Original Article

Suzuki - Miyaura Cross-Coupling Of Cetirizine Impurity A : Synthesis, Charactrization, Molecular Docking And Antioxidant Activity

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Abstract

The study involved the creation of several heterocyclic derivatives, which are significant in the field of medicinal chemistry, as well as a nucleus for the creation of other chemical derivatives of the cetirizine impurity A ,In this study prepared some derivatives by Suzuki - Miyaura Cross-coupling to formation c-c bond by reflex method , at the first react 1-((4-chlorophenyl)(phenyl)methyl)piperazine with different arylboronic acid followed by addition of $Pd(0)(PPh_3)_4$ then add EtOAc after cooling, The reaction was monitored by thin-layer chromatography (TLC) technique. All new compounds were characterized by elemental analysis, FT-IR, ^{1}H-NMR, and ^{13}CNMR spectroscopy. Study of derivatives ability to coupling with the protein of cancerous cells to undermine their growth by simulating the process using one of the molecular docking programs (MOE 2015) to find out their effectiveness compounds and study antioxidant activity.

INTRODUCTION

The progress of organic chemistry has been significantly influenced by reactions that lead to the creation of carbon-carbon bonds[1,2]. Palladium-catalyzed cross-coupling reactions, which are defined as the transition-state catalyzed substitution of an organ halide or related electrophilic material by a nucleotide, have been shown to be particularly significant for carbon-carbon bond formation reactions because of their numerous advantages, including high throughput, atom-cost efficiency, the potential for catalyst recycling, and mild reaction conditions. [3-5] Boron acids have different properties than organic reagents, which are non-toxic and unaffected by moisture, and the possibility of crystallizing in ethanol, as well as their selectivity is very high, in addition to the fact that the time required to complete the reaction is a little slow. [6-7]

2-EXPERIMENTAL

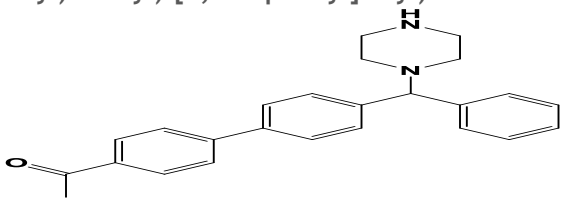
2-1-Materials and methods

All the used chemicals were obtained from commercial sources, with a purity range of 95-98%, that were used as received (without further purification). Melting points of all synthesized compounds were measured in open capillary tubes in a Gallen-Kamp MFB-600 melting point apparatus. FT-IR spectra measurements were recorded using FT-IR-8400S-Shimadizu spectrophotometer.^{1}H-NMR and ^{13}C-NMR spectra were recorded on VARIAN-INOVA 500MHZ spectrophotometer (Germany), CDCl3 and DMSO were used as solvents, and tetramethylsilane TMS as internal standard.

2-2 General procedure for the synthesis of diaryl derivatives by Suzuki cross-coupling reaction(1-0)[8,9]

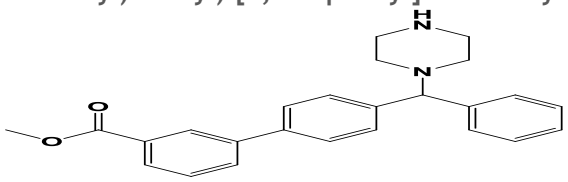
To a solution of 1-((4-chlorophenyl)(phenyl)methyl)piperazine (0.5 g; 1.7434 mmol) in 1-propanol (25 ml) was added arylboronic acid (2.0921 mmol) and the mixture was stirred for 15 min at ambient temperature followed by addition of $Pd(0)(PPh_3)_4$ (0.141 g, 7% mmol) and aq. solution of 2 M K_2CO_3 (7 ml). The reaction mixture was heated under reflux for 18– 24 h under N_2 . After cooling, water (5 ml) was added and the mixture was partitioned with EtOAc (3 X 10 ml). The combined organic extracts were washed with aq. solution of 5% Na_2CO_3 (30 ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified on a short SiO_2 column using [Toluene: EtOAc (6:1)] as eluent to give the desired product.

2-2-1 1-(4'-(phenyl(piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)ethan-1-one (1)



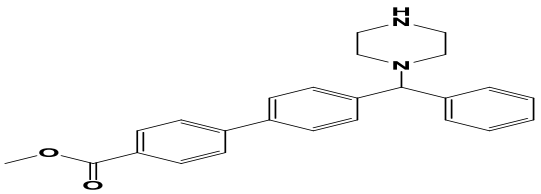
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and (4-acetylphenyl) boronic acid as a gum matter with yellow color as a yield (0.5491 g; 85%)***Rf*** =0.71 **,FT-IR (KBr, cm^{-1})** : (2962,2806) C-$H_{al.}$, (3055,3025) C-$H_{ar.}$,(1600,1488) C=$C_{ar.}$,(3411) N-H, 1679 (C=O).[10] **^{1}H-NMR (400 MHz, DMSO)** δ =2.59 (s,3H, H-19), 2.63,2.82 (m, 8H, H-Piperazine), , 4.44 (s, 1H, H-5), 7.20-8.15 (m, H-ar.).[11,12] **^{13}C NMR (100 MHz, DMSO)** δ=27.32 (C-19), 43.96, 44.00, 51.82, 51.94 (C- Piperazine), 74.99(C-5), 127.28-129.29 (C-ar.),133.68 (C-17), 136.78 (C-13), 141.64 (C-6), 142.57 (C-4), 143.66 (C-14), 198.02 (C-18). [13] **Anal. calc**. for $C_{25}H_{26}N_2O$ (370.50) : C, 81.05; H, 7.07; N, 7.56 Found: C, 81.00; H, 7.05; N, 7.49.

2-2-2 methyl 4'-(phenyl(piperazin-1-yl)methyl)-[1,1'-biphenyl]-3-carboxylate (2)



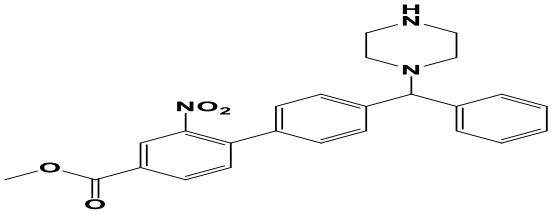
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and (3-(methoxycarbonyl)phenyl)boronic acid as a gum matter with yellow color as a yield (0.5458 g; 81%)***Rf*** =0.74 **FT-IR (KBr, cm^{-1})** : (2952,,2925 , 2808,2870) C-$H_{al.}$, (3057,3025) C-$H_{ar.}$,(1596,1489) C=C_{ar},(3391) N-H.**^{1}H-NMR (400 MHz, DMSO)** δ =2.14 (s,1H,H-9), 2.84,2.94 (m, 8H, H-Piperazine), 3.91 (s,3H,H-22), 4.29 (s, 1H, H-5), 7.09-8.69 (m, H-ar.).**^{13}C NMR (100 MHz, DMSO)** δ= 45.19 ,51.69 (C- Piperazine), 53.18(C-22), 75.73 (C-5), 127.35 (C-1),127.52-129.29 (C-ar.), 129.92 (C-16),132.00(C-19), 139.02 (C-13), 142.09 (C-10),143.02 (C-14), 143.37(C-4),166.55 (C-20). **Anal. calc**. for $C_{25}H_{26}N_2O_2$ (386.50): C, 77.69; H, 6.78; N, 7.25; O, 8.28 Found: C, 77.61; H, 6.69; N, 7.17**.**

2-2-3 methyl 4'-(phenyl(piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-carboxylate (3)



This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and (4-(methoxycarbonyl)phenyl)boronic acid as a gum matter with yellow color as a yield (0.5391 g; 80%) ,***Rf*** =0.77 **,FT-IR (KBr, cm^{-1})** : (2957 ,2807) C-$H_{al.}$, (3056,3025) C-$H_{ar.}$,(1601,1487) C=C_{ar},(3405) N-H. **^{1}H-NMR (400 MHz, DMSO)** δ =2.23 (s,1H,H-9), 2.97,2.80 (m, 8H, H-Piperazine), 3.78 (s,3H,H-20), 4.41 (s, 1H, H-5), 7.20-8.07 (m, H-ar.). **^{13}C NMR (100 MHz, DMSO)** δ= 44.29 ,44.36, 50.06 (C- Piperazine), 53.16 (C-20), 74.15(C-5), 127.28-129.29 (C-ar.), 137.38 (C-13),141.75 (C-10), 142.67 (C-4),143.40 (C-14), 166.53 (C-18) .**Anal. calc**. for $C_{25}H_{26}N_2O_2$(386.50): C, 77.69; H, 6.78; N, 7.25 Found: C, 77.58; H, 6.66; N, 7.14

