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3-Oxobutanamides in Heterocyclic Synthesis: Synthesis, Reactions and Biological Evaluation of Novel Thiophene, Pyridine, Pyrimidine, 1,2,4-Triazine Derivatives.

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ABSTRACT

Number of thiophene, pyridine, pyrimidine, and 1,2,4-triazine derivatives were obtained via interaction of 3-Oxo-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino)sulphonyl]phenyl} butanamide (1) with different reagents. The new synthesized compounds were confirmed by their infrared, mass spectrum, ^{1}H-NMR, ^{13}C-NMR and elemental analyses, and further screened for antimicrobial activity.

Introduction

Simple nitrogen-containing heterocycles attached to sulfonamido moieties have received a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Heterocyclic sulfonamides are used as carbonic anhydrase inhibitors [1], antimicrobial [2], anesthetic [3], anti-Alzheimer [4], anticarcinogenic [5], anti- inflammatory [6] and anti-diabetic agents [7]. Liver cancer (hepatocellular carcinoma) remains one of the most important health problems in the world because it is the third foremost cause of cancer-related deaths worldwide [8,9]. Thiophene and its derivatives constitute one of the major classes in heterocyclic chemistry, thus some of these compounds has interesting biological properties [10,11]. Also, pyridine is another important nitrogen-containing heterocycle with various bioactivities [12]. The pyrimidine is a wide spread heterocyclic moiety, present in numerous natural products as well as synthetic pharmacophores with biological activities [13,14]. In view of the above mentioned findings and in continuation of our work in heterocycles of biological interest [2,14, 15–18] , prompted us to devise an efficient and convenient method of synthesis of hitherto unknown and novel thiophene, pyridine, pyrimidine, and 1,2,4-triazine derivatives with a sulfonamide nucleus. Results from assessment of the antimicrobial activity of these newly synthesized compounds are reported in this study.

Experimental

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^{1}H NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 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 analyses were carried out by the Micro analytical Research Center, Faculty of Science, Cairo University and Assiut University. Compound 1 was prepared according literature procedure [19].

2-Cyclohexylidene-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)-3-oxobutanamide (3)

To a dray solid of acetoacetanilide **1** (0.01 mole) containing ammonium acetate (0.50 g) cyclohexanone (**2**) (0.01 mole) was added. The reaction mixture was heated in an oil bath at 120°C for 5h then left to cool then triturated with ethanol and the formed solid product was collected by filtration and recrystallized from ethanol to give **3** (90%) as pale brown crystals, m.p. 140°C. IR (KBr): υ cm^{-1} 3300, 3268 (2NH), 3066 (CH-arom.), 2944 (CH-aliph.), 1690, 1665 (2CO); ^{1}H NMR (DMSO-d_6): δ = 1.45-1.48 (m, 6H, 3CH$_2$), 2.11-2.15 (m, 4H, 2CH$_2$), 2.23 (s, 3H, CH$_3$), 3.72, 3.76 (2s, 6H, 2OCH$_3$), 4.12 (s, 1H, NH), 6.70 (s, 1H, pyrimidine-H), 7.62, 7.74 (d-d, 4H, Ar-H), 10.16 (s, 1H, NH). MS: m/z 474 (M^{+}; 36.50%). Anal. Calc. for $C_{22}H_{26}N_4O_6S$ (474.16): C, 55.68; H, 5.52; N, 12.17; S, 6.76%. Found: C, 55.92; H, 5.81; N, 11.62; S, 6.94%.

Preparation of Compounds 5a, b: General Procedure

To a solution of compound **3** (0.01 mole) in ethanol (50 ml) containing piperidine (0.5 ml), either malononitrile (**4a**) (0.01 mole) or cyanothioacetamide (**4b**) (0.01 mole) was added. The reaction mixture was heated under reflux for 5 h then left to cool and the solid product was formed in each case upon pouring onto ice/water containing few drops of hydrochloric acid, the solid product was collected by filtration and recrystallized from the proper solvent

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to give **5a,b** respectively.

4.4-Dicyano-2-cyclopentylidene-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-3-methylbut-3-enamide (5a)

It was obtained as yellow crystals from ethanol; yield 83%; m.p. 163˚C; IR (KBr): υ cm^{-1} 3436, 3315 (2NH), 3058 (CH-arom.), 2925 (CH-aliph.), 2222, 2220 (2CN), 1675 (CO); ^{1}H NMR (DMSO-d_6): δ = 1.43-1.46 (m, 6H, $3CH_2$), 2.13-2.17 (m, 4H, $2CH_2$), 2.21 (s, 3H, CH_3), 3.68, 3.71 (2s, 6H, $2OCH_3$), 4.15 (s, 1H, NH), 5.96 (s, 1H, pyrimidine-H), 7.64, 7.77 (d-d, 4H, Ar-H), 9.90 (s, 1H, NH). Anal. Calc. for $C_{25}H_{26}N_6O_5S$ (522.17): C, 57.46; H, 5.01; N, 16.08; S, 6.14%. Found: C, 57.74; H, 5.30; N, 16.36; S, 6.43%.

5-Amino-4-cyano-2-cyclohexylidene-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-3-methyl-5-thioxopent-3-enamide (5b)

It was obtained as yellow crystals from ethanol; yield 80%; m.p. 158˚C; IR (KBr): υ cm^{-1} 3435, 3384 (NH_2), 3275, 3215 (2NH), 3050 (CH-arom.), 2943 (CH-aliph.), 2223 (CN), 1685 (CO); ^{1}H NMR (DMSO-d_6): δ = 1.41-1.44 (m, 6H, $3CH_2$), 2.10-2.14 (m, 4H, $2CH_2$), 2.44 (s, 3H, CH_3), 3.65, 3.69 (2s, 6H, $2OCH_3$), 4.18 (s, 1H, NH), 5.92 (s, 1H, pyrimidine-H), 7.23- 7.65 (m, 6H, Ar-H + NH_2), 9.83 (s, 1H, NH). Anal. Calc. for $C_{25}H_{28}N_6O_5S_2$ (556.16): C, 53.94; H, 5.07; N, 15.10; S, 11.52%. Found: C, 53.65; H, 5.34; N, 15.38; S, 11.82%.

Preparation of Compounds 6a, b: General Procedure

To a solution of each compound **5a** (0.01 mole) or compound **5b** (0.01 mole) in ethanol (40 ml) containing triethylamine (0.5 ml), elemental sulfur (0.01 mole) was added. The reaction mixture was heated under reflux for 5 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration and recrystallized from the proper solvent to give **6 a, b**.

2-(5-Amino-4-cyanothiophen-3-yl)-2-cyclohexylidene-N-(4-(N-(2,6-dimethoxy pyrimidin-4-yl)sulfamoyl)phenyl)acetamide (6a)

It was obtained as buff crystals from dioxane; yield 72%; m.p. 181˚C IR (KBr): υ cm^{-1} 3427, 3378 (NH_2), 3242, 3222 (2NH), 3058 (CH-arom.), 2925 (CH-aliph.), 2224 (CN), 1687 (CO); ^{1}H NMR (DMSO-d_6): δ = 1.39-1.42 (m, 6H, $3CH_2$), 2.03-2.09 (m, 4H, $2CH_2$), 3.68, 3.70 (2s, 6H, $2OCH_3$), 4.21 (s, 1H, NH), 6.92 (s, 1H, CH-thiophene), 7.27- 7.75 (m, 7H, Ar-H + NH_2), 9.32 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): 23.4 ($2CH_3$), 25.6 (CH_2), 27.2 ($2CH_2$), 32.0 ($2CH_2$), 115.7 (CN), 122.5 (C=C), 123.1, 124.3, 125.2, 126.7, 129.0, 130.8, 135.6, 140.4, 148.3, 150.1, 152.5, 154.3 (Ar-C), 160.6 (C=C-cyclohexylidene), 170.2 (CO). MS: m/z = 554 (M^+; 65.20%). Anal. Calc. for $C_{25}H_{26}N_6O_5S_2$ (554.14): C, 54.14; H, 4.72; N, 15.15; S, 11.56%. Found: C, 54.45; H, 4.43; N, 15.41; S, 11.85%.

