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Synthesis of some new aminothiophene, pyridazine, pyrimidine and thienopyrimidine derivatives with expected biological activity

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ABSTRACT

Treatment of 1 with active methylene reagents 2a, b and elemental sulfur furnished aminothiophene derivatives 3a, b. diazotization of 3a with active methylene compounds, namely malononitrile (5a) and acetylacetone (5b) afforded the corresponding hydrazono derivatives 6a, b. pyridazine derivatives 9a, b, 10 and 12a, b were obtained by reaction of 6a with ethylcyanoacetae, ethylacetoacetate, malononitrile and arylidinemalononitrile 11a, b, respectively. Furthermore, the reaction of 6b with urea and/or thiourea afforded the pyrimidine derivatives 14a, b. Also, the interaction of 3a with phenyl isothiocyanate, thiourea and formamide afforded the corresponding thienopyrimidine derivatives 16, 17 and 18 respectively. Schiff base 19 was obtained from the reaction of 3a with benzaldehyde. Condensation of 3a with DMF-DMA afforded the derivative 20. Compound 20 cyclized with hydrazine hydrate to give 23. Also, when compound 3b reacted with triethylorthoformate afforded the intermediate 21, which cyclized into the thienopyrimidine derivative 25. The reaction of 3b with phenyl isothiocyanate in boiling ethanol furnished the thiourea derivative 26. Treatment of 26 with hydrazine hydrate produced thienopyrimidine derivative 27. © 2015 Trade Science Inc. - INDIA

KEYWORDS

Aminothiophenes;
Pyridazines;
Pyrimidines;
Thienopyrimidines;
Antimicrobial activity.

INTRODUCTION

Aminothiophene derivatives are an important class of heterocycles found in several biologically active and natural compounds. This class of compounds has demonstrated a broad spectrum of activities and applications as pharmaceuticals and agrochemicals, dyes, biodiagnostics, and electronic and optoelectronic devices[1]. They have been reported to exert antitubercular[2], anti-inflammatory[3], antimicrobial[4] and ntianxiety[5] properties. A survey of the literature also reveals that substituted aminothiophenes are potent, and tyrosine kinases of the fibroblast growth factor receptors (FGRF)[6]. Antifungal[7] and antitumor[8] properties have also been extensively described, resulting in marketed antifungal agents such as sertaconazol. On the other hand, pyridazines posses a wide variety of biological activities such as, antidepressant[9], antihypertensive[10], anticancer[11] and antimicrobial[12] activities. Recently, pyridazinone nucleus has been extensively studied in the search for new and selective medicinal agents as drugs acting on the cardiovascular system[13]. In chemotherapy pyrimidines are considered as privileged structures with a large spectrum of biological activities. They are known very widely in Nature since they are components of RNA and DNA. Several pyri-

midine derivatives exhibit diverse pharmacological activities as antiviral[14], antimalarial[15], antithyroid[16] and antimicrobial[17] agents. Moreover, thienopyrimidine derivatives, which are structure analogues of purines, have been focus of great interest because of their large range of pharmacological activities[18] as antibacterial[19], antifungal[20], analgesic[21], antipyretic[22], antihistaminic[23], radioprotective[24]. Many thieno [2,3-*d*]pyrimidine derivatives were reported as phosphodiesterase inhibitors[25] insecticidal, pesticidal and acaricidal activities[26]. In connection with our efforts to synthesize heterocycles[27-30] from readily available starting materials, we report here in the synthesis of some novel pyridazine, pyrimidine and thienopyrimidine derivatives in order to investigate the antimicrobial activity.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (υ, cm-1). The ^{1}H NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 200, 300 MHz on a Varian Gemini NMR spectrometer (d, 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. Microbiology screening was carried out in Botany Department, Faculty of Science, Al-Azhar University, Assiut.

Preparation of compounds 3a, b: general procedure

A mixture of compound 1 (0.01 mole), elemental sulfur (0.01 mole) and malononitrile or ethyl cyanoacetate (0.01mole) in absolute ethanol (30 mL) containing few drops of triethylamine was refluxed for 6 h. The reaction mixture was cooled and the solid product so formed was collected and crystallized from the proper solvent to give 3a, b.

4-((5-Amino-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (3a)

It was obtained as brown crystals from dioxane; yield 85%; mp. 232°C; IR (KBr) υ cm-1 3400, 3345 (NH_2), 3226, 3190 (2NH), 3052 (CH-arom.), 2925 (CH-aliph.), 2207 (CN); ^{1}H NMR (DMSO-d_6) δ = 3.45 (s, 1H, NH), 5.26 (s, 1H, NH_2), 6.22 (s, 1H, CH-thiophene), 7.24-8.05 (m, 8H, Ar-H+ NH), ^{13}C-NMR (DMSO-d_6): 115.3 (CN), 79.4, 106.5, 113.2, 116.6, 125.5, 129.3, 130.7, 149.1, 150.4, 153.2, 155.8 (Ar-C). Anal. Calc. For $C_{15}H_{12}N_6O_2S_2$ (372.43): C, 48.38; H, 3.25; N, 22.57; S, 17.22%. Found: C, 48.60; H, 3.46; N, 22.78; S, 17.44%.

Ethyl2-amino-4-((4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)amino)thiophene-3-carboxylate (3b)

It was obtained as brown crystals from ethanol; yield 80%; mp. 183°C; IR (KBr): υ cm-1 3412, 3357 (NH_2), 3247, 3186 (2NH), 3049 (CH-arom.), 2928 (CH-aliph.), 1722 (CO).^{1}H NMR (DMSO-d_6) δ = 1.34 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 3.15 (s, 1H, NH), 4.24 (q, *J* = 7.0 Hz, 2H, CH_2, OCH_2CH_3), 5.98 (s, 1H, CH-thiophene), 7.20-8.08 (m, 10H, Ar-H+ NH + NH_2). Anal. Calc. for $C_{17}H_{17}N_5O_4S_2$ (419.48): C, 48.68; H, 4.08; N, 16.70; S, 15.29%. Found: C, 48.90; H, 4.32; N, 16.95; S, 15.53%.

Preparation of compounds 6a, b: general procedure

To a cold solution (0–5 °C) of malononitrile (5a) (0.01 mol) and acetylacetone (5b) (0.01 mole) in ethanol (20 mL) containing sodium acetate (2 g) an equimolar amount of diazotized 4-((5-amino-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl) benzenesulfonamide (3a) [which was prepared by adding $NaNO_2$ (0.01 mol) solution to a cold solution of 3a (0.01 mol) in acetic acid (3 mL), HCl (2 mL)] was gradually added while stirring. The solid product formed upon cooling in an ice-bath was collected by filtration, washed with water and crystallized from ethanol to give 6a, b.

