Synthesis and Characterization of Schiff Base 1-Amino-4-methylpiperazine Derivatives

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Received / Geliş: 15th August (Ağustos) 2016
Accepted / Kabul: 15th December (Aralık) 2016
DOI: 10.18466/cbayarfbe.280600

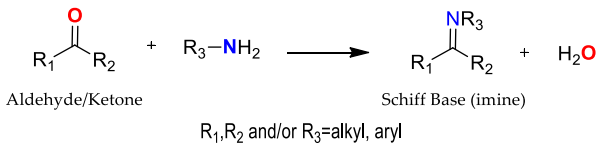
Abstract

In this study, potentially biological active new Schiff bases were synthesized in good yield from 1-amino-4-methylpiperazine and aromatic aldehydes as a 3-nitro-benzaldehyde, 4-fluoro-benzaldehyde, 3,4,5-trimethoxybenzaldehyde, 3,4-dichlorobenzaldehyde, 4-diethylaminobenzaldehyde, 2,5-dimethoxybenzaldehyde and 5-nitro-2-furaldehyde and structure of the synthesized compounds were elucidated by FTIR, LC-MS, ^{1}H-NMR and ^{13}C-NMR techniques.

Key Words: 1-Amino-4-methylpiperazine, aromatic aldehydes, hydrazone, imine, Schiff base.

1 Introduction

Schiff bases are very important structures for synthetic organic chemistry. They were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Compounds that containing an azomethine group (-CH=N-), known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound such as aldehyde and ketone (**Scheme 1.**) Also, Schiff bases are known as imines. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable while those of aromatic aldehydes, having a conjugation system, are more stable [1-9].



Scheme 1. General Pathway for Synthesis of a Schiff Base

Schiff bases, in other words imines, exhibit a broad range of biological activities. These compounds are very important in medicinal fields because of their wide spectrum of biological activities. Most of them have antibacterial, antifungal and antitumor activities as biologically important molecules [8-10].

In addition to their biological activities, they are used in many fields such as dyes, analytical chemistry, pigments, polymer stabilizers, corrosion inhibitors, fungicidal, agrochemical, electrical conductivity, magnetism, ion exchange, nonlinear optics and catalysis [4].

Schiff bases are versatile molecules. Schiff bases are generally bi- or tridentate ligands which are capable of forming very stable complexes with transition metals such as cobalt, nickel, iron and copper etc. Zoubi reported that most of the metal chelates had higher antimicrobial activity than the free ligands. Moreover, they have a variety of biological applications in pharmacological areas. Some transition metal complexes were reported to have antimicrobial activities. For example, copper complexes showed numerous biological activities such as antitumor, antifungal, antimicrobial activities [1, 2, 7, 10].

Not only Schiff bases are obtained synthetically but also are extracted from plants. There are many of

antibacterial Schiff bases derived from plants. For example, the compound, *Ancistrocladidine* **(Figure 1)**, obtained from members of *Ancistrocladaceae* and *Dioncophyllaceae* families has an antimalarial activity [2].

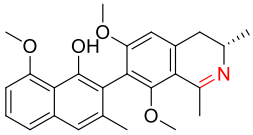
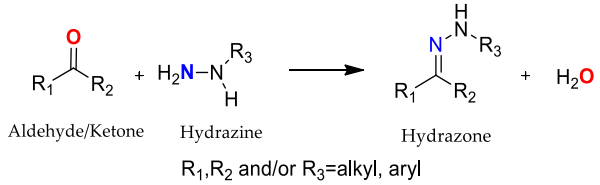


Figure 1. Ancistrocladidine (Antimalarial activity)

Hydrazones are very similar to imines. Hydrazones are formed in reactions between aldehydes/ketones and hydrazines, functional groups containing a nitrogen-nitrogen single bond (**Scheme 2.**)[11-15].



Scheme 2. General Pathway for Synthesis of a Hydrazone

Hydrazone derivatives are important class of biologically active compounds as well. Studies on hydrazones have shown that these derivatives possess a wide variety of biological functions such as antitumor, antibacterial, antiviral, antihypertensive, analgesic etc. [6, 8, 10, 11, 16].

The piperazine nucleus (**Figure 2.**) is often found in biologically active compounds used in a number of different therapeutic areas with their antimicrobial, anti-tubercular, antipsychotic, anticonvulsant, antidepressant, anti-inflammatory, cytotoxic, antimalarial, antiarrhythmic, antioxidant and antiviral activities [6, 17-20].

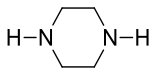


Figure 2. Piperazine molecule

1-Amino-4-methylpiperazine (**Figure 3.**), a derivative of piperazine, is used widely as an intermediate in the synthesis of pharmaceutical agents [21-25].

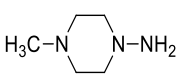


Figure 3. 1-Amino-4-methylpiperazine molecule

For example, 1-Amino-4-methylpiperazine is an important intermediate for *Rifampicin*. *Rifampicin* (**Figure 4**.), known as rifampin, is an antibiotic used to treat a several kinds of bacterial infections such as tuberculosis, leprosy and Legionnare's disease [26]. *Rifampisin* has an active side that is showed as red colour on **Figure 4.** As shown below**,** this active side consists of 1-amino-4-methylpiperazine [28].

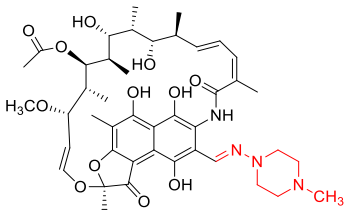


Figure 4. Rifampicin (Antitubercular Activity)

With respect to the previous information, in this study, it was aimed to synthesize new Schiff bases with 1-amino-4-methylpiperazine as hydrazine/primer amine and seven different aromatic aldehyde derivatives as carbonyl containing groups. (**Scheme 3.**). Their spectroscopic analysis was performed and explained for each compound in experimental section. In addition to, related spectrums were added to behind references. The numbers that on molecule structures are only used for spectroscopic analysis. It did not apply to the IUPAC nomenclature.

2 Materials and Methıds

2.1. Chemicals, Reagents and Analysis

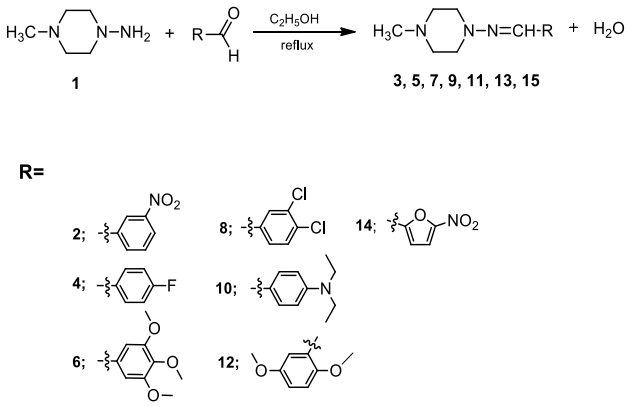
Commercially available reagent grade solvents and chemicals were bought from Merck, TCI, Sigma-Aldrich, and Alfa Aesar and used without further purification. TLC were performed on precoated aluminium silica gel plates G-60 F254 (Merck 5554). All reactions were monitored by TLC, detection for spots using UV light at 254 nm and spraying on ethanolic solution of H_2SO_4 (5%, v/v) followed by heating at 100°C. Melting points were determined in open capillary tubes using on a Electrothermal IA9300 capillary melting point apparatus and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer using KBr discs. ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz), spectra were

recorded on a Varian AS 400 NMR spectrometer in Ege University and the following multiplicity abbreviations were used: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet; *J* in hertz. The mass spectra were recorded on Agilent LC-MS/TOF spectrometer (HPLC unit: 1260 Infinitiy Series and TOFMS unit: Agilent 6230) using electrospray as an ionization source in Giresun University.

2.2. Experiments

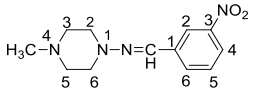
General Method (**Scheme 3.**):

1-amino-4-methylpiperazine (**1;** 1,25 eq, 0,57 mL, d=0,957 g/mL,) was slowly added to a solution of aromatic aldehyde derivative (respectively**, 2**, **4**, **6**, **8**, **10**, **12**, **14;** 1 eq.) in absolute ethanol (10 mL). The stirred reaction mixture was refluxed for 3 h. After cooling, a precipitate was formed which was collected by filtration, then washed with cold ethanol, and recrystallized from ethanol [15, 27]. **3**, **5**, **7**, **9**, **11**, **13**, **15** numbered compounds were obtained, respectively.



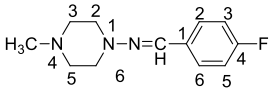
Scheme 3. General synthesis reaction of this study

2.2.1. 4-Methyl-*N*-(3-nitrobenzylidene)piperazin-1-amine (3):



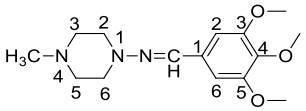
1-Amino-4-methylpiperazine (**1**) with 3-nitrobenzaldehyde (**2**) were reacted according to the general method. The product (**3**) was obtained as yellow solid. Yield 88%, mp 105 °C. FTIR (KBr Disc): 2841-2947 cm^{-1} Aliphatic -C-H, 1586 cm^{-1} C=N, 3079 cm^{-1} Aromatic C-H, 1521 cm^{-1} $-NO_2$, ^{1}H-NMR ($CDCl_3$, 400 MHz); δ = 8.34 (s, 1H, -N=CH-), 7.99 (d, 1H, $J_{9,10}$= 8.4 Hz, H-9), 7.81 (d, 1H, $J_{10,11}$= 7.6 Hz, H-11), 7.43 (s, 1H, H-7), 7.41 (dd, 1H, H-10), 3.21 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0.0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 5.2 Hz, H-1a, H-1b, H-4a and H-4b), 2.55 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.30 (s, 3H, N-CH_3) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 148.6 (C-8), 138.4 (C-5), 131.5 and 131.3 (C-6 and C-11), 129.2 (C-10), 122.0 (C-9), 120.4 (C-7), 57.3 (C-1 and C-4), 50.6 (C-2 and C-3), 45.9 (N-CH_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{12}H_{17}N_4O_2$ [M+H]: calc. 249.1352, found 249.1469.

