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CONVERSION OF 2-METHYLCHROMONES TO PYRIMIDINE DERIVATIVES

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2-Methylchromones Ia-d were converted to 4-methyl-6-(substituted phenyl) -2-[1H]-thiopyrimidines IIa-d, via the condensation with thiourea. These thiopyrimidines were converted to other pyrimidine derivatives e.g. bis pyrimidinyl disulphides, oxopyrimidines, ethoxycarbonylmethylmercaptopyrimidines, ethoxycarbonylmethyl-mercaptopyrimidine acid hydrazides, triazolylpyrimidines, pyrimidin-2-ylmercaptoacetyl-thiosemicarbazides and dimethyl oxalacetate 2-carboxymethyl-mercaptopyrimidine acid hydrazides.

Key words: Methyl chromones, Thiopyrimidines, Pyrimidine derivatives.

Introduction

Flavones have been examined to give 2-[1H]-thiopyrimidines [1] on condensation with thiourea. But no 2-methyl-chromones have been treated with the same reagent. When 2-methylchromones I(a-d) were condensed with excess thiourea in alcoholic potassium hydroxide solution 4-Methyl-6-(substituted phenyl)2-[1H]-thiopyrimidines II(a-d) were obtained. All compounds II were soluble in aqueous alkali and gave a colour reaction with ferric chloride; their IR spectra showed bands at 3190-3170 (NH), 2900 (OH. Br), 1625-1620 (C=N) and at 1240-1230 cm^{-1} (C=S). The PMR spectrum of IIb taken as an example showed signals at δ 12.4 (s, 1H, OH), 7.76-6.76 (m, 5H, phenyl and pyrimidine protons), 2.37 (s, 3H, pyrimidine CH_3) and at 2.27 (s, 3H, phenyl CH_3).

Experimental

Melting points were recorded. The IR spectra (potassium bromide) were recorded on a Pye Unicam SP-1100 spectrophotometer. ^1H NMR spectra were measured in DMSO-d_6 on a Varian EM-360 60MHz or Brucker 250 MHz spectrophotometers. Chemical shifts were quoted as δ values in relation to TMS as internal standard.

4-Methyl-6-(substituted phenyl)-2-[1H]-thiopyrimidines II(a-d). A mixture of chromone (0.01 mole), thiourea (0.025 mole), potassium hydroxide (0.02 mole : dissolved in a small amount of water) and ethanol (50 ml) was refluxed for 3 hrs. The solution was cooled and acidified with dilute hydrochloric acid on which a yellow crystalline solid was obtained. It was filtered off and crystallized from the proper solvent to give compounds II.

Bis-[4-methyl-6-(substituted phenyl)-pyrimidin-2-yl] disulphides III (a-d). A mixture of thiopyrimidine II (1g), dioxane (30 ml) and hydrogen peroxide (1 ml, 30%) was heated for 5 mins, then cooled. A white crystalline solid was deposited which was filtered off and recrystallized from the proper solvent to give compounds III.

4-Methyl-6-(substituted phenyl)-2-[1H]-oxopyrimidines IV(a-d). To a solution of thiopyrimidine II (1 g) in 10% aqueous sodium, hydroxide (10 ml), hydrogen peroxide (10 ml, 30%) was added and the mixture was allowed to stand for 24 hrs at room temperature. The yellow sodium salt that separated was filtered off, acidified with dilute hydrochloric acid and recrystallized from the proper solvent to give the oxopyrimidines IV.

2-Ethoxycarbonylmethylmercapto-4-methyl-6-(substituted phenyl) pyrimidines V a and b. A mixture of compound IIa or IIb to (0.01 mole), ethyl chloroacetate (0.012 mole), pyridine (20 ml) and anhydrous sodium carbonate (4 g) was heated under reflux for 10 mins, allowed to cool, then poured into water. A white crystalline solid was obtained which was filtered and crystallized from the proper solvent to give Va or Vb.

