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# Synthesis, characterization, antioxidant and quantum chemical calculations of some new thiophene, diazepine and pyrimidine derivatives containing sulfamoyl moiety

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**Abstract**
Novel ketene *N*, *S*-acetal 4 was readily prepared by the reaction of 3-oxo-butanamide 1with isothiocyanate sulfonamide 2 in the presence of potassium hydroxide, followed by alkylation of the non-isolated salt with methyl iodide. Also, Treatment of non- isolated 3 with dilute HCl afforded the corresponding thiocarbamoyl derivative 5. The reaction of compound 4 with various bifunctional nucleophilic reagent such as thiourea, hydrazine, ethylenediamine and *o*-phenylenediamine to produce pyrimidine, pyrazole, diazepine and benzodiazepine derivatives 6, 7, 8 and 9, respectively. The non-isolated intermediate 3 was reacted with $\alpha$ -halo carbonyl, such as ethyl chloroacetate, p-methoxy-phencyl bromide, chloroacetonitrile and chloro arylacetamide afforded the corresponding thiophene derivatives 10, 12, 14 and 17a,b. Finally, compound 3 reacted with chloroacetyl chloride to give thiozolidinone derivative 19. These compounds have been characterized using IR, $^1$H NMR and mass spectra. Some of the new synthesized compounds were evaluated as antioxidant agents by phosphomolybdenum method. The results indicated that the derivative 4 exhibited more potency than standard ascorbic acid. Quantum chemical calculations used for predict the stability and reactivity of some new synthesized compounds through energy gap between $E_{HOMO}$ and $E_{LUMO}$. The quantum chemical calculation gives good approval according to experimental characterization of some new compounds as IR, $^1$H NMR and mass spectra.

**Keywords:** Butanamide, isothiocyanate sulfonamide, ketene N, S-acetal**,** antioxidant

## 1. Introduction
Sulfonamides were the first drugs largely employed and systematically used as preventive and chemotherapeutic agents against various diseases [1]. Sulfonamide derivatives have biological activities including antibacterial [2], carbonic anhydrase inhibitor [3], antifungal [4], anti-inflammatory [5], antiprotozoal [6], nonpeptidic vasopressin receptor antagonists [7] and translation initiation inhibitors [8]. They are also effective for the treatment of urinary, intestine, and ophthalmic infections, scalds, ulcerative colitis [9], rheumatoid arthritis [10] and obesity [11]. More recently, sulfonamides are used as an anticancer agent [12], as the antiviral HIV protease inhibitor amprenavir [13], and in Alzheimer's disease [14]. Also, thiophenes have been reported to possess interesting biological and pharmacological activities where several derivatives are used as antibacterial [15-17], anticancer [18, 19], anti-inflammatory [20] and antiviral agents [21]. In addition, pyrimidine derivatives have been reported to exhibit important biological activities [22], antioxidant [23, 24], anti-inflammatory [22], antitubercular [25-28], antibacterial activity [29-31]. Reactive oxygen species (ROS), such as superoxide radicals, hydroxyl (OH) radicals and peroxyl radicals, are natural by products of the normal metabolism of oxygen in living organisms with important roles in cell signaling. However, excessive amounts of ROS may be a primary cause of biomolecular oxidation and may result in significant damage to cell structure, DNA, protein, and lipid contributing to various diseases, such as cancer, stroke, diabetes and degenerative processes associated with ageing. Minimizing oxidative damage may be an important approach to the primary prevention or treatment of these diseases. Antioxidants are important inhibitors of lipid peroxidation not only for food protection but also as a defense mechanism of living cells against oxidative damage since they may stop the free-radical formation, or interrupt an oxidizing chain reaction [32-35].

In continuation of our work [36-41], it seemed of interest to design and synthesize a novel series of thiophene and pyrimidine derivatives bearing antioxidant active and sulfonamide moiety. To overcome this, investigates aimed at the synthesis of new antioxidants with better properties from a pharmacological point of view have been performed. Also, calculations are performed by using restricted Hartree-Fock level using chemoffice 2015 to get molecular orbital by Huckel calculation. Semi-empirical methods are involved in the evaluation of organic molecules by correlating analysis experimental data with quantum chemical properties such as energy of the highest molecular orbital ($E_{HOMO}$), the energy of the lowest unoccupied molecular orbital ($E_{LUMO}$) and energy gap ($E_{LUMO} - E_{HOMO}$) to predict the reactivity or the stability of tested compounds [42, 43].

## 2. Materials and Methods

### 2.1. Materials

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, $cm^{-1}$). The $^1H$ NMR and $^{13}C$ NMR spectra were recorded in DMSO-d6 at 200, 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analysis was carried out by the Micro analytical Research Center, Faculty of Science, Cairo University. The starting materials were obtained from Sigma Aldrich and El-Gomhouria for Trading Chemicals and Medical Appliances **(**Egypt**).**

### 2.2. Methods

#### 2.2.1. Synthesis

***2-(methylthio)-((4-sulfamoyl phenyl) amino) methylene-3-oxo-N-(pyrimidin-2-yl)- butanamide (4)***

To a cold suspension of finally divided KOH (0.01 mole) in dry dimethylformamide (20 mL), butanamide 1 (0.01 mole) was added. After stirring for 30 min., isothiocyanate sulfonamide 2 (0.01 mole) was added to the resulting mixture, stirring was continued for 5 h., then cooled again to 0ºC, treated with methyl iodide (0.01 mole), and the stirring was continued at room temperature for 6 h. The reaction mixture was poured into ice cold water. The resulting precipitate was filtered off dried then recrystallized from ethanol to give 4. Orange crystals, yield (75%), m.p 192-194ºC, IR (KBr) ν $cm^{-1}$; 3362, 3255, 3140 (NH, $NH_2$), 1688, 1655 (2C = O), 1327, 1158($SO_2$). $^1H$ NMR (DMSO-$d_6$), δ ppm = 2.24 (s, 3H, $CH_3$), 2.71 (s, 3H, $CH_3$), 7.12–7.99 (m, 9H, Ar-H and $NH_2$), 10.18 (s, 1H, NH), 12.82 (s, 1H, NH). Anal. calcd for $C_{16}H_{17}N_5O_4S_2$ (407.47); C,47.16, H, 4.21; N,17.19; S, 15.74; found; C,47.20; H, 4.31; N,17.40; S,15.52%.

***2-mercapto ((4-sulfamoyl phenyl) amino) methylene-3-oxo-N (pyrimidin-2-yl)- butanamide (5)***

To a solution of potassium hydroxide (0.01 mole) in dimethylformamide (15 mL), 3-oxo-butanamide 1 (0.01 mole) was added. After stirring for 30 min., sulfonamide isothiocyanate 2 (0.01 mole) was added to the resulting mixture. Stirring was continued for 6 h, and then poured into iced water containing a few drops of hydrochloric acid. The solid product that formed was filtered off, washed with water, dried and re-crystallized from ethanol to afford compound **5**.Yellow crystals, yield (65%) m.p 130-132ºC IR (KBr) ν $cm^{-1}$; 3380, 3275, 3197 (2NH/$NH_2$), 1688, 1655 (2C=O), 1315, 1155($SO_2$). $^1H$ NMR (DMOS-$d_6$) ; δ ppm = 2.49 (s, 3H, $CH_3$), 7.08 (s, 2H, $NH_2$) , 6.91 (t, 1H, CH-pyrimidine), 7.11-7.98 (m, 4H, Ar-H), 8.55 (d, 2H, CH-pyrimidine), 9.58 (s,1H, NH), 10.29 (s, 1H, NH), 13.19 (s, 1H, SH). Anal. Calcd. for $C_{15}H_{15}N_5O_4S_2$ (393.44): C, 45.79 ; H, 3.84 ; N, 17.80 ; S, 16.30. Found: C, 45.89, H, 3.92; N, 17.92; S, 16.41%.

***4-methyl-N-(pyrimidin-2-yl)-6-((4-sulfamoyl phenyl) amino)-2-thioxo- 1,2-dihydro pyrimidine-5-carboxamide (6)***

To a solution of compound 4 (0.01 mole) in ethanol (30 mL) containing triethylamine (0.5 mL) was treated with thiourea (0.01 mole). The reaction mixture was heated under reflux for 8 hr. The reaction mixture was poured into ice-cold water. The solid product that formed was filtered off, dried and recrystallized from methanol to give 6. pale yellow, yield (70%) m.p. 190-192 ºC IR (KBr) ν $cm^{-1}$; 3462, 3354, 3226 (2NH, $NH_2$) 1655 (C=O), 1320, 1153 ($SO_2$). $^1H$ NMR (DMSO- $d_6$) δ ppm = 1.25 (s, 3H, $CH_3$), 7.10-7.96 (m, 9H, Ar-H and $NH_2$), 10.53 (s, 1H, NH), 11.20 (br, 1H,NH), 13.17 (s, 1H, NH). Anal. Calcd for $C_{16}H_{15}N_7O_3S_2$ (417.47); C, 46.03; H, 3.62; N, 23.49; S, 15.36. Found: C, 46.31, H, 3.71; N, 23.58, S, 15.43%.

***3-methyl-N-(pyrimidine-2-yl)-5-((4-sulfamoyl phenyl) amino)-1-H-pyrazole-4-carbox-amide (7)***

A mixture of compound 4 (0.01 mole), hydrazine hydrate (0.01 mole) in ethanol (30 mL) was heated under reflux for 12 h. The reaction was concentrated and the obtained product was collected and recrystallized from ethanol to give **7**. Brown crystals, yield (55%), m.p.120-122 ºC, IR (KBr) ν $cm^{-1}$; 3477, 3383, 3242, 3165 (3NH, $NH_2$), 1645 (C=O), 1312, 1150 ($SO_2$). $^1H$ NMR (DMSO-$d_6$), δ ppm =2.25(s, 3H, $CH_3$), 6.78-7.48 (m, 9H, Ar–H and $NH_2$), 9.41 (s, 1H, NH), 10.22 (br, 1H, NH), 11.30 (s, 1H, NH). MS (EI, m/z (%)): 373 ($M^+$, 1.22), 343 (1.39), 254 (5.59), 126 (2.31), 108 (31.76), 92 (40), 79 (16.16), 59 (100 %). Anal. calcd for $C_{15}H_{15}N_7O_3S$ (373.39); C, 48.25; H, 4.05; N, 26.26; S, 8.59. Found: C, 48.39; H, 4.16; N, 26.42; S, 8.68%.