2-(5-Amino-4-carbamothioylthiophen-3-yl)-2-cyclohexylidene-N-(4-(N-(2,6-dimethoxypyrimidin-4- yl) sulfamoyl)phenyl)acetamide (6b)

It was obtained as Pale yellow crystals from dioxane; yield 70%; m.p. 186˚C IR (KBr): υ cm^{-1} 3448, 3391 ($2NH_2$), 3284, 3237 (2NH), 3067 (CH-arom.), 2955 (CH-aliph.), 1677 (CO); ^{1}H NMR (DMSO-d_6): δ = 1.48-1.51 (m, 6H, $3CH_2$), 2.12-2.18 (m, 4H, $2CH_2$), 3.66, 3.69 (2s, 6H, $2OCH_3$), 4.26 (s, 1H, NH), 6.88 (s, 1H, CH-thiophene), 7.12- 7.95 (m, 9H, Ar-H + $2NH_2$), 9.27 (s, 1H, NH) Anal. Calc. for $C_{25}H_{28}N_6O_5S_3$ (588.13): C, 51.00; H, 4.79; N, 14.28; S, 16.34%. Found: C, 51.28; H, 4.50; N, 14.57; S, 16.62%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-l)sulfamoyl)phenyl)-2-(mercapto (phenylamino)methylene)-3-oxobutanamide (8)

To a stirred solution of potassium hydroxide (0.1 mole) in dimethylformamide (20 mL) the **1** (0.1 mole) was added. After stirring for 30min, phenylisothiocyanate (0.1 mole) was added to the resulting mixture and stirring was continued for 6 h; then it was poured over crushed ice containing hydrochloric acid. The solid product formed was filtered off, washed with water, dried, and finally recrystallized from dioxane as pale yellow crystals; yield 52%; m.p. 225˚C IR (KBr): υ cm^{-1} 3385 , 3223, 3156 (3NH), 3072 (CH-arom.), 2940 (CH-aliph.), 1688, 1662 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.27 (s, 3H, CH3), 3.58, 3.57 (2s, 6H, $2OCH_3$), 3.76 (s, 1H, NH), 6.92- 7.80 (m, 10H, Ar-H), 10.15 (s, 1H, D_2O-exchangeable NH), 11.27 (s, 1H,D_2O-exchangeable NH), 12.65 (s, 1H, SH). MS: m/z = 531 (M^++2). Anal. Calc. for $C_{23}H_{23}N_5O_6S_2$ (529.11): C, 52.16; H, 4.38; N, 13.22; S, 12.11%. Found: C, 52.38; H, 4.60; N, 13.45; S, 12.33%.

5-Benzoyl-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)-4-methyl-2-(phenylamino)thiophene-3-carboxamide (9)

To a mixture of 8 (0.1 mole) and 2-bromo-1-phenylethanone (0.1mole) in dimethylformamide (20 mL), triethylamine (0.5 mL) was added and the reaction mixture was refluxed for 6 hrs; then it was left to cool. The precipitated product was filtered off and purified by recrystallization from dioxane as brown crystals; yield 50%; m.p. 275˚C IR (KBr): υ cm^{-1} 3390 , 3244, 3120 (3NH), 3062 (CH-arom.), 2960 (CH-aliph.), 1698, 1665 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.19 (s, 3H, CH_3), 3.30, 3.32 (2s, 6H, $2OCH_3$), 4.03 (s, 1H, NH), 7.05- 8.91 (m, 15H, Ar-H), 9.14 (s, 1H, NH), 10.12 (s, 1H, NH). MS: m/z = 629 (M^+). Anal. Calc. for $C31H_{27}N_5O_6S_2$ (629.71): C, 59.13; H, 4.32; N, 11.12; S, 10.18%. Found: C, 59.34; H, 4.52; N, 11.33; S, 10.40%.

Preparation of Compounds 10, 11, 12 and 14: General Procedure

To a stirred solution of potassium hydroxide (0.1 mole) in DMF (20 mL), compound **1** (0.1mole) was added. After stirring for 30min, phenyl isothiocyanate (0.1mole) was added to the resulting mixture. Stirring was continued for 6 hrs, and then chloroacetonitrile, ethyl chloroacetate, methyl iodide, or *N*-(2-chlorophenyl)-2-oxopropane hydrazonoyl chloride (0.1mole) was added portion wise over a period of 30 min. After the addition was complete, the reaction mixture was stirred for additional 12 h, The solid product formed on standing was collected by filtration and recrystallized from the appropriate solvent to gives **10, 11, 12 and 14.**

5-Cyano-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)-4-methyl-2-(phenylamino)thiophene-3-carboxamide (10)

It was obtained as yellow crystals from ethanol/ dioxane; yield 68%; m.p. 264˚C IR (KBr): υ cm^{-1} 3387 , 3262, 3146 (3NH), 3072 (CH-arom.), 2925 (CH-aliph.), 2220 (C≡N), 1653 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.16 (s, 3H, CH_3), 3.47, 3.49 (2s, 6H, $2OCH_3$), 3.97 (s, 1H, NH), 7.21- 7.99 (m, 10H, Ar-H), 9.22 (s, 1H, NH), 9.80 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): 14.3 (CH_3), 26.1 ($2CH_3$), 115.3 (CN), 118.5, 120.6, 121.1, 122.4, 124.3, 126.8, 130.4, 132.7, 135.4, 138.1, 140.7, 154.3, 156.2, 157.7, 160.3 (Ar-C), 165.2 (CO).MS: m/z = 550 (M^+). Anal. Calc. for $C_{25}H_{22}N_6O_5S_2$ (550.61): C, 54.53; H, 4.03; N, 15.26; S, 11.65%. Found: C, 54.75; H, 4.26; N, 15.48; S, 11.87%.

Ethyl4-((4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)carbamoyl)-3-methyl-5-(phenylamino) thiophene-2-carboxylate (11)

It was obtained as yellow crystals from ethanol/ dioxane; yield 70%; m.p. 288˚C IR (KBr): υ cm^{-1} 3371 , 3281, 3165 (3NH), 3050 (CH-arom.), 2935 (CH-aliph.), 1715 (C=O), 1645 (C=O); ^{1}H NMR (DMSO-d_6): δ = 1.24 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.15 (s, 3H, CH_3), 3.45, 3.47 (2s, 6H, $2OCH_3$), 3.95 (s, 1H, NH), 4.19 (q, *J* = 7.2 Hz, 2H , $O\underline{CH_2}CH_3$), 7.35- 7.87 (m, 10H, Ar-H), 9.18 (s, 1H, NH), 9.76 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): 12.3 (CH_3), 14.1 (CH_3), 25.8 ($2CH_3$), 60.4 (CH_2), 102.4, 117.6, 118.1, 119.2, 122.7, 129.4, 131.2, 136.5, 140.2, 142.8, 150.6, 152.3, 155.1, 157.4, 160.7 (Ar-C), 164.9, 168.7 (2CO). Anal. Calc. for $C_{27}H_{27}N_5O_7S_2$ (597.66): C, 54.26; H, 4.55; N, 11.72; S,10.73%. Found: C, 54.49; H, 4.77; N, 11.93; S, 10.95%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4yl)sulfamoyl)phenyl)-2-((methylthio)(phenylamino)methylene)-3-xobutanamide (12)

It was obtained as yellow crystals from ethanol/ dioxane; yield 66%; m.p. 258˚C IR (KBr): υ cm^{-1} 3391 , 3265, 3147 (3NH), 3064 (CH-arom.), 2933 (CH-aliph.), 1698, 1655 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H, CH_3), 2.85 (s, 3H, SCH_3), 3.61, 3.63 (2s, 6H, $2OCH_3$), 3.72 (s, 1H, NH), 7.05- 7.84 (m, 10H, Ar-H), 10.12 (s, 1H, D_2O-exchangeable NH), 11.03 (s, 1H,D_2O-exchangeable NH). MS: m/z = 543 (M^+). Anal. Calc. for $C_{24}H_{25}N_5O_6S_2$ (543.62): C, 53.03; H, 4.64; N, 12.88; S, 11.80%. Found: C, 53.35; H, 4.89; N, 12.65; S, 11.58%.