2-Carboxymethylmercapto-4-methyl-6-(substituted) pyrimidine hydrazides VIa and b. Compound Va or Vb (0.01 mole), hydrazine hydrate (0.012 mole, 98%) and ethanol (20 ml) were heated on a steam bath for 6 hrs. The colourless crystals which separated on cooling were recrystallized from the proper solvent to give acid hydrazides VIa or b.

2-Carboxymethylmercapto-4-methyl-6-(substituted phenyl) pyrimidine anisylidenehydrazides VIIa and b. A mixture of VIa or VIb (0.001 mole), ethanol (20 ml), acetic acid

(3 ml) and anisaldehyde (0.001 mole) was heated under reflux for 1 hr. The product which separated on cooling was filtered off and recrystallized from the proper solvent to give VIIa, or b.

2-[(4-amino-1,2,3-triazol-5-thione-3-yl) carbonylmethylthio]-4-methyl-6-(substituted phenyl) pyrimidines IXa and b. Carbon disulphide (12 ml) was added dropwise to an ice-cold solution of potassium hydroxide (0.025 mole in absolute ethanol (200 ml) containing VIa or b (0.01 mole). The mixture was stirred at room temperature for 14 hrs, then dry ether (200 ml) was added and filtered off, washed with ether to give the dithiocarbazates VIIIa or b in nearly quantitative yield and they were used without further purification. VIIIa or VIIIb (0.01 mole), hydrazine hydrate (0.02 mole) and water (2 ml) were heated under reflux for half an hour. Cold water (10 ml) was added and the mixture was neutralized with diluted hydrochloric acid. The separated product was filtered off and crystallized from the proper solvent to give IX a and b respectively.

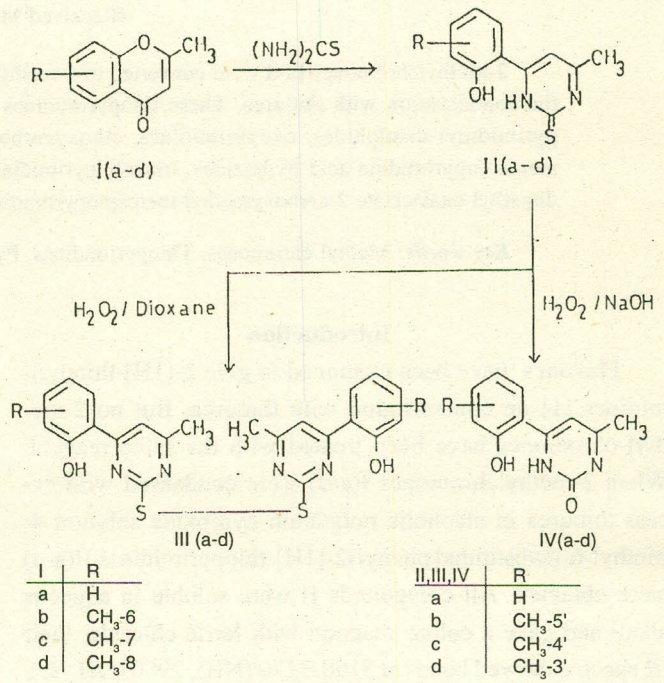
2-[4-anisylideneamino-1,2,3-triazol-5-thione-3-yl) carbonylmethylthio]-4-methyl-6-(substituted phenyl) pyrimidines Xa and b. A mixture of IXa or b (0.001 mole), ethanol (20 ml), acetic acid (3 ml) and anisaldehyde (0.001 mole) was heated under reflux for 20 mins. The product which separated on cooling was filtered off and recrystallized from the proper solvent to give Xa or b respectively.

4-Methyl-6-(substituted phenyl) pyrimidin-2-ylmercapto-methylcarbonylthiosemicarbazides XI a and b. A mixture of VIa or b (0.01 mole), ammonium thiocyanate (2.3g, 0.03 mole), concentrated hydrochloric acid (4 ml) and ethanol (200 ml) was heated under reflux for 22 hrs. The solvent was distilled and the solid residue was crystallized from the proper solvent to give XIa or b respectively.