***5-methyl-N-(pyrimidin-2-yl)-7-((4-sulfamoylphenyl)amino)-2,3-dihydro-1H-1,4-diazepine-6-carboxamide(8)***

A solution of *N, S*-keten acetal 4 (0.01 mole) and ethylenediamine (0.01 mole) in methanol (30 mL) containing triethylamine was refluxed for 4 h. The reaction was kept overnight in ice bath. The solid formed was filtered off and recrystallized from ethanol to give 8. This compound was obtained as pale yellow crystals from ethanol (yield 70%), m.p. 214 -216 ºC; IR (KBr) *ν* $cm^{-1}$; 3460, 3370, 3280, 3160 (3NH, $NH_2$), 1656 (C= O), 1360, 1155 ($SO_2$) . $^1H$ NMR (DMSO-$d_6$) δ ppm= 1.72 (q, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$), 3.41(t, 2H, $CH_2$), 5.68 (s, 2H, $NH_2$), 6.63(t, 1H,CH-pyrimidine),7.29 –7.89 (m, 5H, Ar-H and NH), 8.62 (d, 2H, CH-pyrimidine), 11.22( br, 1H, NH), 13.17( s, 1H, NH). Anal. calcd. for $C_{17}H_{19}N_7O_3S$ (401.44): C, 50.86; H, 4.77; N, 24.42; S, 7.99. Found: C, 50.90; H, 4.81; N, 24.50; S, 7.85%.

***4-methyl-N-(pyrimidin-2-yl)-2-((4-sulfamoylphenyl)amino)-1H-benzo[b][1,4]-diazepine-3-carboxamide (9)***

A mixture of compound 4 (0.01 mole) and *o*-phenylenediamine (0.01 mole) in DMF (20 mL) containing triethylamine (0.5 mL). The reaction mixture was heated under reflux for 6 h. until the evolution of methylthioal was ceased. The solid product that formed was filtered off, dried well and re-crystallized from ethanol to give 9. Brown crystal, yield (65%), m. p 210-212 ºC. IR (KBr) *ν* $cm^{-1}$; 3468, 3375, 3270, 3135(2NH, $NH_2$), 1642 (C=O), 1332, 1144 ($SO_2$). $^1H$ NMR (DMSO-d6) δ ppm=1.25 (s, 3H, $CH_3$); 6.93 (t, 1H, CH-

pyrimidine), 6.79 (s, 2H, $NH_2$), 7.20–7.71 (m, 9H, Ar-H and NH), 8.25 (d, 2H, pyrimidine-H), 8.60 (s, 1H, NH), 9.31 (br, 1H, NH). MS (EI, m/z (%)): 449 (M+, 1.42), 367 (5.10), 264 (13.17), 198 (4.97), 1.34 (9.7), 94 (29), 79 (52.70), 57.10 (100). Anal. calcd. for $C_{21}H_{19}N_7O_3S$ (449.49); C, 56.11; H, 4.26 ; N, 21.81; S, 7.13. Found: C, 56.20; H, 4.31; N, 21.98; S, 7.21 %.

***Synthesis of compounds 10 and 12***

**General procedure**:

To a solution 3-oxo-*N*-(pyrimidin-2-yl) butanamide (1) (0.1 mole) in DMF (20 mL). The mixture was stirred for 30 min., and then isothiocyanate sulfonamide 2 (0.01 mole) was added. Stirring was continued for 6 h. and then (ethyl chloroacetate or chloroacetonitrile) was added dropwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for 12 h., and then acidified with HCl. The precipitated products that obtained were filtered, dried and recrystallized from the proper solvent to give thiophene derivatives 10 and 12.

***Ethyl 3-methyl-4-(pyrimidin-2-ylcarbamoyl)-5-((sulfamoyl phenyl) amino) thiophene-2-carboxylate (10)***

This compound was obtained as yellow crystals from ethanol (yield 70%), m.p 184 -186 °C; IR (KBr) ν $cm^{-1}$; 3462, 3380, 3355, 3254 (2NH, $NH_2$), 1725, 1640 (2C=O), 1331, 1157 ($SO_2$). $^1$H NMR (DMSO–d6) δ ppm =1.19 (t, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 4.02 (q, 2H, $CH_2$) , 6.91 (t, 1H, CH-pyrimidine), 7.24 (s, 2H, $NH_2$), 7.29-7.85 (m, 4H, Ar-H), 8.48 (d, 2H, CH-pyrimidine), 10.42 (s, 1H, NH); 11.89 (br, 1H, NH). $^{13}$C NMR (ppm) 14.46 ($CH_3$), 20.87 ($CH_3$), 61.81 ($CH_2$), 113.17, 119.73, 122.98, 123.33, 124.28, 126.74, 127.13, 129.02, 129.79, 137.51, 145.10, 158.70 (CO), 171.89 (CO). MS (EI, m/z (%)): 461 (M+, 1.29), 429 (0.40), 253(3.27), 214 (6.93), 156 (17.07), 134 (19.25) , 92 (100%). Anal calcd. for $C_{19}H_{19}N_5O_5S_2$ (461.51); C,49.45; H, 4.15; N, 15.17; S, 13.90. Found: C, 49.52; H, 5, 24; N, 15.32, S, 14.02%.

***5-cyano-4-methyl-N-(pyrimidin-2-yl)-2-((4-Sulfamoyl phenyl) amino) thiophene -3-carboxamide (12).***

This compound was obtained as brown crystals from dioxane yield (60%), m.p. 169-171 °C; IR (KBr) ν $cm^{-1}$; 3455, 3331, 3228, 3110 (2NH, $NH_2$), 2204 (CN), 1635 (C=O), 1330, 1157($SO_2$). $^1$H NMR (DMSO-d6), δ ppm =1.95 (s, 3H, $CH_3$) ,6.97-8.03 (m, 9H, Ar-H and $NH_2$), 10.51 (s, 1H, NH), 11.13 (br, 1H, NH), MS (EI, m/z (%) ): 414 ($M^+$, 6.0%), 399 (0.57), 306 (1.11), 172 (13.17), 134 (2.40), 108 (73.85), 92 (100%). Anal. calcs. for $C_{17}H_{14}N_6O_3S_2$ (414.48); C, 49.26; H, 3.40; N, 20.28; S, 15.47. Found: C, 49.42; H, 3.50; N, 20.62; S, 15.50%.

***5-(4-methoxybenzoyl)-4-methyl-N-(pyrimidin-2-yl)-2-((4-sulfamoyl phenyl)amino)-thiophene-3-carboxamide (14).***

To a suspension of potassium hydroxide (0.01 mole) in DMF (20 mL), compound 1 was added (0.01 mole) and followed by isothiocyante sulfonamide 2 (0.01 mole). The mixture was stirred for 6 h. at room temperature and treated with the *p*-methoxy phenacyl bromide (0.01 mole), stirring was continued for 6h the reaction the mixture was poured onto ice-cold water. Acidify by dilute HCl, the precipitated product that obtained was filtered and recrystallized from ethanol to give 14. Yield (55%), m.p 172-174 °C; IR (KBr) *ν* $cm^{-1}$, 3410, 3370, 3265(2NH, $NH_2$), 1668, 1659(2C=O), 1339, 1152($SO_2$). $^1$H NMR (DMSO-d6), δ ppm = 2.73(s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 6.63 (t, 1H, CH-pyrimidine), 6.78 (s, 2H, $NH_2$), 7.02–7.95 (m, 9H, Ar-H and NH), 8.64 (d, 2H, CH-pyrimidine), 11.41(br, 1H, NH). Anal. Calcd. for $C_{24}H_{21}N_5O_5S_2$ (523.58): C, 55.05, H 4.04; N, 13.38; S, 12.25. Found: C, 55.13; H, 4.16; N, 13.50; S, 12.22%.

***Synthesis of compounds 17a, b*. General procedure**:

To a stirred suspension of finely powdered potassium hydroxide (0.01 mole) in dry DMF (15 mL) cooled to 0 °C compound 1 (0.01 mole) was added followed by sulfonamide isothiocyanate 2 (0.01 mole). The reaction mixture was stirred at room temperature for 6 h., and then cooled again to 0 °C. Treated with 2-chloro-*N*-[3-methyl-pyrazol-3-yl] acetamide (16a), or 2-chloro-*N*-[4-chloro-phenyl]acetamide (16b), (0.01 mole) and stirred at room temperature for on additional 6 h. It was poured into ice-water; the resulting precipitate was filtered off, dried and recrystallized from the proper solvent to give 17a, b.

***3-methyl-$N^2$-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-$N^4$-(pyrimidin-2-yl)-5-((4-sulfamoyl phenyl) amino) thiophene-2, 4-dicarboxamide (17 a)***

Yellow powder, yield (75%), m.p. 194-196 °C IR (KBr) ν $cm^{-1}$; 3465, 3375, 3250, 3135 (3NH, $NH_2$), 2950 (CH aliph.), 1668, 1653 (2C=O), 1320, 1157($SO_2$). $^1$H NMR (DMSO –d6) δ ppm = 2.20 (s, 3H, $CH_3$), 2, 49 (s, 3H, $CH_3$), 6.22 (s, H, CH-pyrozole), 7.29-7.83 (m, 8H, Ar-H and $NH_2$) 8.78 (br, 1H, NH), 10.41 (hump, 2H, 2NH). Anal calcd. for $C_{27}H_{24}N_8O_4S_2$ (588.66); C, 55.09; H, 4.11; N, 19.04; S, 10.89 found: C,55.18; 4.25; N 19.60; S, 10.97.

***$N^2$-(4-chlorophenyl)-3-methyl-$N^4$-(pyrimidin-2-yl)-5-((4-sulfamoy l- phenyl)amino) thiophene-2,4-dicarboxamide (17b).***

This compound was, obtained as yellow crystals from ethanol, yield (65%) m.p 156-158 °C, IR(KBr) *ν* $cm^{-1}$; 3466, 3331, 3228, 3110 (3NH, $NH_2$), 1680, 1651 (2C=O), 1335, 1155($SO_2$). $^1$H NMR (DMSO–d6), $\delta$ ppm = 2.57 (s, 3H, $CH_3$), 7.20-7.98 (m, 13H, Ar–H and $NH_2$), 10.21 (s, 1H, NH), 10.47 (s, 1H, NH), 13.17(s, 1H, NH). Anal. calcd. for $C_{23}H_{19}Cl\ N_6O_4S_2$. (542.03): C, 50.96; H, 3.53; N, 15.50; S, 11.81. Found: C, 50.98; H, 3.65; Cl, 6.62; N, 15.61; S, 11.92%.