(3-Cyano-4-((4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)amino)thiophen-2-yl)carbonohydraz- noyl dicyanide (6a)

It was obtained as Pale yellow crystals from ethanol; yield 71%; m.p. 182°C IR (KBr): υ cm-1 3382, 3270, 3192 (3NH), 3055 (CH-arom.), 2927 (CH-aliph.), 2203, 2215 (CN); ^{1}H NMR (DMSO-d_6) δ = 4.12 (s, 1H, NH), 5.42 (s, 1H, CH-thiophene), 7.24-8.02 (m, 8H, Ar-H+ NH), 11.34 (s, 1H, NH). Anal. Calc. for $C_{18}H_{11}N_9O_2S_2$ (449.48): C, 48.10; H, 3.43;

N, 2.47; S, 14.27%. Found: C, 48.31; H, 2.68; N, 28.26; S, 14.48%.

4-((4-Cyano-5-(2-(2,4-dioxopentan-3-ylidene)hydrazinyl)thiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (6b)

It was obtained as Pale yellow crystals from ethanol; yield 70%; m.p. 162°C IR (KBr): υ cm-1 3362, 3212, 3175 (3NH), 3055 (CH-arom.), 2927 (CH-aliph.), 2202 (CN), 1718 (2CO); ^{1}H NMR (DMSO-d_6) δ=2.42 (s, 6H, $2CH_3$) 3.36 (s, 1H, NH), 5.59 (s, 1H, CH-thiophene), 7.17-8.03 (m, 8H, Ar-H+ NH), 8.12 (s, 1H, NH). Anal. Calc. for $C_{20}H_{17}N_7O_4S_2$ (483.53): C, 49.68; H, 3.54; N, 20.28; S, 13.26%. Found: C, 49.88; H, 3.75; N, 20.49; S, 13.47%.

Preparation of compounds 9a, b and 10: general procedure

Equimolar amounts of 6a (0.01 mole) and an active methylene compound, namely ethyl cyanoacetate, ethyl acetoacetate or malononitrile (0.01 mole) in ethanol (40 mL) containing piperidine (5 drops), were heated under reflux for 8–10 h. The solid product so obtained on cooling was collected by filtration and crystallized from the appropriate solvent to give compounds 9a, b and 10, respectively.

4-((5-Amino-3,5-dicyano-6-oxopyridazin-1(6H)-yl)-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl) benzenesulfonamide (9a)

It was obtained as green crystals from DMF/ethanol; yield 50%; m.p. 300°C IR (KBr): υ cm-1 3420, 3354 (NH_2), 3241, 3179 (2NH), 3056 (CH-arom.), 2947 (CH-aliph.) 2205, 2218 (3Ca"N), 1690 (C=O); ^{1}H NMR (DMSO-d_6): δ = 3.25 (s, 1H, NH), 5.88 (s, 1H, CH-thiophene), 7.27-8.23 (m, 8H, Ar-H+ NH), 8.29 (s, 2H, NH_2). ^{13}C-NMR (DMSO-d_6): 115.2 (CN), 115.8 (2CN), 75.9, 77.7, 95.3, 113.9, 116.2, 125.2, 129.1, 130.4, 149.8, 154.5, 155.3, 157.6, 158.2, 158.8 (Ar-C), 166.7 (CO). Anal. Calc. for $C_{21}H_{12}N_{10}O_3S_2$ (516.52): C, 48.83; H, 2.34; N, 27.12; S, 12.42%. Found: C, 48.62; H, 2.56; N, 27.35; S, 12.63%.

4-((5-(5-Acetyl-4-amino-3-cyano-6-oxopyridazin-1(6H)-yl-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (9b)

It was obtained as green crystals from DMF/ethanol; yield 55%; m.p. 265°C IR (KBr): υ cm-1 3423, 3352, 3249, 3169 (NH_2, 2NH), 3050 (CH-arom.), 2928 (CH-aliph.) 2207, 2215 (2Ca"N), 1692, 1667 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 2.68 (s, 3H, $COCH_3$), 4.28 (s, 1H, NH), 6.26 (s, 1H, CH-thiophene), 7.22-8.42 (m, 10H, Ar-H + NH+ NH_2). Anal. Calc. for $C_{22}H_{15}N_9O_4S_2$ (533.55): C, 49.52; H, 2.83; N, 23.63; S, 12.02 %. Found: C, 49.73; H, 2.61; N, 23.85; S, 12.23 %.

4-((5-(4-Amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (10)

It was obtained as light brown crystals from DMF/ethanol; yield 55%; m.p. 294æ%C. IR (KBr): υ cm-1 3430, 3379, (NH_2), 3312, 3225, 3176 (3NH), 3048 (CH-arom.), 2926 (CH-aliph.), 2207, 2220 (3Ca"N); ^{1}H NMR (DMSO-d_6) δ = 4.22 (s, 1H, NH), 5.64 (s, 1H, CH-thiophene), 7.26-8.18 (m, 10H, Ar-H+ NH+ NH_2), 8.45 (s, 1H, C=NH). Anal. Calc. for $C_{21}H_{13}N_{11}O_2S_2$ (515.54): C, 48.93; H, 2.54; N, 29.89; S, 12.44%. Found: C, 48.71; H, 2.76; N, 29.67; S, 12.67%.

Preparation of compounds 12a, b: general procedure

A mixture of 6a (0.01 mole), arylidinemalononitriles 11a, b (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 8 hrs.

The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and recrystallized from the proper solvent to give 12a, b.

4-((4-Cyano-5-(3,5-dicyano-4-imino-6-phenylpyridazin-1(4H)-yl)thiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (12a)

It was obtained as yellow crystals from dioxane; yield 70%; m.p. 235°C. IR (KBr): υ cm-1 3394, 3282, 3193 (3NH), 3057 (CH-arom.), 2920 (CH-aliph.), 2202, 2220 (3CN); ^{1}H NMR (DMSO-d_6) δ = 3.27 (s, 1H, NH), 5.72 (s, 1H, CH-thiophene), 7.08-8.16 (m, 13H, Ar-H+ NH), 8.29 (s, 1H, C=NH). Anal. Calc. for $C_{27}H_{16}N_{10}O_2S_2$ (576.62): C, 56.24; H, 2.80; N, 24.29; S, 11.12%. Found: C, 56.45; H, 2.58; N, 24.50;

S, 11.33%.

