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Facile and Convenient Synthesis of Novel Benzopyranopyrimidine Derivatives

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A series of new 2-alkyl thiopyrimidines (**2a-e**) were synthesized by reaction of the 2-mercaptopyrimidine (**1**) with some alkylating agents. When compound **1** reacted with activated unsaturated compounds, under Michael conditions, adducts **3a,b** were obtained which on turn reacted with hydrazine to give pyridazine **4**. Pyrimidine derivatives **6**, **7** were synthesized by treatment of **1** with benzylidine-malononitrile in basic medium. While treatment of **1** with α,β-unsaturated acids gave the S-substituted derivatives **8** and **9** which on reacting with hydrazine afforded compounds **12** and **16**, respectively. The triazole **11** was obtained by treatment of **1** with aminodithiocarbamic acid. When **2a** reacted with hydrazine, primary aromatic amines or *o*-phenylenediamine, derivatives **18**, **21** and **22** were obtained, respectively. Compound **18** in turn reacted with carbon disulphide to give dithiocarbamate **23** which on reacting with sodium chloroacetate or methyl iodide afforded the thiazole **26** and triazole **28**, respectively. Moreover, condensation of **18** with aromatic aldehyde furnished the Schiff's base **29** which underwent cyclization upon treatment with chloroacetyl chloride to give azetidine **30**.

Key Words: Benzopyranopyrimidines, Oxazole, Thiazole, Triazole, Michael addition, Cyclization, Alkylation, Chlorination.

INTRODUCTION

Benzopyranopyrimidine derivatives are reported to possess significant applications as anticoagulant[1], antithrombotics[2], estrogenic activity on MCF-7 breast carcinoma cells[3] and antagonists as potential antipsychotic agents[4].

It was reported that[5] the interaction between 3-ethoxycarbonylcoumarin with thiourea in ethanol in presence of anhydrous potassium carbonate gave the benzopyrano[3,4-d]pyrimidine-4,5-dione derivative (**1**).

EXPERIMENTAL

All melting points are uncorrected and determined on Stuart electric melting point apparatus. Elemental analysis was performed by the microanalytical center, Faculty of Science, Cairo University. Infrared spectra were recorded on Bruker or Satellite 2000 spectrometer using KBr discs. Mass spectra were determined on

GC-MS (QP/000 EX) Shimadzu spectrometer at an ionizing voltage of 70 eV. Nuclear magnetic reasonance spectra were recorded on Varian Mercury 300 MHz spectrometer using TMS as internal standard; chemical shifts are recorded in δ units. Characterization data of all the compounds prepared given in Table-1.

TABLE-1
CHARACTERISTIC DATA OF COMPOUNDS PREPARED

Compd.	m.p. (ºC) / Colour	Solvent of crystallization / Yield (%)	m.f. (m.w.)	Elemental analysis (%)		
					Calcd.	Found
2a	247 / Colourless	Dioxane (80)	$C_{15}H_{12}N_2O_5S$ (332.33)	C	54.21	54.40
				H	3.63	3.72
				N	8.42	8.55
				S	4.64	9.76
2b	234 / Colourless	Dioxane (76)	$C_{19}H_{14}N_2O_4S$ (366.39)	C	62.28	62.54
				H	3.85	3.91
				N	7.64	7.82
				S	8.75	8.89
2c	276 / Greenish white	Ethanol (73)	$C_{13}H_8N_2O_5S$ (304.27)	C	51.31	51.31
				H	2.65	2.44
				N	9.20	9.32
				S	10.53	10.32
2d	225-227 / Faint brown	Ethanol (60)	$C_{22}H_{12}N_2O_6S$ (432.40)	C	61.08	61.43
				H	2.79	2.88
				N	6.47	6.62
				S	7.41	7.59
2e	287 / Colourless	Dioxane (71)	$C_{12}H_8N_2O_3S$ (260.26)	C	55.37	54.96
				H	3.09	3.22
				N	10.76	10.56
				S	12.32	12.41
3a	312 / Pale green	Ethanol (71)	$C_{14}H_{11}N_3O_3S$ (301.32)	C	55.8	55.40
				H	3.67	3.70
				N	13.94	13.77
				S	10.64	10.55
3b	335 / Buff	DMF (65)	$C_{15}H_8N_2O_6S$ (344.29)	C	52.32	52.44
				H	2.34	2.28
				N	8.13	8.21
				S	9.31	9.42
4	>340 / Buff	DMF (35)	$C_{15}H_{12}N_4O_5S$ (360.34)	C	49.99	50.32
				H	3.35	3.01
				N	15.54	15.32
				S	8.89	8.65
6	314-316 / Dark yellow	Ethanol (45)	$C_{14}H_8N_4O_3$ (280.23)	C	60.0	60.33
				H	2.87	2.95
				N	10.99	10.81
7	>340 / Yellowish brown	Dioxane (40)	$C_{14}H_8N_4O_2S$ (296.30)	C	56.74	56.59
				H	2.72	2.88
				N	18.90	18.22
				S	10.82	10.69