***3-oxo-2-(5-oxo-3-(4-sulfamoyl phenyl) thiazolidin-2-ylidene)-N-(pyrimidin-2-yl) butanamide(19)***

To a solution 3-oxo-*N*-(pyrimidin-2-yl)butanamide (1) (0.1 mole) in DMF (20 mL). The mixture was stirred for 30 min., and then isothiocyanate sulfonamide 2 (0.01 mole) was added. Stirring was continued for 6 h., and then chloroacetyl chloride was added dropwise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for addition 12 h. and then acidified with HCl. The precipitated products that obtained were filtered, dried and recrystallized from the ethanol to give thiazole derivative 19. Yield (65%), m.p 235-337 °C; IR (KBr) ν $cm^{-1}$, 3450, 3395, 3261 (NH, $NH_2$), 1742, 1685, 1655 (3C=O), 1323, 1154($SO_2$). $^1$H NMR (DMSO-d6) δ ppm = 2.56 (s, 3H, $CH_3$), 4.19 (s, 2H, $CH_2$), 6.85 (t, 1H, CH-pyrimidine), 7.29 (s, 2H, $NH_2$), 7.45 –7.95 (m, 4H, Ar-H) 8.62 (d, 2H,CH-pyrimidine), 10.31 (s, 1H, NH). Anal. calcd. for: $C_{17}H_{15}N_5O_5S_2$ (433.48): C, 47.10; H, 3.49; N, 16.16; S, 14.79. Found: C, 47.32; H, 3.51; N, 16.30; S, 14.80%.

**2.2.2. Evaluation of antioxidant activity**

The antioxidant activity of tested synthesized compounds derivatives was evaluated by the phosphomolybdenum method according to Prieto et *al*., (1999). This method is

based on the reduction of Mo (VI) to Mo (V) by the tested compounds followed by formation of a green to blue phosphate/Mo(V) complex at acid pH. An aliquot of sample solution (100 µL, 2 mM in DMSO) is mixed with the reagent solution (1 mL, 0.6 M sulphuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The samples are incubated in a water bath at 95 °C for 90 minutes. Samples are cooled to room temperature and the absorbance was measured at 695 nm. The antioxidant activity was expressed relative to the antioxidant activity of same concentration of ascorbic acid as a standard.

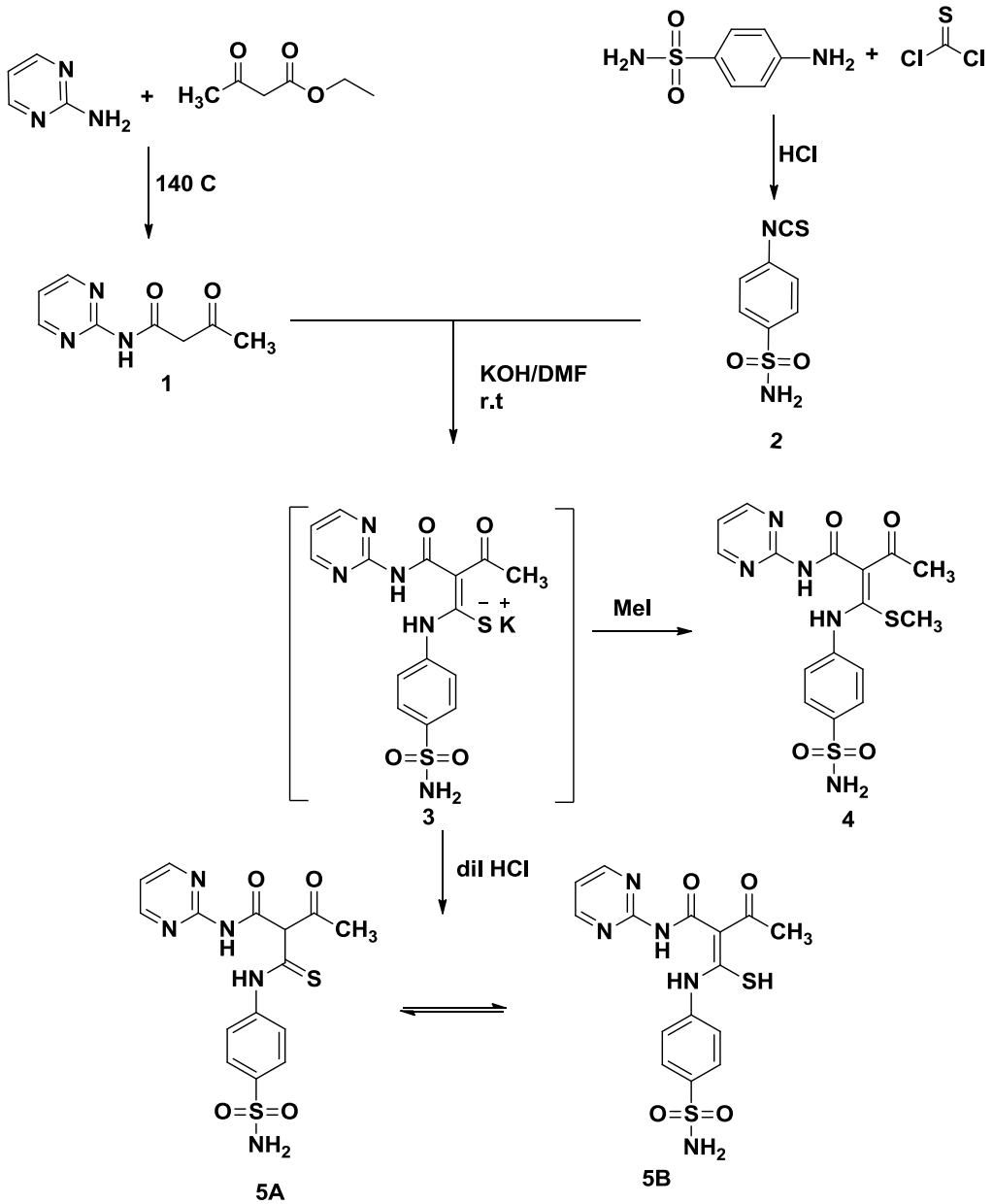
### 2.2.3. Quantum Chemical Calculations

Quantum chemical analysis was performed using chemoffice 2015 to calculate the molecular orbital which useful in reactivity arrangement of synthesized compounds. The following quantum chemical indices were taken into consideration: the energy of the highest occupied molecular orbital ($E_{HOMO}$), the energy of the Lowest unoccupied molecular orbital ($E_{LUMO}$), energy band gap, $\Delta E = E_{LUMO}-E_{HOMO}$.

## 3. Results and Discussion

The starting material, 3-oxo-*N*-(pyrimidin-2-yl) butanamide (**1**), was prepared by the solvent free reaction of 2-aminopyrimidine with ethyl acetoacetate, according to a literature procedure [44]. Also, isothiocyanate sulfonamide (**2**) [45] was synthesized by treatment of sulfonamide with thiophosgene in the presence of dilute hydrochloric acid at room temperature, (Scheme 1). The base catalyzed reaction of active compound (1) with isothiocyanate sulfonamide (2) in dry DMF at room temperature yields the non-isolated potassium salt 3, (Scheme 1).

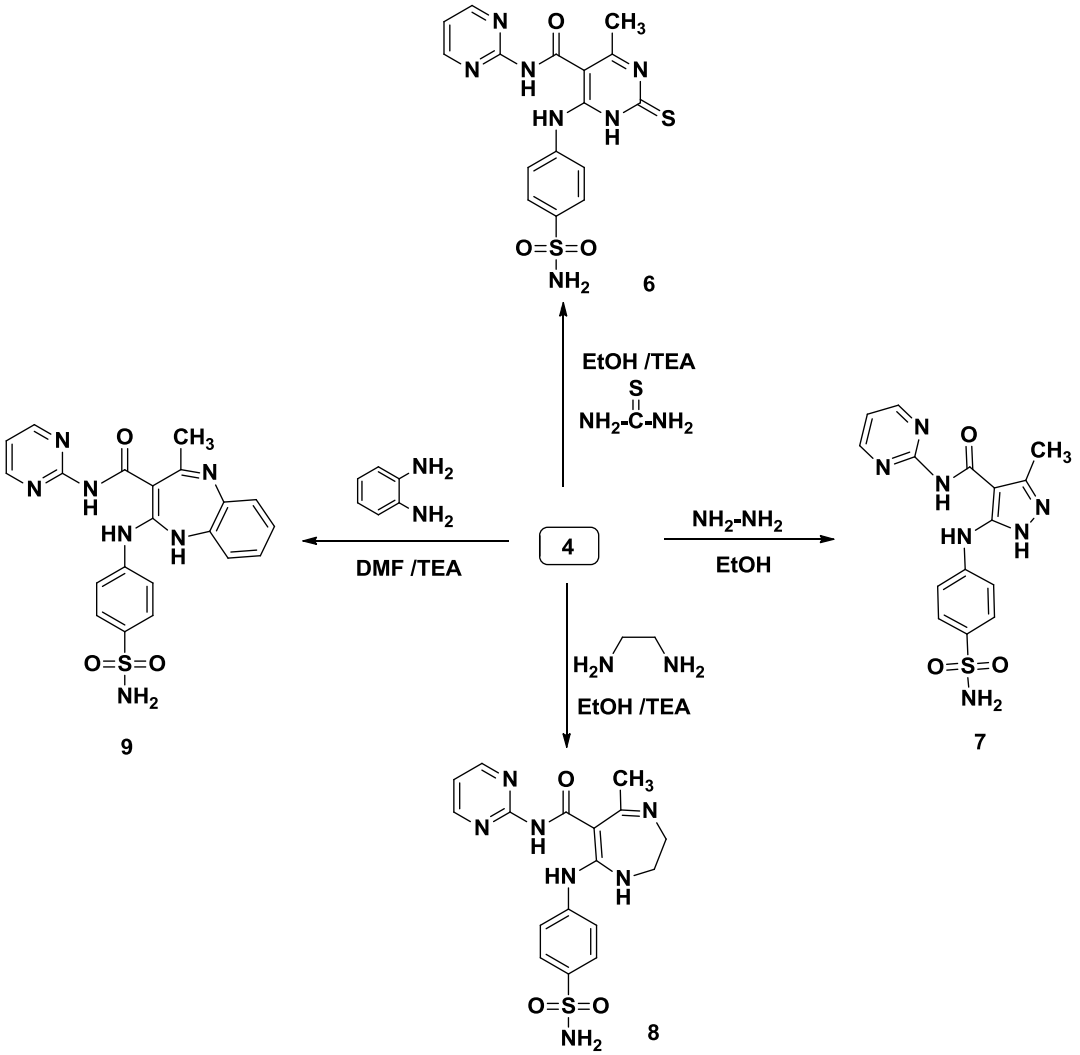
The non-isolated potassium salt 3 was methylated by treatment with methyl iodide to afford the novel ketene *N*, *S*-acetal 4. The structure of compound 4 was elucidated from its spectroscopic and analytical date. Treatment of non-isolated intermediate 3 with dilute HCl afforded the corresponding thiocarbamoyl derivative (5). The structure of 5 was confirmed on the basis of its elemental analysis and spectral data. This can exit in two tautomeric thione, thiol forms (5A and 5B) [46]. The thiol form (5B) was verified by its $^1$H NMR spectrum which display a singlet signal at 13.4 ppm due to SH proton, besides the other expected signals.