2.2.2. *N*-(4-Fluorobenzylidene)-4-methylpiperazin-1-amine (5):



1-Amino-4-methylpiperazine (**1**) with 4-fluorobenzaldehyde (**4**) were reacted according to the general method. The product (**5**) was obtained as white solid. Yield: 62%, mp 77-78 °C. FTIR (KBr Disc): 2799-2912 cm^{-1} Aliphatic -C-H, 1601 cm^{-1} -C=N-, 3040-3030 cm^{-1}aromatic C-H, 1003 cm^{-1} C-F, ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.47 (s, 1H, -N=CH-), 7.55 and 7.54 (dd, 2H, $J_{7,8}$= $J_{10,11}$=8.8 Hz, $J_{8,F}$= $J_{10,F}$=1.2 Hz, H-7 and H-11), 7.01 and 6.99 (dd, 2H, $J_{8,F}$= $J_{10,F}$=1.6 Hz, H-8 and H-10,), 3.17 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0.0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 4.8 Hz, H-1a, H-1b, H-4a and H-4b), 2.58 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.32 (s, 3H, N-CH_3) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 162.7 (d, $J_{9,F}$= 246.0 Hz, C-9), 134.5 (C-5), 132.5 (d, $J_{6,F}$= 3.1 Hz, C-6), 127.6 (d, $J_{7,F}$= $J_{11,F}$= 8.0 Hz, C-7 and C-11), 115.4 (d, $J_{8,F}$= $J_{10,F}$= 21.6 Hz, C-8 and C-10), 54.5 (C-1 and C-4), 51.0 (C-2 and C-3), 45.9 (N-CH_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{12}H_{17}FN_3$ [M+H]: calc. 222.1407, found 222.1621.

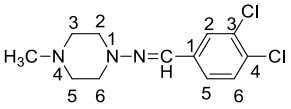
2.2.3. 4-Methyl-*N*-(3,4,5-trimethoxybenzylidene) piperazin-1-amine (7):



1-Amino-4-methylpiperazine (**1**) with 3,4,5-trimethoxybenzaldehyde (**6**) were reacted according to the general method. The product (**7**) was obtained as white solid. Yield: 81%, mp 141-142 °C. FTIR (KBr

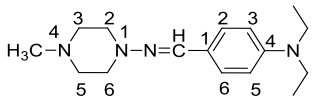
Disc): 2815-2933 cm^{-1} Aliphatic -C-H, 1601 cm^{-1} C=N, 3080 cm^{-1} Aromatic C-H, 1229 cm^{-1} -C-O-C-, ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.41 (s, 1H, -N=CH-), 6.81 (s, 2H, H-7 and H-11), 3.83 and 3.80 (s, 9H, 3×OCH_3), 3.15 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0,0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 5.2 Hz, H-1a, H-1b, H-4a and H-4b), 2.56 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.30 (s, 3H, N-CH_3) ppm; ^{13}C NMR (CDCl3, 100 MHz): δ = 153.3 (C-8 and C-10), 138.3 (C-9), 135.5 (C-5), 131.9 (C-6), 103.1 (C-7 and C-11), 60.8 and 56.0 (3×OCH_3), 54.5 (C-1 and C-4), 51.0 (C-2 and C-3), 45.9 (N-CH_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{15}H_{24}N_3O_3$ [M+H]: calc. 294.1818, found 294.2127.

2.2.4. *N*-(3,4-Dichlorobenzylidene)-4-methylpiperazin-1-amine (9):



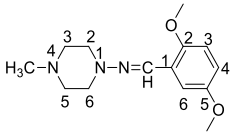
1-Amino-4-methylpiperazine (**1**) with 3,4-dichlorobenzaldehyde (**8**) were reacted according to the general method. The product (**9**) was obtained as white solid. Yield: 70%, mp 63-64 °C. FTIR (KBr Disc): 2800-2971 cm^{-1} aliphatic -C-H 1584 cm^{-1} -C=N-bond, 3081 cm^{-1} aromatic -C-H bond, 898 cm^{-1} C-Cl, ^{1}H-NMR ($CDCl_3$, 400 MHz); δ = 7.70 (s, 1H, -N=CH-), 7.34 (d, 2H, $J_{10,11}$=6.8 Hz, H-10 and H-11), 3.19 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0.0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 5.2 Hz, H-1a, H-1b, H-4a and H-4b), 2.56 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.32 (s, 3H, N-CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.6, 132.6, 132.0, 131.2, 130.3 and 127.3 (C-5, C-6, C-7, C-8, C-9 and C-10), 125.7 (C-11), 54.3 (C-1 and C-4), 50.7 (C-2 and C-3), 45.9 (N-CH_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{12}H_{16}Cl_2N_3$ [M+H]: calc. 272.0721, found 272.0921.

2.2.5. *N*-(4-(Diethylamino)benzylidene)-4-methylpiperazin-1-amine (11):



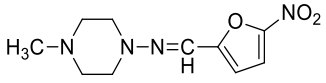
1-Amino-4-methylpiperazine (**1**) with 4-diethylaminobenzaldehyde (**10**) were reacted according to the general method. The product (**11**) was obtained as bright yellow solid. Yield: 79%, mp 102 °C. FTIR (KBr Disc): 1605 cm^{-1} C=N, 3037-3085 cm^{-1}Aromatic C-H, 2825-2970 cm^{-1}Aliphatic -C-H. ^{1}H-NMR ($CDCl_3$, 400 MHz); δ = 7.56 (s, 1H, -N=CH-), 7.45 (d, 2H, $J_{7,8}$= $J_{10,11}$=8.8 Hz, H-7 and H-11), 6.93 (d, 2H, H-8 and H-10), 3.35 (dd, 4H, $J_{CH2,\ CH3}$= 6.8 Hz, $J_{CH2a,CH2b}$= 14.0 Hz, 2×-C<u>H</u>$_2$-CH_3), 3.13 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0.0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 4.8 Hz, H-1a, H-1b, H-4a and H-4b), 2.59 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.32 (s, 3H, N-CH_3), 1.15 (dd, 6H, 2×-CH_2-C<u>H</u>$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 148.0 (C-9), 138.7 (C-5), 127.7 (C-7 and C-11), 123.5 (C-6), 111.5 (C-8 and C-10), 54.7 (C-1 and C-4), 51.7 (C-2 and C-3), 45.9 (N-CH_3), 44.4 (2×-<u>C</u>H_2-CH_3), 12.6 (2×-CH_2-<u>C</u>H_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{16}H_{27}N_4$ [M+H]: calc. 275.2236, found 275.2542.

2.2.6. *N*-(2,5-Dimethoxybenzylidene)-4-methylpiperazin-1-amine (13):



1-Amino-4-methylpiperazine (**1**) with 2,5-dimethoxybenzaldehyde (**12**) were reacted according to the general method. The product (**13**) was obtained as light yellow syrup. Yield: 72%. FTIR (KBr Disc): 2796-2939 cm^{-1} Aliphatic -C-H, 1589 cm^{-1} C=N bond, 1217 cm^{-1} -C-O-C- bond, ^{1}H NMR ($CDCl_3$, 400 MHz); δ = 7.85 (s, 1H, -N=CH-), 7.42 (s, 1H, H-7), 6.77-6.76 (m, 2H, H-9 and H-10), 3.76 and 3.75 (s, 6H, 2×OCH_3), 3.20 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0,0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 5.2 Hz, H-1a, H-1b, H-4a and H-4b), 2.58 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.32 (s, 3H, N-CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.9 and 151.5 (C-8 and C-11), 131.5 (C-5), 125.4, 115.5, 112.5 and 109.3 (C-6, C-7, C-9 and C-10), 56.2 and 55.7 (2×OCH_3), 54.5 (C-1 and C-4), 51.0 (C-2 and C-3), 45.9 (N-CH_3) ppm; LC-MS (ESI) (pos): *m*/*z* for $C_{14}H_{22}N_3O_2$ [M+H]: calc. 264.1712, found 264.1960.

2.2.7. 4-Methyl-*N*-((5-nitrofuran-2-yl)methylene)piperazin-1-amine (15):

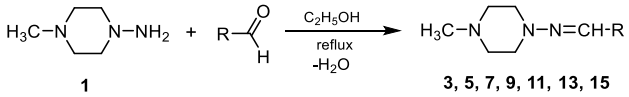


1-Amino-4-methylpiperazine (**1**) with 5-nitro-2-furaldehyde (**14**) were reacted according to the general method. The product (**15**) was obtained as light brown solid. Yield: 97%, mp 114-115 °C. FTIR

(KBr Disc): 2800-2950 cm^{-1} Aliphatic -C-H, 1594 cm^{-1} C=N, 2800-2957 cm^{-1} Aliphatic C-H, 1555 cm^{-1} NO_2(O=N=O), ^{1}H-NMR ($CDCl_3$, 400 MHz); δ = 7.22 (d, 1H, $J_{7,8}$= 4.0 Hz, H-8), 7.12 (s, 1H, -N=CH-), 6.51 (d, 1H, H-7), 3.15 (dd, 4H, $J_{1a,1b}$= $J_{4a,4b}$= 0,0 Hz, $J_{1a,2a}$= $J_{1a,2b}$ = $J_{4a,3a}$= $J_{4a,3b}$ = 5.2 Hz, H-1a, H-1b, H-4a and H-4b), 2.43 (dd, 4H, $J_{2a,2b}$= $J_{3a,3b}$= 0.0 Hz, H-2a, H-2b, H-3a and H-3b), 2.19 (s, 3H, N-CH_3) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 155.6 (C-6), 150.9 (C-9), 120.6 (C-5), 114.5 and 108.0 (C-7 and C-8), 53.9 (C-1 and C-4), 50.1 (C-2 and C-3), 45.8 (N-CH_3) ppm; LC-MS (ESI) (pos): *m/z* for $C_{10}H_{15}N_4O_3$ [M+H]: calc. 239.1144, found 239.1225.

3 Results and Discussion

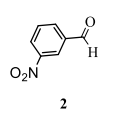
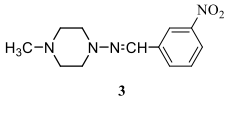
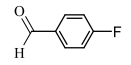
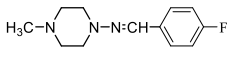
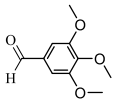
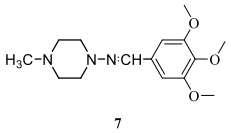
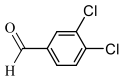
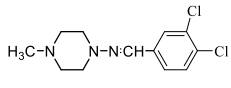
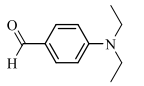
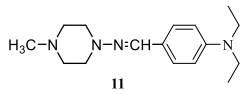
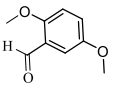
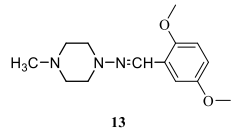
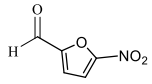
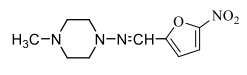
Schiff bases, in other words hydrazones, are versatile molecules. They have a variety of biological applications in pharmacological areas. Some transition metal complexes were reported to have antimicrobial activities. [1, 2, 7, 10]. With respect to the previous information, in this study, it was aimed to synthesize new Schiff bases with 1-amino-4-methylpiperazine (**1**) as hydrazine/primer amine and seven different aromatic aldehyde derivatives as carbonyl containing groups (**Scheme 3.**, **Table 1.**). They were synthesized one step according to the literature [15, 27]. All of this reaction have been performed without catalyst under reflux in absolute ethanol. The yields of potentially biological active new products of were presented in **Table 1**. Hydrazone derivatives (**3-15**) were prepared between 62% and 97% yields under mentioned conditions. ^{1}H-NMR, ^{13}C NMR, and mass spectrums are given after references.



