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Proceeding Paper

Synthesis, Characterization and Molecular Docking of New Derivatives that Contain Thiazole Moieties and Study Antioxidant Properties †

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Abstract: An important class of heterocyclic chemicals are thiazole derivatives, providing a wide spectrum of biological activities in the form of antibacterial and antifungal, anti-HIV, anti-hypertensive, anti-inflammatory, anti-cancer, anti-convulsant, anti-depressant, and anti-tuberculosis acts In this study we are prepared some novel derivatives from cetirizine Impurity A by react 1-((4-chlorophenyl)(phenyl) methyl)piperazine with with 2-chloro acetyl chloride to prepared 2-chloro-1-(4-((4-chlorophenyl) (phenyl) methyl)piperazin-1-yl)ethan-1-one (1) then react with 2-aminothiazole derivatives to the derivatives (2–11) .The reaction was monitored by thin-layer chromatography (TLC) technique. All new compounds were characterized by melting points, elemental analysis, FT-IR, ^{1}H-NMR, and ^{13}CNMR spectroscopy. The molecular docking of these derivatives was also determined and study as antioxidant efficiently.

Keywords : Thiazole ; Cetirizine impurity A ; Antioxidant ,Molecular docking

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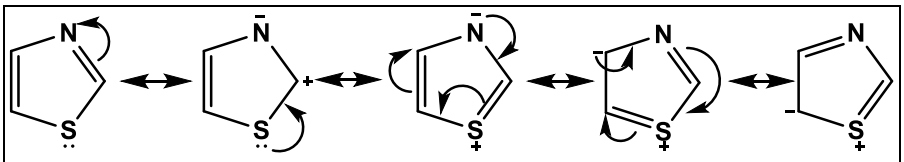
1. Introduction

Synthetic organic chemicals have the extension ability to replace of the nature's most interesting molecules invitro and apply their advanced synthetic strategies and techniques to construct various forms of them [1]. These molecules facilitate biology and medicine, as they are often used as biological tools and drug candidates for clinical development, In organic chemistry, the largest families of organic compounds belong to heterocyclic compounds [2]. In our daily life, heterocyclic compounds are very important. It has a wide range of applications in medicinal chemistry and agrochemical products [3]. Heterocyclic structures are essentially composed of elements other than carbon, with the most common substituents being oxygen, nitrogen, and sulfur [4]. Thiazoles are one of the most intensively scrutinized classes of 5-membered aromatic heterocycles. Many natural and synthesized thiazole and its derivatives showed significant biological activity [5]. Due to its unique properties, thiazole derivatives show significant antibacterial activity against various bacteria and pathogens. Large extent research on thiazole ring from the past two to three decades has proven that the thiazole scaffold has various active biological properties such as antioxidant, antibacterial, anti-viral, diuretic, antitumor and anticonvulsing properties [6]. Thiazole has an electron-donating group (-S-) and an electron-accepting group (-N-). The aromaticity of thiazole was only due to the delocalization of a non-bonding pair of electrons from the sulfur atom to fulfill the vacant 6p electrons to fulfill Hackle's rule (Scheme-1) this type of biological investigation takes us to a new

world of research to synthesize newly novel derivatives with strong biological activity [7,8].



Scheme 1. Resonating structure of thiazole

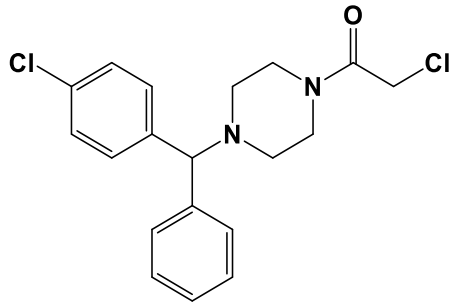
2. Experimental

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 [9] were recorded using FT-IR-8400S-Shimadizu spectrophotometer.^{1}H-NMR and ^{13}C-NMR [10,11] spectra were recorded on VARIAN-INOVA 400MHZ spectrophotometer (Germany), $CDCl_3$ and DMSO were used as solvents, and tetramethylsilane TMS as internal standard.

2-4-2 General procedure for the synthesis chloro-1-(4-((4-chloro phenyl)(phenyl)methyl)piperazin-1-yl)ethan-1-one (1)

To a solution of 1-((4-chlorophenyl)(phenyl) methyl)piperazine (3.4868 mmol) and triethylamine (0.37mL, 5.2302 mmol) in dry dichloromethane at 0 °C was added 2-chloroacetyl chloride (0.21mL, 5.2302 mmol) drop wise. The reaction mixture was stirred at 0°C about 2 h and the stirring was continued at room temperature for enough time. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with distilled water and extracted with chloroform (30 mL × 3). The organic layer was washed with 10% ammonium chloride solution and then water and dried over anhydrous $MgSO_4$. The crude product was recrystaled from ethanol to give the desired product as a solid matter with color light brown as a yield (0.68 g, 68%) that purified by chromatographic purification (toluene:ethyl acetate, 6:1) afforded intermediate [12–14].

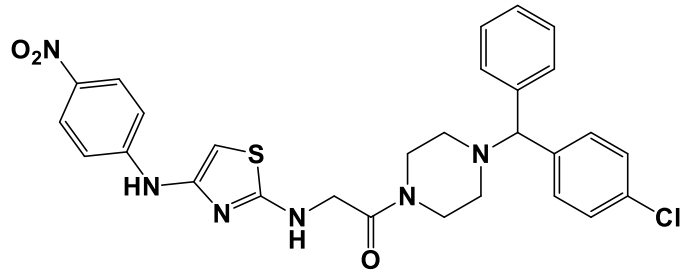


m.p = 88–90 °C, *Rf* =0.55 FT-IR (KBr, cm^{-1}): (2980,2939) C-H$_{al.}$,(1590) C=C$_{ar.}$ (1661) C=O, (3050) C-H$_{ar.}$ (1015) C-Cl$_{ar.}$^{1}H-NMR (400 MHz, DMSO-d^6) δ =2.67,3.64 (m,8H,H-piprazine), 4.89,4.90 (s,1H,H-5), 4.35 (s,2H,H-15),7.24-7.77 (m, H-ar.).^{13}C-NMR (100 MHz, DMSO-d^6) δ= 41.38 (C-15), 42.24, 51.32, 51.75 (C-piprazine), 74.00 (C-5), 126.36 (C-9), 128.25 (C-7+C-7`), 129.21,129.32 (C-3+C-3`& C-8+C-8`), 130.11 (C-2+C-2`) ,131.97 (C-1), 141.34 (C-6), 142.67 (C-4), 165.04 (C-14).Anal. calc. For $C_{19}H_{20}Cl_2N_2O$ (363.28) : C, 62.82; H, 5.55; N, 7.71; Found: C, 62.74; H, 5.48; N, 7.63.

2-4-6-A- General procedure for the synthesis of amine derivatives 3(a–j)

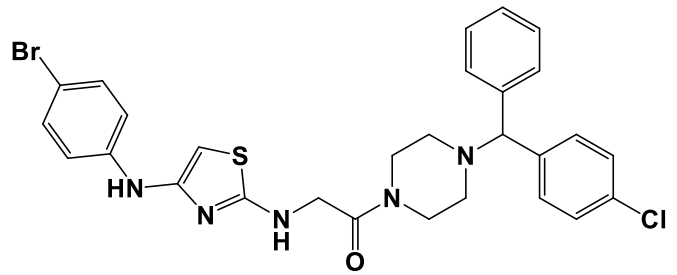
To a suspension of 1 (0.3 g, 0.8258 mmol) and K_2CO_3 (0.1712 g, 1.2387 mmol) in ethanol (20.0 mL), 2-aminothiazole derivatives (0.8258 mmol) and a catalytic amount of KI (0.0081 g, 0.0487 mmol) were added. The resulting mixture was refluxed for enough time (followed by TLC). After filtering, the resulting filtrate was evaporated to dryness under reduced pressure. The residue was suspended in water (10.0 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were evaporated under reduced pressure, and the residue was recrystallized from EtOH to yield compounds [15,16].

2-4-6-A-9-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((4-((4-nitrophenyl) amino)thiazol-2-yl)amino)ethan-1-one (a)



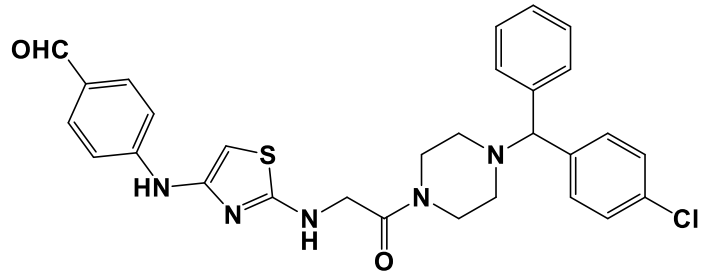
This compound was prepared according to the general method from the derivative 1 and N4-(4-nitrophenyl)thiazole-2,4-diamine as a solid matter with yellowish brown color as a yield (0.358 g, 77%) *m.p*= 70-72°C, *Rf* =0.74 FT-IR (KBr, cm^{-1}) : (2970, 2854) C-$H_{al.}$, (1632) C=O , (3361,3219) N-H, (3080) C-$H_{ar.}$, (1401,1370) NO_2, (998) C-Cl, (1597,1484) C=$C_{ar.}$ ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.94, 3.34 (m, 8H, H-Piperazine), 3.90 (s, 2H ,H-15), 5.44 (s, 1H, H-5), 5.68 (s,1H,H-19), 6.83 (br., 1H, H-16), 7.19-8.04 (m, H-ar.). 8.79 (br, 1H, H-22). ^{13}C NMR (100 MHz, DMSO-d^6) δ= 44.29, 51.47, 51.82 (C- Piperazine), 60.38 (C-15), 74.14 (C-5), 108.36 (C-19), 119.38- 131.93 (C-ar.), 136.10 (C-26), 141.93 (C-4), 142.30 (C-6), 145.94 (C-20), 150.44 (C-23), 156.19 (C-17), 170.35 (C-14). Anal. calc. For $C_{28}H_{27}ClN_6O_3S$ (563.07) : C, 59.73; H, 4.83; N, 14.93; S, 5.69 Found: C, 59.63; H, 4.72; N, 14.83; S, 5.58.