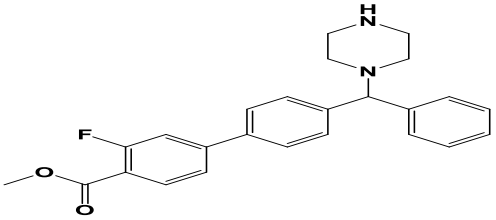
2-4-8-4 methyl 2-nitro-4'-(phenyl(piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-carboxylate (4)



This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and (4-(methoxycarbonyl)-2-nitrophenyl)boronic acid as a gum matter with blackish brown color as a yield (0.6169 g, 82%)***Rf*** = 0.70 **FT-IR (KBr, cm^{-1})** : (2960 ,2921,2849,2805) C-$H_{al.}$, (3057,3024) C-$H_{ar.}$,(1595,1486) C=C_{ar},(3411) N-H, (1420,1347) NO_2. **^{1}H-NMR (400 MHz, DMSO)** δ =2.14 (s,1H,H-9), 2.54 ,2.99,3.01 (m, 8H, H-Piperazine), 3.93 (s.,3H,H-22), 4.42 (s, 1H, H-5), 7.16-8.90 (m, H-ar.).**^{13}C NMR (100 MHz, DMSO)** δ= 44.04 , 51.80, 51.71 (C-

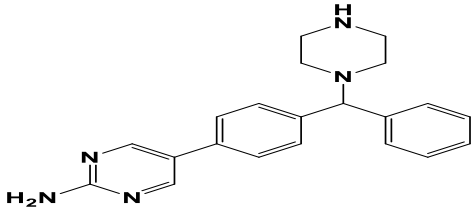
Piperazine), 55.18 (C-22), 74.08(C-5), 124.06 (C-16) 127.47 (C-1), 128.07-129.29 (C-ar.), 129.62 (C-19), 133.64 (C-18), 135.69 (C-13), 141.68 (C-4), 142.76 (C-10), 146.09 (C-14), 147.95 (C-15), 173.26 (C-20).**Anal. calc**. for $C_{25}H_{25}N_3O_4$ (431.49) : C, 69.59; H, 5.84; N, 9.74Found: C, 69.48; H, 5.75; N, 9.63

2-2-4 methyl 3-fluoro-4'-(phenyl(piperazin-1-yl)methyl)-[1,1'-biphenyl]-4-carboxylate (5)



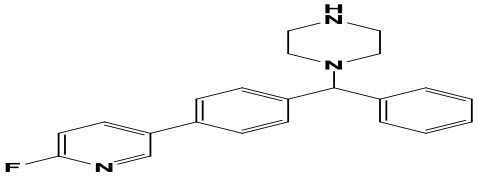
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and (3-fluoro-4-(methoxycarbonyl)phenyl) boronic acid as a gum matter with yellow color as a yield 5 g (0.5571 g, 79%), ***Rf*** =0.73 **FT-IR (KBr, cm^{-1})** : (2959 ,2925,2806) C-$H_{al.}$, (3056,3024) C-$H_{ar.}$,(1597,1488) C=C_{ar},(3391) N-H, (1025) C-$F_{ar.}$,(1731) C=O. **^{1}H-NMR (400 MHz, DMSO)** δ =2.28 (s,1H,H-9), 2.52,2.99 (m, 8H, H-Piperazine), 3.45 (s,3H,H-22), 4.43 (s, 1H, H-5), 7.15-8.21 (m, H-ar.).**^{13}C NMR (100 MHz, DMSO)** δ= 44.08 , 44.14, 51.81, 51.94 (C- Piperazine), 56.51 (C-22), 74.08 (C-5), 116.40 (C-15), 117.86 (C-17), 123.52 (C-19), 127.16 (C-1) ,129.28-123.52 (C-ar.), 133.70 (C-18), 137.50 (C-13), 141.69 (C-10), 142.61(C-4), 143.36 (C-14), 161.11 (C-16), 175.21(C-20) . **Anal. calc**. for $C_{25}H_{25}FN_2O_2$ (404.49) : C, 74.24; H, 6.23; F, 4.70; N, 6.93Found: C, 74.12; H, 6.14; N, 6.82

2-2-5 5-(4-(phenyl(piperazin-1-yl)methyl)phenyl)pyrimidin-2-amine (6)



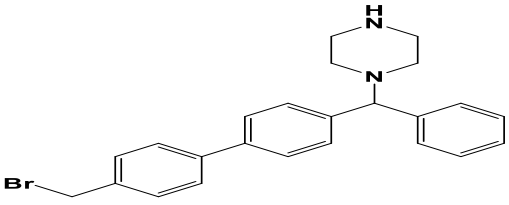
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and 2-Aminopyrimidine-5-boronic acid pinacol ester as a gum matter with yellow color as a yield (0.4457 g, 74%), ***Rf*** =0.83 **FT-IR (KBr, cm^{-1})**: (2967,2805) C-$H_{al.}$, (3057,3025) C-$H_{ar.}$,(1598,1562,1486) C=C_{ar}, (3388) N-H,(1652) C=N. **^{1}H-NMR (400 MHz, DMSO)** δ =2.38 (s,1H,H-9), 2.56,2.87 (m, 8H, H-Piperazine), 4.37 (s,1H,H-5), 6.54 (s,2H,H-18), 7.18-8.73 (m, H-ar.). **^{13}C NMR (100 MHz, DMSO)** δ= 44.97 , 51.14 (C- Piperazine), 74.53 (C-5), 119.67 (C-14), 127.57 (C-1), 130.06 (C-13), 142.40, 142.32 (C4+C-10), 150.65 (C-15+C-15`), 158.46 (C-17), 128.10 -129.16 (C-ar.) **Anal. calc**. for $C_{21}H_{23}N_5$ (345.45): C, 73.02; H, 6.71; N, 20.27 Found: C, 72.94; H, 6.61; N, 20.16

2-2-6 1-((4-(6-fluoropyridin-3-yl)phenyl)(phenyl)methyl)piperazine (7)



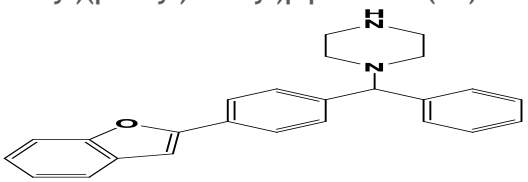
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and 6-Fluoropyridine-3-boronic acid pinacol ester as a gum matter with color greenish brown as a yield (0.4785 g, 79%), ***Rf*** =0.66 **FT-IR (KBr, cm^{-1})** : (2975,2813) C-$H_{al.}$, (3057,3026) C-$H_{ar.}$,(1599,1547,1485) C=C_{ar}, (3406) N-H,(1656) C=N,(1026) C-F. **^{1}H-NMR (400 MHz, DMSO)** δ =2.54 ,2. 97, 2.98 (m, 8H, H-Piperazine), 2.29 (br.,1H,H-9), 4.43 (s, 1H, H-5), 7.21-8.50 (m, H-ar.). **^{13}C NMR (100 MHz, DMSO)** δ= 44.22 ,53.15 (C- Piperazine), 74.00(C-5), 107.41 (C-18) 127.69-129.29 (C-ar.), 133.70 (C-13), 136.24 (C-14), 139.60 (C-19), 141.66 (C-15), 142.02 (C-10), 142.42 (C-4), 158.97 (C-17). **Anal. calc**. for $C_{22}H_{22}FN_3$ (347.44): C, 76.05; H, 6.38; N, 12.09 Found: C, 75.96; H, 6.26;; N, 12.00

2-2-7 1-((4'-(bromomethyl)-[1,1'-biphenyl]-4-yl) (phenyl) methyl) piperazine (8)



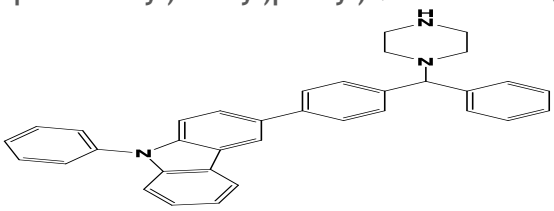
This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and 4-(Bromomethyl)benzeneboronic acid pinacol ester as a gum matter with yellow color as a yield (0.5216 g, 71%), ***Rf*** =0.59 **FT-IR (KBr, cm^{-1})** : (2975,2925,2808) C-$H_{al.}$, (3057,3025) C-$H_{ar.}$,(1612,1514,1488) C=C_{ar}, (3390) N-H.**^{1}H-NMR (400 MHz, DMSO)** δ =2.30 (s,1H,H-9), 3.39, 3.47 (m, 8H, H-Piperazine), 4.30(s,1H,H-5), 4.31(s,2H,H-18), 7.18-8.73 (m, H-ar.).**^{13}C NMR (100 MHz, DMSO)** δ= 25.14 (C-18), 51.82, 53.12 (C- Piperazine), 74.53 (C-5), 127.46 (C-1), 128.77-129.83 (C-ar.), 142.73, 142.37 ,142.06 (C-4+C-10+C-14), 135.13 (C-13), 134.82 (C-17).**Anal. calc**. for $C_{24}H_{25}BrN_2$ (421.38): C, 68.41; H, 5.98; N, 6.65 Found: C, 68.32; H, 5.88; N, 6.55