Dimethyl oxalacetate 2-carboxymethylmercapto-4-methyl-6-(substituted phenyl) pyrimidine acid hydrazides XIIa and b. Dimethyl acetylenedicarboxylate (0.005 mole), was added to a warm solution of VIa or VIb (0.005 mole) in methanol (50 ml). The reaction mixture was heated under reflux on a steam bath for 20 mins. A white crystalline solid was obtained which was filtered off and re-crystallized from the proper solvent to give XIIa or b respectively.

Results and Discussion

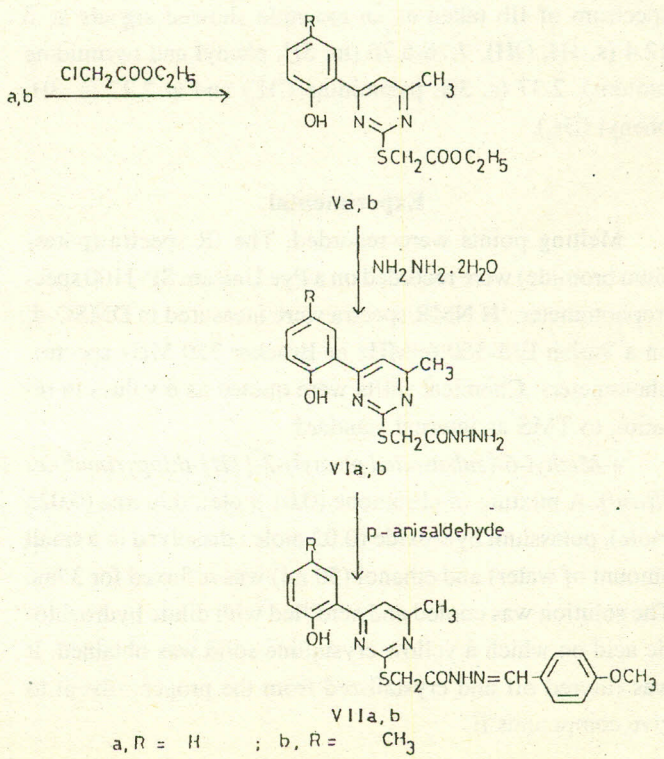
It is known that oxidation of thiopyrimidines give different products depending on the oxidation conditions [2]. Thus when thiopyrimidines IIa-d were oxidized with hydrogen peroxide in boiling dioxane, they were converted quantitatively to the corresponding disulphides III(a-d). However, if the oxidation with hydrogen peroxide was conducted in aqueous sodium hydroxide, desulphurization took place and 2-[1H]-oxopyrimidines IV(a-d) were obtained.



I	R
a	H
b	CH_3-6
c	CH_3-7
d	CH_3-8

II,III,IV	R
a	H
b	CH_3-5'
c	CH_3-4'
d	CH_3-3'