2-4-6-A-10-2-((4-((4-bromophenyl)amino)thiazol-2-yl)amino)-1-(4-((4-chlorophenyl) (phenyl)methyl)piperazin-1-yl)ethan-1-one (b)



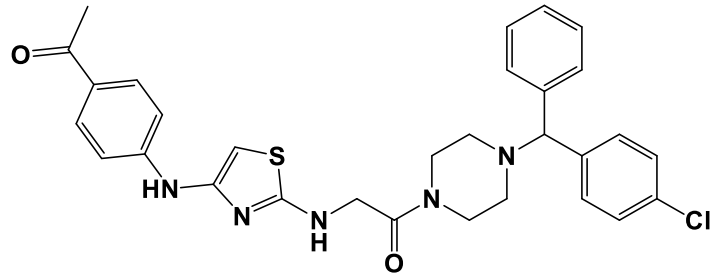
This compound was prepared according to the general method from the derivative R10 and N^4-(4-bromophenyl)thiazole-2,4-diamine as a solid matter with reddish brown color as a yield (0.3944 g, 80%) *m.p*= 76-78°C. *Rf* =0.60 FT-IR (KBr, cm^{-1}) : (2929, 2813) C-$H_{al.}$, (1650) C=O , (3390,3243) N-H, (3028) C-$H_{ar.}$, (1018) C-Br , (998) C-Cl, (1564,1488) C=$C_{ar.}$ ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.95, 3.34 (m, 8H, H-Piperazine), 3.71 (s, 2H ,H-15), 5.64 (s, 1H, H-5), 5.89 (s,1H,H-19), 7.19-8.47 (m, H-ar.), 7.00 (br., 1H, H-16), 8.13 (br, 1H, H-22). ^{13}C NMR (100 MHz, DMSO-d^6) δ= 43.99, 51.48, 51.84 (C- Piperazine), 60.38 (C-15), 74.12 (C-5), 105.40 (C-19), 115.58-142.31 (C-ar.), 144.84 (C-20), 163.73 (C-17), 170.53 (C-14). Anal. calc. For $C_{28}H_{27}BrClN_5OS$ (596.97) : C, 56.34; H, 4.56; N, 11.73; S, 5.37 Found: C, 56.23; H, 4.34; N, 11.62; S, 5.25.

2-4-6-A-11-4-((2-((2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-oxoethyl) amino)thiazol-4-yl)amino)benzaldehyde (c)



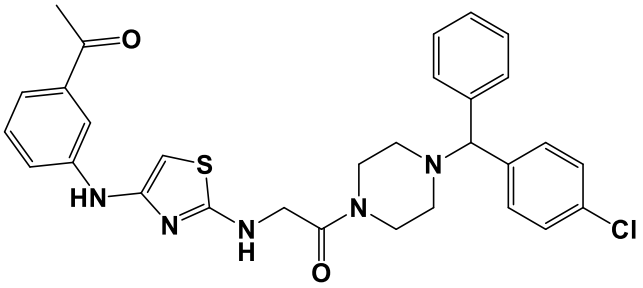
This compound was prepared according to the general method from the derivative R10 and 4-((2-aminothiazol-4-yl)amino)benzaldehyde as a solid matter with yellowish brown color as a yield (0.3563 g, 79%) *m.p*= 72-74°C, *Rf* =0.71 FT-IR (KBr, cm^{-1}) : (2923, 2816) C-$H_{al.}$, (1720) C=$O_{ald.}$, (3390) N-H, (3050) C-$H_{ar.}$, (1638) C=O amid., (1565,1489) C=$C_{ar.}$ ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.69, 3.33, 3.34 (m, 8H, H-Piperazine) , 3.90 (s, 2H ,H-15), 5.52 (s, 1H, H-5), 5.88 (s,1H,H-19), 7.18-7.72 (m, H-ar.). 8.97 (br., 1H, H-22), 6.62 (s, 1H, H-16), 9.57 (s,1H-H-27) ^{13}C NMR (100 MHz, DMSO-d^6) δ= 43.97, 51.49,51.85 (C- Piperazine), 60.39 (C-15), 74.11 (C-5), 106.36 (C-19), 111.67-149.42 (C-ar.),166.03 (C-17), 145.51 (C-20),170.40 (C-14). 201.12 (C-27). Anal. calc. For $C_{29}H_{28}ClN_5O_2S$ (546.09) : C, 63.78; H, 5.17; N, 12.82; S, 5.87 Found: C, C, 63.70; H, 5.09; N, 12.72; S, 5.76.

2-4-6-A-12 2-((4-((4-acetylphenyl)amino)thiazol-2-yl)amino)-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethan-1-one (d)



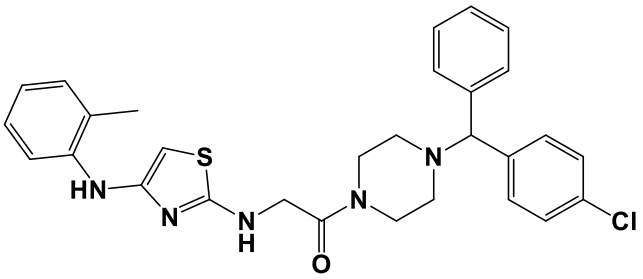
This compound was prepared according to the general method from the derivative 1 and 1-(4-((2-aminothiazol-4-yl)amino)phenyl)ethan-1-one as a solid matter with yellowish brown color as a yield (0.3793 g, 82%) *m.p* 79-81°C, *Rf* =0.80 FT-IR (KBr, cm^{-1}) : (2931, 2816) C-$H_{al.}$, (1651) C=O_{amid} , (3384) N-H, (3050) C-$H_{ar.}$, (1720) C=O ketone, , (1593 ,1563,1489) C=$C_{ar.}$,(999) C-Cl. ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.54 (s,3H, H-28) , 2.94-3.35 (m, 8H, H-Piperazine) , 3.88 (s, 2H ,H-15), 5.62 (s, 1H, H-5), 6.12 (s,1H,H-19), 7.19-8.44 (m, H-ar.). 9.10 (br., 1H, H-22), 6.54 (s, 1H, H-16). ^{13}C NMR (100 MHz, DMSO-d^6) δ= 26.31 (C-28), 47.75, 51.49, 51.86 (C- Piperazine), 60.41 (C-15), 74.11 (C-5), 110.97 (C-19), 112.91-142.32 (C-ar.), 154.15 (C-23), 152.75 (C-20). 170.48 (C-17), 174.78 (C-14). 195.43 (C-27). Anal. calc. For $C_{30}H_{30}ClN_5O_2S$ (560.11) : C, 64.33; H, 5.40; N, 12.50; S, 5.72 Found: C, 64.29; H, 5.27; N, 12.38; S, 5.59.

2-4-6-A-13 2-((4-((3-acetylphenyl)amino)thiazol-2-yl)amino)-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethan-1-one (e)



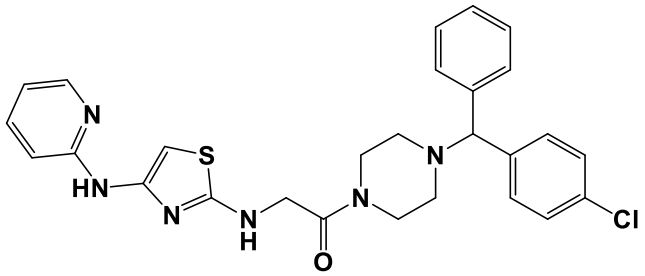
This compound was prepared according to the general method from the derivative 1 and 1-(3-((2-aminothiazol-4-yl)amino)phenyl)ethan-1-one as a semisolid matter with yellowish brown color as a yield (0.3747 g, 81%) *Rf* =0.82 FT-IR (KBr, cm^{-1}) : (2923, 2817) C-$H_{al.}$, (1647) C=O_{amid} , (3369) N-H, (3050) C-$H_{ar.}$, (1720) C=O_{ketone}, , (1562, 1480) C=$C_{ar.}$,(1016) C-Cl. ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.35 (s,3H, H-30) , 2.59, 3.36 (m, 8H, H-Piperazine) , 3.79 (s, 2H ,H-15), 5.38 (s, 1H, H-5), 5.67 (s,1H,H-19), 5.87 (s, 1H, H-16), 7.14-7.50 (m, H-ar.), 8.57 (br., 1H, H-22), ^{13}C NMR (100 MHz, DMSO-d^6) δ= 25.92 (C-30), 49.21,51.54 (C-Piperazine), 60.44 (C-15), 74.12 (C-5), 127.84-131.68 (C-ar.), 110.98 (19), 116.31(C-24), 120.64 (C-26), 124.14 (C-28), 133.71 (C-27),138.20 (C-25), 140.35 (C-23), 141.95 (C-4), 142.67 (C-6), 143.22 (C-20), 166.70 (C-17), 174.77 (C-14) ,190.34 (C-29). Anal. calc. For $C_{30}H_{30}ClN_5O_2S$ (560.11) : C, 64.33; H, 5.40; N, 12.50; S, 5.72 Found: C, 64.23; H, 5.29; N, 12.40; S, 5.61.

