Accepted Manuscript

A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction

Satheesh Gujarathi , Xingui Liu , Lin Song , Howard Hendrickson , Guangrong Zheng

PII: S0040-4020(14)00767-4

DOI: 10.1016/j.tet.2014.05.073

Reference: TET 25622

To appear in: *Tetrahedron*

Received Date: 10 April 2014

Revised Date: 16 May 2014

Accepted Date: 19 May 2014

Please cite this article as: Gujarathi S, Liu X, Song L, Hendrickson H, Zheng G, A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.05.073.

Tetrahedron
journal homepage: www.elsevier.com

A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction

Satheesh Gujarathi, Xingui Liu, Lin Song, Howard Hendrickson, Guangrong Zheng*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

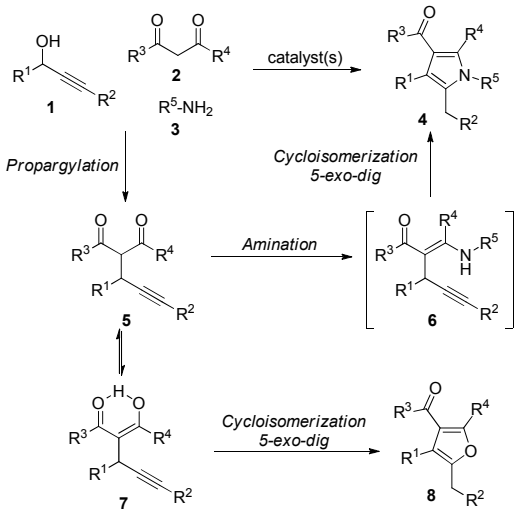
Keywords:
Propargylation
$AgSbF_6$
Cycloisomerization
Pyrrole
Heterocycles

ABSTRACT

Development of an efficient synthesis of fully substituted pyrroles via a sequential propargylation/amination/cycloisomerization was accomplished using $AgSbF_6$ as a catalyst. The one-pot three-component reaction of propargylic alcohols, 1,3-dicarbonyl compounds, and primary amines proceeds at a mild temperature, which prevents the formation of furan by-product. The reaction was also successfully applied to the more basic aliphatic amines with the addition of 1.1 eq. of acetic acid.

1. Introduction

There is a great interest in developing efficient synthetic routes to structurally diverse heterocycles from readily available simple starting materials, especially in pharmaceutical chemistry where heterocycles are predominant building blocks.[1] Pyrrole, one of the major heterocycles, is embedded in many biologically active compounds of both natural and synthetic origin, and is also present in many organic materials.[2,3] Compounds with pyrrole ring as a key structural motif display an impressive range of biological properties,[3] such as antibacterial,[4] antifungal,[5] anti-inflammatory,[6] antitubulin,[7] anticonvulsant,[8] and hypnotic[9] activities. Consequently, considerable efforts have been made in developing methods for construction of the pyrrole ring.[10] The most efficient and versatile strategy for the assembly of pyrroles is via multicomponent reactions in which three or more starting materials undergo a series of chemical reactions in a single-pot without separation and purification of intermediates.[3,10a,10h,11] One prominent example of this strategy is the synthesis of fully substituted pyrroles **4** through a sequential propargylation/amination/cycloisomerization reaction of propargylic alcohols **1**, 1,3-dicarbonyl compounds **2**, and primary amines **3** (Scheme 1).[12-14] Three methods have been reported for this type of one-pot process, including a cooperative [Ru(η^3-2-C_3H_4Me)(CO)(dppf)][SbF_6]/trifluoroacetic acid (TFA) catalytic system,[12] a single metal catalyst $InCl_3$,[13] and more recently, a heterobimetallic catalyst [Ir(COD)($SnCl_3$)Cl(μ-Cl)]$_2$ (Ir^{III}-Sn^{IV}).[14] A noticeable limitation of the first method is the high cost of catalyst and the propargylic alcohols used in the method appear to be limited to the ones with a terminal alkyne group (R^2 = H, Scheme 1). The Ir^{III}-Sn^{IV} method only works on aromatic primary amines.[14] The $InCl_3$ method appears to be the most attractive because of the low cost of catalyst and the wide substrate compatibility, but a relatively high temperature (reflux in toluene) is required.[13] Therefore, it is still desirable to further develop mild, highly efficient, and inexpensive reaction systems for this one-pot transformation.



Scheme 1. One-pot synthesis of fully substituted pyrroles and the competing furan formation.

* Corresponding author. Tel.: +1-501-526-6787; fax: +1-501-526-5945; e-mail: gzheng@uams.edu

A number of Brønsted and Lewis acid catalysts have been reported for the nucleophilic substitution of propargylic alcohols **1** with 1,3-dicarbonyl compounds **2** to form compounds **5** (Scheme 1).[15] Some of these catalysts have been shown to facilitate the subsequent amination/cycloisomerization for the conversion of **5** to pyrroles **4**, although in poor yields.[13] In relation to our recent efforts on the synthetic application of propargylic alcohols,[16] we expanded the list of catalytic systems for the conversion of 1,3-diphenylpropargylic alcohol **1a** and ethyl acetoacetate **2a** to compound **5a** (Table 1). Further exploration of these catalysts on the subsequent amination/cycloisomerization with aniline **3a** led to the discovery of a novel $AgSbF_6$-catalyzed, efficient and mild one-pot synthesis of fully substituted pyrroles that we report herein.

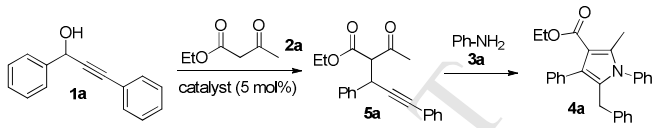
2. Results and discussion

We selected **1a**, **2a**, and aniline **3a** as the model starting materials to survey catalysts and reaction conditions for the one-pot propargylation/amination/cycloisomerization reaction. In addition to Amberlite IR-120H in acetonitrile (CH_3CN) (Table 1, entry 1),[16] we found a number of catalytic systems, including $Zn(OTf)_2$ in toluene, $Sc(OTf)_3$ in toluene, $Yb(OTf)_3$ in BMIM-PF_6, $Bi(NO_3)_3$ in toluene, $Bi(OTf)_3$ in toluene, $AgPF_6$ in toluene, $AgBF_4$ in toluene, and $AgSbF_6$ in toluene, were also capable of facilitating the nucleophilic substitution of **1a** with **2a** to form intermediate **5a** under mild heating (60 °C) (Table 1, entries 2-9). Upon completion of the conversion from **1a** to **5a** (0.5-3 hours, monitored by TLC and GC-MS), aniline **3a** was added to the reaction mixture to carry out the subsequent amination/cycloisomerization reaction. We were delighted to find that the fully substituted pyrrole **4a** was formed in the presence of $Zn(OTf)_2$, $Yb(OTf)_3$, $Bi(NO_3)_3$, $Bi(OTf)_3$, $AgPF_6$, $AgBF_4$, and $AgSbF_6$ (Table 1, entries 2, 5-9), among which $AgSbF_6$ gave the best results with 82% isolated yield (Table 1, entry 9). With $AgSbF_6$, the amination/cycloisomerization reaction proceeded smoothly at 60 °C, no by-products were observed from TLC and GC-MS analysis. The reaction took place without exclusion of air or moisture from the reaction mixture. However, when other catalysts were used, reflux temperature of toluene (110 °C) was required for the conversion of **5a** to **4a**. Due to the high temperature used in these reactions, a significant amount of **5a** was converted into furan **8a** (Scheme 1, where R^1=R^2=Ph, R^3=OEt, R^4=Me), which was partially co-eluted with **4a** on a silica gel column, leading to low yields of **4a** and tedious purification process. The side reaction was somewhat predictable since several Lewis acids, including $InCl_3$,[15e] $FeCl_3$,[17] and $Cu(OTf)_2$,[15g] have previously been shown to efficiently catalyze furan formation at high temperature (from 1 and 2 to 8 via 5, Scheme 1). Although not explicitly discussed, we suspect that the furan formation could have occurred in the previously reported $InCl_3$–catalyzed pyrrole formation reaction due to the high temperature.[13,18] Interestingly, we observed that in the absence of catalysts, intermediate **5a** could also be converted into the corresponding furan in toluene under reflux, albeit in low rate.[19] Thus, reaction temperature played a key role in the formation of furan by-product. The superior results obtained under $AgSbF_6$ are likely due to its ability of facilitating the amination/cycloisomerization reaction at a temperature not high enough for the furan formation.

The reaction also tested in CH_3CN, 1,2-dichloroethane (1,2-DCE), and nitromethane (CH_3NO_3) (Table 1, entries 10-12). The results indicated that the propargylation reaction could tolerate different solvents; **5a** was rapidly formed at 60 °C when 1,2-DCE was used as solvent or at room temperature when CH_3CN or CH_3NO_3 was used as solvent. However, the amination/cycloisomerization reaction was remarkably sensitive to solvents. Toluene was found to be the most effective for the conversion of **5a** to **4a**. Compared to toluene, a longer reaction time was required with 1,2-DCE as solvent (Table 1, entry 11), while CH_3CN did not promote the formation of **4a** and the yield of **4a** was poor when CH_3NO_3 was used as solvent.

The mechanism for the present $AgSbF_6$-catalyzed one pot pyrrole formation is likely to be similar to previously proposed $InCl_3$-catalyzed reaction.[13]

Table 1. Screening of reaction conditions for the formation of fully substituted pyrroles



Entry[a]	Catalyst	Solvent	Temp (°C)[b]	Time (h)[c]	Temp (°C)[d]	Time (h)[e]	Yield (%)[f]
1	Amberlite IR-120H[g]	CH_3CN	reflux	2	reflux	12	0
2	$Zn(OTf)_2$	toluene	60	1	reflux	12	37
3	$Sc(OTf)_3$	toluene	60	1	reflux	14	0
4	$Yb(OTf)_3$	BMIM-PF_6	60	0.5	100	10	0
5	$Bi(NO_3)_3$	toluene	60	2	reflux	12	35
6	$Bi(OTf)_3$	toluene	60	2	reflux	14	54
7	$AgPF_6$	toluene	60	2	reflux	14	25
8	$AgBF_4$	toluene	60	3	reflux	14	18
9	**$AgSbF_6$**	**toluene**	**60**	**0.5**	**60**	**6**	**82**
10	$AgSbF_6$	CH_3CN	Rt	1	reflux	12	0
11	$AgSbF_6$	1,2-DCE	60	0.5	reflux	12	76
12	$AgSbF_6$	CH_3NO_2	Rt	1	60	12	31

[a]Reaction conditions: **1a**/**2a**/catalyst = 0.5:0.55:0.025 in 2 mL solvent; **3a** (0.55 mmol) added after **1a** fully consumed; reaction temperature and time as indicated.

[b]Reaction temperature for **5a** formation.

[c]Reaction time for **5a** formation.

[d]Reaction temperature for amination/cycloisomerization.

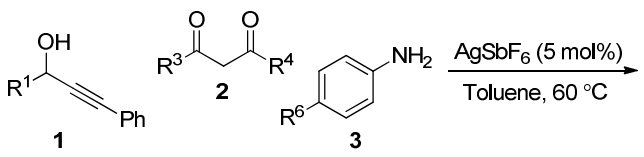
[e]Reaction time for amination/cycloisomerization.

[f]Isolated yields of **4a**.

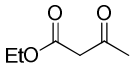
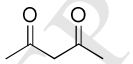
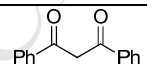
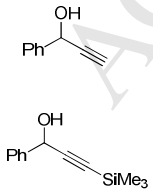
[g]150 mg catalyst was used.

The scope and limitations of this novel $AgSbF_6$-catalyzed one-pot pyrrole synthesis was then explored under the standard conditions (Table 1, entry 9). We initially applied the reaction procedure to **1a** and **2a** with a series of substituted anilines (Table 2, entries 2-6). The reactions proceeded smoothly, yielding the corresponding pyrroles in good isolated yields. It is interesting to note that every reaction gave a single product peak on GC-MS and practically identical isolated yields were obtained with different anilines, although electron-donating group (entry 5, methoxy) substituted aniline appeared to react slightly faster when compared to electron-withdrawing group (entries 2-4, and 6, halogens and methyl ester) substituted anilines.

Table 2. Synthesis of fully substituted pyrroles **4** from anilines **3**[a]



The scope of the application was then extended to various benzylic phenyl ring-substituted 1,3-diphenyl propargylic alcohols (Table 2, entries 7-13). Both electron-donating group (entries 8 and 13) substituted and electron-withdrawing group (entries 7, 9, 10 and 11, halogens) substituted 1,3-diphenyl propargylic alcohols participated well in the reaction. However, no propargylation of **2a** with 4-cyano substituted 1,3-diphenyl propargylic alcohol **1f** was observed in toluene even at reflux temperature. This can be explained by the destabilization effect of the strong electron-withdrawing cyano group on the putative carbocation intermediate from propargylic alcohol. It appeared the destabilization effect could be compensated by an increase in solvent polarity; when toluene was replaced by 1,2-DCE, the one-pot reaction proceeded smoothly at reflux temperature, and completed in 16 h to afford **4k** in 75% isolated yield (Table 2, entry 11). Good yields were also obtained when acetylacetone **2b** was used in place of **2a** (Table 2, entries14-18). However, when

Entry	Propargylic alcohol	Dicarbonyl compound	Amine	Product	Time (h)[b]	Isolated yield
1	**1a** (R^1=Ph)		**3a** (R^6=H)	**4a**	6	82%
2	**1a**		**3b** (R^6=Cl)	**4b**	6	74%
3	**1a**		**3c** (R^6=Br)	**4c**	8	75%
4	**1a**		**3d** (R^6=I)	**4d**	7	76%
5	**1a**	**2a**	**3e** (R^6=OMe)	**4e**	5	74%
6	**1a**		**3f** (R^6=CO_2Me)	**4f**	8	77%
7	**1b** (R^1=4-F-Ph)	**2a**	**3a** (R^6=H)	**4g**	8	73%
8	**1c** (R^1=4-MeO-Ph)	**2a**	**3a** (R^6=H)	**4h**	6	75%
9	**1d** (R^1=3-Cl-Ph)	**2a**	**3a** (R^6=H)	**4i**	6	73%
10	**1e** (R^1=4-Cl-Ph)	**2a**	**3b** (R^6=Cl)	**4j**	5	74%
11	**1f** (R^1=4-CN-Ph)	**2a**	**3b** (R^6=Cl)	**4k**	16[c]	75%[d]
12	**1b (** R^1=4-F-Ph)	**2a**	**3b** (R^6=Cl)	**4l**	10	74
13	**1g** (R^1=3,4-(OCH_2O)-Ph)	**2a**	**3b** (R^6=Cl)	**4m**	7	71%
14	**1a** (R^1=Ph)		**3a** (R^6=H)	**4n**	8	73%
15	**1c** (R^1=4-MeO-Ph)		**3a** (R^6=Cl)	**4o**	7	73%
16	**1h** (R^1=3,4,5-$(MeO)_3$Ph)		**3f** (R^6=CO_2Me)	**4p**	8	73%
17	**1h** (R^1=3,4,5-$(MeO)_3$Ph)	**2b**	**3b** (R^6=Cl)	**4q**	10	73%
18	**1h** (R^1=3,4,5-$(MeO)_3$Ph)		**3c** (R^6=Br)	**4r**	8	78%
19	**1a** (R^1=Ph)	 **2c**	**3a** (R^6=H)	-	12[e]	0
20	 **1i**	**2a**	**3a** (R^6=H)	**4s**	6	Trace
21	**1j**	**2a**	**3a** (R^6=H)	**4s**	6	30%

[a]Reaction conditions: $AgSbF_6$ (0.025 mmol), **1** (0.5 mmol), and **2** (0.55 mmol) in 2 mL toluene at 60 °C for 0.5-2 h, **3** (0.55 mmol) then added and reaction continued at 60 °C for the period of time indicated.

[b]Time for amination/cycloisomerization.

[c]Reflux in 1,2-DCE.

[d]Isolated yield from reaction in 1,2-DCE; no reaction was observed in toluene.

[e]Reflux in toluene.

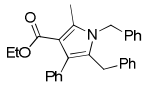
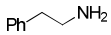
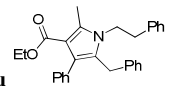
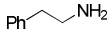
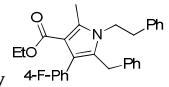
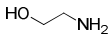
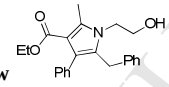
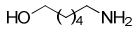
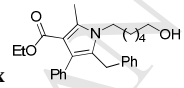
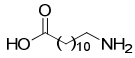
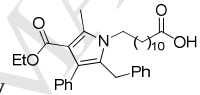
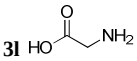
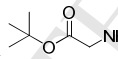
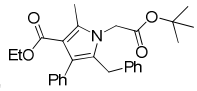
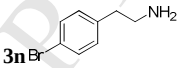
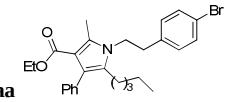
1,3-diphenyl diketone **2c** was used, the propargylation of **2c** with **1a** went smoothly, but no subsequent amination/cycloisomerization with aniline occurred after 12 h reflux in toluene (Table 2, entry 19). We also investigated the reactivity of 1-phenyl propargylic alcohol **1i** under the standard conditions (Table 2, entry 19). Treatment of **1i** with **2a** followed by adding aniline **3a** resulted in a complex mixture. Trace amount of compound **4s** was detected by GC-MS, but purification attempts of by column chromatography on silica gel were unsuccessful. When the terminal alkyne of **1i** was capped with a trimethylsilyl group, the resulting propargylic alcohol **1j** reacted smoothly with **2a** and **3a**. Surprisingly, the resulting pyrrole product turned out to be 4s (Table 2, entry 20). Cleavage of the trimethylsilyl group occurred during the process.

We extended the scope of the one-pot procedure by employing aliphatic primary amines (Table 3). Propargylation of **2a** with **1a** followed by the addition of benzylamine **3g** or phenethylamine **3h** afforded the corresponding pyrroles **4t** and **4u**, respectively. Unfortunately, the purification process for these products was tedious. Unlike the reactions involving aniline derivatives which routinely afforded a single product, reactions using **3g** and **3h** resulted in the formation of furan **8** (general structure as in Scheme 1) by-products as determined by GC-MS. We reasoned that the higher basicity of aliphatic amines, relative to anilines, was responsible for promoting the *O*-cycloisomerization. In fact, furan formation from propargylated dicarbonyl intermediates under stoichiometric amount of inorganic bases has been reported.[14,15b] Gratifyingly, modification of the reaction by adding 1.1 equiv (relative to amine) of acetic acid to the reaction mixture completely eliminated the formation of furans; **4t** and **4u** were isolated in good yields (Table 3, entries 1 and 2). Thus, the key to avoiding the furan by-product is to maintain the reaction at near neutral or slightly acidic pH. Under this modified method, 1-phenylhept-2-yn-1-ol (**1k**) also worked well with 4-bromo phenethylamine **3n**, yielding the corresponding pyrrole in good yield (entry 9). Amino alcohols **3i** and **3j** also gave satisfactory results with the addition of acetic acid; clean and complete conversion to the corresponding pyrroles **4w** and **4x**, respectively, was observed (entries 4 and 5). In addition, amino acids as substrates were examined, in which 12-aminododecanoic acid **3k** proceeded smoothly to the corresponding pyrrole **4y** in 71% isolated yield (entry 6). However, no desired product was obtained when glycine **3l** was used (entry 7), likely due to the poor solubility of glycine in toluene. After protection of the carbonyl acid group of glycine with a *t*-butyl group, the resulting compound **3m** worked well to afford the corresponding pyrrole **4z** in 73% isolated yield (entry 8).

3. Conclusions

In summary, we have developed a highly efficient method for the direct nucleophilic substitution of the hydroxyl group of propargylic alcohols with 1,3-dicarbonyl compounds, and the sequential formation of fully substituted pyrroles with a wide range of primary amines in a simple one-pot operation. The $AgSbF_6$ catalyzed sequential propargylation/amination/cycloisomerization reaction proceeds at a relatively mild temperature (60 °C), which is advantageous in preventing the formation of furan byproduct. In addition, furan formation when aliphatic primary amines are used can be effectively avoided by adding 1.1 equiv. of acetic acid to the reaction. The method presented here could be a valuable addition to the available strategies of pyrrole synthesis.

Table 3. Synthesis of fully substituted pyrroles **4** from aliphatic primary amines **3**

Entry[a]	Propargylic alcohol	Amine	Product	Time (h)[b]	Isolated yield
1	**1a** (R^1=Ph, R^2=Ph)	**3g** 	**4t** 	6	77%
2	**1a**	**3h** 	**4u** 	1[c]	82%
3	**1b** (R^1=4-F-Ph, R^2=Ph)	**3h** 	**4v** 	3	77%
4	**1a**	**3i** 	**4w** 	6	76%
5	**1a**	**3j** 	**4x** 	7	76%
6	**1a**	**3k** 	**4y** 	14	71%
7	**1a**	**3l** 	-	14[d]	0
8	**1a**	**3m** 	**4z** 	6	73%
9	**1k** (R^1=Ph, R^2=n-Bu)	**3n** 	**4aa** 	14	67%

[a]Reaction conditions: same as in Table 2 except 1.1 equiv of HOAc was added together with **3**.

[b]Reaction time for amination/cycloisomerization.

[c]50 °C.

[d]Reflux.

