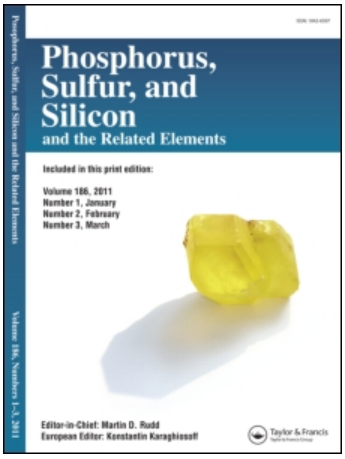

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STUDIES OF BIOLOGICALLY ACTIVE SULFUR COMPOUNDS-PART I: REACTIONS OF BIS(MERCAPTOTHIOFOR-MYLHYDRAZID0)PHTHALATE WITH SOME DIFFERENT α,β - BIWNCTIONAL COMPOUNDS

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STUDIES OF BIOLOGICALLY ACTIVE SULFUR COMPOUNDS-PART I: REACTIONS OF BIS(MERCAPTOTHIOFORMYLHYDRAZIDO)PHTHALATE WITH SOME DIFFERENT α,β - BIFUNCTIONAL COMPOUNDS

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The reactions of bis(mercaptothioformylhydrazido)phthalate (2) moiety with nitrogen, sulfur and / or halogen α,β – bifunctional compounds have been studied. Structures of the products have been deduced from elemental analysis and spectral data (UV, IR, ^{1}HNMR & mass spectra). Most of the products showed moderate activity against some bacteria.

Keywords: bifunctional compounds; sulfur hetero-cycles

1. INTRODUCTION

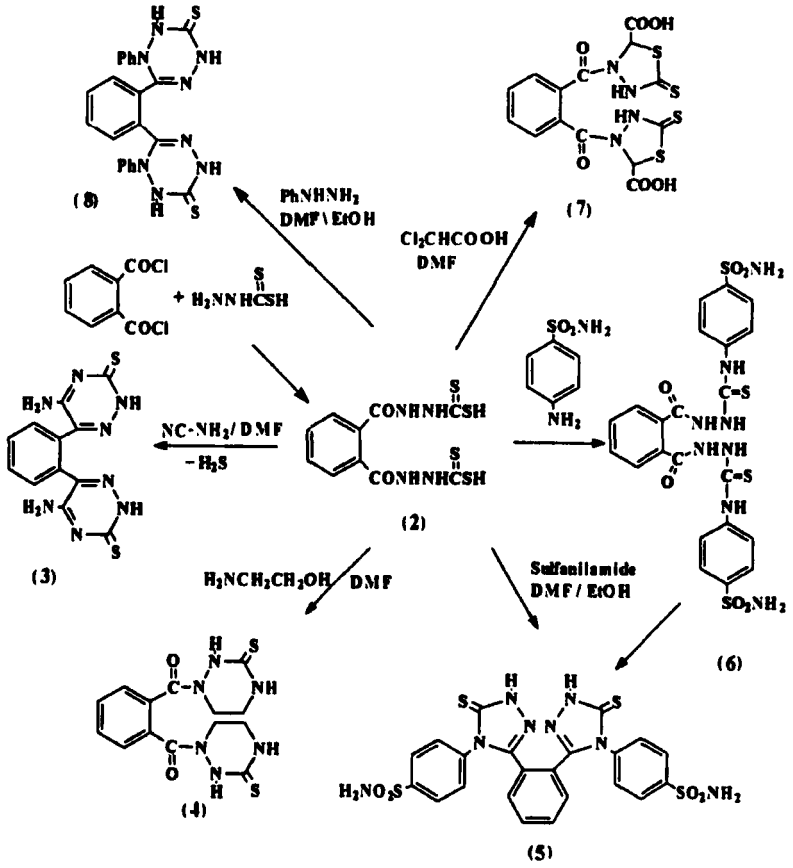
Different types of sulfur containing heterocyclic systems exhibit a wide spectrum of biological activities [1–5]. Recently, reported that 3-thioxo-1,2,4-triazines can be used as anticancer and anti HIV drugs [6–10]. On the other hand, a little works have been done on mercapto-thioformic acid hydrazide. It was worthwhile to prepare bis(mercaptothio-formylhydrazido)phthalate (2) and investigate the behavior of it towards nitrogen, sulfur and / or halogen α,β-bifunctional compounds and study their effect on the biological activities.