8	130 / Yellow	Methanol (42)	$C_{26}H_{20}N_2O_4S$ (456.51)	C H N S	68.40 4.00 6.13 7.02	68.63 3.89 6.32 7.11
9	305-307 / Faint yellow	Dioxane (48)	$C_{27}H_{18}N_2O_6S$ (498.50)	C H N S	65.05 3.63 5.61 6.43	65.55 3.98 5.46 6.25
10	>340 / Pale yellow	Dioxane (68)	$C_{13}H_8N_6O_2S_3$ (376.43)	C H N S	41.47 2.14 22.32 25.55	41.12 2.01 22.11 25.21
11	315 / Colourless	Acetic acid (47)	$C_{13}H_6N_6O_2S_2$ (342.35)	C H N S	45.60 1.76 24.54 18.73	45.31 1.63 24.37 18.52
12	230 / Pale yellow	Ethanol (35)	$C_{26}H_{22}N_4O_3S$ (470.54)	C H N S	66.36 4.71 11.9 6.81	66.85 4.55 11.31 6.64
14	118-120 / Dark brown	Dioxane (53)	$C_{27}H_{14}N_2O_4S$ (462.47)	C H N S	70.11 3.05 6.05 6.93	69.79 3.01 5.85 6.73
15	135 / Yellow	Methanol (38)	$C_{27}H_{16}N_4O_4$ (460)	C H N	70.43 3.5 12.16	70.12 3.39 12.25
16	165 / Brownish	Ethanol (59)	$C_{27}H_{20}N_4O_4S$ (496.53)	C H N S	65.30 4.05 11.28 6.45	65.62 4.20 11.43 6.67
17	273-275 / Yellowish brown	Ethanol (69)	$C_{11}H_5N_2O_2SCl$ (264.68)	C H N S Cl	49.91 1.90 10.58 2.11 13.39	49.76 1.95 10.37 12.12 13.33
18	>340 / Yellowish orange	DMF (47)	$C_{11}H_8N_4O_3$ (244.20)	C H N	54.10 3.30 22.94	53.85 3.45 22.82
19	285 / Yellow	Dioxane (32)	$C_{13}H_8N_2O_5$ (272.21)	C H N	57.35 2.96 10.29	56.95 3.01 10.43
21a	270 / Brown	Ethanol 58	$C_{17}H_{12}N_4O_3$ (320)	C H N	63.74 3.77 17.49	63.43 3.65 17.51
21b	338-340 / Buff	DMF (60)	$C_{18}H_{13}N_3O_3$ (319.31)	C H N	67.70 4.10 13.15	67.32 4.39 13.21
21c	323 / Yellow	Dioxane (57)	$C_{18}H_{11}N_3O_5$ (349.29)	C H N	61.89 3.17 12.02	61.44 3.49 11.72

22	>340 / Yellowish orange	DMF (43)	$C_{23}H_{14}N_4O_3$ (337.37)	C H N	70.04 3.57 14.20	70.32 3.50 14.34
23	267-269 / Orange	Methanol (52)	$C_{12}H_{11}N_5O_3S_2$ (337.37)	C H N S	42.72 3.28 20.75 19.0	42.53 3.19 20.42 18.61
24	198-200 / Pale green	Ethanol (38)	$C_{14}H_9N_4O_4S_2Cl$ (396.83)	C H N S Cl	42.36 2.28 14.11 16.16 8.93	42.50 2.34 14.33 16.26 8.61
26	230 / Gray greenish	Ethanol (53)	$C_{14}H_{14}N_4O_3S_2$ (350.41)	C H N S	47.98 4.02 15.98 18.30	48.41 3.89 16.23 18.07
28	303-304 / Lemon yellow	DMF (62)	$C_{14}H_{10}N_4O_3S$ (314.32)	C H N S	53.49 3.20 17.82 10.20	53.32 3.22 17.65 10.31
29a	245 / Yellow	Methanol (57)	$C_{19}H_{14}N_8O_4$ (362.33)	C H N	62.28 3.89 15.46	62.65 3.75 15.23
29b	287 / Brown	Methanol (52)	$C_{18}H_{12}N_5O_5$ (378.31)	C H N	57.14 3.19 18.51	57.34 3.22 18.21
29c	214 / Brown	Methanol (43)	$C_{18}H_{12}N_3O_3Cl$ (367.76)	C H N Cl	58.78 3.28 15.23 9.64	58.6 3.19 15.47 9.73
30a	172 / Yellow	Methanol (51)	$C_{21}H_{17}N_4O_5Cl$ (440.83)	C H N Cl	57.21 3.88 12.70 8.04	57.53 3.79 12.54 8.21
30b	235 / Yellow	Ethanol (48)	$C_{20}H_{14}N_5O_6Cl$ (455.80)	C H N Cl	52.70 3.09 15.36 7.77	52.44 3.18 15.12 7.58

Synthesis of 2-substituted-thio-3[*H*],4[*H*],5[*H*][1]benzopyrano[3,4-d]pyrimidine-4,5-dione (2a-e)

Method A: A mixture of **1** (2.46 g, 0.01 mol), ethyl bromoacetate (1.1 mL, 0.01 mol) and anhydrous potassium carbonate (2 g) in dry acetone (30 mL) was stirred at room temperature for 2 h. The solvent left to evaporate, then the residue was treated with dilute acetic acid, the solid product that obtained was collected by filtration, washed with water and crystallized from dioxane as colourless crystals to give compound **2a**.

Method B: To a mixture of **1** (2.46 g, 0.01 mol), proper alkylating agent (0.01 mol) in 40 mL dry acetone, 2 g of anhydrous potassium carbonate was added; the

reaction mixture was refluxed with stirring for 12 h. The solvent was evaporated at room temperature and then neutralized with dilute acetic acid, the solid product that separated was filtered, washed with water and crystallized from proper solvent to yield compounds **2b-d**.

Method C: To a solution of **1** (2.46 g, 0.01 mol) in ethanol (30 mL) 0.62 mL (0.01 mol) of methyl iodide and (5 mL) of 10 % aqueous sodium hydroxide were added. The reaction mixture was heated under reflux on water bath for 1.5 h then cooled and poured into dilute acetic acid, the solid product formed was collected by filtration and crystallized from dioxane to give compound **2e** as colourless crystals in 71 % yield, m.p. 287 ºC.

Reaction of 1 with acrylonitrile and maleic anhydride to give compounds 3a,b: A mixture of **1** (2.46 g, 0.01 mol) and acrylonitrile (0.65 mL, 0.01 mol) or maleic anhydride (0.98 g, 0.01 mol) in pyridine (synthesis of 30 mL) was heated under reflux with stirring for 25 h. The reaction mixture was cooled and poured into a mixture of crushed ice and HCl, the solid product that separated was filtered off and crystallized from the proper solvent to give compounds **3a,b**.

Synthesis of 2-(3,6-dihydroxy-4,5-dihydropyridazine-4-yl)-thio-3[*H*],4[*H*], 5[*H*]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidine-4,5-dione (4): To a solution of compound **3b** (3.46 g, 0.01 mol) in absolute ethanol (40 mL), 0.75 mL (0.015 mol) of hydrazine hydrate (98 %) was added. The reaction mixture was heated under reflux for 7 h then concentrated to give a buff precipitate which was collected by filtration and crystallized.