2-2-8 1-((4-(benzofuran-2-yl)phenyl)(phenyl)methyl)piperazine (R9)



This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and Benzofuran-2-boronic acid as a gum matter with color brown as a yield (0.4947 g, 77%), ***Rf*** =0.68 **FT-IR (KBr, cm^{-1})** : (2957,2925,2809) C-$H_{al.}$, (3056,3025) C-$H_{ar.}$,(1597,1488) C=C_{ar},(3390) N-H,(1667) C=$C_{benzofuran}$.**^{1}H-NMR (400 MHz, DMSO)** δ =2.29 (s,1H,H-9), 2.94,3.60 (m, 8H, H-Piperazine), 4.40 (s,1H,H-5), 7.15-7.96 (m, H-ar.).**^{13}C NMR (100 MHz, DMSO)** δ= 44.40, 44.47, 51.81, 51.93 (C- Piperazine), 74.24 (C-5), 104.72 (C-22), 111.75 (C-17), 121.64 (C-20), 122.21 (C-19), 124.19 (C-18), 126.04-129.91 (C-ar.), 142.68 (C-4), 142.11 (C-10), 154.96 (C-16), 161.12 (C-14). **Anal. calc**. for $C_{25}H_{24}N_2O$ (368.48): C, 81.49; H, 6.57; N, 7.60 Found: C, 81.36; H, 6.45; N, 7.48

2-2-9 9-phenyl-3-(4-(phenyl(piperazin-1-yl)methyl)phenyl)-9H-carbazole (R10)

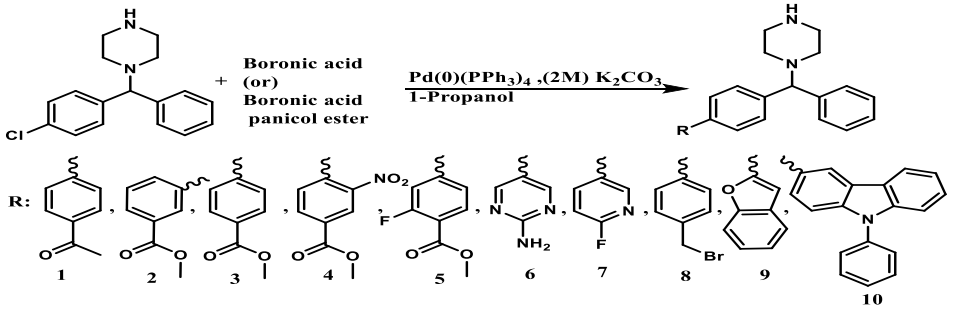


This compound was prepared according to the general method from 1-((4-chlorophenyl) (phenyl)methyl)piperazine and 9-Phenyl-9H-carbazole-3-boronic acid as a gum matter with yellowish brown color with a yield (0.6971 g, 81%), ***Rf*** =0.52 **FT-IR (KBr, cm^{-1})** : (2957, 2920, 2850, 2811) C-$H_{al.}$, (3054,3025) C-$H_{ar.}$, (1658, 1595, 1500, 1451) C=C_{ar},(3390) N-H, (1658) C=C $_{pyrrole\ ring}$. **^{1}H-NMR (400 MHz, DMSO-*d*^{6})** δ =2.24 (s,1H,H-9), 3.08,3.09, 3.35 , 3.36 (m, 8H, H-Piperazine), 4.47 (s,1H,H-5), 7.20-8.70 (m, H-ar.). **^{13}C NMR (100 MHz, DMSO)** δ= 43.52, 51.16, 51.22 (C- Piperazine), 74.04 (C-5), 109.04 (C-23), 110.04 (C-21), 110.62 (C-16), 115.90 (C-15), 119.02 (C-19),119.88 (C-25), 121.31 (C-26), 126.01(C-30), 126.48 (C-24), 126.57 (C-1), 126.72 (28+C-28`), 128.07-129.89 (C-ar.), 131.90 (C-18), 134,65 (C-22), 137.33 (C-27), 137.81 (C-13), 141.35 (C-10), 142.28 (C-4),143.84 (C-14),144.57 (C-17). **Anal. calc**. for $C_{35}H_{31}N_3$ (493.65): C, 85.16; H, 6.33; N, 8.51 Found: C, 84.96; H, 6.12; N, 8.31

3- RESULT AND DISCUSSION:

3-1 Chemistry:

Derivatives were prepared from reaction of 1-((4-chlorophenyl) (phenyl)methyl)piperazine with aryl boronic acid derivatives in the presence of K_2CO_3 as base, $Pd(0)(PPh_3)_4$ as catalytic and 1-propanol as a reaction medium in an atmosphere of N_2 gas, then refluxed until end of the reaction after following it up using TLC. As shown in the following equation:



Scheme 1: Equation Of Cetirizine Impurity A Derivatives Formation

The **FT-IR** spectrum in Figure (3-3) of (1) showed the appearance of the band at the frequencies (3411 cm^{-1}) to the group (N-H) with band of carbonyl group at (1679 cm^{-1}) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed

the single at δ= 2.63, 2.82 ppm belonging to the protons of piprazine ring, displacement at δ= 4.44 ppm due to chiral center (methyne group) (H-5), in other hand show single at δ = 2.59 refer to proton of thiazol ring (H-19), displacements at δ = 7.20-8.15 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings. Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=27.32 due to methyl group and the single at δ = 43.96, 44.00, 51.82, 51.94 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.99 ppm of due to methyne group (charial center C-5), as well as show single in δ=127.28-129.29 ppm due to carbone of aromatic rings and also single at δ= 198.02 ppm to carbonyl group. The **FT-IR** spectrum of (2) in Figure (3-4) showed the appearance of the band at the frequencies (3391 cm^{-1}) to the group (N-H) with band of carbonyl group at (1721 cm^{-1}) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ= 2.84,2.94 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.29 ppm due to chiral center (methyne group) (H-5), displacements at δ = 7.09-8.69 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as show single at δ = 2.14 due to amine group (H-9), in other hand show single at 3.91 ppm due to methyl group. Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=53.18 due to methyl group and the single at δ = 45.19 , 51.69 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 75.73 ppm of due to methyne group (charial ce+-nter C-5), as well as show single in δ=127.35 -143.37 ppm due to carbone of aromatic rings and also single at δ= 166.55 ppm to carbonyl group.The **FT-IR** spectrum of (3) in Figure (3-5) showed the appearance of the band at the frequencies (3405 cm^{-1}) to the group (N-H) with band of carbonyl group at (1719 cm^{-1}) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.23 ppm refer to amine group (H-9), and also show δ= 2.97, 2.80 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.41 due to chiral center (methyne group) (H-5), displacements at δ = 7.20-8.07 (m, H-ar.) ppm belonging to the protons of aromatic rings, in other hand show single of proton at δ =3.78 ppm due to methoxy group (H-20). Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=55.18 due to methoxy group and the single at δ = 44.29 ,44.36, 50.06 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.15ppm of due to methyne group (charial center C-5), as well as show single in δ=127.28-129.29 ppm due to carbone of aromatic rings and also single at δ= 166.53 ppm to carbonyl group. The **FT-IR** spectrum of (4) in Figure (3-6) showed the appearance of the band at the frequencies (3411 cm^{-1}) to the group (N-H) with band of carbonyl group at (1727 cm^{-1}) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.14 ppm refer to amine group (H-9), and also show δ= 2.54, 2.99, 3.01 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.42 due to chiral center (methyne group) (H-5), displacements at δ = 7.16-8.90 (m, H-ar.) ppm belonging to the protons of aromatic rings, in other hand show single of proton at δ =3.93 ppm due to methoxy group (H-22). Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=55.18 due to methoxy group (C-22) and the single at δ = 44.04 , 51.80, 51.71 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.08 ppm of due to methyne group (charial center C-5), as well as show single in δ=124.06-147.95 ppm due to carbone of aromatic rings and also single at δ= 173.26 ppm to carbonyl group (C-20). The **FT-IR** spectrum of (5) in Figure (3-7) showed the appearance of the band at the frequencies (3391 cm^{-1}) to the group (N-H) with band of carbonyl group at (1731 cm^{-1}) and disappearance chloro group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.28 ppm refer to amine group (H-9), and also show δ= 2.52,2.99 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.43 due to chiral center (methyne group) (H-5), displacements at δ = 7.15-8.21 (m, H-ar.) ppm belonging to the protons of aromatic rings, in other hand show single of proton at δ =3.45 ppm due to methoxy group (H-22). Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=56.51 due to methoxy group (C-22), and the single at δ = 44.08 , 44.14, 51.81, 51.94 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.08 ppm of due to methyne group (charial center C-5), as well as show single in δ=123.52-143.36 ppm due to carbone of aromatic rings and also single at δ= 175.21 ppm to carbonyl group (C-20). The **FT-IR** spectrum of (6) in Figure (3-8) showed the appearance of the band at the frequencies (3388 cm^{-1}) to the group (N-H) and disappearance chloro group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.38 ppm refer to amine group (H-9), and also show δ= 2.56, 2.87 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.37 due to chiral center (methyne group) (H-5), displacements at δ = 7.18-8.73 (m, H-ar.) ppm belonging to the protons of aromatic rings, in other hand show single of proton at δ =6.54 ppm due to amine group (H-18). Also, the spectrum of **(^{13}C-NMR)** showed signal at δ = 44.97 , 51.14 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.53 ppm of due to methyne group (charial center C-5), as well as show single in δ=127.57 -142.32 ppm due to carbone of aromatic rings and also singles at δ= 119.67 , 150.65 and 158.46 ppm to dihydropyrizine ring. The **FT-IR** spectrum of (7) in Figure (3-9) showed the appearance of the band at the frequencies (3406 cm^{-1}) to the group (N-H) with band of carbonyl group at (1026 cm^{-1}) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ= 2.54 2.97,2.98 ppm belonging to the protons of piprazine ring, displacement at δ= 4.43 ppm due to chiral center (methyne group) (H-5), displacements at δ = 7.21-8.50 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as show single at δ = 2.92 due to amine group (H-9). Also, the spectrum of **(^{13}C-NMR)** showed signal at frequency signals at δ=53.18 due to methyl group and the single at δ = 44.22 ,53.15 ppm that belong to the carbons of Piperazine ring, , also show frequency signal at δ= 74.00 ppm of due to methyne group (charial center C-5), as well as show single in δ=107.41 -142.42 ppm due to carbone of aromatic rings and also single at δ= 158.97 ppm to carbon associated with fluoro group (C-17). The **FT-IR** spectrum of (8) in Figure (3-10) showed the appearance of the band at the frequencies (3390 cm^{-1}) to the group (N-H) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.30 ppm refer to amine group (H-9), and also show δ= 3.39, 3.47 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.30 due to chiral center (methyne group) (H-5), displacements at δ = 7.18-8.73 (m, H-ar.) ppm belonging to the protons of aromatic rings, in other hand show single of proton at δ = 4.31 ppm due to methylene group (H-18). Also, the