* Corresponding Author.

2. INVESTIGATIONS AND RESULTS

2.1. Chemistry

The starting material bis(mercaptothioformylhydrazido)phthalate (**2**), was prepared from boiling phthaloyl chloride with two moles of mercaptothioformyl hydrazide (**1**) in DMF (Scheme 1).



SCHEME 1

Structure of compound **2** was deduced from elemental analysis and spectral data. IR spectrum exhibited γ_{max} at 3163 (NH), 1660 (CONH) and

1129, 1079 cm^{-1} (C=S, C-S). The ^{1}HNMR spectrum showed signals at δ 3.5 (SH), 7.7–8.2 (aromatic protons), 8.5 (NHCS), 11.5 (NHCO) ppm, while the mass spectrum of that compound recorded the m/z at 104 as the base peak which characteristic the postulated structure (Chart I).

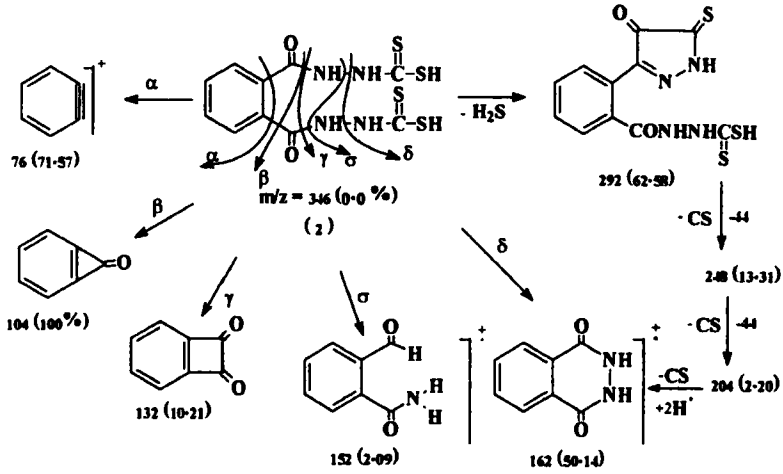
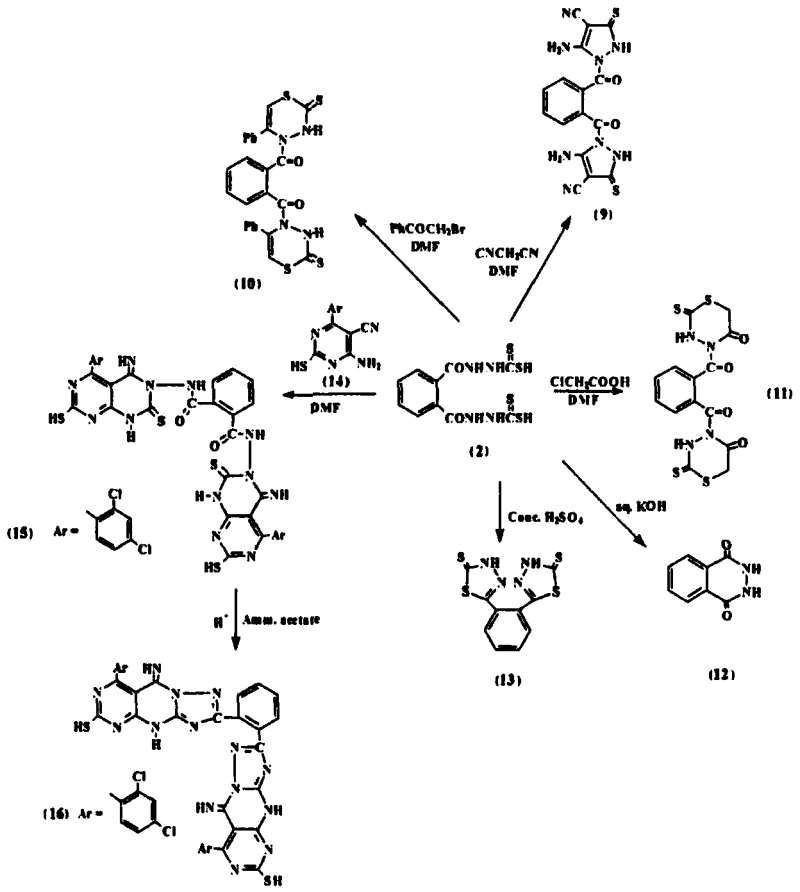


