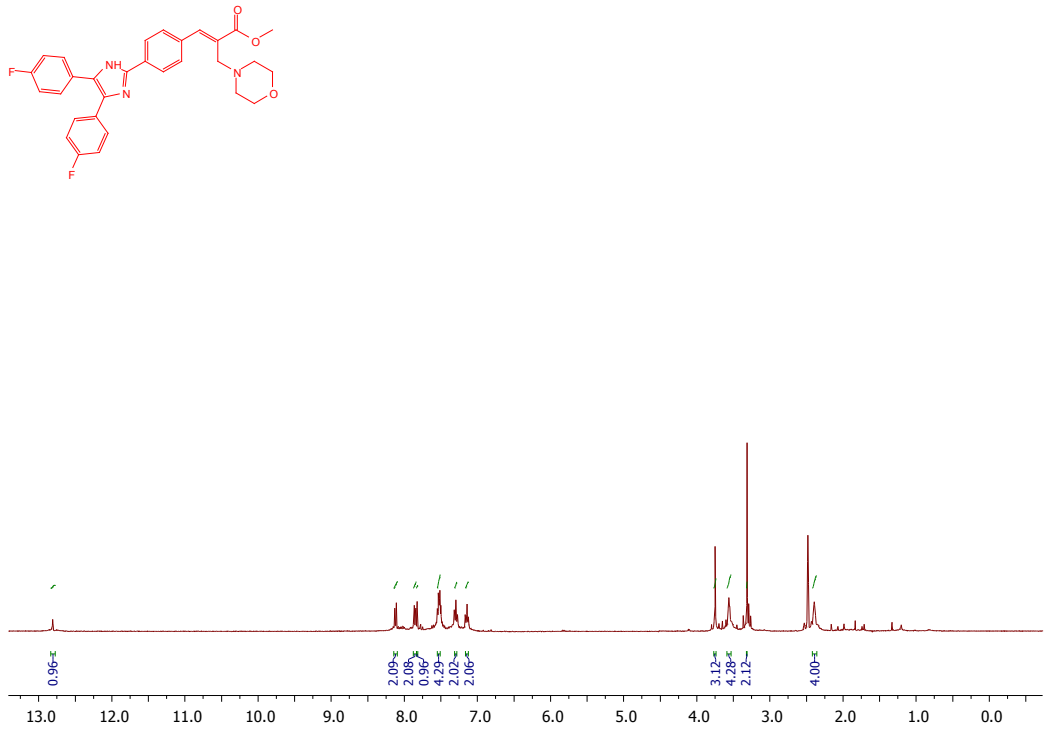


Figure 35. 400 MHz ^{1}H NMR of Compound **9m** in $CDCl_3$

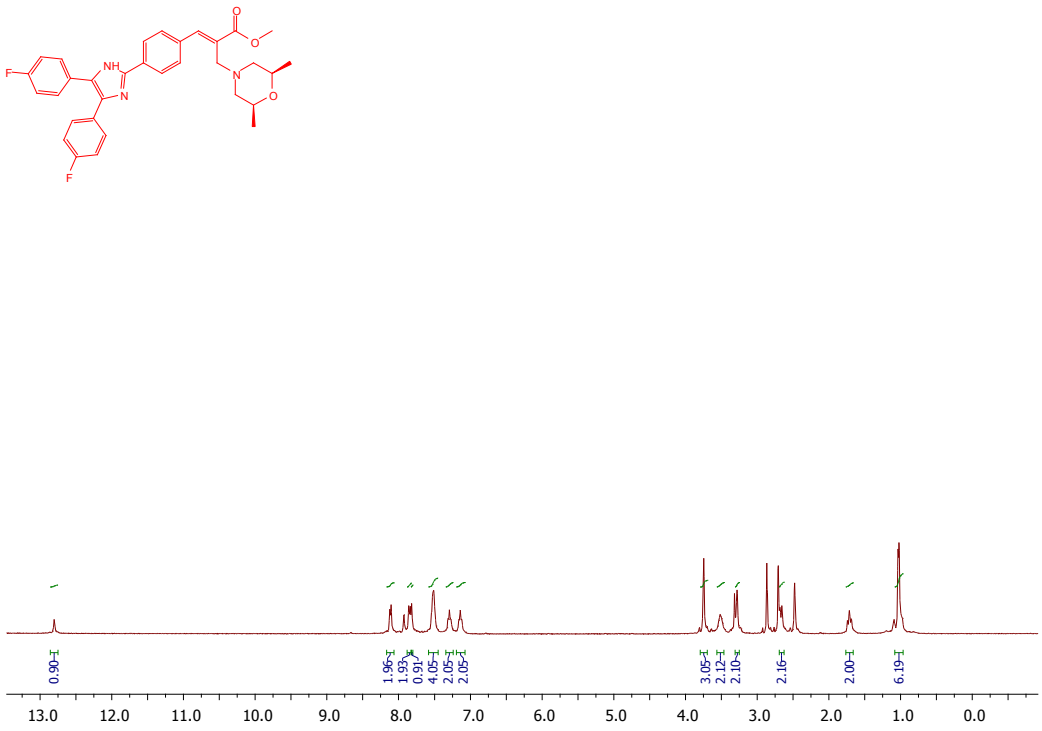


Figure 36. 400 MHz ^{1}H NMR of Compound **9n** in $CDCl_3$

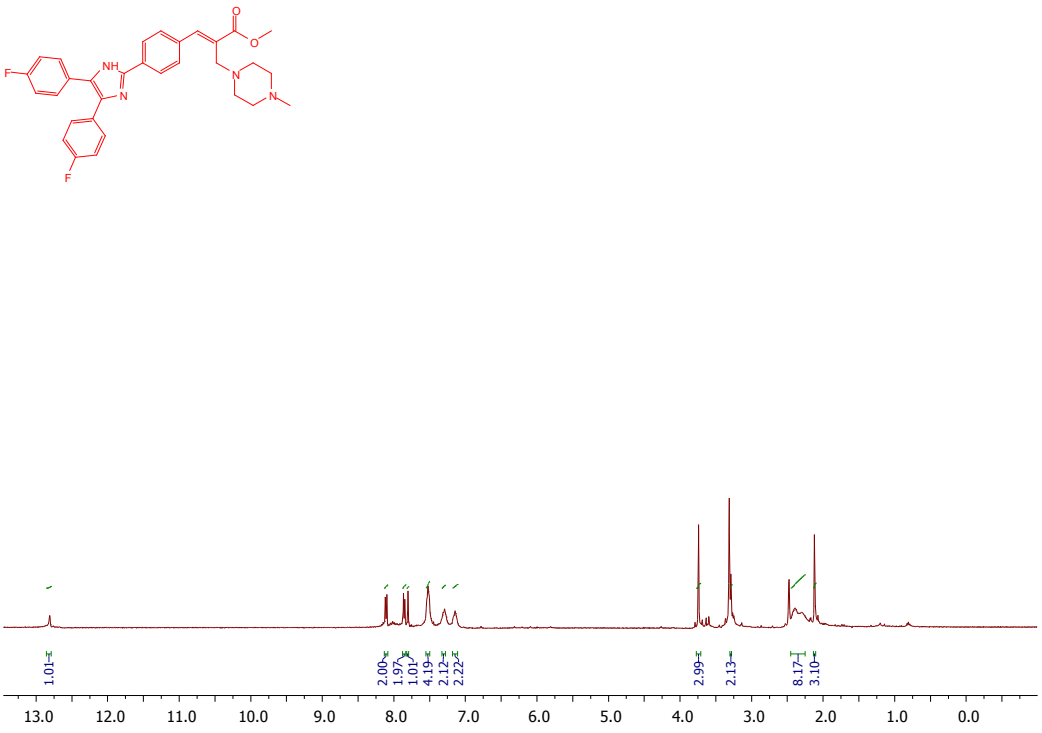