Structure 1

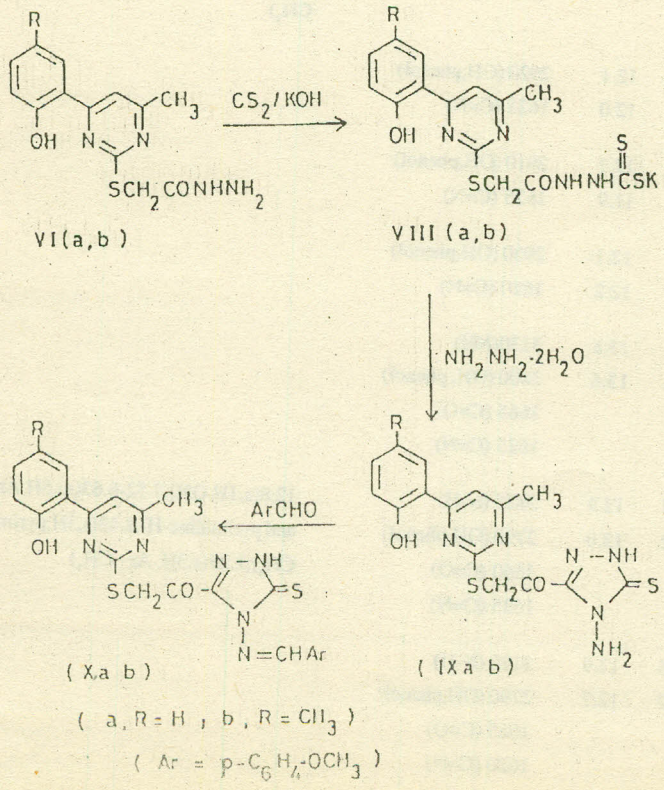


Structure 2

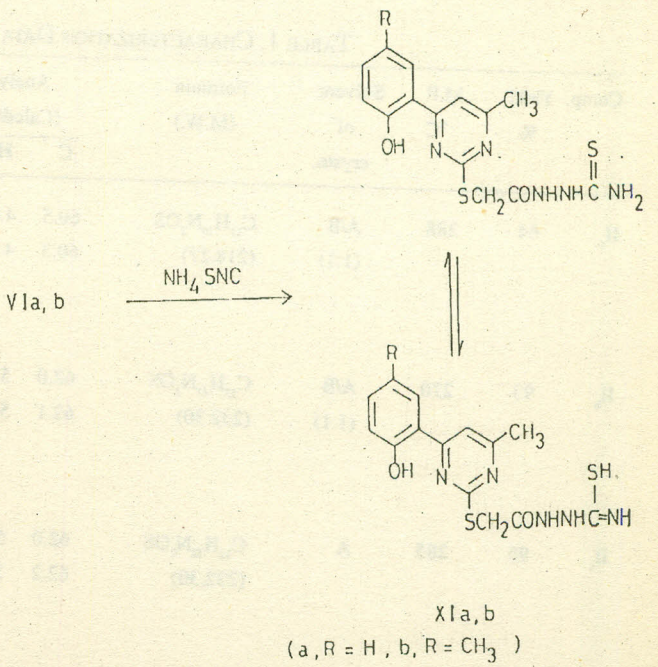
Reaction of compounds II(a and b) with ethyl chloroacetate in pyridine containing anhydrous sodium carbonate yielded the corresponding 2-ethoxy-carbonylmethyl-mercaptopyrimidines V(a and b) respectively, which upon reaction with hydrazine hydrate in boiling alcohol gave the corresponding acid hydrazides VI(a and b). These acid hydrizides condensed easily with anisaldehyde to give the hydrazones VII (a and b) respectively.

The acid hydrazides VI were used for the synthesis of other pyrimidine derivatives. Thus aminotriazolylpyrimidines IX(a and b) were prepared via the conversion of the hydrazides VI to the corresponding potassium 3-(pyrimidin-2-yl mercaptomethylenecarbonyl) dithiocarbazates VIII (a and b) using CS_2 in alcoholic potassium hydroxide, then reacting VIII with hydrazine hydrate. The structures of compounds IX were confirmed through their correct elemental analysis, spectral data (IR and PMR) and similarly to the synthesis of other aminotriazoles from acid hydrazides [3]. The aminotriazoles IX (a and b) condensed with anisaldehyde to give the azomethine derivatives X (a and b) respectively.

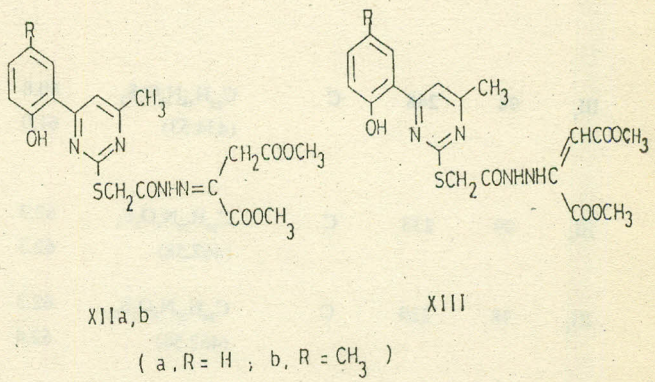
Like other acid hydrazides [4], compounds VI(a and b) reacted with ammonium thiocyanate in ethanolic hydrochloric acid to give pyrimidylmercaptomethylcarbonyl thiosemicarbazides XI(a and b), which might have existed in the imino form since the PMR spectra displayed no signal



Structure 3



Structure 4



Structure 5

for NH_2 but showed a sharp signal at δ 9.37 for SH and a broad signal at δ 7.44 for -C=N-H.

