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Synthesis and biological activity of some new heterocyclic systems derived from 5-carboxyhydrazide-4, 5-dihydro-1-phenylpyrazolo[3,4-d] pyrimidin-4-one

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ABSTRACT

Several new heterocyclic systems bearing a 4,5-dihydro-1-phenylpyrazolo[3,4-d] pyrimidin-4-one-5-yl moiety have been synthesized through acylation of 5-carboxyhydrazide-4,5-dihydro-1-phenylpyrazolo [3,4-d] pyrimidin-4-one(II) followed by cyclization reactions. Structure of the products have been established by elemental analyses and spectral data(UV, lR, ^{1}H NMR and mass). Some of them have been screened for their antibacterial and antifungal activity. © 2008 Trade Science Inc. -INDIA

INTRODUCTION

Carboxyhydrazides are convenient intermediates for the synthesis of oxadiazoles, thiadiazoles, triazoles, triazines and tetrazines[1-3]. They are also known as biologically active agents. Phenylpyrazolo[3,4-d] pyrimidines reported from this laboratory were found to possess considerable anti-tumor activity and various DNA viruses[4,5]. Also they are useful for treatment of cardio vascular diseases[6,7]. In view of these reports and in continuation of our work in this area. the synthesis of some heterocyclic moieties are reported to explore the possibility of obtaining biologically useful compounds.

RESULTS AND DISCUSSION

The key intermediate,5-carboxyhydrazide-4,5-dihydro-1-phenylpyrazolo[3,4-d] pyrimidin-4-one (II) was synthesized by treatment of the corresponding ethyl ester I with hydrazine hydrate in EtOH. The structure of II was confirmed from UV, lR and mass spectral studies. Its UV spectra showed an intense band at 285nm and another less prominent band at 260nm. lR spectra of II showed peaks at 3340, 3268 and 1710, 1640cm^{-1} due to two NH and C=O groups. The mass spectral fragmentation pattern of II has been presented in chart 1.

Acylation of II using acetyl chloride, chloroacetyl chloride, ethyl chloroformate, p-nitrobenzoylchloride, allyl/phenyl isothiocyanate and benzenesulphonyl chloride in DMF gave the corresponding monoacyl derivative IIIa-g.

Cyclocondensation of compounds IIIa,b in ammonium acetate and gl AcOH Afforded 3-methyl/methylchloride-4H-5-(4`,5`-dihydro-`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5‘-yl)-s-triazoles (IVa,b) while IIIb on treatment with liq ammonia-ammonium acetate in ethanol afforded 2,5-dihydro-6-(4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5‘-yl)-1,2,4-triazine-3(4H)-one (V).