4-((4-Cyano-5-(3,5-dicyano-4-imino-6-p-toly)pyridazin-1(4H)-yl)thiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (12b)

It was obtained as yellow crystals from dioxane; yield 72%; m.p. 278°C. IR (KBr): υ cm-1 3382, 3264, 3179 (3NH), 3047 (CH-arom.), 2928 (CH-aliph.), 2205, 2222 (3CN); ^{1}H NMR (DMSO-d_6) δ = 2.32 (s, 3H, CH_3), 4.16 (s, 1H, NH), 5.43 (s, 1H, CH-thiophene), 7.15-8.27 (m, 13H, Ar-H+ NH+ C=NH). Anal. Calc. for $C_{28}H_{18}N_{10}O_2S_2$ (590.65): C, 56.94; H, 3.07; N, 23.71; S, 10.86 %. Found: C, 56.72; H, 3.28; N, 23.92; S, 10.65%.

Preparation of compounds 14a, b: general procedure

To a mixture of 6b (0.01 mole) and urea or thiourea (0.01 mole) in absolute ethanol (30 mL), sodium ethoxide (0.01 mole of Na in 10 mL ethanol) was added. The reaction mixture was refluxed for 8 h, concentrated and cooled. The separated solid was filtered off, washed with water several times and crystallized from the proper solvent to afford compounds 14a, b.

4-((4-Cyano-5-(2-(4,6-dimethyl-2-oxopyrimidin-5(2H)-ylidene)hydrazinyl)thiop-hen-3-yl) amino)-N- (pyrimidin-2-yl)benzenesulfonamid (14a)

It was obtained as orange yellow crystals from dioxane; yield 66%; m.p. 289°C. IR (KBr): υ cm-1 3347, 3216, 3162 (3NH), 3055 (CH-arom.), 2936 (CH-aliph.), 2203 (CN), 1673 (CO); ^{1}H NMR (DMSO-d_6) δ = 2.12 (s, 6H, $2CH_3$), 4.02 (s, 1H, NH), 6.32 (s, 1H, CH-thiophene), 7.36-8.25 (m, 8H, Ar-H+ NH), 11.48(s, 1H, hydrazinyl NH).^{13}C-NMR (DMSO-d_6): 15.2 ($2CH_3$), 80.2, 106.4, 113.7, 116.6 125.8, 129.2, 130.4, 137.9, 148.7, 151.6, 155.2, 155.9, 157.5, 158.8 (Ar-C), 167.3 (CO). Anal. Calc. for $C_{21}H_{17}N_9O_3S_2$ (507.56): C, 49.69; H, 3.38; N, 24.84; S, 12.64%. Found: C, 49.92; H, 3.59; N, 24.63; S, 12.85%.

4-((4-Cyano-5-(2-(4,6-dimethyl-2-thioxopyrimidin-5(2H)-ylidene)hydrazinyl) thiophen-3-yl) amino)-N-(pyrimidin-2-yl)benzenesulfonamid (14b)

It was obtained as Orange crystals from dioxane; yield 68%; m.p. 296°C. IR (KBr): υ cm-1 3365, 3232, 3178 (3NH), 3050 (CH-arom.), 2924 (CH-aliph.), 2208 (CN); ^{1}H NMR (DMSO-d_6) δ = 2.07 (s, 6H, $2CH_3$), 4.13 (s, 1H, NH), 5.44 (s, 1H, CH-thiophene), 7.32-8.19 (m, 8H, Ar-H+ NH), 11.22 (s, 1H, hydrazinyl NH). Anal. Calc. for $C_{21}H_{17}N_9O_2S_3$ (507.56): C, 48.17; H, 3.27; N, 24.08; S, 18.37%. Found: C, 48.38; H, 3.49; N, 24.30; S, 18.58%.

4-((4-Imino-3-phenyl-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (16)

To a solution of compound 3a (0.01 mol) in pyridine (30 mL), phenyl isothiocyanate (0.01 mol) was added. The mixture was heated under reflux for 24 h. The solid product that formed after cooling was collected by filtration and recrystallized from dioxane to give 16 (57%) as brown crystals, m.p. >300°C. IR (KBr): υ cm-1 3374, 3310, 3228, 3152 (4NH), 3056 (CH-arom.), 2947 (CH-aliph.); ^{1}H NMR (DMSO-d_6): δ = 3.25 (s, 1H, NH), 6.47 (s, 1H, CH-thiophene), 7.23-8.20 (m, 14H, Ar-H+ 2NH), 8.24 (s, 1H, C=NH). MS, m/z (%): 508 [M^+] (16.85), 77 (100%). Anal. Calc. for $C_{22}H_{18}N_7O_2S_3$ (508.63): C, 51.95; H, 3.57; N, 19.28; S, 18.91%. Found: C, 51.73; H, 3.78; N, 19.51; S, 18.68%.

4-((4-Amino-2-thioxo-1,2-dihydrothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl) benzenesulfonamide (17)

A mixture of compound 3a (0.01 mole) and thiourea (0.01 mole) was heated on an oil bath for 4 h. On cooling the product solidiûed, which was recrystallized from DMF / ethanol to give 17 as yellow crystals, yield 71%; m.p. >300°C. IR (KBr): υ cm-1 3415, 3373 (NH_2), 3315, 3278, 3181 (3NH), 3050 (CH-arom.), 2928 (CH-aliph.); ^{1}H NMR (DMSO-d_6) δ = 4.28 (s, 1H, NH), 5.25 (s, 1H, CH-thiophene), 6.68 (s, 2H, NH_2), 7.34-8.28 (m, 9H, Ar-H+ 2NH). Anal. Calc. for $C_{16}H_{13}N_7O_2S_3$ (431.52): C, 44.54; H, 3.04; N, 22.72; S, 22.29%. Found: C, 44.75; H, 3.26; N, 22.95; S, 22.50%.

4-((4-Aminothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl)benzene sulfonamide (18)

A solution of compound 3a (0.01 mol) in formamide (10 mL) was heated under reflux for 5 h, then allowed to cool and poured into cold water. The solid product

was collected and crystallized from ethanol / dioxan to give 18 as green crystals, yield 69%; m.p. > 300°C. IR (KBr): υ cm-1 3426, 3378 (NH_2), 3225, 3189 (2NH), 3048 (CH-arom.), 2926 (CH-aliph.); ^{1}H NMR (DMSO-d_6) δ = 3.22 (s, 1H, NH), 6.02 (s, 1H, CH-thiophene), 7.38-8.13 (m, 10H, Ar-H+ NH+ NH_2), 8.24 (s, 1H, CH-pyrimidine), Anal. Calc. for $C_{16}H_{13}N_7O_2S_2$ (399.46): C, 48.11; H, 3.28; N, 24.55; S, 16.05%. Found: C, 48.33; H, 3.49; N, 24.77; S, 16.28%.