Synthesis of 2-dicyanomethyl-3[*H*],4[*H*],5[*H*]-3,4-dihydro[1]benzo-pyrano-[4,3-d]pyrimidine-4,5-dione (6) and 2-mercapto-4-dicyanomethyl-3[*H*],5[*H*]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidine-5-one (7): A solution of **1** (2.46 g, 0.01 mol) and benzylidinemalononitrile (1.54 g, 0.01 mol) in pyridine (30 mL) was refluxed with stirring for 25 h. The reaction mixture was cooled, then poured into a mixture of crushed ice and hydrochloric acid and the solid product that obtained was fractionally crystallized.

Synthesis of 2-[4-phenyl-benzoyl]-ethylthio-3[*H*],4[*H*],5[*H*]3,4-dihydro[1]-benzopyrano[4,3-d]-pyrimidine-4,5-dione (8) and 2-[(3[H], 4[H], 5[H][1-benzopyrano[4,3-d]-pyrimidine-4,5-dione-2-yl)-thio]-3-(4-phenyl-benzoyl)-propanoic acid (9): A mixture of **1** (2.46 g, 0.01 mol) and aroyl acrylic acid (Ar = biphenyl, 2.52 g, 0.01 mol) in pyridine (30 mL) was heated under reflux with stirring for 25 h. The reaction mixture was cooled, poured into ice/HCl. The solid product that formed was collected by filtration and fractionally crystallized.

Synthesis of 4-mercapto-2[*H*],7[*H*][1]benzopyrano[4,3-d]pyrimidino[2,1-c]-1,2,4-triazol-5-imino-dithiocarbamic acid (10) and 2[*H*],6[*H*][1]benzo-pyrano[4,3-d]pyrimidino[1,2-c]-1,2,4-triazolo[3,4-c]-1,2,4-triazlo-6-one-5-dithiocarboxylic acid (11): A mixture of compound **1** (2.46 g, 0.01 mol) and N-amino dithiocarbamic acid (1.08 g, 0.01 mol) in DMF (30 mL) was heated under reflux for 3 h in case of compound **10** and for 10 h in case of compound **11**, the

reaction mixture was cooled, poured into crushed ice, the formed solid product was filtered off, dried and crystallized from proper solvent to give compounds **10** and **11**.

Synthesis of 1-(4)-biphenyl-2-(3[*H*],4[*H*],5[*H*]-3,4-dihydro[1]benzo-pyrano-[4,3-d]pyrimidine-4,5-dione-2-yl)-thio-propionaldehyde hydrazone (12): A mixture of compound **8** (2.28 g, 0.005 mol) and hydrazine hydrate (98 %) (0.5 mL, 0.01 mol) in absolute ethanol (30 mL) was heated under reflux for 3 h then cooled, the precipitated solid was filtered off and crystallized.

Synthesis of 4-biphenyl-6[*H*],7[*H*][1]benzopyrano[4,3-d]pyrimidino[2,1-b]thiazolo[4,5-b]furan-6,7-dione (14): A mixture of compound **9** (2.49 g, 0.005 mol) and acetic anhydride (excess) was heated under reflux on water bath for 6 h then poured into ice cold water, the precipitated solid was collected by filtration and recrystallized.

Synthesis of 2-amino-4-biphenyl-6[*H*],7[*H*][1]benzopyrano[4,3-d]-pyrimidino[1,2-a]imidazo[4,5-b]furan-6,7-dione (15): To a solution of compound **14** (2.31 g, 0.005 mol) in absolute ethanol (40 mL), (0.5 mL, 0.01 mol) of hydrazine hydrate was added. The reaction mixture was refluxed for 3 h then cooled, the solid product formed was collected by filtration and crystallized.

Synthesis of 2-(3-biphenyl-1[*H*]-4,5-dihydropyridazine-6-one-5yl)-thio-3[*H*],4[*H*],5[*H*][1]benzopyrano-[4,3-d]pyrimidin-4,5-dione (16): To a solution of compound **9** (2.49 g, 0.005 mol) in DMF (30 mL), 0.5 mL (0.01 mol) of hydrazine hydrate (98 %) was added. The reaction mixture was refluxed for 5 h then poured into ice-cold water, the brownish solid product formed was collected by filtration and crystallized.

Synthesis of 2-mercapto-4-chloro-5[*H*][1]benzopyrano[4,3-d]pyrimidin-5-one (17): A mixture of **1** (2.46 g, 0.01 mol), phosphorous pentachloride (1 g) and phosphorous oxychloride (15 mL) was heated under reflux on water bath for 7 h. The reaction mixture was poured into a mixture of crushed ice and dilute hydrochloric acid, the solid product that obtained was filtered off, washed several times with water, dried and recrystallized.

Synthesis of 2-hydrazino-3[*H*],4[*H*],5[*H*][1]benzopyrano[4,3-d]pyrimidine-4,5-dione (18) and 3[*H*],4[*H*],5[*H*],6[*H*]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidino[2,1-b]-oxazol-4,5,6-trione (19): To a solution of compound **2a** (3.32 g, 0.01 mol) in DMF (30 mL), 0.75 mL (0.01 mol) of 98 % hydrazine hydrate was added. The reaction mixture was heated under reflux with stirring for 1 h. The yellowish orange solid formed during reflux was collected by filtration while hot and crystallized from DMF to give compound **18**.

On concentrating the filtrate and cooling a yellow solid formed which filtered and crystallized from dioxane to give compound **19**.

Reaction of compound 2a with aromatic amines to give compounds 21a-c and 22: To a solution of compound **2a** (3.32 g, 0.01 mol) in DMF (30 mL). 0.01 mol of appropriate aromatic amine was added and the reaction mixture was refluxed

with stirring for 3 h. The solid products formed on hot in case of compound **22** and after cooling in case of compounds **21a-c** were collected by filtration and crystallized from proper solvents to give compounds **21a-c** and **22**. On concentrating the filtrate and cooling, the solid that obtained was filtered off and crystallized from dioxane and identified as compound **19**.

