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Research Article

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β-Oxoanilides in heterocyclic synthesis : Synthesis of Some New Pyrimidine containing Sulphonamido moiety Derivatives

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ABSTRACT

*Butanamide derivative **(1)** coupls smoothly with arenediazonium salts to afford the hydrazone **(3)**. The latter product reacts with dimethylformamide – dimethylacetal (DMF-DMA) and or malononitrile to afford the substituted 1,4-dihydropyridazines **(5,6)**. Several new pyran **(8)**, thiophene **(9)**, pyrazole **(14)** and isothiocyanate derivatives **(17,18)** have been synthesized by the reactions of butanamide with 4-chloro-benzylidenemalonitrile, malononitrile and elemental sulfur, and hydrazine hydrate respectively. Refluxing of butanamide **(1)** with p-chlorobenzaldhyde afforded compound **(10)**. Treating butanamide derivative **(1)** with (DMF-DMA) afforded compound **(11)** and when reacting with triethylorthoformate and hydroxylamine hydrochloride afforded compounds **(13, 15).** Treating of sulfonamide with thiophosgene afforded isothiocyanate product **(16)** which on refluxing with p-toulidine or methanol afforded compounds (**17**, **18)** respectively.*

Keywords: Pyridazine, pyran, thiophene, pyrazole and isothiocynate derivatives.

INTRODUCTION

The sulphonamides are generally known as sulpha drugs. They are groups of drugs derived from sulphanilamide that prevents the growth of bacterial and therefore they are bacteriostatic[(1)]. Sulfa drugs are a group of compounds used for eliminating a wide range of infections in human and other animal systems. Sulfonamides posses SO_2NH moiety which is an important toxophoric functions[(2)]. Sulfonamides with varying, chemical, pharmacological and antibacterial properties are produced by attaching substituents to the amido group (SO_2NHR) or the amino group ($-NH_2$) of the sulfonamide nucleus. They inhibit the incorporation of p-aminobutyric acid into folic acid[(3,4)]. They therefore inhibit DNA synthesis. Sulfonamides have been reported to exhibit antimicrobial[(5,6)], antifungal[(7)], insulin releasing[(8)], carbonic anhydrase inhibitory[(9)], anti-inflammatory[(10)] and antitumor properties[(11)]. Some active sulfanilamides as antibacterial are also known for their immunodifying effects[(12)]. In view of these facts and as a continuation of the research program on the chemistry of butanamide[(13-17)]. It is reported herein a facile route for the synthesis of various hydrazone , pyridazine, pyran, thiophene, pyrazole derivatives and incorporating (4-dimethoxinesulfamoylphenyl) amide I has found that N-[4-(2,6-dimethoxypyrimidin-2-ylamino) sulfonyl] phenyl-3-oxo-butanamide **(1)** is an excellent building block for the synthesis of the target objectives. The required starting material N-[4-(2,6-dimethoxypyrimidin-2-ylamino) sulfonyl] phenyl-3-oxo-butanamide **(1)** was prepared as previously described[(18)].

EXPERIMENTAL SECTION

Melting points were determined on an electrothermal melting point apparatus and were uncorrected. IR (cm^{-1}) spectra were recorded (KBr discs), on a FT-IR 8201 PC Shimadzu spectrophotometer ^{1}HNMR spectra were obtained on a BRUKER proton NMR-Avance (300 MHz), in DMSO-d_6 and $CDCl_3$ as a solvent, using

tetramethylsilan (TMS) as internal standard. Mass spectra were run on HP model MS-5988, elemental analyses were performed at the microanalytical center, Cairo University, Giza, Egypt.

3-Oxo-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino)sulphonyl] phenyl} butanamide (1) obtained as previously described[18].

3-Oxo-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino)sulphonyl] phenyl} -2-(arylhydrazono)butanamide (3).
To a cold mixture of compound **1** (2 mmol) and sodium acetate trihydrate (3g) in ethanol (40 ml), while the mixture in an ice bath and being stirred, a solution of the appropriate arenediazonium chloride was added dropwise over a period of 20 min [prepared as usual by diazotizing the respective aniline (2mmol) in hydrochloric acid (6M, 1.2 mL) with sodium nitrite (0.138g, 2mmol)]. After complete addition, the reaction mixture was stirred for further 4h. The resulting solid was filtered off, and recrystallized from ethanol to afford the respective hydrazone **3**. The mass spectrum of compound **(3)** showed a molecular at m/z=512, 10%. The ^{1}HNMR spectrum of compound **(3)** showed the signals at δ 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.73 (s, 6H, 2-0CH_3) 4.0 (s, 1H, NH), 7.0(s,1H,NH), 7.23-7. 85(m, 9H, HAr), 8.47 (s, 1H, NH).

N-{4-[(2,6-dimethoxy pyrimidin-2-yl-amino)sulphonyl]phenyl}-1-(4-methyl phenyl)-4-oxo-1,4-dihydropyrida -zine-3-carboxamide (5)
A mixture of hydrazone **3** (10 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (1.32 ml, 10 mmol) in dry dioxane (20 mL) was refluxed for 6h, and the resulting solid was filtered off, and recrystallized from ethanol to give 1,4-dihydropyridazine derivative **5**. The mass spectrum of compound **(5)** showed a molecular at m/z=522, 8%. The ^{1}HNMR spectrum of compound **(5)** showed a signals at δ 2.3 (s, 3H, CH_3), 3.73 (s, 6H, 2OCH_3), 4.0(s, 1H, NH), 7.23-7.85 (m, 11H, HAr), 8.0 (s, 1H,NH).