4. Experimental section

4.1. General

NMR spectra were recorded with 400 MHz spectrometers for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm using tetramethylsilane as an internal standard. Multiplicities of NMR signals are designated as singlet (s), broad singlet (*br* s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). High resolution mass spectra (HRMS) were taken with Q-TOF mass spectrometer. Flash chromatography was performed using silica gel (100-200 mesh) as the stationary phase. Reaction progress was monitored by thin layer chromatography (silica-coated glass plates and visualized under UV light and in iodine) and gas chromatography-mass spectrometer (GC-MS). Melting points were measured on a capillary melting point apparatus and are uncorrected. All reagents and solvents were purchased from commercial sources and used without further purification. Propargylic alcohols **1b-1h** and **1k** were prepared by reacting lithium phenylacetylide (10 mmol, 1M in THF) with an appropriate aldehyde (10 mmol) at -78 °C.

4.2. General Procedure for the Synthesis of Fully Substituted Pyrroles

To a stirred solution of propargylic alcohol (**1a-1k**, 0.5 mmol) in toluene (2 mL) was added 1,3-dicarbonyl compound (**2a-2c**, 0.55 mmol) and $AgSbF_6$ (0.025 mmol, purchased from Sigma-Aldrich Co.) and the mixture were heated at 60 °C. After consumption of the starting materials, an appropriate amine (0.55

mmol) was added and the reaction continued at the same temperature until completion (GC and TLC analysis). When an aliphatic amine (**3g-3n**) was used, 0.55 mmol HOAc was added prior to the addition of amine. The reaction mixture was diluted with ethylacetate (10 mL), and then washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to give desired products.

*4.2.1. Ethyl 1,4-diphenyl-2-methyl-5-benzyl-1H-pyrrole-3-carboxylate (**4a**).*[20] Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.39 (m, 8H), 7.00 (t, *J* = 3.6 Hz, 3H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.95-6.64 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.68 (s, 2H), 2.27 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 139.7, 137.5, 136.6, 136.4, 130.5, 129.5, 129.0, 128.6, 128.5, 128.1, 127.9, 127.6, 126.2, 125.7, 124.2, 111.2, 59.2, 30.8, 14.0, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{26}NO_2$ 396.1964; found 396.1968.

*4.2.2. Ethyl 1-(4-chlorophenyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4b**).* Solid, mp 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.21 (m, 7H), 7.02-6.06 (m, 3H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.66 (t, *J* = 4.0 Hz, 2H), 4.09 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 2H), 2.27 (s, 3H), 1.02 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 139.5, 136.5, 136.2, 136.0, 134.5, 130.4, 129.9, 129.4, 129.5, 128.1, 127.6, 126.4, 125.9, 124.5, 111.6, 59.3, 30.8, 14.0, 12.5 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}{}^{35}ClNO_2$ 430.1575; found 430.1590.

*4.2.3. Ethyl 1-(4-bromophenyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4c**).* Solid, mp 95-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.29 (m, 7H), 7.04 (s, 3H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.69-6.62 (m, 2H), 4.09 (q, *J* = 8.0 Hz, 2H), 3.67 (s, 2H), 2.26 (s, 3H), 1.02 (t, *J* = 8. 0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 139.5, 136.5, 136.4, 136.1, 132.2, 130.4, 130.2, 129.3, 128.1, 127.6, 126.3, 125.9, 124.5, 122.5, 111.6, 59.3, 30.7, 14.0, 12.5 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}{}^{79}BrNO_2$ 474.1069; found 474.1085.

*4.2.4. Ethyl 1-(4-iodophenyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4d**).* Solid, mp 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.39-7.21 (m, 6H), 7.04 (s, 3H), 6.67-6.61 (m, 4H), 4.08 (q, *J* = 8.0 Hz, 2H), 3.67 (s, 2H), 2.26 (s, 3H), 1.01 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 139.5, 138.2, 137.2, 136.3, 136.1, 130.4, 129.3, 128.1, 127.6, 126.3, 125.9, 124.5, 111.6, 94.0, 59.3, 30.7, 14.0, 12.5 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}INO_2$ 522.0930; found 522.0920.

*4.2.5. Ethyl 1-(4-methoxyphenyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4e**).* Solid, mp 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.16 (m, 5H), 7.05-7.01 (m, 3H), 6.78 (q, *J* = 8.0 Hz, 4H), 6.69-6.63 (m, 2H), 4.08 (q, *J* = 8.0 Hz, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 2.26 (s, 3H), 1.01 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 159.4, 139.9, 136.9, 136.5, 130.5, 130.2, 129.7, 129.6, 128.1, 127.9, 127.6, 126.2, 125.7, 124.0, 114.1, 111.0, 59.1, 55.5, 30.8, 14.0, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{28}NO_3$ 426.2069; found 426.2057.

*4.2.6. Ethyl 1-(4-methoxycarbonylphenyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4f**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.42-7.23 (m, 5H), 7.05-6.95 (m, 5H), 6.63-6.58 (m, 2H), 4.09 (q, *J* = 8.0 Hz, 2H), 3.92 (s, 3H), 3.69 (s, 2H), 2.27 (s, 3H), 1.02 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.8, 141.6, 139.3, 136.3, 136.1, 130.4, 130.3, 130.2, 129.2, 128.7, 128.1, 128.0, 127.6, 126.4, 125.9, 124.7, 111.8, 59.3, 52.4, 30.7, 14.0, 12.5 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{28}NO_4$ 454.2018; found 454.2031.

*4.2.7. Ethyl 1-phenyl-2-methyl-4-(4-fluorophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4g**).* Solid, mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 7.05-6.97 (m, 5H), 6.94-6.85 (m, 2H), 6.62-6.53 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 2.27 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 163.0, 160.6, 139.6, 137.4, 136.7, 132.4, 132.3, 132.0, 132.0, 129.6, 129.1, 128.6, 128.6, 128.0, 128.0, 125.8, 123.1, 114.5, 114.3, 111.2, 59.3, 30.7, 29.8, 14.1, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}FNO_2$ 414.1869; found 414.1884.

*4.2.8. Ethyl 1-phenyl-2-methyl-4-(4-methoxyphenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4h**).*[20] Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 7.02 (t, *J* = 4.0 Hz, 3H), 6.97-6.85 (m, 4H), 6.82 (bt, 2H), 4.11 (q, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 2H), 2.26 (s, 3H), 1.07 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 158.2, 139.8, 137.5, 136.4, 131.5, 129.5, 128.9, 128.7, 128.6, 128.4, 128.1, 127.9, 125.7, 123.8, 113.1, 111.2, 59.2, 55.2, 30.7, 14.2, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{28}NO_3$ 426.2069; found 426.2063.

*4.2.9. Ethyl 1-phenyl-2-methyl-4-(3-chlorophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4i**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.39 (m, 8H), 7.03 (t, *J* = 4.0 Hz, 3H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.60 (dd, *J* = 3.6 and 6.8 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 2.27 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 139.4, 138.4, 137.3, 137.0, 133.3, 130.8, 129.7, 129.1, 128.8, 128.7, 128.6, 128.6, 128.0, 126.4, 125.9, 122.8, 111.1, 59.3, 30.8, 14.0, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}{}^{35}ClNO_2$ 430.1574; found 430.1565.

*4.2.10. Ethyl 1-(4-chlorophenyl)-2-methyl-4-(4-chlorophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4j**).* Solid, mp 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 6H), 7.08-7.03 (m, 3H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.64 (t, *J* = 4.0 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 2.26 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 139.2, 136.7, 135.8, 134.7, 134.7, 132.3, 131.8, 129.8, 129.5, 129.3, 128.2, 128.0, 127.8, 126.0, 123.3, 111.4, 59.4, 30.7, 14.1, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}{}^{35}Cl_2NO_2$ 464.1184; found 464.1176.

*4.2.11. Ethyl 1-(4-chlorophenyl)-2-methyl-4-(4-cyanophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4k**).* Solid, mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 4.0 Hz, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.64 (t, *J* = 3.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 2.27 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 141.6, 138.9, 137.3, 135.6, 134.9, 131.5, 131.2, 129.8, 129.4, 128.3, 127.9, 126.3, 123.0, 119.4, 111.2, 110.0, 59.6, 30.7, 14.1, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{24}{}^{35}ClN_2O_2$ 455.1526, found 455.1545.

*4.2.12. Ethyl 1-(4-chlorophenyl)-2-methyl-4-(4-fluorophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4l**).* Solid, mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 4H), 7.08-6.91 (m, 5H), 6.90-6.83 (m, 2H), 6.65 (dd, *J* = 3.6, 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 2.26 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 163.0, 160.6, 139.3, 136.6, 135.9, 134.6, 132.1, 132.1, 132.0, 131.9, 129.9, 129.5, 129.3, 128.1, 128.0, 126.0, 123.4, 114.6, 114.4, 111.5, 59.4, 30.7, 14.1, 12.6 ppm; ; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}{}^{35}ClFNO_2$ 448.1479, found 448.1475.

*4.2.13. 1-(4-Chlorophenyl)-2-methyl-3-acetyl-4-(3,4-methylenedioxidephenyl)-5-benzyl-1H-pyrrole (**4m**).* Solid, mp 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.0 Hz, 2H), 7.07-7.02 (m, 3H), 6.86-6.78 (m, 5H), 6.65 (dd, *J* = 4.0, 8.0 Hz, 2H), 4.13 (q, *J* = 8.0 Hz, 2H), 3.67 (s, 3H), 2.24 (s, 3H), 1.11 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 147.0, 146.2, 139.4, 136.3, 136.0, 134.5, 129.9, 129.9, 129.6, 129.2, 128.1, 128.1, 126.0, 124.1, 123.5, 111.6, 111.3, 107.7, 100.8, 59.4, 30.8, 14.2, 12.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{25}ClNO_4$ 474.1472, found 474.1456.

*4.2.14. 1,4-Diphenyl-2-methyl-3-acetyl-5-benzyl-1H-pyrrole (**4n**).*[20] Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.24 (m, 8H), 7.01 (t, *J* = 4.0 Hz, 3H), 6.95-6.91 (m, 2H), 6.62-6.56 (m, 2H), 3.65 (s, 2H), 2.28 (s, 3H), 1.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 139.5, 137.3, 136.8, 136.0, 130.7, 129.5, 129.1, 128.6, 128.5, 128.4, 128.1, 128.0, 127.0, 125.8, 123.8, 121.9, 31.1, 30.8, 13.0 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{24}NO$ 366.1853, found 366.1837.

*4.2.15. 1-(4-Chlorophenyl)-2-methyl-3-acetyl-4-(4-methoxyphenyl)-5-benzyl-1H-pyrrole (**4o**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 5H), 7.07-7.02 (m, 3H), 6.92 (d, *J* = 8.0 Hz, 2H), 6. 83 (d, *J* = 8.0 Hz, 2H), 6.63 (dd, *J* = 4.0, 8.0 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 2H), 2.22 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 158.8, 139.4, 135.8, 135.7, 134.5, 131.6, 129.8, 129.4, 129.2, 128.5, 128.1, 128.0, 125.9, 123.6, 122.1, 113.9, 55.3, 31.0, 30.8, 13.0 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{25}{}^{35}ClNO_2$ 430.1574, found 430.1574.

*4.2.16. Methyl 4-[2-methyl-3-acetyl-4-(3,4,5-trimethoxyphenyl)-5-benzyl-1H-pyrrol-1-yl]benzoate (**4p**).* Solid, mp 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.02-7.09 (m, 5H), 6.67-6.71 (m, 2H), 6.56, (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.77 (s, 6H), 3.70 (s, 2H), 2.25 (s, 3H), 2.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 166.1, 153.1, 141.2, 139.4, 137.1, 135.4, 131.7, 130.5, 130.3, 129.1, 128.5, 128.1, 127.9, 126.0, 124.2, 122.2, 107.6, 61.0, 56.1, 52.4, 30.9, 30.8, 12.9 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{31}H_{32}NO_6$ 514.2229; found 514.2220.

*4.2.17. 1-(4-Chlorophenyl-2-methyl-3-acetyl-4-(3,4,5-trimethoxyphenyl)-5-benzyl)-1H-pyrrole (**4q**).* Solid, mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 2H), 7.09-7.06 (m, 3H), 6.93-6.85 (d, *J* = 8.8 Hz, 2H), 6.72-6.70 (m, 2H), 6.55 (s, 2H), 3.87 (s, 3H), 3.76 (s, 6H), 3.67 (s, 2H), 2.24 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 153.1, 139.6, 137.1, 135.7, 135.6, 134.7, 131.8, 129.7, 29.4, 129.2, 128.2, 128.0, 126.0, 124.0, 122.0, 107.7, 61.0, 56.1, 30.9, 30.8, 12.9 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{29}{}^{35}ClNO_4$ 490.1785; found 490.1797.

*4.2.18. 1-(4-Bromophenyl-2-methyl-3-acetyl-4-(3,4,5-trimethoxyphenyl)-5-benzyl)-1H-pyrrole (**4r**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.13-7.05 (m, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.73-6.69 (m, 2H), 6.55 (s, 2H), 3.86 (s, 3H), 3.75 (s, 6H), 3.68 (s, 2H), 2.24 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 153.0, 139.5, 37.1, 136.2, 135.5, 132.4, 131.8, 130.0, 129.2, 128.1, 127.9, 126.0, 124.0, 122.7, 122.0, 107.6, 61.0, 56.1, 30.8, 30.8, 12.9 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{29}{}^{78}BrNO_4$ 534.1280; found 534.1293.

*4.2.19. Ethyl 1,4-diphenyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (**4s**).*[20] Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.41 (m, 3H), 7.38-7.22 (m, 7H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.88 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 137.9, 136.6, 135.8, 130.5, 129.5, 128.6, 128.4 127.5, 126.8, 126.0, 122.4, 111.1, 59.2, 14.0, 12.7, 11.3 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{22}NO_2$ 320.1651; found 320.1665.

*4.2.20. Ethyl 1,5-dibenzyl-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate (**4t**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.12 (m, 11H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.84 (d, *J* = 7.2 Hz, 2H), 4.85 (s, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 2H), 2.47 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 139.6, 137.1, 136.5, 136.0, 130.4, 128.9, 128.6, 128.0, 127.9, 127.5, 127.4, 126.3, 126.2, 125.6, 124.9, 111.2, 59.2, 47.2, 30.4, 13.9, 11.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{28}NO_2$ 410.2120; found 410.2118.

*4.2.21. Ethyl 1-phenethyl-2-methyl-4-phenyl-5-benzyl-1H-pyrrole -3-carboxylate (**4u**).* Solid, mp 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.14 (m, 11H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.80 (t, *J* = 7.2 Hz, 2H), 3.70 (s, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.55 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 139.9, 137.9, 136.7, 135.4, 130.5, 128.8, 128.7, 128.1, 127.7, 127.5, 126.9, 126.4, 126.1, 124.6, 111.1, 59.1, 46.0, 36.9, 30.5, 14.0, 11.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{30}NO_2$ 424.2276; found 424.2263.

*4.2.22. Ethyl 1-phenethyl-2-methyl-4-(4-fluorophenyl)-5-benzyl-1H-pyrrole-3-carboxylate (**4v**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.16 (m, 8H), 7.02-6.75 (m, 6H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.81 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 2H), 2.63 (t, *J* = 8.0 Hz, 2H), 2.55 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 163.0, 160.5, 139.7, 137.8, 135.5, 132.7, 132.6, 132.0, 131.9, 128.8, 128.8, 128.7, 128.0, 127.9, 126.9, 126.5, 123.5, 114.4, 114.2, 111.1, 59.2, 45.9, 36.9, 30.4, 14.0, 11.7 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{29}FNO_2$ 442.2182; found 442.2175.

*4.2.23. Ethyl 1-(2-hydroxyethyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4w**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.15 (m, 8H), 7.04 (d, *J* = 7.6 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.56 (s, 3H), 1.56 (*br* s, 1H), 0.97 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 139.7, 136.5, 135.9, 130.4, 128.7, 128.0, 127.5, 126.4, 126.2, 124.8, 111.3, 61.8, 59.2, 46.0, 30.5, 13.9, 11.9 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{26}NO_3$ 364.1912; found 364.1918.

*4.2.24. Ethyl 1-(6-hydroxyhexyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4x**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.15 (m, 8H), 7.05 (d, *J* = 7.6 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 3.57 (t, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.63 (*br* s, 1H), 1.58-1.17 (m, 8H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 139.9, 136.7, 135.3, 130.4, 128.6, 128.0, 127.5, 127.4, 126.3, 126.1, 124.4, 110.8, 62.7, 59.1, 44.2, 32.5, 30.6, 30.5, 26.7, 25.4, 13.9, 11.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{34}NO_3$ 420.2539; found 420.2556.

*4.2.25. 12-(2-Benzyl-3-phenyl-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-1-yl)dodecanoic acid (**4y**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.28 (m, 8H), 7.05 (d, *J* = 7.6 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 3.57 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.72-1.60 (m, 2H), 1.40-1.12 (m, 18H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 166.1, 139.9, 136.8, 135.4, 130.4, 128.5, 127.9, 127.5, 127.4, 126.3, 126.0, 124.4, 110.7, 59.1, 44.3, 34.1, 30.6, 30.5, 29.5, 29.4, 29.4, 29.2, 29.1, 29.1, 26.9, 24.7, 13.9, 11.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{33}H_{44}NO_4$ 518.3270; found 518.3271.

*4.2.26. Ethyl 1-(2-tert-butoxy-2-oxoethyl)-2-methyl-4-phenyl-5-benzyl-1H-pyrrole-3-carboxylate (**4z**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.04 (m, 10H), 4.27 (s, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 2H), 2.48 (s, 3H), 1.35 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 165.8, 139.0, 136.5, 136.2, 130.5, 128.7, 128.0, 127.8, 127.4, 126.4, 126.2, 124.7, 111.3, 82.6, 59.1, 46.3 30.5, 27.9, 13.9, 11.5 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{32}NO_4$ 434.2331; found 434.2317.

*4.2.27. Ethyl 1-(4-bromophenethyl)-2-methyl-4-phenyl-5-pentyl-1H-pyrrole-3-carboxylate (**4aa**).* Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.41 (m, 2H), 7.34-7.16 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.04-3.97 (m, 4H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.38-1.34 (m, 2H), 1.18-1.10 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 137.1, 136.9, 134.2, 131.9, 130.5, 130.5, 130.3, 127.4, 125.9, 122.9, 120.9, 111.2, 59.0, 45.1, 36.9, 31.5, 30.5, 24.3, 22.2, 14.0, 13.9, 11.6 ppm; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{33}{}^{79}BrNO_2$ 482.1695; found 482.1678.

Acknowledgements

The authors thank the College of Pharmacy of University of Arkansas for Medical Sciences and National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program (UL1TR000039 and KL2TR000063) for financial support.

Supplementary data

^{1}H and ^{13}C NMR spectra for all compounds are available online. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.xxxxxxx.