Synthesis of ammonium-N(3[*H*], 4[*H*], 5[*H*][1]benzopyrano-[4,3-d]pyrimidine-4,5-dione-2-yl)-N-amino-dithiocarbamate (23): To a solution of the hydrazino compound **18** (2.44 g, 0.01 mol), in ammonium hydroxide (40 mL), 2 mL of carbon disulfide was added drop wise. The reaction mixture was stirred at room temperature for 3 h and left overnight, the solid product formed was filtered off and crystallized.

Synthesis of N-chloroacetyl-N-[N(3[*H*],4[*H*],5[*H*][1]benzopyrano[4,3-d]pyrimidin-4,5-dione-2-yl)amino]dithiocarbamic acid (24): To an aqueous solution of sodium chloroacetate (0.01 mol), (3.37 g, 0.01 mol) dithiocarbamate **23** was added portion wise during 10 min with stirring. The stirring was continued at room temperature for 3 h. Then a hot solution (85-90 ºC) of concentrated hydrochloric acid (66 mL) and water (26 mL) was added. On cooling a pale green precipitate was formed which was filtered off and crystallized.

Synthesis of 4-mercapto-1[*H*],2[*H*], 8[*H*],9[*H*]-3,4-dihydro[1]benzopyrano-[4,3-d]pyrimidino[2,1-c]-1,2,4-triazolidino[5,1-c]-thiazolidin-8,9-dione (26): A solution of compound **23** (1.98 g, 0.05 mol) in pyridine (30 mL) was heated under reflux for 5 h. Then cooled and poured into a mixture of crushed ice and hydrochloric acid, the obtained solid product was collected by filtration and crystallized.

Synthesis of 2-methyl-4-methylthio-6[*H*],7[*H*][1]benzopyrano[4,3-d]-pyrimidino[1,2-d]-1,2,4-triazol-6,7-dione (28): To a solution of dithiocarbamate compound **23** (3.37 g, 0.01 mol) in DMF (30 mL), (0.93 mL, 0.015 mol) of methyl iodide was added, the reaction mixture was refluxed for 5 h. Then cooled and poured into ice-cold water, the solid product that separated out was filtered off and crystallized.

Synthesis of 2-arylidinehydrazino-3[*H*],4[*H*],5[*H*][1]benzopyrano[4,3-d]-pyrimidine-4,5-dione (29a-c): A mixture of hydrazino compound **18** (2.44 g, 0.01 mol), appropriate aromatic aldehyde (0.01 mol) and piperidine (few drops) was fused on oil bath, the reaction mixture was cooled. The solid product was collected by filtration and recrystallized from proper solvent to give compounds **29a-c**.

Synthesis 2-(4-aryl-3-chloro-2-azetidinone-1-yl)-amino-3[*H*],4[*H*],5[*H*]-3,4-dihydro[1]benzopyrano[4,3-d]pyrimidine-4,5-dione (30a,b): To a well-stirred solution of Shiff base **29a,b** (0.01 mol) and triethyl amine (0.02 mol, 2.8 mL) in dry dioxane (30 mL) chloroacetyl chloride (1.59 mL, 0.02 mol) was added drop wise at room temperature. After all the acid chloride was added, the mixture was stirred for 12 h. The precipitated triethyl amine hydrochloride salt was filtered and washed thoroughly with dioxane. The combined solvent and filtrate was evaporated to small volume, poured into cold acidified water and the solid product obtained was collected by filtration, dried and recrystallized from proper solvent to give compounds **30a,b**.

RESULTS AND DISCUSSION

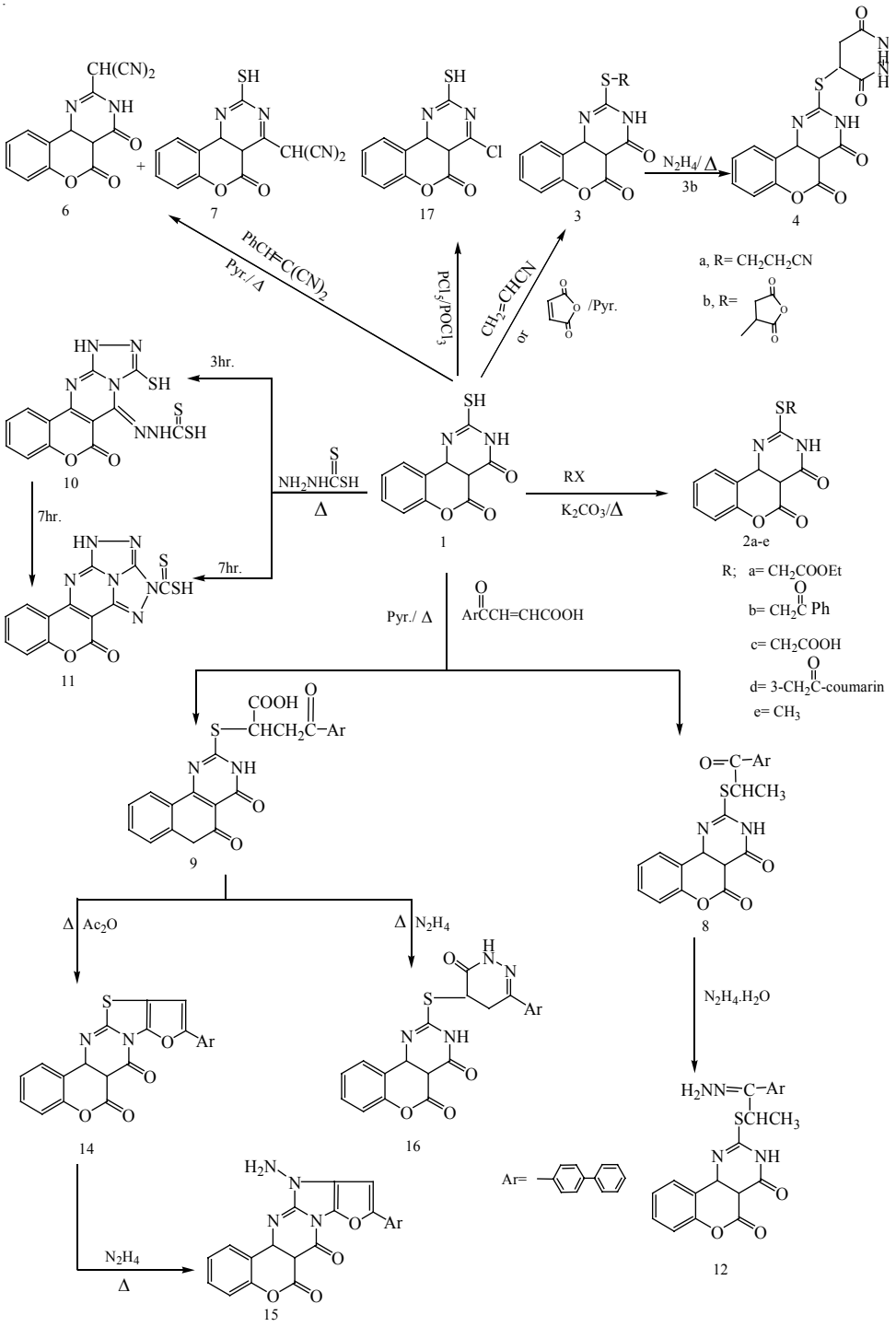
Alkylation of compound **1** with different alkylating agents such as ethyl bromoacetate, phenacyl bromide, chloroacetic acid, 3-bromoacetyl coumarin and methyl iodide under different conditions gave the 2-substituted thio derivatives **2a-e** (**Scheme-I**).The structure of compounds **2a-e** were confirmed from their elemental analysis and spectral data: The IR spectra of **2a-e** showed strong absorption bands at 3420-3216 cm^{-1} due to ν(NH), at 1743-1725 cm^{-1} due to ν(CO) of δ-lactone, at 1686-1649 cm^{-1} due to ν(CO) of cyclic amide. ^1H NMR (DMSO-d_6) spectrum of compound **2a** showed a triplet at δ 1.219 attributable to (3H, CH_3), a singlet at δ 3.57 due to (CH_2) protons adjacent to sulfur atom, a quartet at δ 4.20 referred to (CH_2) protons of ethyl group, a multiplet at δ 7.35-8.23 due to (4H, Ar-H) and a singlet at δ 13.57 due to (NH). The mass spectrum of compound **2b** revealed a parent peak at m/e = 366 (39.7 %) equivalent to molecular formula $C_{19}H_{14}N_2O_4S$.