It is known that hydrazines, arylhydrazines [5] and aroyl hydrazines [6] condense with dimethyl acetylene dicarboxylic ester (DMAD) to yield the hydrazones (imines) or the enehydrazines (enamines). Herein when acid hydrazides VI (a and b) were allowed to react with (DMAD), they gave dimethyl oxalacetate hydrazones XII (a and b) (imine form) but not the enehydrazines XIII (enamine form). This was confirmed from the PMR spectra of XII (a and b) which showed no signals for vinyl absorption at 5.40 ± 0.54 [5] but showed a methylene resonance at 3.72 for XIIa and at 3.79 for XIIb (Table 1).

TABLE 1. CHARACTERIZATION DATA OF THE NEWLY SYNTHESIZED COMPOUNDS.

Comp.	Yield %	M.P. °C	Solvent of crystn.	Formula (M.W.)	Analysis % (Calcd/Found) C	H	N	$IR_{(cm^{-1})}$	^1H NMR
II_a	64	288	A/B (1:1)	$C_{11}H_{10}N_2OS$ (218.27)	60.5 60.3	4.6 4.5	12.8 12.6	3170 (NH) 2875 (OH, phenol) 1620 (C=N) 1235 (C=S)	
II_b	93	270	A/B (1:1)	$C_{12}H_{12}N_2OS$ (232.30)	62.0 62.1	5.2 5.2	12.1 11.9	3185 (NH) 2900 (OH,phenol) 1624 (C=N) 1240 (C=S)	12.4 (s,1H,OH),7.76-6.76 (m,5H, Ar - H and pyrimidine - H), 237 (s, 3H, pyrimidine CH_3), 2.27 (s,3H,Ar-CH_3)
II_c	95	285	A	$C_{12}H_{12}N_2OS$ (232.30)	62.0 62.2	5.2 5.1	12.1 12.2	3190 (NH) 2890 (OH, phenol) 1620 (C=N) 1230 (C=S)	
II_d	91	275	A	$C_{12}H_{12}N_2OS$ (232.30)	62.0 61.9	5.2 5.3	12.1 12.3	3180 (NH) 2910 (OH, phenol) 1625 (C=N) 1240 (C=S)	
III_a	98	248	C	$C_{22}H_{18}N_4O_2S_2$ (434.53)	60.8 61.0	4.2 4.1	12.9 12.7	2875 (OH, phenol) 1620 (C=N)	11.9(s,1H,OH),7.96-6.82(m,10H, Ar - H and pyrimidine-H), 2.33 (s,6H,pyrimidine CH_3)
III_b	99	233	C	$C_{24}H_{22}N_4O_2S_2$ (462.58)	62.3 62.3	4.8 4.6	12.1 12.0	2920 (OH,phenol) 1625 (C=N)	
III_c	98	229	C	$C_{24}H_{22}N_4O_2S_2$ (462.58)	62.3 62.4	4.8 4.8	12.1 11.9	2910 (OH,phenol) 1625 (C=N)	
III_d	95	244	C	$C_{24}H_{22}N_4O_2S_2$ (462.58)	62.3 62.5	4.8 4.6	12.1 12.2	2930 (OH,phenol) 1620 (C=N)	
IV_a	81	>300	D	$C_{11}H_{10}N_2O_2$ (202.21)	65.3 65.1	4.9 5.0	13.8 13.6	3130(NH) 2800 (OH, phenol) 1665 (C=O) 1625 (C=N)	
IV_b	85	>300	D	$C_{12}H_{12}N_2O_2$ (216.24)	66.6 66.7	5.5 5.2	12.9 13.0	3125 (N-H) 2790 (OH,phenol) 1660 (C=O) 1625 (C=N)	12.8(s,1H,OH),7.52-6.63(m,5H,Ar - H) and pyrimidine-H),2.43(s,3H,pyrimidine CH_3),2.25(s,3H, Ar - CH_3)
IV_c	80	>300	D	$C_{12}H_{12}N_2O_2$ (216.24)	66.6 66.4	5.5 5.7	12.9 12.7	3120 (N-H) 2790 (OH,phenol) 1665 (C=O) 1620 (C=N)	