**Scheme 1**: Synthesis of ketene *N*, *S*-acetal **4** and thiocarbamoyl derivative **5**

Compound 4 was utilized as a starting material for preparation of wide variety of heterocyclic compound by reaction with bifunctional nucleophilic reagents. Refluxing of compound 4 with thiourea in DMF containing triethyl amine afforded pyrimidine derivative 6. The structure of compound 6 was elucidated from its spectroscopic and analytical data. The IR spectrum of 6 displayed stretching bands at 4362, 3354, 3226, for $NH_2$ and three NH groups, while carbonyl group absorption appeared at 1655cm$^{-1}$. Also, $^1$H NMR spectrum of this compound 6 exhibited a singlet signal at δ 1.25 ppm for methyl protons, signals at 10.53, 11.20, and 13.17due to three NH protons, and an aromatic multiplet and amino group in the region δ 7.10-7.96 ppm.

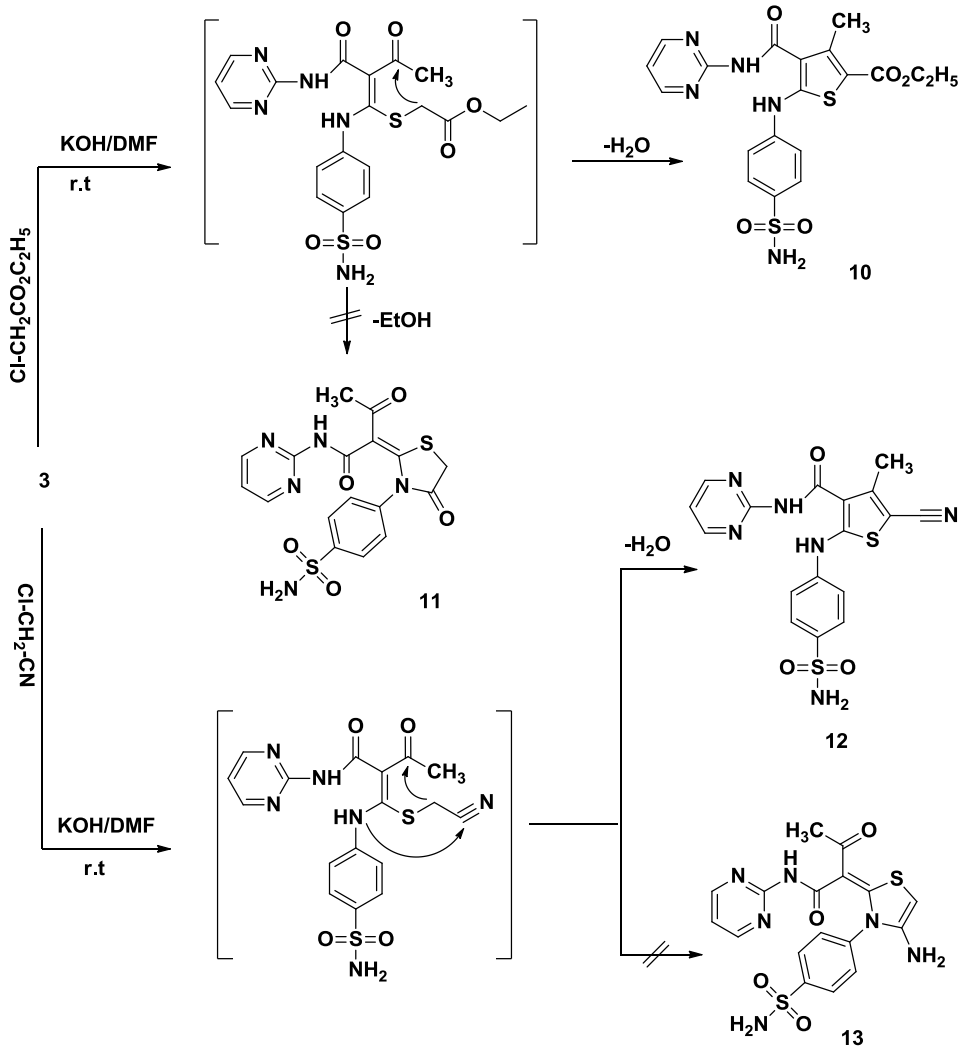
Compound 4 on treatment with hydrazine hydrate in refluxing ethanol, afforded the corresponding pyrazole derivative 7, Scheme (2). The chemical structure of compound 7 was established on the basis of its elemental analysis and spectral data. The IR spectrum of compound **7** showed absorption bands at 3383, 3318, 3242, 3165 and 1627 due to three NH, $NH_2$ and amidic carbonyl functions. It's $^1$H NMR showed singlet signal at $\delta$ 2.34 due to $CH_3$ protons, 7.19-7.97 ppm corresponding to the aromatic protons together with $NH_2$ proton and the presence of three singlet signals at 10.51, 10.96 and 13.17 ppm due to three NH protons. Similarly, *N*,*S*-ketene acetal 4 condensed with ethylene diamine in methanol in presence of triethyl amine afforded 1,4-diazepine derivative 8. The structure of compound 8 was elucidated from its spectroscopic and analytical data. On the other hand, benzodiazepine derivative 9 was synthesized by the condensation of *o*-phenylenediamine and *N*,*S*-ketene acetal 4 in refluxing dimethylformamide containing triethylamine. Establishing compound 9 based on spectral data. Its infrared spectrum exhibited absorption bands at 3375, 3270, 3135 and 1642 cm$^{-1}$ due to NH, $NH_2$ and C=O groups, respectively. The $^1$H NMR spectrum showed a singlet signal at $\delta$ ppm 1.25 for $CH_3$ and the presence of two singlet signals at 8.90 and 9.31 ppm due to two NH protons, beside the expected multiplet signal for aromatic protons together with NH and $NH_2$ groups in the region 6.55-8.25 ppm. The mass spectrum of compound 9 was compatible with molecular formula $C_{21}H_{19}N_7O_3S$. The base peak was found in the spectrum at m/z = 57 (100%) and molecular ion peak at m/z = 449 ($M^+$, 1.42), (Scheme 2).




**Scheme 2**: Synthesis of pyrimidine **6**, pyrazole **7** and diazepine derivatives **8** and **9**

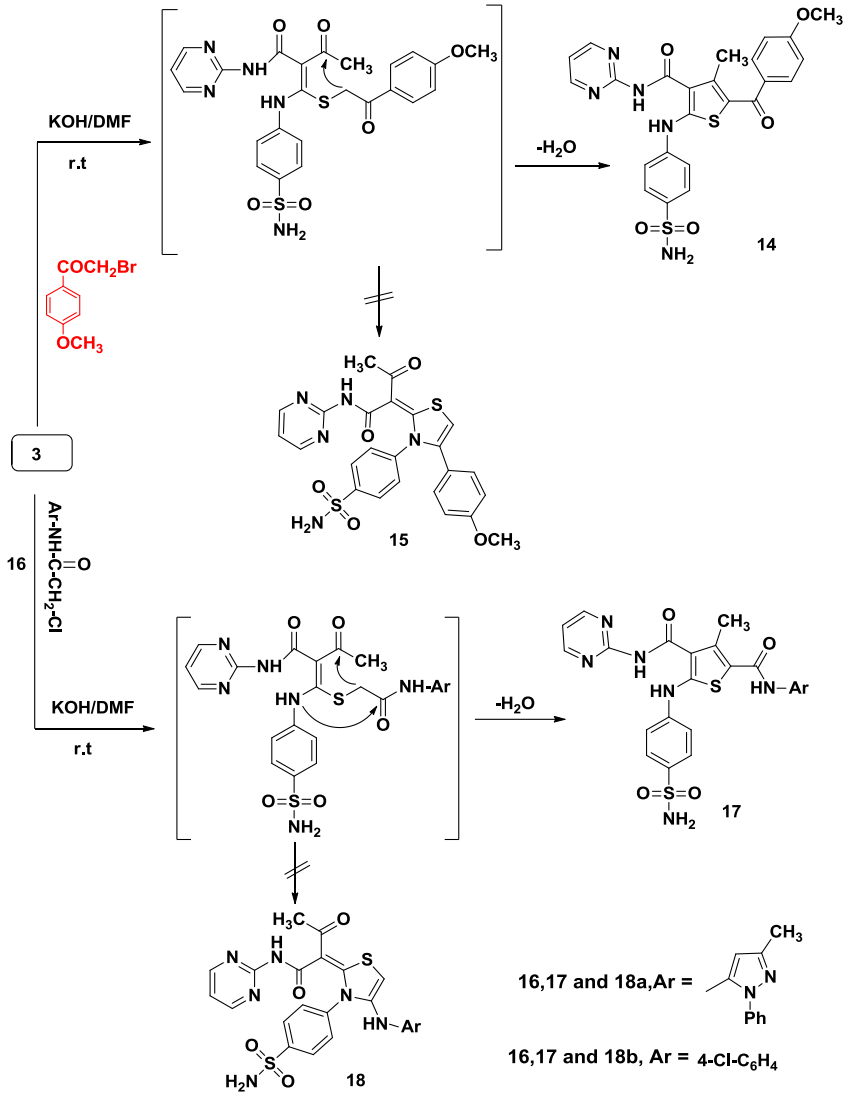
The non-isolated potassium salt (**3**) was allowed to react with $\alpha$ -halo-carbonyl compounds such as ethyl chloroacetate at room temperature gave the thiophene derivative 10 and discarded the other possible structure 11 on the basis of analytical and spectral data. The infrared spectrum of compound 10 was characterized by the appearance of absorption bands corresponding to NH, $NH_2$, C=O ester and C=O amide at 3480–3254, 1725 and 1640 cm$^{-1}$, respectively. It's $^1$H NMR spectrum showed appearance of a signal for methyl protons at $\delta$ ppm 1.95, triplet signals at $\delta$ ppm 1.19