CHART I Mass Fragmentation pattren of compound (2)

The chemical reactivity of the nitrogen compounds as well as active methylene compounds towards compound **2** has been studed in this work. Thus, 1,2-bis(5-amino-3(2H)thioxo-6-(1,2,4,-triazino) benzene (**3**) was obtained from reaction of compound 2 with cyanamide [11] in a mixture of DMF and abs. EtOH, while bis(2,4,5,5,6,6-hexahydro-3-thioxo-1-(1,2,4-triazino) phthalate (**4**) produced upon treatment of **2** with ethanolamine under the same conditions (Scheme 1).

Compounds having both sulfa and heterocyclic moieties together gave some interesting results [12]. Thus, compound **2** on reaction with sulfanilamide in a mixture of DMF and abs. EtOH resulted in the formation of 1,2-bis(4-(p-benzenesulfonamido)-5(1H)-thioxo-3-(1,2,4-triazolo) benzene (**5**), while warming compound **2** with sulfanilamide in DMF furnished bis(1-phthaloyl-4-(p-benzenesulphonamido) thiosemicarbazide (**6**) and upon heterocyclization by refluxing with 1,1-dichloroacetic acid in DMF afforded bis(5-carboxy-2(3H)thioxo-4-(1,3,4-thiadiazolo) phthalate (**7**) (Scheme 1).



SCHEME 2

Compound **2** on treatment with phenyl hydrazine in abs. EtOH led to the direct formation of 1,2-bis(1-phenyl-3-(2H,4H)thioxo-6-(1,2,4,5-tetrazino) benzene (**8**) (Scheme 1).

In the present investigation, the chemical reactivity of methylene group as compared with amino groups was found to be depend out mainly on the nature of nucleophile, neighboring group, and also the reaction conditions. Thus, refluxing compound **2** with malononitrile, phenacyl bromide and monochloroacetic acid in DMF [13] yielded bis(5-amino-4-cyano-3(2H)thioxo-1-pyrazolo) phthalate (**9**), bis(5-phe-

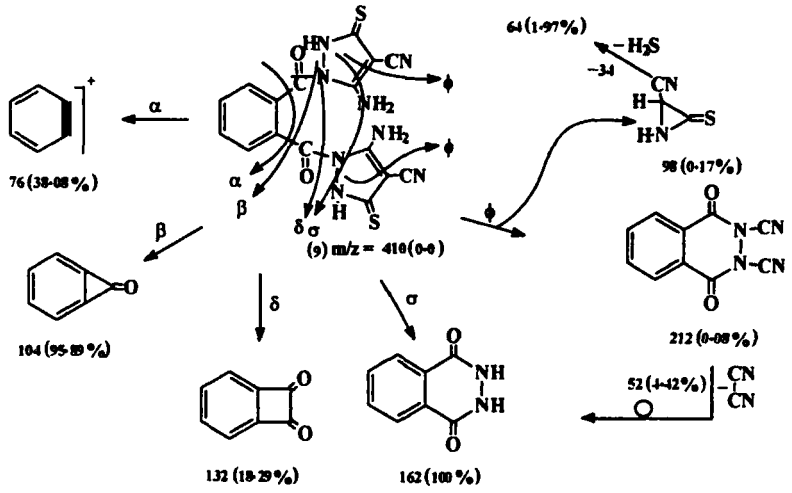


CHART II Mass fragmentation pattren for compound (9)

nyl-2(3H)thioxo-4-(1,3,4-thiadiazino) phthalate (**10**) and bis(6,6-dihydro-5-oxo-2(3H)thioxo-1-(1,3,4-thiadiazino) phthalate (**11**) respectively (Scheme 2).