4-((5-(Benzylideneamino)-4-cyanothiophen-3-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (19)

A mixture of compound 3a (0.01 mole), benzaldehyde (0.01 mole) and a few drops of piperidine in ethanol (30 mL) was refluxed for 7 h. The solid precipitate produced on hot was collected by filtration and recrystallized from dioxane to give 19 as white crystals, yield 72%; mp. 280°C. IR (KBr): υ cm-1 3282, 3193 (2NH), 3057 (CH-arom.), 2920 (CH-aliph.), 2208 (CN); ^{1}H NMR (DMSO-d_6) δ = 3.27 (s, 1H, NH), 5.20 (s, 1H, CH-thiophene), 7.21-8.14 (m, 14H, Ar-H+ NH+ N=CH). Anal. Calc. for $C_{22}H_{16}N_6O_2S_2$ (460.54): C, 57.38; H, 3.50; N, 18.25; S, 13.92%. Found: C, 57.60; H, 3.72; N, 18.48; S, 13.70%.

4-[4-Cyano-5-(dimethylamino-methyleneamino)-thiophen-3-ylamino]-N-pyrimidin-2-yl-benzenesulfonamide (20)

A solution of 3a (0.01 mol) in dry xylene (30 mL) and DMF-DMA (0.015 mol) was heated under reûux for 5 h. The reaction mixture was then cooled. The solid product thus formed was filtered off and crystallized from ethanol to give 20 as yellow crystals, yield 64%; m.p. 168°C. IR (KBr): υ cm-1 3347, 3198 (2NH), 3048 (CH-arom.), 2984 (CH-aliph.), 2208 (CN); ^{1}H NMR (DMSO-d_6) δ = 2.60 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.64 (s, 1H, NH), 5.52 (s, 1H, CH-thiophene), 7.25-7.98 (m, 8H, Ar-H+ NH), 8.05 (s, 1H, N=CH). Anal. Calc. $C_{18}H_{17}N_7O_2S_2$ (427.51): C, 50.57; H, 4.01; N, 22.93; S, 15.00%. Found: C, 50.78; H, 4.22; N, 22.71; S, 15.23%.

4-((3-Amino-4-imino-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl) benzenesulf- onamide (23)

To a solution of 20 (0.01 mol) in ethanol (30 mL), hydrazine hydrate (2 mL) was added. The reaction mixture was heated under reflux for 4 h. The solid product that formed was collected by filtration and recrystallized from dioxane to give 23 as yellow crystals, yield 57%; mp. 276°C. IR (KBr): υ cm-1 3412, 3384 (NH_2), 3308, 3266, 3195 (3NH), 3060 (CH-arom.), 2945 (CH-aliph.); ^{1}H NMR (DMSO-d_6) δ = 3.18 (s, 1H, NH), 5.12 (s, 2H, NH_2), 6.65 (s, 1H, CH-thiophene), 7.33-8.26 (m, 10H, Ar-H+ 2NH+ CH-pyrimidine). Anal. Calc. for $C_{16}H_{14}N_8O_2S_2$ (414.47): C, 46.37; H, 3.40; N, 27.04; S, 15.47%. Found: C, 46.58; H, 3.62; N, 27.26; S, 15.69%.

4-((3-Amino-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl) benzenesulfon amide (25)

A mixture of 3b (0.01 mol) and triethylorthoformate (5 mL) was heated under reflux for 6 h. After cooling, the solvent was removed in vacuo and the brownish red oil obtained was used directly without purification in the next step. A mixture of the latter intermediate (0.01 mol) and excess of hydrazine hydrate (2 mL) in ethanol (10 mL) was refluxed for 3 h. The solvent was then removed under reduced pressure. The solid product obtained was triturated with water, filtered and recrystallized from dioxane to give 25 as pale buff crystals, yield 70%; m.p. 240°C. IR (KBr): υ cm-1 3410, 3355 (NH_2), 3246, 3191 (2NH), 3064 (CH-arom.), 2947 (CH-aliph.), 1675 (CO); ^{1}H NMR (DMSO-d_6) δ = 2.47 (s, 2H, NH_2), 4.20 (s, 1H, NH), 6.49 (s, 1H, CH-thiophene), 7.31-8.11 (m, 8H, Ar-H+ NH), 8.26 (s, 1H, CH-pyrimidine). Anal. Calc. for $C_{16}H_{13}N_7O_3S_2$ (415.46): C, 46.26; H, 3.15; N, 23.60; S, 15.44%. Found: C, 46.47; H, 3.38; N, 23.82; S, 15.66%.

Ethyl2-(3-phenylthioureido)-4-((4-(N-(pyrimidin-2-yl)sulfamoylphenyl)am-ino)thiophene-3-carboxylate (26)

A mixture of 3b (0.01 mol) and phenyl isothiocyanate (0.01 mol) in absolute ethanol (20 mL) was heated under reflux for 4 h. The solid product that formed after cooling was collected by filtration and recrystallized from ethanol to give 26 as buff crystals, yield 62%; mp. 220°C. IR (KBr): υ cm-1 3358, 3265, 3220, 3168 (4NH), 3060 (CH-arom.), 2954 (CH-aliph.),

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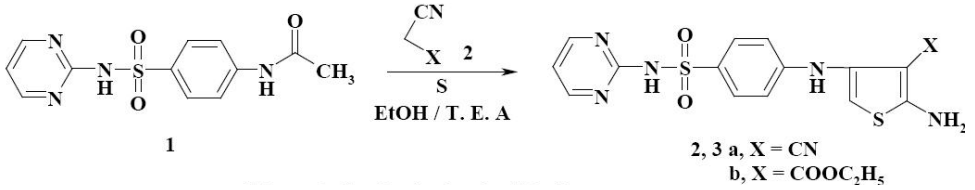


Scheme 1 : Synthesis of aminothiophenes

1780, (CO); ^{1}H NMR (DMSO-d_6): δ = 1.36 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.15 (s, 1H, NH), 3.72 (s, 1H, NH), 4.21 (q, J = 7.2 Hz, 2H, CH_2, OCH_2CH_3), 4.46 (s, 1H, NH), 6.27 (s, 1H, CH-thiophene), 7.18-8.13 (m, 13H, Ar-H+ NH). Anal. Calc. for $C_{24}H_{22}N_6O_4S_3$ (554.67): C, 51.97; H, 4.00; N, 15.15; S, 17.34%. Found: C, 51.75; H, 4.20; N, 15.36; S, 17.56%.