2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-N-(4-(N-(2,6-dimethoxy-pyrimidin-4-yl)sulfamoyl)phenyl)-3-oxobutanamide (14)

It was obtained as yellow crystals from ethanol/ dioxane; yield 71%; m.p. 291˚C IR (KBr): υ cm^{-1} 3363 , 3220 (2NH), 3040 (CH-arom.), 2926 (CH-aliph.), 1725, 1713,1647 (3C=O); ^{1}H NMR (DMSO-d_6): δ = 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.73, 3.76 (2s, 6H, $2OCH_3$), 4.14 (s, 1H, NH), 7.10- 7.79 (m, 10H, Ar-H), 10.25 (s, 1H, NH). MS: m/z = 596 (M^+). Anal. Calc. for $C_{26}H_{24}N_6O_7S_2$ (596.63): C, 52.34; H, 4.05; N, 14.09; S, 10.75%. Found: C, 52.57; H, 4.26; N, 14.33; S, 10.96%.

Preparation of compounds 16a, b; General procedure

A mixture of compound **1** (0.01 mole), aromatic aldehyde **15a,b** (0.01mole) and few drops of piperidine in ethanol (30ml) was refluxed for 8hrs. The solid precipitate produced on hot was collected by filtration and recrystallized from the proper solvent to give **16a, b**.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl) phenyl) -2-(4-methylbenzyl-idene)-3-oxobutanamide (16a)

It was obtained as yellow crystals from ethanol; yield 83%; m.p. 231˚C; IR (KBr): υ cm^{-1} 3348 , 3232 (2NH), 3065 (CH-arom.), 2950 (CH-aliph.), 1695, 1670 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.22 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.41, 3.44 (2s, 6H, $2OCH_3$), 3.77 (s, 1H, NH), 7.36–7.94 (m, 9H, Ar-H), 8.38 (s,1H, olefinic-H), 10.18 (s, 1H, NH). Anal. Calc. for $C_{24}H_{24}N_4O_6S$ (496.54): C, 58.05; H, 4.87; N, 11.28; S, 6.46%. Found: C, 58.26; H, 4.65; N, 11.49; S, 6.68%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl) phenyl)-2-(4-methoxybenzyl-idene)-3-oxobutanamide (16b)

It was obtained as yellow crystals from ethanol; yield 81%; m.p. 239˚C; IR (KBr): υ cm^{-1} 3370, 3258 (2NH), 3055 (CH-arom.), 2943 (CH-aliph.), 1698, 1675 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 3.34, 3.38 (3s, 9H, $3OCH_3$), 3.69 (s, 1H, NH), 7.30- 8.03 (m, 9H, Ar-H+ C=CH-olefinic), 10.28 (s, 1H, NH). Anal. Calc. for $C_{24}H_{24}N_4O_7S$ (512.53): C, 56.24; H, 4.72; N, 10.93; S, 6.26%. Found: C, 56.44; H, 4.51; N, 10.72; S, 6.47%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl)phenyl) -5-methyl-1-phenyl-3-(p-tolyl)-1H-pyrazole-4-carboxamide (17a)

A mixture of compound **16a** (0.01 mole), and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was refluxed for 8 hrs. The reaction mixture was left to cool and the solid precipitate so formed was collected by filtration and recrystallized from ethanol as orange crystals; yield 54 %; m.p. 163°C; IR (KBr) ν cm^{-1} 3300 , 3221 (2NH), 3074 (CH-arom), 2989 (CH-aliph), 1665 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.60, 3.64 (2s, 6H, $2OCH_3$), 4.10 (s, 1H, NH), 7.22- 7.93 (m, 14H, Ar-H), 9.15 (s, 1H, NH). MS: m/z = 586 (M^{+2}). Anal. Calc. for $C_{30}H_{28}N_6O_5S$ (584.65): C, 61.63; H, 4.83; N, 14.37; S, 5.48%. Found: C, 61.84; H, 4.62; N, 14.58; S, 5.70%.

4-(3-Acetyl-2-oxo-4,6-diphenylpyridin-1(2H)-yl)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (19)

A mixture of compound **1** (0.01 mole) and 1,3-diphenyl propenone (**18**) in ethanol (30 mL) containing a few drops of piperidine was heated under reflux for 6 hrs. The solid product formed after cooling was collected by filtration and recrystallized from ethanol to give (**19**; 82%) as yellow crystals; mp. 152°C; IR (KBr) ν cm^{-1} 3225 (NH), 3060 (CH-arom), 2924 (CH-aliph), 1685, 1647 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.28 (s, 3H, CH_3), 3.57, 3.59 (2s, 6H, $2OCH_3$), 4.11 (s, 1H, NH), 5.82 (s, 1H, CH-pyridine), 7.30-7.85 (m, 15H, Ar-H); ^{13}C-NMR (DMSO-d_6): 24.3 (CH_3), 29.8 ($2CH_3$), 108.6, 111.8, 121.2, 127.1, 127.8, 128.3,128,7, 129.9,130.5, 131.2, 132.8, 134.1, 136.3, 137.8, 141.4, 145.5, 154.1, 157.2, 159.3, 161.5 (Ar-C), 163.1(CO), 196.4 ($COCH_3$). MS: m/z = 582 (M^+). Anal. Calc. for $C_{31}H_{26}N_4O_6S$ (582.63): C, 63.91; H, 4.50; N, 9.62; S, 5.50 %. Found: C, 63.70; H, 4.73; N, 9.95; S, 5.80 %.

4-((5-Cyano-4,6-dimethylpyridin-2-yl)amino)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (20)

To a solution of compound **1** (0.01 mole), 3-aminocrotonitrile (0.01 mole) in ethanol (30 mL) treated with a few drops of piperidine was heated under reflux for 15 hrs. Then cool, the solid product so formed was collected by filtration and recrystallized from dioxane as brown crystals; yield 69%; m.p. 273˚C IR (KBr): υ cm^{-1} 3368 , 3255 (2NH), 3078 (CH-arom.), 2951 (CH-aliph.), 2214 (C≡N). ^{1}H NMR (DMSO-d_6): δ = 2.75 (s, 6H, $2CH_3$), 3.67, 3.72 (2s, 6H, $2OCH_3$), 4.24 (s, 1H, NH), 5.77 (s, 1H, CH-pyridine), 7.15-7.78 (m, 5H, Ar-H) 9.60 (s, 1H, NH). Anal. Calc. for $C_{20}H_{20}N_6O_4S$ (440.48): C, 54.54; H, 4.58; N, 19.08; S, 7.28%. Found: C, 54.83; H, 4.82; N, 19.35; S, 7.56%.