The structure of **9** was established upon analysis the spectral data. The UV spectrum data of **9** exhibited bands at 225,236 and 218 nm, while the IR spectrum showed ν_{max} at 3650 (NH_2), 2199 (CN), 1747 (C=O) and 1217 (C=S) cm^{-1}. ^{1}HMNR of compound **9** exhibited peaks at δ 3.3 (NH_2), 7.6–8.0 (aromatic CH), and 11.5 (NH) ppm. The mass spectrum of **9** showed the elimination of pyrazoline thione to give the stabilized phthalizin-1,4-dione moity at m/z 162 as a base peak (Chart 2).

The action of pH of medium on the heterocyclization of compound **2** also was studied. Thus, refluxing compound **2** with 5% aq. KOH yielded phthalazin-1,4-dione (**12**). The formation of **12** may be occurred as showen in schem 3. While warming that with conc. H_2SO_4 [14] produced 1,2-bis(2(3H)thioxo-5-(1,3,4-thiadiazolo)benzene (**13**). IR spectrum of **12** exhibited characteristic absorptions at 3165 (NH-NH) and 1661 cm^{-1} (CONH). Its UV spectrum revealed λ_{max} 260–250, 230 and 218 nm due to the bathochromic shifts. The mass spectrum of **12** showed molecular ion at m/z 162 (100 %) which under further fragmentation process by loss of N, N_2, O, O_2 supported the postulated structure (Chart 3).

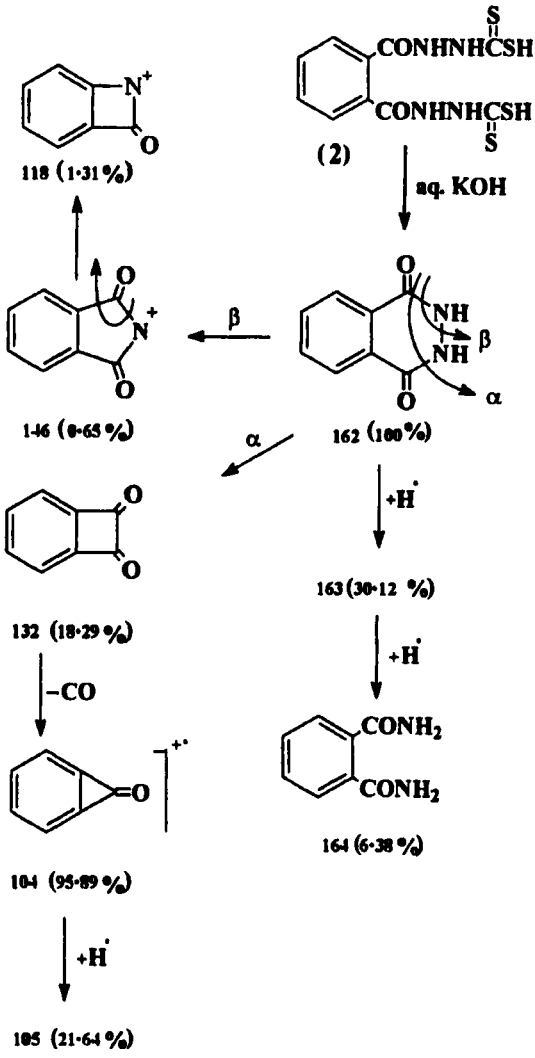


CHART III Mass fragmentation pattren for compound (12)

Finally, heterocyclization of compound **2** with 4-amino-6-aryl-5-cyano-primidin-3(2H)thione (**14**) via refluxing in DMF-abs. EtOH gave **15** which on boiling with ammonium acetate in acetic acid [15] afforded the fused poly heterocyclic system **16** (Scheme 2).

2.2. Antimicrobial activity

Some of obtained compounds were screened for antibacterial activity against Bacteria, R. Legs, E. Coli, P. aeruginosa, B. Cereas, Staph. Aureus and Sarcina sp. [16].

The antibacterial activities of the test compounds were compared with standard sulfanilamide and salicylic acid respectively [17]. DMF was used as solvent control.