4-((3-Amino-4-oxo-2-(phenylamino)-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (27)

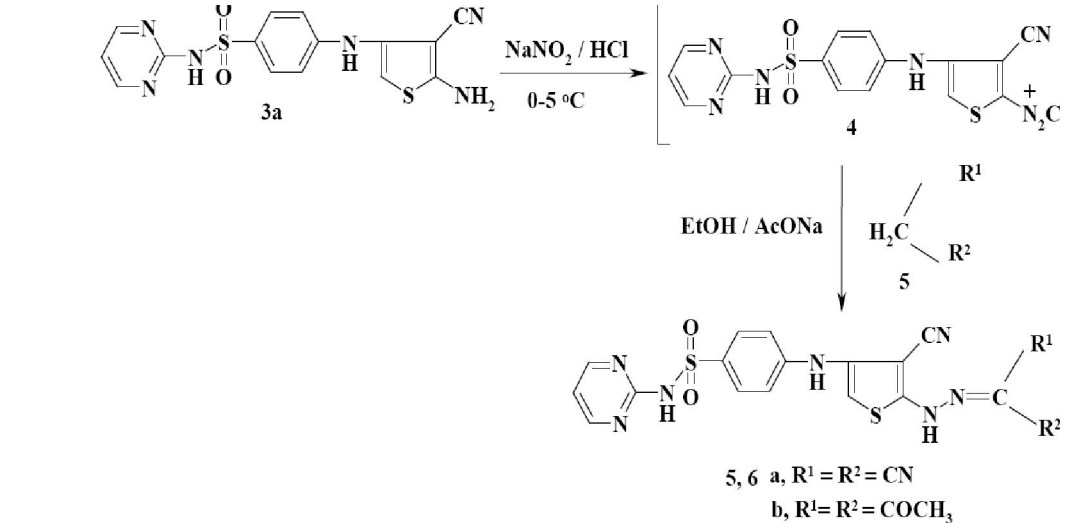
A mixture of 26 (0.01 mol) and excess hydrazine hydrate (3 mL) was heated under reflux for 15 h. The solid product that formed after cooling was collected by filtration and recrystallized from ethanol / dioxane to give 27 as brown crystals, yield 64%; mp. 292°C. IR (KBr): υ cm^{-1} 3400, 3350 (NH_2), 3272, 3215, 3175 (3NH), 3055 (CH-arom.), 2928 (CH-aliph.), 1668 (CO); ^{1}H NMR (DMSO-d_6) δ = 2.74 (s, 2H, NH_2), 3.12 (s, 1H, NH), 4.11 (s, 2H, 2NH), 6.63 (s, 1H, CH-thiophene), 7.35-8.32 (m, 13H, Ar-H+ NH). MS, m/z (%): 506 [M$^+$] (11.83), 93 (100%). Anal. Calc. for $C_{22}H_{18}N_8O_3S_2$ (506.57): C, 52.16; H, 3.58; N, 22.12; S, 12.66%. Found: C, 52.37; H, 3.80; N, 22.33; S, 12.89%.

RESULTS AND DISCUSSION

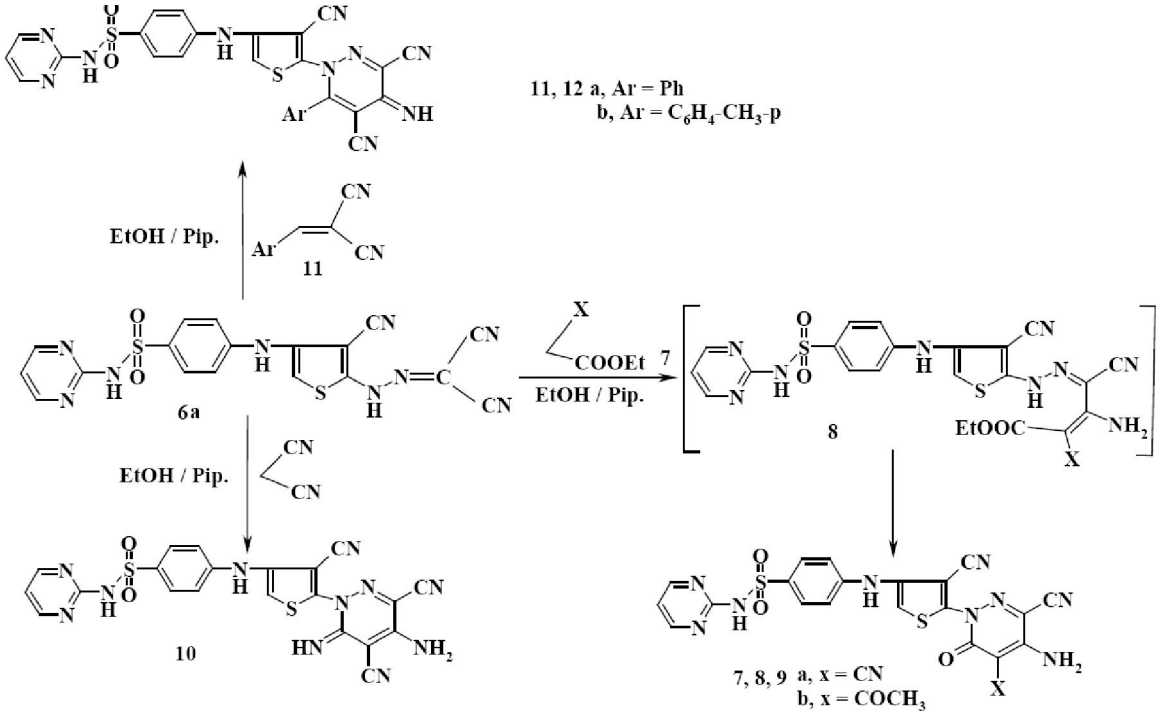
Treatment of N-[4-(Pyrimidin-2-ylsulfamoyl)-phenyl]-acetamide (1)[31] with either malononitrile 2a or ethyl cyanoacetate 2b and elemental sulfur in presence of few drops of triethyl amine under Gewald reaction conditions[32] furnished aminothiophene derivatives 3a, b (Scheme 1). The IR spectrum of compound 3a exhibited the appearance of absorption band due to the NH_2 and CN group. The ^{1}H NMR spectrum of compound 3a revealed the presence of two protons as a singlet at δ = 5.26 ppm assignable to the NH_2 group beside the other protons in their proper positions.

The starting material 3a, b was proved to be a versatile for synthesis of some novel pyridazine, pyrimidine and thienopyrimidine derivatives. diazotization of compound 3a was accomplished through its reaction with cold hydrochloric acid and saturated aqueous sodium nitrite solution to yield diazonium chloride 4 which was further coupled with compounds bearing active methylene functions namely; malononitrile (5a) and acetylacetone (5b) to afford the corresponding hydrazono derivatives[33] 6a, b (Scheme 2). Compounds 6a, b were characterized by their elemental analysis, IR and ^{1}H-NMR data (see Experimental). For example, the IR spectrum of 6a shows an absorption band at 3382, 3270, 3192 cm^{-1} corresponding to the vibrations of the 3NH groups and the presence of the absorption band of the 3CN functional groups at υ 2203, 2215 cm^{-1}. The spectral data revealed that this compound exists in the hydrazone form, as the ^{1}H-NMR spectrum showed a signal at 11.34 corresponding to NH hydrazo group.