References and notes

1. Gomtsyan, A. *Chem. Heterocycl. Compd.* **2012**, *48*, 7-10
2. Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. *Chem. Rev.* **2008**, *108*, 264-287.
3. Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402-4421.
4. Bijev, A.; Radev, I.; Borisova, Y. *Pharmazie* **2000**, *55*, 568-571.
5. Wang, M. Z.; Xu, H.; Liu, T. W.; Feng, Q.; Yu, S. J.; Wang, S. H.; Li, Z. M. *Eur. J. Med. Chem.* **2011**, *46*, 1463-1472.
6. Battilocchio, C.; Poce, G.; Alfonso, S.; Porretta, G. C.; Consalvi, S.; Sautebin, L.; Pace, S.; Rossi, A.; Ghelardini, C.; Di Cesare Mannelli, L.; Schenone, S.; Giordani, A.; Di Francesco, L.; Patrignani, P.; Biava, M. *Bioorg. Med. Chem.* 2013, *21*, 3695-3701.
7. Da, C.; Telang, N.; Hall, K.; Kluball, E.; Barelli, P.; Finzel,K.; Jia, X.; Gupton, J. T.; Mooberry, S. L.; Kellog, G. E.*Med. Chem. Comm* **2013**, *4*, 417-421.
8. Carson, J. R.; Carmosin, R. J.; Pitis, P. M.; Vaught, J. L.; Almond, H. R.; Stables, J. P.; Wolf, H. H.; Swinyard, E. A.; White, H. S. *J. Med. Chem.* **1997**, *40*, 1578-1584.
9. Desai, R.; Miller, K. W.; Raines, D. E. *Anesth. Analg.* **2013**, *116*, 573-579.
10. For recently reported pyrrole synthesis, see: (a) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Commun.* **2013**, *49*, 591-593; (b) Billedeau, R. J.; Klein, K. R.; Kaplan, D.; Lou, Y. *Org. Lett.* **2013**, *15*, 1421-1423; (c) Bharathiraja, G.; Sakthivel, S.; Sengoden, M.; Punniyamurthy, T. *Org. Lett.* **2013**, *15*, 4996-4999; (d) Narayan, R.; Frohlich, R.; Wurthwein, E. U. *J. Org. Chem.* **2012**, *77*, 1868-1879; (e) Maehara, T.; Kanno, R.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2012**, *14*, 1946-1948; (f) Geng, W.; Zhang, W. X.; Hao, W.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 20230-20233; (g) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Maggi, S.; Aresta, B. M. *J. Org. Chem.* **2012**, *77*, 4005-4016; (h) Dhara, D.; Gayen, K. S.; Khamarui, S.; Pandit, P.; Ghosh, S.; Maiti, D. K. *J. Org. Chem.* **2012**, *77*, 10441-10449; (i) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926-4929; (j) Yoshida, M.; Maeyama, Y.; Al-Amin, M.; Shishido, K. *J. Org. Chem.* **2011**, *76*, 5813-5820; (k) Wang, H. Y.; Mueller, D. S.; Sachwani, R. M.; Kapadia, R.; Londino, H. N.; Anderson, L. L. *J. Org. Chem.* **2011**, *76*, 3203-3221;(l) Trost, B. M.; Lumb, J. P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740-743; (m) Sai, M.; Matsubara, S. *Org. Lett.* **2011**, *13*, 4676-4679; (n) Wang, H. Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290-2293; (o) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339;(p) Robles-Machin, R.; Lopez-Perez, A.; Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chemistry* **2010**, *16*, 9864-9873; (q) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585-9587; (r) Morin, M. S.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916-4919; (s) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140-144; (t) Ngwerume, S.; Lewis, W.; Camp, J. E. *J. Org. Chem.* **2013**, *78*, 920-934; (u) Reddy, B. V. S.; Reddy, M. R.; Rao, Y. G.; Yadav, J. S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 464-467; v) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176-179; (w) Wang, P.; Song, S.; Miao, Z.; Yang, G.; Zhang, A. *Org. Lett.* **2013**, *15*, 3852-3855; (x) Teo, W. T.; Rao, W.; Koh, M. J.; Chan, P. W. *J. Org. Chem.* **2013**, *78*, 7508-7517.
11. (a) Lin, M.; Hao, L.; Ma, R. D.; Zhan, Z. P. *Synlett* **2010**, 2345-2351; (b) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312-315. (c) Liu, X. T.; Hao, L.; Lin, M.; Chen, L.; Zhan, Z. P. *Org. Biomol. Chem.* **2010**, *8*, 3064-3072.
12. Cadierno, V.; Gimeno, J.; Nebra, N. *Chemistry* **2007**, *13*, 9973-9981.
13. Liu, X. T.; Huang, L.; Zheng, F. J.; Zhan, Z. P. *Adv. Synth. Catal.* **2008**, *350*, 2778-2788.
14. Chatterjee, P. N.; Roy, S. *Tetrahedron* **2011**, *67*, 4569-4577.
15. (a) Zhan, Z. P.; Wang, S. P.; Cai, X. B.; Liu, H. J.; Yu, J. L.; Cui, Y. *Adv. Synth. Catal.* **2007**, *349*, 2097-2102; (b) Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 727-730; (c) Kuninobu, Y.;Ueda, H.; Takai, K. *Chem. Lett.* **2008**, *37*, 878-879; (d) Fan, J.; Wan, C.; Sun, C.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 8608-8611; (e) Feng, X. B.; Tan, Z.; Chen, D.; Shen, Y. M.; Guo, C. C.; Xiang, J. N.; Zhu, C. L. *Tetrahedron Lett.* **2008**, *49*, 4110-4112; (f) Yadav, J. S.; Reddy, B. V. S.; Pandurangam, T.; Rao, K. V. R.; Praneeth, K.; Kumar, G. G. K. S. N.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 4296-4301; (g) Pan, Y. M.; Zhao, S. Y.; Ji, W. H.; Zhan, Z. P. *J. Comb. Chem.* **2009**, *11*, 103-109; (h) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Narender, R. *Tetrahedron Lett.* **2009**, *50*, 3963-3965; (i) Funabiki, K.; Komeda, T.; Kubota, Y.; Matsui, M. *Tetrahedron* **2009**, *65*, 7457-7463; (j) Reddy, C. R.; Vijaykumar, J.; Gree, R. *Synthesis- Stuttgart* **2010**, 3715-3723; (k) Zhang, M.; Yang, H. W.; Cheng, Y. X.; Zhu, Y. H.; Zhu, C. J. *Tetrahedron Lett.* **2010**, *51*, 1176-1179; (l) Maiti, S.; Biswas, S.; Jana, U. *Syn. Commun.* **2011**, *41*, 243-254; (m) Aridoss, G.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 6859-6864 (n) Das, D.; Pratihar, S.; Roy, U. K.; Mal, D.; Roy, S. *Org. Biomol. Chem.* , *10*, 4537-4542.

16. Gujarathi, S.; Hendrickson, H. P.; Zheng, G. R. *Tetrahedron lett.* **2013**, *54*, 3550-3553.
17. Ji, W. H.; Pan, Y. M.; Zhao, S. Y.; Zhan, Z. P. *Synlett* **2008**, 3046-3052.
18. In our hands, significant amount of furan was detected by GC-MS and TLC when $InCl_3$ was used as a catalyst for the one-pot pyrrole formation in toluene under reflux.
19. Intermediate **5a** was synthesized by either Amberlite IR-120H- or $AgSbF_6$-catalyzed method. Purification was carried out by column chromatography on silica gel. Furan formation was detected by TLC and GC-MS. No difference in furan formation was observed between these two different batches of **5a**.
20. The compound was reported in ref. 13. The NMR data for the compound was in agreement with those reported.

Supplementary Material

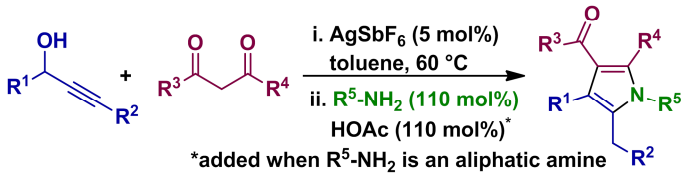
Copies of all of the ^{1}H and ^{13}C NMR spectra.

Graphical Abstract

A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction

Leave this area blank for abstract info.

Satheesh Gujarathi, Xingui Liu, Lin Song, Howard Hendrickson, Guangrong Zheng*
Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States



A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction

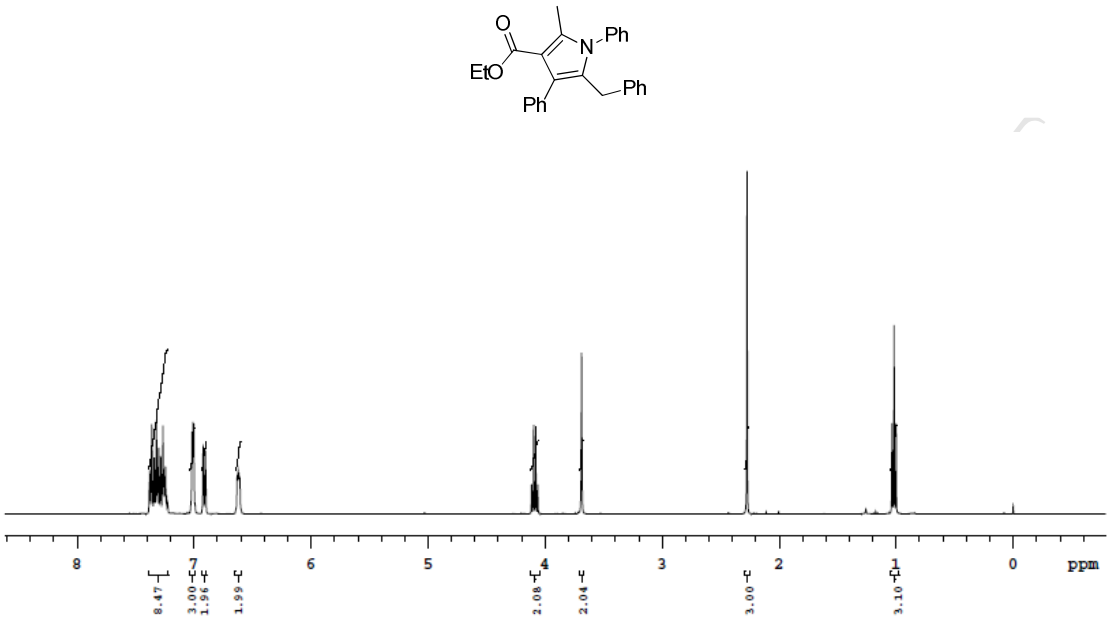
Satheesh Gujarathi, Xingui Liu, Lin Song, Howard Hendrickson, Guangrong Zheng*