5-Cyano-6-imino-4-methyl-N{4-[(2,6-dimethoxy pyrimidin-2-yl-amino) sulphonyl]phenyl}-1,6-dihydropyrida -zin-3-carboxamide (6)
To an ethanolic solution of hydrazone **3** (1mmol) and malonanitrile (1 mmol) was add few drops of piperdine and the reaction mixture was refluxed for 4h. The solvent was evaporated under reduced pressure and the residue was triturated with ethanol, filtered off, washed with ethanol and finally purified by recrystallized from DMF to afford the product **(6)**. The mass spectrum of compound **(6)** showed a molecular at m/z = 560, 20%. The ^{1}HNMR spectrum of compound **6** showed the signals at δ 1.71 (s, 3H, CH_3), 3.75 (s, 6H, 20CH_3), 4.0(s,1H, NH), 7.2 (s, 1H, NH), 8.2 (s, 1H, NH).

6-Amino-N-{4-[(2,6-dimethoxypyrimidin-2-yl-aminosulphonyl] phenyl]phenyl}-5-cyano-4-(4-chlorophenyl)-2-methyl-4H-pyran-3-carboxamide (8):
To a solution of the p-chlorobenzlidene malononitrile **7** (10 mmol) in absolute ethanol (20 mL) was added acetoacetanilide **(1)** (10 mmol), and few drops of piperidine and the reaction mixture was refluxed for 6h. The resulting solid was filtered off, and recrystallized from ethanol to give compound **8.** The mass spectrum of compound **8** showed a molecular at m/z=581, 10%. The ^{1}HNMR spectrum of compound **8** showed signals at δ 2.35 (s, 3H, CH_3), 3.75 (s, 6H, 2OCH_3), 4.2 (s, 1H, NH), 5.66 (s,1H, pyran H),6.99-7.091(m,10H,HAr,NH_2), 7.47 (s, 2H, NH_2), 8.1 (s, 1H, NH).

5-Amino-N-{4-[(2,6-dimethoxy pyrimidin-2-yl-amino)sulphonyl] phenyl}-4-cyano-3-methyl thiophene-2-carboxamide (9).
Elemental sulfur (10 mmol) was added to a solution of acetoacetanilide **1** (10 mmol) and malononitrile (10 mmol) in ethanol (30 mL), few drops of triethylamine (0.5ml) was added and the mixture was refluxed for 4h and then left to cool. The resulting solid was filtered off, washed with water and recrystallized from ethanol. The mass spectrum of compound **9** showed molecular at m/z : 474, 8%. The ^{1}HNMR spectrum of compound **9** showed the signals at δ 2.25 (s, 3H, CH_3), 3.75 (s, 6H, 2OCH_3), 4.2 (s, 1H, NH), 7.22-7.50(m, 5H, HAr), 7.79 (s, 2H, NH_2), 8.4 (s, 1H, NH).

2-Acetyl-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl]phenyl}-3-(4-chlorophenyl) acrylamide (10)
To a solution of p-chlorobenzaldehyde (10 mmol) in absolute ethanol (30 mL) was added acetoacetanilide **1** (10 mmol) and few drops of piperidine and the reaction mixture was refluxed for 6h. The resulting solid was filtered off and recrystallized from ethanol to give compound **10**. The mass spectrum of compound **10** showed a molecular at m/z 516, 18%. The ^{1}HNMR spectrum of compound **10** showed the signals at δ 2.49 (s, 3H, CH_3), 3.79 (s, 6H, 2OCH_3), 4.8 (s, 1H, NH) 5.77 (s, 1H, CH), 6.86-7.82 (m, 9H, HAr), 8.62 (m, 1H, NH).

2-Acetyl-3-(dimethylamino)-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl] phenyl} acrylamide (11).
A mixture of acetoacetanilide **1** (10 mmol) and DMF-DMA (Dimethylformamide-Dimethylacetal) (10 mmol) in dry dioxane was heated under reflux for 3hrs, the solvent was evaporated under vacuum. The solid product was

collected by filtration and recrystallized from ethanol to give compound **11**. The mass spectrum of compound **11** showed a molecular at m/z 449, 30%. The ^{1}HNMR showed signals at δ 2.30 (s, 3H, CH_3), 2.47(s, 6H, $2CH_3$), 3.73 (s, 6H, $2OCH_3$), 7.0.42 (m, 5H, aromatic protons and 1H CH), 8.2 (s, 1H, NH).

2-Acetyl-3-ethoxy-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl]phenyl}acryalmide (13).
A mixture of acetoacetanilide (0.01 mol) and triethylorthoformate (0.01 mol) in acetic anhydride (20 mL) was heated under reflux for 4hrs, then the solvent was evaporated under vacuum. The solid product that formed was collected by filtration and recrystallized from ethanol to give compound **13**. The mass spectrum of compound **13** showed a molecular at m/z 450,12%. The ^{1}HNMR spectrum showed signals at δ 1.25 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.75(s, 6H, $2OCH_3$), 4.0 (s, 1H,NH), 7.0-77 (m, 5H, aromatic protons and 1H CH), 8.4 (s, 1H, NH).

4-(5-Methyl-1H-pyrazol-3-ylamino)-N-2,6-dimethoxypyrimidin-2-yl-benzenesulphonamide (14).
A mixture of acetoacetanilide **1** (0.01 mol) and excess of hydrazine hydrate was fused together in sand bath for **15** min, then pet. ether (60-80) was added. The solid product that formed was collected by filtration and recystallized from ethanol to give compound **14**. The mass spectrum of compound **14** showed a molecular at m/z 390, 20%.