The reactivity of compound 6a with active methylene compounds, such as ethyl cyanoacetate, ethyl cetoacetate and malononitrile, was investigated. Thus, when compound 6a reacted with active methylene compounds 7a, b in refluxing ethanol in the presence of catalytic amounts of piperidine, the pyridazinone derivatives 9a, b were obtained. Formation of 9 is believed to be formed via the intermediate 8 followed by the intramolecular cyclization with loss of an ethanol molecule (Scheme 3). The structures of the synthesized compounds were elucidated based on their spectral data. The IR spectrum of compound 9a, for example, indicated the presence of the absorption band due to the NH_2 functional group at υ 3420, 3354 cm^{-1} and a carbonyl group at υ 1690 cm^{-1}. The ^{1}H NMR spectrum of compound 9a revealed the disappearance of any signal corresponding to NH function of hydrazo group at high down field, and revealed the presence of two protons



Scheme 2 : Synthesis of hydrazono derivatives 6a,b



Scheme 3 : synthesis of pyridazines

as a singlet at δ = 8.29 ppm assignable to the NH_2 group beside the other protons in their proper positions. Also, the ^{13}C NMR of compound 9a revealed a signal at 115.2 ppm (CN), 115.8 ppm (2CN) and 166.7 ppm (CO), in addition to the *sp*^{2} carbon atoms as in the experimental section. Similarly, reaction of hydrazone 9a with malononitrile under the same reaction conditions afforded the pyridazine derivative 10 (Scheme 3 and Experimental part). Also, the behavior of 9a towards electrophilic reagents under alkaline conditions was investigated. Thus, the reaction of 9a with arylidinemalononitrile 11a, b in refluxing ethanol containing a cartalytic amount of piperidine afforded the pyridazine derivatives 12a, b. The reaction occurs via â-attack followed by 1,6-dipolar intramolecular cyclization. However, the IR spectrum of compound 12a as example revealed the presence of 3NH groups at υ = 3394, 3282, 3193 cm^{-1} and indicated the presence of absorption bands at υ = 2202, 2220 cm^{-1} which attributed to three CN function groups. The ^1H-NMR of

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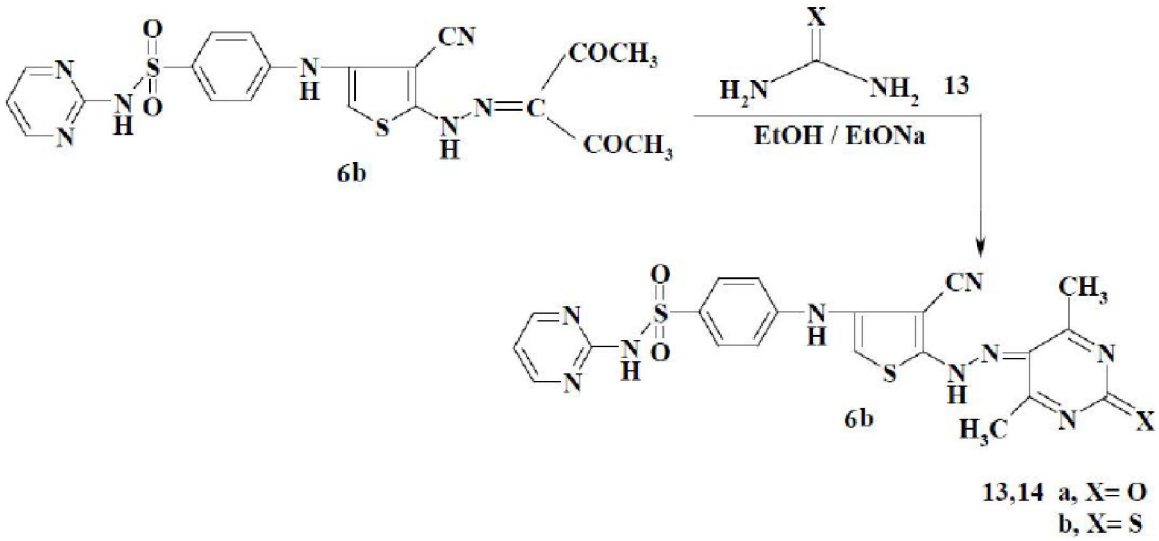
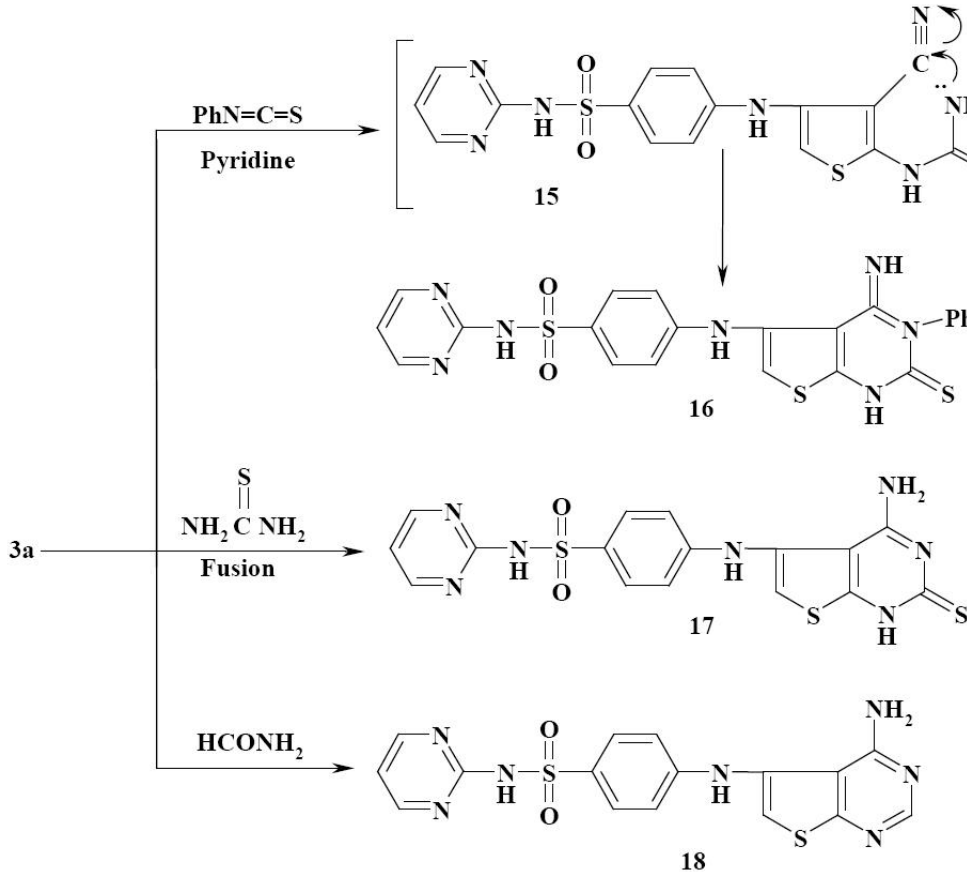