Figure 37. 400 MHz ^{1}H NMR of Compound **9o** in $CDCl_3$

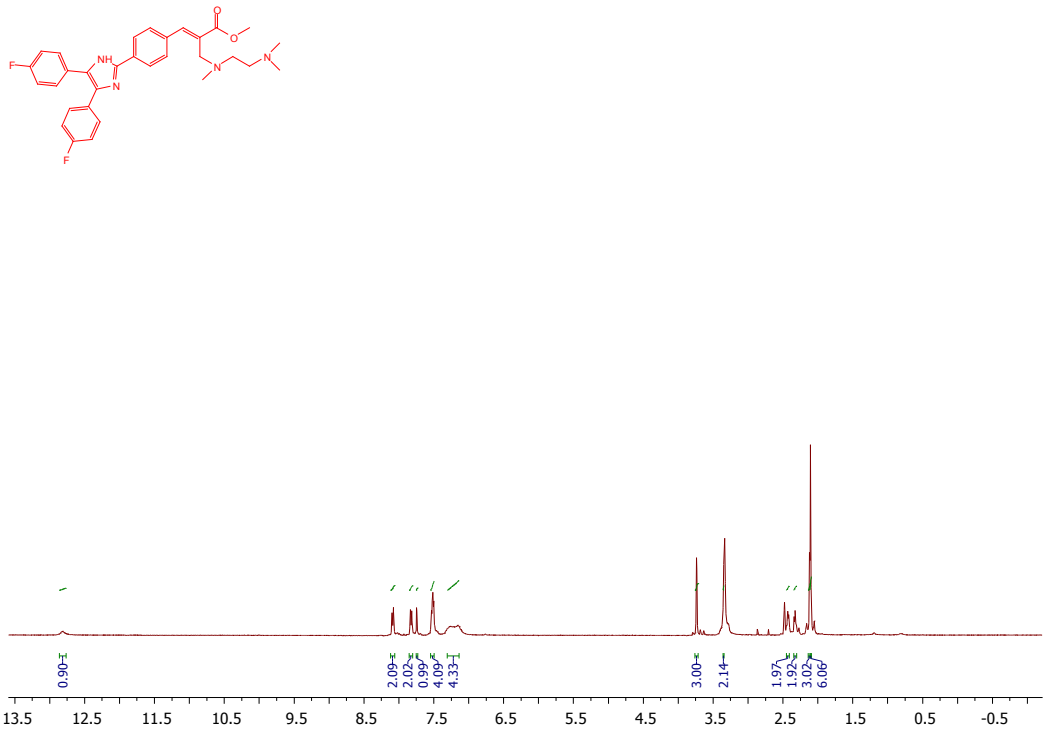


Figure 38. 400 MHz ^{1}H NMR of Compound **9p** in $CDCl_3$

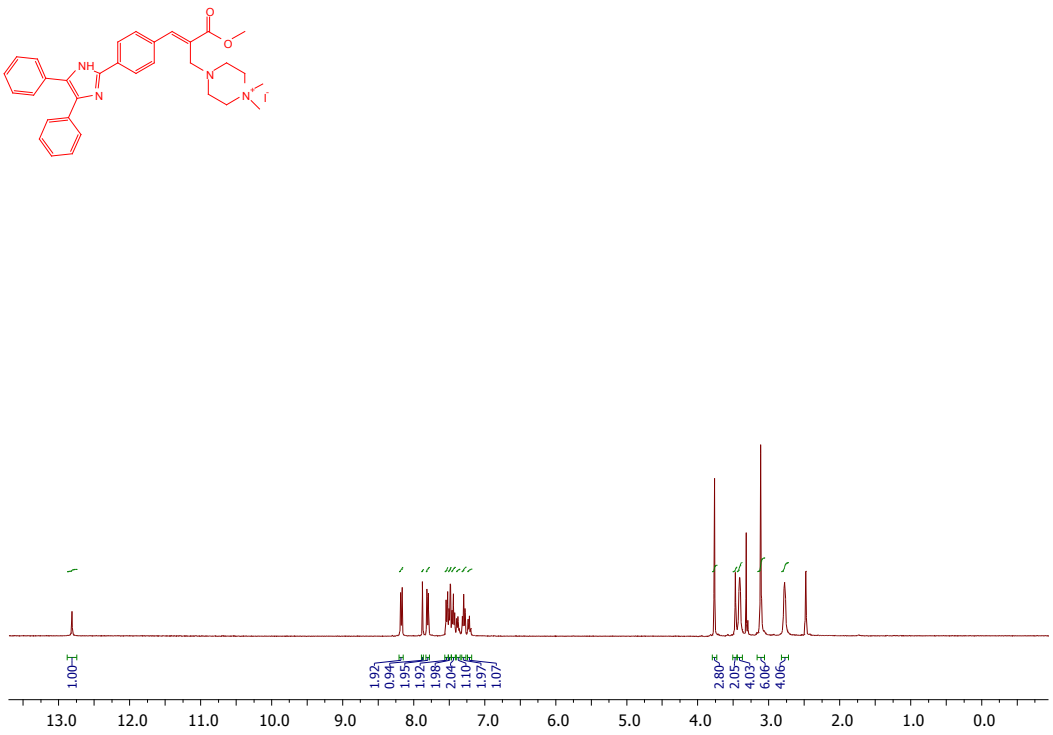