3-Hydroxyimino-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl] phenyl} butamide (15)
To a mixture of acetoacetanilide **1** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in ethanol (20 ml), sodium acetate (0.01 mol) was added. The reaction mixture was heated under reflux for 2hrs. The solid product was collected by filtration and recrystallized from dioxane to give compound **15**. The mass spectrum of compound **15** showed a molecular at m/z: 409, 22%. The ^{1}HNMR showed the signals at δ 1.90 (s, 3H, CH_3), 2.0 (s, 1H, OH) 3.73 (s, 6H, $2OCH_3$), 4.2(s, 1H, NH) ,6.54-8.09 (m, 5H, Ar–H and NH proton).

Table (1): Physical Data of the synthesized compounds

Compd. No.	Yield (%)	M.P. (°C)	Cryst. Solvent	Mol. Formula (mole. Wt)	Analyses required/found			
					C	H	N	S%
3	32	60—62	Ethanol	$C_{23}H_{24}N_6O_6S$ 512.5	53.90 53.75	4.72 4.60	16.40 16.22	6.26 6.35
5	39	150-152	Ethanol	$C_{24}H_{22}N_6O_6S$ 522.5	55.17 56.20	4.24 4.80	16.08 16.20	6.14 6.12
6	34	220-223	DMF	$C_{26}H_{24}N_8O_5S$ 560.5	55.71 55.33	4.32 4.95	19.99 19.03	5.72 5.30
8	35	165-167	Ethanol	$C_{26}H_{23}ClN_6O_6S$ 583.5	53.56 53.22	3.98 3.32	14.41 14.39	5.50 5.92
9	32	160-162	Ethanol	$C_{19}H_{18}N_6O_5S_2$ 474.5	48.09 48.63	3.82 3.20	17.71 17.02	13.51 13.23
10	37	200-202	Ethanol	$C_{23}H_{21}ClN_4O_6S$ 516.9	53.44 53.03	4.09 4.10	10.84 10.09	6.20 6.35
11	80	170-172	Ethanol	$C_{19}H_{23}N_5O_6S$ 449.4	50.77 50.04	5.16 5.98	15.58 15.03	7.13 7.90
13	86	170-172	Ethanol	$C_{19}H_{22}N_4O_7S$ 450.4	50.66 50.13	4.92 4.14	12.44 12.16	7.12 7.94
14	32	160-162	Ethanol	$C_{16}H_{18}N_6O_4S$ 390.4	49.22 49.39	4.65 4.22	21.53 21.09	8.21 8.90
15	84	210-212	Dioxane	$C_{16}H_{19}N_5O_6S$ 409.4	46.94 46.20	4.68 4.02	17.11 17.90	7.83 7.22
16	75	120-122	Ethanol	$C_{13}H_{12}N_4O_4S_2$ 352.3	44.31 44.02	3.43 3.04	15.90 15.03	18.20 18.95
17	75	180-182	Ethanol	$C_{20}H_{21}N_5O_4S_2$ 459.5	52.27 52.19	4.61 4.11	15.24 15.88	13.96 13.11
18	85	220-222	Ethanol	$C_{14}H_{16}N_4O_5S_2$ 384.4	43.74 43.02	4.20 4.20	14.57 14.11	16.68 16.12

4-Isothiocyanato-N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl)phenyl} (16):
To a suspension of sulfadimethoxine (0.01 mol) in water (30 mL), thiophosgene (0.01 mol) was added and the reaction mixture was stirred for 1 h until red color of the thiophosgene disappeared and a white precipitate was formed. The precipitate was filtered off and washed with water to give compound **16**. The mass spectrum of compound **16** showed molecular at m/z: 352, 15%. The ^{1}HNMR showed the signals at δ 3.75 (s, 6H, $2OCH_3$), 4.3 (s,1H, NH), 7.40- 7.50 (2d, 5H, Ar–H).

4-Methylphenyl-N-{4-(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl] phenyl} thiourea (17).
A mixture of isothiocyanate **(16)** (0.01 mol) and p-toulidine (0.01 mol) in dioxane (20 mL) with 3 drops of TEA, was refluxed for 1h, the solid obtained was precipitated when cold and filtered to give compound **17** and

recrystallzied from ethanol to give compound **17.** The mass spectrum of compound **17** showed a molecular at m/z: 459, 30%. The ^{1}HNMR showed a signals at δ 2.35 (s, 3H, CH_3), 3.73 (s, 6H, $2OCH_3$), 4.3 (s, 1H, NH), 7.20-7.70 (d, 9H, Ar–H), 10.60 (s, 1H, NH).

N-{4-[(2,6-dimethoxypyrimidin-2-yl-amino) sulphonyl] phenyl}-4-methylthiocarbamate (18)

A solution of isothiocyante **16** (0.01 mol) in methanol (10 ml) was heated under reflux for 8h and left to cool. The crystalline product thus formed was filtered off, washed with pet. ether (60-80) and recrystallized from ethanol to give compound **18**. The mass spectrum of compound **18** showed a molecular at m/z= 384, 25%. The ^{1}HNMR showed a signals at δ 3.39 (s, 3H, CH_3), 3.75 (s, 6H, $2OCH_3$), 4.22 (s, 1H, NH), 7.22-7.95 (m, 5H, Ar-H + NH).

Table (2) IR spectra of synthesized compounds

Comp. No	$\upsilon_{max}(cm^{-1})$
3	3496(NH), 3564(NH), 3300(NH), 1693(CO), 1662(CO)
5	3496(NH), 3380(NH), 1695(CO), 1630(CO).
6	3497(NH), 3243(NH), 3200(NH), 2203(CN), 1668(CO).
8	3240(NH), 3200(NH), 3262(NH_2), 2216(CN), 1638 (CO).
9	3436(NH), 3360(NH), 3220(NH_2), 2210(CN), 1632(CO).
10	3476(NH), 3240(NH), 1689(CO), 1645(CO).
11	3300(NH), 3200(NH), 1710(CO), 1660(CO).
13	3300(NH), 3100(NH), 1700(CO), 1650(CO).
14	3400(NH), 3343(NH), 3221(NH).
15	3500(OH), 3400(NH), 3200(NH), 1650(CO).
16	3070(CH arom.), 3290(NH), 2160(NCS), 1593(C=S).
17	3442(NH), 3360(NH), 3198(NH), 3072 (CH arom.), 1593 (C=S).
18	3290(NH), 3197(NH), 3070(CH arom.), 1393 (C=S).