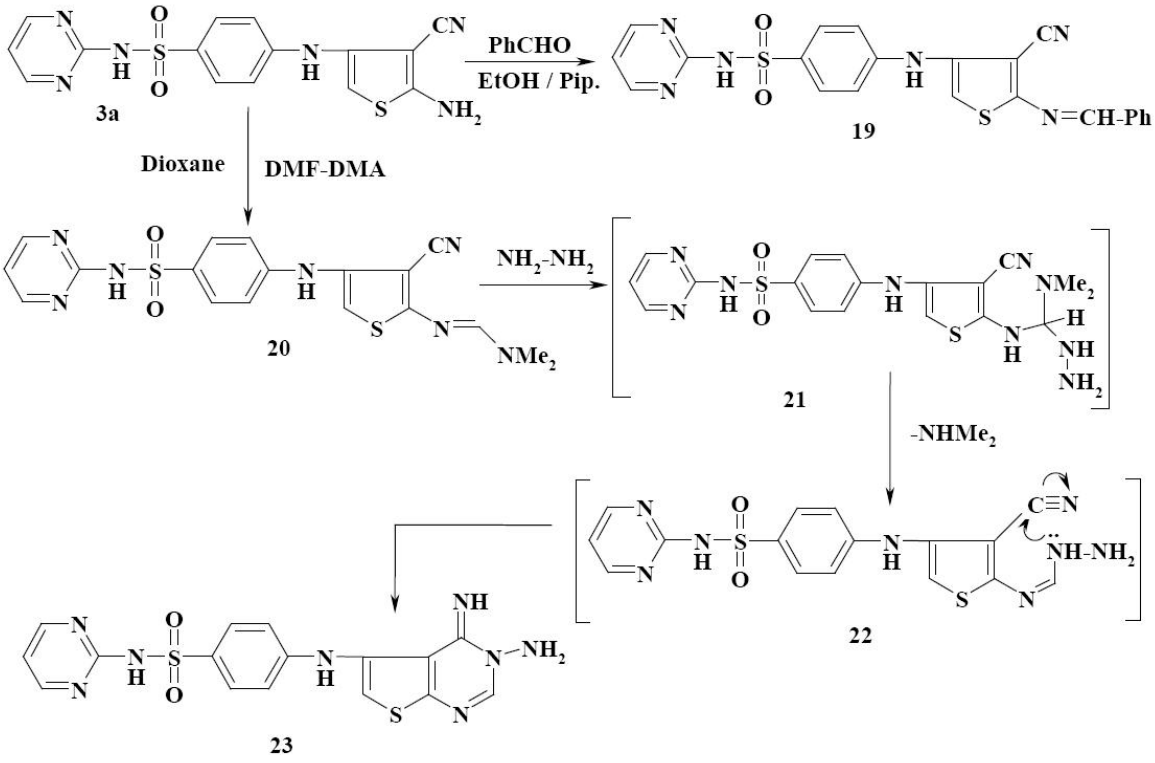
Scheme 4 : synthesis of pyrimidines



Scheme 5 : Synthesis of thienopyrimidines

12a revealed signals at δ = 3.27 (s, 1H, NH), 5.72 (s, 1H, CH-thiophene), 7.08-8.16 (m, 13H, Ar-H+ NH), 8.29 (s, 1H, C=NH).

Furthermore, treatment of hydrazone 6b with either urea or thiourea as binucleophlic reagents in ethanolic sodium ethoxide solution afforded the pyrimidine derivatives 14a, b. The reaction took place via 1,3-intermolecular cyclization of compound 9b with 1,3-dinucleophiles 13a and 13b via loss of two moles of water. The analytical and spectral data of the latter products were based on analytical and spectral data (Scheme 4 and Experimental part).



Scheme 6 : Synthesis of thienopyrimidines

The ^{1}H NMR spectrum of (14a in DMSO-d_6) revealed signals at δ = 2.12 (s, 6H, 2CH_3), 4.02 (s, 1H, NH), 6.32 (s, 1H, CH-thiophene), 7.36-8.25 (m, 8H, Ar-H+ NH), 11.48(s, 1H, hydrazinyl NH). Furthermore, the structure of compound 14a was supported by ^{13}C NMR spectrum (Scheme 4 and Experimental part).

Moreover, the interaction of 3a with phenyl isothiocyanate in pyridine led to the formation of thiourea intermediate derivative 15 which cyclized at adjacent cyano group to form thienopyrimidine derivative 16 (Scheme 5).

The mass spectrum of 16 exhibited a molecular ion peak m/z at 508 corresponding to molecular formula $C_{22}H_{18}N_7O_2S_3$. Also, compound 3a was cyclized with thiourea under the condition of fusion to yield thienopyrimidine derivative 17 through the elimination of ammonia followed by intramolecular cyclization at the cyano group and tautomerization to yield 17. This structure was confirmed based on the elemental analysis and spectral data. The IR spectrum of compound 17 exhibited the disappearance of the absorption band due to the CN function group and appearance of absorption band due to NH_2 group at 3415, 3373 cm^{-1}. Furthermore, treatment of compound 3a with formamide solution under reflux gave the expected 4-((4-Aminothieno [2,3-*d*]pyrimidin-5-yl)amino)-N-(pyrimidin-2-yl) benzenesulfonamide (18). The analytical and spectral data are in agreement with the proposed structure (Scheme 5 and Experimental part). On the other hand, Schiff base 19 was obtained from the reaction of 3a with benzaldehyde in ethanolic piperidine. Also, Condensation of 3a with DMF-DMA in dry dioxane under reûux yielded the 4-Cyano-5-(dimethylamino-methyleneamino)-thiophen-3-ylamino derivative 20. The structure of 20 was inferred via elemental analysis, spectral data, and chemical transformations (See Scheme 6 and the Experimental section). The reaction of 20 with hydrazine hydrate in ethanol under reflux gave the corresponding thienopyrimidine derivatives 23. The structure of 23 was established based on elemental analysis and spectral studies. The IR spectra of 23 showed the absorption bands of NH_2, 3NH groups, and absence of CN group, and their ^{1}H NMR spectra revealed the signals of NH_2, NH, pyrimidine protons, and absence of the signals of $N(CH_3)_2$ protons. The formation of 23 in this reaction proceed