2-4-6-A-14-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((4-(o-tolylamino) thiazol-2-yl)amino)ethan-1-one (f)



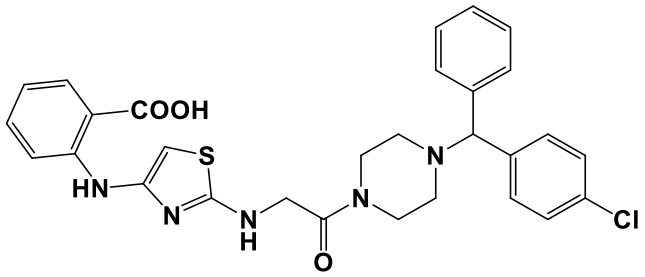
This compound was prepared according to the general method from the derivative 1 and N^4-(o-tolyl)thiazole-2,4-diamine as a solid matter with light brown color as a yield (0.3747 g, 78%) *m.p*= 73-75 °C, *Rf* =0.73 FT-IR (KBr, cm^{-1}) : (2930, 2813) C-$H_{al.}$, (1644) C=O , (3385) N-H, (3050) C-$H_{ar.}$,(1569,1488) C=$C_{ar.}$,(1000) C-Cl .^{1}H-NMR (400 MHz, DMSO-d^6) δ =2.27 (s,3H,H-29), 2.94, 3.34 (m,8-H,H-piprazine), 5.60 (s,1H,H-5), 3.88 (br.,1H,H-15), 5.71 (s,1H-H-19), 5.98 (br.,1H, H-16), 7.18-7.85 (m, H-ar.) 8.09 (br.,1H, H-22).^{13}C-NMR (100 MHz, DMSO-d^6) δ= 17.35 (C-29), 43.98, 51.85 (C-piprazine), 60.38 (C-15), 74.12 (C-5), 109.63 (C-19), 123.13 (C-26), 123.84 (C-28),126.24 (C-27), 127.63(C-9), ,128.07 -129.31 (C-ar.), 129.51 (C-24), 131.37 (C-1), 131.91 (C-25),141.96 (C-4+C-6), 146.49 (C-20), 147.64 (C-23), 170.49 (C-17), 174.81 (C-14). **Anal. calc**. For $C_{29}H_{30}ClN_5OS$ (532.10) : C, 65.46; H, 5.68; N, 13.16; S, 6.03 Found: C, 65.41; H, 5.62; N, 13.10; S, 5.96

2-4-6-A-15-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((4-(pyridin-2-ylamino)thiazol-2-yl)amino)ethan-1-one (g)



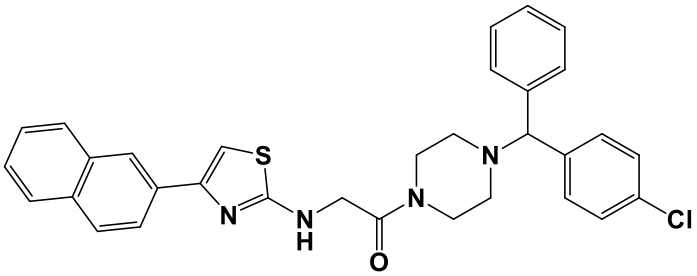
This compound was prepared according to the general method from the derivative 1 and N^4-(pyridin-2-yl)thiazole-2,4-diamine as a solid matter with dark yellow color as a yield (0.3343 g, 78%) *m.p*= 82-84°C, *Rf* =0.69 FT-IR (KBr, cm^{-1}) : (2923, 2816) C-$H_{al.}$, (1647) C=O , (3407,3347) N-H, (3050) C-$H_{ar.}$,(1568) C=$C_{ar.}$,(1014) C-Cl .^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.94, 3.34-3.36 (s, 8H, H-Piperazine) , 3.88,3.89 (s, 2H ,H-15), 5.62 (s, 1H, H-5), 5.98 (br.,1H,H-19), 7.19-7.96 (m, H-ar.), 8.53 (br., 1H, H-22), 6.94 (br., 1H, H-16) .^{13}C NMR (100 MHz, DMSO-d^6) δ= 47.91, 51.49, 51.86 (C- Piperazine), 60.42 (C-15), 74.12 (C-5), 127.63-131.92 (C-ar.), 108.52 (C-28), 111.73 (C-19),116.71 (C-26),137.39 (C-27), 141.95, 142.31 (C-4+C-6), 145.76 (C-20), 148.62 (C-25), 157.13 (C-23), 170.48 (C-17), 174.81 (C-14). Anal. calc. For $C_{27}H_{27}ClN_6OS$ (519.06) : C, 62.48; H, 5.24; N, 16.19; S, 6.18 Found: C, 62.41; H, 5.17; N, 16.13; S, 6.10.

2-4-6-A-16-2-((2-((2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-oxoethyl) amino)thiazol-4-yl)amino)benzoic acid (h)



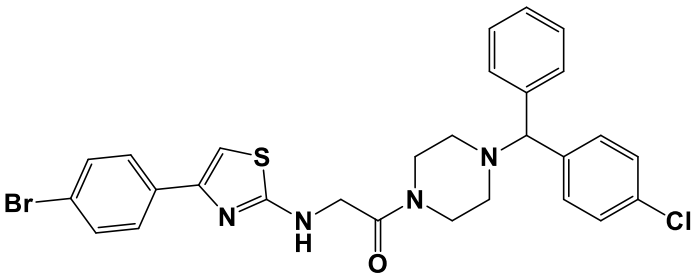
This compound was prepared according to the general method from the derivative 1 and 2-((2-aminothiazol-4-yl)amino)benzoic acid as a solid matter with yellowish brown color as a yield (0.3481 g, 75%) *m.p*= 75-77°C, *Rf* =0.84.FT-IR (KBr, cm^{-1}) : (2923, 2818) C-$H_{al.}$, (1641) C=O_{amid} , (3411) N-H&COOH , (3050) C-$H_{ar.}$,(1564,1410) C=$C_{ar.}$,(1000) C-Cl, (1700) C=O. ^{1}H-NMR (400 MHz, DMSO-d^6) δ = 3.17, 3.35 (s, 8H, H-Piperazine) , 3.89 (s, 2H ,H-15), 5.32 (br., 1H, H-5), 5.61 (br.,1H,H-19), 7.19-8.49 (m, H-ar.). 8.97 (br., 1H, H-22), 6. 28 (s, 1H, H-16), 14.04 (s,1H,H-30).^{13}C NMR (100 MHz, DMSO-d^6) δ= 44.01 , 51.84 (C-Piperazine), 60.39 (C-15), 74.12 (C-5), 108.03 (C-28), 110.11 (C-19), 118.94 (C-26), 120.05 (C-27), 127.63-141.95 (C-ar.), 142.32 (C-4+C-6), 143.44 (C-20), 144.21 (C-23), 162.03 (C-17), 170.52 (C-14), 175.17 (C-29).Anal. calc. For $C_{29}H_{28}ClN_5O_3S$ (562.09) : C, 61.97; H, 5.02; N, 12.46; S, 5.70 Found: C, 61.85; H, 4.90; N, 12.33; S, 5.62.

2-4-6-A-17-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((4-(naphthalen-2-yl)thiazol-2-yl)amino)ethan-1-one (i)



This compound was prepared according to the general method from the derivative 1 and 4-(naphthalen-2-yl)thiazol-2-amine as a solid matter with yellowish brown color as a yield (0.3334 g, 73%) *m.p*= 124-126°C. *Rf* =0.64 FT-IR (KBr, cm^{-1}) : (2920, 2816) C-$H_{al.}$, (1646) C=O , (3250) N-H, (3055) C-$H_{ar.}$,(1515, 1487) C=$C_{ar.}$,(999) C-Cl .^{1}H-NMR (400 MHz, DMSO-d^6) δ = 2.75, 2.78, 3.19 (s, 8H, H-Piperazine) , 3.53 (s, 2H ,H-15), 5.03 (s, 1H, H-5), 5.49 (s, 1H, H-16), 6.61 (s,1H,H-19), 7.13-8.25 (m, H-ar.). ^{13}C NMR (100 MHz, DMSO-d^6) δ= 46.01 ,51.44, 51.78 (C- Piperazine), 60.42 (C-15), 74.06 (C-5), 102.92 (C-19), 124.01-142.07 (C-ar.), 141.78 (C-4), 142.07 (C-6), 147.95(C-20), 168.78 (C-17), 170.42 (C-14). Anal. calc. For $C_{32}H_{29}ClN_4OS$ (553.12) : C, 69.49; H, 5.28; N, 10.13; S, 5.80 Found: C, 69.30; H, 5.09; N, 9.92; S, 5.61.