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States

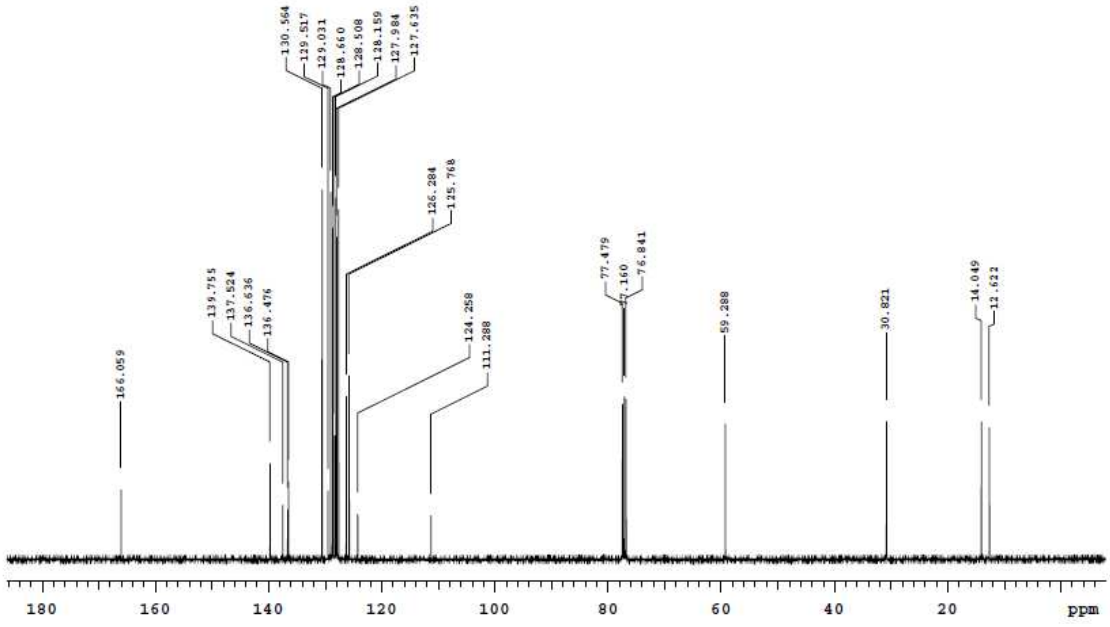
Supporting Information

Table of Contents

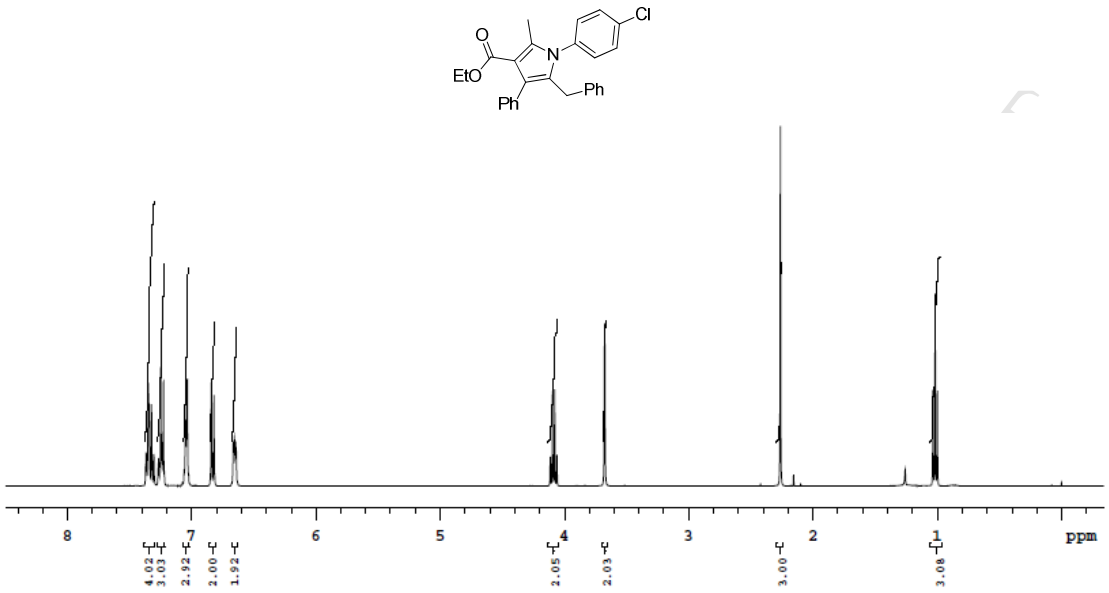
^{1}H NMR Spectrum of Compound 4a



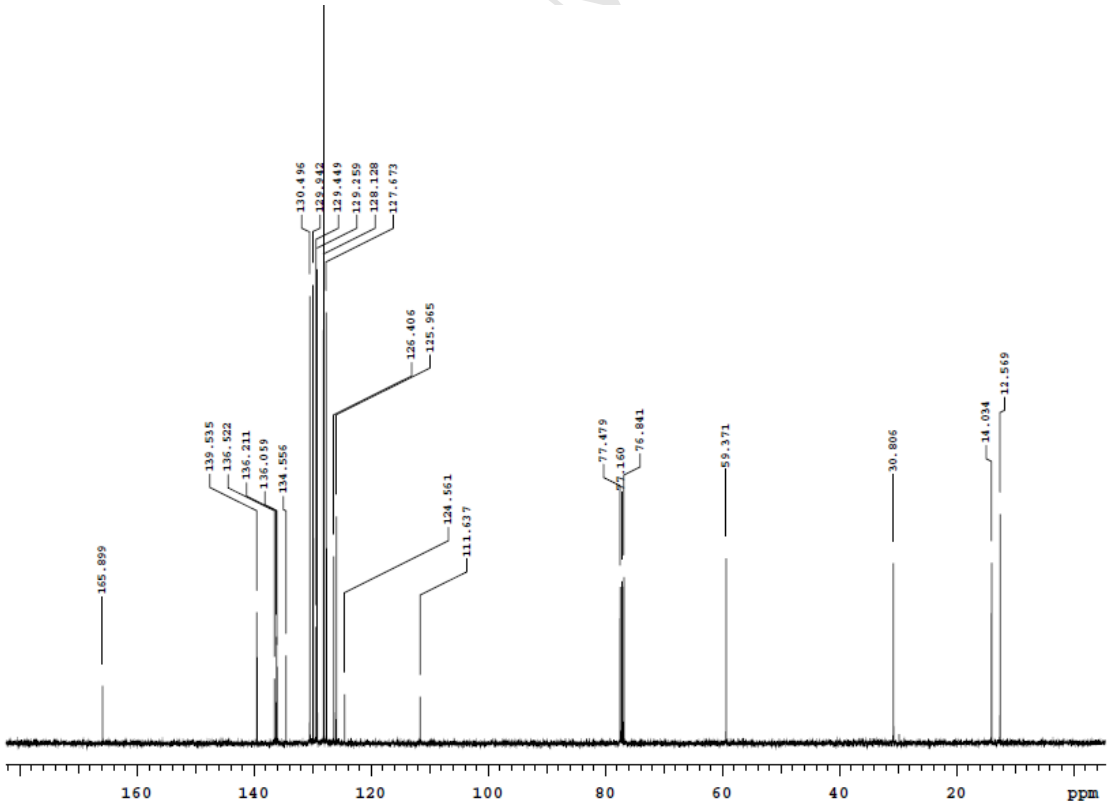
^{13}C NMR Spectrum of Compound 4a



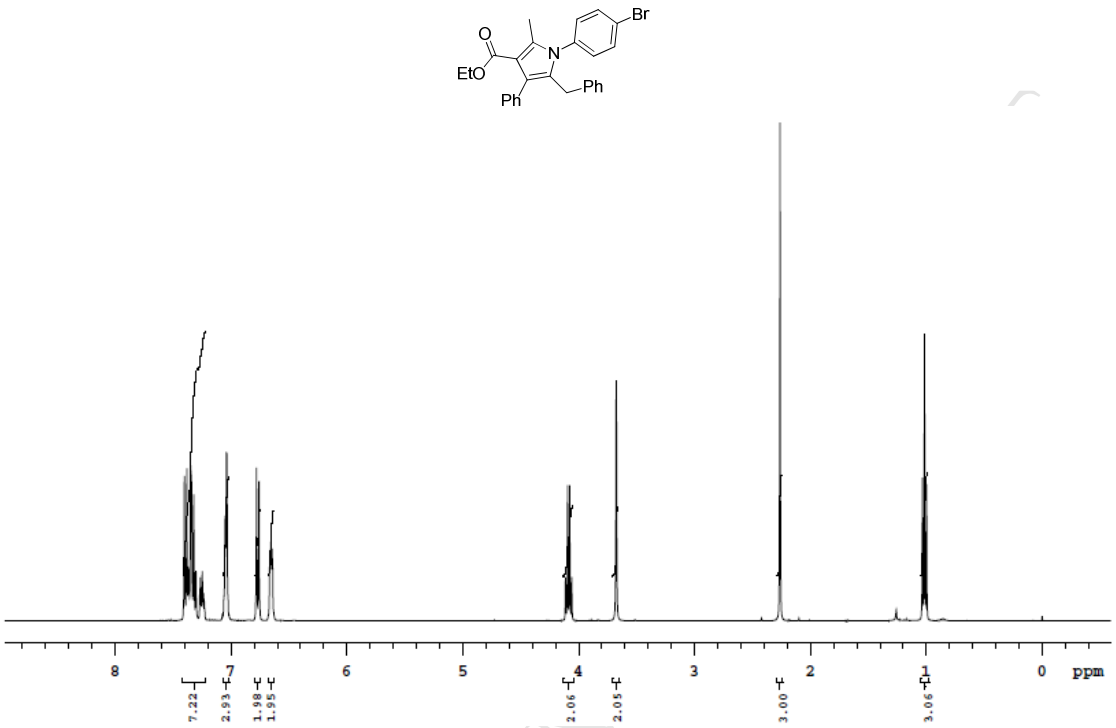
^{1}H NMR Spectrum of Compound 4b



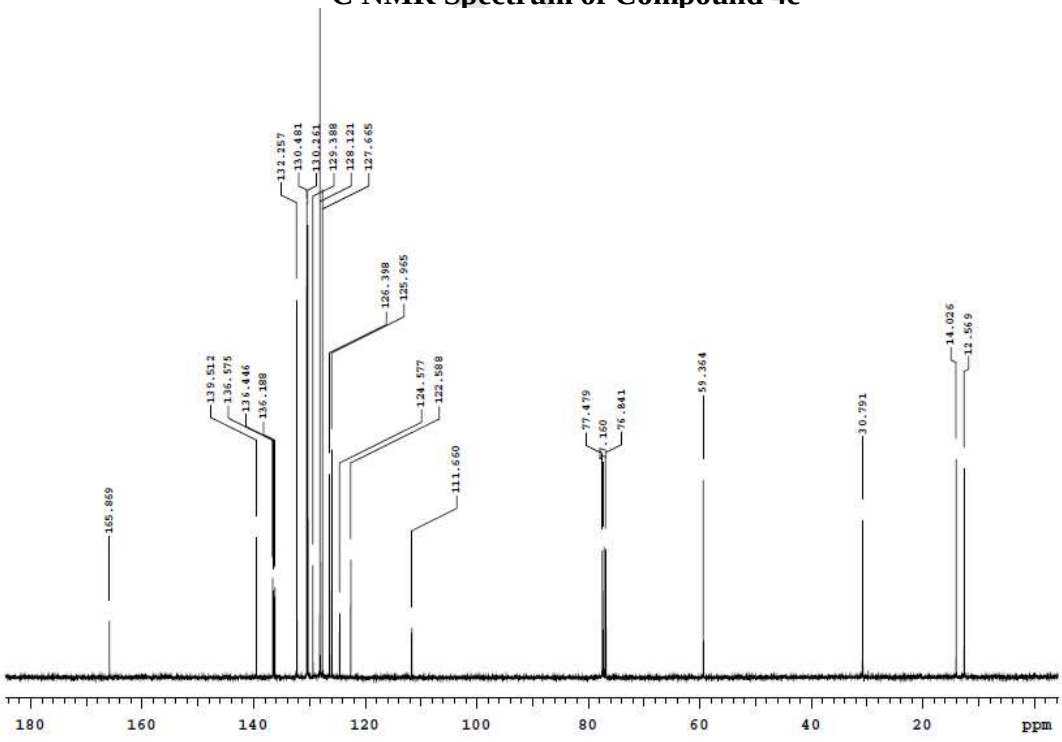
^{13}C NMR Spectrum of Compound 4b



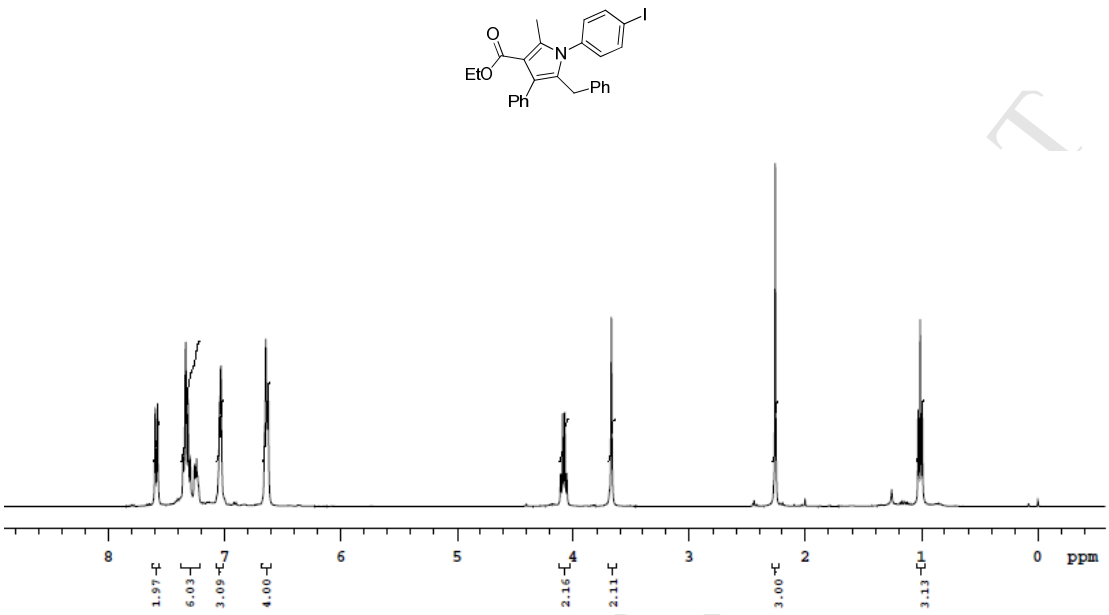
^{1}H NMR Spectrum of Compound 4c



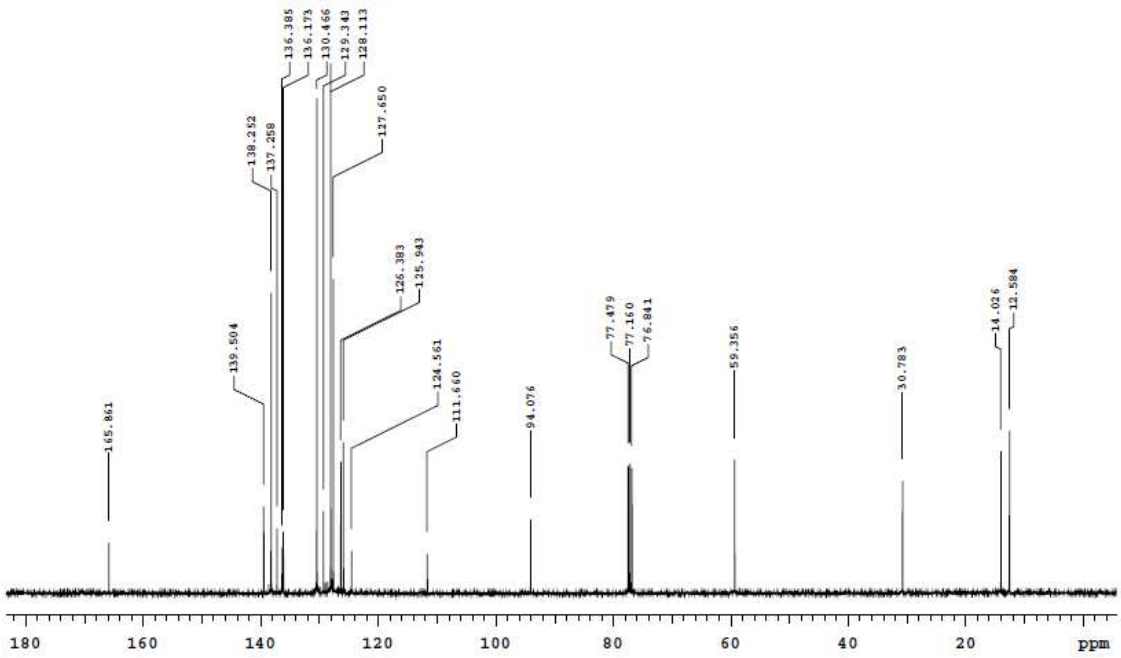
^{13}C NMR Spectrum of Compound 4c



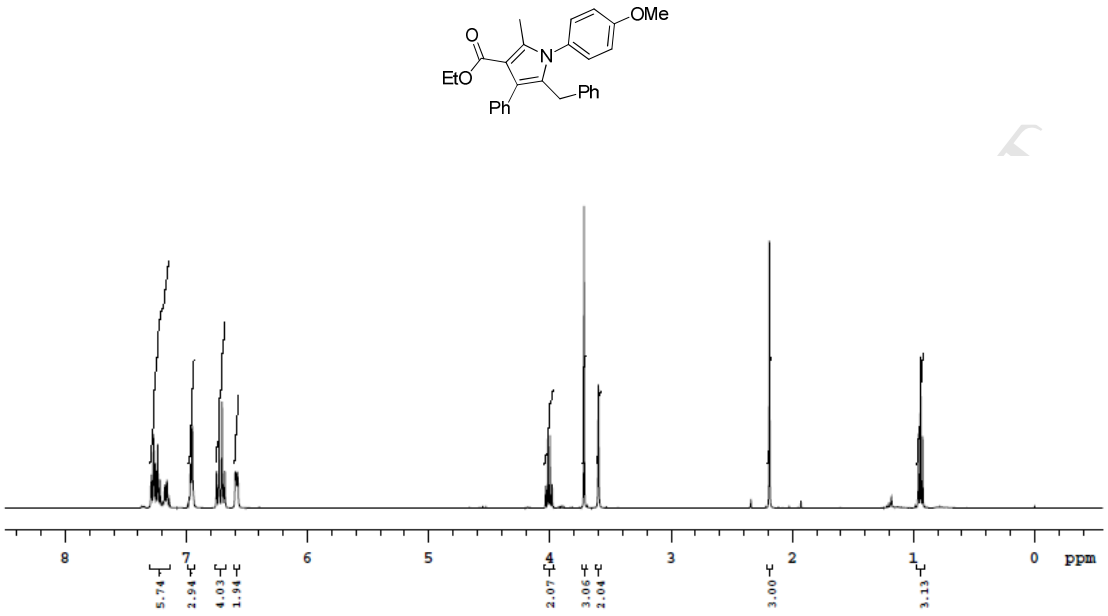
^{1}H NMR Spectrum of Compound 4d



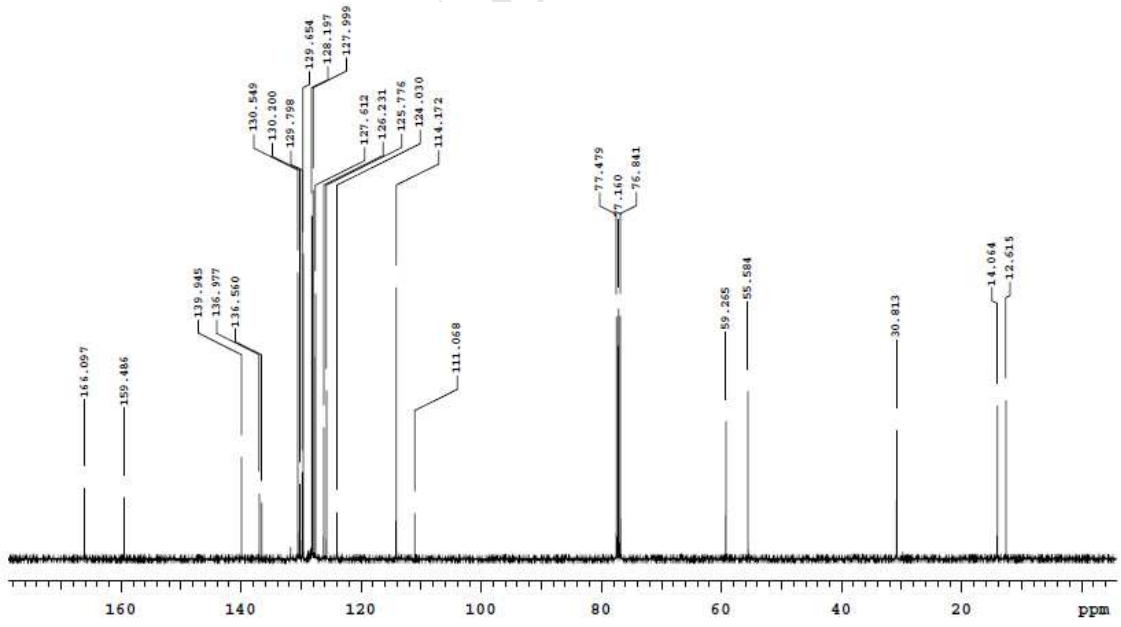
^{13}C NMR Spectrum of Compound 4d



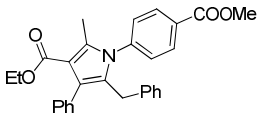
^{1}H NMR Spectrum of Compound 4e