Antimicrobial Activity

1- Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against two species of Gram-positive bacteria, namely *Staphylococcus aureus* (NCTC-7447), *Bacillus subtilis* (NCIB-3610)) and two species of Gram negative bacteria namely *Escherichia coli* (NCTC-10416) and *Pseudomonas aeruginosa*(NCIB-9016) using Miphinicol at conc. 1 mg/ml for gram positive bacteria, while keflex was used as standard for gram negative bacteria at concentration 1 mg/ml as the reference compound. Table (3) shows the effect of compounds on the microorganisms tested using the agar diffusion method.[25-27] It was found that all compounds **5,6,9,10,11** and **15** were shown to exhibit an activity pattern which suggests that they may have a broad spectrum antibacterial effect with a sustained high degree of inhibition against all of the test organisms.

Table (3): Antimicrobial activity of some prepared compounds

Sample No.	Mean Diameter of Inhibition Zone (mm)			
	Bacillus subtillus	***E.coli***	***Staphylococcus aureus***	***Pseudomonas aeruginosa***
5	15	20	15	13
6	-	15	14	-
9	-	17	-	-
10	-	15	-	-
11	22	16	-	18
15	23	16	-	15
St.	315	30	32	37.5

Well diameter . 1 cm……. (100 ul of each one was tested)

Table (4): Antifungal activity of synthesized compounds

Sample No.	Mean Diameter of Inhibition Zone (mm)	
	Candida albicans	***Aspergillus niger***
5	14	13
6	15	-
9	-	12
10	-	-
11	20	-
15	22	-
St.	25	23

2-Antifungal activity

The newly synthesized compounds were screened for their antifungal activity against two species of fungi, *Candida albicans* (CBS-562) and *Aspergillus niger* (LTV 131) using Flucoral as the reference compound. Table 4 showed the effect of compounds **(5,6,9,10,11** and **15**) on the microorganism tested using the agar diffusion method .[25-27] It

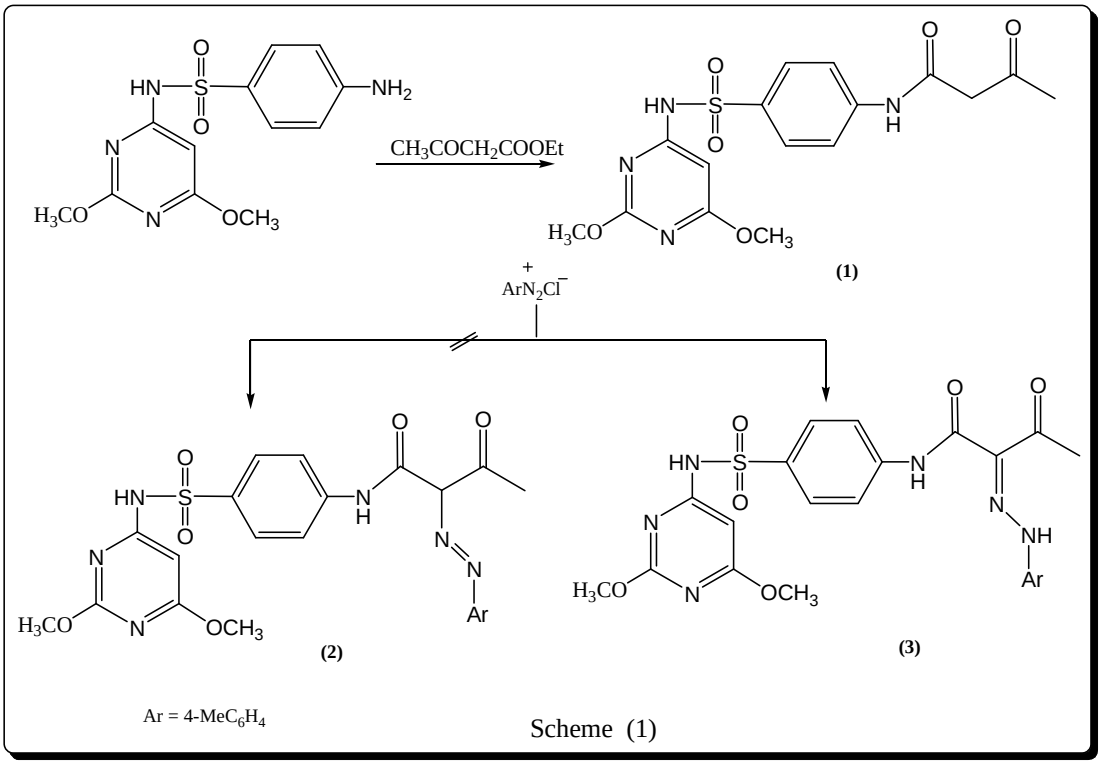
was found that all compounds were shown on exhibit an activity pattern which suggested that they may have broad spectrum of antifungal action with a sustained high degree of inhibition, against all of the test organisms.

RESULTS AND DISCUSSION

Treatment of compound **1** with diazotized 4-toluidine in ethanol buffered with sodium acetate afforded the respective arylhydrazo derivative **3** instead of arylazo derivative **2** (scheme 1).

On the basis of their spectral data (^{1}HNMR, IR). For example, ^{1}HNMR spectrum revealed three characteristic signals in the region δ 4.0, 7.0, 8.47 ppm assignable to a three NH protons in hydrazone structure **3**[19].