2-4-6-A-18-2-((4-(4-bromophenyl)thiazol-2-yl)amino)-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)ethan-1-one (j)



This compound was prepared according to the general method from the derivative 1 and 4-(4-bromophenyl)thiazol-2-amine as a solid matter with yellowish brown color as a yield (0.3604 g, 75%) *m.p*= 105-107°C. *Rf* =0.59 FT-IR (KBr, cm^{-1}) : (2962, 2920, 2811) C-$H_{al.}$, (1638) C=O , (3283) N-H, (3085, 3030) C-$H_{ar.}$,(1534,1485) C=$C_{ar.}$,(1000) C-Cl , (1008) C-Br. ^{1}H-NMR (400 MHz, DMSO-d^6) δ =2.98,3.39 (m,8-H,H-piprazine), 5.48 (s,1H,H-5), 3.53 (br.,1H,H-15), 6.87 (br.,1H, H-16), 7.14-7.81 (m, H-ar.).^{13}C-NMR (100 MHz, DMSO-d^6) δ= 43.95, 51.48 ,51.84 (C-piprazine), 60.38 (C-15), 74.12 (C-5), 102.87 (C-19), 120.56 (C-24), 127.63 (C-9), 128.01 -131.92 (C-ar.), 134.57 (C-24), 141.95 ,142.31 (C-4+C-6), 131.91 (C-1),149.09 (C-20) 168.80 (C-17), 170.34 (C-14). Anal. calc. For $C_{28}H_{26}BrClN_4OS$ (581.96) : C, 57.79; H, 4.50; N, 9.63; S, 5.51 Found: C, 57.64; H, 4.35; N, 9.37; S, 5.35.

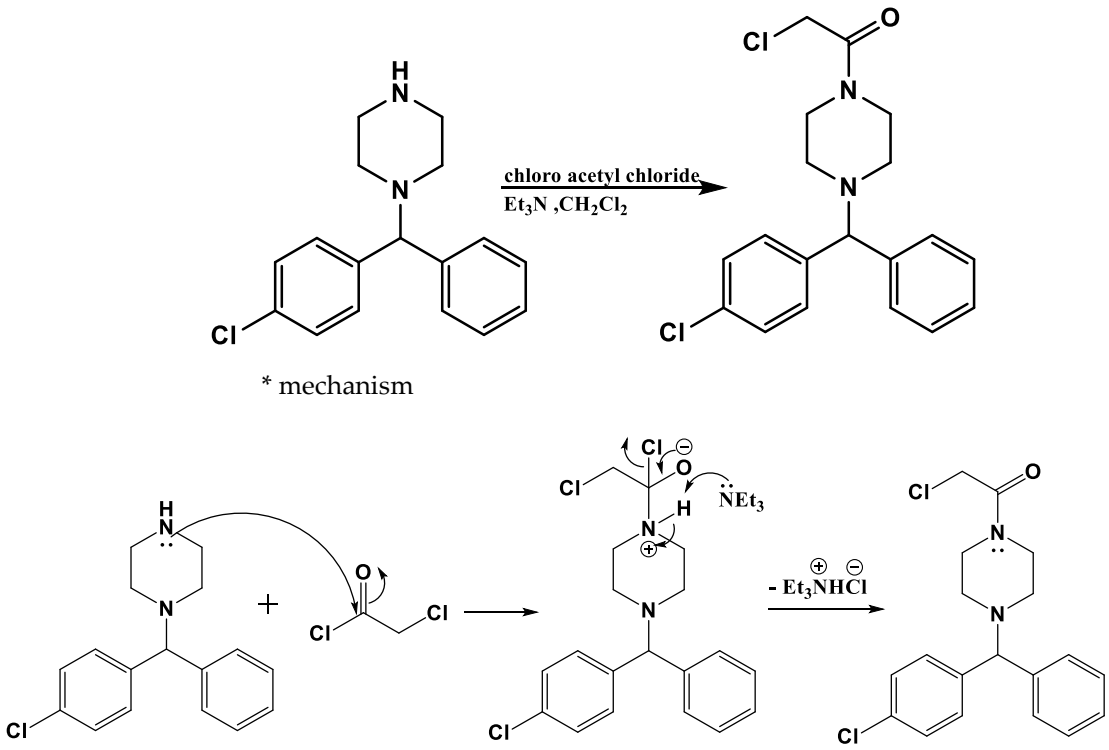
3. Result and Discussion:

3.1. Chemistry

3.1.2. Preparation and Characterization of Derivative (1)

The derivative was prepared from reaction of 1-((4-chlorophenyl)(phenyl) methyl)piperazine with 2-chloroacetyl chloride in the presence of triethylamine and CH_2Cl_2 as a reaction medium, then stirred the mixture for 2 h at 0°C and then at room temperature until end of the reaction after following it up using TLC. As shown in the following equation & mechanism :

* equation



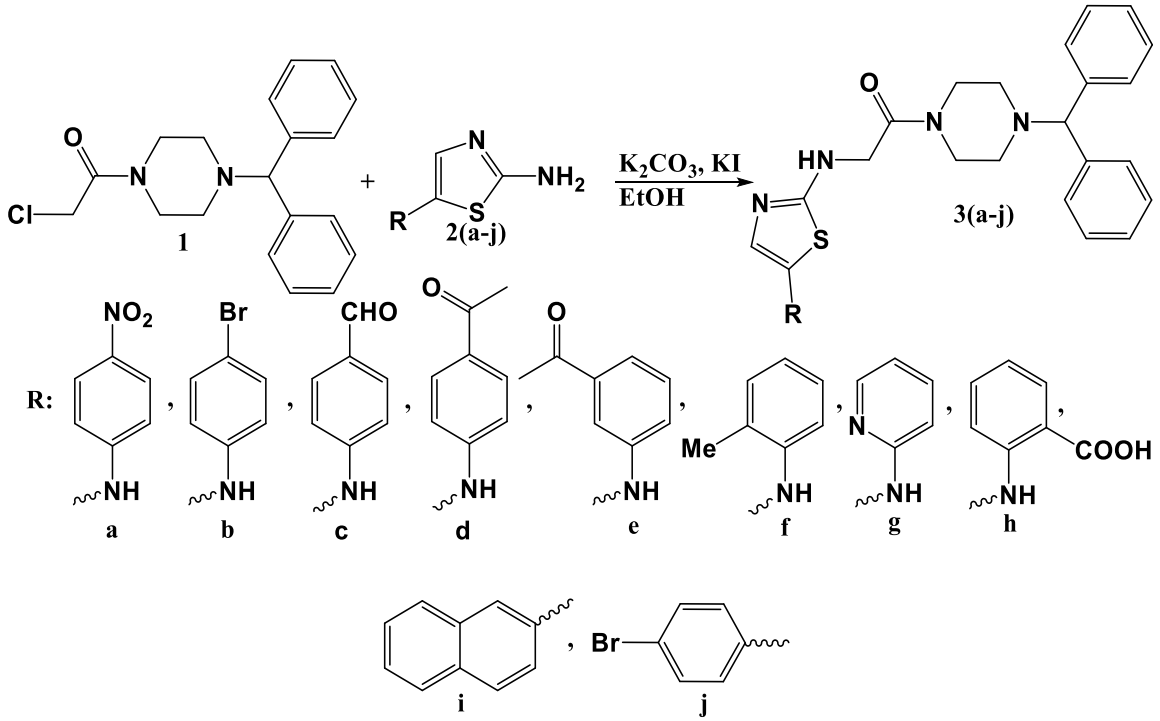
Scheme 3. Equation and mechanism of preparing the derivative (1).

As indicated absorption band of carbonyl group at the frequency (1661 cm^{-1}) and disappearance (N-H) group. The spectrum of (^{1}H-NMR) in Figure (2) showed the signal at δ =4.35 ppm refer to methylene group (H-15), and also shown δ= 2.67, 3.64 ppm belonging to the protons of Piprazine ring, displacements at δ= 4.49, 4.90 ppm due to chiral center (methyne group) (H-5), displacements at δ = 7.24-7.77 ppm (m, H-ar.) belonging to the protons of aromatic rings. Also, the spectrum of (^{13}C-NMR) in Figure (3) showed signal at frequency signals at δ=41.38 ppm due to methylene group and the signals at δ = 42.24, 51.32, 51.75 ppm that belong to the carbons of Piperazine ring, also shown frequency signal at δ= 74.00 ppm of due to methyne group (charial center C-5), as well as shown in δ=126.36 -142.67 ppm due to carbons of aromatic rings and also signal at δ= 165.04 ppm to carbonyl group (C-14).

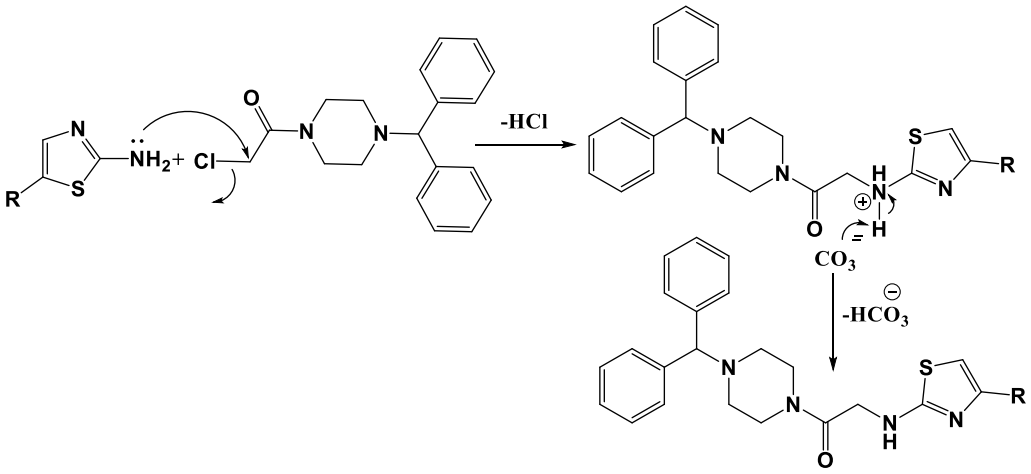
3.1.2. Preparation and Characterization of the Derivatives (a–j)

Derivatives were prepared from reaction of 2-aminothiazole derivatives with **1** in the presence of K_2CO_3 as base, KI as catalytic and ethanol as a reaction medium, then refluxed until end of the reaction after following it up using TLC. As shown in the following equation & mechanism :

* equation:



* mechanism:



Scheme 3. Equation and mechanism of preparing the derivatives3 (a-j).