and quartet signals at 4.02 ppm characterized for $CO_2C_2H_5$ ester and two singlet signals at 10.42, 13.22 pm for two NH protons. The mass spectrum showed a molecular ion peak at m/z = 461 corresponding to a molecular formula $C_{19}H_{19}N_5O_5S_2$. The formation of thiophene derivative 10 in this reaction was assumed to proceed via initial alkylation followed by intramolecular cyclization with the loss of $H_2O$ molecule to give the final reaction product (10) Scheme 3. Similarly, when non-isolated potassium salt (3) is stirred with chloroacetonitrile in DMF at room temperature to afford the thiophene derivative 12 and not thiazole structure 13. The thiophene derivative 12 was established on the basis of its IR spectrum with showed band related CN group at 2204 $cm^{-1}$.



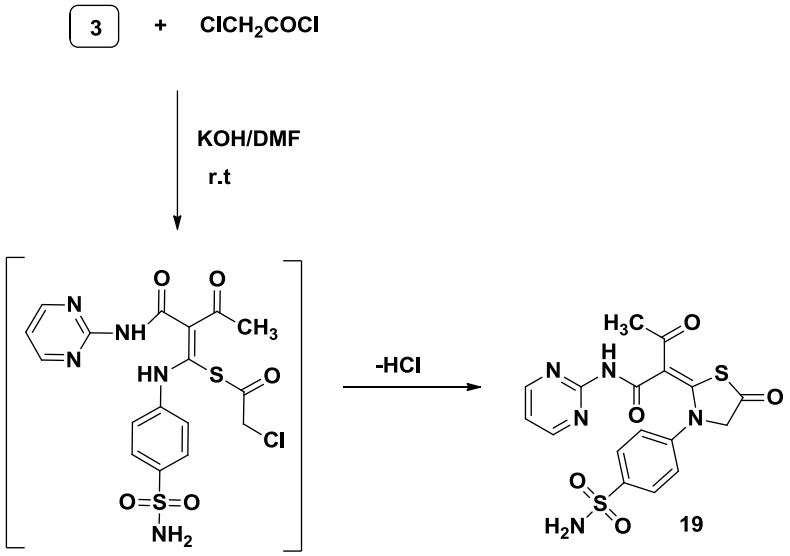

**Scheme 3**: Synthesis of thiophene derivatives **10** and **12**

In a similar sequence, when the non-isolated potassium salt (3) was reacted with *p*-methoxy phenacyl bromide at room temperature gave the corresponding thiophene derivative 14, rather than the compound 15, Scheme (4). Evidence for the structure of thiophene 14 was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at 3410 – 3270, 1668 and 1659 $cm^{-1}$, corresponding to 2NH, $NH_2$, and two carbonyl groups. It's $^1H$ NMR spectrum showed two singlet signals at $\delta$ 2.37 and 3.84 ppm due to the protons of $CH_3$ and $OCH_3$, besides singlet, and multi-plet signals to $NH_2$, 2NH and aromatic protons. Also, treatment of no-isolated potassium salt (3) underwent hetero-cyclization with cholor-*N*-Heteroaryl-acetamide reagents, namely 2-chloro-N-(3-methyl-pyrazol-5-yl) acetamide 16a and chloro-*N*-(4-chloro-phenyl)acetamide 16b were stirring in DMF at room temperature, the corresponding thiophene derivative 17a,b rather than the thiazole derivatives 19a,b (Scheme 4). Evidence for the structure of thiophene 17a,b were elucidated on the basis of their elemental analysis and spectral data (see experimental sections).




**Scheme 4**: Synthesis of thiophene derivatives **14** and **17**

Finally, when intermediate 3 was reacted with chloroacetyl chloride in dimethylformamide at room temperature afforded the thiazolidin-5-one was isolated in good yield. The structure of compound 19 was established by the presence of a strong absorption band at 1742, 1682 and 1655 $cm^{-1}$ due to three carbonyl groups in the IR spectrum. This is considered to be a strong conformation for the thiazolidinone nucleus formation. Furthermore, conformation for the cyclization is the presence of a singlet signal, equivalent to protons in $^1H$ NMR spectrum at $\delta$ 4.19 ppm which represents the C-4 protons of the thiozolidinone nucleus, (scheme 5).




**Scheme 5**: Synthesis of thiazole derivative **19**

**In-vitro total antioxidant activity**

The total antioxidant activity was determined using phophomolybdenum blue complex with a maximum absorption at 695 nm. The data presented in Fig (1) show that the tested compound 4a are more active than standard ascorbic acid. The activities of the compounds appeared in the following order: 4 > vit C > 12 > 7 > 10 >6 > 5 > 14> 9 >8 >17b > 17a.