spectrum of **(^{13}C-NMR)** showed signal at δ = 51.82, 53.12 ppm that belong to the carbons of Piperazine ring, and also show single at δ=25.14 ppm refer to methylene group (H-18), also show frequency signal at δ= 74.53 ppm of due to methyne group (charial center C-5), as well as show single in δ=127.46 -142.73 ppm due to carbon of aromatic rings. The **FT-IR** spectrum of (9) in Figure (3-11) showed the appearance of the band at the frequencies (3390 cm^{-1}) to the group (N-H) and disappearance chloride group. The spectrum of **(^{1}H-NMR)** showed the single at δ =2.29 ppm refer to amine group (H-9), and also show δ= 2.94,3.60 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.40 due to chiral center (methyne group) (H-5), displacements at δ = 7.15-7.96 (m, H-ar.) ppm belonging to the protons of aromatic rings. Also, the spectrum of **(^{13}C-NMR)** showed signal at δ = 44.40, 44.47, 51.81, 51.93 ppm that belong to the carbons of Piperazine ring, also show frequency signal at δ= 74.24 ppm of due to methyne group (charial center C-5), as well as show single in δ=104.72 -161.12 ppm due to carbon of aromatic rings. The **FT-IR** spectrum of (10) in Figure (3-12) showed the appearance of the band at the frequencies (3390 cm^{-1}) to the group (N-H) and disappearance chloride group.The spectrum of **(^{1}H-NMR)** showed the single at δ =2.24 ppm refer to amine group (H-9), and also show δ= 3.09, 3.08, 3.36, 3.35 ppm belonging to the protons of Piprazine ring, displacement at δ= 4.47 due to chiral center (methyne group) (H-5), displacements at δ = 7.20-8.70 (m, H-ar.) ppm belonging to the protons of aromatic rings. Also, the spectrum of **(^{13}C-NMR)** showed signal at δ = 43.52, 51.16, 51.22 ppm that belong to the carbons of Piperazine ring, also show frequency signal at δ 74.04 ppm of due to methyne group (charial center C-5), as well as show single in δ= 109.04 - 144.57 ppm due to carbon of aromatic rings.

3-2 Biological Activity By Insilco

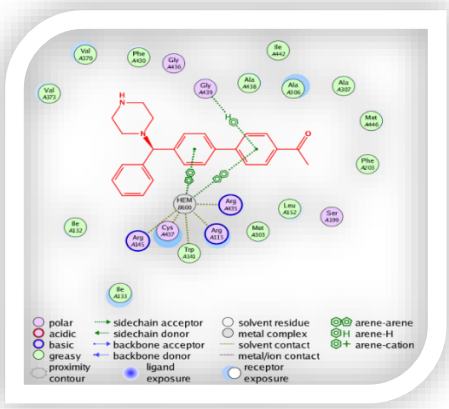
The ability of compounds to inhibit breast cancer was analyzed using the program (moe 2015) by coupling compounds with two proteins (PDB: 3eqm & 3s7s)[14,15]. Compounds gave good efficacy compared to the drug compound available for treatment through a group of factors:

1) The value of the correlation energy. 2) The number of bindings between the ligand (complex) and the receptor (protein). 3) The type of correlation and the value of (rmsd) where less than 2 is better. 4) The extent of the association of the prepared ligand with the original ligand available with the protein in the binding sites. 5) The efficiency of the probability of association compared to the other available possibilities during the docking work[16,17]. As shown in tables (3-1)

Tables (3-1): Molecular Docking Of The Derivatives Prepared

No.	1	2	3	4	5	6	7	8	9	10
Binding energy	**-7.9326**	**-8.4048**	**-8.1357**	**-9.1219**	**-8.0456**	**-7.4996**	**-7.4371**	**-7.8650**	**-8.0125**	**-8.8638**
Rmsd	**0.8869**	**1.4979**	**1.1317**	**1.1488**	**1.8379**	**1.9076**	**1.921**	**0.9099**	**1.3198**	**1.1591**

1



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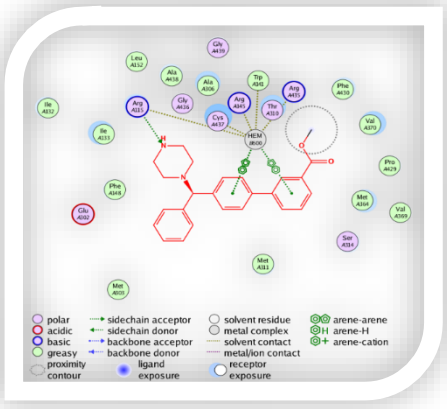

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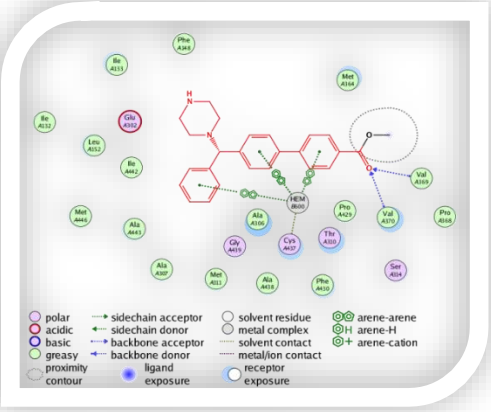

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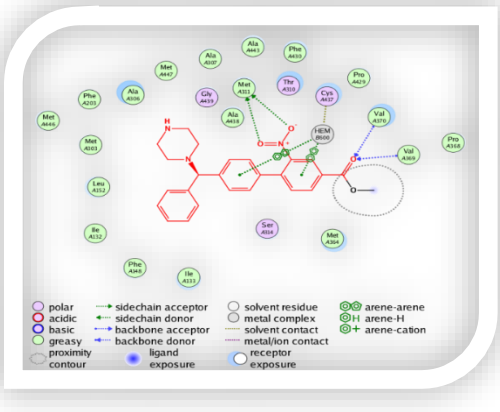