Figure 39. 400 MHz ^{1}H NMR of Compound **10c** in $CDCl_3$

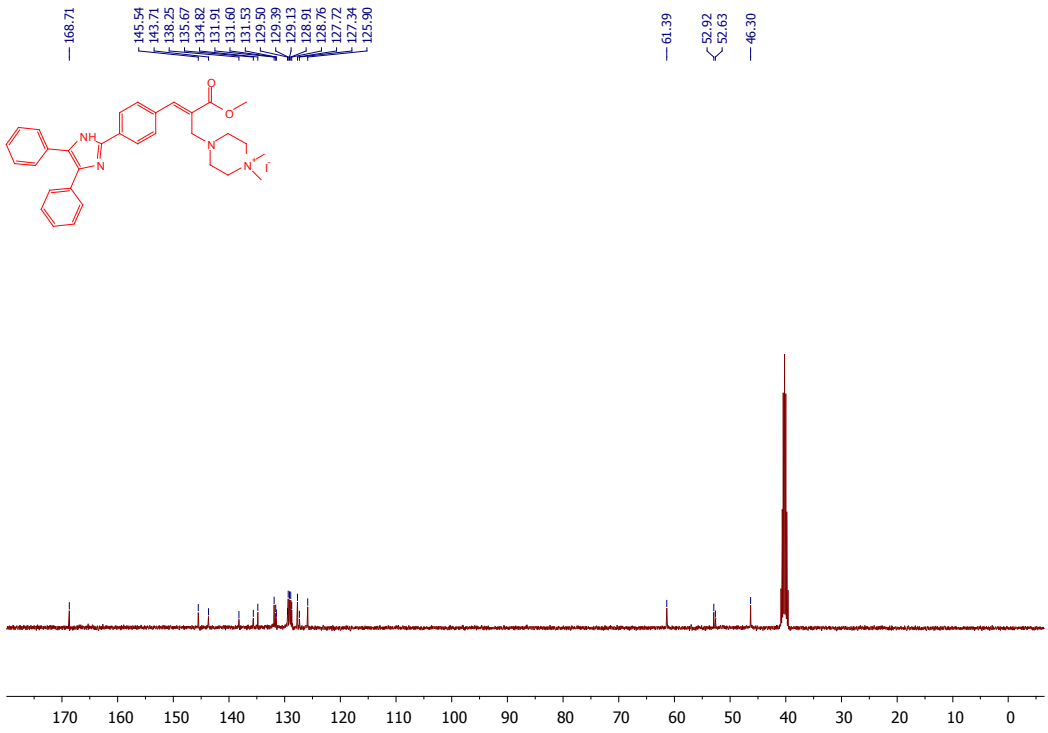


Figure 40. 101 MHz ^{13}C NMR of Compound **10a** in $CDCl_3$

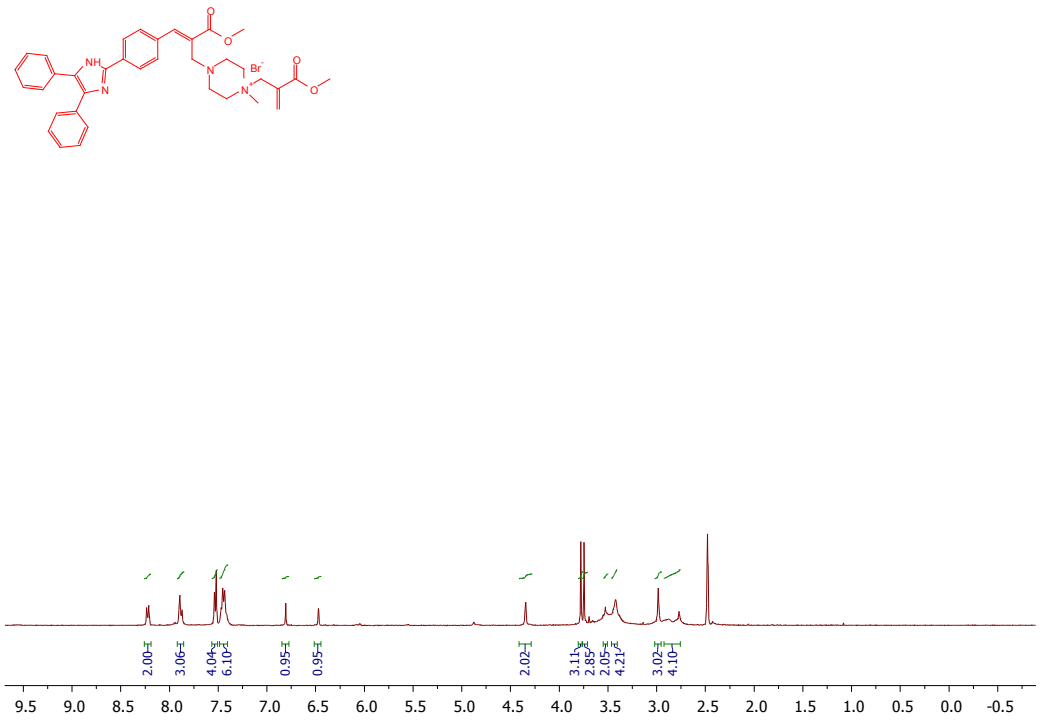


Figure 41. 400 MHz ^{1}H NMR of Compound **10b** in $CDCl_3$