The FT-IR spectrum of derivative **3a** showed the appearance of the two bands at the two frequencies (3361 and 3219 cm^{-1}) to the group (N-H) with band of NO_2 group at 1401 and 1370 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (5) showed the signals at δ= 2.94, 3.34 ppm belonging to the protons of piprazine ring, displacement at δ= 5.44 ppm due to chiral center (methyne group) (H-5), in other hand shown signals at δ = 3.90 ppm refer to methylene group, displacements at δ = 7.19-8.04 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 5.68 ppm due to methylene group, and also shown signals at δ =8.79 and 6.83 ppm due to amines group (H-22 & H-16) respectively. Also, the spectrum of (^{13}C-NMR) in Figure (6) showed signals at δ = 44.29, 51.47, 51.82 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.38 refer to methylene gruop (C-15), also shown frequency signal at δ= 74.14 ppm of due to methyne group (charial center C-5), as well as shown signals in δ=119.38- 131.93 ppm due to carbons of aromatic rings, and also signals at δ= 108.36 ,156.19 and 145.94 ppm to protons of thiazole ring as well as shown signal at δ=170.35 ppm due to carbonyl group.

The FT-IR spectrum of derivative **3b** showed the appearance of the two bands at the two frequencies (3390 cm^{-1} and 3243 cm^{-1}) to the group (N-H) with band of carbonyl group at 1650 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (8) showed the signals at δ= 2.95, 3.34 ppm belonging to the protons of piprazine ring, displacement at δ= 5.64 ppm due to chiral center (methyne group) (H-5), in other hand show signal at δ =5.89 refer to proton of thiazole ring (H-19), displacements at δ = 7.19-8.47 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.71 ppm due to methylene group, and also shown signals at δ =7.00 and 8.13 ppm due to amines group (H-16 & H-22) respectively .

Also, the spectrum of (^{13}C-NMR) in Figure (9) showed signals at δ = 43.99, 51.48, 51.84 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.38 ppm refer to methylene gruop (C-15), also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown signals in δ=115.58-142.31 ppm due to carbons of aromatic rings, and also signals at δ= 163.73, 105.40 and 144.84 ppm to protons of thiazole ring (C-17, C-19, C-20), as well as shown signal at δ=170.53 ppm due to carbonyl group.

The FT-IR spectrum of derivative **3c** showed the appearance of the two bands at the frequencies (3390 cm^{-1}) to the group (N-H) with band of carbonyl of aldehyde group at 1720 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (11) showed the single at δ= 2.69, 3.33, 3.34 ppm belonging to the protons of piprazine ring, displacement at δ= 5.52 ppm due to chiral center (methyne group) (H-5), in other hand shown signal at δ =5.88 ppm refer to proton of thiazole ring (H-19), displacements at δ = 7.18-7.72 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.90 ppm due to methylene group (H-15), and also shown signals at δ = 88.97 and 6.45 ppm due to amines group (H-16 & H-22) respectively, and appear signal at 9.57 ppm to H-27 due to proton aldehyde. Also, the spectrum of (^{13}C-NMR) in Figure (12) showed signals at δ = 43.97, 51.49, 51.85 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.39 ppm refer to methylene gruop (C-15), also shown frequency signal at δ= 74.11 ppm of due to methyne group (charial center C-5), as well as shown signals in δ=111.67-149.42 ppm due to carbons of aromatic rings, and also signal at δ= 166.03 , 106.36 and 145.51 ppm to protons of thiazole ring (C-17, C-19, C-20), as well as shown signals at δ=170.40 and 201.12 ppm due to carbonyl groups.

The FT-IR spectrum of derivative **3d** showed the appearance of the two bands at the two frequencies (3384 cm^{-1}) to the group (N-H) with band of carbonyl of ketone group at 1720 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (14) showed the signals at δ= 2.94-3.55 ppm belonging to the protons of piprazine ring, displacement at δ= 5.62 ppm due to chiral center (methyne group) (H-5), in other hand shown signal at δ =6.12 ppm refer to proton of thiazole ring (H-19), displacements at δ = 7.19-8.44 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.88 ppm due to methylene group, and also shown signals at δ =9.10 and 6.54 ppm due to amines group (H-16 & H-22) respectively, and appear signal at 2.54 ppm to H-28 due to protons of methyl group. Also, the spectrum of (^{13}C-NMR) in Figure (15) showed signals at δ = 47.75, 51.49, 51.86 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.41 ppm refer to methylene gruop (C-15), also shown frequency signal at δ= 74.11 ppm of due to methyne group (charial center C-5), as well as shown signals in δ=112.91-142.32 ppm due to carbons of aromatic rings, and also signals at δ= 110.97, 170.48 and 152.75 ppm to protons of thiazole ring (C-17, C-19, C-20), as well as shown signals at δ=174.78 and 195.43 ppm due to carbonyl groups (C-14) & (C-27) respectively.

The FT-IR spectrum of derivative **3e** showed the appearance of the two bands at the two frequencies (3369 cm^{-1}) to the group (N-H) with band of carbonyl group of ketone at 1720 cm^{-1}.As well as the spectrum of (^{1}H-NMR) in Figure (17) showed the signal at δ= 2.59, 3.36 ppm belonging to the protons of piprazine ring, displacement at δ= 5.38 ppm due to chiral center (methyne group) (H-5), in other hand shown signal at δ =5.67 ppm refer to proton of thiazole ring (H-19), displacements at δ = 7.14-7.50 ppm (m, H-ar.) ppm

belonging to the protons of aromatic rings, as well as shown signal at δ = 2.35 ppm due to methylene group, and also show signals at δ = 5.87 and 8.57 ppm due to amines group (H-16 & H-22) respectively

Also, the spectrum of (^{13}C-NMR) in Figure (18) showed signal at frequency signals at the signal at δ = 49.21, 51.54 ppm that belong to the carbons of Piperazine ring, the dispacements at δ = 60.44 ppm refer to methylene gruop (C-15), also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown signal in δ=127.84-131.68 ppm due to carbons of aromatic rings, and also signal at δ=166.70, 110.98 and 143.22 ppm to protons of thiazole ring (C-17, C-19, C-20) respectively, as well as shown signal at δ=174.77 and 190.34 ppm due to carbonyl groups (C-14 & C-29) respactively.

The FT-IR spectrum of derivative **3f** showed the appearance of the two bands at the two frequencies (3385 cm^{-1}) to the group (N-H) with band of carbonyl group at 1644cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (20) showed the signal at δ =3.88 ppm refer to methylene group (H-15), and also shown δ= 2.94,3.34 ppm belonging to the protons of piprazine ring, displacement at δ= 5.60 ppm due to chiral center (methyne group) (H-5), displacements at δ = 7.18-8.85 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, and also shown signals at δ = 8.09 & 5.98 ppm refer to amines group (H-22& H-16) respectively as well as shown signal at δ = 2.27 ppm to methyl group H-29.

Also, the spectrum of (^{13}C-NMR) in Figure (21) showed signal at frequency signals at δ=54.22 ppm due to methylene group and the signal at δ = 43.98, 51.85 ppm that belong to the carbons of Piperazine ring, also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown in δ=128.07-129.31 ppm due to carbons of aromatic rings, and also signal at δ=170.49, 109.63 and 146.49 ppm to protons of thiazole ring (C-17, C-19, C-20) respectively, and also signal at δ= 174.81 ppm to carbonyl group (C-14).

The FT-IR spectrum of derivative **3g** showed the appearance of the two bands at the two frequencies (3407 and 3347 cm^{-1}) to the group (N-H) with band of carbonyl group at 1647 cm^{-1}.As well as the spectrum of (^{1}H-NMR) in Figure (23) showed the signal at δ= 2.94, 3.34-3.36 ppm belonging to the protons of piprazine ring, displacement at δ= 5.62 ppm due to chiral center (methyne group) (H-5), in other hand show signal at δ = 5.98 refer to proton of thiazole ring (H-19), displacements at δ = 7.19-7.96 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.88, 3.89 ppm due to methylene groups, and also shown signals at δ =6.94 and 8.53 ppm due to amines group (H-16 & H-22) respectively.

Also, the spectrum of (^{13}C-NMR) in Figure (24) showed signals at δ = 47.91, 51.49, 51.86 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.42 refer to methylene gruop (C-15), also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown signals in δ=127.63-131.92 ppm due to carbons of aromatic rings, and also signals at δ=170.48, 111.73 and 145.76 ppm to protons of thiazole ring (C-17, C-19, C-20), as well as shown signal at δ=174.81 ppm due to carbonyl group (C-14).

The FT-IR spectrum of derivative **3h** showed the appearance of the broad band at the frequencies (3384 cm^{-1}) to the group amine and carboxyl group with band of carbonyl group of carboxyl at 1700 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (26) showed the signals at δ= 3.17, 3.35 ppm belonging to the protons of piprazine ring, displacement at δ= 5.32 ppm due to chiral center (methyne group) (H-5), in other hand shown signal at δ = 5.61 ppm refer to proton of thiazole ring (H-19), displacements at δ = 7.19-8.49 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.89 ppm due to methylene group, and also shown signals at δ =6.28 and 8.97 ppm due to amines group (H-16 & H-22) respectively, and appeared signal at δ =14.04 ppm to H-30 due to proton of carboxyl group.