The IR spectra revealed a ketone carbonyl absorption band in the region 1685-1720cm^{-1}. The observed low frequency of the latter group may be the result of conjugation with C=N bond and possible strong chelation with the hydrazone NH. The electronic absorption spectra of this dye **3** in dioxane showed two absorption maxima in the regions 380-395 and 285-320 nm. This absorption pattern is similar to that of hydrazone chromophore[20,21].

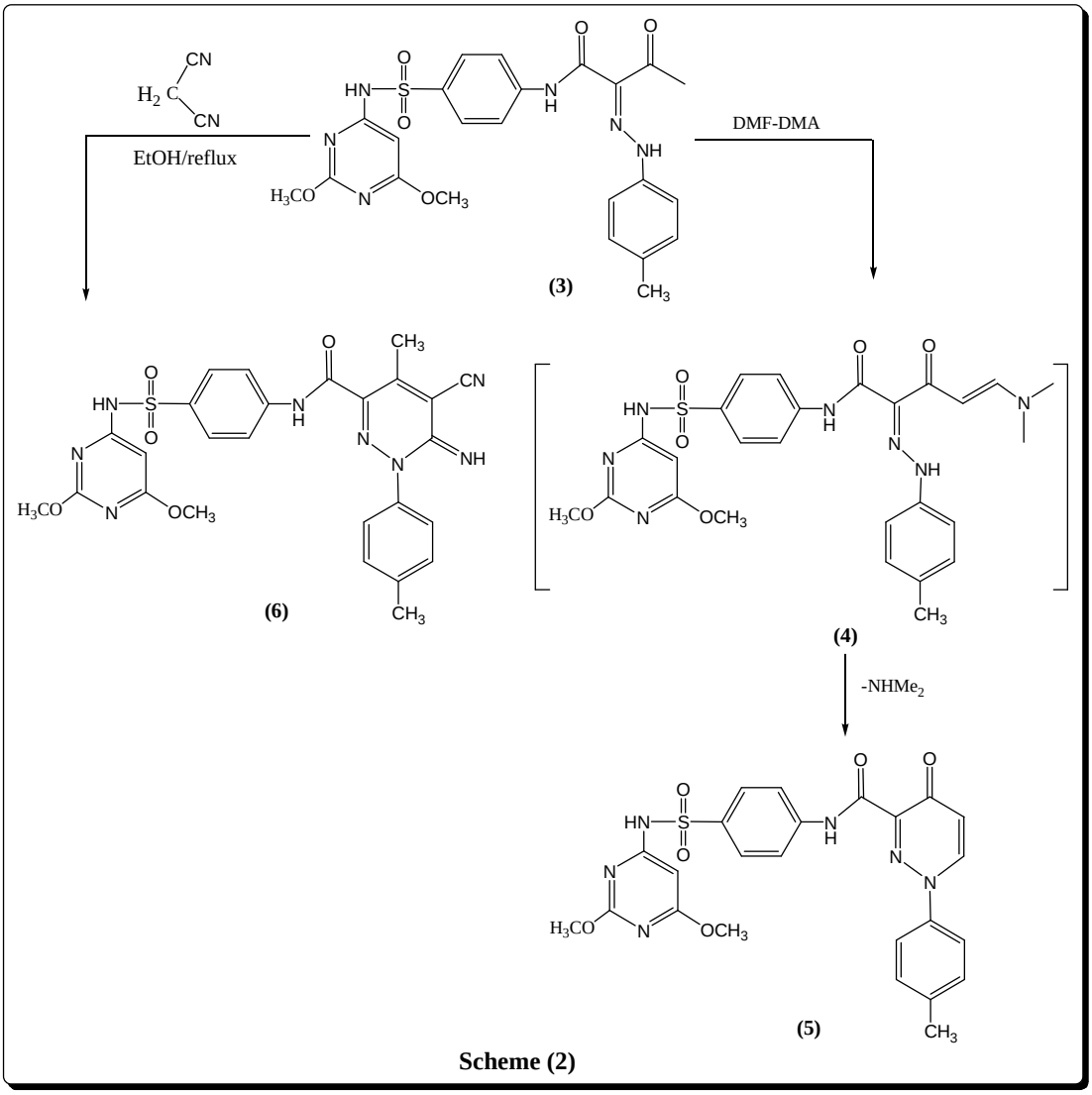


Scheme (1)

In addition treatment of butanamide **(3)** with dimethylformamide – dimethylacetal (DMF-DMA) in refluxing dry dioxane afforded pyridazine derivative **5** in good yield. This process is assumed to follow route in which underwent intramolecular ring closure and dimethylamine elimination to form compound **5** (scheme 2).

The structure of compound **5** has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectra of compound **5** showed characteristic band for the vibration of the 2NH and amidic C=O, function groups at 3496, 3546 and 1630cm^{-1} respectively. The ^{1}HNMR spectra exhibited two broad singlet at δ 4.0 and 8.0 ppm assignable to 2NH protons and a multiplet signals at δ 7.23-7.85ppm region owing to the aromatic protons. The mass spectra showed a molecular ion peak at m/z: 522 corresponding to a molecular formulae $C_{24}H_{22}N_6O_6S$.

Compound **3** readily reacted with malononitrile in refluxing ethanolic piperidine solution to yield the pyridazine derivative **6**. The IR spectrum showed an absorption band at 1668cm^{-1} due to conjugation carbonyl of amide group, in addition to absorption bands at 2203 and 3280cm^{-1} due to nitrile function and NH groups. The ^{1}HNMR spectrum revealed signals at 1.71 ppm due to CH_3 and three signals at 4.0, 7.17 and 8.0 ppm due to three NH protons, in addition to an aromatic multiplet in the region δ 7.73-7.99 ppm.