5-Cyano-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)-2-methyl-6-thioxo-4-(p-tolyl)-1,6-dihydropyridine-3-carboxamide (24)

A mixture of compound **1** (0.01 mole) and 2-cyano-3-(p-tolyl) prop-2-enethioamide (**21**) (0.01 mole) in ethanol (30 mL) was treated with piperidine (0.5 mL) and heated under reflux for 8h. then it was poured over crushed ice containing hydrochloric acid. The solid product formed was filtered off, washed with water, dried, and finally recrystallized from ethanol/ dioxane as yellow crystals; yield 80%; m.p. 233˚C IR (KBr): υ cm^{-1} 3375 , 3218, 3175 (3NH), 3042 (CH-arom.), 2930 (CH-aliph.), 2222 (CN), 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.17 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.32,

3.35 (2s, 6H, $2OCH_3$), 3.60 (s, 1H, NH), 6.95- 7.70 (m, 9H, Ar-H), 9.54 (s, 1H, NH), 11.17 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): 18.3 (CH_3), 20.3 (CH_3), 26.8 ($2CH_3$), 116.7 (CN), 118.4, 120.8, 124.9, 128.6, 131.2, 132.8, 135.1, 136.5, 137.3, 140.8, 153.7, 156.2, 157.1, 160.3, 161.5 (Ar-C), 166.7 (CO), 175.1 (CS). MS: m/z = 576 (M^+). Anal. Calc. for $C_{27}H_{24}N_6O_5S_2$ (576.65): C, 56.24; H, 4.20; N, 14.57; S, 11.12%. Found: C, 56.46; H, 4.43; N, 14.80; S, 11.35%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl)phenyl) -6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (25)

To a solution of **1** (0.01 mole) in absolute ethanol (30 mL) and (1 mL) HCl. aromatic aldehyde **15a** (0.01 mole) and thiourea (0.01 mole) was added. The reaction mixture was refluxed for 10 hrs. The solid product was produced on hot was collected by filtration and recrystallized from ethanol as yellow crystals; yield 83%; m.p. 262˚C IR (KBr): υ cm^{-1} 3397, 3355, 3242 (4NH), 3069 (CH-arom.), 2948 (CH-aliph.), 1645 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.63, 3.68 (2s, 6H, $2OCH_3$), 3.83 (s, 1H, NH), 5.47 (s, 1H, CH-pyrimidine), 7.11- 7.84 (m, 9H, Ar-H), 9.82 (s, 1H, NH), 10.01 (s, 1H, NH), 10.52 (s, 1H,NH). MS: m/z = 554 (M^+). Anal. Calc. for $C_{25}H_{26}N_6O_5S_2$ (554.64): C, 54.14; H, 4.72; N, 15.15; S, 11.56%. Found: C, 54.36; H, 4.93; N, 15.38; S, 11.77%.

N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl)phenyl) -7-methyl-3-oxo-5-(p-tolyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxamide (26)

To a solution of pyrimidine derivative **25** (0.01 mole) in ethanol (30mL) was added ethylchloroacetate (0.01 mole). the reaction mixture was refluxed for 12 h. Then cool, the solid product so formed was collected by filtration and recrystallized from ethanol/ dioxane as orange crystals; yield 71%; m.p. 243˚C IR (KBr): υ cm^{-1} 3257, 3172 (2NH), 3045 (CH-arom.), 2927 (CH-aliph.), 1697, 1655 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.72 (s, 2H, CH_2), 3.76, 3.78 (2s, 6H, $2OCH_3$), 4.05 (s, 1H, NH), 5.86 (s, 1H, CH-pyrimidine), 7.13- 7.88 (m, 9H, Ar-H), 10.11 (s, 1H, NH). MS: m/z = 594 (M^+). Anal. Calc. for $C_{27}H_{26}N_6O_6S_2$ (594.66): C, 54.53; H, 4.41; N, 14.13; S, 10.78%. Found: C, 54.74; H, 4.63; N, 14.37; S, 10.55%.

2-(2-(4-Chlorophenyl)hydrazono)-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-3-oxobutanamide (28)

A solution of **1** (0.01 mole) in ethanol (30 mL) containing sodium acetate (2.0g) was cooled to 0^0C, stirred and treated gradually with cooled solution of diazonium chloride **27** (prepared from 0.01 mole of amine and the appropriate quantities of HCl and $NaNO_2$). The solid product formed on standing was collected and recrystallized from ethanol as red crystals; yield 80%; m.p. 128˚C; IR (KBr): υ cm^{-1} 3378 , 3267, 3179 (3NH), 3045 (CH-arom.), 2937 (CH-aliph.), 1718, 1668 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.47 (s, 3H, CH_3), 3.71, 3.75 (2s, 6H, $2OCH_3$), 4.08 (s, 1H, NH), 7.25- 7.86 (m, 9H, Ar-H), 9.17 (s, 1H, NH), 11.23 (s, 1H, NH). MS: m/z = 532 (M^+). Anal. Calc. for $C_{22}H_{21}ClN_6O_6S$ (532.96): C, 49.58; H, 3.97; Cl, 6.65; N, 15.77; S, 6.02%. Found: C, 49.79; H, 3.73; Cl, 6.87; N, 15.56; S, 6.25%.

4-((6-Acetyl-2-(4-chlorophenyl)-4-phenyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-ylidene)amino)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (30)

To a solution of compound **28** (0.01 mole) in 1,4-dioxane (40 mL) containing catalytic base triethylamine (0.5 ml), phenylisothiocyanate (0.01 mole) was added. The reaction mixture was heated under reflux for 6 h. then left to cool. Poured into cold water and acidified with HCl. The solid product obtained was collected by filtration and recrystallized from DMF as brown crystals; yield 70 %; m.p. 179°C; IR (KBr) ν cm^{-1} 3228 (NH), 3060 (CH-arom), 2966 (CH-aliph), 1695 (CO); ^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 3.61, 3.66 (2s, 6H, $2OCH_3$), 4.16 (s, 1H, NH), 6.99- 7.96 (m, 14H, Ar-H). MS: m/z = 551 (M^+ +1). Anal. Calc. for $C_{29}H_{24}ClN_7O_5S_2$ (650.13): C, 53.58; H, 3.72; Cl, 5.45; N, 15.08; S, 9.86%. Found: C, 53.80; H, 3.93; Cl, 5.66; N, 15.30; S, 9.64%.

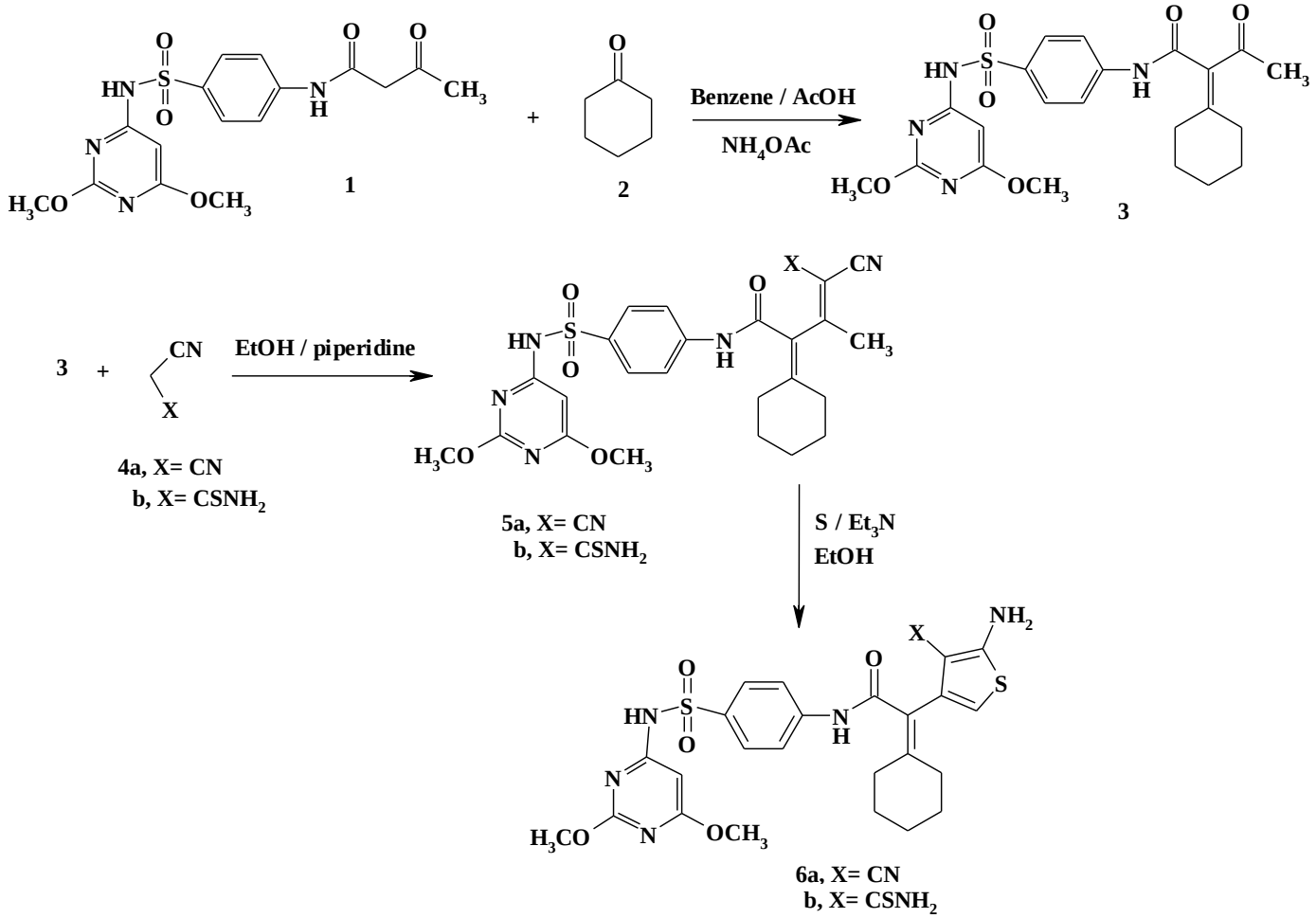
4-(6-Acetyl-2-(4-chlorophenyl)-5-oxo-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5H)-yl)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (31)