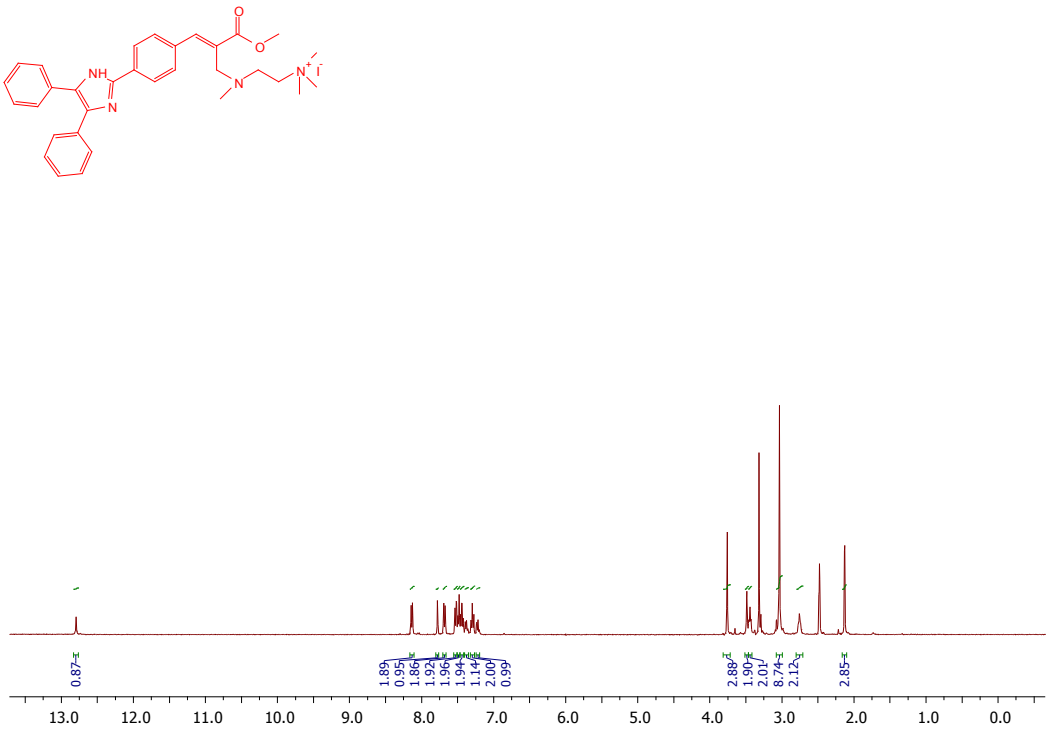


Figure 42. 400 MHz ^{1}H NMR of Compound **10g** in $CDCl_3$

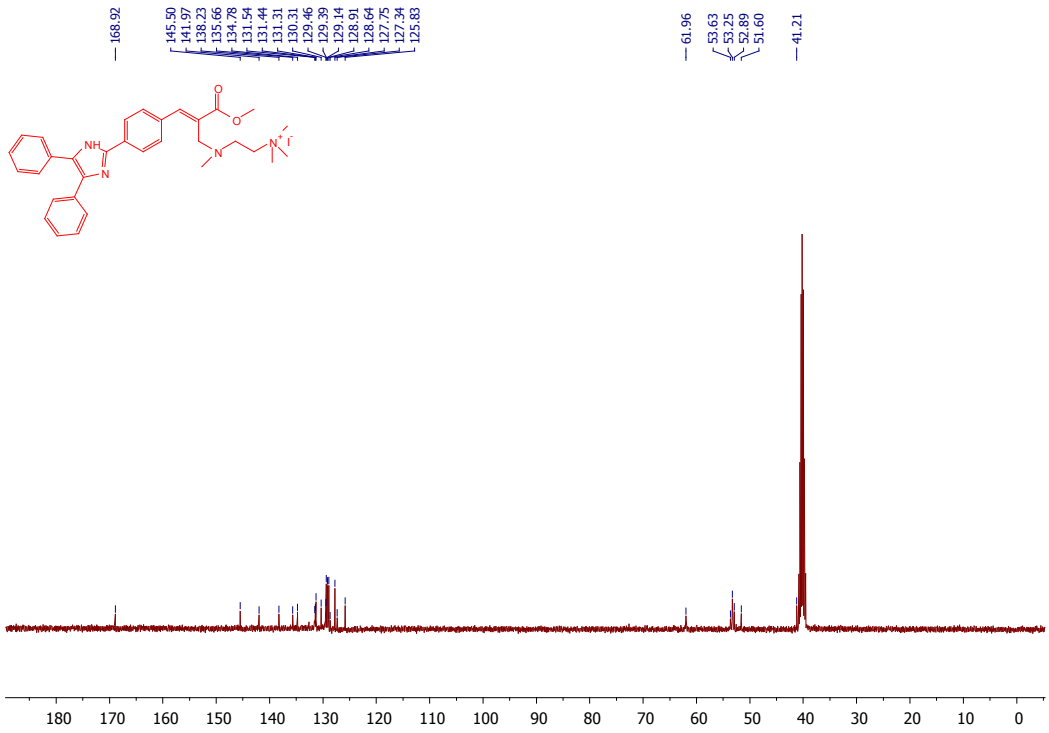


Figure 43. 101 MHz ^{13}C NMR of Compound **10g** in $CDCl_3$

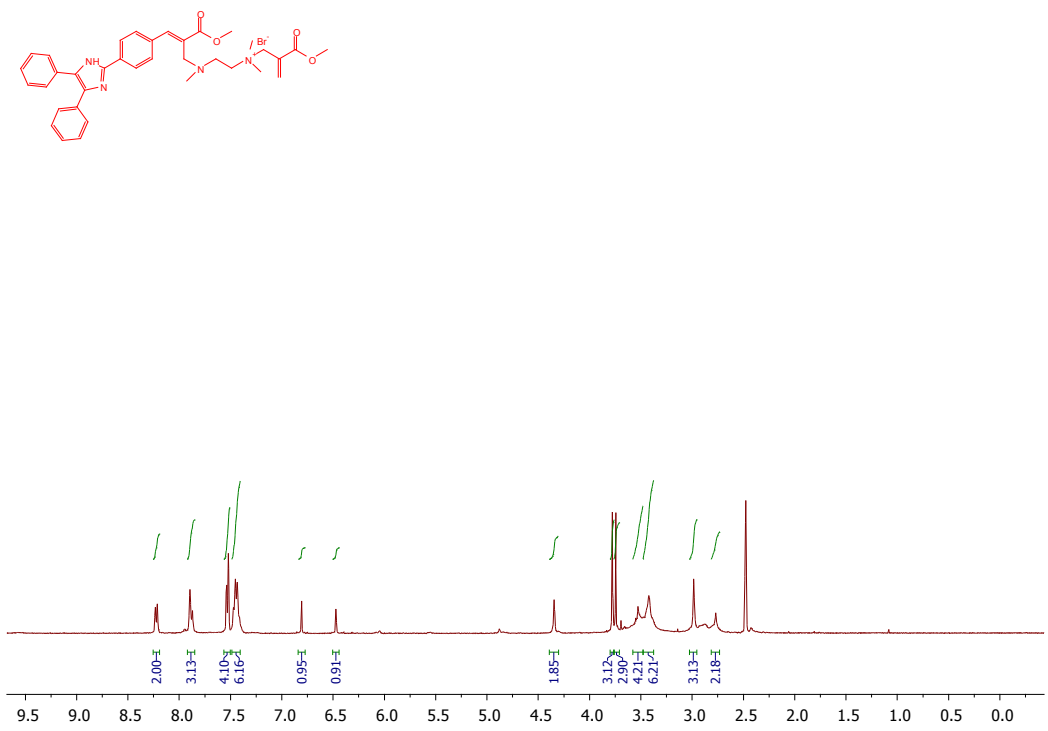