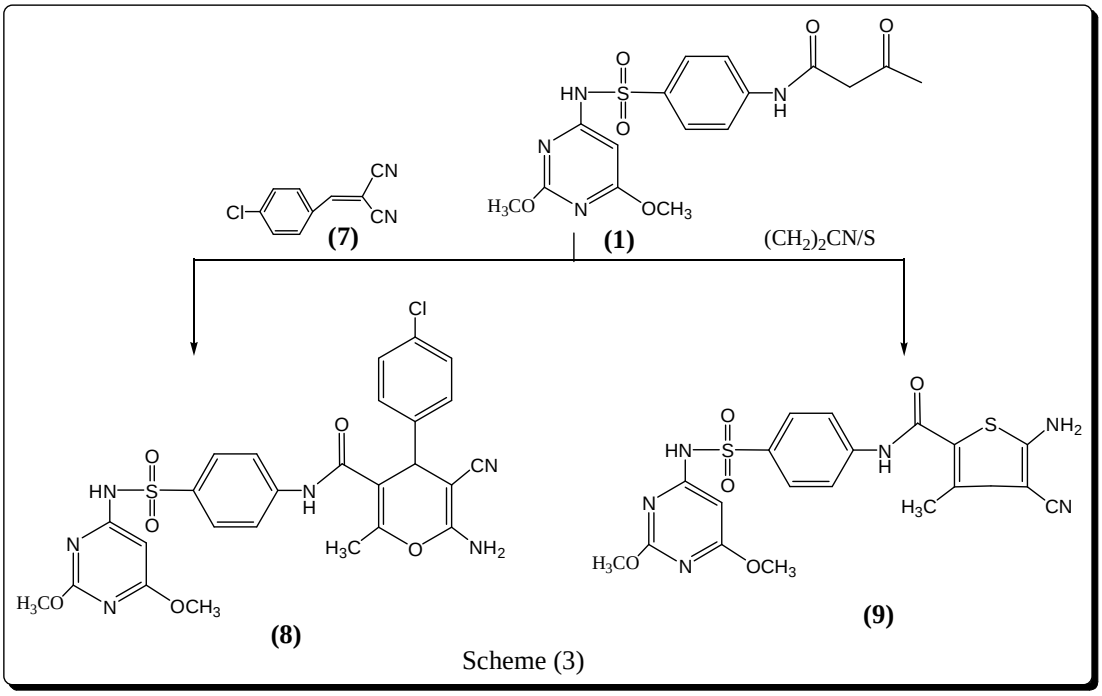


Scheme (2)

The reactivity of compound **1** towards p-chlorobenzylidene malononitrile, malononitrile and elemental sulfur was studied. Thus, treatment of compound **1** with p-chlorbenzylidenemalonitrile (7), in refluxing ethanol in the presence of piperidine, afforded the expected compound **8** (scheme 3). This is formed most likely, via an established reaction sequence of benzylidenemalononitrile with diketone[22]. The structure of the synthesized product was established on the basis of the elemental analysis and spectral data.

Treatment of compound **1** with elemental sulfur and malononitrile, in refluxing ethanol in the presence of catalytic amount of triethylamine, furnished a single product identified as 5-amino-N-{4-[(2,6-dimethyoxypyrimidin-2-ylamino)sulphonyl]phenyl}-4-cyano-3-methyl-thiophene-2-carboxamide **(9)** according to its elemental analysis and spectral data. The IR spectrum of **9** showed absorption bands at 1632, 2210, 3320, 3436 and 3360cm^{-1} due to amidic C=O, CN, NH_2 and 2NH function groups, respectively. This is are compatible with the assigned structure which assumed to be formed via application of Gewald synthesis to alkyl heterocyclic carbonitriles to afford the thiophene derivative**9**[23] (scheme 3).

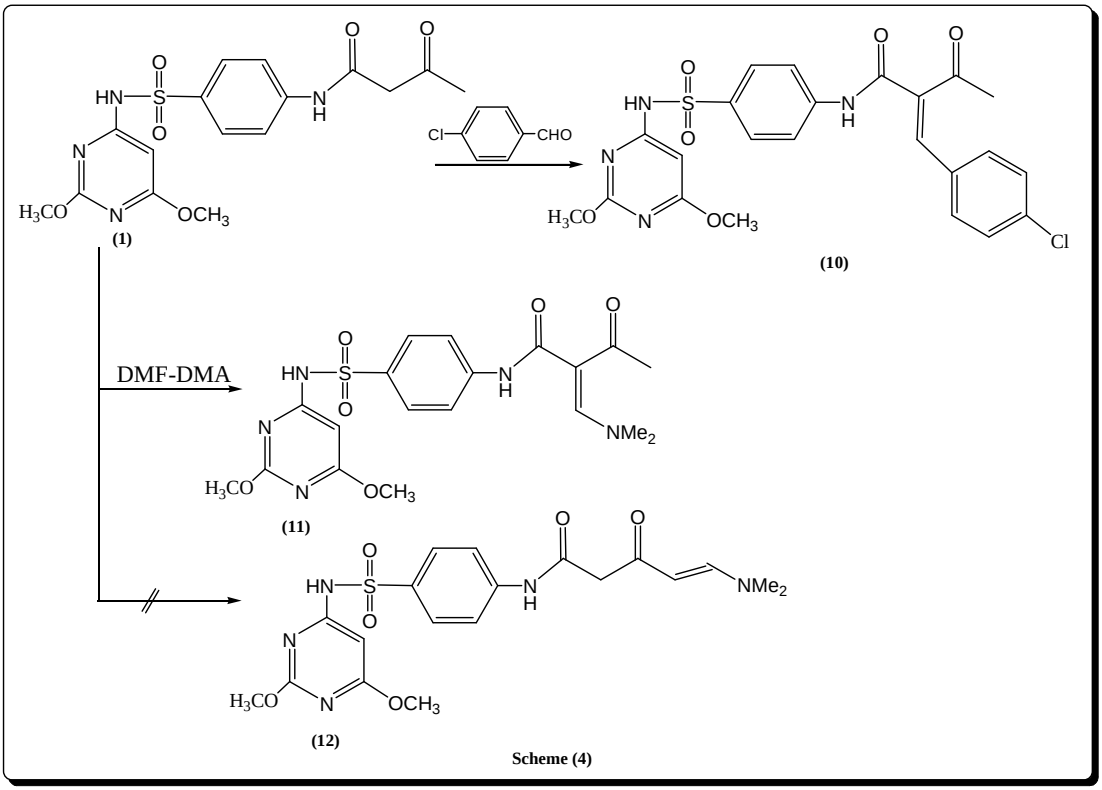
Also, treatment of compound **1** with p-chlorobenzaldehyde in refluxing ethanol containing catalytic amount of piperidine afforded the corresponding,2-acetyl-N-{4-[(2,6-dimethoxypyrimidin-2-ylamino) sulphonyl) phenyl}-3-(4-chlorophenyl)acrylamide **(10).** The structure of the synthesized product was established on the basis of elemental analysis and spectral data (see the experimental part). Compound **1** was condensed with *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing dry dioxane to yield a product that may be either structure **11** or its isomeric **12.** Establishing the exact structure of the reaction product as structure **11** rather than **12** was based on elemental analysis and spectral data. ^{1}HNMR spectrum revealed the presence of a δ 2.3 ppm assigned to the acetyl functional group for structure **11** and absence of olefinic double doublet which would be observed for structure **12** (scheme 4).