Compound **1** undergo Michael addition reactions to activated unsaturated compounds such as acrylonitrile, maleic anhydride, benzylidine malononitrile and aroyl acrylic acid to give addition products depending on the nature of the unsaturated compound.

Compound **1** when reacted under reflux with acrylonitrile or maleic anhydride, in pyridine, it underwent simple Michael like type addition to afford the adducts **3a,b** (**Scheme-I**). The structures **3a,b** assigned to the product were based on analytical and spectral data. The IR spectra showed strong absorption bands at 3455-3158 cm^{-1} which are equivalent to ν(NH), at 2899-2858 cm^{-1} due to ν(CH) aliphatic, at 2191 cm^{-1} due to ν(CN) (for compound **3a**) at 1759-1744 cm^{-1} due to ν(CO) of δ-lactone and at 1647-1643 cm^{-1} due to ν(CO) of cyclic amide.

The action of hydrazine on succinic anhydride derivative **3b** as a nucleophilic attack resulted in the formation of pyridazinyl thiobenzo-pyranopyrimidine derivative **4** (**Scheme-I**) the structure of compound **4** was proved *via* its analytical and spectral data. The IR spectrum showed strong absorption bands at 3417 cm^{-1}, 3240 cm^{-1} due to bonded and nonbonded NH, at 2923, 2854 cm^{-1} due ν(CH_2), at 1735 cm^{-1} equivalent to ν(CO) of δ-lactone and at 1651 cm^{-1} due to ν(CO) of cyclic amide.

The reaction of compound **1** with benzylidine malononitrile was found to proceed an a different manner and does not give the expected addition product 2[1-phenyl-2-carbonitry-ethyl]mercapto-3[*H*],4[*H*],5[*H*][1]benzopyrano[3,4-d]pyrimidine-4,5-dione but it afforded both compounds **6** and **7** together (**Scheme-I**). A reasonable explanation for this behaviour is the breakdown of benzylidine malononitrile into its initial species (benzaldehyde and malononitrile) and the regenerated malononitrile acts as a nucleophilic reagent for attacking both the carbon atom bearing the mercapto group and the carbonyl carbon atom of the pyrimidine nucleus and afforded compounds **6** and **7**, respectively. Supporting evidences for the structures of compound **6** was provided from its analytical and spectral data. The IR spectra of **6** showed strong absorption bands at 3235 cm^{-1} characteristic for ν(NH) group, at 2209, 2178 cm^{-1} equivalent to both CN groups, at 1761 cm^{-1} due to ν(CO) of δ-lactone and at 1645


6
7
17
3
4
3b
a, R= CH2CH2CN
b, R=
PhCH=C(CN)2
Pyr./Δ
PCl5/POCl3
CH2=CHCN
or
/Pyr.
3hr.
7hr.
7hr.
10
11
NH2NHCSH
Δ
1
RX
K2CO3/Δ
2a-e
R; a= CH2COOEt
b= CH2C Ph
c= CH2COOH
d= 3-CH2C-coumarin
e= CH3
Pyr./ Δ
ArCCH=CHCOOH
9
8
Δ Ac2O
Δ N2H4
N2H4.H2O
14
16
12
Ar=
N2H4
Δ
15

Scheme-I

cm^{-1} due to ν(CO) of cyclic amide. The mass spectrum of compound **6** showed a parent peak at m/e = 280 (1.4 %) equivalent to the formula $C_{14}H_8N_4O_3$. The IR spectrum showed strong absorption bands at 2859 cm^{-1} due to ν(CH) aliphatic, at 2546 cm^{-1} due to ν(CO) ν(SH), at 2206, 2183 cm^{-1} due to both CN groups and 1760 cm^{-1} due to ν(CO) of saturated δ-lactone. Further confirmation of the structures of **6** and **7** was accomplished their formation on refluxing compound **1** with malononitrile in pyridine.