(Contd...)

furic acid. The methyl esters were purified by column chromatography on silica gel by eluting with hexane/diethyl ether (99.5:0.5 v/v). The purity of esters was monitored by TLC and infrared (IR) spectroscopy.

Methyl esters of triglycerides were prepared by using a mixture of boron trifluoride in methanol [9].

Identification by GC and GC/MS. Methyl esters were analysed using a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and packed glass column (1.6 m x mm i.d.) containing 15% diethylene glycol succinate on Shimalite (AW) (201), mesh size 60-80. Nitrogen was used as a carrier gas with a pressure of 0.3 kg/cm^2. The column temperature was maintained at 200°C, while the detector and injector temperatures were 300° and 250°C respectively. The fatty acid methyl esters were identified by their retention times and peak enhancement using authentic standards. The percentage composition of each individual component was calculated on the basis of peak area using a Shimadzu C-R4A (chromatopac) data processor (Table 2).

Jeol model JMS-AX505H Mass Spectrometer combined with Hewlett 5890 Packard gas chromatograph was used for GC/MS analysis. Samples were injected on to a column (25 m x 0.22 mm i.d.; phase thickness 0.25 μ) containing 5 % phenyl siloxane and 95 % dimethyl siloxane, coated with BP-5 (bonded phase) and helium as carrier gas, split ratio 1:100, EI positive mode, electron energy 70 eV, ionization current 300 μA, ionization source temperature 250°C, interface temperature 230°C, column temperature programmed at 60°C for 4 min with a 6°C/min. rise to 230°C. Data acquisition and reprocessing were performed by Jeol JMA-DA 5500 system with MS-48TK library search system. The fatty acid components of the total lipids were confirmed by this method (Table 3

Results and Discussion

The physico-chemical characteristics of the oil are shown in Table 1. The oil content of *T. Portulacastrum* is found to be 12.5%. It consists primarily of neutral lipids (95.2%) mainly triglycerides, including hydrocarbons, wax-esters, free fatty acids, mono and diglycerides with small amounts of polar lipids (4.8%). The fatty acid composition of total lipids and isolated triglycerides are reported for the first time (Table 2&3). A comparison of fatty acid composition of the triglycerides (84.5%) and total lipids (95.2%) (Table 2) indicates that the total oil consists mainly of unsaturated fatty acids. Although Osman *et al.* [10] have investigated two different

TABLE 2. FATTY ACID COMPOSITION OF THE SEED OIL AND TRIGLYCERIDES OF *TRIANTHEMA PORTULACASTRUM* LINN.

Fatty acids (%)	Total lipids	Triglycerides
C_8 : 0	Trace	Traces
C_{10} : 0	Traces	Traces
C_{14} : 0	0.6	0.7
C_{16} : 0	13.1	15.0
C_{18} : 0	5.6	6.2
C_{18} : 1	23.0	23.3
C_{18} : 2	55.6	52.8
C_{18} : 3	0.8	0.4
C_{20} : 0	1.2	1.2

TABLE 3. CHARACTERISTIC MASS FRAGMENTS OF METHYL ESTER OF FATTY ACID.