To a solution of **28** (0.01 mole) in pyridine (20 mL), CS_2 (0.02 mole) was added. The reaction mixture was refluxed for 15 hrs. Then left to cool, poured into cold water and acidified with HCl. The product formed was collected by filtration and recrystallized from DMF as brown crystals; yield 62 %; m.p. 192°C; IR (KBr) ν cm^{-1} 3212 (NH), 3065 (CH-arom), 2952 (CH-aliph), 1722, 1685 (2CO); ^{1}H NMR (DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 3.74, 3.77 (2s, 6H, $2OCH_3$), 4.02 (s, 1H, NH), 7.28- 7.79 (m, 9H, Ar-H); ^{13}C-NMR (DMSO-d_6): 26.3 (CH_3), 32.2 ($2CH_3$), 111.7, 120.1, 129.6, 131.8, 133.4, 134.1, 136.5, 138.3, 141.2, 155.6, 157.9, 161.2 (Ar-C), 164.6 (CO), 175.2 (CS), 188.1 ($COCH_3$). Anal. Calc. for $C_{23}H_{19}ClN_6O_6S_2$ (575.02): C, 48.04; H, 3.33; Cl, 6.17; N, 14.62; S, 11.15%. Found: C, 48.28; H, 3.55; Cl, 6.38; N, 14.83; S, 11.37%.

Results and Discussion

The required starting material *N*-[4-(2,6-dimethoxypyrimidin-2-ylamino) sulfonyl] phenyl-3-oxo-butanamide (**1**) was prepared as previously described [19]. Treatment of compound **1** with cyclohexanone (**2**) in benzene/AcOH containing ammonium acetate gave the Knoevenagel condensation product **3**. The structure of compound **3** was confirmed based on the analytical and spectral data. Thus, the ^{1}H NMR spectrum of compound **3** showed two multiplets at δ 1.45-1.48 & 2.11-2.15 ppm indicating the five CH_2 groups, a singlet at δ 2.23 ppm corresponding to CH_3 group, two doublets at δ 7.62, 7.74 ppm for the C_6H_4 group and two broad singlet at δ 4.12 , 10.16 ppm assignable to 2NH protons. The mass spectra showed a molecular ion peak at m/z: 474 corresponding to a molecular formulae $C_{22}H_{26}N_4O_6S$.

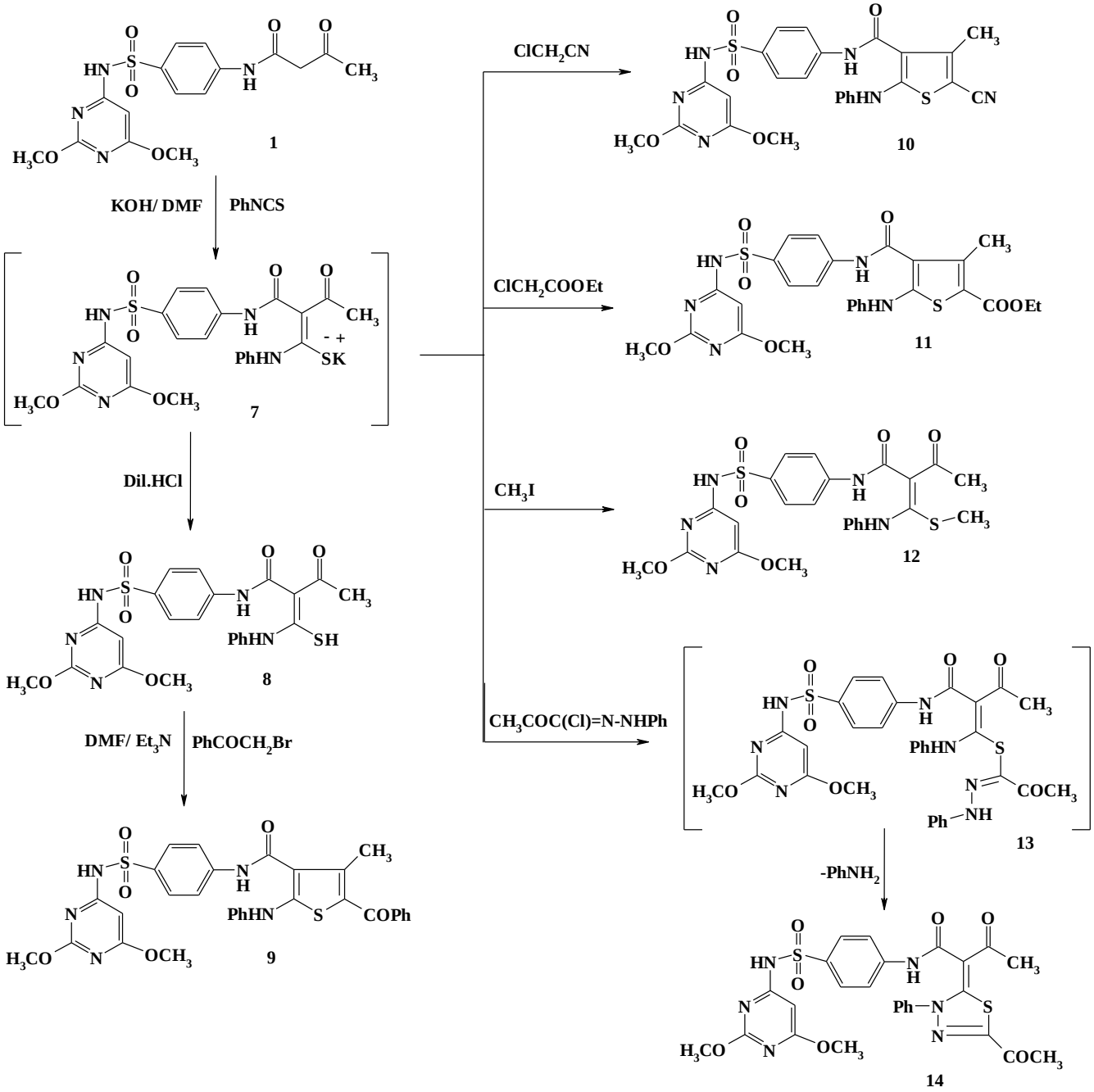
Compound **3** reacted with either malononitrile (**4a**) or cyanothioacetamide (**4b**) afforded compounds **5a** and **5b** respectively. The existence of the methyl group in conjugation with the cyano group enhances the reactivity of the first. Thus, the reaction of compounds **5a** and **5b** with elemental sulfur in ethanol containing a catalytic amount of triethylamine to give the thiophene derivatives **6a** and **6b**



Scheme 1

respectively. The analytical and spectral data of compounds **6a** and **6b** were consistence with their respective structures. Thus, the ^{1}H NMR spectrum of **6a** showed two multiplets at δ 1.39-1.42 & 2.03-2.09 ppm indicating the five CH_2 groups, a singlet at δ 6.92 ppm corresponding to 1H (thiophene ring)a multiplet at δ 7.27-7.75 ppm for the C_6H_5 with NH_2 groups and a singlet at δ 9.32 ppm for the NH amid group. Furthermore, the structure of compound **6a** was supported by ^{13}C-NMR spectrum (Scheme 1 and Experimental part).