3. DISCUSSION

The results have bccn shown in the following table:

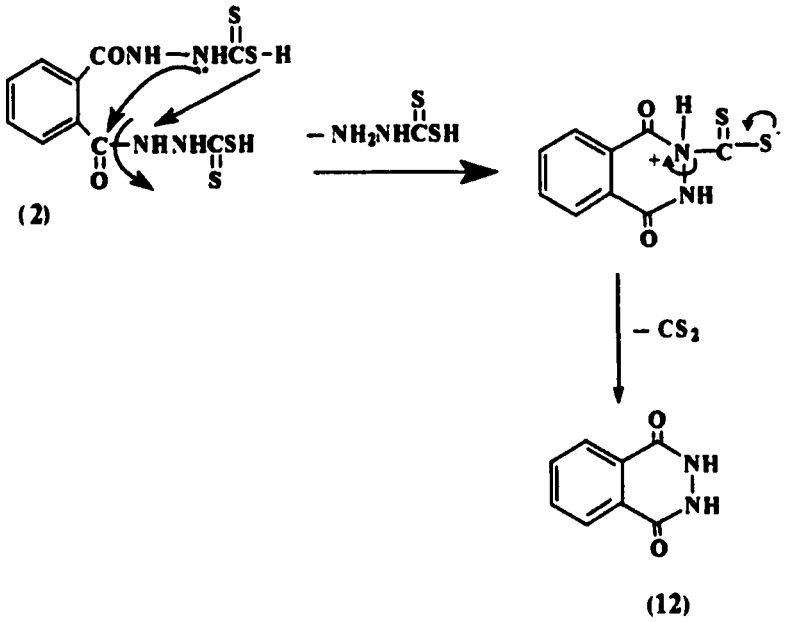
Sample no.	*R. Legs*	*E. Coli*	*P. Aeruginosa*	*B. Cereas*	*Staph. Aureus*	*Sarcina sp.*
3	+++	–	+++	–	++	+
6	++	+++	+++	+++	++	++
7	–	+	+	–	+++	+
8	+++	–	++	++	+++	–
11	–	–	++	++	–	–
13	+++	+++	++	+++	–	+
16	+++	+++	++	++	++	–

Diameter of the zone is as following:
+++ = 4cm = 400mm
++ = 3cm = 300mm
+ = 2cm= 200mm
– = Negative assay = 4cm = 400mm

From the above data we sec that compounds **6, 8, 13** and **16** exihibited significant antibacterialwhile **7** and **11** have moderate activity towards tested bacteria.

4. EXPERIMENTAL

Melting points reported are uncorrected. IR spectra in KBr pellets on a Perkin-Elmer, 1430 ratio recording spectrophotometer (ν_{max} in cm^{-1}). UV spectra were recorded in pure ethanol on a Perkin-Elmer, Lambda 4B con-



SCHEME 3

troller accessory interface, UV-VIS spectrophotometer (λ_{max} in nm). ^{1}HNMR spectra were recorded on EM NMR Spectrometer 200 MHz using DMSO-d_6 as a solvent and TMS as an internal reference (chemical shifts reported in δ, ppm). Mass spectra were recorded on a gas chromatographic $GCMS_{qp}$ 1000ex Schimadzu instrument at 70 eV.

4.1. Preparation of bis(mercaptothioformylhydrazido) phthalate (2)

A mixture of compound **1** (0.02 mol) phthaloyl chloride (0.01 mol) in DMF (10 ml) were refluxed for 1hr, cooled, then poured onto ice. The solid obtained filtered off and recrystallized to give **2** (Table I).

IR: 3163 (NH), 3012 (aromatic CH), 1660 (C=O), 1601 (C=N), 1347 (NCS), 1219, 1166, 1127, 1079 and 1021 (C=S, C-S). **^{1}HNMR**: 3.5 (s, 2H, SH), 7.7–8.2 (m, 4H, aromatic protons), 8.5 (s, 2H, NHCS) and 11.5 (s, 2H, NHCO). **M/Z** (Int. %): 51(12.65), 55(9.26), 76(71.57), 77(19.51),

78(2.56), 104(100), 105(17.10), 132(10.21), 162(50.14), 163(6.15), 248(13.31), 292(62.58), 293(11.51) and 346(1.00)