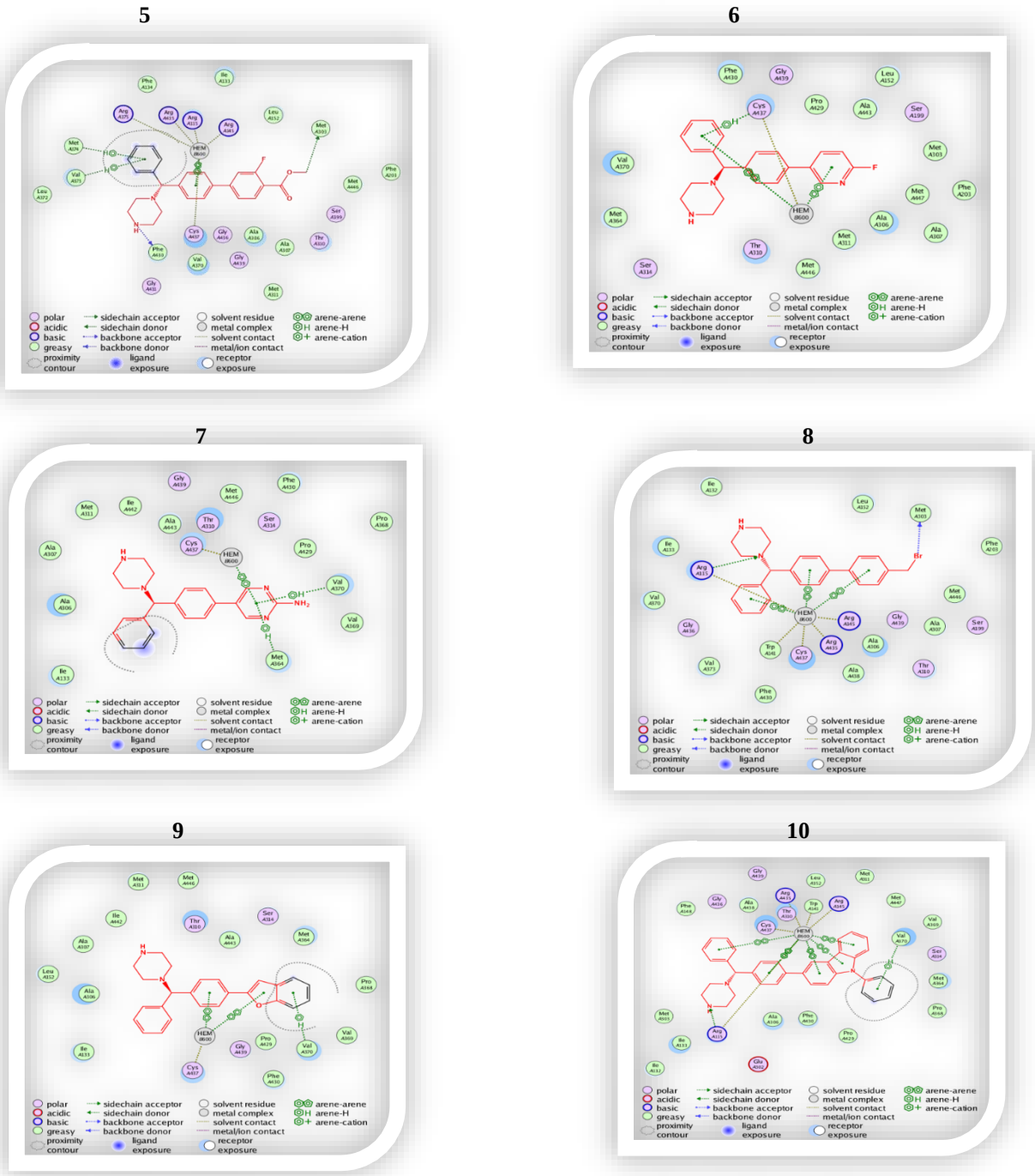
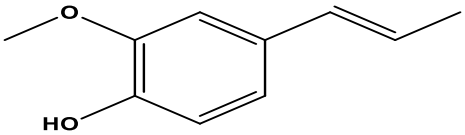


Figure (3-1) A 2D Shape Showing The Binding Sites Of The Ligand (1-10) With The Protein

3-3 Antioxidant activity

In recent years, there has been an increased interest in the application of antioxidants to medical treatment as information is constantly gathered linking the development of human diseases to oxidative stress. This study focused on the antioxidant activity of title compounds based on screening using free-radical assays (DPPH), as oxidative stress may be the main cause of neurodegenerative diseases. The brain's dependence on oxygen (O_2) and high consumption of glucose makes it highly susceptible to oxidative stress, as leaked O2 has been implicated in the generation of free radicals, such as superoxide anions, hydrogen peroxide (H_2O_2), and OH[17,18]. Some molecules have both active antioxidant and tyrosinase activities, such as isoeugenol. Designing antioxidant molecules using biosystems can protect inhibit tyrosinase enzymes and prevents related diseases[19,20].



structure of isoeugenol

Tables (3-2): Table Showing The Inhibitory Effect Of The Derivative Compounds By Changing The Concentrations

Series		Concentration (µg/ml)										Inhibition(%)
No.	Compounds	1000	900	800	700	600	500	250	125	62.5	31.25	
1	1	95.0	93.9	92.5	91.4	85.4	72.7	66.9	63.5	60.5	54.4	
2	2	86.5	85.4	82.6	81.2	80.1	77.1	72.7	66.9	63.0	56.9	
3	3	94.2	93.1	85.4	81.5	79.0	75.4	73.2	69.6	63.0	57.2	
4	4	80.4	76.5	73.5	71.5	63.0	57.5	55.5	48.1	47.0	32.9	
5	5	93.9	93.1	90.6	89.2	84.3	72.9	67.4	63.5	58.0	55.2	
6	6	92.3	88.7	85.6	76.5	72.7	66.9	59.9	57.5	54.7	52.2	
7	7	96.1	95.3	93.4	92.3	90.9	89.2	87.6	61.3	28.2	20.2	
8	8	59.9	57.2	32.3	29.8	25.7	25.4	23.5	20.7	16.3	15.5	
9	9	90.9	87.6	86.2	81.8	75.7	69.6	60.5	57.2	45.3	42.0	
10	10	85.9	83.7	78.7	78.5	77.3	76.5	73.5	66.9	63.5	62.2	

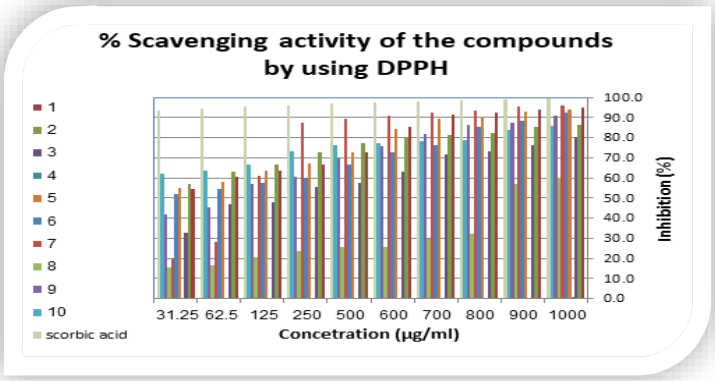


Figure (3-2) Shows The Relationship Between The Percentage And Concentration Of The Effect Of The Derivative (1-10) On DPPH

CONCLUSION

In this study we are reported synthesis of many cetirizine Impurity A derivatives The work included preparation of C-C bond by Suzuki compounds. These derivatives were study molecular docking Study of derivatives ability to coupling with the protein of cancerous cells to undermine their growth by simulating the process using one of the molecular docking programs (MOE 2015) . The compounds were studied as antioxidants, and it was found that a good number of prepared derivatives are highly effective.