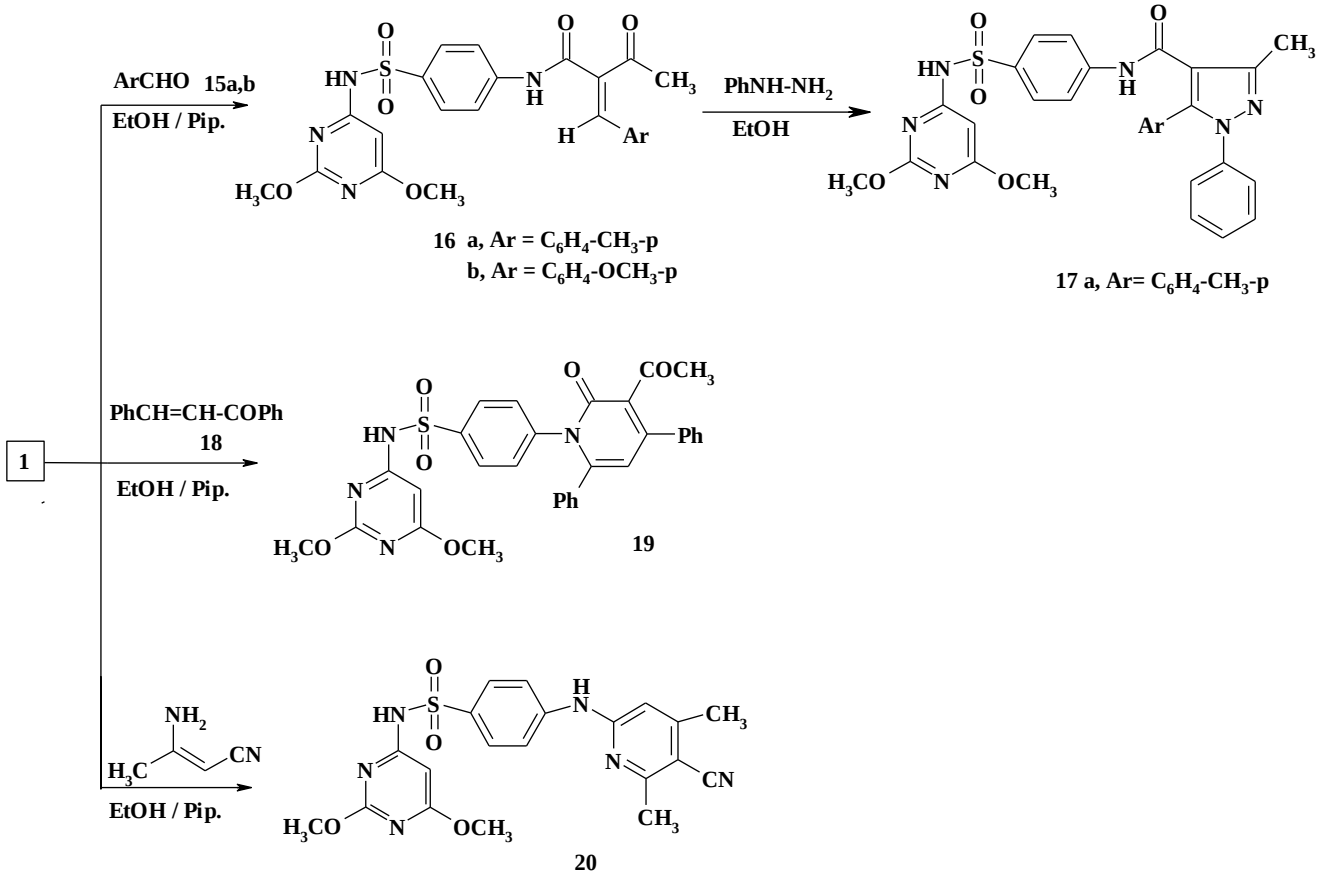
Next, the nucleophilic addition of **1** to phenyl isothiocyanate in dimethylformamide, in the presence of potassium hydroxide, afforded the corresponding potassium salt **7**. When the intermediate potassium salt was treated with dilute HCl, it gave the corresponding N-(4-(N-(2,6-Dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-2-(mercapto(phenylamino)methylene)-3-oxobutanamide **(8)** (Scheme 2). The IR spectrum of compound **8** revealed the absorption bands at 3385, 3223, 3156 and 1688, 1662 cm^{-1} corresponding to 3NH and 2CO groups, respectively. Its ^{1}H NMR spectrum showed four signals at 3.76, 10.15, 11.27, and 12.65 corresponding to 3NH and SH proton, respectively. Moreover, the mass spectrum of the product **8** exhibited a molecular ion peak at *m/z* 531 (M^++2). Treatment of compound **8** with 2-bromo-1-phenylethanone in dimethylformamide, in the presence of a catalytic amount of triethylamine, afforded the carboxamide **9** [20] (Scheme 2). The structure of compound **9** was elucidated from its spectroscopic and elemental analytical data. Thus, it showed absorption bands at 3390, 3244, 3120 and 1698, 1665 cm^{-1}due to 3NH and 2CO functions, whereas its ^{1}H NMR spectra revealed three signals at 4.03, 9.14 and 10.12 corresponding to 3NH protons beside the other protons in their proper positions. Heterocyclisation of the intermediate with chloroacetonitrile and ethyl 2-chloroacetate furnished in each case one isolable product (as tested by TLC). The reaction products were identified as 5-Cyano-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl) phenyl)-4-methyl-2-(phenylamino)thiophene-3-carboxamide (**10**) and ethyl 4-((4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)carbamoyl)-3-methyl-5-(phenyl amino)thiophene-2-carboxylate (**11**). The reaction proceeds *via* nucleophilic displacement of bromide to give *S*-alkylated intermediate followed by loss of water of the latter intermediate to give thiophene derivatives **10** or **11** as the final products. The structures of the products **10** and **11** were determined from spectroscopic and elemental analytical data. The IR spectrum of **10**, for example, indicated the presence of the absorption band at 3387 , 3262, 3146, 2220 and 1653 cm^{-1} corresponding to 3NH, C≡N, and C=O groups, respectively. Its ^{1}H NMR spectrum revealed the absence of CH_2 protons of chloroacetonitrile and showed signals at δ 3.97, 9.22 and 9.80 due to 3NH protons, in addition to an aromatic multiplet in the region δ 7.21- 7.99. The mass spectrum of **10** exhibited a molecular ion peak m/z at 550 corresponding to molecular formula $C_{25}H_{22}N_6O_5S_2$. The ^{13}CNMR of compound **10** revealed signals at 14.3 ppm (CH_3), 26.1 ppm ($2CH_3$),



Scheme 2

115.3 ppm (CN) and 165.2 ppm (CO), in addition to the sp^2 carbon atoms as in the experimental section. Furthermore, the nonisolated potassium salt was methylated by treatment with methyl iodide to afford the novel ketene *N*, *S*-acetal **12**. The structure of the synthesized product was established on the basis of their elemental analysis and spectral data [See the Experimental Part]. Heterocyclisation of the intermediate **7** with 2-oxo- *N*-phenylpropane hydrazonoyl chloride [21] furnished one isolable product (as tested by TLC).The reaction product was identified as 2-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl) sulfamoyl)phenyl)-3-oxobutanamide (**14**) (Scheme 2).