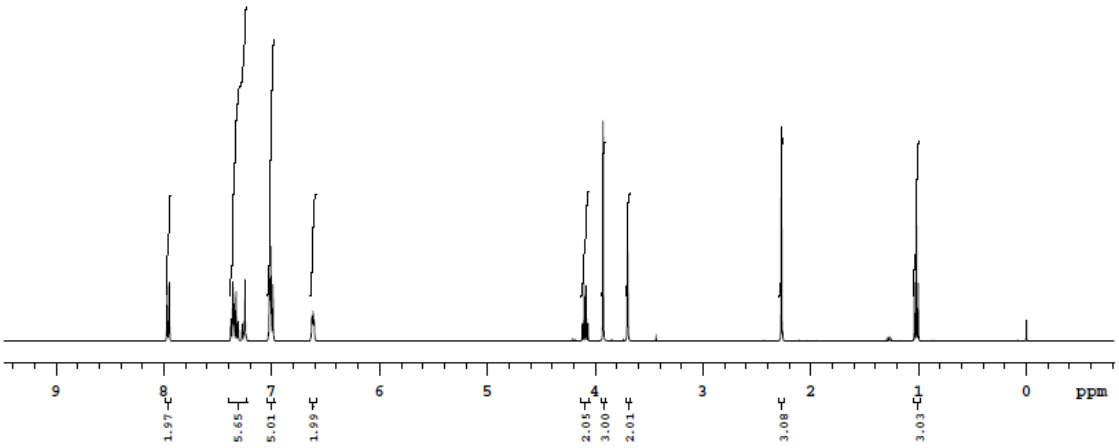


^{13}C NMR Spectrum of Compound 4e

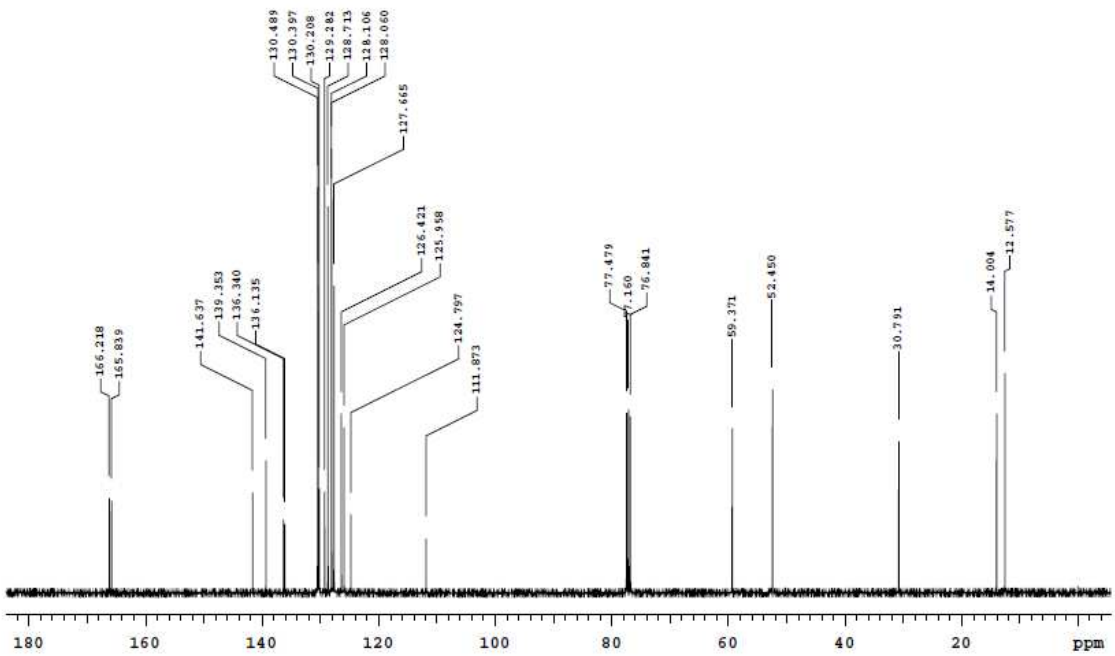


^{1}H NMR Spectrum of Compound 4f

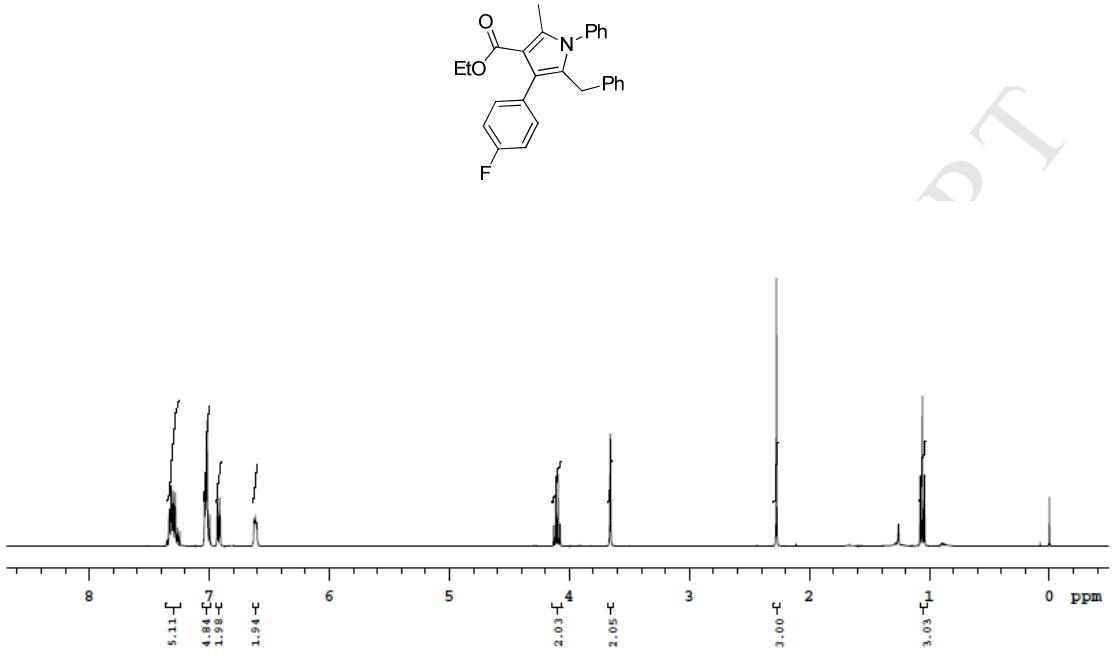




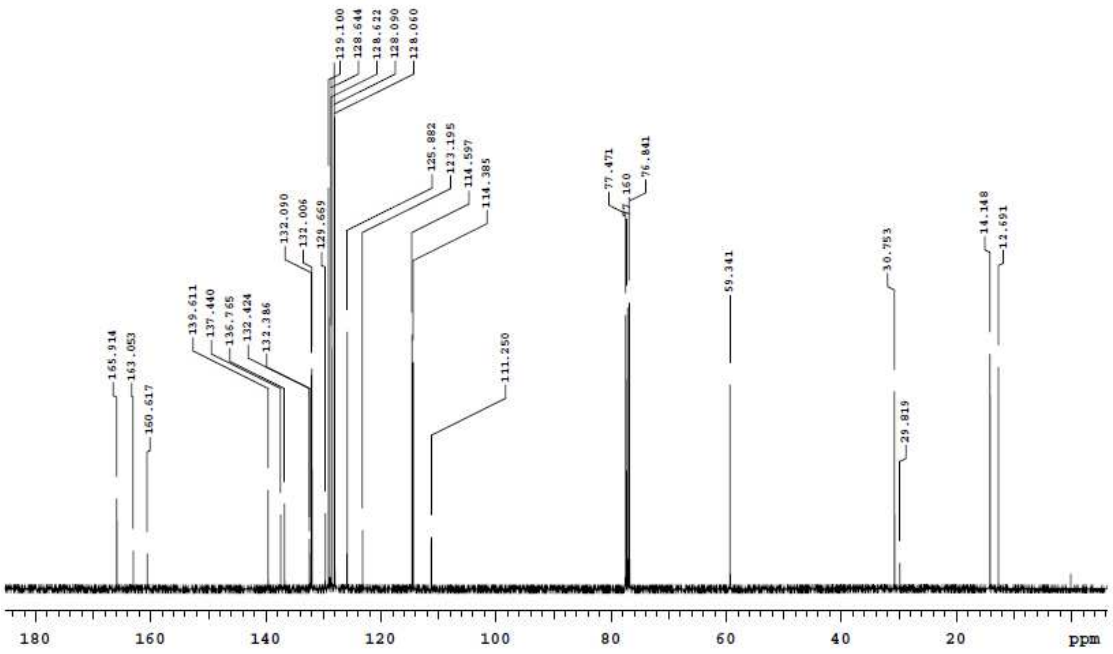
^{13}C NMR Spectrum of Compound 4f



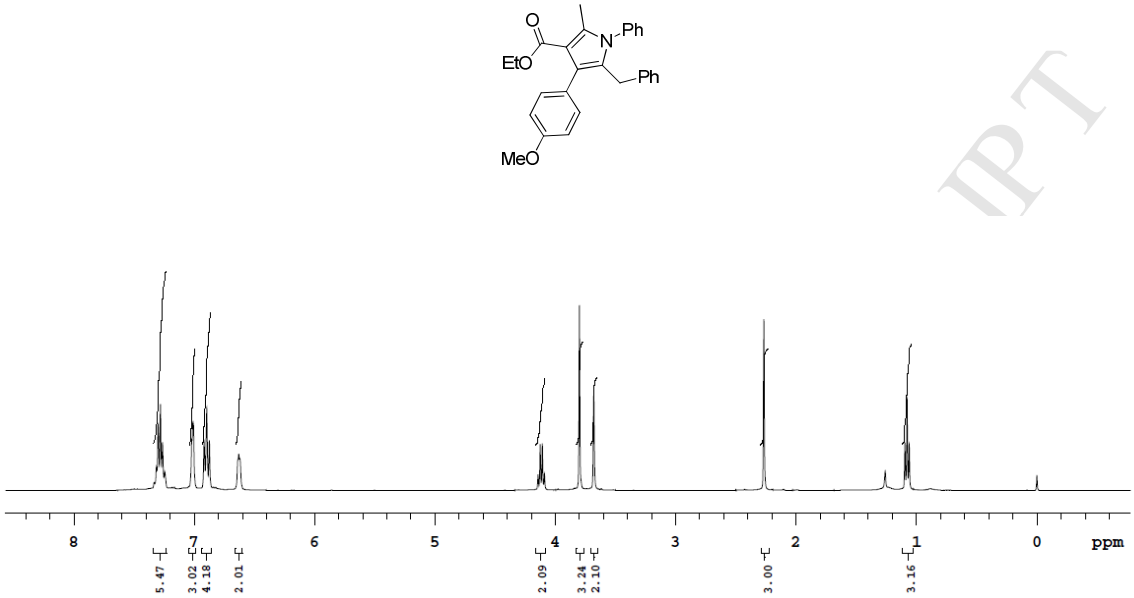
^{1}H NMR Spectrum of Compound 4g



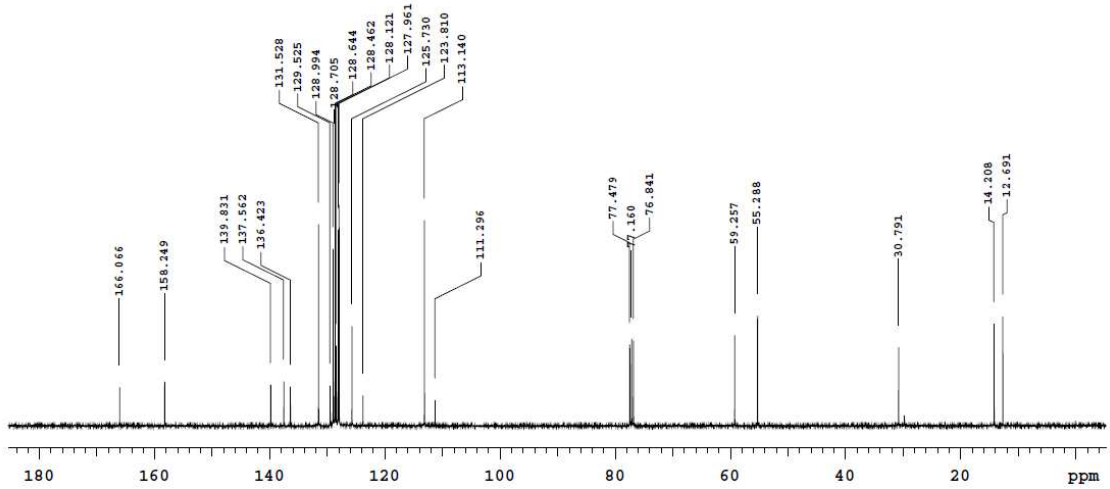
^{13}C NMR Spectrum of Compound 4g



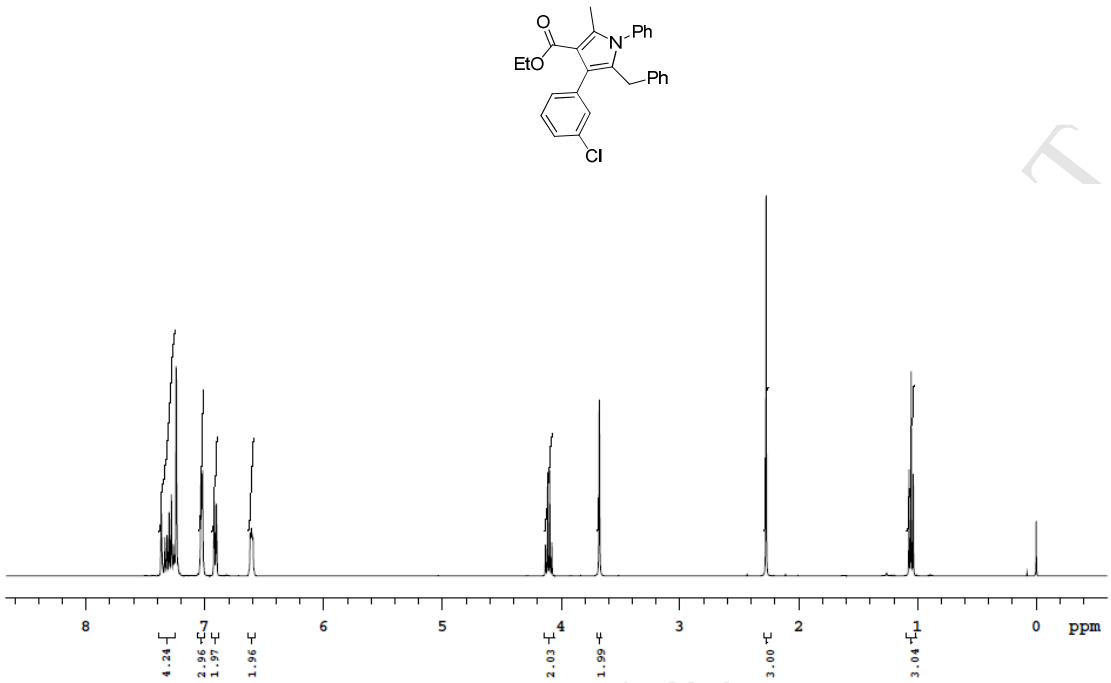
^{1}H NMR Spectrum of Compound 4h



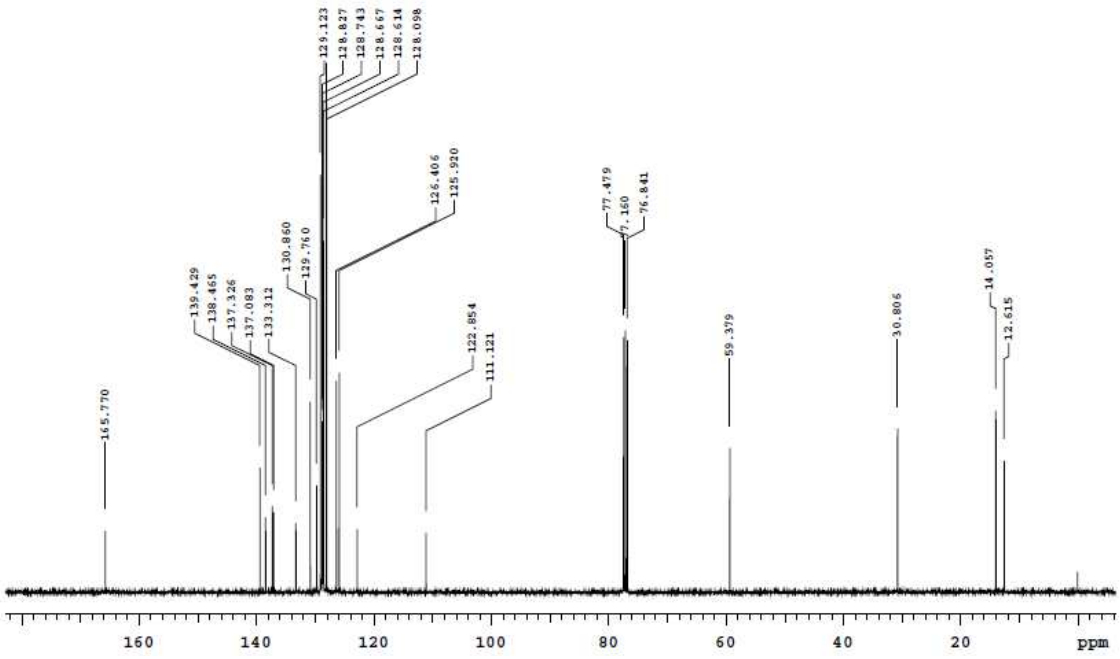
^{13}C NMR Spectrum of Compound 4h



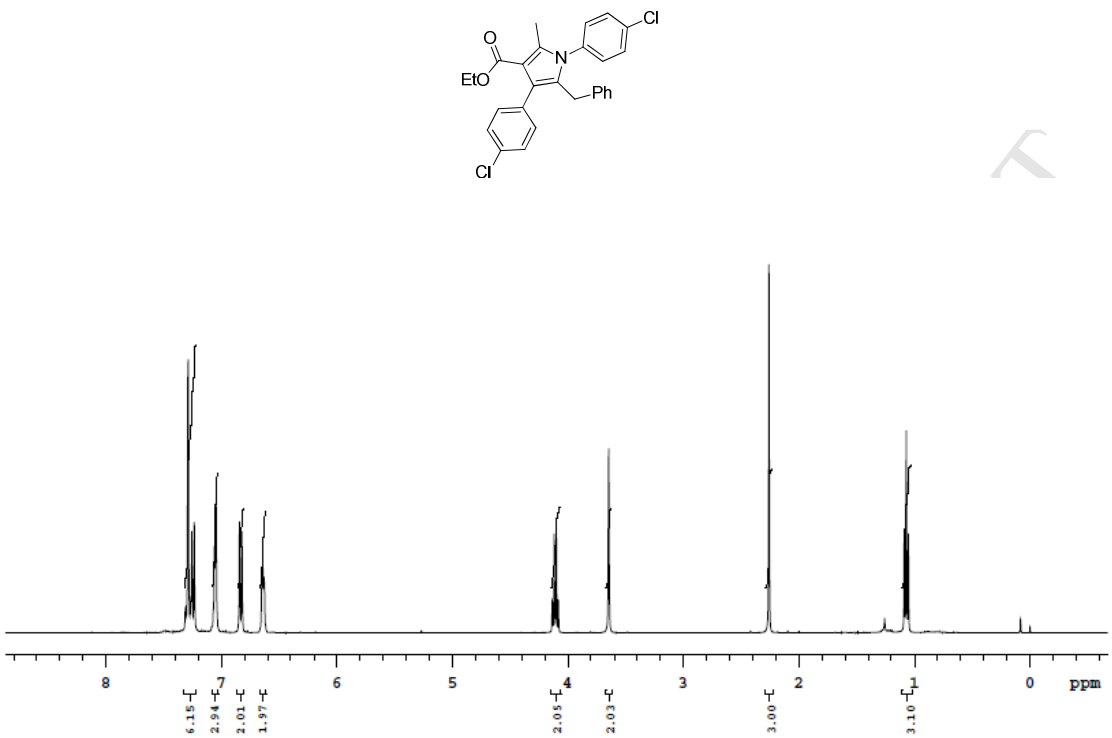
^{1}H NMR Spectrum of Compound 4i



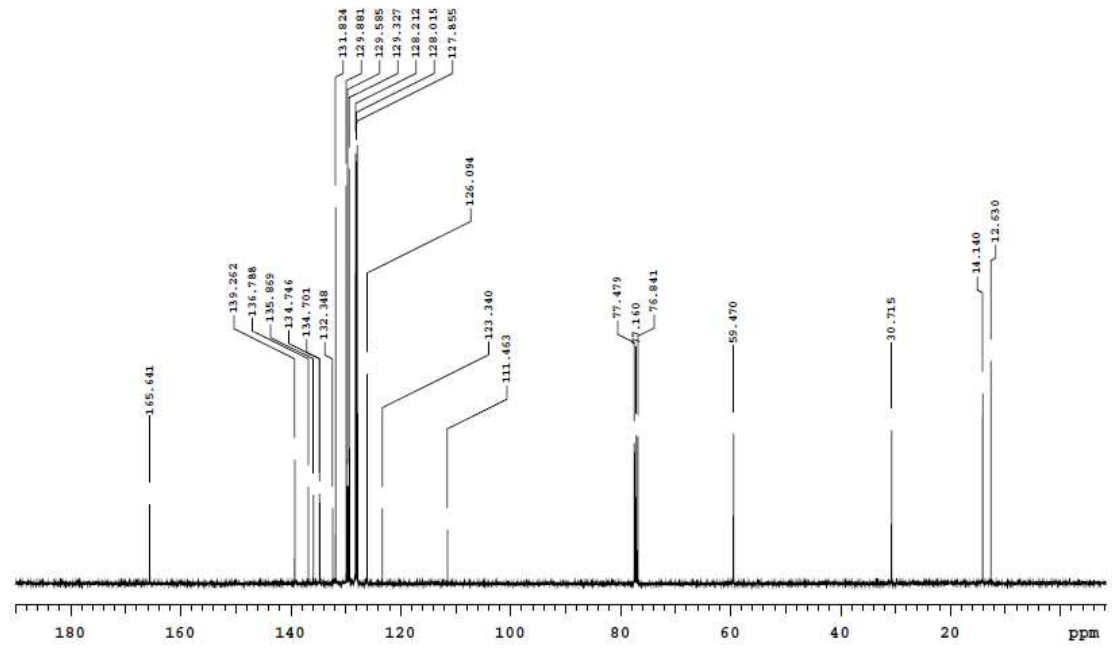
^{13}C NMR Spectrum of Compound 4i



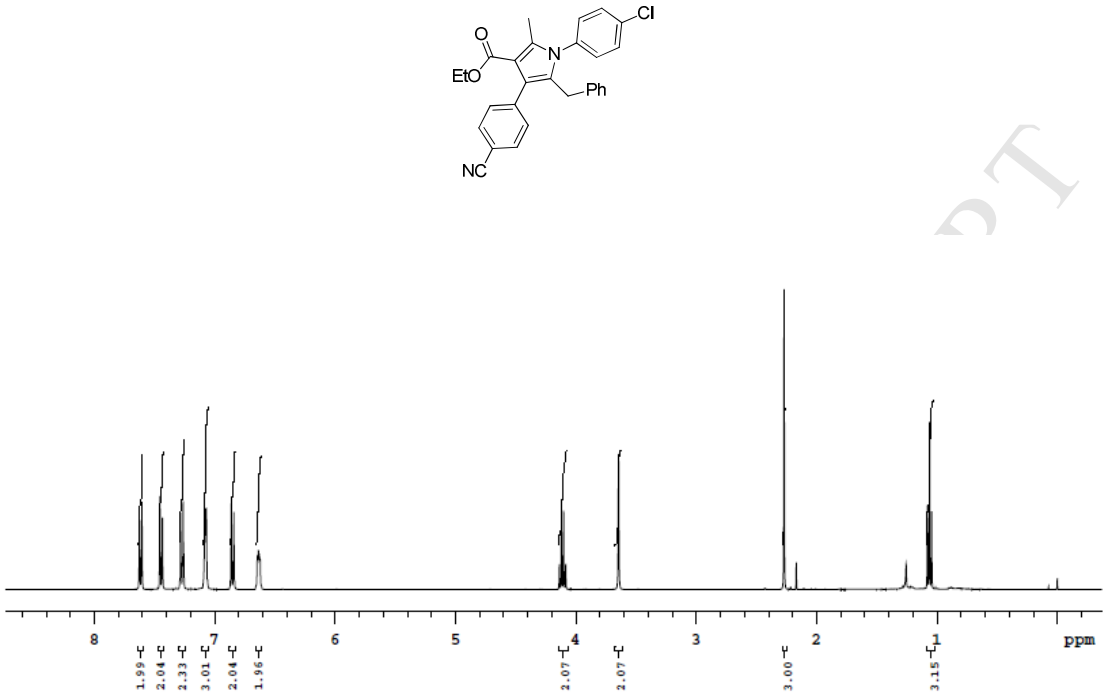
^{1}H NMR Spectrum of Compound 4j



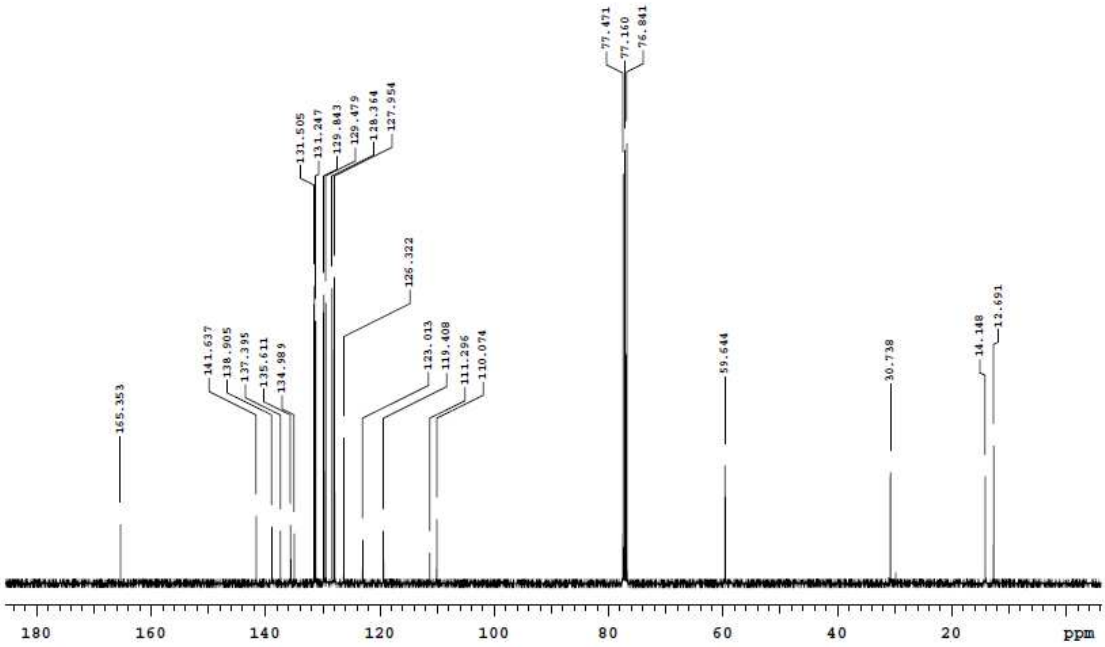