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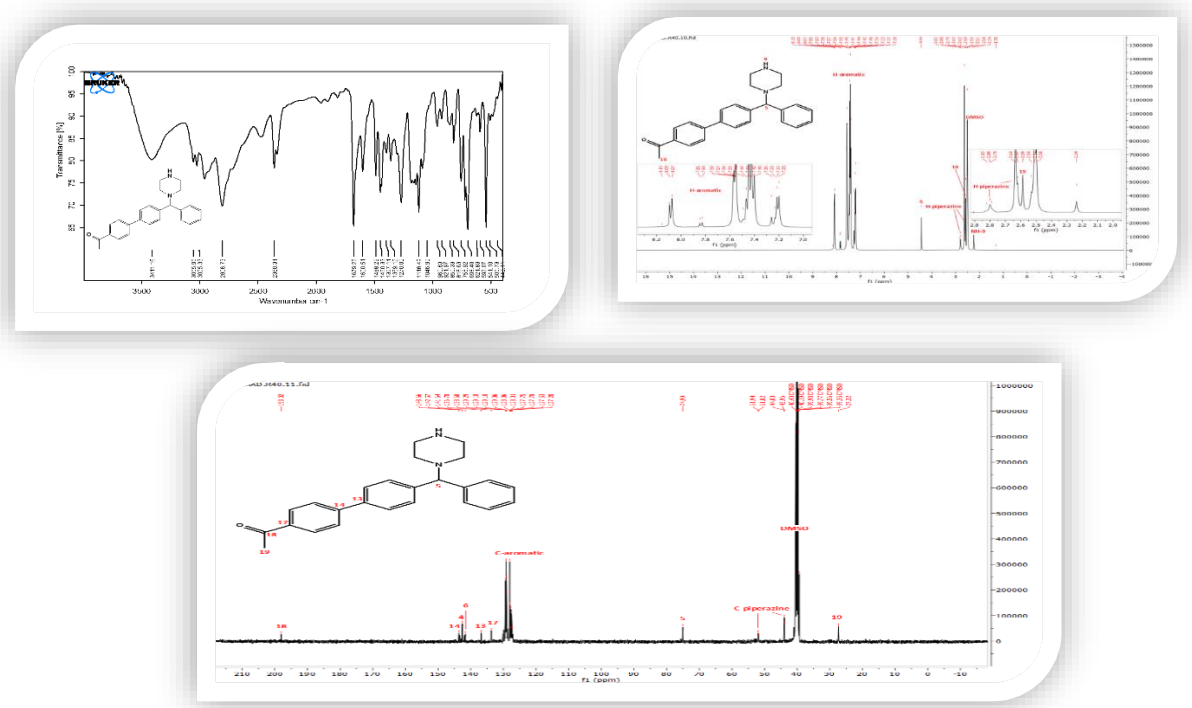


Figure (3-4): FT-IR- Spectrum Of R61
Figure (3-3):FT-IR, ^{1}H-NMR&^{13}C-NMR- Spectrum Of Derivative 1

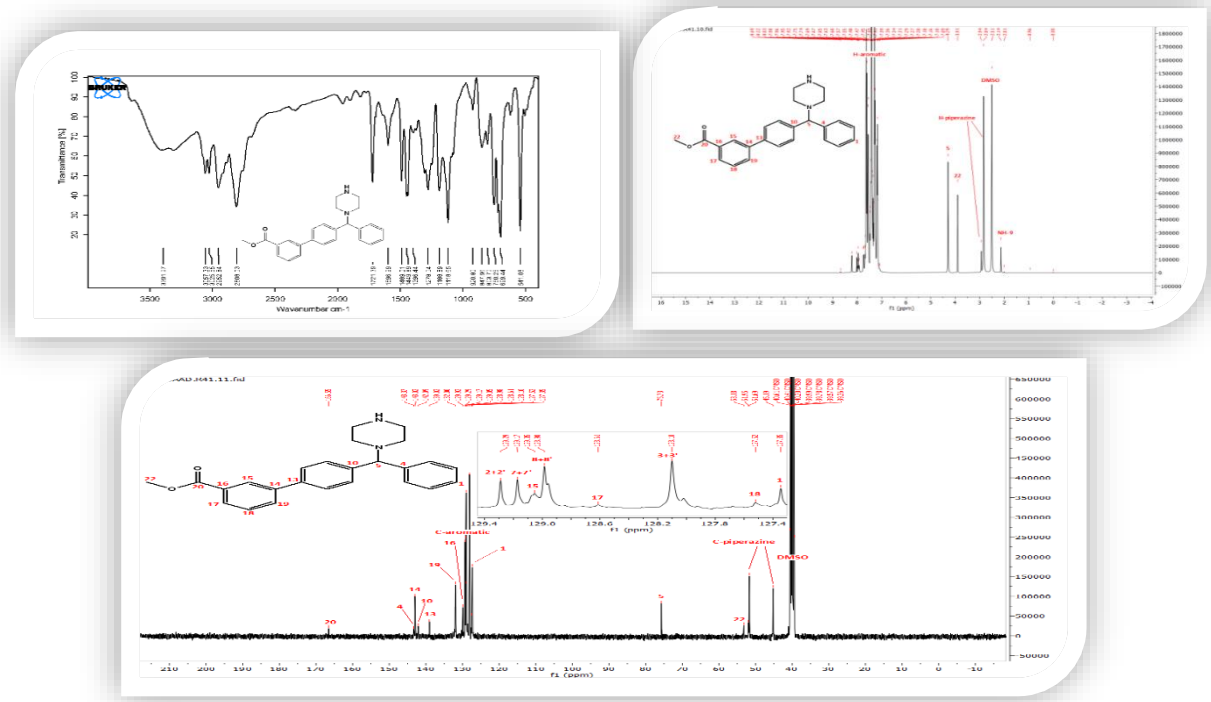


Figure (3-4): FT-IR, ^{1}H-NMR&^{13}C-NMR- Spectrum Of Derivative 2

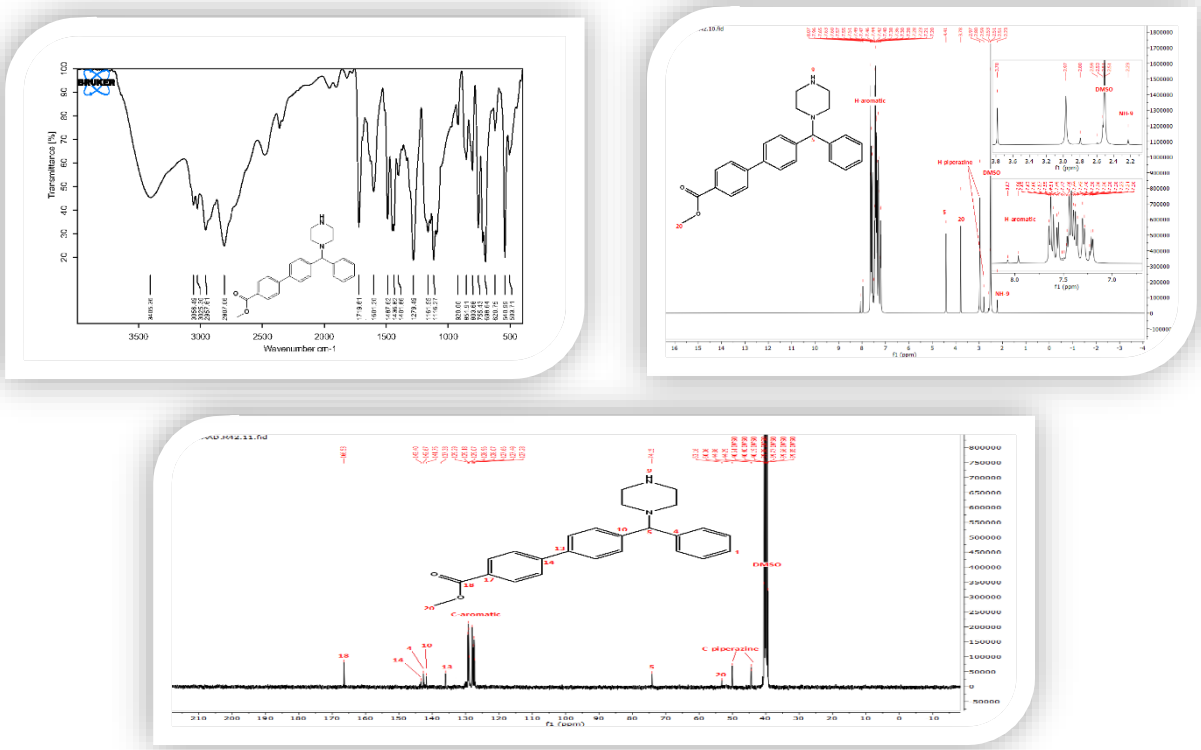
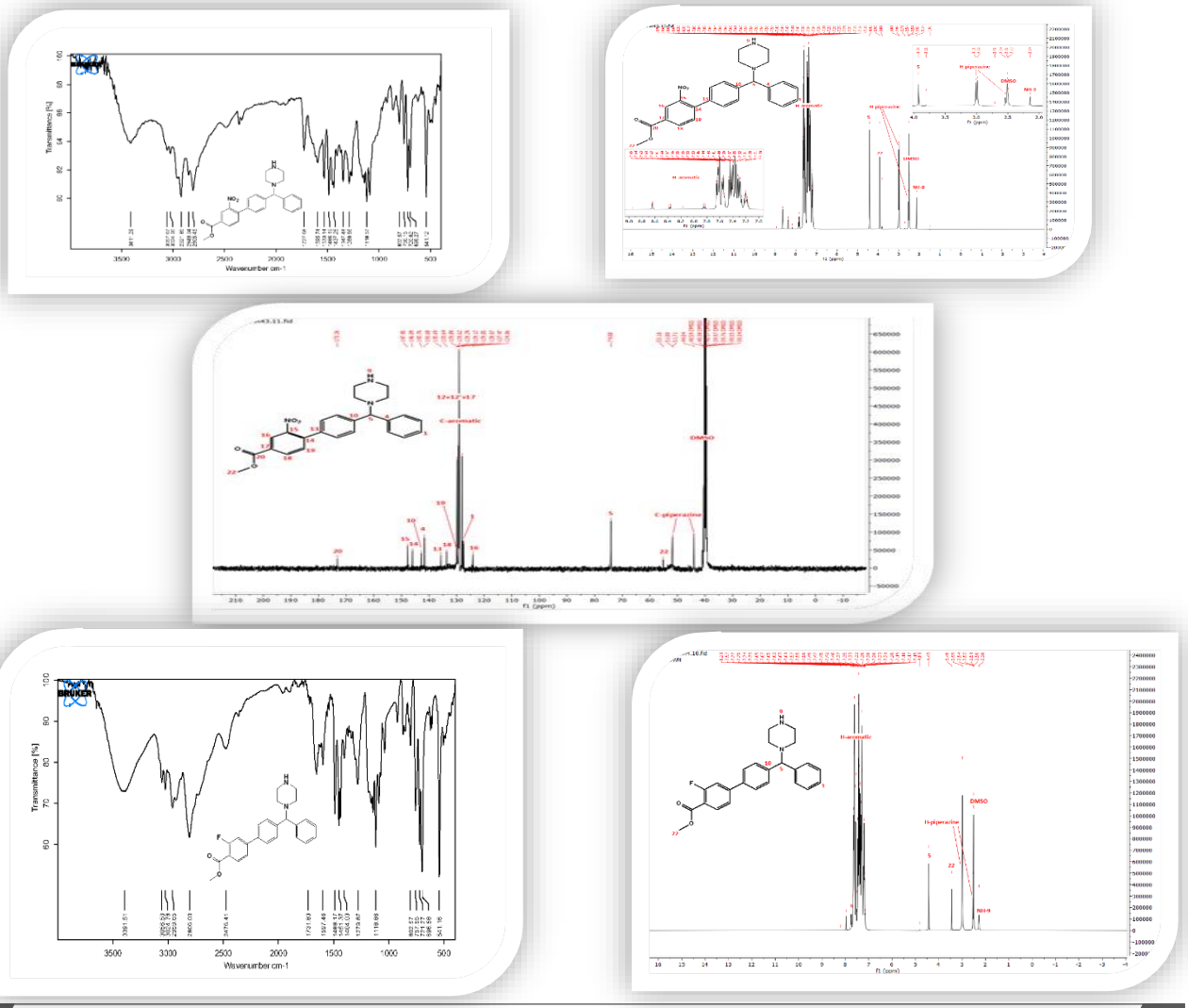