Scheme 3. General synthesis reaction of this study

The IR spectra of compounds were evaluated as follows. The stretching frequencies of the -C=N- groups of Schiff bases with the compound numbers of **3**-**15** were observed at 1586, 1601, 1601, 1584,1605 and 1589 cm^{-1} respectively. All of these compounds have characteristic aromatic -C-H peaks that observed at 3030-3040 cm^{-1} ca. Because they are weak, it is difficult to see them. Also, compound **5** and **9** have strong C-X (X; halogen) peaks 1003 and 898 cm^{-1} respectively. Compound **3** and **15** have -NO_2 group. The stretching frequencies of the -NO_2 groups were observed at 1555 and 1521 cm^{-1} as very sharp peaks. Furthermore, the peaks observed at 1217 and 1229 cm^{-1} in the spectra of the compounds **7** and **13** relate to -C-O-C-(methoxy) groups.

Table 1. Synthesized new Schiff base derivatives

Entry	Aldehyde	Product	% Isolated yield
1	 **2**	 **3**	88
2	 **4**	 **5**	62
3	 **6**	 **7**	81
4	 **8**	 **9**	70
5	 **10**	 **11**	79
6	 **12**	 **13**	72
7	 **14**	 **15**	97

^{1}H-NMR spectra of the compounds (**3-15**) has showed a sharp singlet peak within the 8.34-7.12 ppm region, corresponding to the azomethine (-C**H**=N) proton. This peak is characteristic for identification of Schiff Base derivatives. It is remarkable that the downfield chemical shift (8.34 ppm) corresponds to the azomethine proton of the *m*-NO_2 derivative (compound **3**), having has the highest electron affinity. ^{1}H-NMR spectra of Schiff base derivatives (**3-13**) were showed peaks at 6.99-7.99 ppm belong to aromatic protons. For compound **3**, aromatic protons were observed at 7.99-7.41 ppm. It was seen that a sharp singlet peak at 2.19-2.32 ppm as 3H. (**3-15**) are belonging to -N-C**H**$_3$ group on piperazine ring. Also, peaks at 2.55 and 3.21 ppm relative to -CH_2 groups on piperazine ring. Because

of the same in the two -CH_2 groups, these peaks were observed and calculated as 4H. For compound **3**, characteristic ^{13}C-NMR signal of the azomethine group (-C=NH, C-5) were observed at 138.4 ppm. This characteristic peak has been seen for the others (**5-15**) at 134.5, 135.5, 132.0, 138.7, 131.5 and 120.6 ppm respectively. Furthermore, signal of aromatic carbons (compound **3**) were observed at 148.6 (C-8), 131.5 and 131.3 (C-6 and C-11), 129.2 (C-10), 122.0 (C-9), 120.4 (C-7) ppm. Finally, signal of -N-C**H**$_3$ groups on piperazine ring were observed at 45.9 ppm. Furthermore, the structure of all new Schiff base compounds (**3-15**) were also confirmed through molecular ion peaks for theirs molecular formula in ESI mass.

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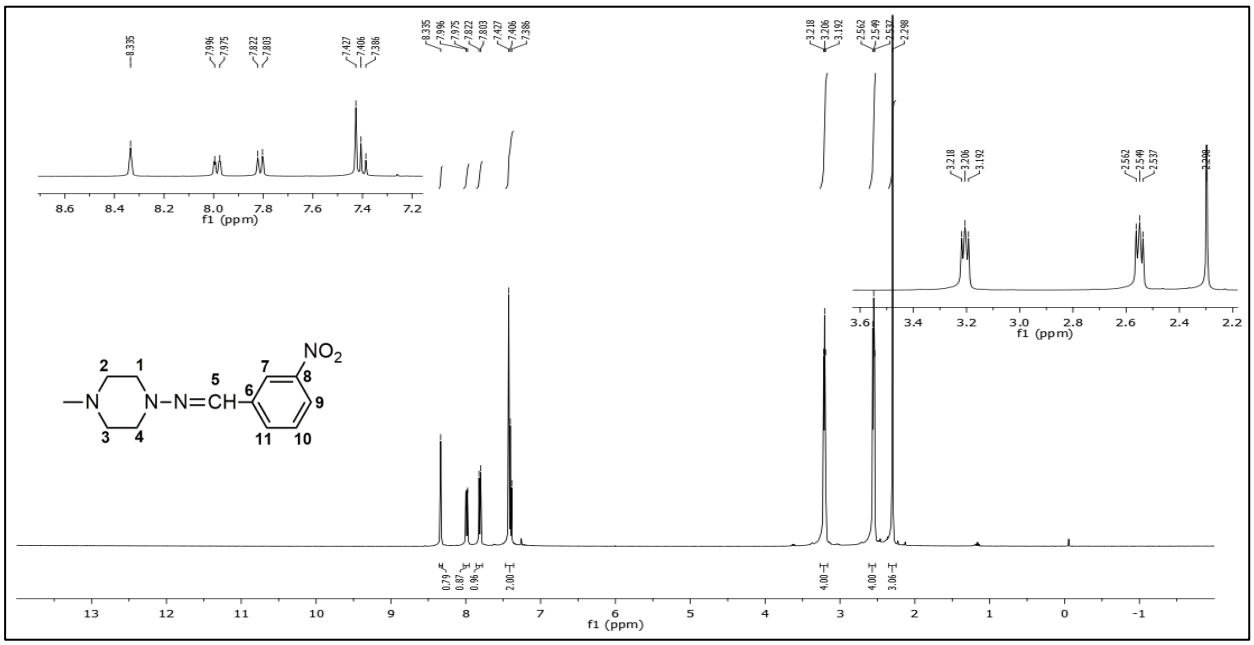
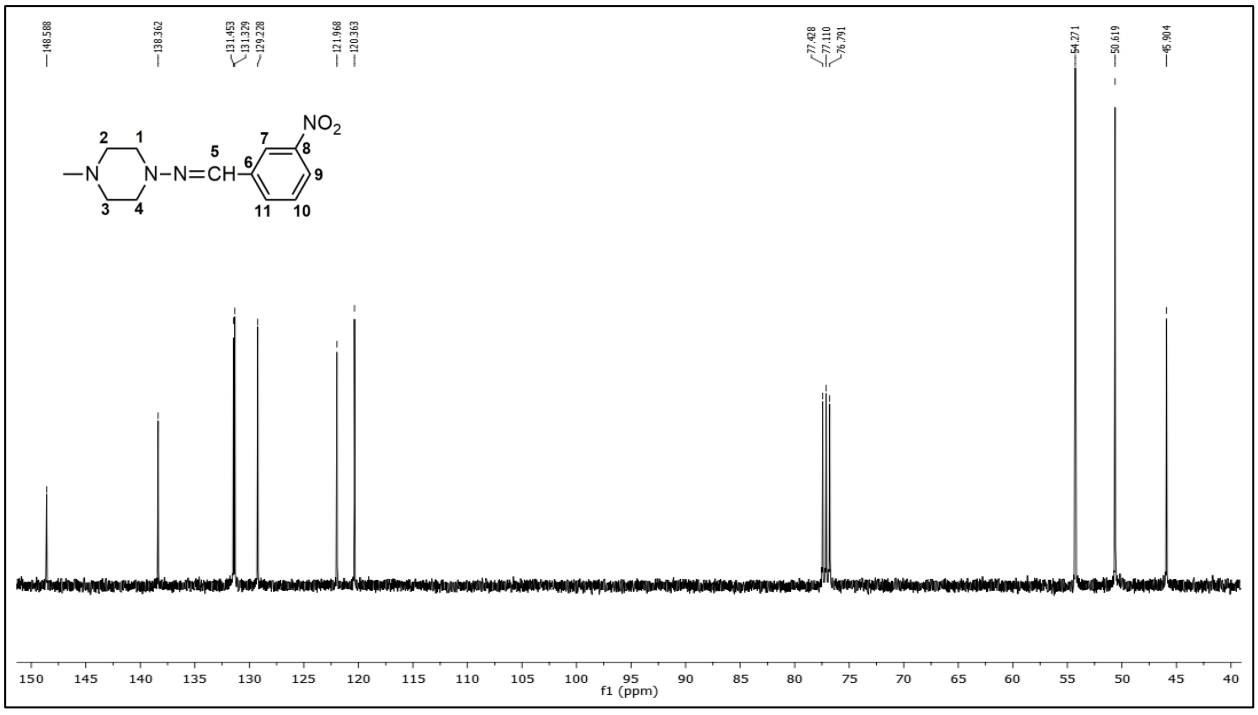
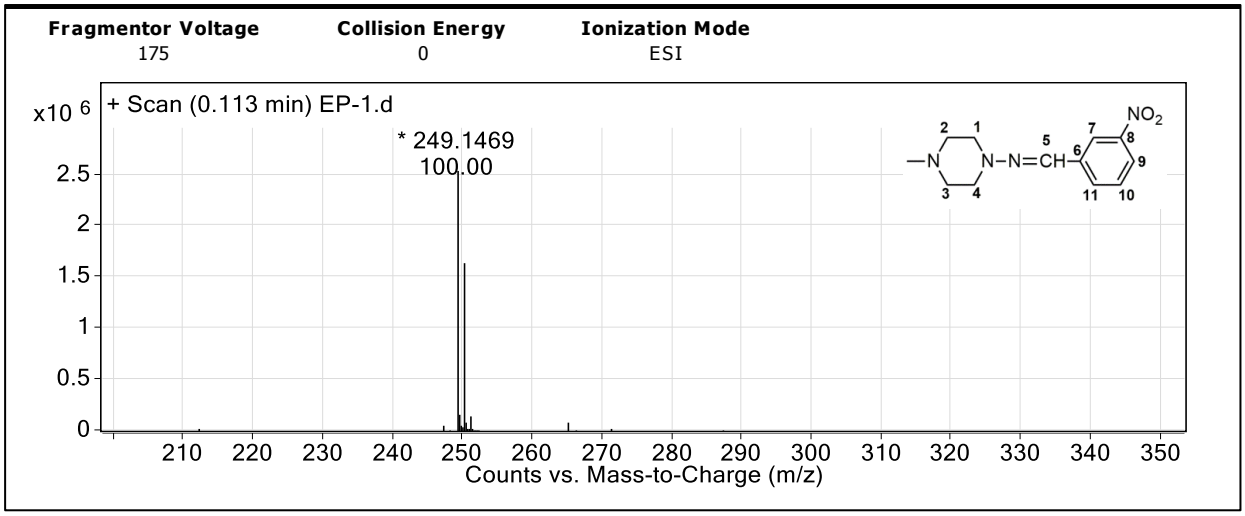