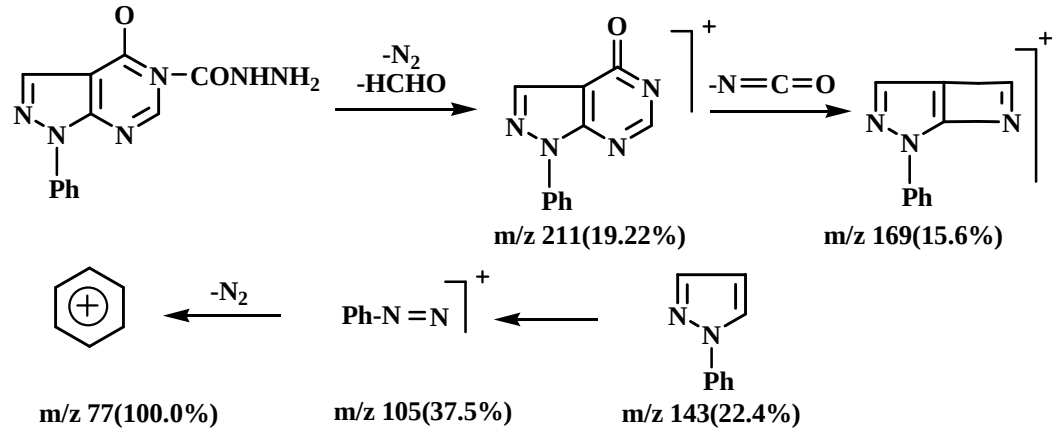
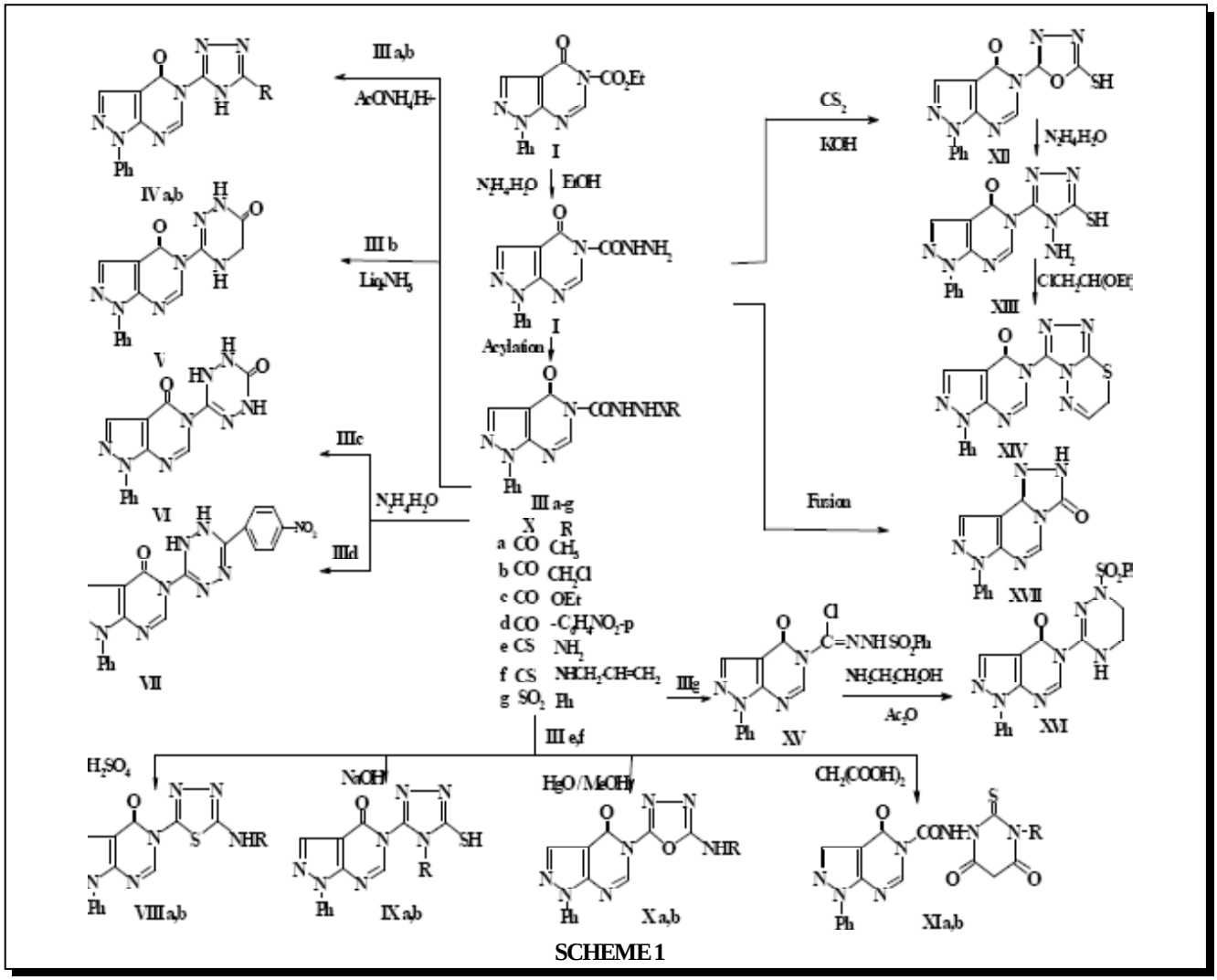