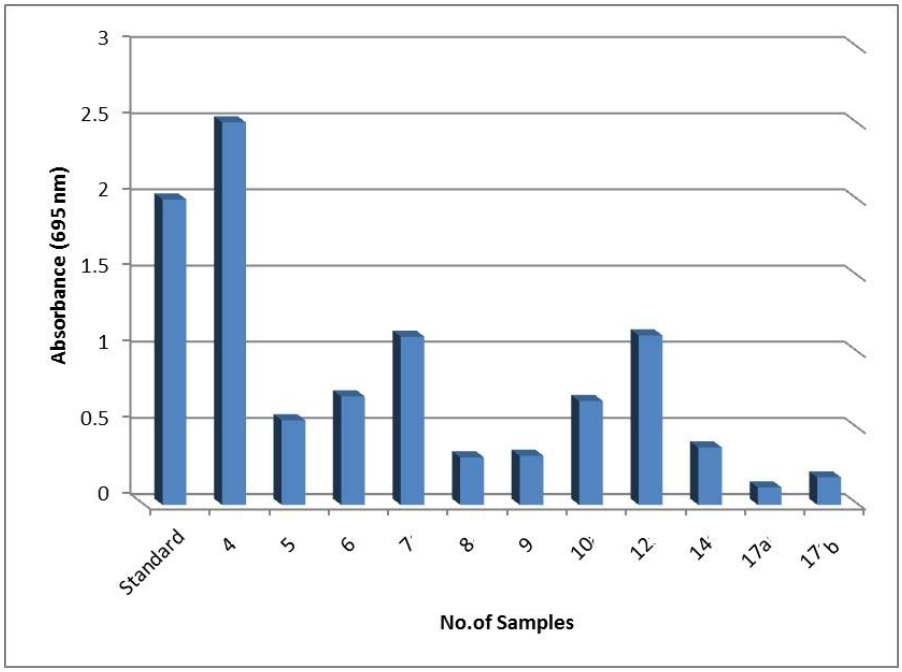
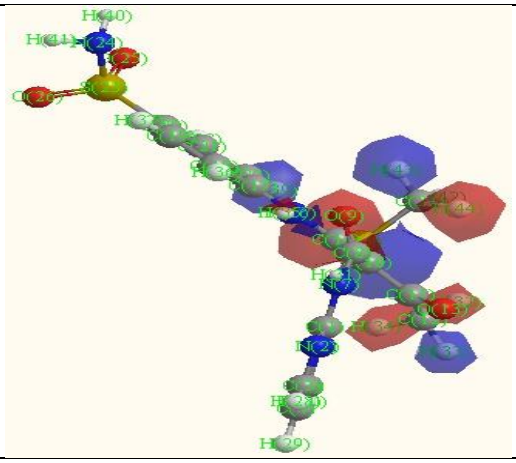
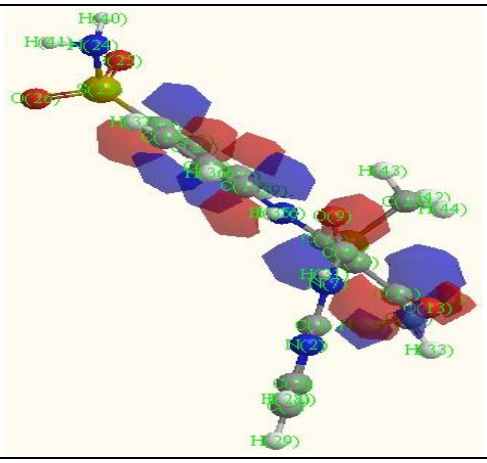
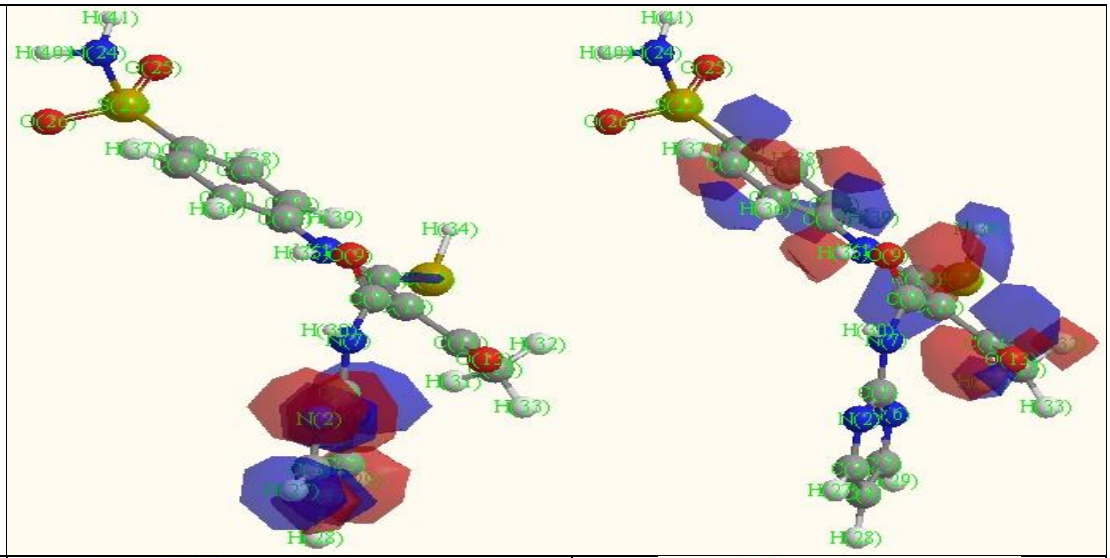
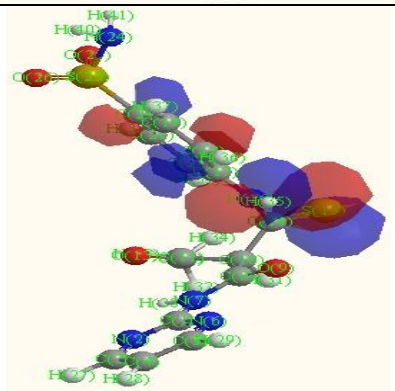
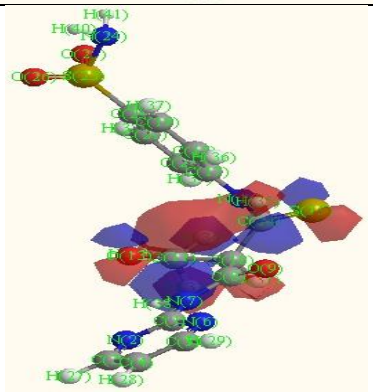
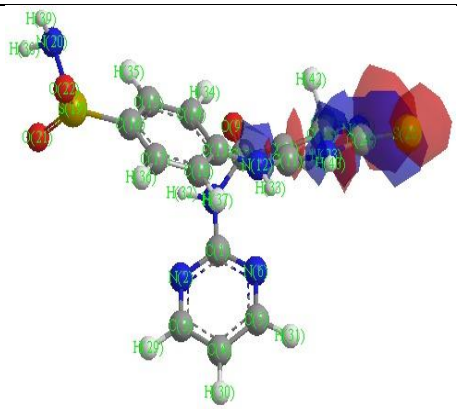
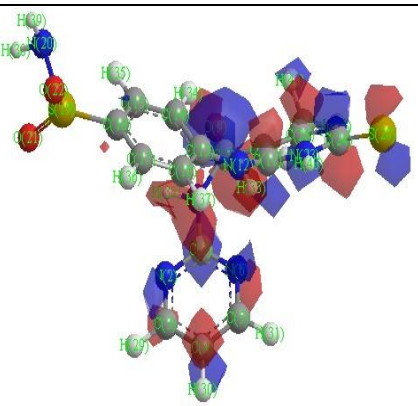
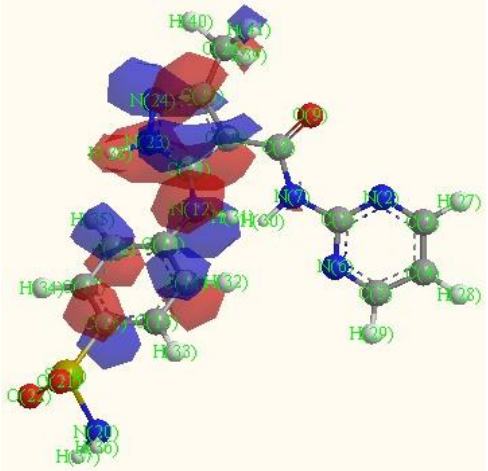
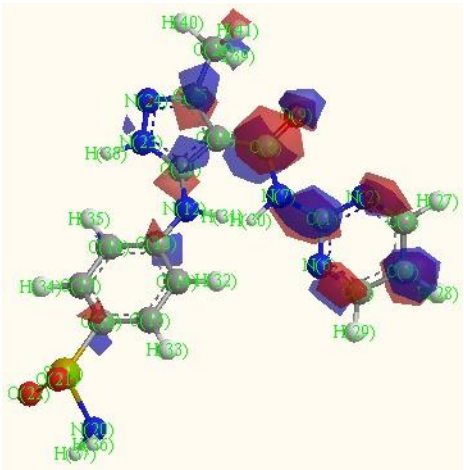


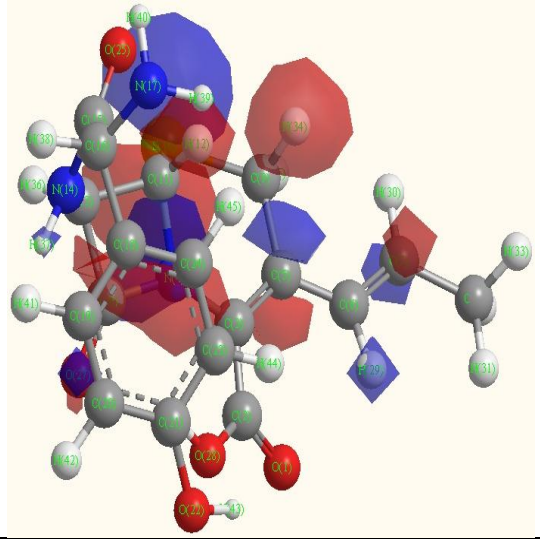
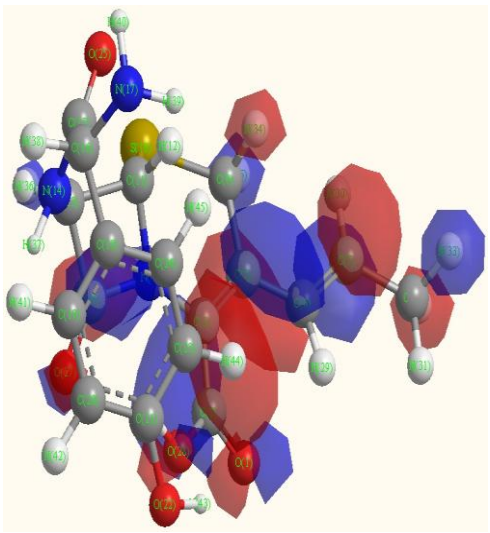

**Fig 1:** Antioxidant activities of synthesized derivatives relative to ascorbic acid

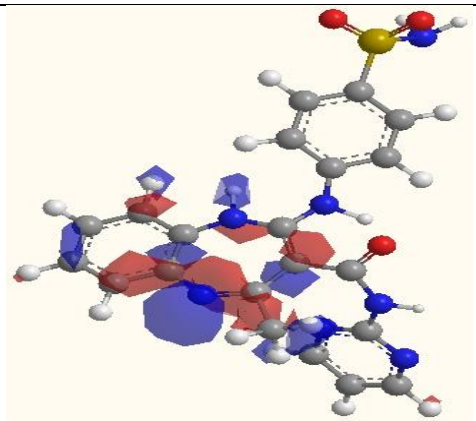
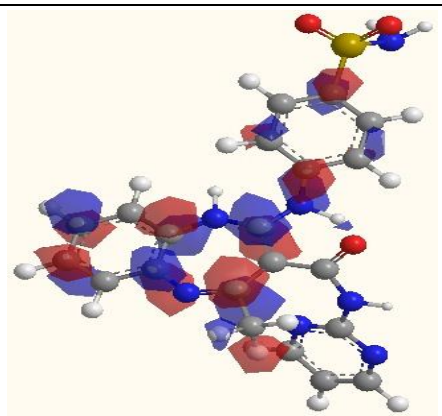
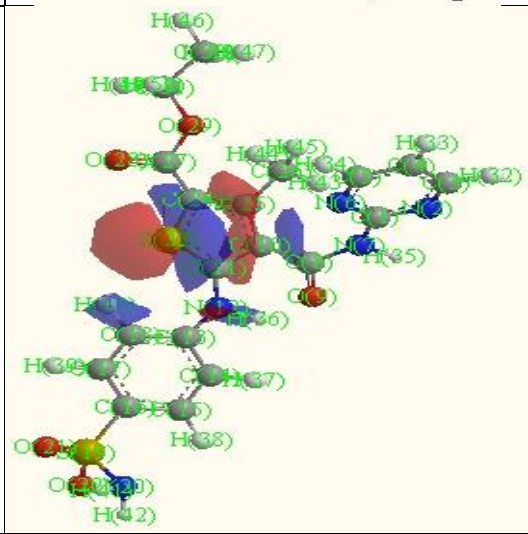
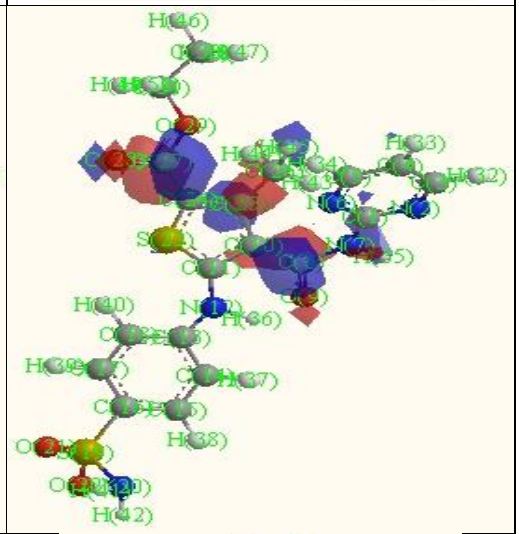
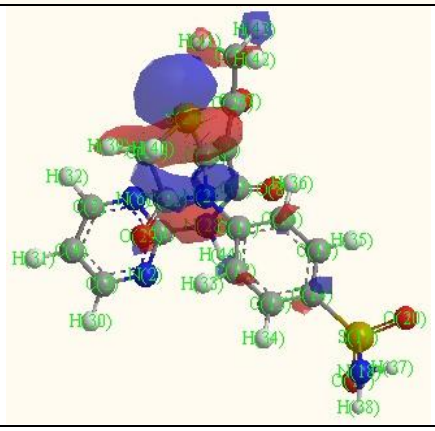
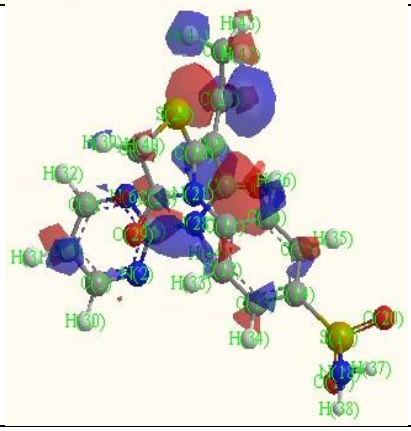
**Quantum chemical calculation** According to the frontier molecular orbital theory (FMO) [47,48], the electron transition is due to an interaction between the frontier orbitals-highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of reacting species. Table (1) presented the parameters of theoretical calculation of EHOMO, ELUMO and energy gap ΔE $_{(ELUMO-EHOMO)}$ which is used to compare between the conformers of some compounds corresponding to reactivity or stability of these compounds and its comparison experimentally by analysis data used for characterization of the synthesized compounds. From the last studies of reactivity of compound, the compound has low energy gap is more reactive than the higher value [49]. Its reveals from data compound **5A** is more stable than **5B** corresponding to the ΔE values where 5.705 ev and 5.518ev for compounds 5A and 5B respectively. Also, compound **10** is more stable than compound 11 due to the ΔE are 5.800ev and 5.245 ev for compounds 10 and 11 respectively. Also, compounds 12 and 13 the reactivity of compound 13 more than compound 12 as values of ΔE are 4.025ev and 6.499ev for compounds 12 and 13 respectively. Compound 14 is more stable than compound 15 as a result of ΔE of compounds 14 and 15 are 3.662ev and 0.076ev, respectively. For compound 17A the value of ΔE 5.819ev and ΔE of compound 18A is 0.283ev, so the compound 17A is more stable than 18A. Finally, for compound 17B is more stable than 18B where the ΔE are 6.562ev and 0.424ev respectively. Quantum chemical calculation can arrange the reactivity and vice versa the stability of all tested compound as follow: **15 > 18a> 18b > 8 > 14 > 13 > 9 > 4 > 10 > 19 > 5B > 5A > 11 > 17a > 12 > 17b > 6 > 7** corresponding to the values of energy gap ΔE as presented in table (**1**). Figure(**2**) shows the molecular orbital structures of the tested compounds through $E_{HOMO}$ and $E_{LUMO}$ structures