Also, the spectrum of (^{13}C-NMR) in Figure (27) showed signals at δ = 44.01, 51.84 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.39 refer to

methylene gruop (C-15), also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown signals in the range δ=127.63-141.95 ppm due to carbons of aromatic rings, and also signal at δ=162.03, 110.11 and 143.44 ppm to protons of thiazole ring (C-17, C-19, C-20), as well as shown signals at δ=170.52 and 175.17 ppm due to carbonyl groups (C-14 and C-29).

The FT-IR spectrum of derivative **3i** showed the appearance of the band at the frequencies (3250 cm^{-1}) to the group (N-H) with band of carbonyl group at 1646 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (29) showed the signal at δ= 2.75, 2.78, 3.19 ppm belonging to the protons of piprazine ring, displacement at δ=5.03 ppm due to chiral center (methyne group) (H-5), in other hand shown signal at δ = 6.61 ppm refer to proton of thiazole ring (H-19), displacements at δ = 7.13-8.25 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings, as well as shown signal at δ = 3.53 ppm due to methylene group (H-15), and also shown signals at δ =5.49 ppm due to amine group (H-16).

Also, the spectrum of (^{13}C-NMR) in Figure (30) showed signals at δ = 46.01 ,51.44, 51.78 ppm that belong to the carbons of Piperazine ring, the dispacements at δ= 60.42 refer to methylene gruop (C-15), also shown frequency signal at δ= 74.06 ppm of due to methyne group (charial center C-5), as well as shown signals in δ= 124.01-142.07 ppm due to carbons of aromatic rings, and also signal at δ=168.78, 102.92 and 147.95 ppm to protons of thiazole ring (C-17, C-19, C-20) respectively, as well as shown signal at δ=170.42 ppm due to carbonyl group (C-14).

The FT-IR spectrum of derivative **3j** showed the appearance of the bands at the frequencies (3283 cm^{-1})to the group of (N-H) with band of bromo group at 1008 cm^{-1}. As well as the spectrum of (^{1}H-NMR) in Figure (32) showed the signal at δ =3.53 ppm refer to methyl group (H-15), and also shown δ= 2.98, 3.39 ppm belonging to the protons of piprazine ring, displacement at δ= 5.48 ppm due to chiral center (methyne group) (H-5), displacements at δ = 7.14-7.81 ppm (m, H-ar.) ppm belonging to the protons of aromatic rings as well as the signal at δ = 6.87 ppm refer to amine group.

Also, the spectrum of (^{13}C-NMR) in Figure (33) showed signal at frequency signals at δ=60.38 due to methyl group and the signals at δ = 43.95, 51.48 ,51.84 ppm that belong to the carbons of Piperazine ring, also shown frequency signal at δ= 74.12 ppm of due to methyne group (charial center C-5), as well as shown in δ=128.01-131.29 ppm due to carbons of aromatic rings and also signals at δ=168.80, 102.87 ppm and 149.09 ppm to protons of thiazole ring (C-17, C-19, C-20) respectively, and also signal at δ= 170.34 ppm to carbonyl group (C-14).

3.2. Biological Activity By Insilco

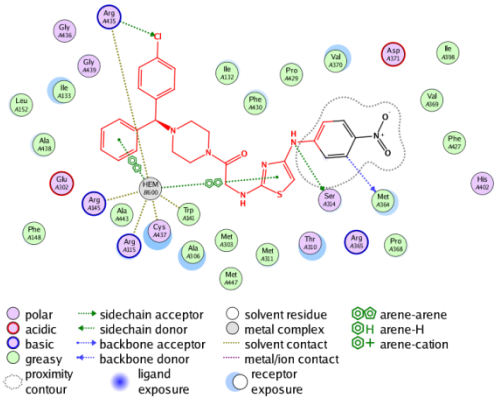
The compounds were analyzed using the program (moe 2015) by coupling compounds with protein (PDB: 3eqm)[17,18]. Compounds gave good efficacy compared to the drug compound available for treatment through a group of factors:

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 [19,20]. As shown in tables 1.

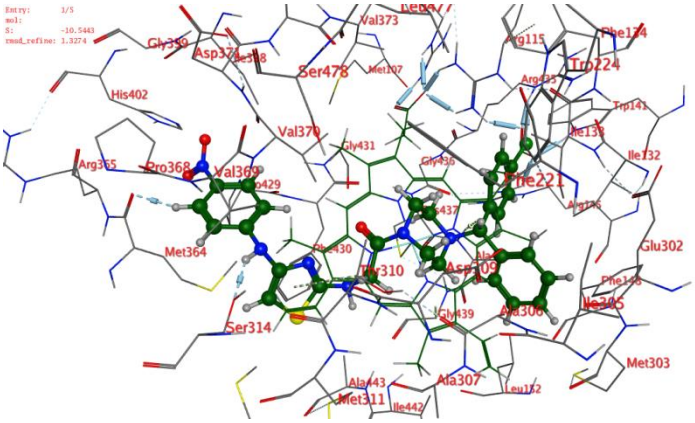
Table 1. Molecular docking of the derivatives prepared.

Compounds (Ligands)	Target protein (3eqm)								
	Binding energy	rmsd	No. of bonds	Rank	Position of interaction		Interaction	Distance (A^O)	Energy of bond (Kcal/mol)
					Ligand	Receptor			

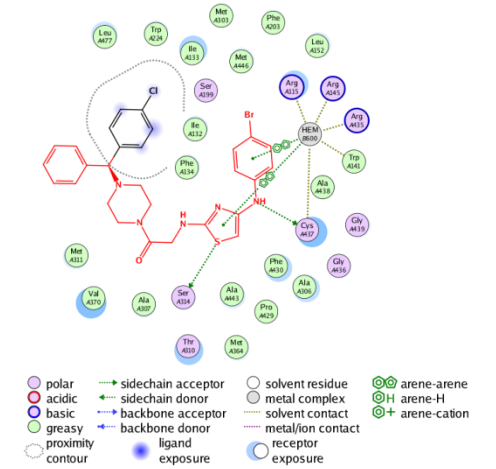
1	-7.0583	1.4284	2	2	6-ring	NH_2(ARG 115)	pi-cation	3.23	-1.0
					6-ring	5-ring(HEM 600)	pi-pi	3.09	0.0
3a	-10.5443	1.3274	5	1	N(52)	OG(SER 314)	H-donor	2.78	-0.3
					C (55)	O(MET 364)	H-donor	3.18	-1.0
					Cl(25)	NE(ARG 435)	H-acceptor	3.19	-0.8
					5-ring	5-ring(HEM 600)	pi-pi	2.76	0.0
					6-ring	5-ring(HEM 600)	pi-pi	3.51	0.0
3b	-9.8533	1.4809	4	1	S (48)	OG(SER 314)	H-donor	3.97	-.06
					N(52)	SG(CYS 437)	H-donor	3.37	-1.1
					5-ring	5-ring(HEM 600)	pi-pi	1.47	0.0
					6-ring	5-ring(HEM 600)	pi-pi	1.65	0.0
3c	-9.6838	2.2153	2	1	6-ring	N(VAL 370)	pi-H	3.62	-1.0
					5-ring	5-ring(HEM 600)	pi-pi	2.83	0.0
3d	-10.3417	1.9371	4	1	6-ring	CB(ALA 438)	pi-H	4.51	-0.8
					5-ring	5-ring(HEM 600)	pi-pi	2.82	0.0
					6-ring	5-ring(HEM 600)	pi-pi	4.00	0.0
					6-ring	5-ring(HEM 600)	pi-pi	3.30	0.0
3e	-9.6761	1.6667	5	3	N(1)	SD(MET 311)	H-donor	4.18	-1.1
					S(48)	SD(MET 311)	H-donor	3.91	-0.4
					6-ring	N(VAL 370)	pi-H	3.66	-0.6
					5-ring	5-ring(HEM 600)	pi-pi	2.38	0.0
					6-ring	5-ring(HEM 600)	pi-pi	2.26	0.0
3f	-9.6166	1.4488	5	1	S(48)	SD(MET 303)	H-donor	3.93	-0.3
					5-ring	5-ring(HEM 600)	pi-pi	3.31	0.0
					5-ring	5-ring(HEM 600)	pi-pi	3,92	0.0
					6-ring	5-ring(HEM 600)	pi-pi	1.55	0.0
					6-ring	5-ring(HEM 600)	pi-pi	1.91	0.0
3g	-9.5553	1.1650	5	1	S(48)	SD(MET 311)	H-donor	3.69	0.0
					6-ring	N(VAL 370)	pi-H	3.62	-0.8
					6-ring	N(ALA 438)	pi-H	4.19	-1.5
					5-ring	5-ring(HEM 600)	pi-pi	2.30	0.0
					6-ring	5-ring(HEM 600)	pi-pi	1.70	0.0
3h	-9.7946	1.9702	7	1	S(48)	SD(MET 303)	H-donor H-	3.86	-0.1
					O(7)	CA(ALA 307)	acceptor	3.30	-0.7
					O(65)	N(ALA 438)	H-acceptor	3.09	-1.6
					5-ring	CA(GLY 439)	pi-H	4.54	-0.6
					5-ring	5-ring(HEM 600)	pi-pi	2.81	0.0
					6-ring	5-ring(HEM 600)	pi-pi	3.39	0.0
					6-ring	5-ring(HEM 600)	pi-pi	3.35	0.0
3i	-9.6107	2.2778	6	1	6-ring	CE2(PHE 430)	pi-H	4.11	-0.6
					5-ring	5-ring(HEM 600)	pi-pi	1.41	0.0
					6-ring	5-ring(HEM 600)	pi-pi	1.60	0.0
					6-ring	5-ring(HEM 600)	pi-pi	2.62	0.0
					6-ring	5-ring(HEM 600) 5-	pi-pi	3.84	0.0
					6-ring	ring(HEM 600)	pi-pi	1.61	0.0
3j	-9.6135	1.4870	8	1	S(48)	SD(MET 311)	H-donor	3.62	0.1
					S(48)	SD(MET 447)	H-donor	3.84	-0.3
					6-ring	N(VAL 370) N(ALA	pi-H	3.73	-1.8
					6-ring	438)	pi-H	3.74	-1.5
					5-ring	5-ring(HEM 600)	pi-pi	2.85	0.0
					6-ring	5-ring(HEM 600)	pi-pi	3.45	0.0
					6-ring	5-ring(HEM 600) 5-	pi-pi	2.74	0.0
					6-ring	ring(HEM 600)	pi-pi	2.41	0.0