Figure (3-5):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 3



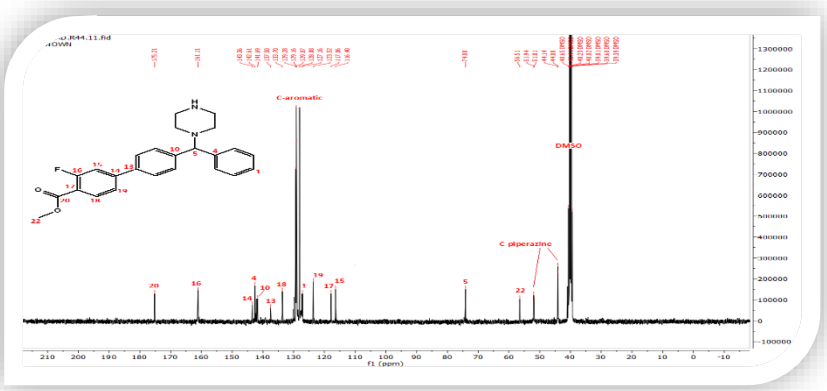


Figure (3-7):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 5

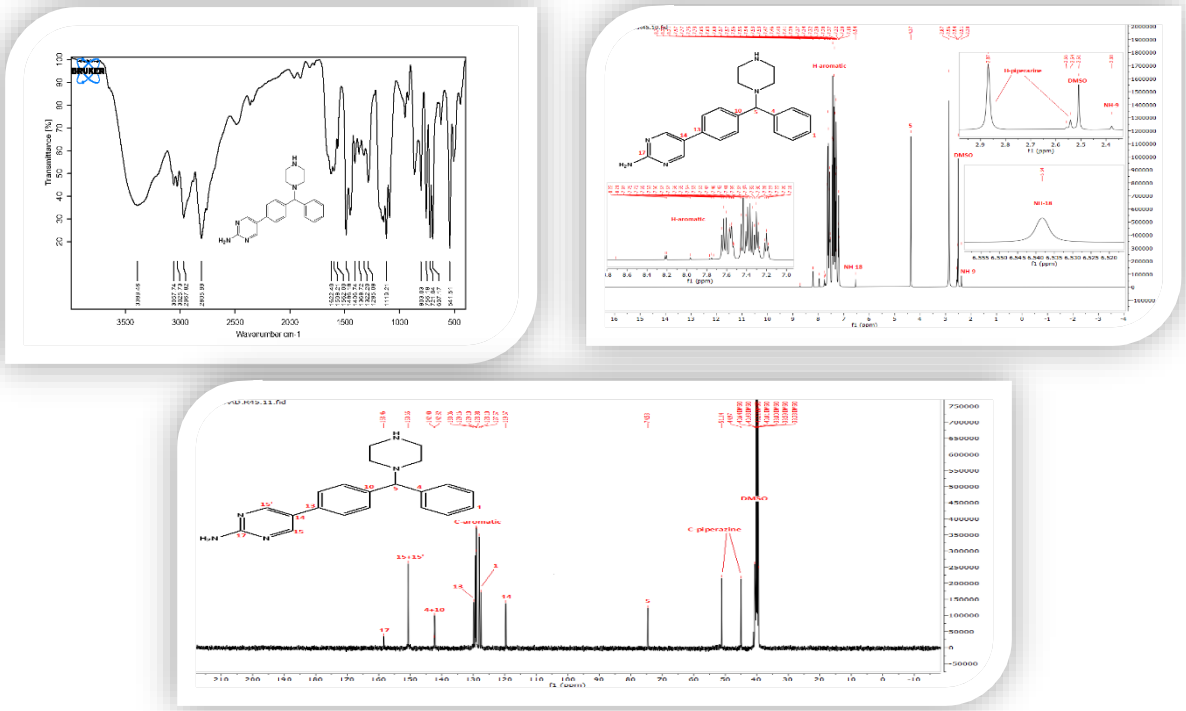
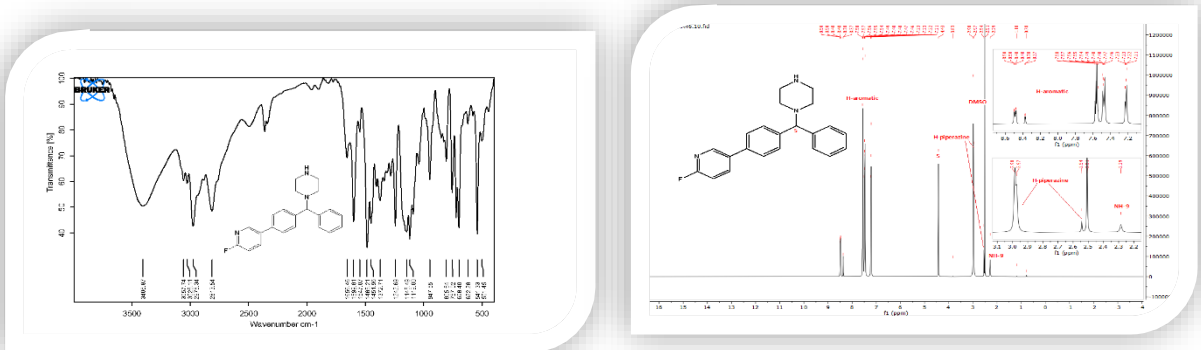