4.2. 1,2-Bis(5-amino-3(2H)thioxo-6-(1,2,4,-triazino) benzene (3)

A mixture of compound **2** (0.01 mol) and cyanamide (0.02 mol) in DMF-abs. EtOH (1:1 50 ml) were refluxed for 4hr, cooled, then poured onto ice. The solid thus obtained was filtered and recrystallized to give **3** (Table I). **UV** (λ_{max}): 250, 230 and 218, **IR**: 3568 (NH_2), 3164 (NH), 3016 (aromatic CH), 1600 (C=C), 1556 (C=N) and 1164 (C=S). ^{1}**HNMR**: 3.3 (s, 2H, SH), 6.5 (s, 2H, NH), 7.7–8.1 (m, 4H, aromatic protons) and 11.8 (s, 4H, NH_2). **M/Z** (Int. %): 51(23.23), 57(7.38), 76(39.19), 77(27.24), 104(85.18), 105(22.41), 132(17.42), 162(100), 163(9.67), 236(1.47), 244(1.54) and 313.3(1.77).

4.3. Bis(2,4,5,5,6,6-hexahydro-3-thioxo-1-(1,2,4-triazino) phthalate (4)

A mixture of compound **2** (0.01 mol) and ethanolamine (0.02 mol) in DMF (20 ml) were refluxed for 4hr, cooled, then poured onto ice. The resultin solid was filtered off and recrystallized to give **4** (Table I).

IR: 3166 (NH), 3023 (aromatic CH), 2895 (aliphatic CH), 1662 (C=O), 1600 (C=C), 1555 (C=N) and 1162 (C=S). **M/Z** (Int. %): 51(19.50), 76(26.30), 77(19.05), 91(3.34), 104(100), 105(16.61), 132(17.14), 162(49.47), 163(7.38), and 364(0.05).

4.4. 1,2-Bis(4-(p-benzenesulfonamido)-5(1H)-thioxo-3-(1,2,4-triazolo) benzene (5)

A mixture of compound **2** (0.01 mol) and sulfanilamide (0.02 mol) in a mixtuer of DMF-abs. EtOH (1:1, 50 ml) were refluxed for 4hr, cooled, then poured onto ice. The resulting solid was filtered off and recrystallized to give **5** (Table I).

IR: 3261 (SO_2NH_2), 3163(NHCS), 3015 (aromatic CH), 1601 (C=C), 1556 (C=N) and 1160 (C=S). **M/Z** (Int. %): 51(40.87), 53(42.31), 64(42.79), 76(100), 77(65.38), 90(10.10), 104(87.98), 105(44.23), 130(11.06), 132(20.19), 146(15.38), 155(10.10), 162(92.79), 163(15.38), 176(19.23), 450(6.73) and 586(0.0).

4.5. Bis(1-phthaloyl-4-(p-benzenesulphonamido) thiosemicarbazide (6)

A mixture of compound **2** (0.01 mol) and sulfanilamide (0.02 mol) in DMF (10 ml) were refluxed for 15 min, cooled, then poured onto ice. The solid obtained filtered and recrystallized to give **6** (Table I).

IR: 3163 (NH_2, NH), 3019 (aromatic CH), 1661 (CONH), 1601 (C=C), 1555 (C=N) and 1164 (C=S).

4.6. Conversion of 6 to 5

A suspension of **5** (1 gm) in abs. EtOH (20 ml) was refluxed for 5hr, cooled, then poured onto ice. The solid obtained filtered and recrystallized to give **5** M.P. and M.M.P. gave no deviation.

4.7. Bis(5-carboxy-2(3H)thioxo-4-(1,3,4-thiadiazolo) phthalate (7)

A mixture of compound **2** (0.01 mol) and 1,1-dichloroacetic acid (0.02 mol) in DMF (20 ml) were refluxed for 4hr, cooled, then poured onto ice. The resulted solid was filtered off and crystallized to give **7** (Table I).

IR: 3586 (OH), 3165 (NH), 3021 (aromatic CH), 2897 (aliphatic CH), 1749 (CO of COOH), 1660 (C=O), 1165 (C=S) and 1080 (C-S). **M/Z** (Int. %): 51(27.28), 76(46.14), 77(37.64), 104(100), 105(32.94), 118(2.10), 132(11.76), 133(5.16), 162(57.50), 163(6.62), 164(1.02), 434(0.22) and 458(0.10).