(3**a**)



(3a)



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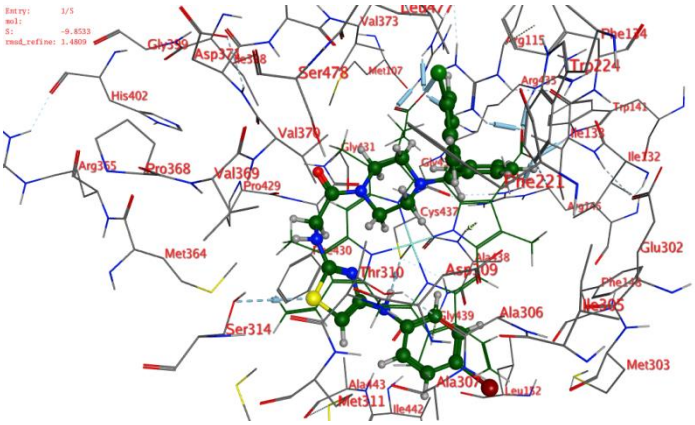

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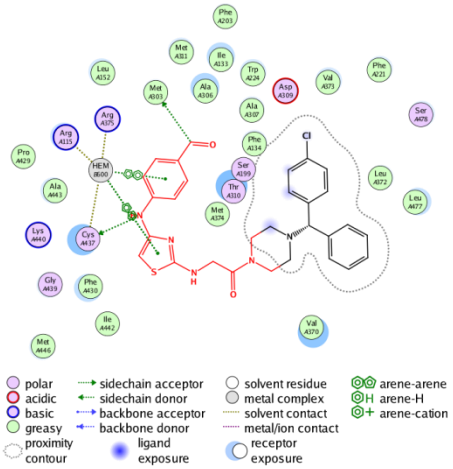

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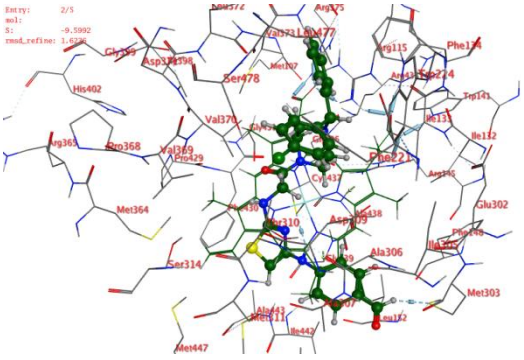

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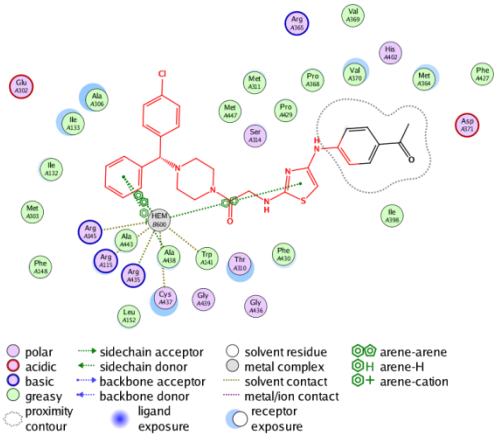

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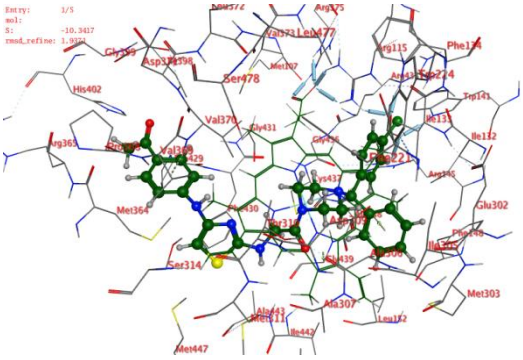

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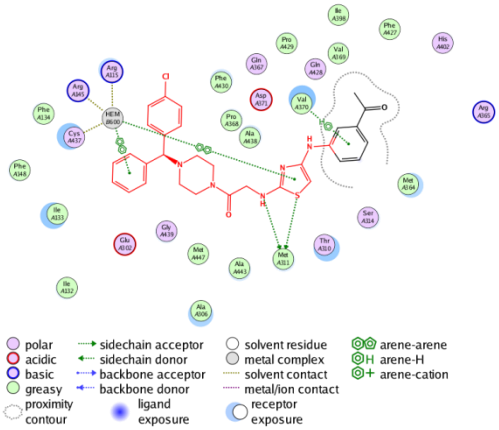

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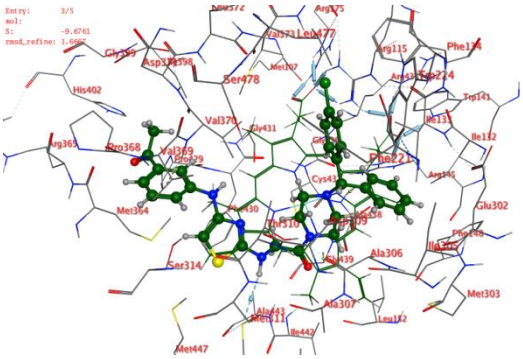

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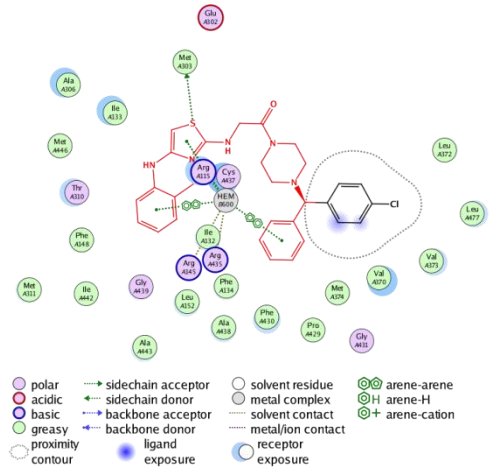

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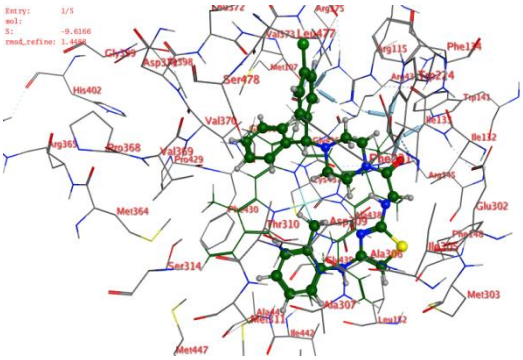

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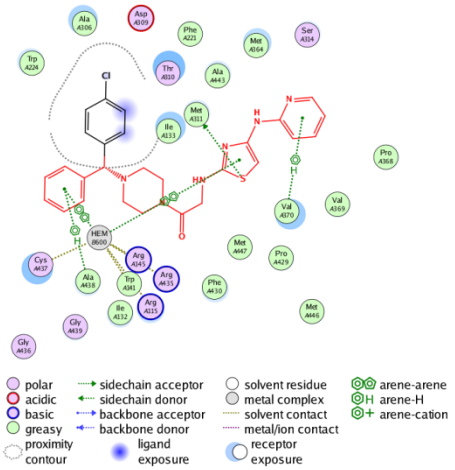
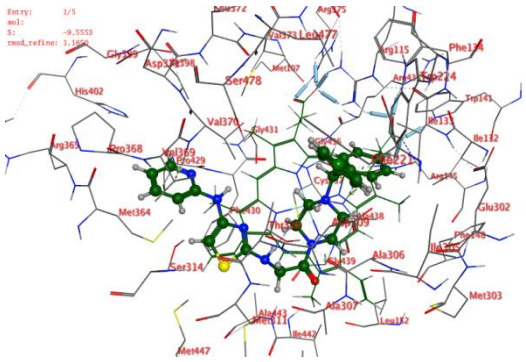


(3g)



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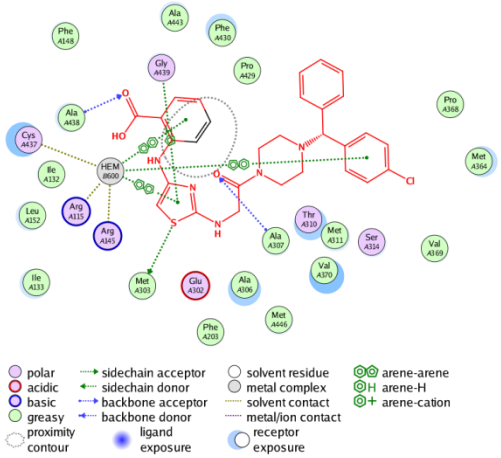