Figure 44. 400 MHz ^{1}H NMR of Compound **10h** in $CDCl_3$

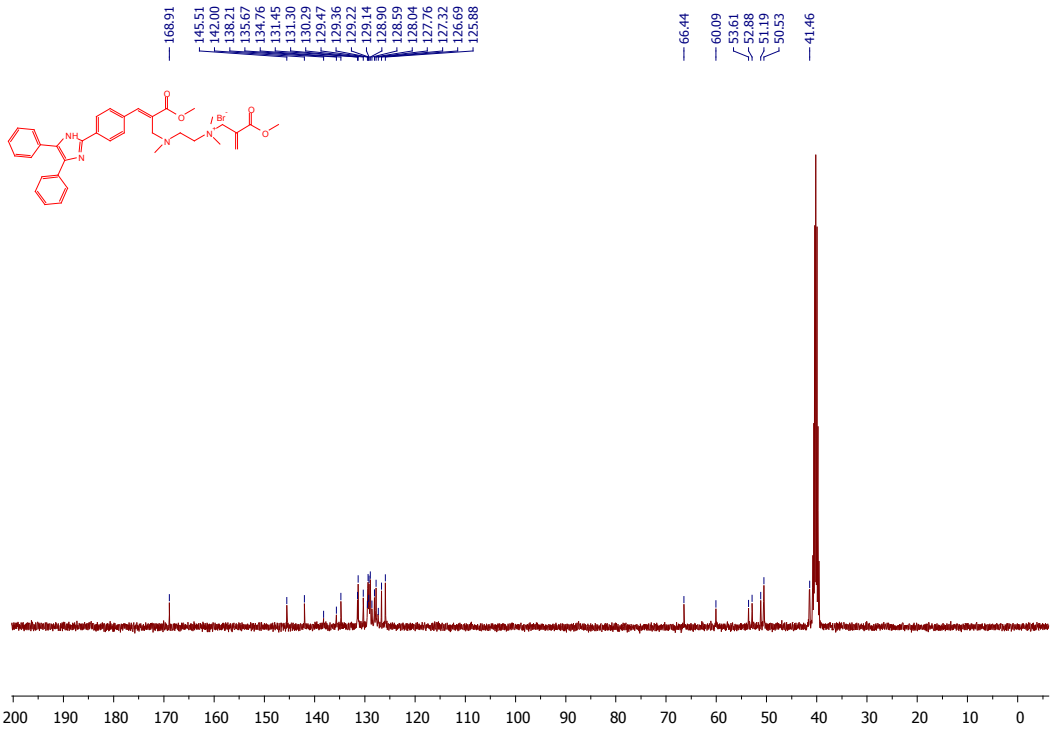


Figure 45. 101 MHz ^{13}C NMR of Compound **10h** in $CDCl_3$

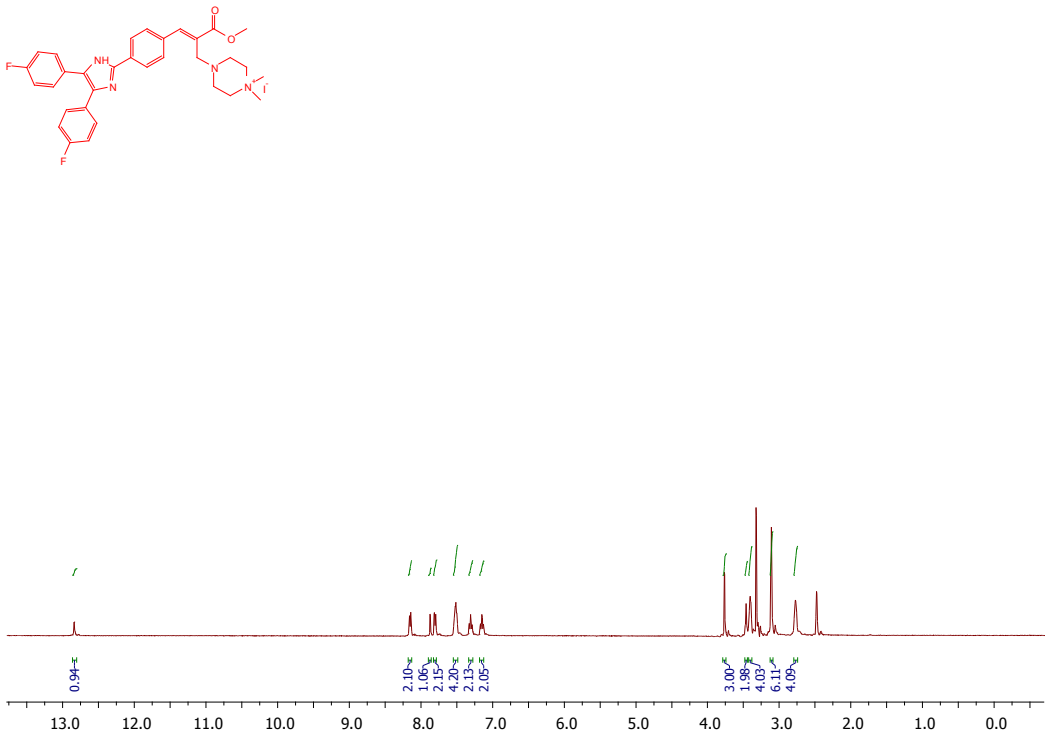