4.8. 1,2-Bis(1-phenyl-3-(2H,4H)thioxo-6-(1,2,4,5-tetrazino) benzene (8)

A mixture of compound **2** (0.01 mol) and phenyl hydrazine (0.02 mol) in DMF-abs. EtOH (1:1, 50 ml) were refluxed for 5hr, cooled, then poured onto ice. The resulting solid was filtered off and recrystallized to give **8** (Table I). **IR**: 3013 (NH), 2581 (SH), 1600 (C=C), 1555 (C=N) and 1163 (C=S).

4.9 Bis(5-amino-4-cyano-3(2H)thioxo-1-pyrazolo) phthalate (9)

A mixture of compound **2** (0.01 mol) and malononitrile (0.02 mol) in DMF (20 ml) were refluxed for 4hr, cooled, then poured onto ice. The resulting solid was filtered off and recrystallized to give **9** (Table I).

UV (λ_{max}): 218, 236, 255; **IR**: 3650 (NH_2), 3163 (NH), 3014 (aromatic CH), 2198 (CN), 1747 (C=O), 1602 (C=C), 1556 (C=N) and 1217 (C=S). **^{1}HNMR**: 3.3 (s, 4H, NH_2), 7.6–8.0 (m, 4H, aromatic protons), 11.5 (s, 2H, NH). **M/Z** (Int. %): 51(18.76), 52(4.42), 64(1.97), 76(38.08), 77(23.72), 91(3.74), 104(95.89), 105(21.64), 132(18.29), 162(100), 163(30.12), 212(0.08), 221(5.83), 410(0.30).

4.10. Bis(5-phenyl-2(3H)thioxo-4-(1,3,4-thiadiazino) phthalate (10)

A mixture of compound **2** (0.01 mol) and phenacyl bromide (0.02 mol) in DMF (20 ml) were refluxed for 4hr, cooled, then poured onto ice. The solid thus obtained was filtered off and recrystallized to give **10** (Table I).

IR: 3067 (NH), 1747 (C=O), 1607 (C=N), 1170 (C=S) and 1077 (C-S).

4.11. Bis(6,6-dihydro-5-oxo-2(3H)thioxo-1-(1,3,4-thiadiazino) phthalate (11)

A mixture of compound **2** (0.01 mol) and monochloroacetic acid (0.02 mol) in DMF (20 ml) were refluxed for 2hr, cooled, then poured onto ice. The solid produced was filtered and recrystallized to give **11** (Table I).

IR: 3160 (NH), 3018 (aromatic CH), 2900 (aliphatic CH), 2583 (SH), 1746 (C=O), 1660 ($COCH_2$), 1166 (C=S) and 1080 (C-S). **^{1}HNMR**: 3.3 (s, 4H, CH_2CO), 7.7–8.0 (m, 4H, aromatic protons), 11.2 (s, 2H, NH).

4.12. Basic hydrolysis of 2: Formation of phthalazin-1,4-dione (12)

A suspension of **2** (1 gm) in aq. KOH (10 %, 20 ml) was refluxed for 4hr, cooled, then pour onto ice – HCl. The solid produced was filtered and crystallized to give **12** (Table I).

UV (λ_{max}): 260–250 (*sh*), 230 and 218; **IR**: 3165 (NH-NH), 3017 (aromatic CH), 1661 (CONH) and 1601 (C=C). **M/Z** (Int. %): 51(18.91), 57(3.89), 76(30.38), 77(24.65), 91(3.70), 104(78.93), 105(21.03), 118(1.44), 132(18.04), 133(3.90), 162(100), 163(9.08).

4.13. Acidic hydrolysis of 2 – Formation of 1,2-bis(2(3H)thioxo-5-(1,3,4-thiadiazolo)benzene (13)

A suspension of **2** (1 gm) in conc. H_2SO_4(10 ml) was stirred for 12hr, then poured onto ice, then neutralized with aq. K_2CO_3. The solid produced, filtered, washed with H_2O and recrystallized to give **13** (Table I).