Chart 1 : Fragmentation pattern of compound II



Reaction of IIIc, and IIId with hydrazine hydrate in EtOH led to the direct formation of 1,2-dihydro-6-(4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5`-yl})1,2,4,5-tetrazin-3(4H)-one(VI) and 3-aryl-1,2-dihydro-6-{4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d]pyrimidin-5`-yl})-1,2,4,5-tetrazine(VII),respectively SCHEME 1.

Acidic cyclization of IIIe,f by treating with conc

H_2SO_4 gave 2-substituted amino-5-(4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5'-yl)-1,3,4-thiadia-zoles (VIIIa,b) while its basic cyclization by boiling with aq NaOH yielded 4-substituted-3 mercapto-5-(4',5'-dihydro-4'-oxo-1-phenylpyrazolo[3,4-d] pyrimidin-5'-yl)-s-triazoles (IXa,b). Further, oxidative cyclization using HgO in MeOH led to the isolation of 2-substituted amino-5-(4',5'-dihydro-4'-oxo-1'-phenylpyrazolo[3,4-d]pyrimidin-5'-yl)-1,3,4-oxadiazole(Xa,b).

Compounds VIII-X exhibited all the characteristic features in IR like NH at 3150 and SH at 1150cm^{-1}, absence of a peak due to the carbonyl (C=O, inside chain) and due to the conjugated C=N at 1590cm^{-1}. This suggests that the thiosemicarbazides have undergo cyclization to give the desired VIII-X.

On the other hand, compounds IIIe,f on refluxing with malonic acid in the presence of acetyl chloride afforded the corresponding 1,3-disubstituted-2- thioxo - 5H-pyrimidin- 4,6-diones (XIa.b).

The synthesis of 2-mercapto-5- (4',5'-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5`-yl)-1,3,4-oxadiazole (XII) was achieved by the reaction of II with $CS_2$ in the presence of KOH. The latter compound XII on treatment with hydrazine hydrate in abs EtOH yielded 4-N-amino-3-mercapto-5-(4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d]pyrimidin-5`-yl)-s-triazole(XIII). The presence of NH_2 group in compound XIII was established from the reaction with chloroacetaldehyde diethyl acetal in sodium ethylate to give 6H-1,3,4-thiadiazino[2,3-c][1,2,4]triazole derivative(XIV).

Chlorination of IIIg using $POCl_3$ yielded the chloro derivative XV which on boiling with ethanolamine in Ac_2O-pyridine gave 1-sulphonylbenzene-3-(4`,5`-dihydro-4`-oxo-1`-phenylpyrazolo[3,4-d] pyrimidin-5 -yl)-4H-5,6-dihydro-1,2,4-triazine(XVI). Finally, fusion of acid hydrazide II alone gave 7-phenylpyrazolo [3`,4`: 4,5]pyrimido[6,1-c]-s-triazole-3(2H)-one (XVII).

The structural assignment of compounds were based on elemental analyses, IR and ^{1}H NMR spectral data showed in TABLE 1 and 2.

Biological activity

Some of the newly synthesized heterocyclic compounds were tested for their antimicrobial activity in DMF at a concentration of 8 mg/ml by cup diffusion techniques[8]. The organisms used were *Escherichia coli*, *Proteus vulgaris*, *Serratia marcescens*, *Bacillus cereus*, *Micrococcus lutea* and *C.albicans*. Compounds, IXb, Xb, and Xlb showed very promising activity of varying degrees against all the tested strains which may be attributed due to the presence of allyl thiocarbamate moiety. Furthermore, compounds VIIIa, IXa and XIII showed moderate effect, may be due to the parent heterocyclic system. On the other hand compounds VII and Xa were least effective towards all the tested organisms.