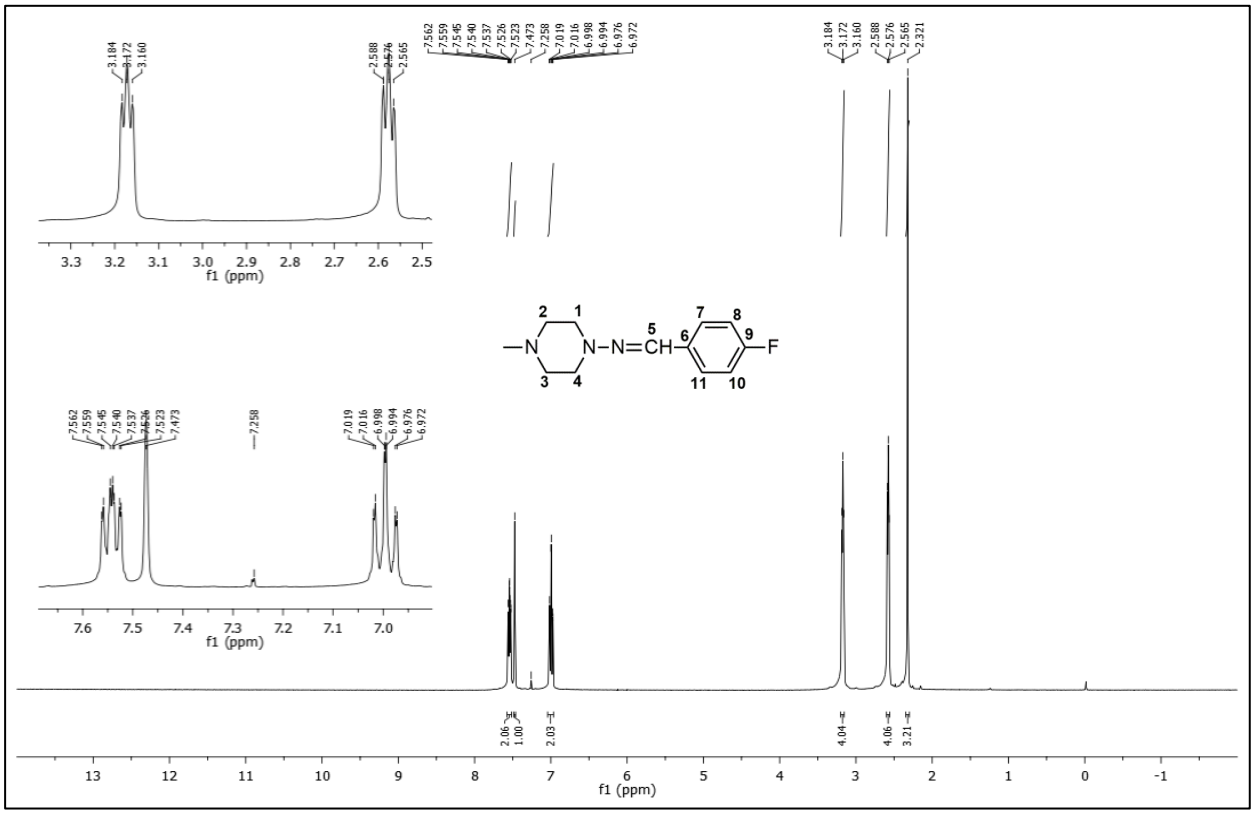
Spectrum 1. ^{1}H NMR (400 MHz) spectrum of compound **3** in $CDCl_3$



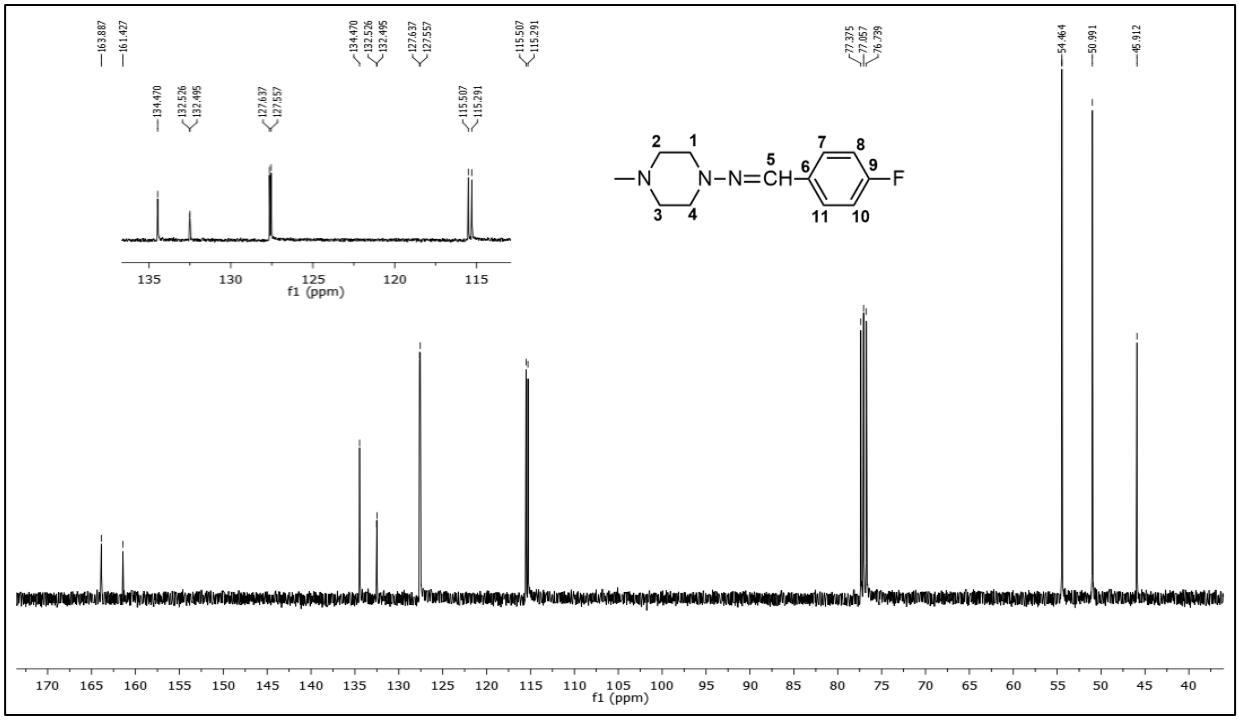
Spectrum 2. ^{13}C NMR (100 MHz) spectrum of compound **3** in $CDCl_3$