Figure (3-8):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 6



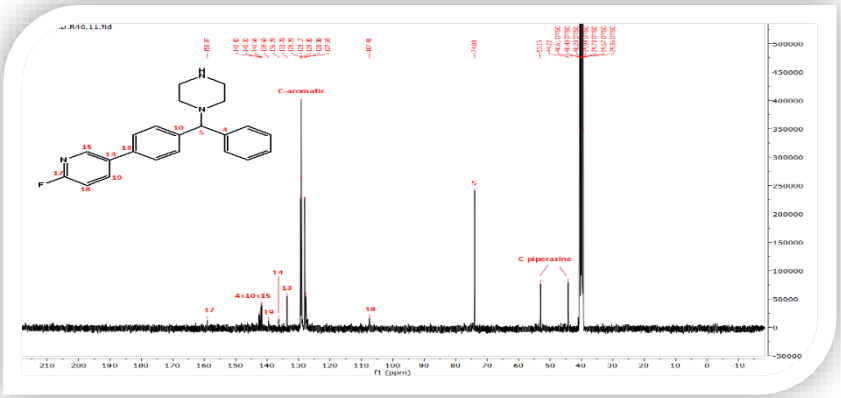
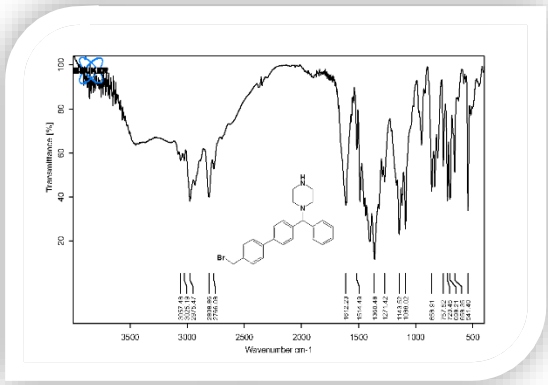
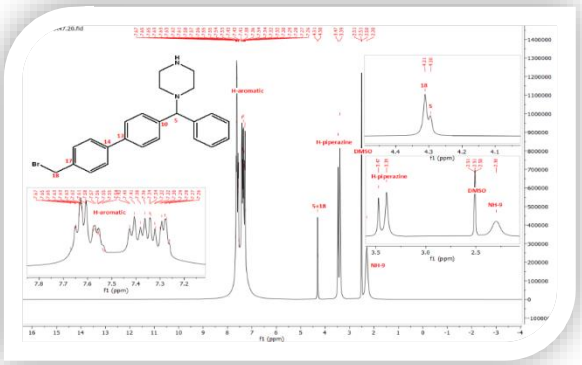


Figure (3-9):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 7





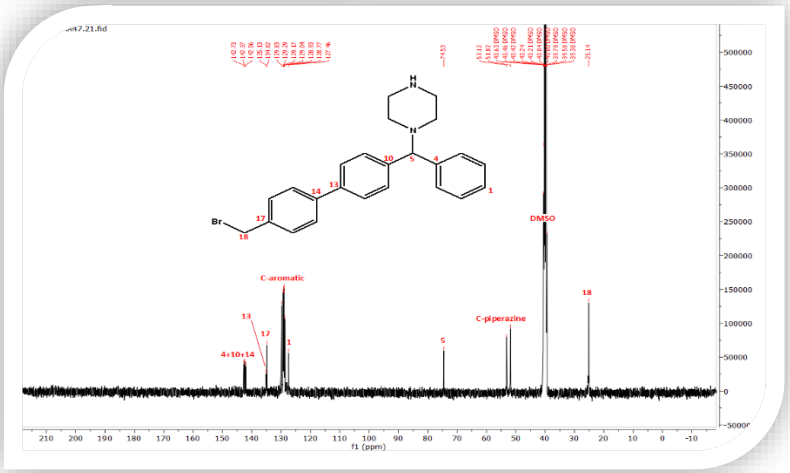
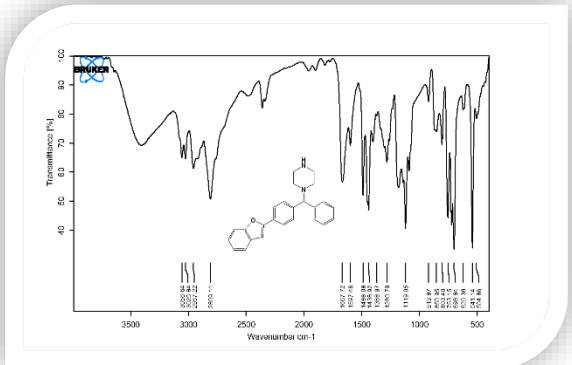
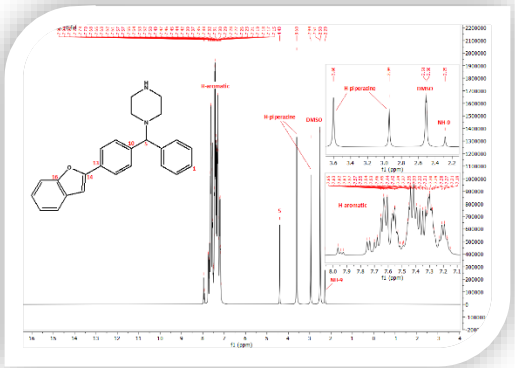


Figure (3-10):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 8





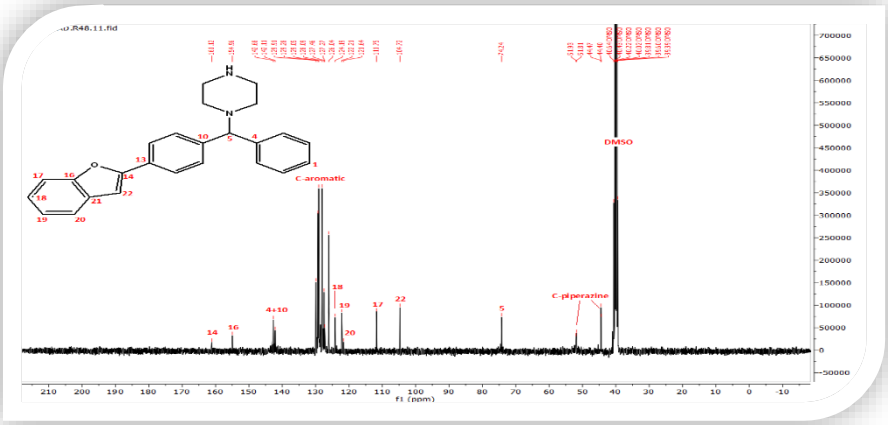
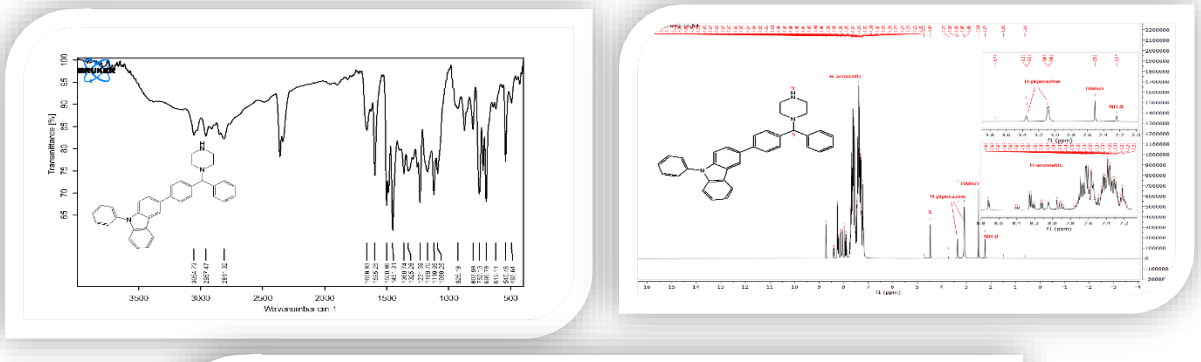


Figure (3-4): ^{13}C-NMR- Spectrum Of R69

Figure (3-11):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 9



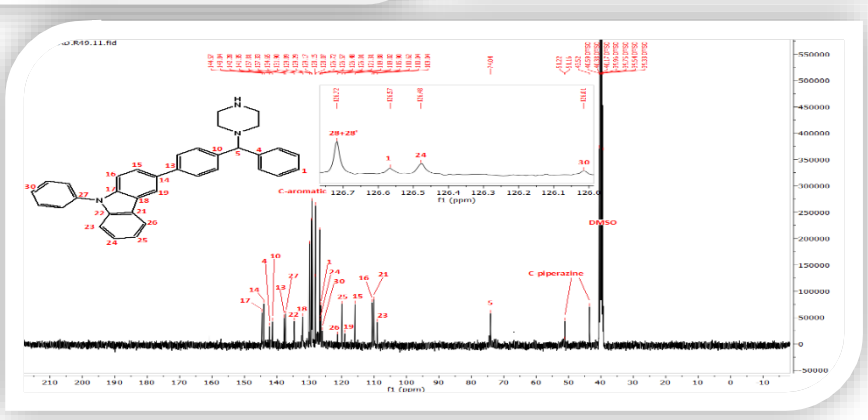


Figure (3-12):FT-IR, ^{1}H-NMR&^{13}C-NMR-Spectrum Of Derivative 10