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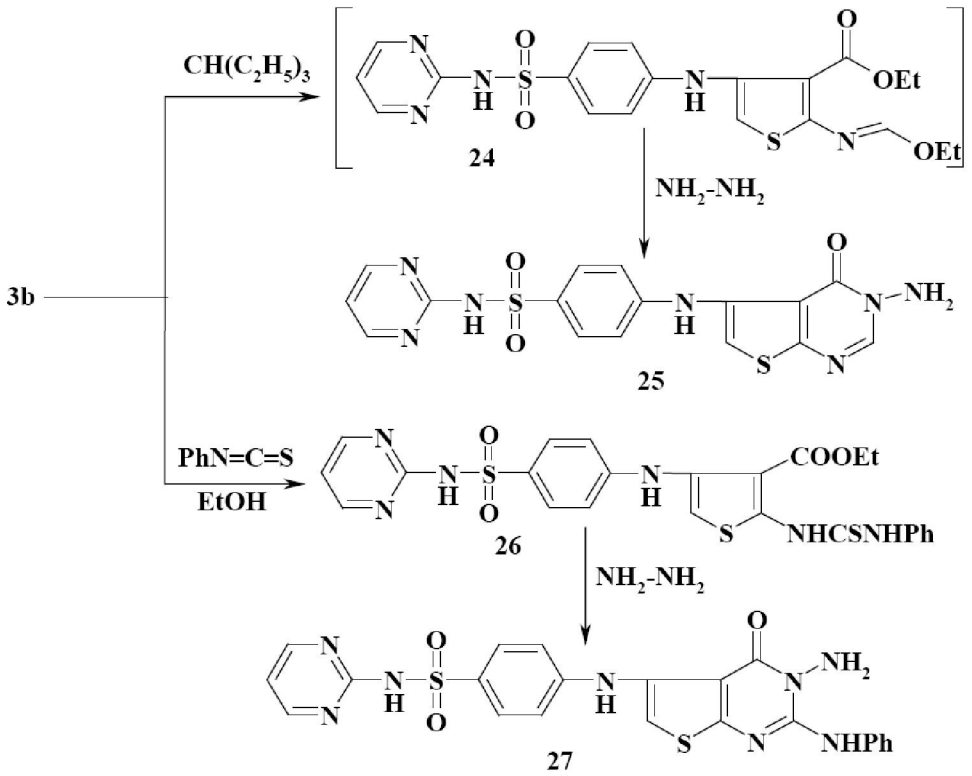

Scheme 7 : Synthesis of thienopyrimidines

via the addition of hydrazine hydrate to 20 followed by cyclization with elimination of dimethylamine, yielding the thieno [2,3-*d*]pyrimidine derivative 14 (cf, Scheme 6 and Experimental Section).

Moreover, the above mention thiophene enaminonitrile was used as intermediate for the synthesis of new thieno [2,3-*d*] pyrimidine derivatives. Also, when the amino ester 3b was reacted with triethylorthoformate the corresponding ethoxymethyleneamino intermediate 24 was obtained as reddish brown oil. This oil was reacted directly without any purification with hydrazine hydrate to give thienopyrimidine derivative 25. The ^{1}H NMR spectrum of 25 revealed the absence of any signals may be attributed to OCH_2CH_3 protons, and appearance the signals assigned to NH_2, 2NH, CH-thiophene and aromatic protons. The reaction of the amino ester 3b with phenyl isothiocyanate in boiling absolute ethanol gave the corresponding thiourea derivative 26. Finally, compound 26 easily reacted with hydrazine hydrate in refluxing ethanol to give the thienopyrimidine derivative 27[34]. Establishing the exact structure of the reaction product is based on the spectroscopic data (cf. scheme 7 and Experimental data).

ANTIMICROBIAL ACTIVITY

Ten compounds were screened in vitro for their antimicrobial activities against two strains of bacteria (Gram positive bacteria; Bacillus cereus (G + ve), and Gram negative bacteria; Klebsiella pneumonia (G " ve) and one fungal specie (Aspergillus flavus) using the filter paper disc method[35]. The filter paper disc method was performed in nutrient agar for bacteria and Dox agar for fungi. These agar media were inoculated with 0.5 mL of the 24 h. liquid cultures. Filter paper discs (5mm diameter) saturated with each compound solution (10 mg/mL of DMSO) was placed on the indicated agar media. The incubation time was (48 h at 37 °C for bacteria and 72 h at 28 °C for fungi). Discs saturated with DMSO were used as control. Ciprofloxacin flucoral was used as a reference substance. The diameter of inhibition zones (mm) were measured and recorded. The results revealed that all the tested compounds were found to possess various antimicrobial activities towards the entire microorgan-

TABLE 1 : Antimicrobial activities of some newly synthesized compounds

Compd. No	Gram positive bacteria	Gram negative bacteria	Fungi
	Bacillus cerecs	Klebsiella pneumonia	Aspergillus flavus
3a	++	+	++
6a	-	++	-
9a	+++	+	+
11a	-	+++	-
14a	++	+	-
16	+	-	+
20	-	+	++
23	+	++	-
25	-	++	-
27	++	-	+
DMF	-	-	-
Ciprofloxacin	++++	++++	++++
Flucoral			

isms used (TABLE 1). Compound 9a exhibited the highest inhibitory activity against Bacillus cereus (G +ve), compound 11a was found to be very active against Klebsiella pneumonia (G -ve). In addition, compounds 3a, 14a, 27 revealed a moderate activity against Bacillus cereus (G +ve). Compounds 6a, 23, 25 showed a moderate activity against Klebsiella pneumonia (G -ve), compounds 3a, 20 showed a moderate activity against Aspergillus flavus. Moreover, compounds 16, 23 showed the lowest inhibitory activity against Bacillus cereus (G +ve), compounds 3a, 9a, 14a and 20 are less active towards Klebsiella pneumonia (G -ve). Whereas compounds 9a, 16, 27 exhibited the lowest inhibitory activity towards Aspergillus flavus. The results indicated that most of the synthesized compounds exhibited noticeable antimicrobial activity, and that the bacterial isolates were less active to the synthesized compounds than the fungal specie.

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, hydrazo, pyridazine, pyrimidine and thienopyrimidine 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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