Spectrum 3. LC-MS (ESI) spectrum of compound **3**



Spectrum 4. ^{1}H NMR (400 MHz) spectrum of compound **5** in $CDCl_3$



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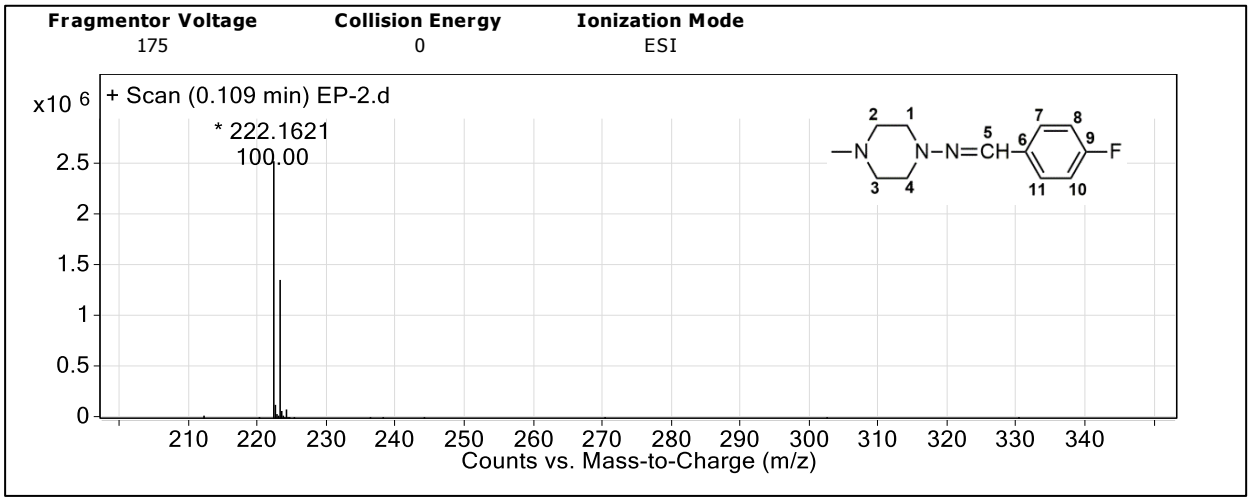
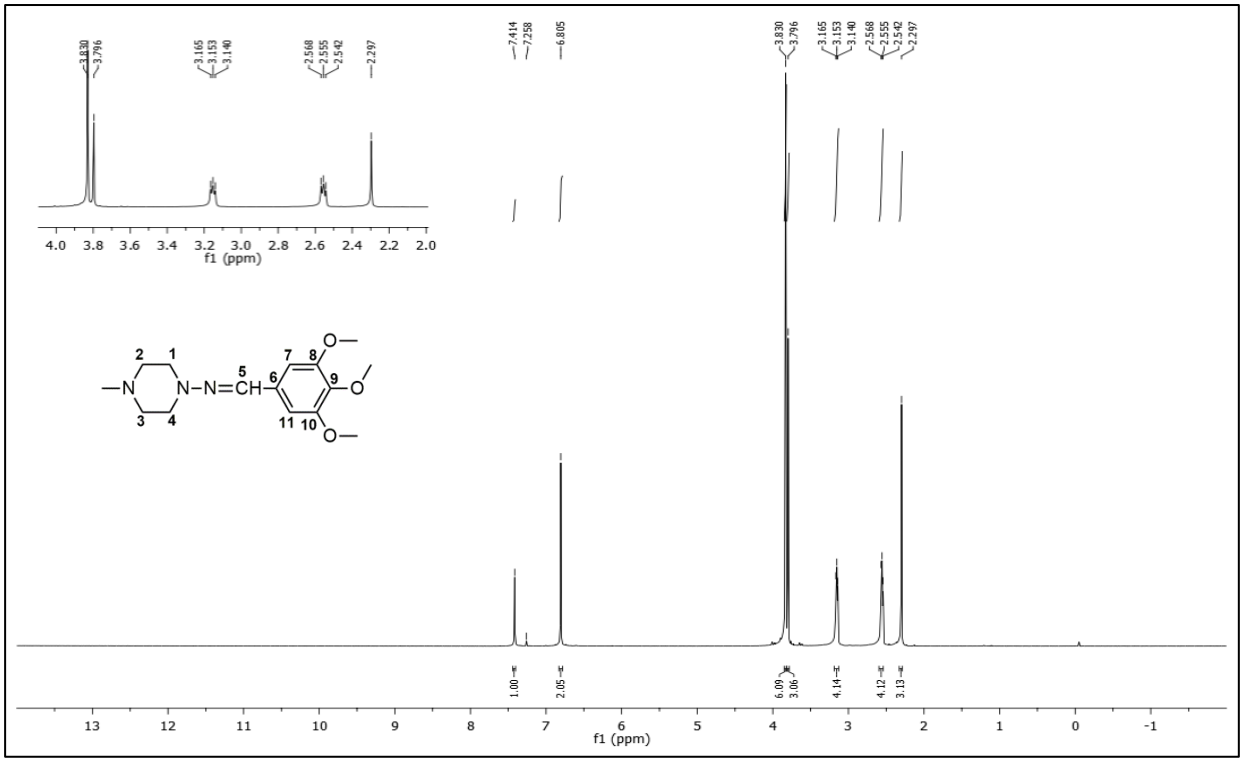
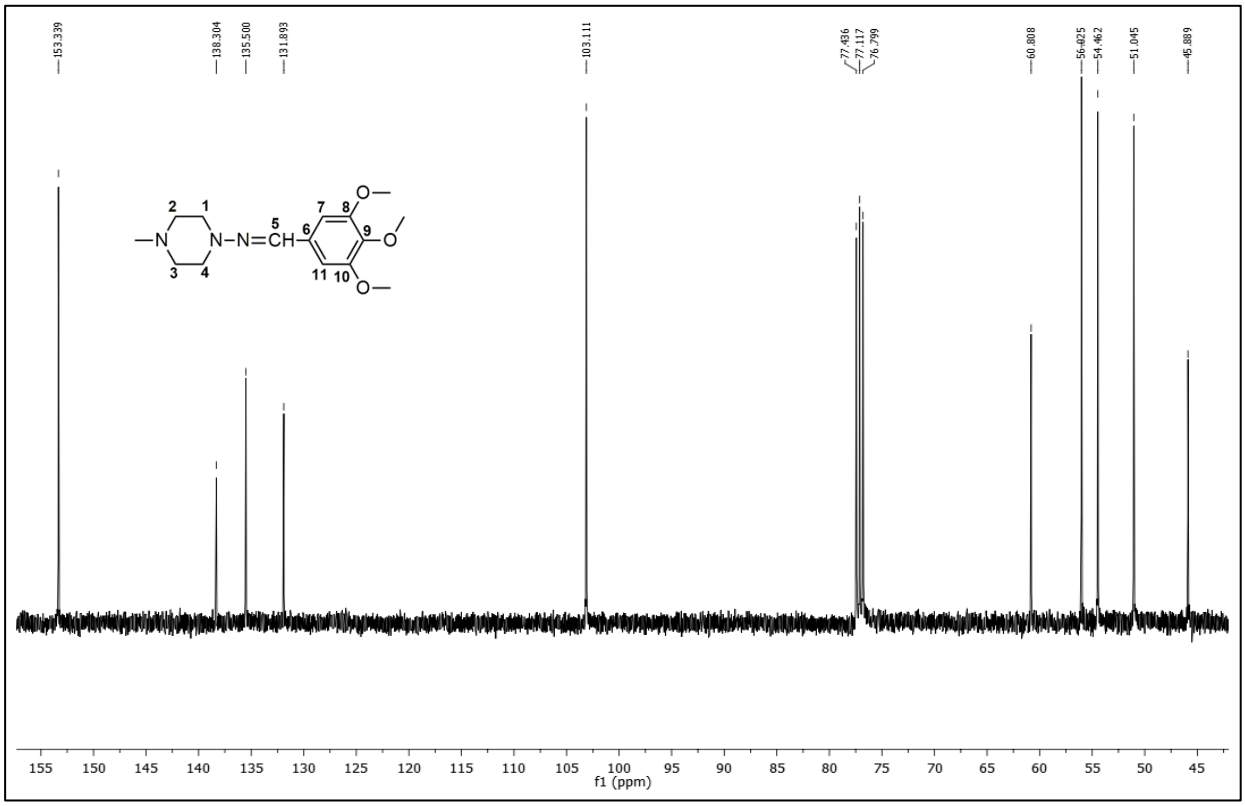


Spectrum 6. LC-MS (ESI) spectrum of compound **5**



Spectrum 7. ^{1}H NMR (400 MHz) spectrum of compound **7** in $CDCl_3$



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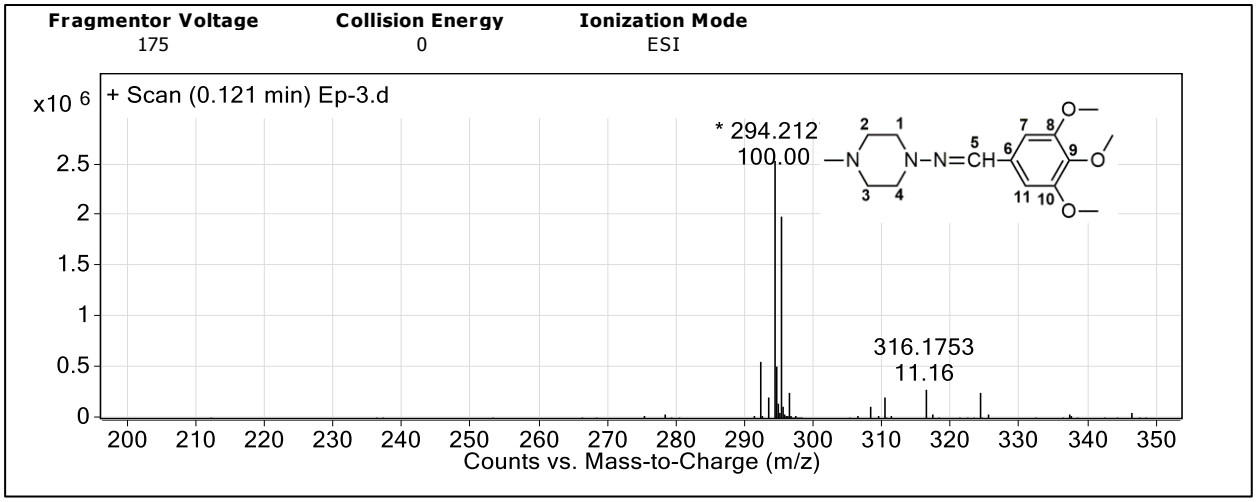
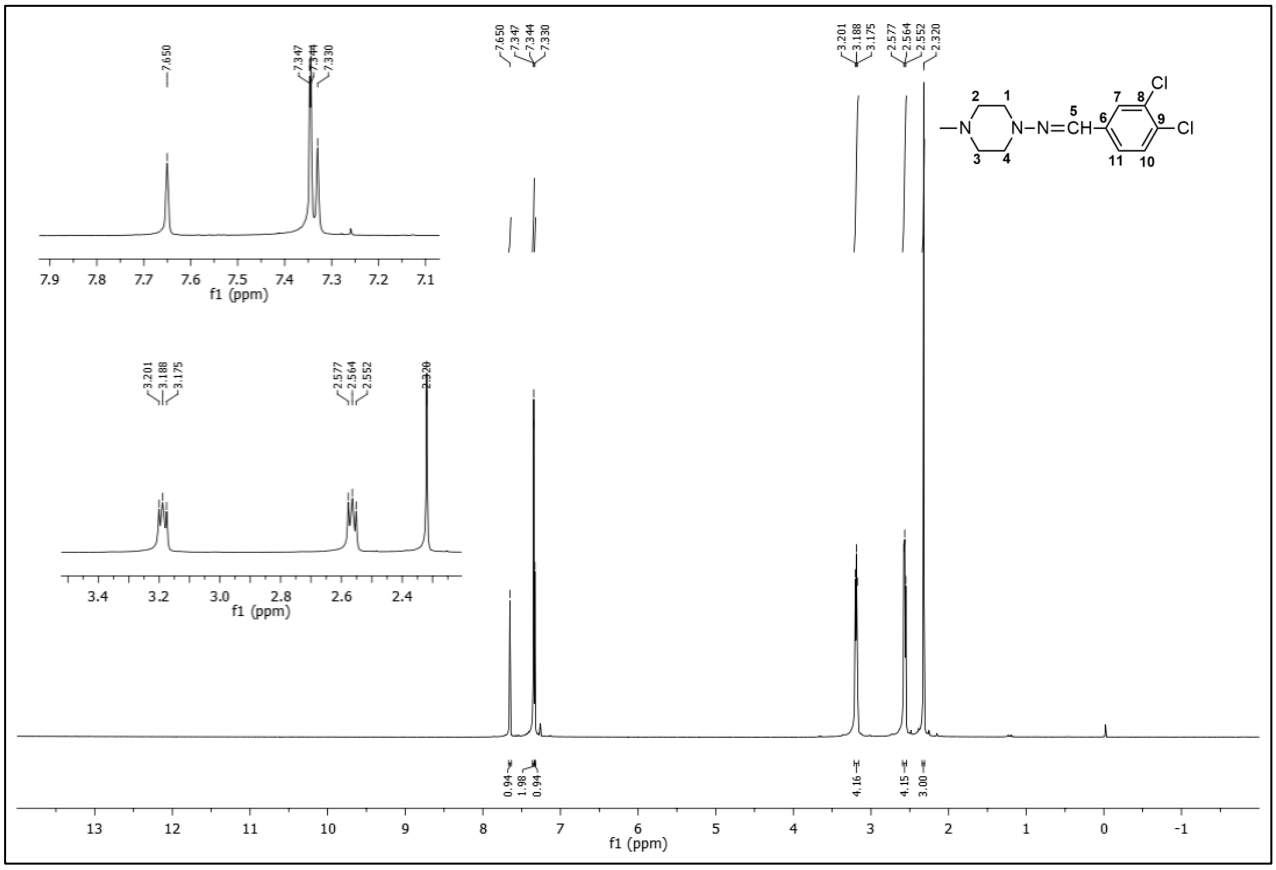
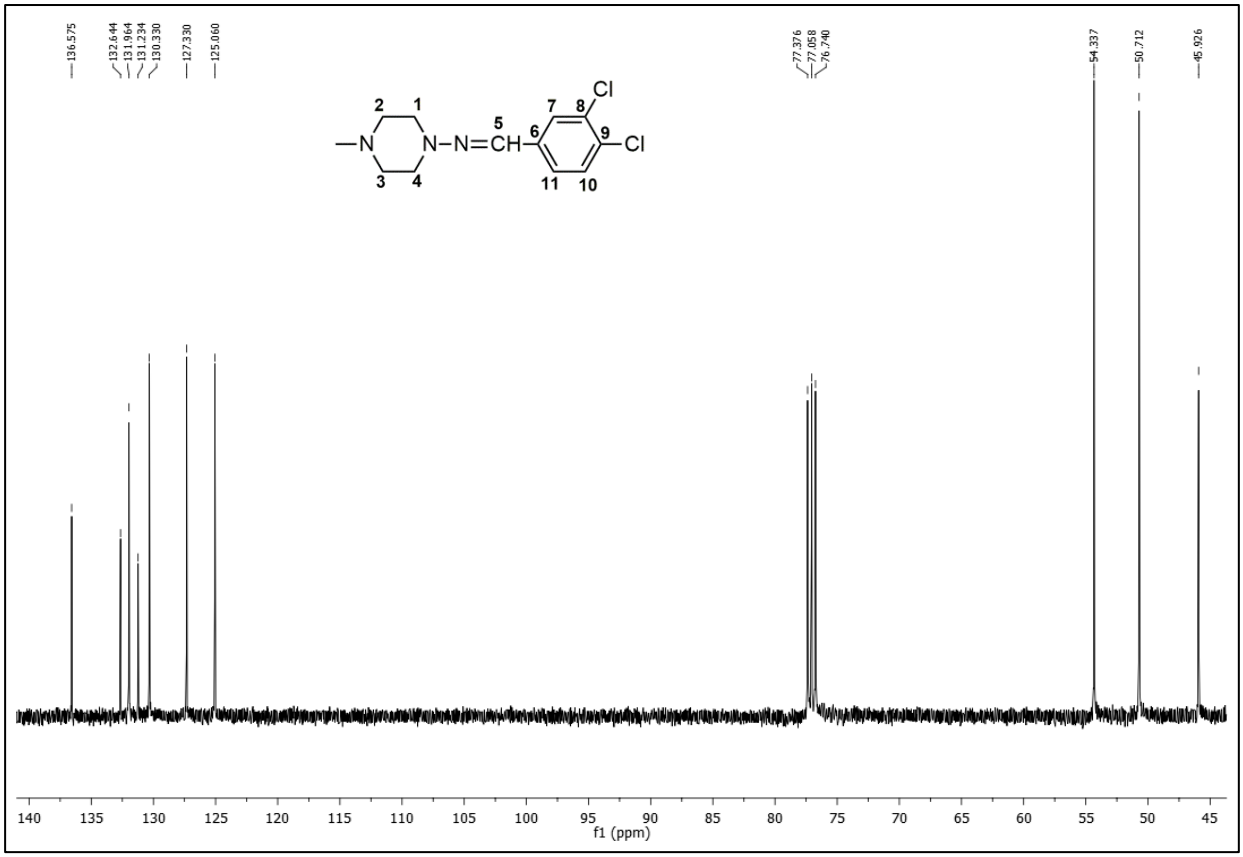