Scheme (3)

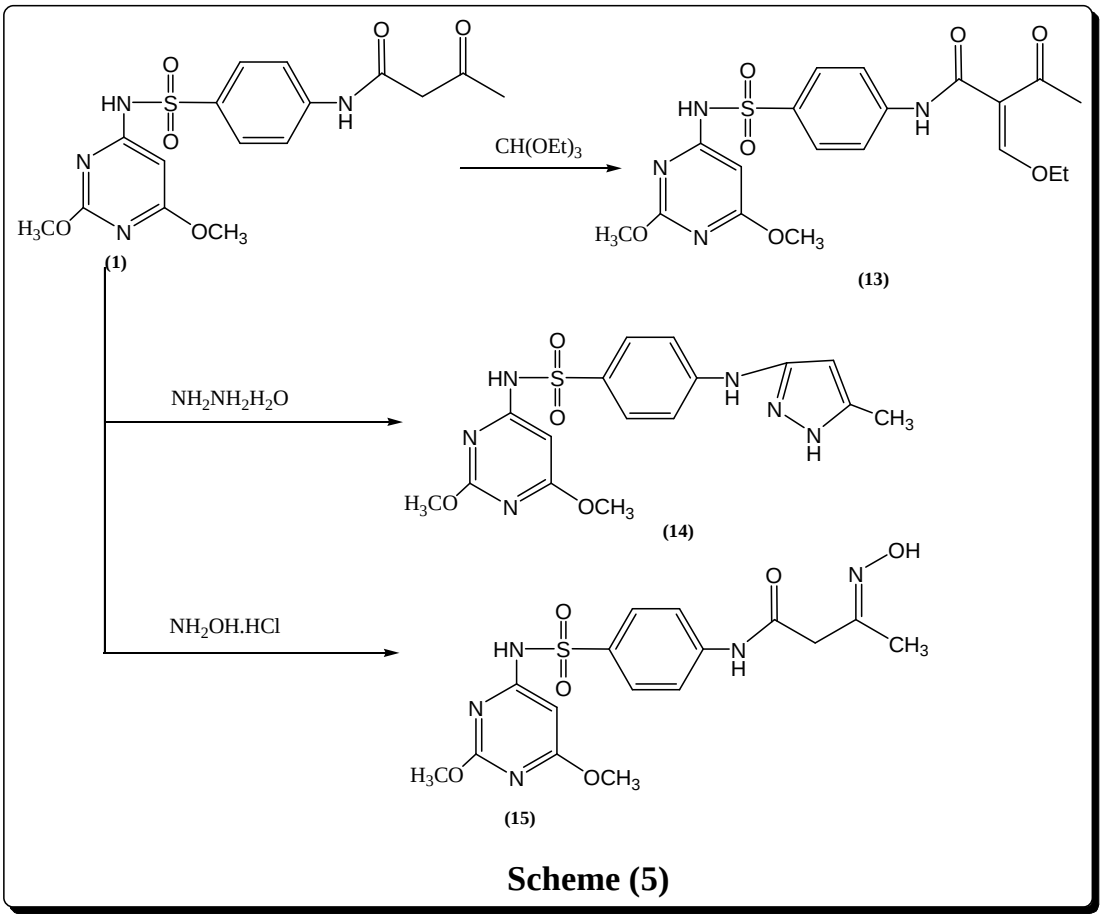
Also, condensation of anilide **1** with triethylorthoformate in refluxing acetic anhydride afforded the ethoxy methylene derivative **13**. Establishing of structure **13** was based on elemental analysis and spectral data.

On the other hand, the reactivity of acetoacetanilide derivative **1** towards hydrazine hydrate and hydroxylamine hydrochloride was investigated. Thus, acetoacetanilide **1** was reacted with hydrazine hydrate to afford the reaction product **14**. Assignment of structure **14** for the reaction product was based on its correct elemental analysis and spectroscopic data.