As a point of interest[6,7], the behaviour of compound **1** towards α,β-unsaturated acids such as 3-(4-phenylbenzoyl) acrylic acid was investigated to prove that the β-aroyl acrylic acid react as α,β-unsaturated acid or α,β-unsaturated ketone. The reaction resulted in formation of both compounds **8** and **9**, respectively (**Scheme-I**). The structure of compound **8** was confirmed by its analytical and spectral data. The IR spectrum showed absorption bands at 3425 cm^{-1} corresponding to ν(NH) group, at 2911 cm^{-1} equivalent to ν(CH) aliphatic, at 1723 cm^{-1} due to ν(CO) of δ-lactone and at 1679 cm^{-1} due to ν(CO) of keto group. The mass spectrum showed a parent peak at m/e = 428 (0.3 %) due to splitting of carbon monoxide molecule. The structure of compound **9** was elucidated *via* elemental analysis and spectral data. The IR spectrum showed absorption bands at 3420 cm^{-1} due to ν(COOH) group, at 3194 cm^{-1} equivalent to ν(NH), at 1720 cm^{-1} is characteristic for ν(CO) of δ-lactone. The carbonyl group of COOH function is being shifted to lower frequency due to H-bonding with NH group of pyrimidine ring and at 1640 cm^{-1} due to ν(CO) of cyclic amide. The mass spectrum of compound **9** revealed a parent peak at m/e = 498 (2.9 %) equivalent to the molecular formula $C_{27}H_{18}N_2O_6S$.

The reactivity of compound **1** towards amino dithiocarbamic acid was studied, the products were found to be dependant on reaction conditions. Thus when the reaction was carried out in DMF under reflux for 3 h, it yielded compound **10** while reflux for 7 h gave compound **11** (**Scheme-I**). The structures of these compounds were established for the reaction products depending on analytical, spectral data and chemical conformations by refluxing the triazole derivative **10** in DMF for 7 h, to give compound **11** *via* loss of hydrogen sulfide molecule. The IR spectrum for compound **10** revealed strong absorption bands at 3204 cm^{-1} due to low ν(NH), at 1722 cm^{-1} equivalent to ν(CO) of δ-lactone and at 1618 cm^{-1} due to ν(C=N). The IR spectrum of compound **11** showed strong absorption bands at 3384 cm^{-1} characteristic for ν(NH), at 1719 cm^{-1} due to ν(CO) of δ-lactone and at 1614 cm^{-1} due to ν(C=N). The mass spectrum which showed a parent peak at m/e = 342 (12.4 %) equivalent to molecular formula $C_{14}H_6N_6O_2S_2$.

Compound **8** undergoes reaction with hydrazine hydrate in refluxing ethanol to yield the corresponding hydrazone derivative **12** (**Scheme-I**). The structure assigned to compound **12** is based on elemental analysis and spectral data. The IR spectrum showed strong absorption bands at 3437 cm^{-1} due to ν(NH), at 3328, 3130 cm^{-1} characteristic for ν(NH_2) group, at 1738 cm^{-1} due to ν(CO) of cyclic amide and 1611 cm^{-1} equivalent to ν(C=N). The mass spectrum showed a parent peak at m/e = 470 (3.9 %) corresponding to the molecular formula $C_{26}H_{22}N_4O_3S$.

The carboxylic acid derivative **9** underwent cyclization to compound **14** when refluxed in acetic anhydride *via* elimination of water (**Scheme-I**). The structure **14** was confirmed on the basis of elemental analysis and spectral data. Thus the IR spectrum showed strong absorption bands at 1720 cm^{-1} characteristic to ν(CO) of δ-lactone and at 1681 cm^{-1} equivalent to ν(CO) of cyclic amide. ^1H NMR (DMSO-d_6) spectrum showed a singlet at δ 6.5 attributed to 1H at C_3 of furan ring and a multiplet at 7.4-8.1 ppm due to aromatic hydrogen (13 H). The mass spectrum revealed a parent peak at m/e = 462 (1.2 %) corresponding to molecular formula $C_{27}H_{14}N_2O_4S$.

Compound **14** when refluxed with hydrazine hydrate yielded the benzopyrano-pyrimidinoimidazofurandione derivative **16** (**Scheme-I**). The structure **15** was established from the correct analytical and spectral data. The IR spectrum showed strong absorption bands at 3405, 3237 cm^{-1} equivalent to the absorption frequency of amino group, at 1711 cm^{-1} is diagnostic for the unsaturated δ-lactone carbonyl group and at 1682 cm^{-1} due to ν(CO) of cyclic amide.

The hydrazinolysis of compound **9** with hydrazine hydrate in DMF give the pyridazinone derivative (**Scheme-I**). The structure of compound **16** was confirmed from its analytical and spectral data. The IR spectrum revealed strong absorption bands at 3415-3312 cm^{-1} due to ν(NH), at 1725 cm^{-1} equivalent to ν(CO) of δ-lactone and at 1670-1644 cm^{-1} due to ν(CO) of amide functions. The mass spectrum is consistent with this proposed structure, it revealed a parent peak at m/e = 496 (1.2 %) corresponding to the molecular formula $C_{27}H_{20}N_4O_4S$.

Chlorination of compound **1** using a mixture of phosphorous pentachloride and phosphoryl chloride under reflux afforded the chloro derivative **17** (**Scheme-I**). The IR spectrum showed the disappearance of the absorption band due to ν(NH) group and also the absorption band of carbonyl group of cyclic amide. Infrared spectrum showed a strong absorption band at 1706 cm^{-1} characteristic for ν(CO) of δ-lactone.