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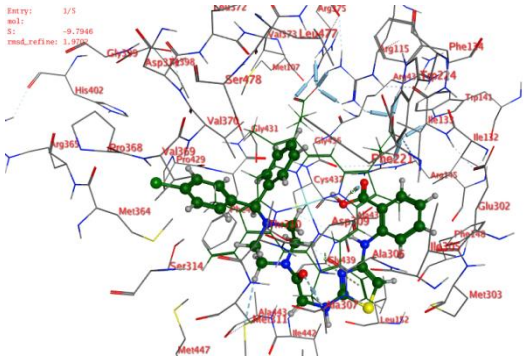

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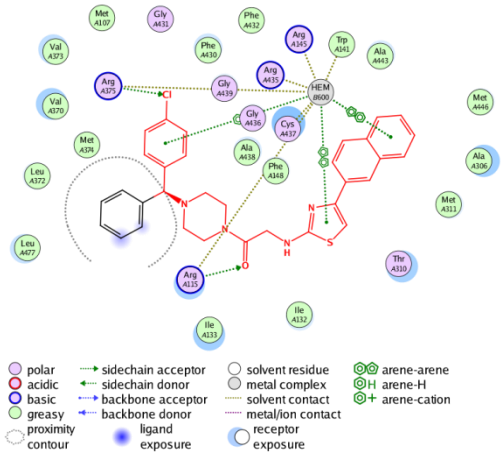
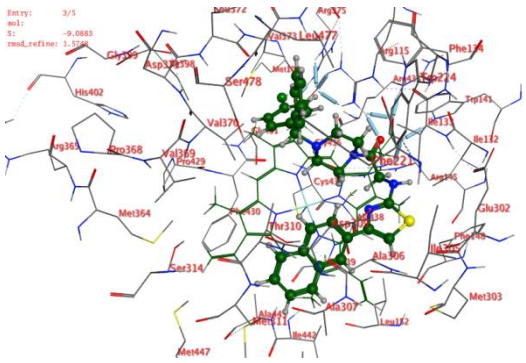
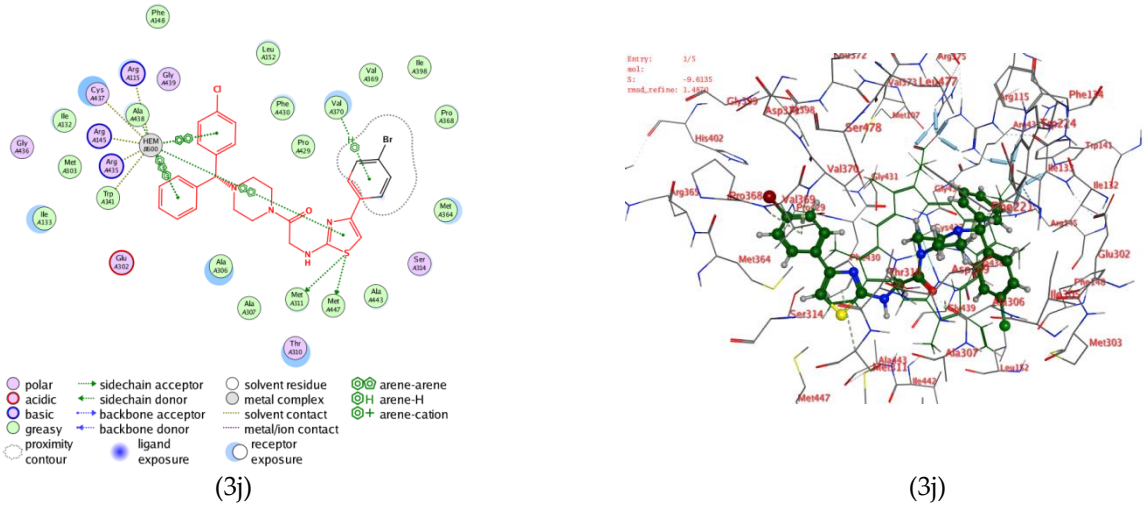


(3i)



(3i)

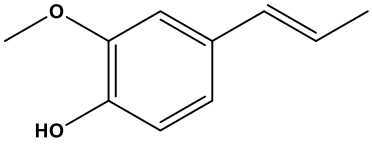


(3j) (3j)

Figure 34. A 2D and 3D shapes showing the binding sites of the ligand (3a–3j) with the protein (PDB:3EQM).

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 [21]. 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 [22].



Scheme . Structure of isoeugenol.

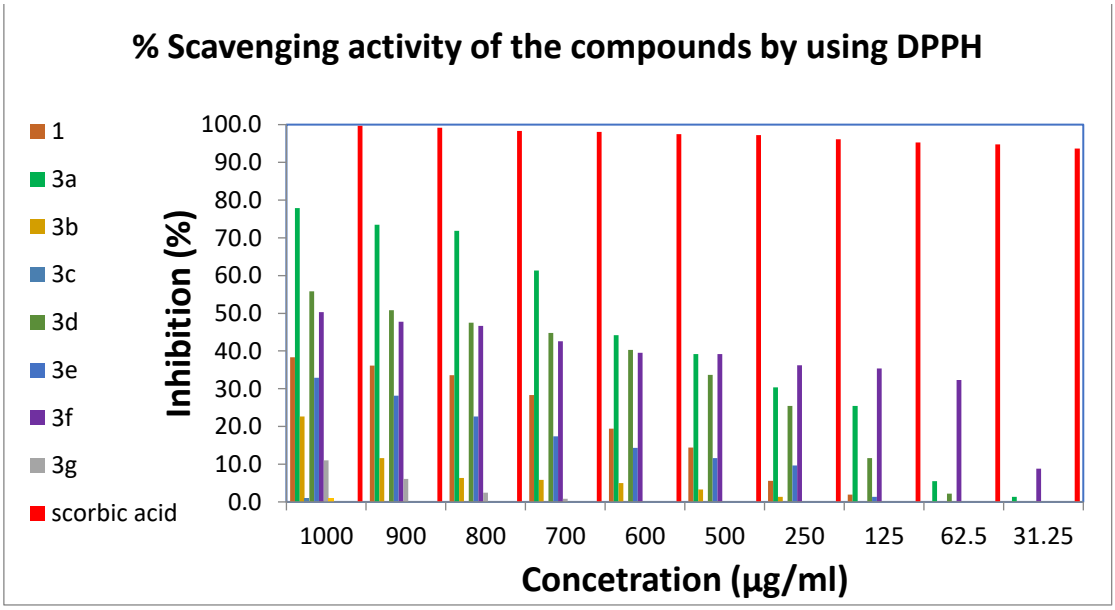


Figure 35. shows the relationship between the percentage and concentration of the effect of the derivative (1-3f) on DPPH.

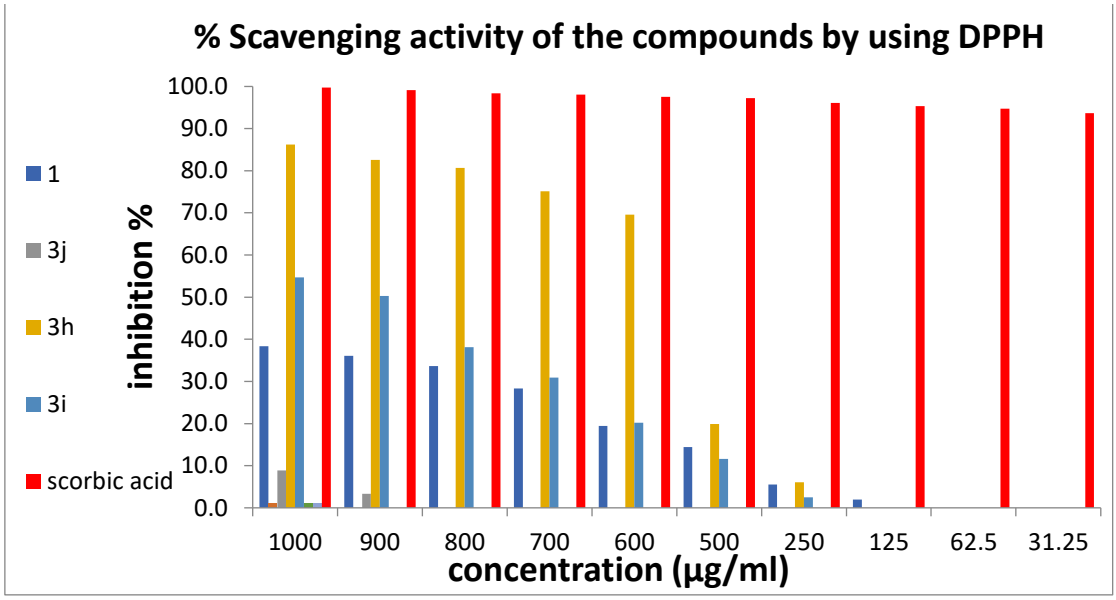


Figure 36. shows the relationship between the percentage and concentration of the effect of the derivative 3(i–j) on DPPH.

4. Conclusion

In this study we are reported synthesis of many cetirizine Impurity A derivatives The work included preparation of thaiazol derivatives. 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 derivatives were studied as antioxidants, and it was found that a good number of some prepared derivatives are highly effective.

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