Figure 46. 400 MHz ^{1}H NMR of Compound **10d** in $CDCl_3$

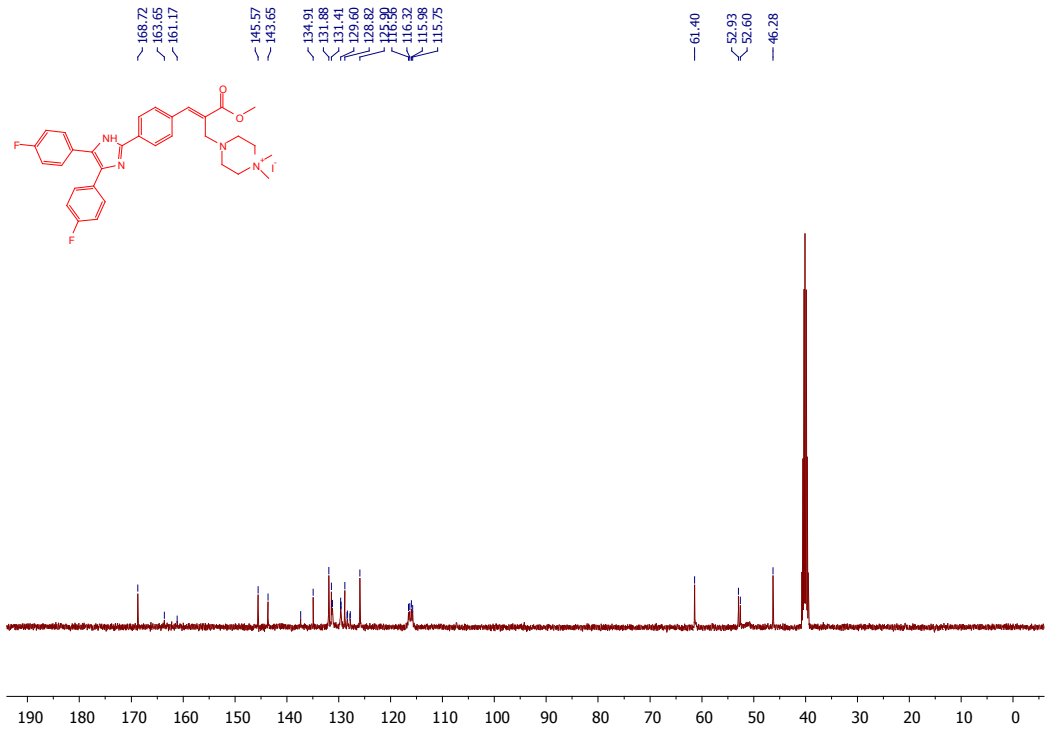


Figure 47. 101 MHz ^{13}C NMR of Compound **10d** in $CDCl_3$

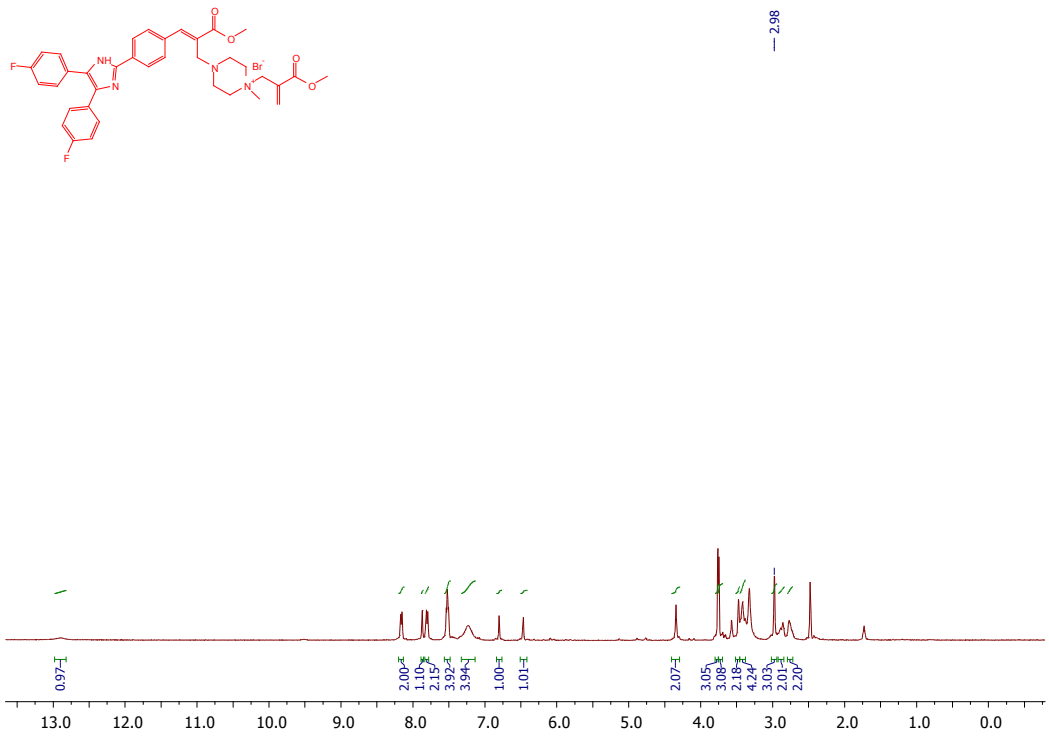


Figure 48. 400 MHz ^{1}H NMR of Compound **10e** in $CDCl_3$