In continuation of our studies[6,7] for developing the behaviour of the sulfide derivative **2a** towards nitrogen nucleophiles, the reaction of compound **2a** with hydrazine hydrate in DMF afforded both hydrazine compound **18** *via* the replacement of the sulfide function in **2a** by nitrogen neucleophile and the cyclized compound **19** which was supposed to be formed photochemically[8] instead of the expected hydrazide compound **20** (**Scheme-II**). The structure of compound **18** was confirmed from its analytical and spectral data. The IR spectrum showed strong absorption bands at 3449, 3355 cm^{-1} due to ν(NH_2), at 3212 cm^{-1} due to ν(CO) of cyclic amide. ^1H NMR (DMSO-d_6) spectrum showed a singlet at δ 3.4 ppm equivalent to two protons of NH_2 group and a multiplet at 7.8-8.2 ppm due to aromatic protons and NH proton. The mass spectrum showed a peak equivalent to (M^+ - 1) at m/e = 243 (11.4 %). Further confirmation of compound **18** was provided chemically by its formation from the thiol compound **1** *via* refluxing with hydrazine hydrate in DMF.

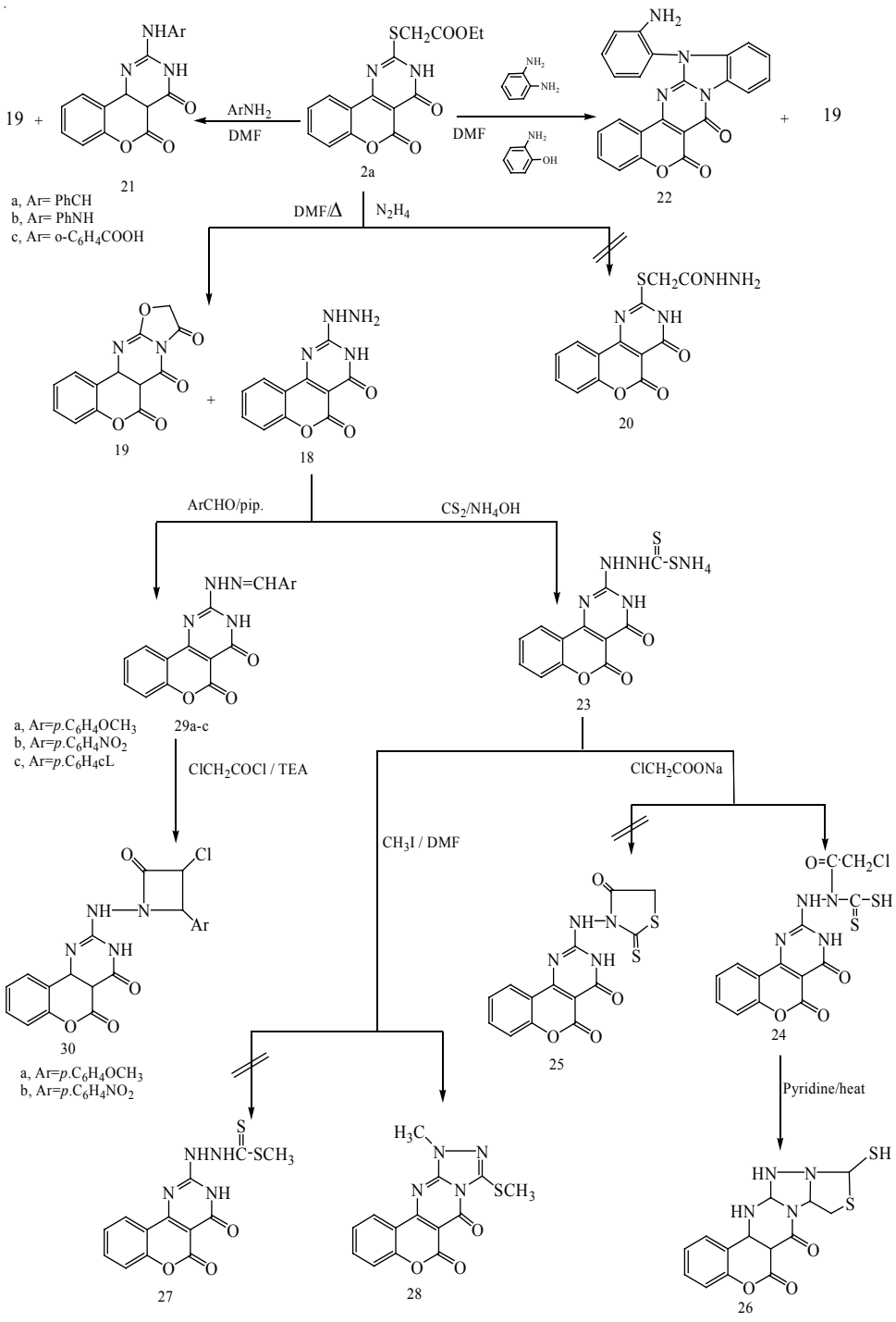
Supporting evidences for the structure of compound **19** were provided from its elemental analysis and spectral data. The IR spectrum showed strong absorption bands at 2926 cm^{-1} due to ν(CH) aliphatic, at 1768 cm^{-1} due to ν(CO) of saturated δ-lactone, at 1735 cm^{-1} due to ν(CO) of oxazole ring and at 1658 cm^{-1} equivalent to ν(CO) of cyclic amide. ^{1}H NMR (DMSO-d_6) spectrum showed signals at δ 3.2 (s, 2H, CH_2) and at 7-8.7 ppm (m, 6H, Ar-H, pyranone H).

It was found that reactions between compound **2a** and substituted hydrazine or aromatic amines proceeded in the same manner as in case of hydrazine hydrate and confirmed the replacement of the ethyl mercaptoacetete group by nitrogen nucleophiles. Thus the interaction of compound **2a** with phenyl hydrazine, benzyl amine and anthranilic acid afforded compounds **21a-c** together with the cyclized compound **19** (**Scheme-II**). The structures of compounds **21a-c** were confirmed based on analytical and spectral data. In the IR spectrum, the bands at 3448-3264 cm^{-1}, due to ν(NH), at 1743-1740 cm^{-1}, characteristic for ν(CO) of δ-lactone and at 1655-1644 cm^{-1}, due to ν(CO) of cyclic amide.