Fatty acid	Common name	Scan no.	Characteristic M/z (Relative intensity)
C_{14} : 0	Myristic acid	519	242(18.6), 211(6.3), 199(14.3) 157(7.1), 143(23.1) 129(7.1), 87(61.4), 74(100), 57(18.6) 55(14.6), 43(22.9) 41(15.7)
C_{16} : 0	Palmitic acid	748	270(58.6), 239(17.9), 227(26.7), 213(5.7), 199(11), 171(12.9), 157(6.2), 143(37.1) 129(16.2), 115(6.7), 101(11.4), 87(100) 74(100), 55(29.5), 43(33.3)
C_{18} : 2	Linoleic acid	954	294(51), 263(23.8), 222 (11), 221(11), 178(12.6) 164(18.1), 150(22), 123 (29.5), 109 (44.8) 95 (77.1), 81(99), 67(100), 55 (76.2), 41(51.4)
C_{18} : 1	Oleic acid	258	296(26.2), 264(94.3) 246(7.6), 222(41.7), 180(31.4), 166(16.4) 137(21), 123(29.5), 110(39.5), 97 (67), 83(72.2), 69(83.3), 55(100),41(59.1)
C_{18} : 0	Stearic acid	974	298(50.5), 267(11.2), 255(20), 241(4.3), 213(6.2) 199(15.7), 185(6.7), 157(5.5) 143(30.5), 129(10.5), 111(4.8), 97(10), 87(71.4), 74(100), 55(23.8),43(26.7)
C_{20} : 0	Arachidic acid	1176	326(61), 195(8.5), 283(16.8)227 (9.3), **213(2.9),199(9.5), 157 (4.3), 143 (29.1), 129(10.7), 97(10.5), 87(73.3), 74(100), 55(25.7), 43(31)**

(Table 1 contd...)

IV_d	83	>300	D	$C_{12}H_{12}N_2O_2$	66.6	5.5	12.9	3125 (N-H)	
				(216.24)	66.3	5.4	12.8	2790 (OH,phenol)	
								1660 (C=O)	
								1625 (C=N)	
V_a	91	96	E	$C_{15}H_{16}N_2O_3S$	59.2	5.3	9.2	2800 (OH,phenol)	
				(304.36)	59.1	5.5	9.4	1720 (C=O,ester)	
								1610 (C=N)	
V_b	95	103	F	$C_{16}H_{18}N_2O_3S$	60.4	5.7	8.8	2800 (OH,phenol)	
				(318.39)	60.7	5.6	8.8	1725 (C=O, ester)	
								1615 (C=N)	
VI_a	76	171	E	$C_{13}H_{14}N_4O_2S$	53.8	4.9	19.3	3310 (NH)	
				(2910.34)	53.6	5.0	19.5	1655 (C=O)	
								1620 (C=N)	
VI_b	81	176	E	$C_{14}H_{16}N_4O_2S$	55.2	5.3	18.4	3300 (NH)	
				(304.36)	55.5	5.4	18.6	1655 (C=O)	
								1610 (C=N)	
VII_a	88	201	D	$C_{21}H_{20}N_4O_3S$	61.7	4.9	13.7	3190 (NH)	
				(408.48)	61.5	4.7	13.5	1680 (C=O)	
								1610 (C=N)	
VII_b	96	227	B	$C_{22}H_{22}N_4O_3S$	62.5	5.2	13.3	3200 (NH)	
				(422.50)	62.3	5.4	13.5	1670 (C=O)	
								(1610 (C=N)	
IX_a	45	214	B	$C_{15}H_{14}N_6O_2S_2$	48.1	3.8	22.4	3275-3100 (NH)	13.89(s,1H,OH),11.35(s,1H,NH),7.83-6.58
				(374.44)	48.3	4.1	22.7	1615 (C=N)	(m,5H,Ar - H and pyrimidine H), 5.56
									(s,2H,NH_2),4.76(s,2H,S-CH_2),2.47(S,3H,
									pyrimidine CH_3).
IX_b	63	239	B	$C_{16}H_{16}N_6O_2S_2$	49.5	4.2	21.6	3310-3110 (NH)	13.63(s,1H,OH),11.38(s,1H,NH),7.81-6.85
				(388.46)	49.8	4.2	21.9	1620 (C=N)	(m,4H, Ar - H and pyrimidine H), 5.64
									(s,2H,NH_2), 4.52(s,2H,S-CH_2),2.46(s,3H,
									pyrimidine CH_3), 2.28(s,3H, Ar - CH_3).
X_a	72	239	B	$C_{23}H_{20}N_6O_3S_2$	56.1	4.1	17.1	3100 (NH)	
				(492.57)	55.9	4.2	16.9	1610 (C=N)	
X_b	75	235	B	$C_{24}H_{22}N_6O_3S_2$	56.9	4.4	16.6	3110 (NH)	13.78(s,1H,OH),11.27(S,1H,NH),9.84
				(506.6)	56.6	4.5	16.8	1610 (C=N)	(s,1H,N=CH),7.81-6.85(m,8H, Ar - H and
									pyrimidine H),4.67(s,2H,SCH_2)3.83
									(s,3H,OCH_3),2.42(s,3H,pyrimidine CH_3),
									2.25 (s,3H, Ar - CH_3)
XI_a	49	214	B	$C_{14}H_{15}N_5O_2S_2$	48.1	4.3	20.0	3430-3280(NH)	11.68(s,1H,OH),10.11(s,1H,NH),9.32(s.1H,
				(349.43)	48.3	4.5	19.8	1695 (C=O)	SH),7.97(s,1H,NHCO),8.15-7.82(m,3H,
								1`605 (C=N)	two Ar - H and pyrimidine H),7.44