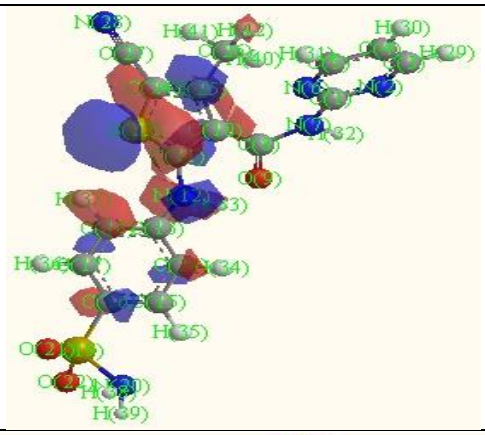
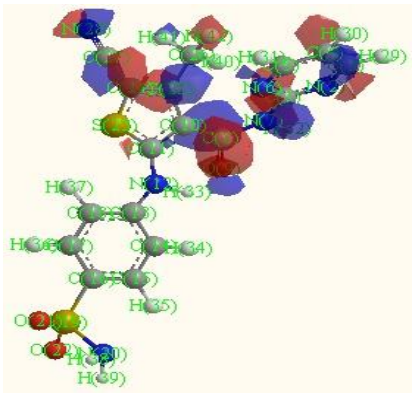
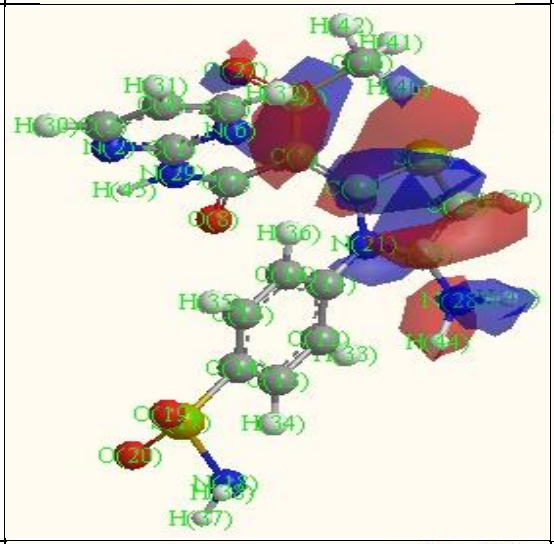
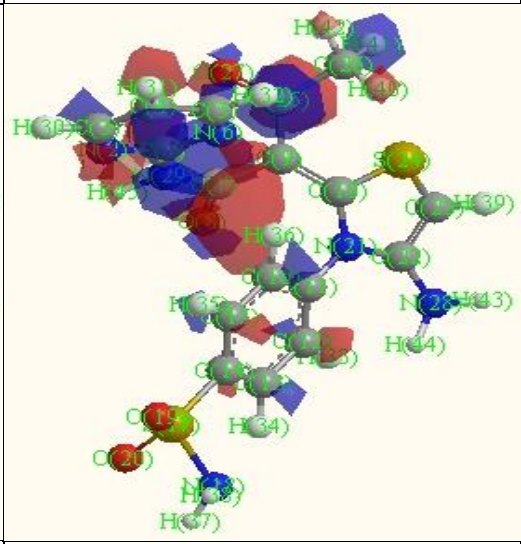
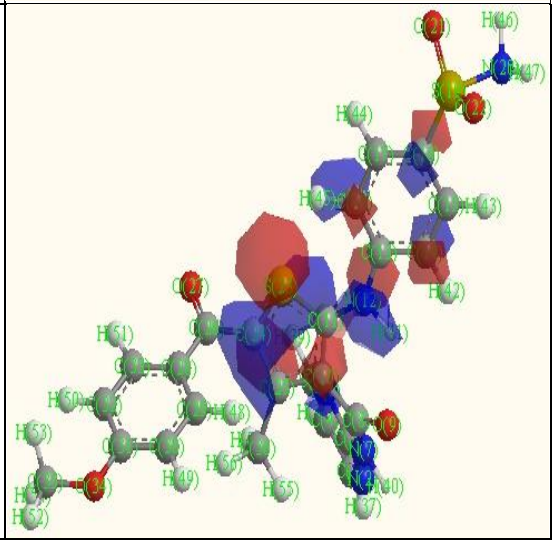
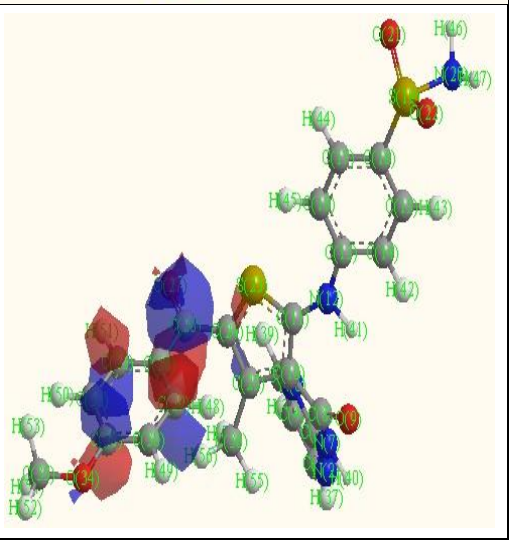
| Comp | HOMO | LUMO |
|---|---|---|
| 4 |  |  |

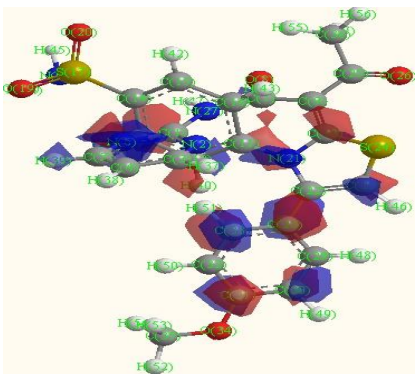
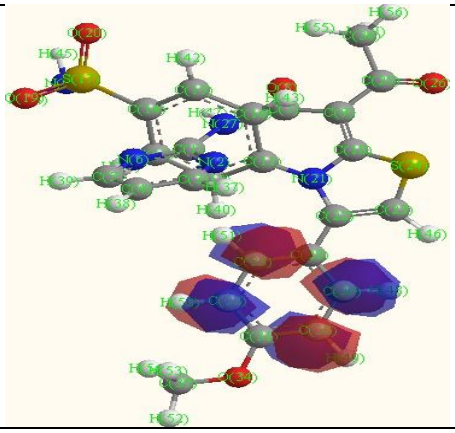
| | | |
|---|---|---|
| **5A** |  | |
| **5B** |  |  |