^{13}C NMR Spectrum of Compound 4j



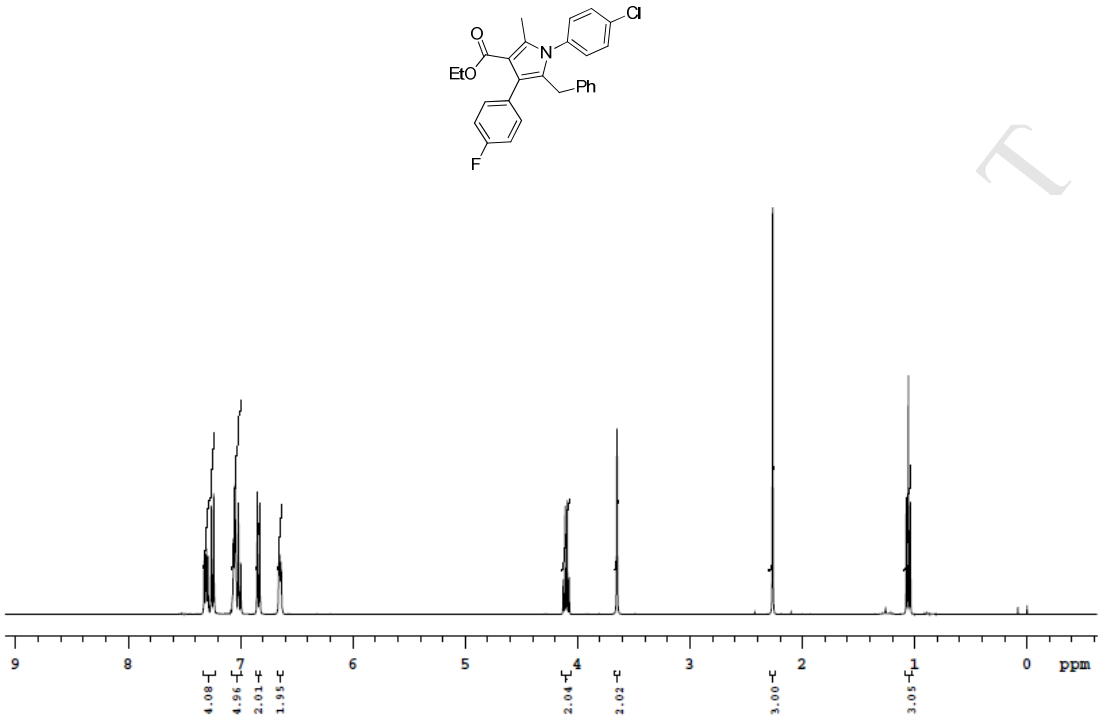
^{1}H NMR Spectrum of Compound 4k



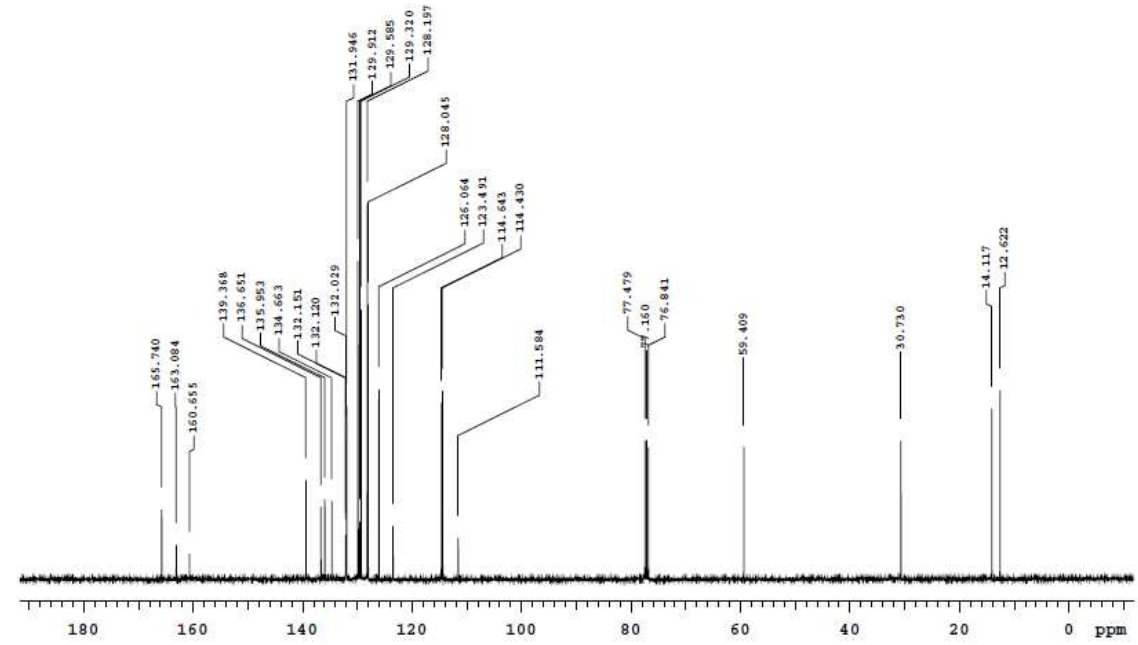
^{13}C NMR Spectrum of Compound 4k



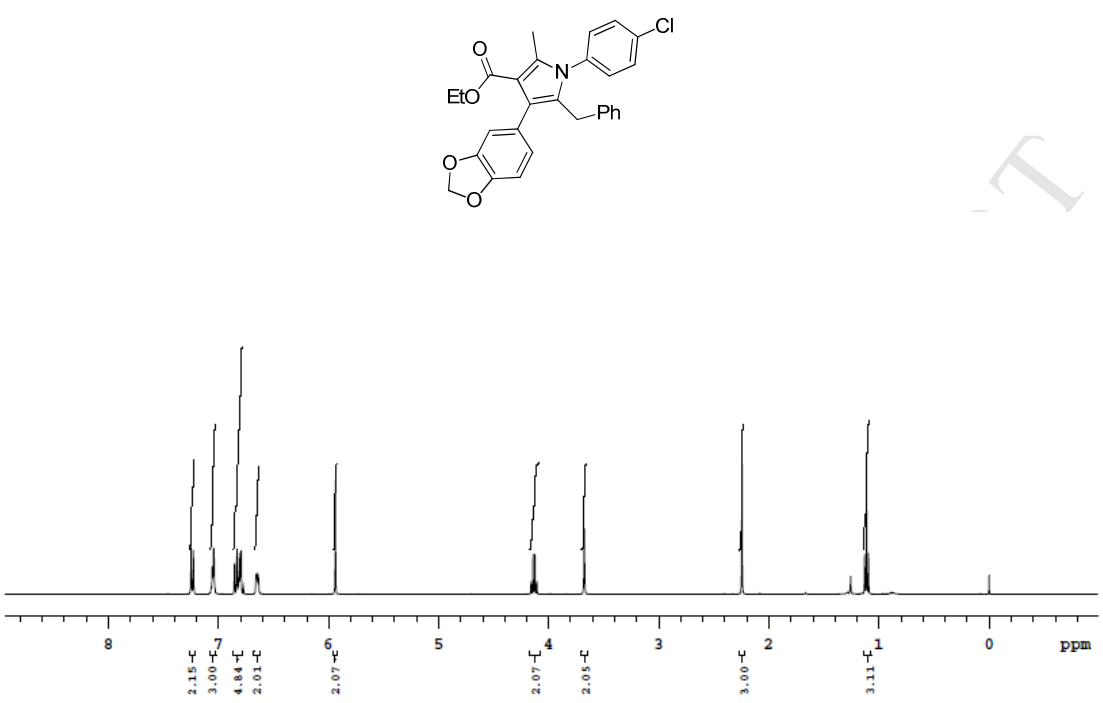
^{1}H NMR Spectrum of Compound 4l



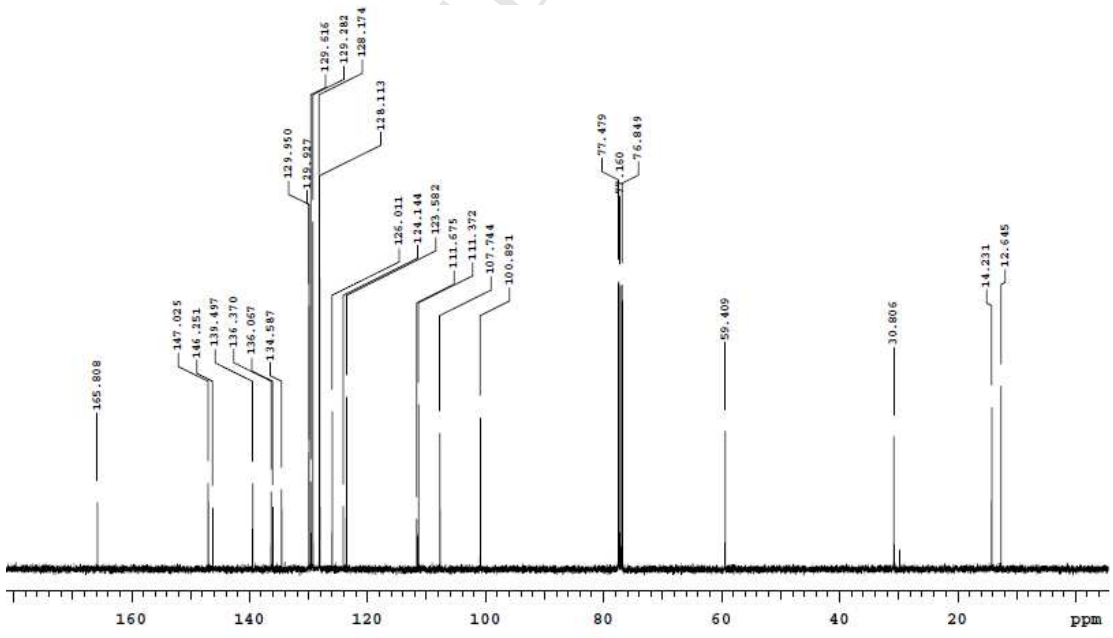
^{13}C NMR Spectrum of Compound 4l



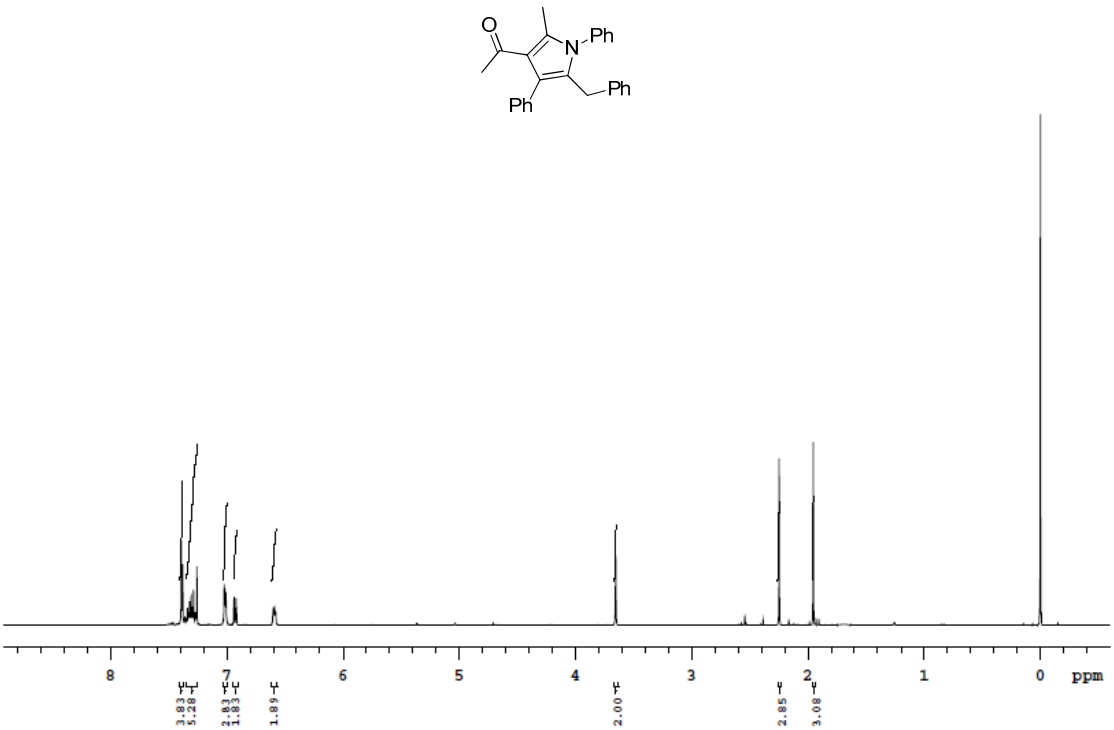
^{1}H NMR Spectrum of Compound 4m



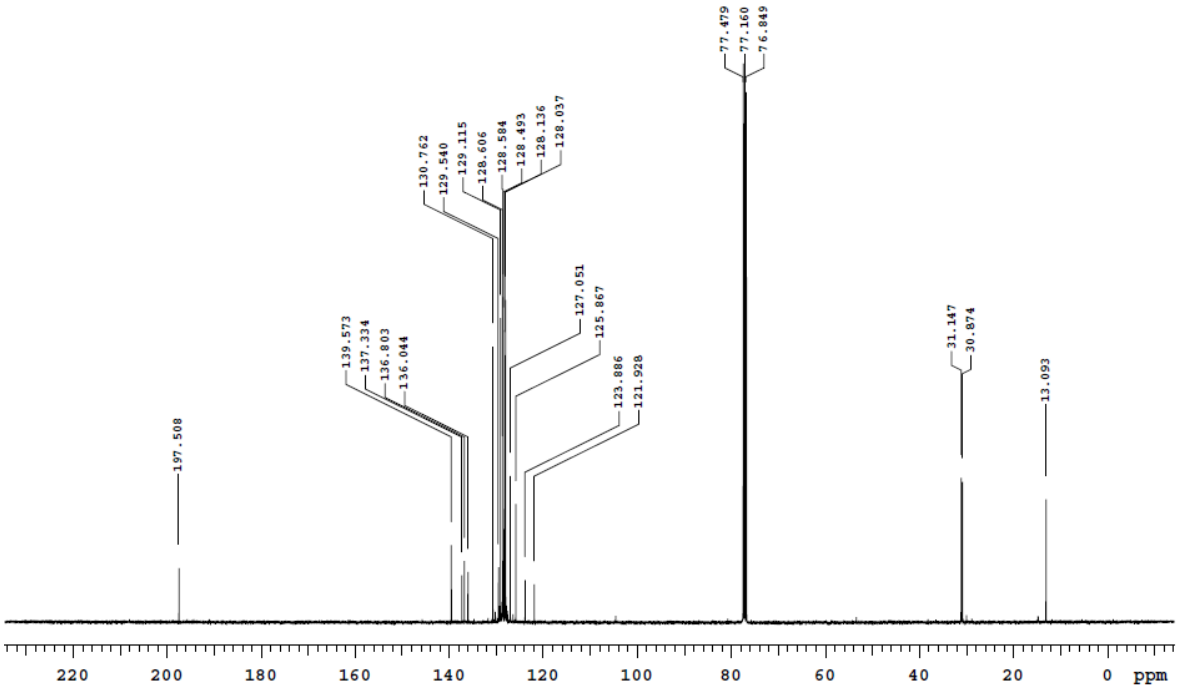
^{13}C NMR Spectrum of Compound 4m



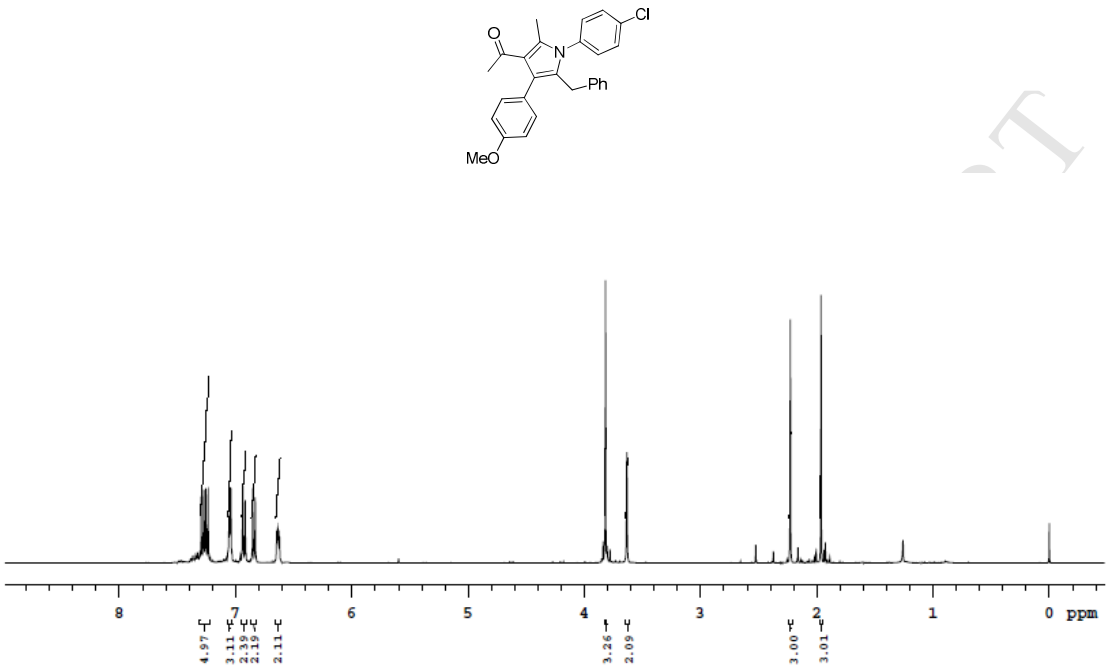
^{1}H NMR Spectrum of Compound 4n



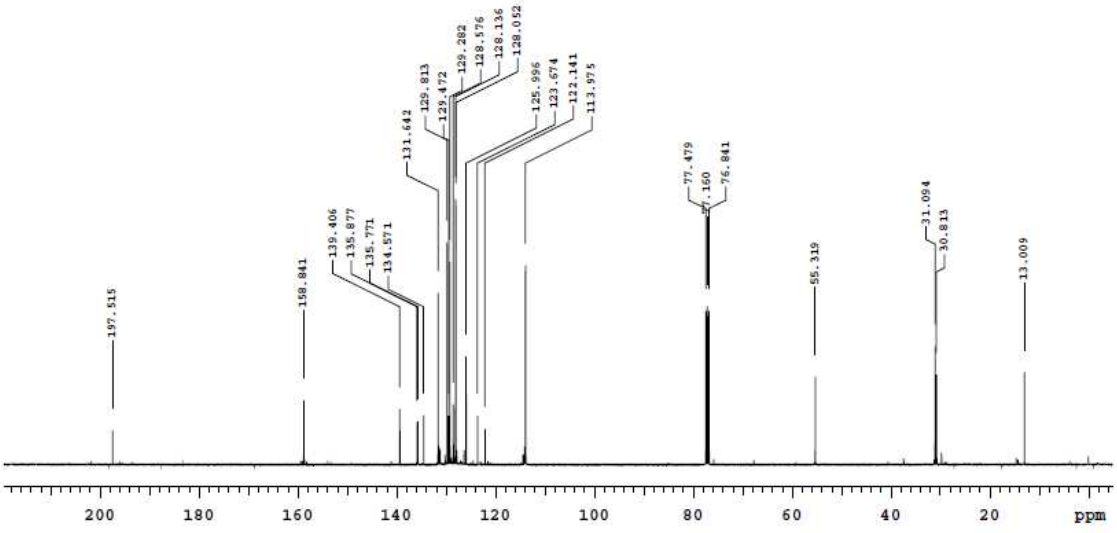
^{13}C NMR Spectrum of Compound 4n



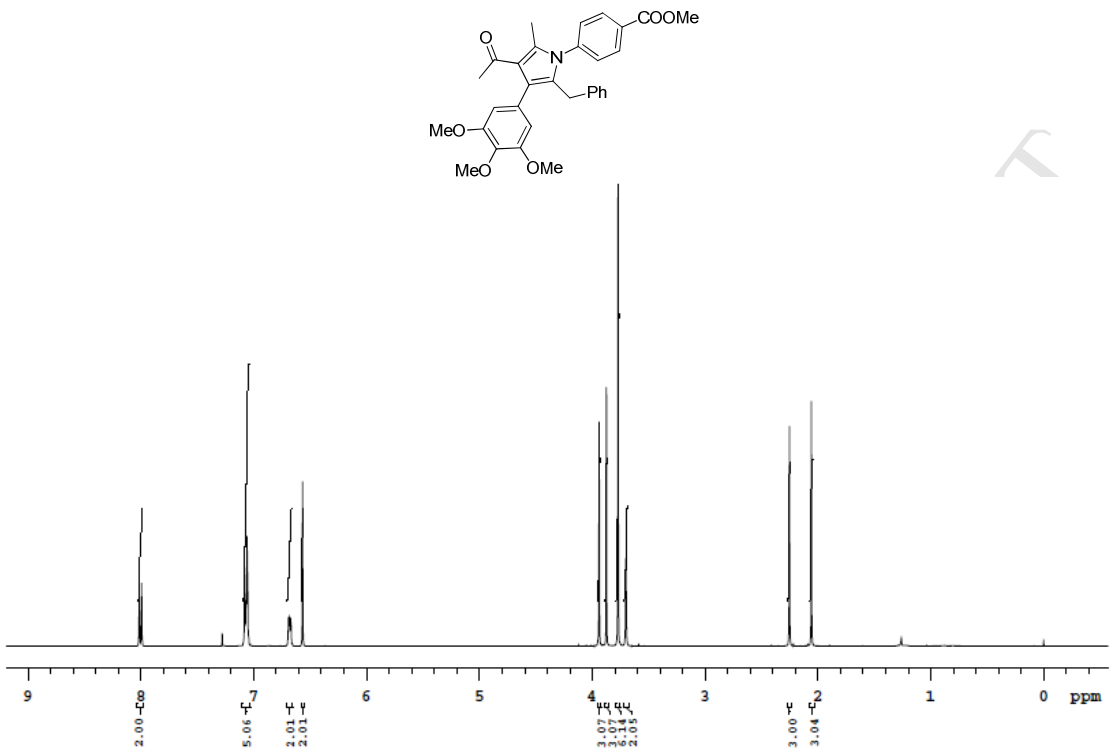
^{1}H NMR Spectrum of Compound 4o



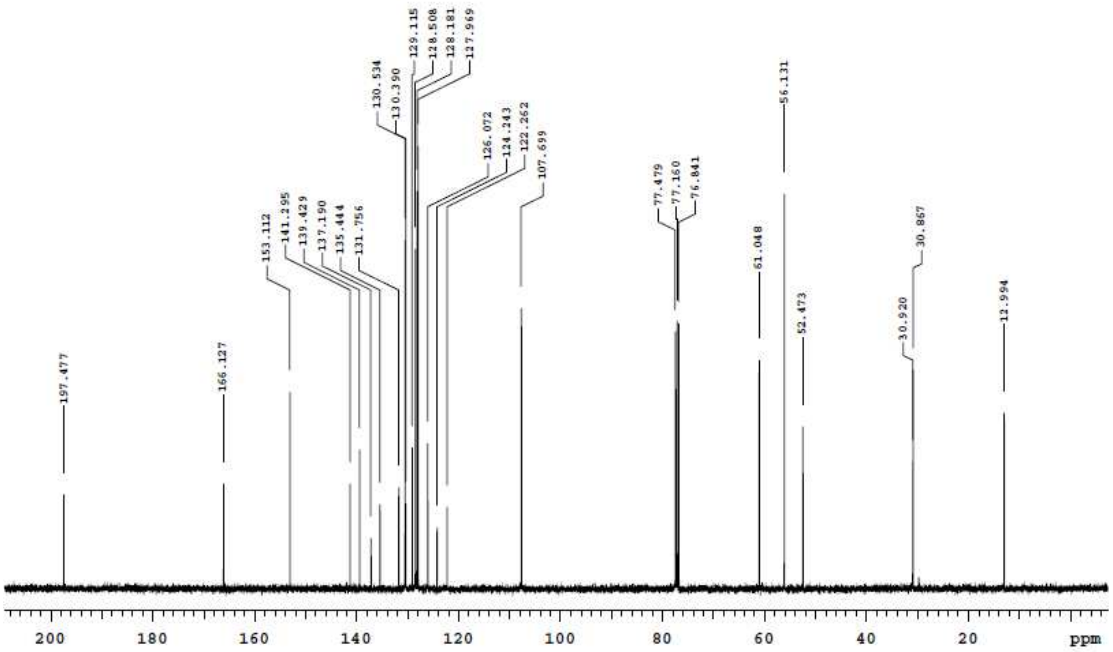
^{13}C NMR Spectrum of Compound 4o



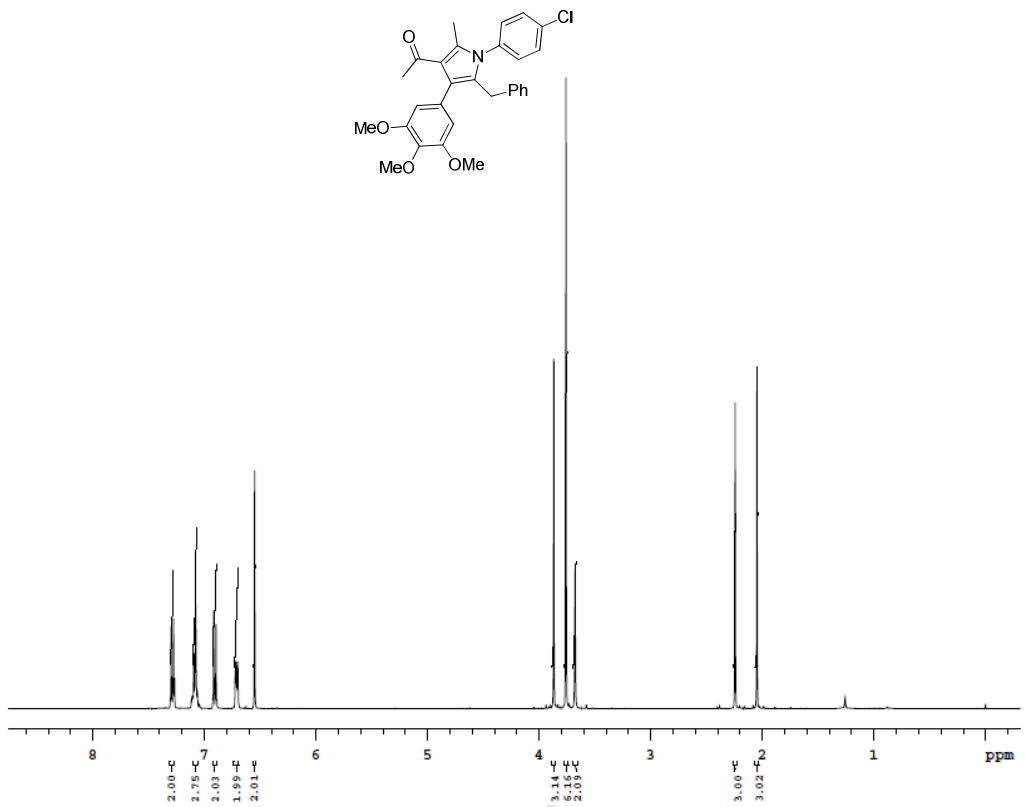