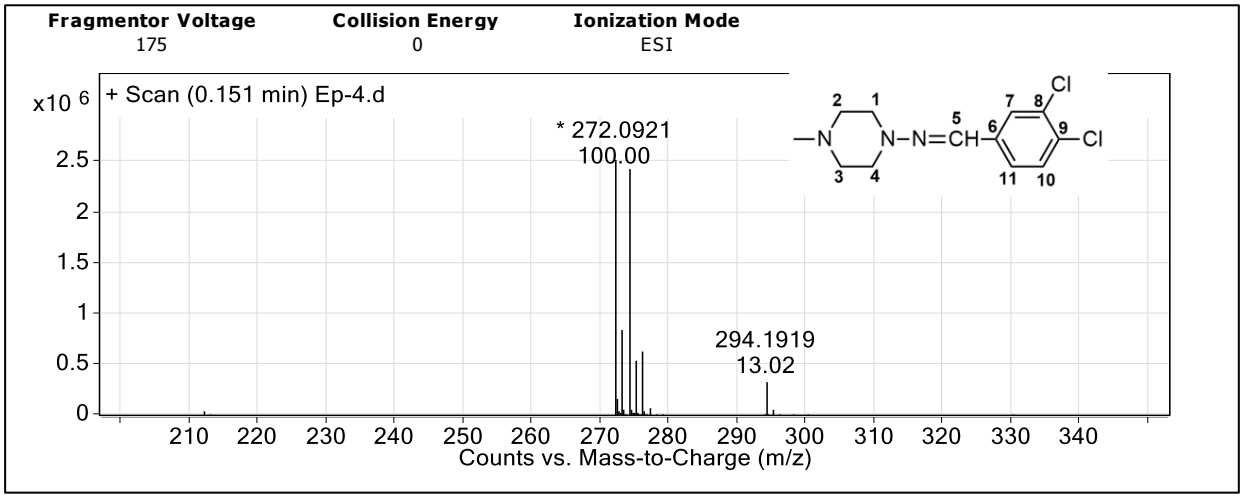
Spectrum 9. LC-MS (ESI) spectrum of compound **7**



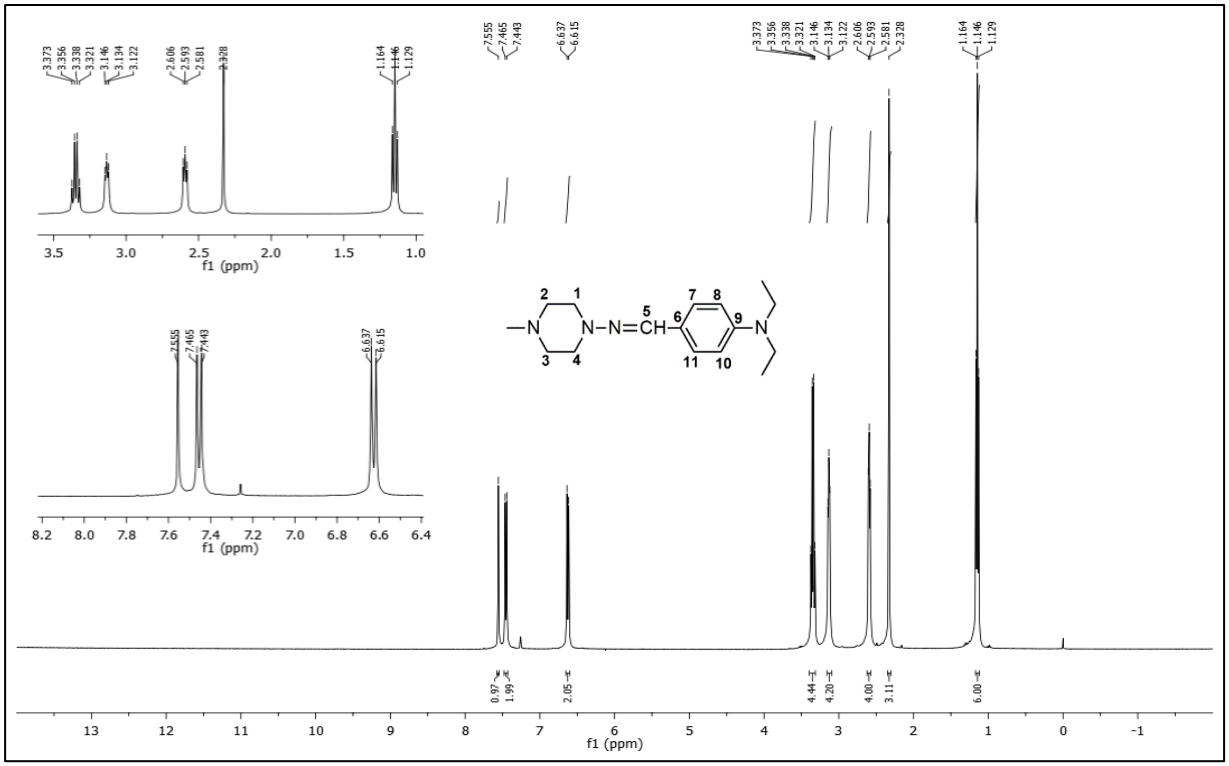
Spectrum 10. ^{1}H NMR (400 MHz) spectrum of compound **9** in $CDCl_3$



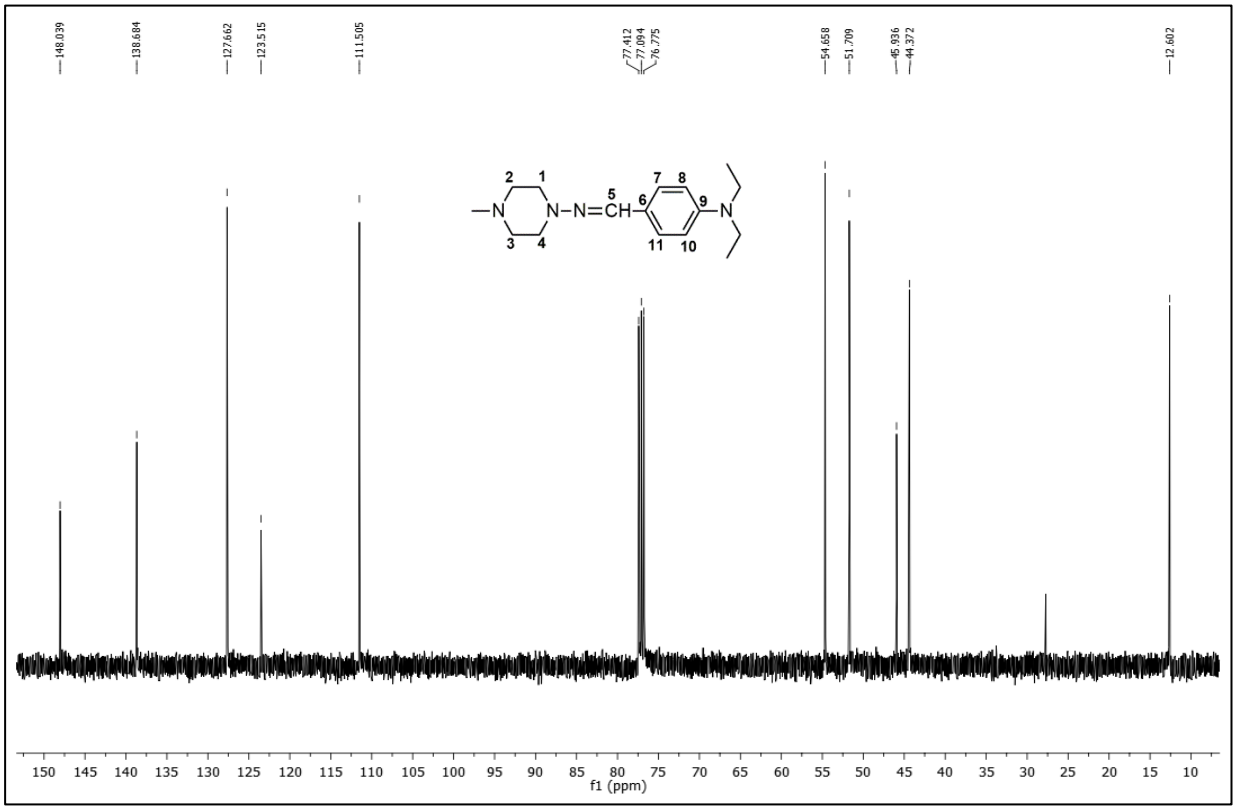
Spectrum 11. ^{13}C NMR (100 MHz) spectrum of compound **9** in $CDCl_3$