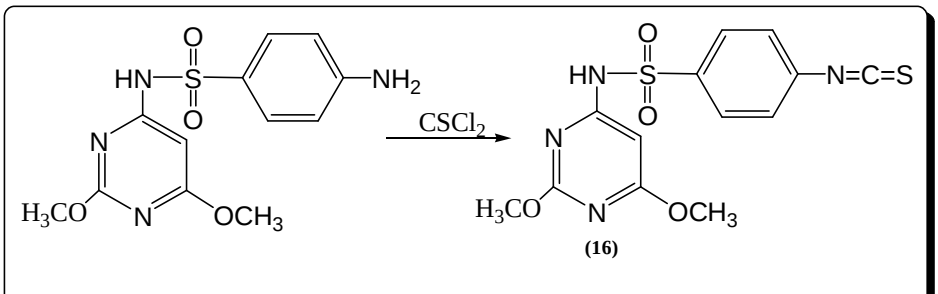
Scheme (4)

Furthermore, acetoacetanilide derivative **1** reacted with hydroxylamine hydrochloride in refluxing ethanol, sodium acetate solution to yield the acylic oxime derivative **15**. Structure **15** was established based on its elemental analysis and spectroscopic data. Thus, the ^{1}HNMR spectrum showed absorption peak at δ 1.9 ppm (CH_3) protons, at δ 2.0 ppm assigned for (OH) proton, at δ 5.97 ppm (CH_2) protons, and δ 8.0 ppm a broad signal assumed for (NH) proton beside the expected signals (scheme 5).



Scheme (5)

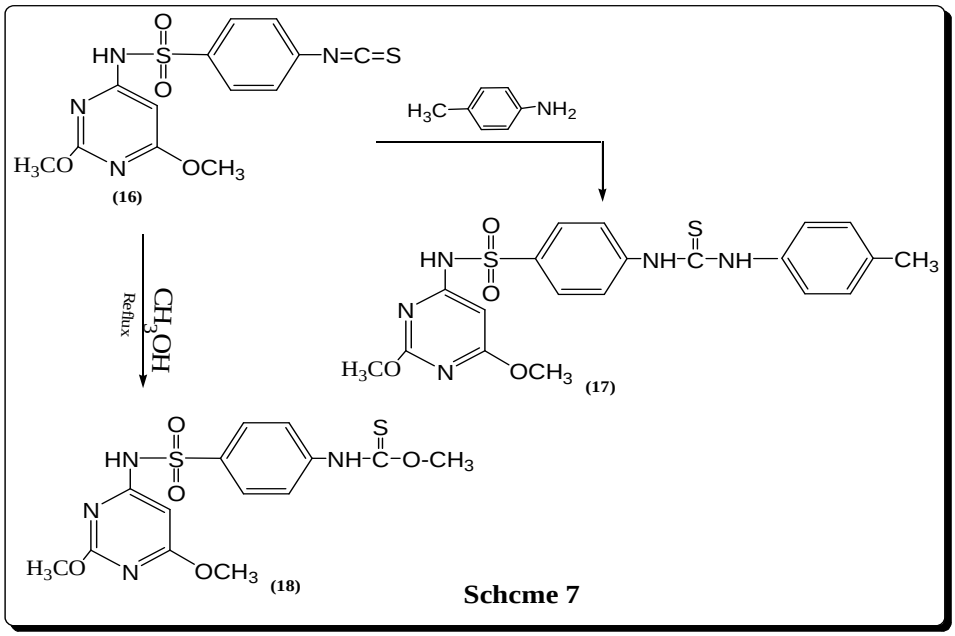
4-Isothiocyanato-N-{4-[(2,6-dimethoxypyrimidin-2-ylamino) sulphonyl] phenyl} **(16)** was synthesized in good yield by treatment of sulfadimethoxine with thiophosgene earlier[24]. Compound **16** was used to prepare different sulfonamide derivatives by incorporating different biologically active moieties. Compound **16** was established by elemental analysis and spectroscopic data. The IR spectrum of compound **16** revealed characteristic band at 3233cm^{-1} (NH) and 2121cm^{-1} (N=C=S). The ^{1}HNMR spectrum of **16** showed the presence of a signal at δ 4.3 (s, 1H, NH) and 7.4-7.5 (d, 4H, Ar–H) (Scheme 6).



Scheme (6)

The reactivity of isothiocyanate **(16)** towards p-toulidine in dioxane containing triethylamine as catalyst was studied. The thiourea was established by analytical and spectral data. The IR spectrum of compound **17** revealed characteristic bands at 3328, 3390 and 3425 cm^{-1} (3NH). The ^{1}HNMR spectrum of compound **17** showed the presence of signals at δ 2.0 (s,3H,CH_3), and 7.2-7.7 (d, 4H, Ar–H).

Methylthiocarbamate derivative **18** was prepared in high yield by refluxing of isothiocyanate **(16)** in methanol. The product was established by analytical and spectral data. The IR spectrum of compound **18** revealed characteristic band at 3232 and 3348 cm^{-1} (2NH). The ^{1}HNMR spectrum of compound **18** showed the presence of signals at δ 3.39 (s, 3H, OCH_3), 4.2 (s, 1H, NH) (Scheme 7).



Schcme 7

CONCLUSION

Butanamide derivative **(1)** coupls smoothly with arenediazonium salts to afford the hydrazone (**3)**. The latter product reacts with dimethylformamide – dimethylacetal (DMF-DMA) and or malononitrile to afford the substituted 1,4-dihydropyridazines **(5,6)**. Several new pyran **(8)**, thiophene **(9)**, pyrazole **(14)** and isothiocyanate derivatives **(17,18)** have been synthesized by the reactions of butanamide with 4-chloro-benzylidenemalonitrile, malononitrile and elemental sulfur, and hydrazine hydrate respectively.

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