On the other hand, the interaction between **2a** and *o*-phenylene diamine or *o*-aminophenol yielded the same compound **22** in addition to the cyclized compound **19** (**Scheme-II**). The isolation of the same product **22** was elucidated *via* matching the thin layer chromatography for both products. The structure of compound **22** was proved *via* elemental analysis and spectral data. The IR spectrum showed strong absorption bands at 3417, 3255 cm^{-1} equivalent to ν(NH_2) group, at 1735 cm^{-1} due to ν(CO) of δ-lactone and at 1640 cm^{-1} due to ν(CO) of cyclic amide. The mass spectrum showed a parent peak at m/e = 394 (9.7 %) that equivalent to molecular formula $C_{23}H_{14}N_4O_3$.

Compound **18** could be converted into the dithiocarbamate salt **23** when it stirred with a mixture of carbon disulfide and ammonium hydroxide at room temperature (**Scheme-II**). The structure of dithiocarbamate salt **23** was proved from analytical and spectral data: IR spectrum showed strong absorption bands at 3412 cm^{-1} due to ν(NH) of pyrimidine ring, at 3245 and 3210 cm^{-1} due to ν(NH) of hydrazine group, at 1732 cm^{-1} due to ν(CO) of δ-lactone and at 1658 cm^{-1} equivalent ν(CO) of cyclic amide.

Moreover, the dithiocarbamate salt **23** can be used to synthesize some interesting compounds. Thus the reaction of compound **23** with sodium chloroacetate in aqueous medium followed by acidification with concentrated hydrochloric acid resulted in the formation of compound **24** and not the expected cyclized compound **25** (**Scheme-II**). The structure of compound **24** was confirmed *via* its elemental analysis and spectral data. The IR spectrum showed strong absorption bands at 3226 cm^{-1} due to ν(NH) of amide ring, at 3184 cm^{-1} equivalent to ν(NH) of hydrazine group, at 2927, 2859 cm^{-1} due to ν(CH) aliphatic, at 2518 cm^{-1} characteristic for ν(SH) group, at 1711 cm^{-1} attributed to ν(CO) of unsaturated δ-lactone and at 1648 cm^{-1} due to ν(CO) of cyclic amide.


19 +
NHAr
21
a, Ar= PhCH
b, Ar= PhNH
c, Ar= o-C6H4COOH
ArNH2
DMF
SCH2COOEt
2a
DMF
NH2
NH2
NH2
OH
22
+ 19
DMF/Δ
N2H4
19
+
NHNH2
18
SCH2CONHNH2
20
ArCHO/pip.
CS2/NH4OH
NHN=CHAr
29a-c
a, Ar=p.C6H4OCH3
b, Ar=p.C6H4NO2
c, Ar=p.C6H4cL
NHNHC-SNH4
23
ClCH2COCl / TEA
CH3I / DMF
ClCH2COONa
30
a, Ar=p.C6H4OCH3
b, Ar=p.C6H4NO2
25
24
Pyridine/heat
NHNHC-SCH3
27
28
26

Scheme-II

Cyclization of compound **24** in a refluxing pyridine afforded compound **26** which was formed *via* elimination of hydrogen chloride molecule followed by loss of water molecule and hydrogenation (**Scheme-II**). Supporting evidences for the structure of compound **26** were provided from its analytical and spectral data. The IR spectrum revealed strong absorption bands at 3442, 3101 cm^{-1} due to two ν(NH), at 2925 cm^{-1} due to ν(CH) aliphatic, at 1740 cm^{-1} equivalent to ν(CO) of saturated δ-lactone and at 1686 cm^{-1} due to ν(CO) of cyclic amide. ^{1}H NMR (DMSO-d_6) spectrum showed signals at δ 3.7 (t, CH-CH_2-S), 3.95 (s, 1H, SH), 4.03 (d, 2H, CH_2-S), 6.3 (s, 1H, S-CH 1H, -SH), 6.87 (d, 1H at C_4 of pyranone), 6.93 (d, 1H at C_3 of pyranone), 7.2-8.2 (m, 4H, Ar-H) and 9.2 ppm (s, 1H, NH). The mass spectrum showed a parent peak at m/e = 350 (12.24%) corresponding to molecular formula $C_{14}H_{14}N_4O_3S_2$.

Alkylation of the dithiocarbamate derivative **23** with methyl iodide in order to prepare the methyl derivative **27**, which could not be obtained but the reaction resulted in the formation of cyclized compound **28** (**Scheme-II**). Confirmatory evidences for the structure of compound **28** were provided from its analytical and spectral data. The IR spectrum showed strong absorption bands at 2927 cm^{-1} due to ν(CH_3) groups, at 1743 cm^{-1} equivalent to ν(CO) of δ-lactone, at 1666 cm^{-1} due to ν(CO) of cyclic amide and at 1624 cm^{-1} due to ν(C=N). The mass spectrum showed a molecular ion peak at m/e = 314 (10 %) corresponding to molecular formula $C_{14}H_{10}N_4O_3S$.

The condensation of the hydrazine derivative **18** with aromatic aldehydes namely, *p*-anisaldehyde, *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde in presence of piperidine as a catalyst yielded the arylidine hydrazino derivatives **29a-c** (**Scheme-II**). The structure of these compounds were confirmed depending on their analytical and spectral data. The IR spectrum revealed strong absorption bands at 3460-3200 cm^{-1} corresponding to ν(NH) group, at 1730-1720 cm^{-1} due to ν(CO) of δ-lactone, at 1680-1654 cm^{-1} due to ν(CO) of cyclic amide and at 1625-1624 cm^{-1} characteristic for ν(C=N).

Furthermore, the behaviour of compounds **29a,b** towards cyclo-addition reactions was studied, thus chloroacetyl chloride cycloadded[9] to the Schiff base **27** in a dry dioxane in presence of triethylamine as a catalyst to afford compounds **30a,b** (**Scheme-II**). Supporting evidences for the structures of these compounds were provided from their elemental analysis and spectral data. The IR spectrum revealed strong absorption bands at 3450-3421 cm^{-1} characteristic for ν(CO), at 1751-1739 cm^{-1} equivalent to ν(CO) of saturated δ-lactone, at 1690-1685 cm^{-1} due to ν(CO) of lactam ring and 1645 cm^{-1} due to ν(CO) of cyclic amide. The mass spectrum of compound **30b** showed a parent peak corresponding to addition product at m/e 456 (1 %) and equivalent to molecular formula $C_{20}H_{14}N_5O_6Cl$.

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