^{1}H NMR Spectrum of Compound 4p



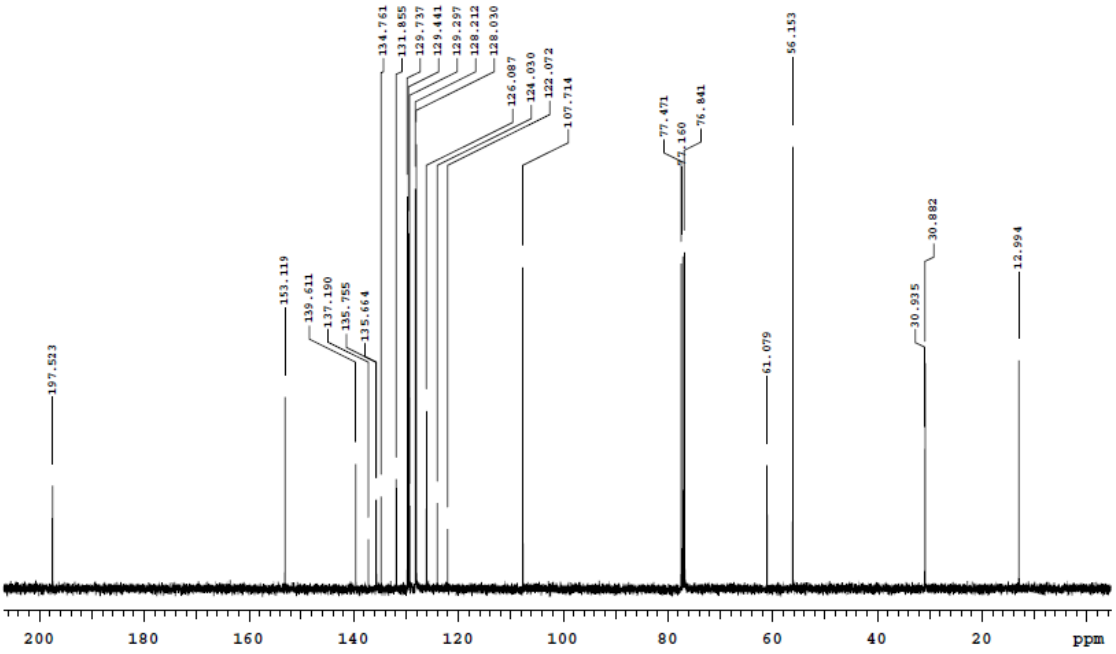
^{13}C NMR Spectrum of Compound 4p



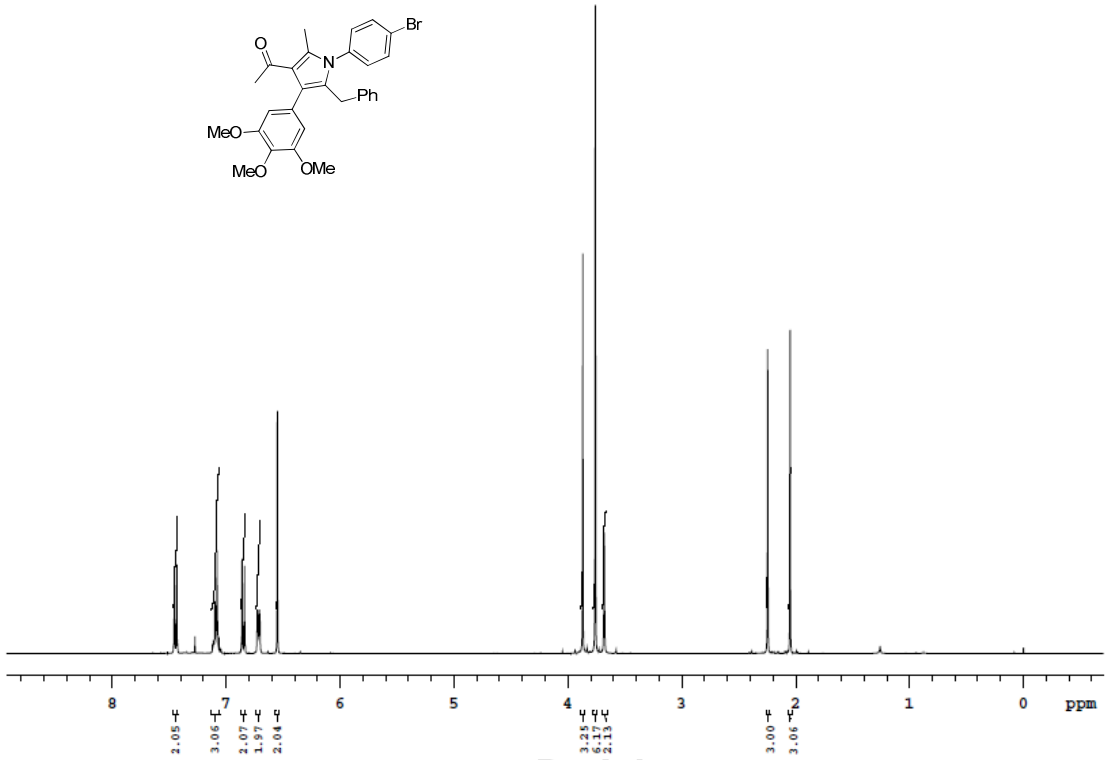
^{1}H NMR Spectrum of Compound 4q



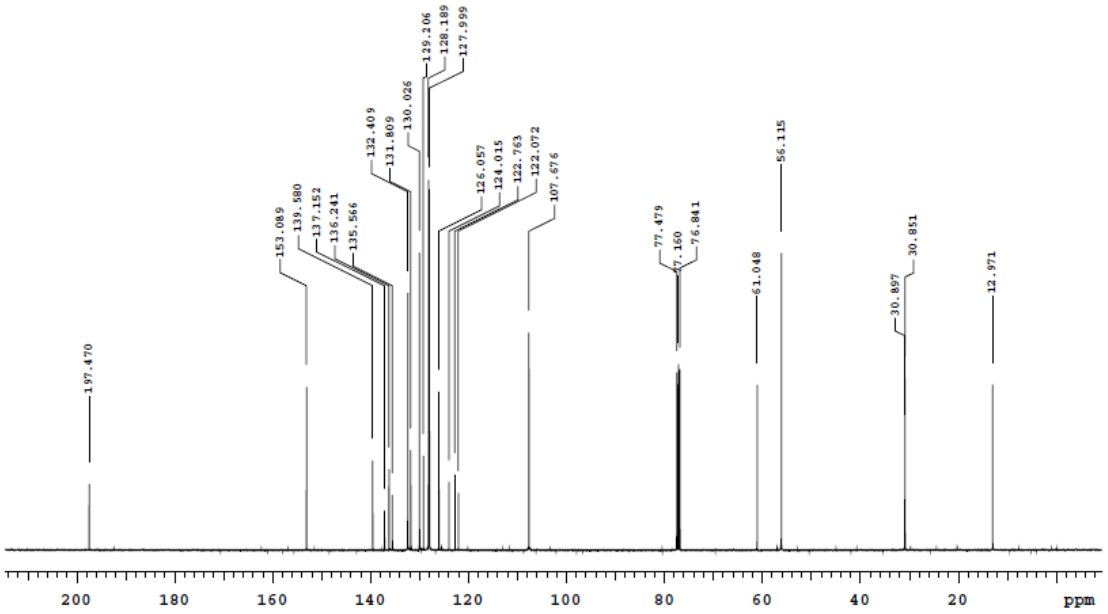
^{13}C NMR Spectrum of Compound 4q



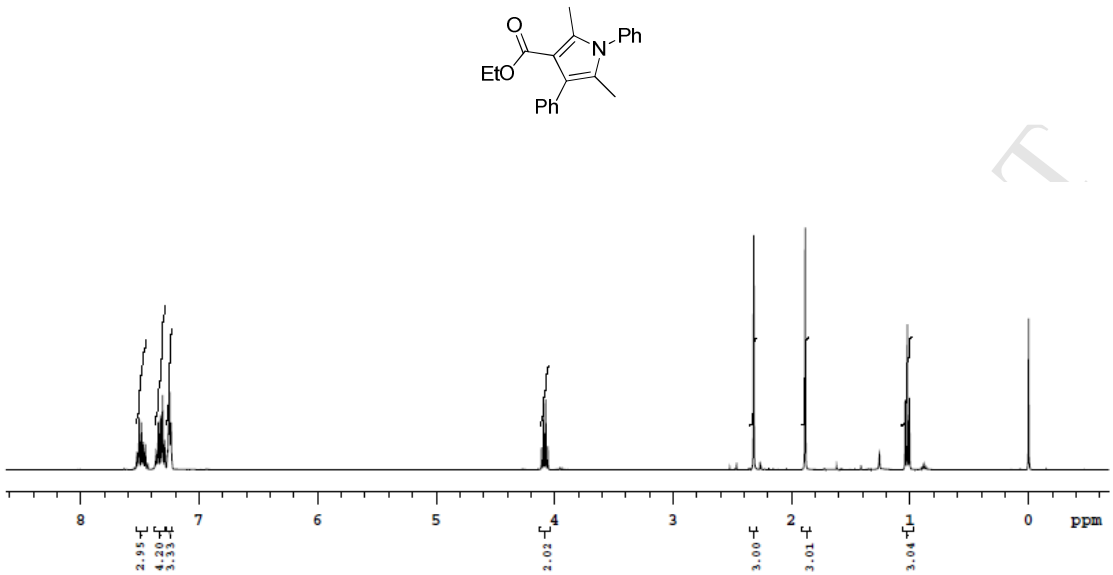
^{1}H NMR Spectrum of Compound 4r



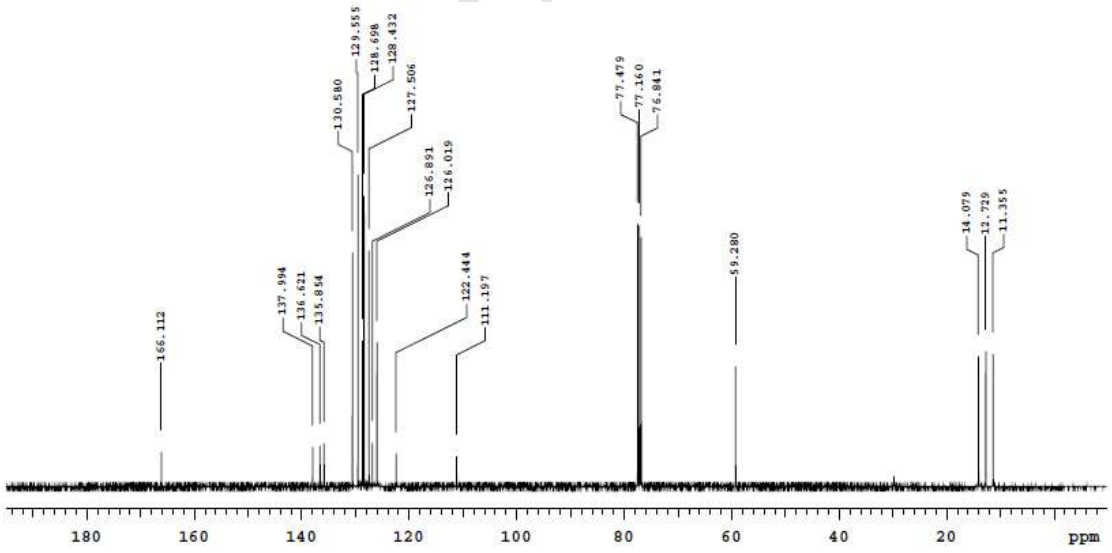
^{13}C NMR Spectrum of Compound 4r



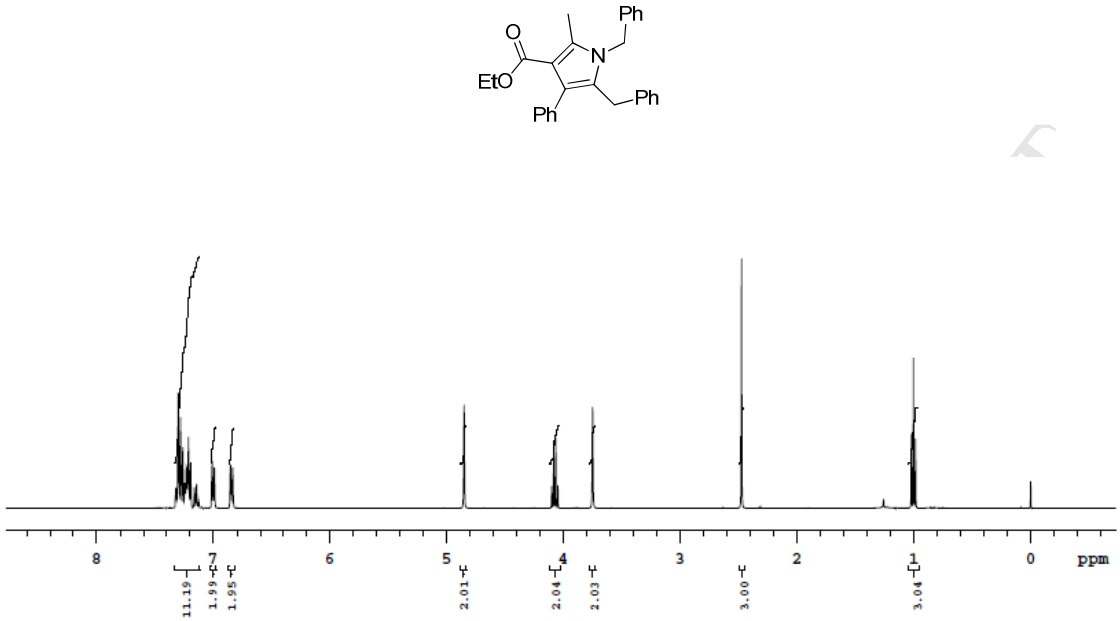
^{1}H NMR Spectrum of Compound 4s



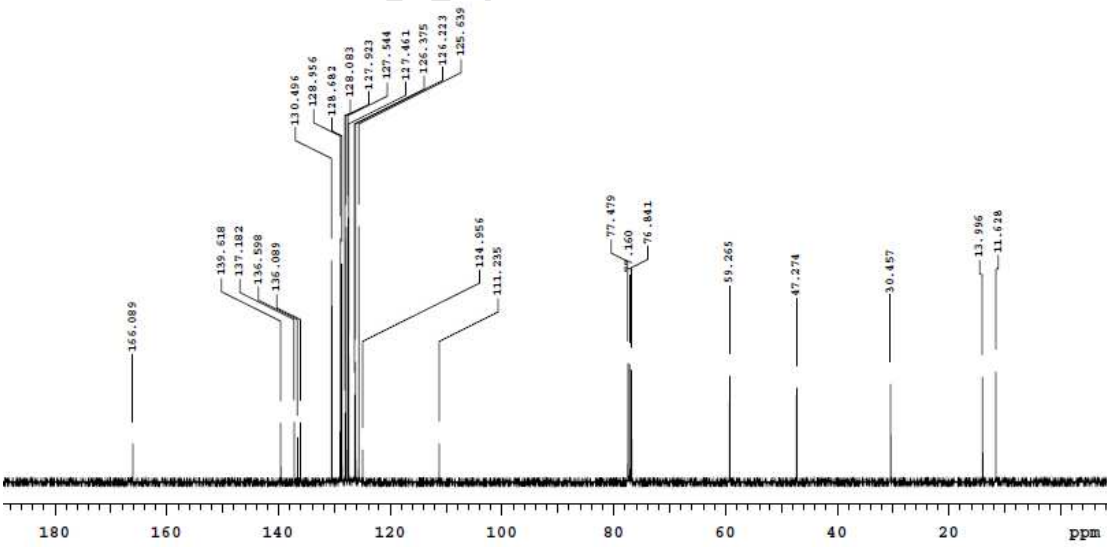
^{13}C NMR Spectrum of Compound 4s



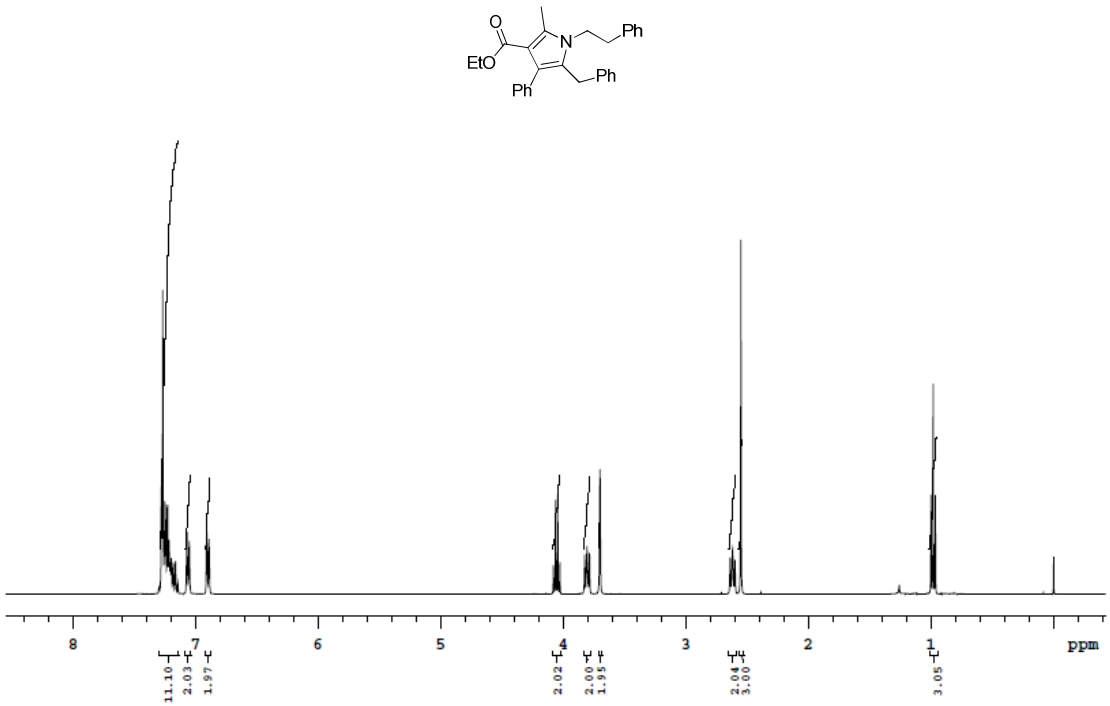
^{1}H NMR Spectrum of Compound 4t



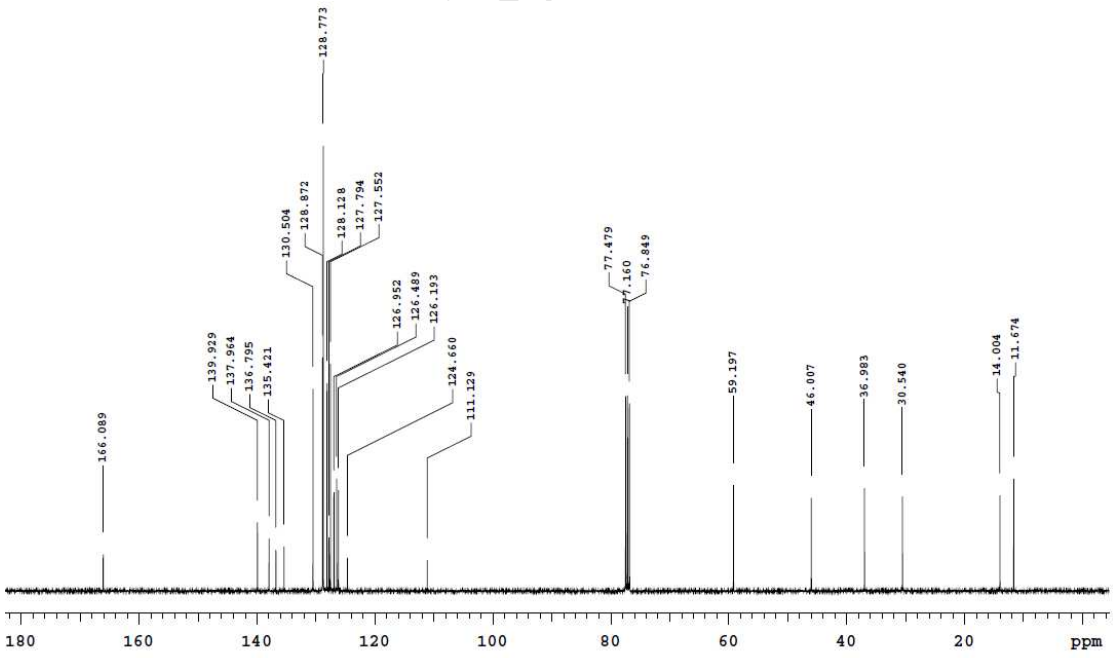
^{13}C NMR Spectrum of Compound 4t



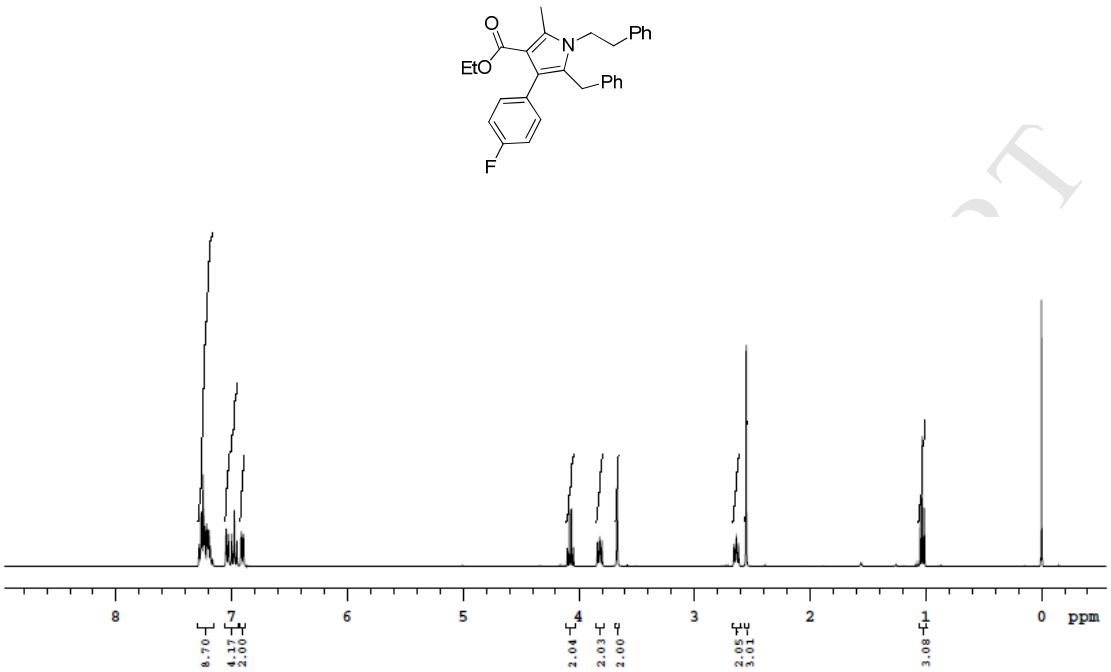
^{1}H NMR Spectrum of Compound 4u



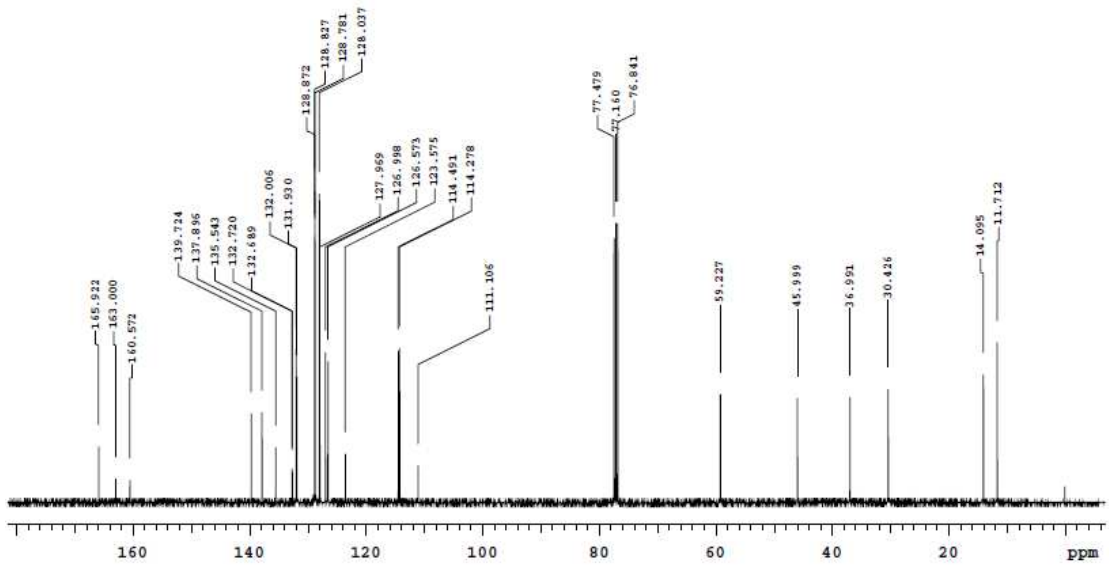