The structure of the product **14** was determined from spectroscopic and elemental analytical data. Thus, the IR spectrum of compound **14** revealed absorption bands at 3363, 3220, and 1725, 1713,1647 cm^{-1} corresponding to 2NH, and 3CO groups, respectively. Its ^1H NMR spectrum revealed signals at δ 2.17, 2.28 and 4.11, 10.25 due to $2CH_3$ and 2NH protons, in addition to an aromatic multiplet in the region δ 7.10- 7.79. The mass spectrum of **14** showed a molecular ion peak at *m/z* 596. The aforementioned results indicate that the reaction proceeds *via S*-alkylation [22], to give *S*-alkylated intermediate **13** which cyclized *in situ* under the employed reaction conditions and elimination of aniline molecule gave the desired product **14** (Scheme 2). Also, **1** reacts with aromatic aldehydes **15a,b** to afford the corresponding 2-(benzylidene)-3-oxobutanamide derivatives **16a**,**b** (Scheme 3). The IR spectrum of compound **16a**, taken as a typical example, revealed absorption bands at 3348 , 3232, and 1695, 1670 cm^{-1} corresponding to 2NH, and 2CO functions, respectively. Its ^1H NMR spectrum showed signals at δ 8.38 and 3.77, 10.18 corresponding to CH and 2NH protons in addition to aromatic protons at δ 7.36–7.94. When the benzylidene derivative **16a** was treated with phenyl hydrazine it afforded the corresponding pyrazole derivative **17a**. The analytical and spectral data are in agreement with the proposed structure (Scheme 3). Its mass spectrum showed a molecular ion peak at *m/z* 586. On the other hand, the



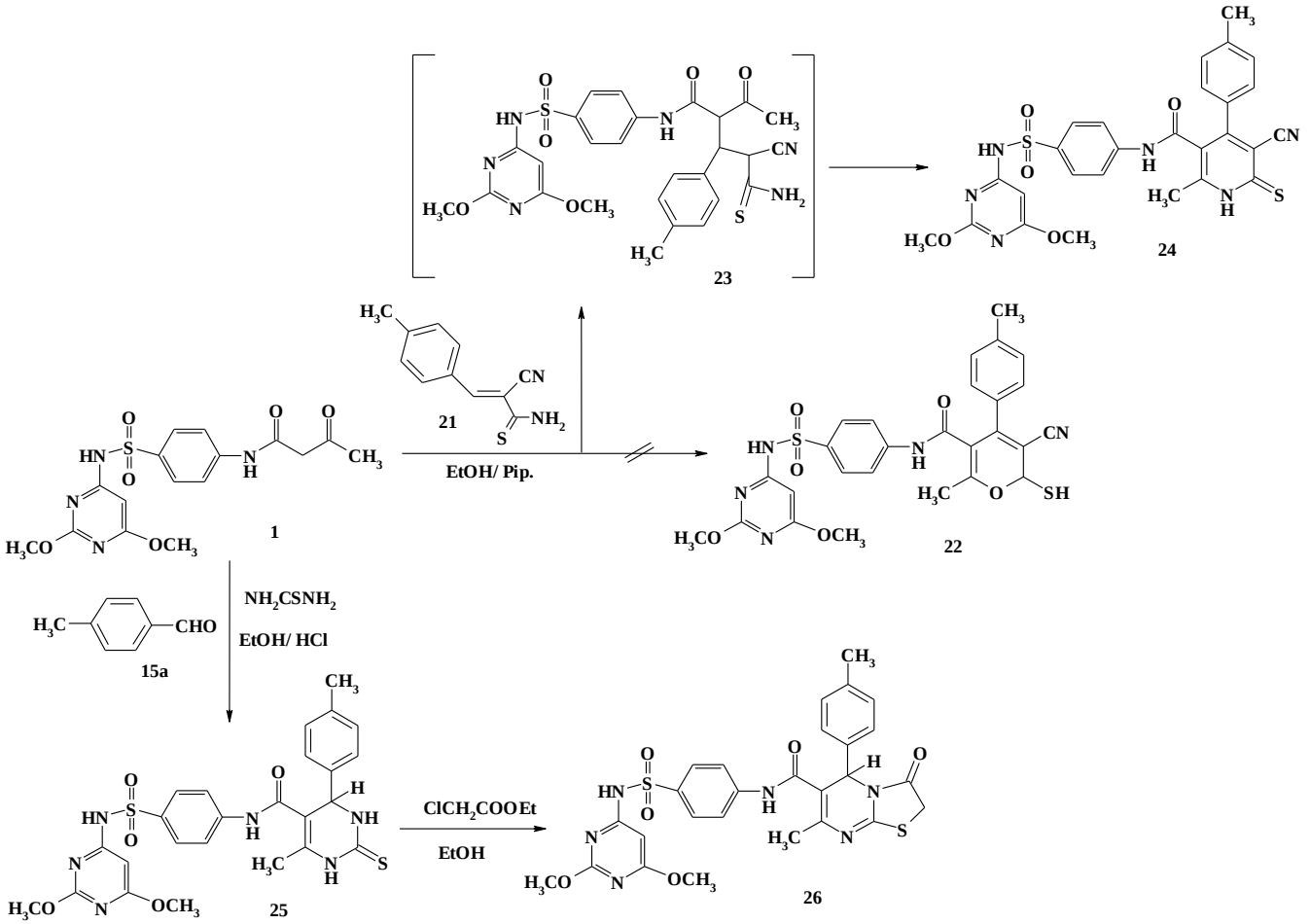
Scheme 3

reactivity of **1** towards chalcone and aminocrotonitrile was investigated. Thus, treatment of compound **1** with 1,3-diphenylpropenone (**18**) afforded a yellow crystalline product the proposed structure. Its ^{1}H NMR spectrum showed signals at δ 2.28 and 5.82 corresponding to CH_3 and CH-pyridine protons in addition to aromatic protons at δ 7.30- 7.85. The mass spectrum of **19** showed a molecular ion peak at *m/z* 582. also, the reaction of **1** with 3-aminocrotonitrile afforded the5-Cyano-4,6-dimethylpyridin-2-yl)amino)-benzenesulfonamide derivative **20**. Compound **20** was confirmed based on the elemental analysis and spectral data (scheme 3 and experimental part).