(Contd...)

(Table 1 contd...)

									(s,1H,NHC=S)7.34-6.92(m,2H, two AR-H), 3.4(s,2H,SCH_2),2.41(s,3H,pyrimidine CH_3)
XI_b	42	230	aq.G	$C_{15}H_{17}N_5O_2S_2$ (363.45)	49.6 49.4	4.7 4.7	19.3 19.5	3430-3160 (NH) 1995 (C-O) 1605 (C=N)	11.73(s,1H,OH),10.19(s,1H,=N-H),9.37(s, 1H,SH),7.99(s,1H,NHCO),7.83-7.82(m,2H, one Ar -H and pyrimidine H),7.44(s,1H, NHCS),6.89-6.23(m,2H, Ar - H), 3.99 (s,2H,SCH_2),2.38(s,3H,pyrimidine CH_3), 2.27(s,3H,ArCH_3)
XII_a	77	173	H/I (1:1)	$C_{19}H_{20}N_4O_6S$ (432.45)	52.8 52.7	4.7 4.5	12.9 12.6	3200 (NH) 1740,1720,1710 1690 (C=O) 1620 (C=N)	11.71(s,1H,OH),10.23(s,1H,NH),8.05-7.82 (m,3H,two Ar - H and pyrimidine H), 7.25-6.94(m,2H,two Ar - H),4.57(s,2H, SCH_2),3.92(s,2H,C-CH_2CO),3.88(s,3H, OCH_3),3.69(s,3H,OCH_3),2.42(S,3H,pyri-midine CH_3).
XII_b	69	180	C/H (1:1)	$C_{20}H_{22}N_4O_6S$ (446.48)	53.8 54.0	4.9 4.7	12.5 12.3	3200 (NH) 1740,1720,1710 1690 (C=O) 1610 (C=N)	11.62(s,1H,OH),10.72(s,1H,NH),7.81(s,1H), pyrimidine H),7.78(d,1H,J=1.7,one Ar - H) 7.49-6.85(m,2H, two Ar -H),4.64(s,2H, SCH_2),3.97(s,2H,C-CH_2-CO),3.76(s,3H, OCH_3),3.63(s,3H,OCH_3),2.43(s,3H,pyri-midine CH_3),2.24(s,3H,ArCH_3)

A = pyridine, B = butanol, C = dioxane, D = acetic acid, E = ethanol, F = petroleum ether (60-80), G = DMF, H = methanol, I = chloroform.

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