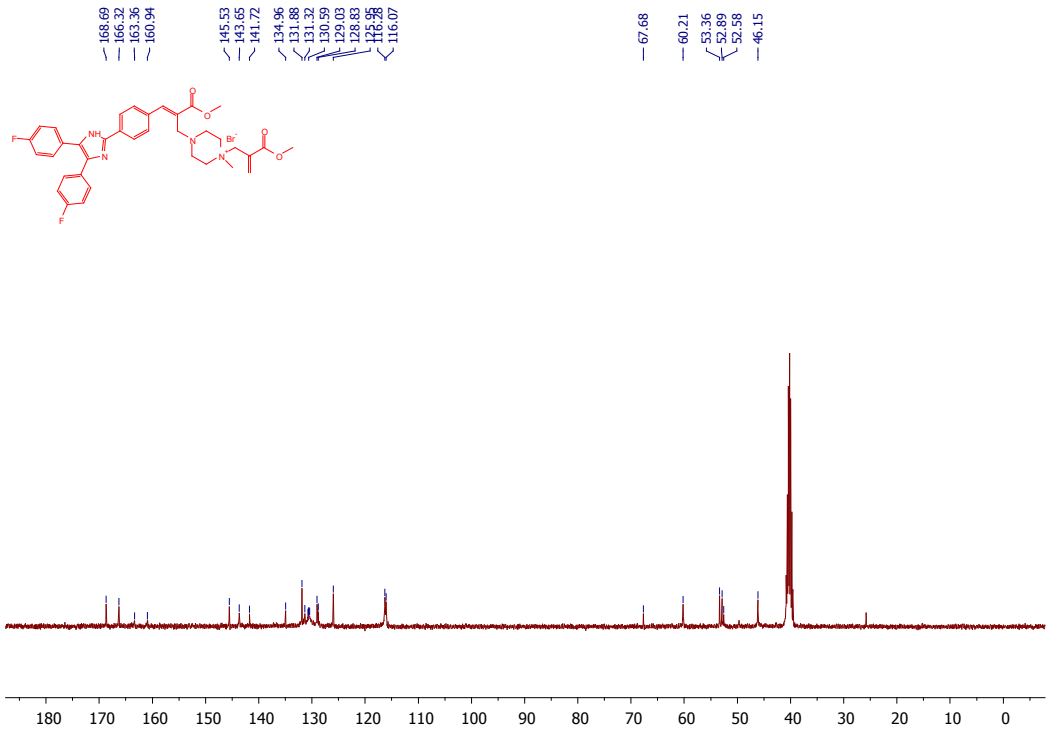


Figure 49. 101 MHz ^{13}C NMR of Compound **10e** in $CDCl_3$

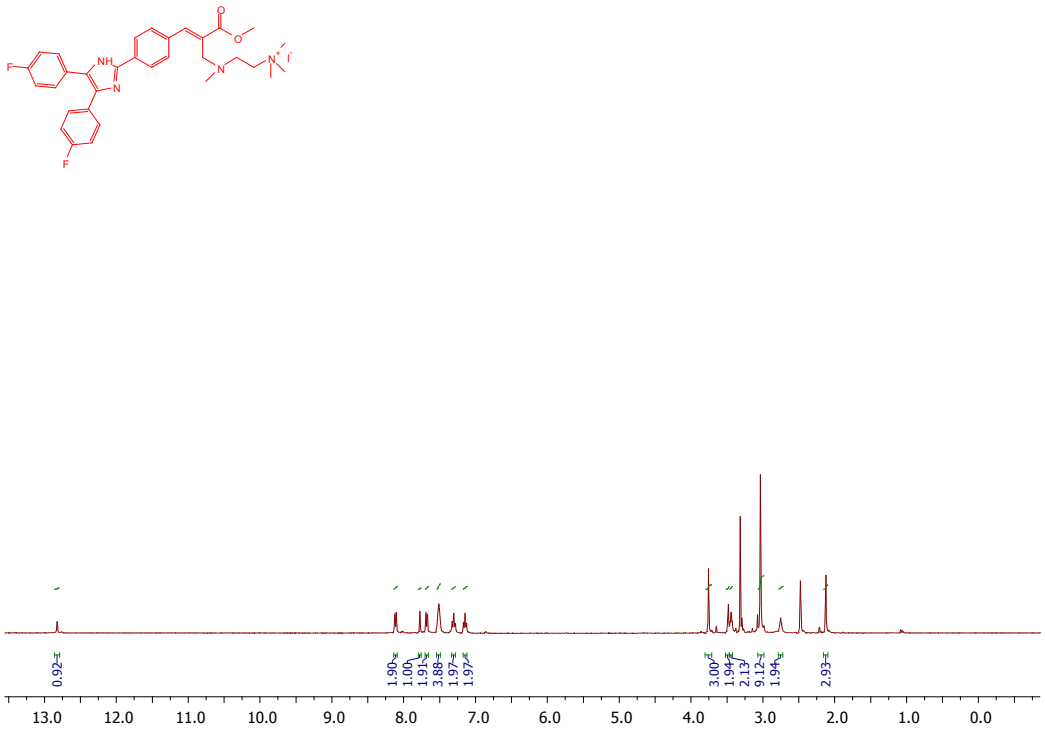


Figure 50. 400 MHz ^{1}H NMR of Compound **10j** in $CDCl_3$