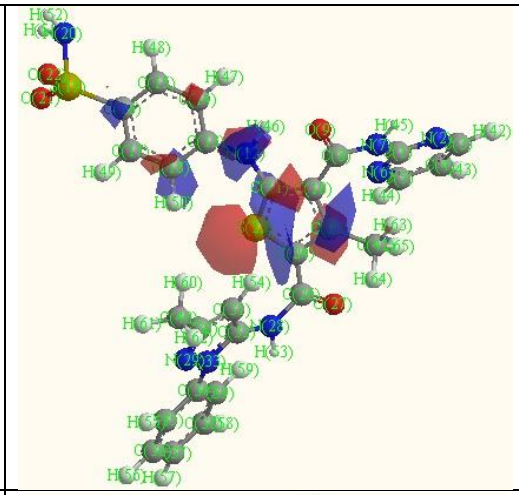
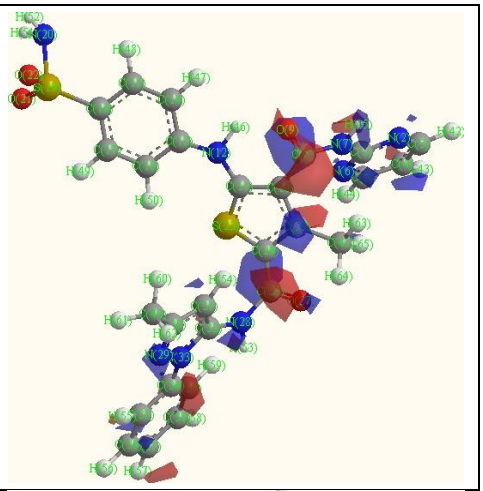
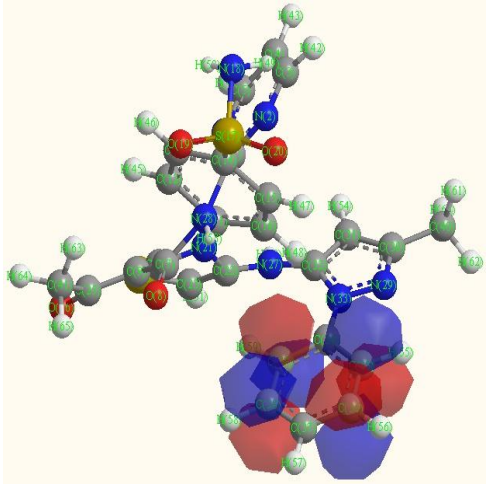
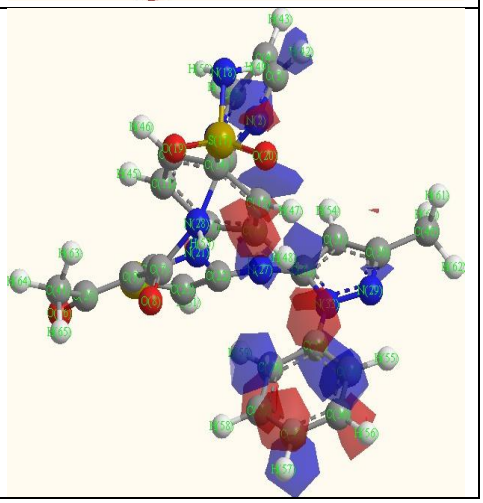
| Comp | HOMO | LUMO |
|---|---|---|
| **6** |  |  |
| **7** |  |  |

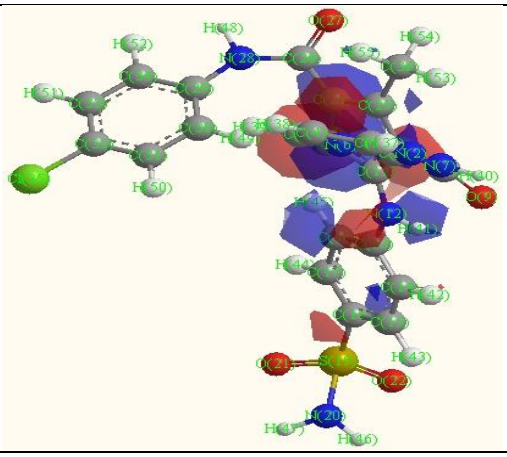
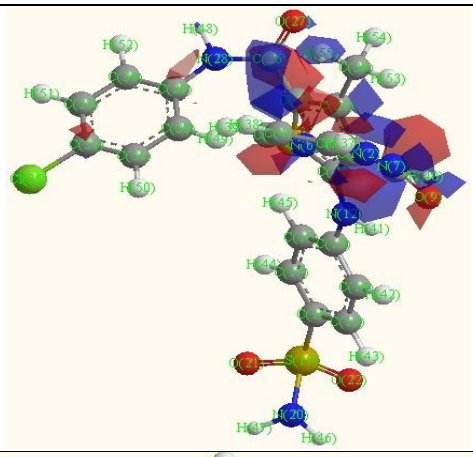
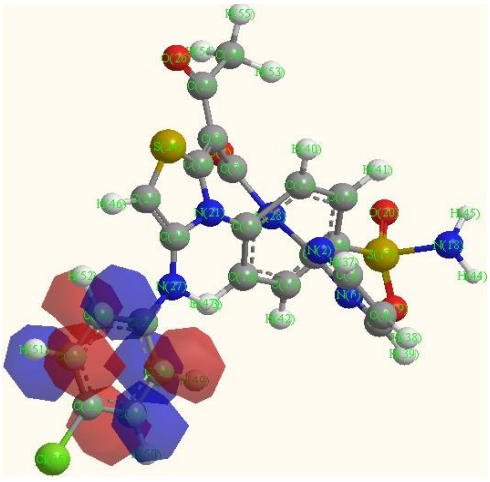
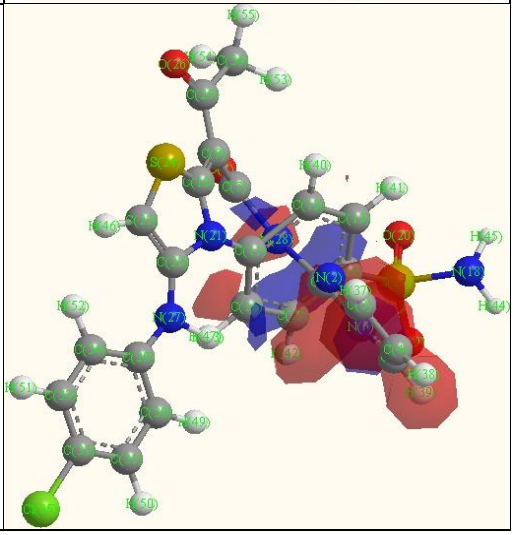
| | | |
|---|---|---|
| **8** |  |  |

| Comp | HOMO | LUMO |
|---|---|---|
| **9** |  |  |
| **10** |  |  |
| **11** |  |  |

| Comp | HOMO | LUMO |
|---|---|---|
| 12 |  |  |
| 13 |  |  |
| 14 |  |  |

| Comp | HOMO | LUMO |
|---|---|---|
| 15 |  |  |

| | | |
|---|---|---|
| **17a** |  |  |
| **18a** |  |  |

| Comp | HOMO | LUMO |
|---|---|---|
| **17b** |  |  |
| **18b** |  |  |

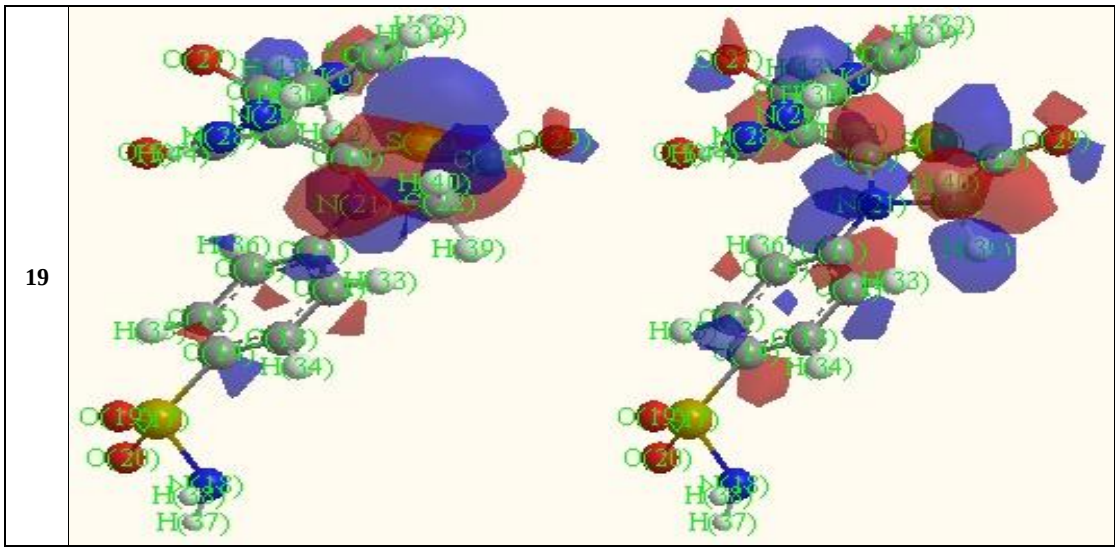



**Fig (2): molecular orbital formers of some synthesized compounds.**

**Table 1:** Quantum Chemical Parameters of the Organic Molecules.

| Compounds | $E_{HOMO}$ | $E_{LUMO}$ | Energy gap |
|---|---|---|---|
| **4** | -7.247 | -2.067 | 5.18 |
| **5A** | -7.6 | -1.895 | 5.705 |
| **5B** | -7.454 | -1.936 | 5.518 |
| **6** | -7.428 | -0.836 | 6.592 |
| **7** | -7.64 | -0.269 | 7.371 |
| **8** | 0.831 | 2.853 | 2.022 |
| **9** | -6.731 | -2.114 | 4.617 |
| **10** | -6.854 | -1.609 | 5.245 |
| **11** | -6.63 | -0.83 | 5.8 |
| **12** | -7.118 | -0.619 | 6.499 |
| **13** | -4.749 | -0.724 | 4.025 |
| **14** | -7.05 | -3.388 | 3.662 |
| **15** | 0.477 | 0.553 | 0.076 |
| **17a** | -6.615 | -0.796 | 5.819 |
| **18a** | 0.444 | 0.727 | 0.283 |
| **17b** | -7.127 | -0.565 | 6.562 |
| **18b** | 0.359 | 0.783 | 0.424 |
| **19** | -7.26 | -1.899 | 5.361 |

## 4. Conclusions

In conclusion, the reactivity of *3-oxo-N-pyrimidin-2-yl butanamide and 4-Isothiocyanato-benzenesulfonamide* (2) was investigated as a versatile and readily accessible building block for the synthesis of new heterocycles incorporating a sulfamoyl moiety. It is noteworthy that, the antioxidant examination of these derivatives exhibited that some of them is potent antioxidants when comparing with vitamin C as reference drug. Thus, further biological studies could be carried out for these compounds as they can be considered as templates for antioxidant supplements. Quantum chemical calculation gives prediction about the reactivity or stability of synthesized compounds which approve the instrumental analysis data.

## 5. Acknowledgments

The authors would like to thank the Chemistry Department, Faculty of Science, Assiut, Al-Azhar University for their financial support to facilitate the publication of this study.

## 6. References

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