^{13}C NMR Spectrum of Compound 4u



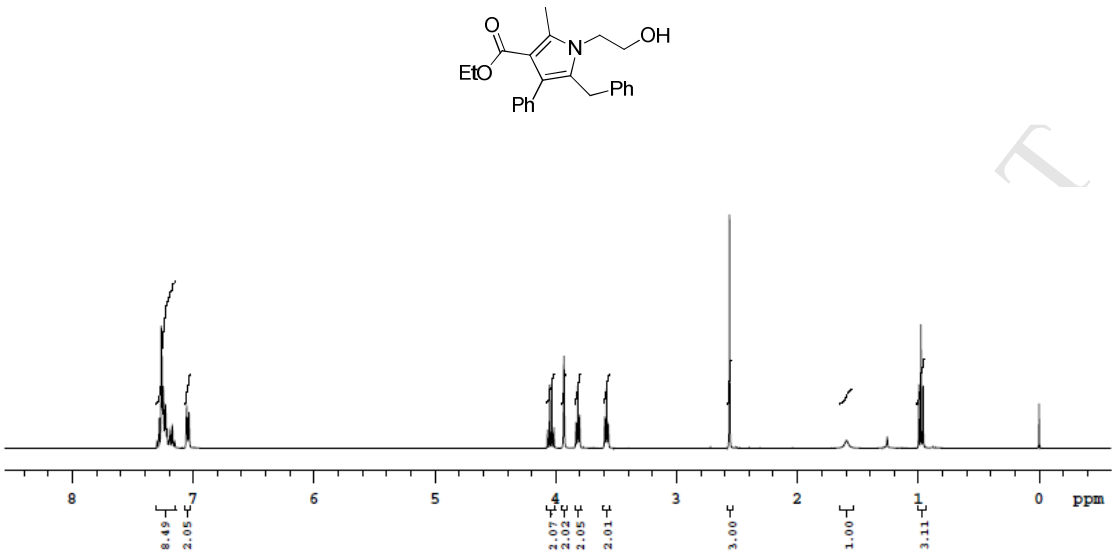
^{1}H NMR Spectrum of Compound 4v



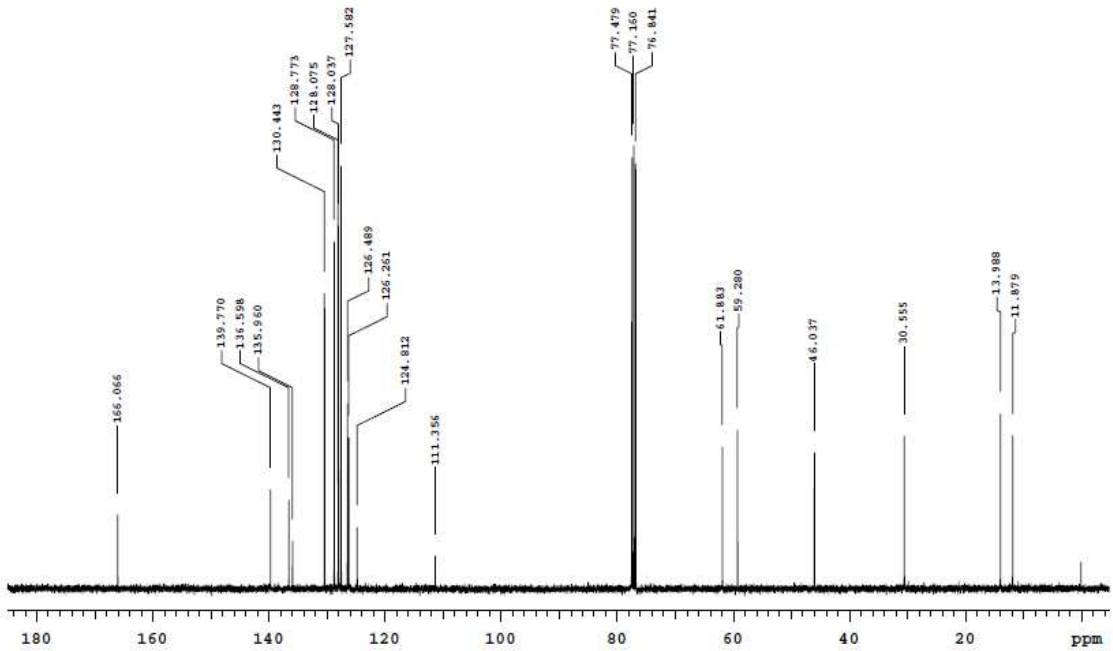
^{13}C NMR Spectrum of Compound 4v



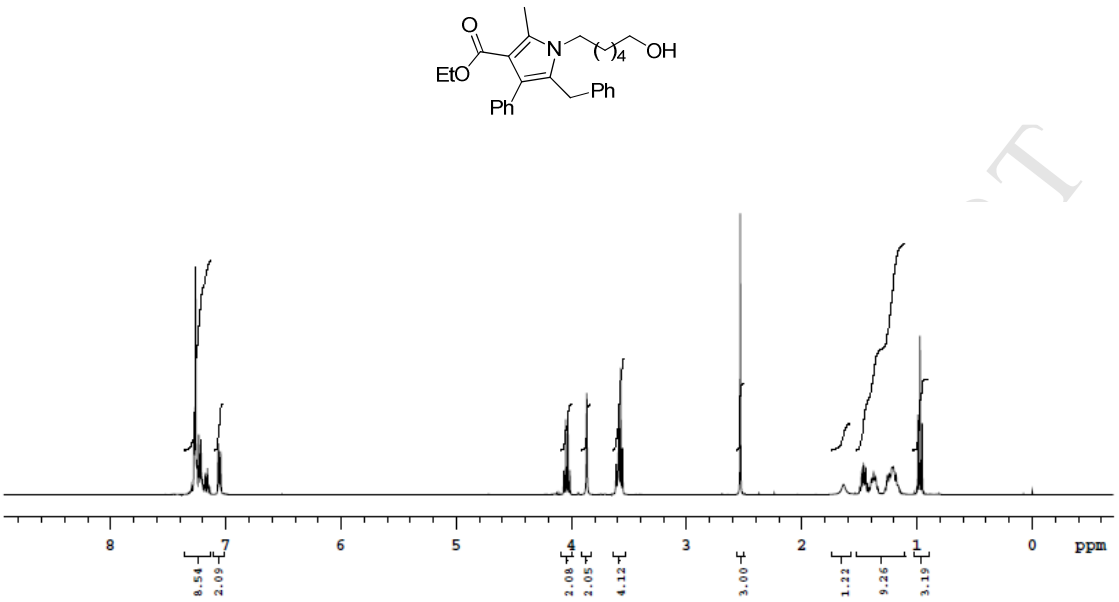
^{1}H NMR Spectrum of Compound 4w



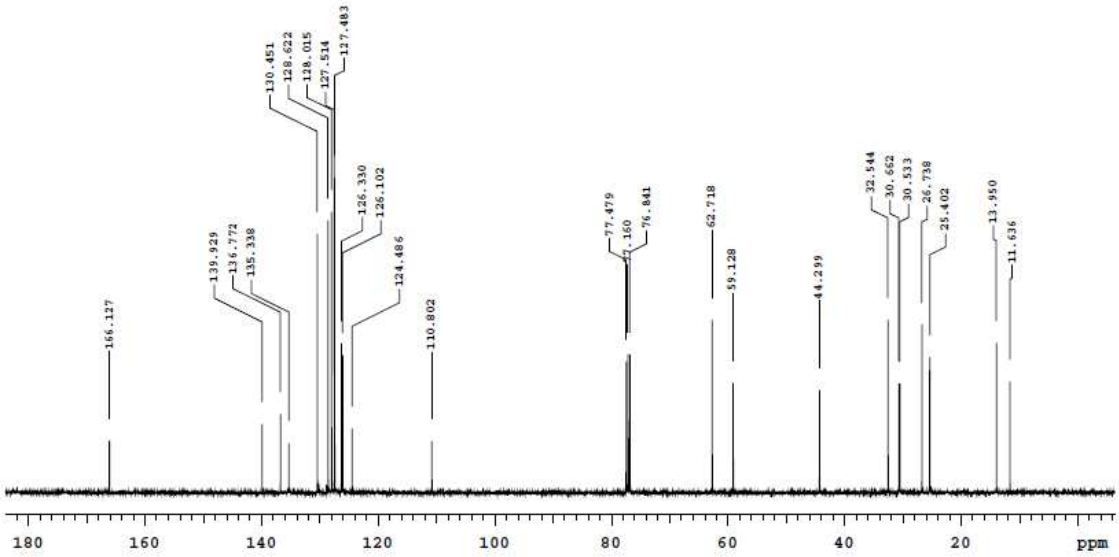
^{13}C NMR Spectrum of Compound 4w



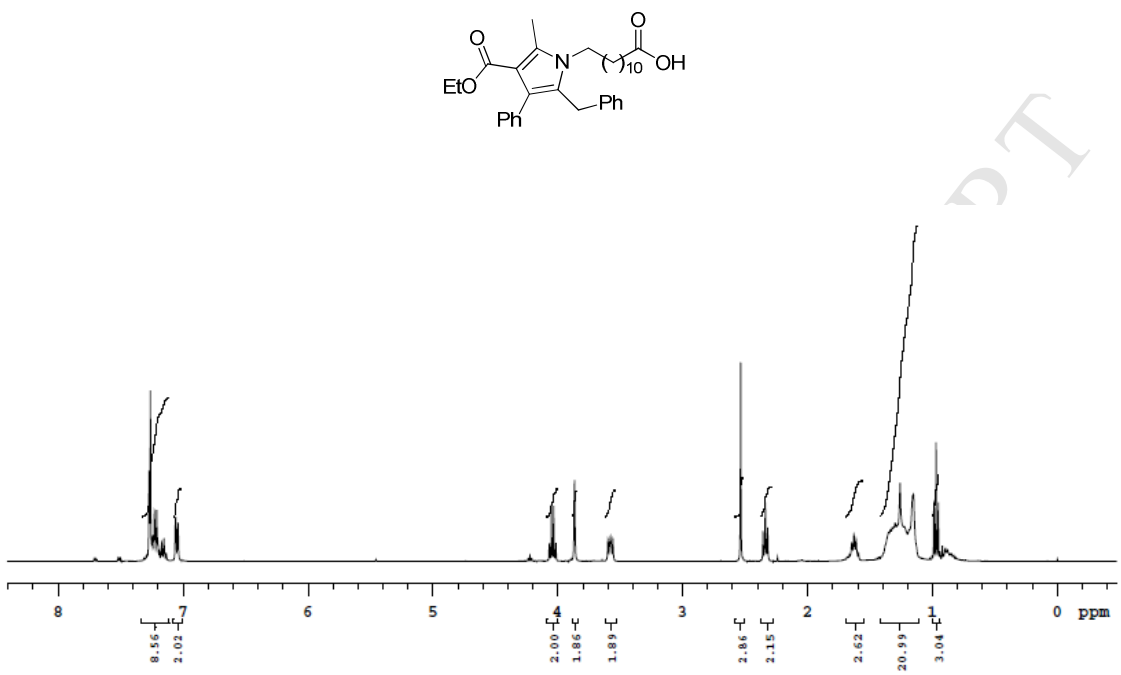
^{1}H NMR Spectrum of Compound 4x



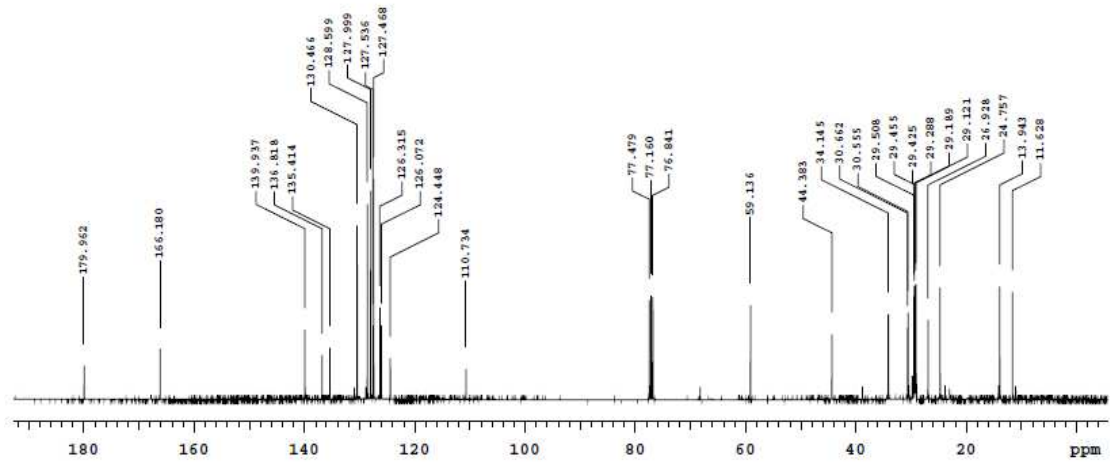
^{13}C NMR Spectrum of Compound 4x



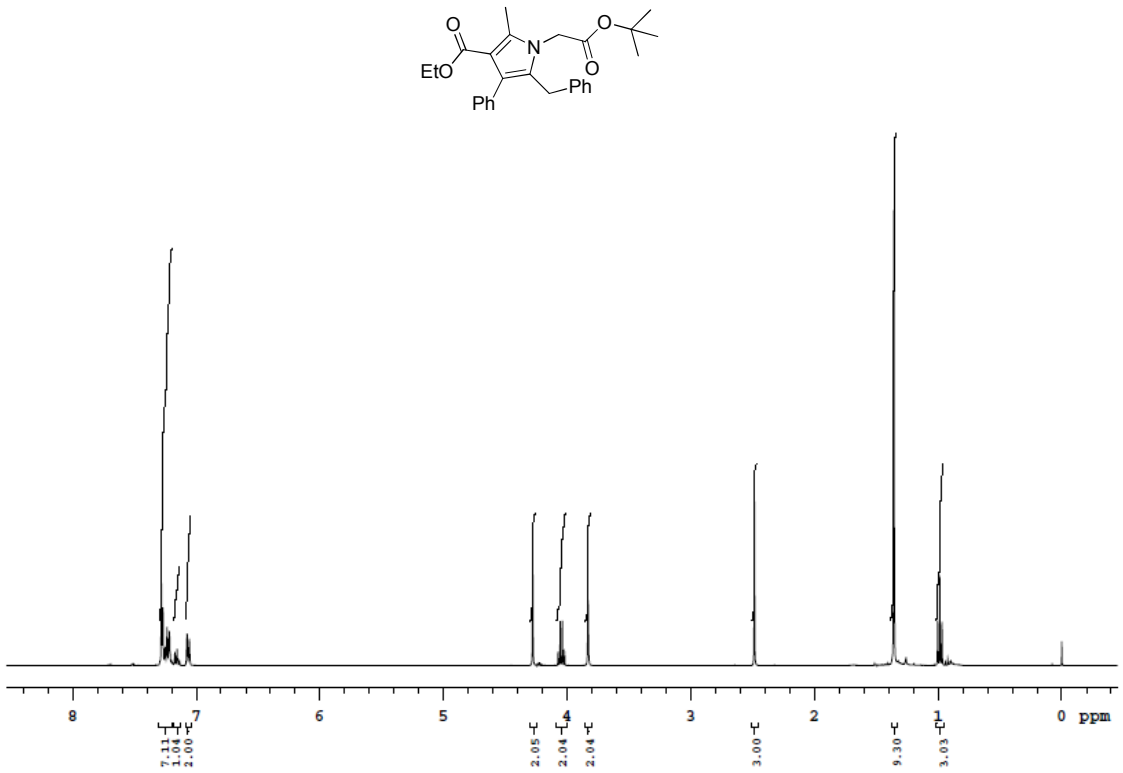
^{1}H NMR Spectrum of Compound 4y



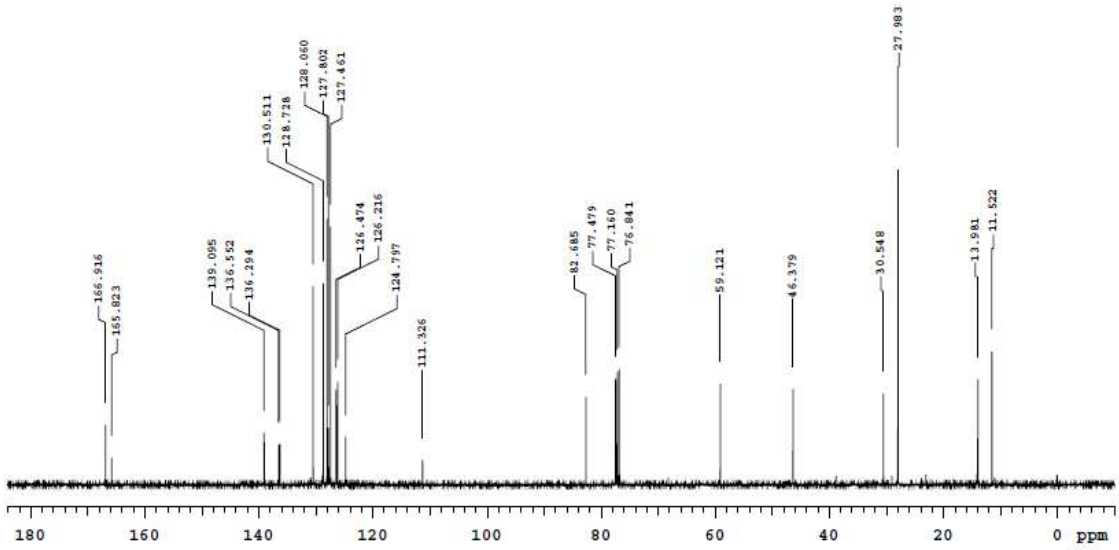
^{13}C NMR Spectrum of Compound 4y



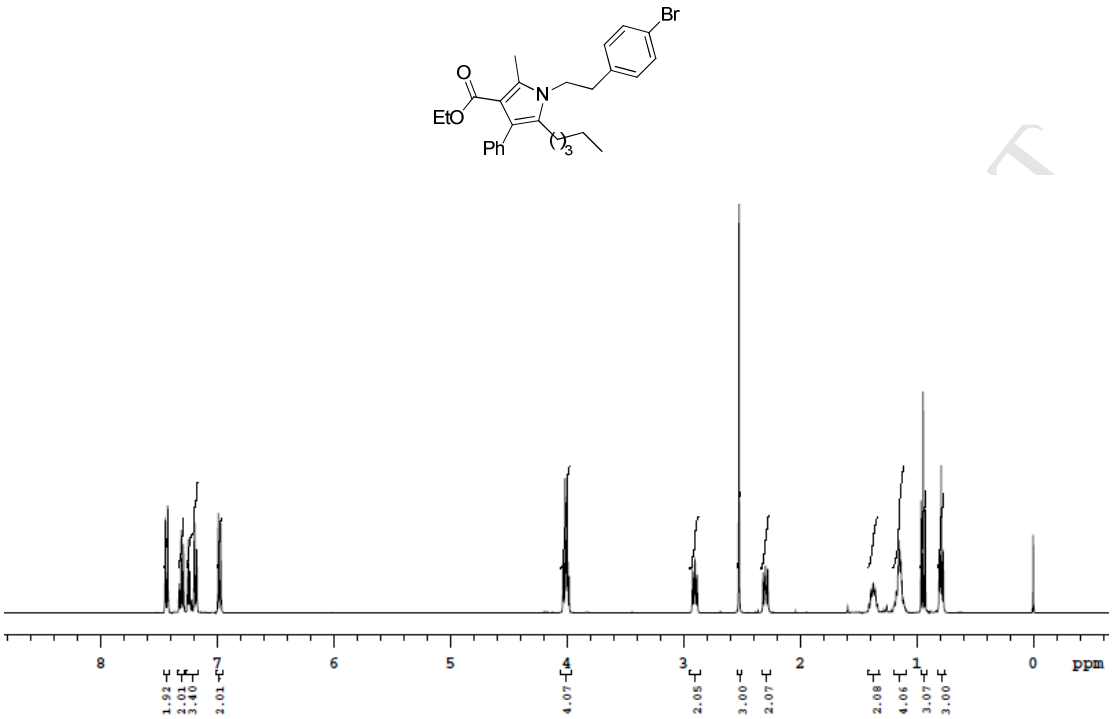
^{1}H NMR Spectrum of Compound 4z



^{13}C NMR Spectrum of Compound 4z



^{1}H NMR Spectrum of Compound 4aa



^{13}C NMR Spectrum of Compound 4aa