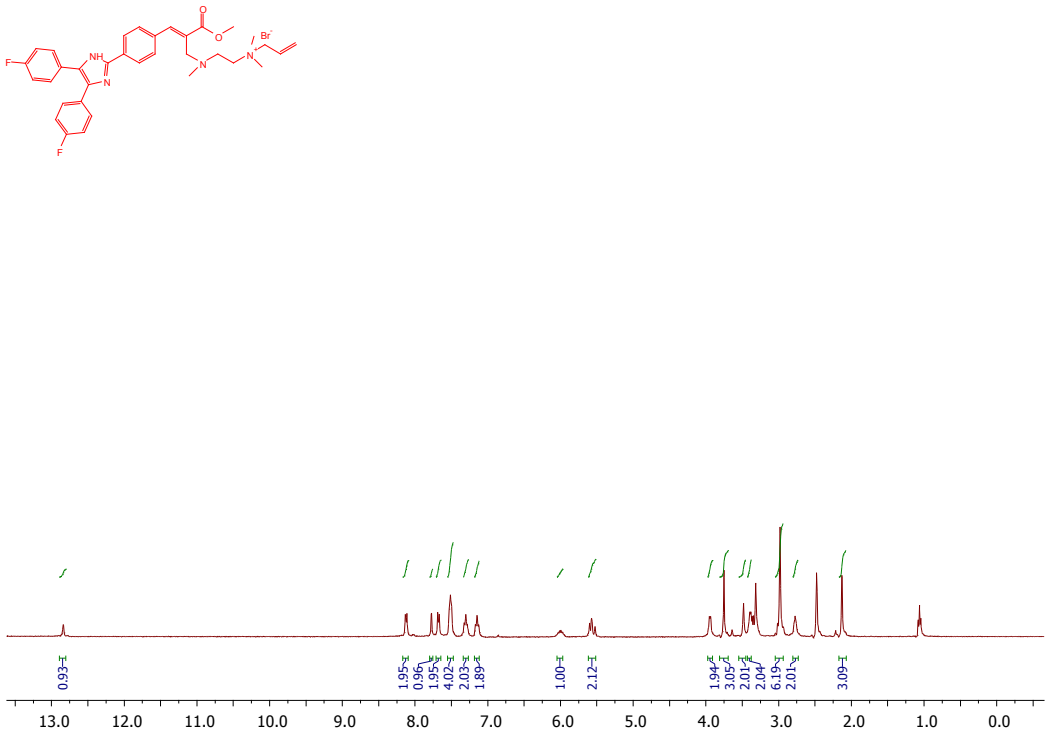


Figure 51. 400 MHz ^{1}H NMR of Compound **10l** in $CDCl_3$

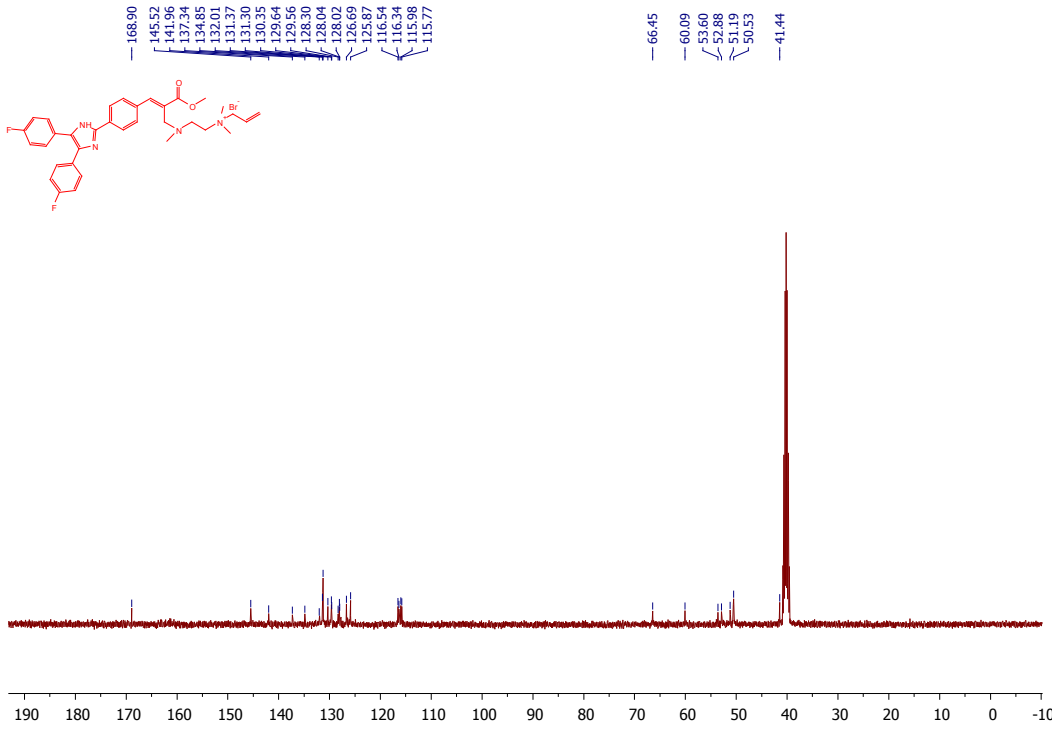


Figure 52. 101 MHz ^{13}C NMR of Compound **10l** in $CDCl_3$

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