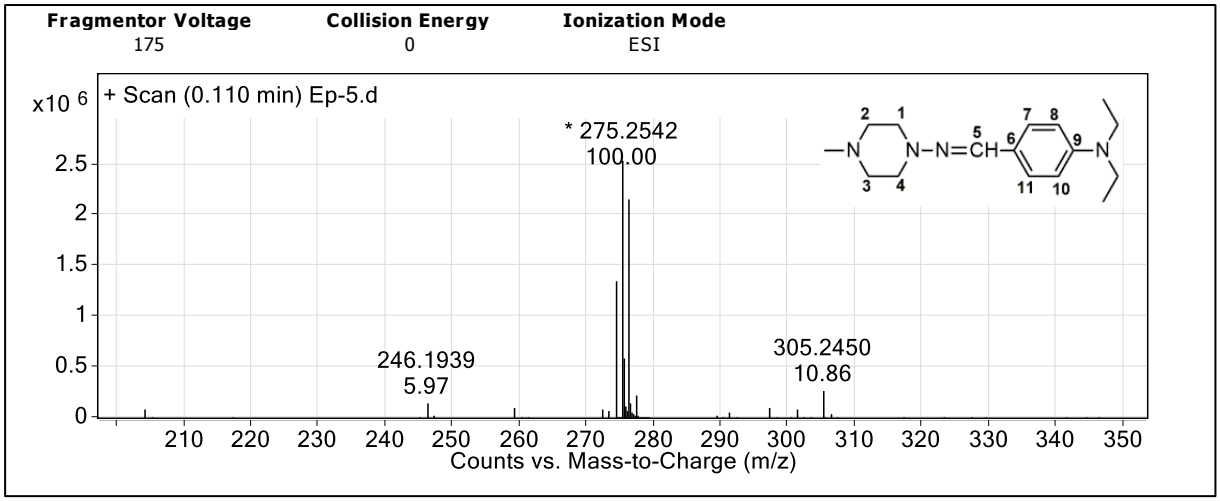
Spectrum 12. LC-MS (ESI) spectrum of compound **9**



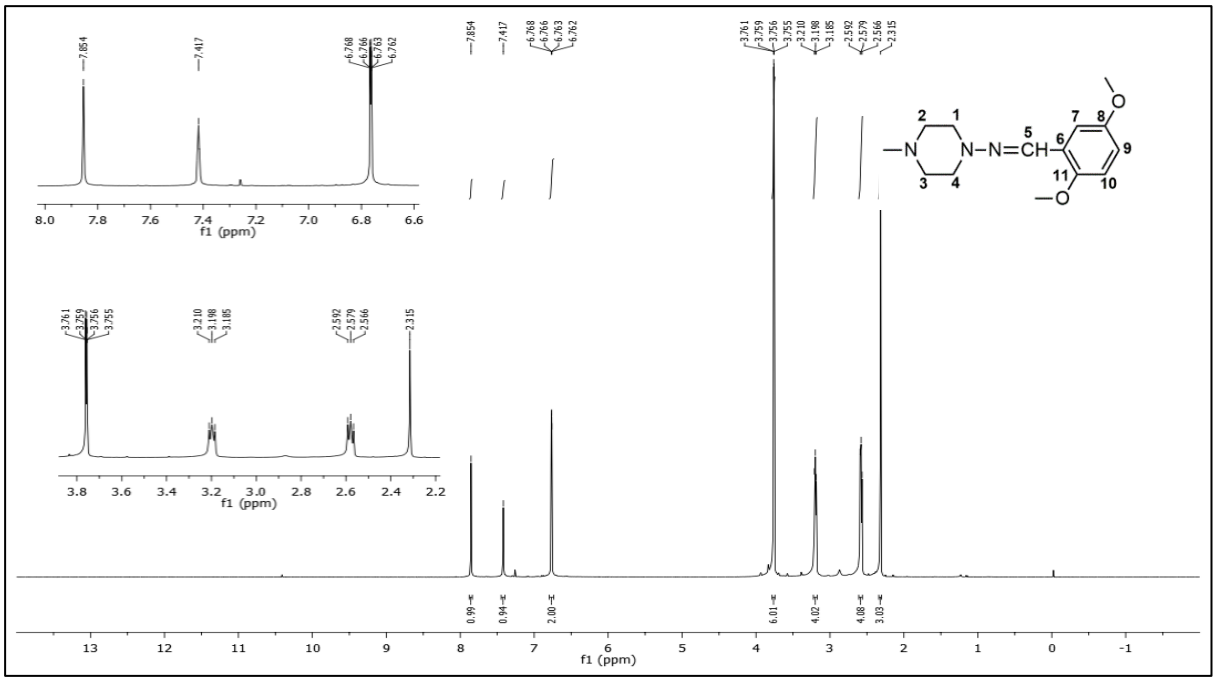
Spectrum 13. ^{1}H NMR (400 MHz) spectrum of compound **11** in $CDCl_3$



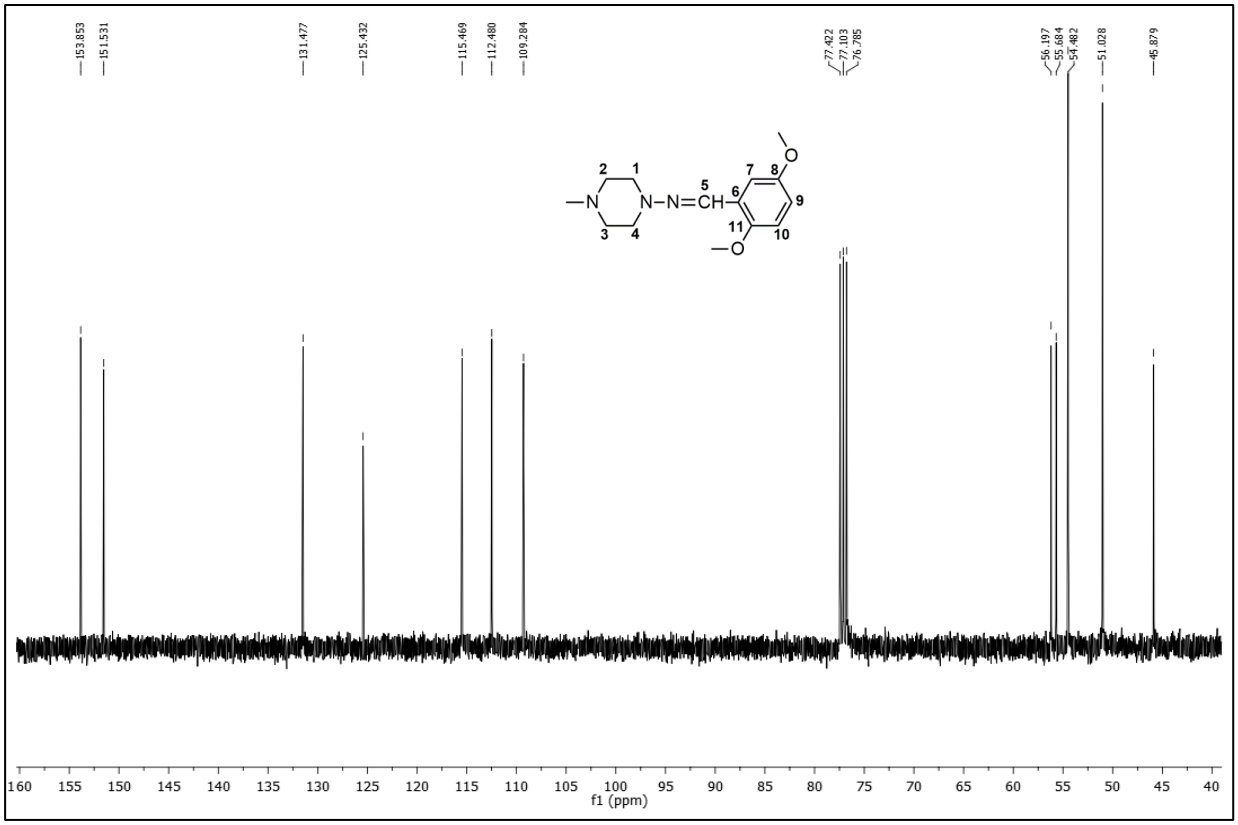
Spectrum 14. ^{13}C NMR (100 MHz) spectrum of compound **11** in $CDCl_3$