TABLE I Characteristic data of the products 2–16

Compd No.	*Formula*	*MWt*	*Crystallized from*	*M.P. / C°*	*Yield %*	*M⁺*	*% C Calc.*	*% C Found*	*% H Calc.*	*% H Found*	*% N Calc.*	*% N Found*	*% S Calc.*	*% S Found*
2	$C_{10}H_{10}N_4O_2S_4$	346.45	DMF	325 – 327	85	346	34.67	34.65	2.91	2.90	16.17	16.20	37.01	36.97
3	$C_{12}H_{10}N_8S_2$	330.38	EtOH	330 – 332	50	330	43.63	43.60	3.05	3.04	33.92	33.90	19.41	19.41
4	$C_{14}H_{16}N_6O_2S_2$	364.44	Dil. DMF	310 – 312	65	364	46.14	46.11	4.42	4.40	23.06	23.00	17.59	17.59
5	$C_{22}H_{18}N_8O_4S_4$	586.68	DMF	285 – 287	55	586	45.04	45.00	3.09	3.06	19.10	19.12	21.86	21.84
6	$C_{22}H_{22}N_8O_6S_4$	622.71	Dil. DMF	295 – 297	45	622	42.43	42.38	3.56	3.52	17.99	17.95	20.59	20.54
7	$C_{14}H_{10}N_4O_6S_4$	458.50	MeOH	315 – 317	60	458	36.68	36.70	2.20	2.15	12.22	12.15	27.97	27.95
8	$C_{22}H_{18}N_8S_2$	458.56	MeOH	335 – 337	90	458	57.62	57.60	3.96	3.99	24.44	24.40	13.98	13.95
9	$C_{16}H_{10}N_8O_2S_2$	410.43	EtOH	317 – 319	70	410	46.82	46.81	2.46	2.45	27.30	27.29	15.62	15.63
10	$C_{26}H_{18}N_4O_2S_4$	546.69	AcOH	300 – 302	60	546	57.12	57.09	3.32	3.33	10.25	10.24	23.46	23.44
11	$C_{14}H_{10}N_4O_4S_4$	426.50	Dil. DMF	305 – 307	80	426	39.43	39.40	2.36	2.33	13.14	13.12	30.07	2.00
12	$C_9H_{10}N_2O_2$	178.19	MeOH	315 – 317	50	178	60.66	60.61	5.66	5.60	15.72	15.70	-	-
13	$C_{10}H_6N_4S_4$	310.42	AcOH	340 – 342	88	310	38.69	38.65	1.95	1.96	18.05	18.06	41.31	41.30
15	$C_{35}H_{30}Cl_4N_{12}O_2S_4$	920.75	EtOH	235 – 237	50	920	45.66	45.63	3.28	3.27	18.25	18.24	13.93	13.91
16	$C_{35}H_{28}Cl_4N_{14}S_2$	850.63	DMF	301 – 203	55	850	49.42	49.38	3.32	3.30	23.05	23.00	7.54	7.52

IR: 3166 (NH), 1601 (C=N), 1166 (C=S), 1080 and 1022 (C-S).

4.14. Reaction of compound 2 with 4-amino-6-aryl-5-cyanoprimidin-3(2H)thione (14) – Formation of 15

A mixture of compound **2** (0.01 mol) and **14** (0.02 mol) in DMF (20 ml) were refluxed for 4hr, cooled, then poured onto ice. The solid thus obtained was filtered off and recrystallized to give **15** (Table I).

UV (λ_{max}): 250, 230 and 216; **IR**: 3023 (NH), 2581 (SH), 1650 (CONH), 1218 and 1080 (C=S).

4.15. Synthesis of poly heterocyclic compound 16

A mixture of compound **15** (0.01 mol) and ammonium acetate (5 gm) in AcOH (10 ml) were refluxed for 12hr, cooled, then poured onto ice. The solid thus obtained washed with cold water, filtered and recrystallized to give **16** (Table I).

UV (λ_{max}): 260–240, 230, 220 and 216; **IR**: 3164 (NH), 2581 (SH), 1659 (=NH), 1591 (C=N) and 1157 (C=S).

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