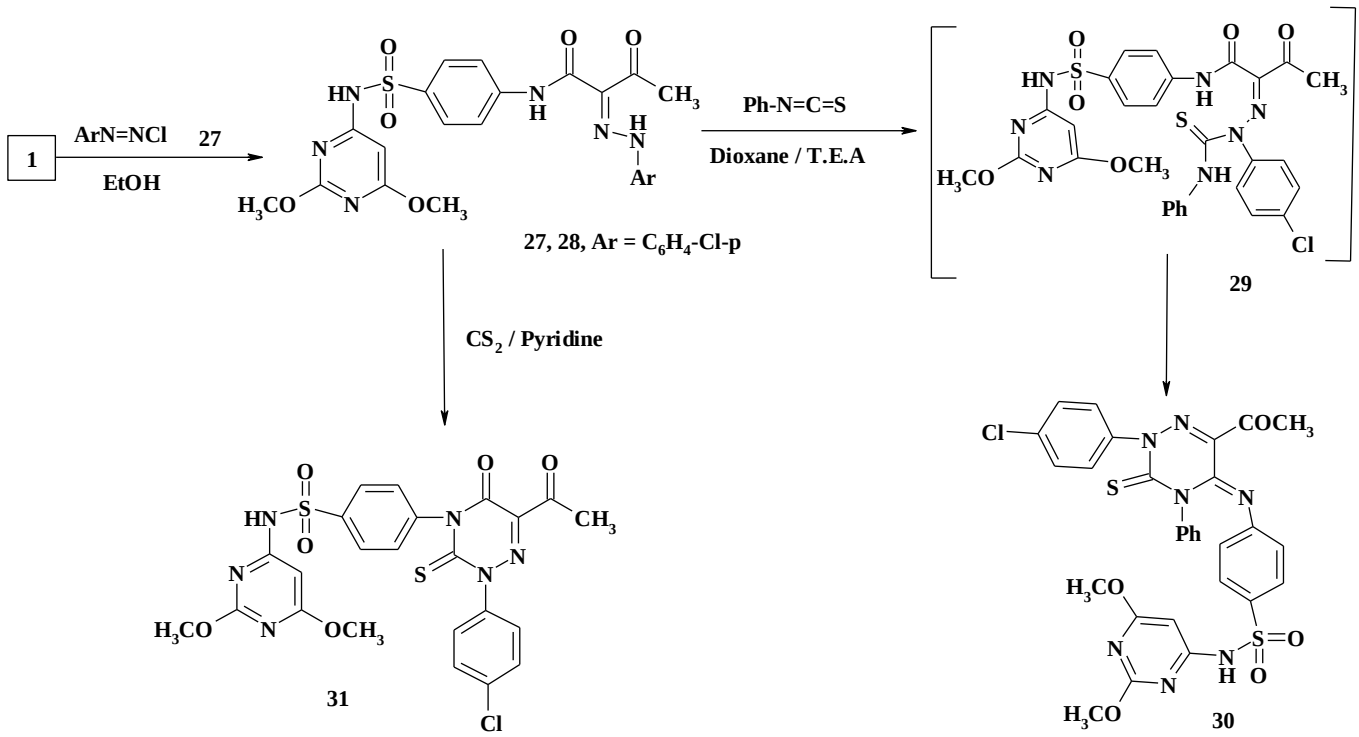
Moreover, the compound **1** reacted with arylidenecyanothioacetamide **21** in refluxing ethanol in the presence of piperidine to give a single product **24** (as examined by TLC). The structure of compound **22** was ruled out on the basis of elemental analysis and spectral data. Thus, the ^{1}H NMR spectrum of compound **24** revealed the presence of a singlet signal at δ = 9.54 and 11.17 ppm assigned to 2NH groups and no signal at rang δ= 4-5 ppm assigned for the thiopyran CH-4. So, the pyridinethione **24** is considered to be only the reaction product. The ^{13}C NMR of compound **24** revealed a signal at 18.3 (CH_3), 20.3 (CH_3), 26.8 ($2CH_3$), 116.7 (CN), and 166.7 ppm (CO), 175.1 ppm (CS), in addition to the sp^2 carbon atoms as in the experimental section.

Also, the mass spectrum of **24** is compatible with the molecular ion peak at m/z=576 (M^+) Corresponding to the molecular formula $C_{27}H_{24}N_6O_5S_2$. The formation of compound **24** can be explained on the basis of an initial Michael addition of the active methylene moiety in compound **1** to the activated double bond in the compound **21** to afford the acyclic Michael adduct intermediate **23** identified as 4-(3-acetyl-2-oxo-4,6-diphenylpyridin-1(2H)-yl)-N-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (**19**). The analytical and spectral data are in agreement with which undergo intramolecular cyclization via loss of H_2O and aromatization takes place during work up via air oxidation afforded compound **24** (Scheme 4).

Compound **1** reacts with a mixture of *p*-methylbenzaldehyde (**15a**) and thiourea in refluxing ethanol in the presence of hydrochloric acid, afforded **25**. The structure of **25** was inferred via elemental analysis, spectral data, and chemical transformations (See Scheme 4 and the Experimental section). Heating of compound **25** with ethylchloroacetate in refluxing ethanol afforded 6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide derivative **26**. This structure was confirmed based on the elemental analysis and spectral data. The IR spectrum of compound **26** exhibited the disappearance of the absorption band due to 2NH groups of thioxopyrimidine ring. The mass spectrum of **26** showed a molecular ion peak at *m/z* 594. The starting material **1** was proved to be a versatile for synthesis of some novel 1,2,4-triazine derivatives. Thus, compound **1** was coupled smoothly with diazonium salt **27**, derived from the appropriate aromatic amine (4-chloroaniline) in ethanol buffered with sodium acetate, to afford the respective hydrazone **28** (Scheme 5). The structure of the product was established on the basis of their elemental analyses and spectral data (IR, ^{1}H NMR, and MS) [see Experimental Part]. The spectral data revealed that this compound exists in the hydrazone form, as the ^{1}H NMR spectrum revealed three characteristic signals in the region δ 4.08, 9.17, 11.23 ppm assignable to a three NH protons in hydrazone structure **28** [19]. Further elucidation of the structure of **28** came from the reaction with phenylisothiocyanate in presence of 1,4-dioxan



Scheme 4



Scheme 5

containing triethylamine afforded 1,2,4-triazine derivative **30** [23] **.**The structure of compound **30** was confirmed based on elemental analysis and spectral data studied (Scheme 5 and ExperimentalPa Finally the reaction of compound **28** with carbon disulphide in pyridine gave the triazine derivative **31**. The analytical and spectral data of compound **31** were in

agreement with the assigned structures. The ^{1}H NMR spectrum of compound **31** revealed the absence of any signal corresponding to NH function of hydrazo group at high down field, beside the other protons in their proper positions. The $^{13}CNMR$ of compound **31** revealed signals at 26.3 (CH_3), 164.6 (CO), 175.2(CS) and 188.1 ($COCH_3$).

Biological Activity:-

Fifteen of the newly synthesized compounds were screened for their in vitro antibacterial activities against Gram positive bacteria; Staphylococcus aureus (G +ve), Gram negative bacteria; Pseudomonas aeruginosa (G -ve) and for their Antifungal activities against Aspergillus niger and Fusarium Oxysporum by the agar diffusion technique[24]. 1 mg/ml solution in dimethylformamide (DMF) was used. The bacteria are maintained on nutrient agar. DMF showed no inhibition zones. The agar media were inoculated with different microorganism's culture tested after 24 hours of inoculation at 37 °C for bacteria and for antifungal tested after 72 hours of inoculation at 28 °C. The diameter of inhibition zone (cm) was measured. The data obtained is summarized in table (1). The results indicated that most of the tested compounds exhibit slightly, moderately to highly active against bacteria but are slightly to moderately active against fungi. Compound **31**, was found to be highly active against Staphylococcus aureus (G +ve) and moderately active against Pseudomonas aeruginosa (G -ve) bacteria, while compound **9** to be highly active against Pseudomonas aeruginosa (G -ve) bacteria.

Table (1). Antimicrobial activity of some newly synthesized compounds.

Compound no.	Staphylococcus aureus (G +ve)	Pseudomonas aeruginosa (G -ve)	Aspergillus niger (fungi)	Fusarium Oxysporum (fungi)
3	+	++	+	-
5a	+	+	-	-
6a	++	+	-	+
9	-	+++	++	+
10	++	-	+	-
14	+	++	-	+
16a	+	-	-	+
17a	++	+	+	-
19	-	+	-	+
20	+	+	+	+
24	++	++	-	-
25	+	-	++	-
26	-	++	+	-
30	++	+	+	++
31	+++	++	-	+
DMF	-	-	-	-
Chloramphenicol	+++	+++		
Clotrimazole	-	-	+++	+++

Inhibition Zone = 0.1 - 0.5 cm beyond control = + (slightly active); Inhibition Zone = 0.6 - 1.0 cm beyond control = + + (moderately active); Inhibition Zone = 1.1 - 1.5 cm beyond control = + + + (highly active); Inhibition Zone = 0.0 cm beyond control = − (inactive).

Conclusion

The achieved derivatives of new thiophene, pyridine, pyrimidine, pyrazole and 1, 2, 4- triazole that are expected to have biological activities, have been synthesized and their structures confirmed by their spectral data, elemental analyses, and with some chemical reactions.

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