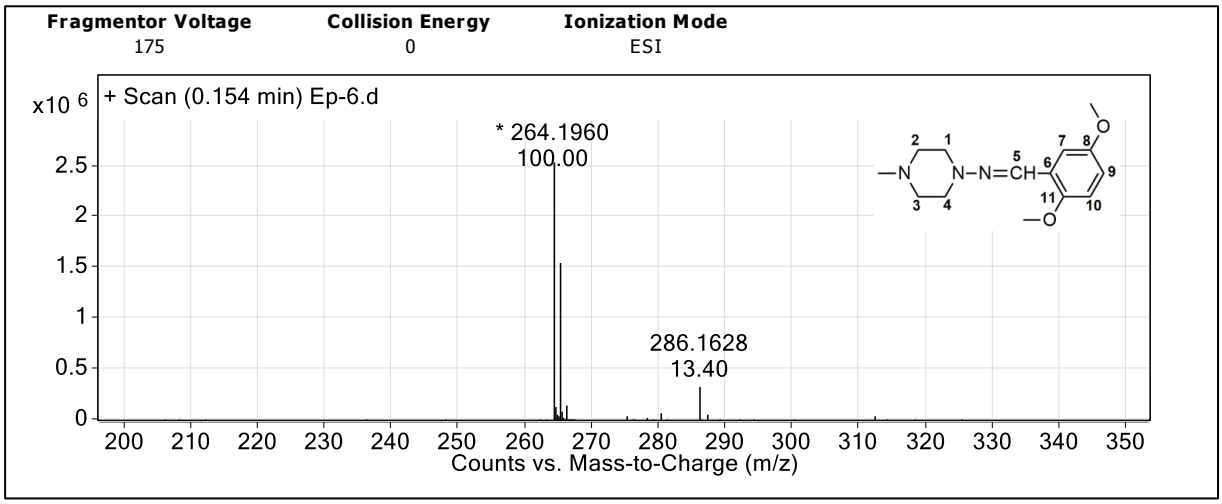
Spectrum 15. LC-MS (ESI) spectrum of compound **11**



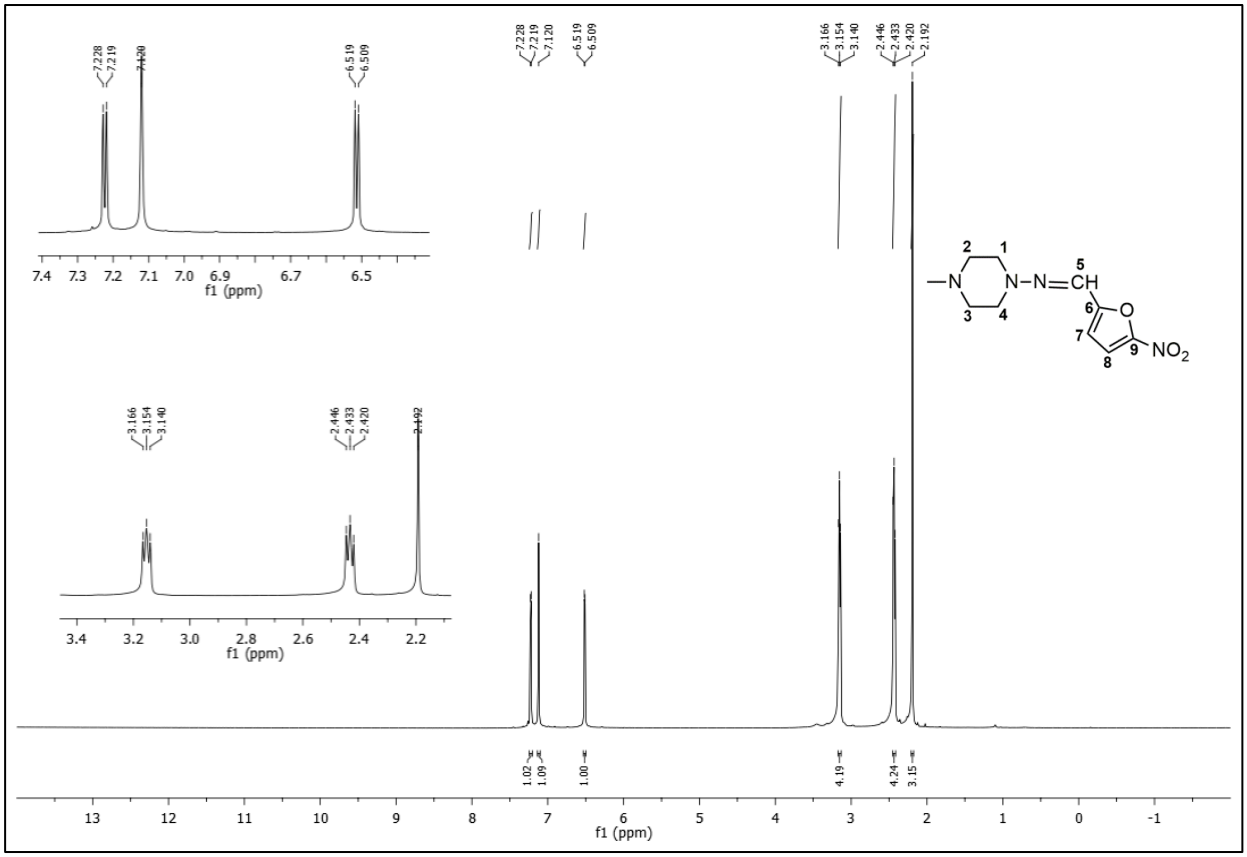
Spectrum 16. ^{1}H NMR (400 MHz) spectrum of compound **13** in $CDCl_3$



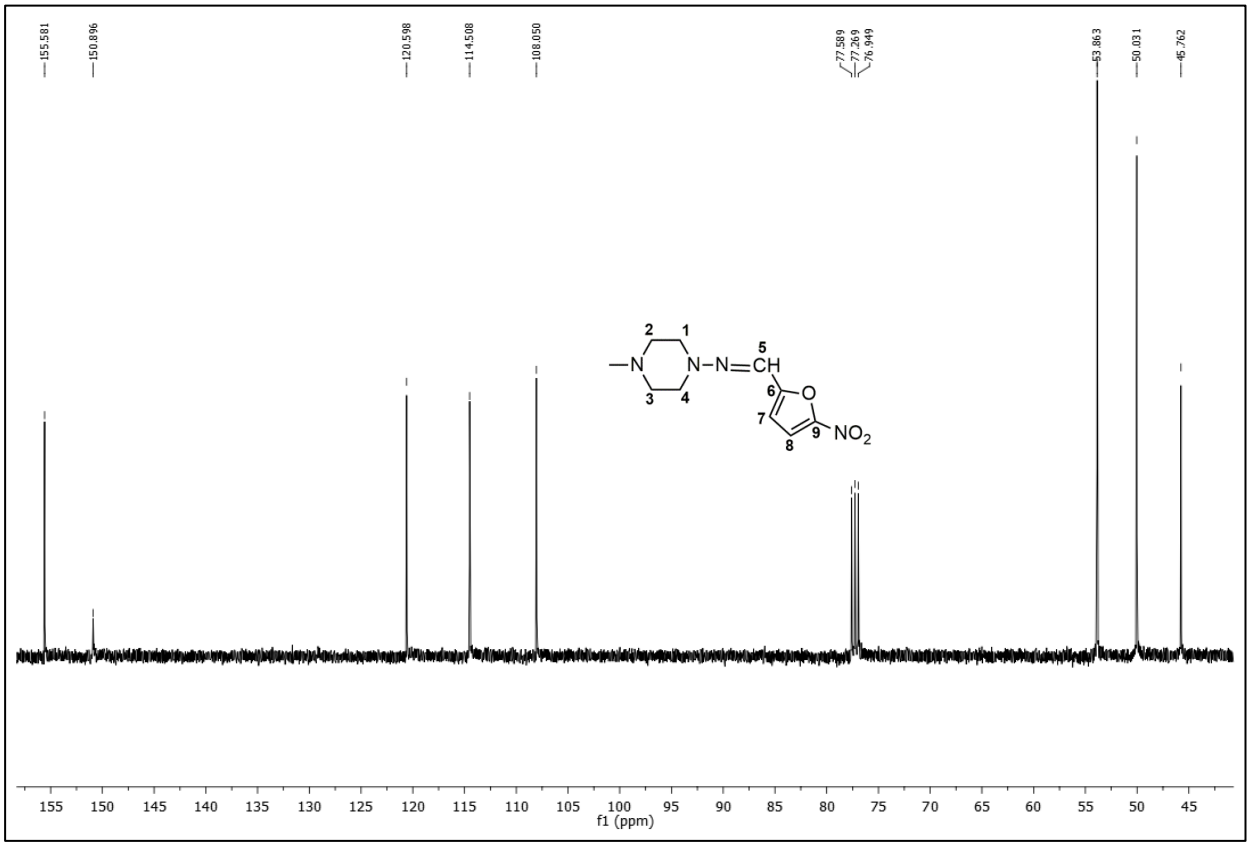
Spectrum 17. ^{13}C NMR (100 MHz) spectrum of compound **13** in $CDCl_3$



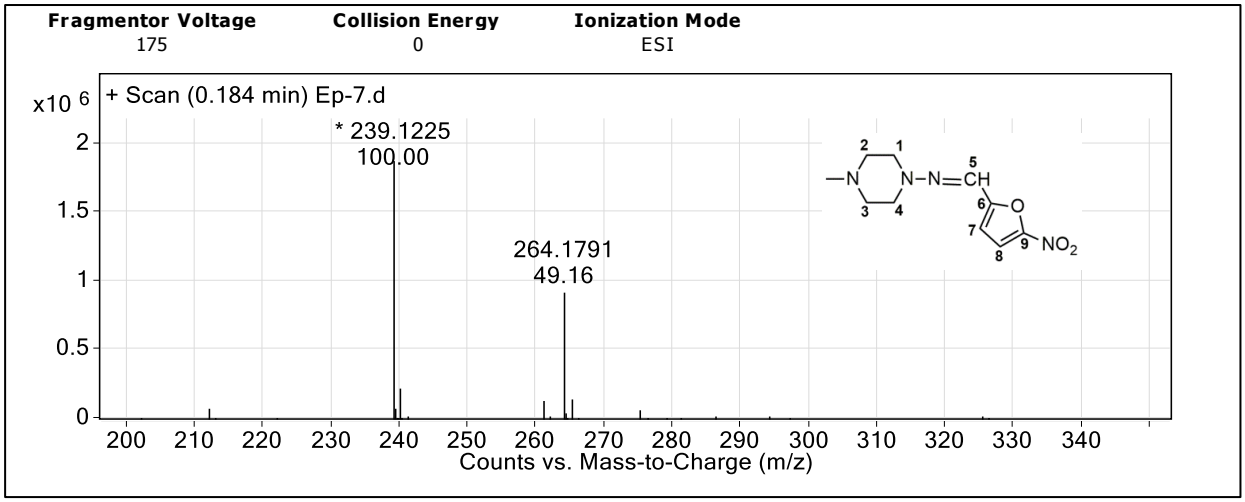
Spectrum 18. LC-MS (ESI) spectrum of compound **13**



Spectrum 19. ^{1}H NMR (400 MHz) spectrum of compound **15** in $CDCl_3$



Spectrum 20. ^{13}C NMR (100 MHz) spectrum of compound **15** in $CDCl_3$



Spectrum 21. LC-MS (ESI) spectrum of compound **15**