EXPERIMENTAL

Melting points are uncorrected. UV spectra (DMF) were recorded on a Perkin-Elmer 550 S spectrophotometer, IR(KBr) on a FT-IR 1650 spectrophotometer and ^{1}H NMR (DMSO-d_6) spectra with TMS as internal standard (δppm) were recorded on a Tesla BS-467(60MHz) spectrometer (JEOL).

Preparation of N-ethyl formate derivative (I)

A mixture of 4-hydroxy-1-phenylpyrazolo[3,4-d]pyrimidine (0.01mol) and ethyl chloroformate (0.02 mol) in DMF (20ml) was refluxed on a water-bath for 3 hr. The reaction mixture was cooled and poured on crushed ice and the solid thus obtained was crystallized to give I.

Synthesis of 5-carboxyhydrazide-4,5-dihydro-1-phenylpyrazolo[3,4-d] pyrimidin-4-one (II)

A mixture of I(0.01mol) and hydrazine hydrate (0.03mol) in ethanol(30ml) was refluxed for 1 hr, cooled and poured onto ice. The solid obtained was filtered off and recrystallized to give II.

Acylation of II: preparation of IIIa-g

A mixture of II(0.01mol) and appropriate acylating agent (0.01mol) in DMF (20 ml) was refluxed for 1 hr, cooled, poured into ice cold aq. HC1. The resultant solid was filtered and crystallized to give IIIa-g.

Synthesis of 3,5-disubstituted-s-triazole derivatives (IVa,b)

A mixture of the appropriate N,N'-diacyl hydrazines (III) (0.01mol), ammonium acetate (0.02mol) and a little

TABLE 1 : Physical and analytical data of the various prepared compounds

Compound	Formula M_t	W_I (calc.)% W_I (found)%			Yield%	M.p.^{0}C	Solvent
		C	H	N			
I	$C_{14}H_{12}N_4O_3$ 284	59.15 59.20	4.22 4.20	19.72 20.00	70	125	Ethanol
II	$C_{12}H_{10}N_6O_2$ 270	53.33 53.31	3.70 3.80	31.11 31.20	72	175	Benzene
IIIa	$C_{14}H_{12}N_6O_3$ 312	53.85 53.80	3.85 3.81	26.92 26.90	66	220	MeOH
IIIb	$C_{14}H_{11}N_6O_2Cl$ 346.5	48.48 48.42	3.17 3.20	24.24 24.21	60	235	DMF/H_2O
IIIc	$C_{15}H_{14}N_6O_3$ 326	55.21 55.10	4.29 4.30	25.77 25.70	72	175	EtOH
IIId	$C_{19}H_{13}N_7O_5$ 419	54.41 54.39	3.10 3.30	23.39 23.35	65	280	EtOH
IIIe	$C_{13}H_{11}N_7SO_2$ 329	47.42 47.40	3.34 3.36	29.79 29.80	69	200	AcOH
IIIf	$C_{16}H_{15}N_7SO_2$ 369	52.03 52.20	4.06 4.00	26.56 26.62	71	230	MeOH
IIIg	$C_{18}H_{14}N_6SO_4$ 410	52.68 52.70	3.41 3.50	20.49 20.40	60	180	Acetone
IVa	$C_{14}H_{11}N_7O$ 293	57.34 57.30	3.75 3.65	33.45 33.50	68	215	EtOH
IVb	$C_{14}H_{10}N_7OCl$ 327.5	51.30 51.20	3.05 3.10	29.92 29.82	58	250	Benzene
V	$C_{14}H_{11}N_7O_2$ 309	54.37 54.22	3.56 4.20	31.71 31.69	71	220	AcOH
VI	$C_{13}H_{10}N_8O_2$ 310	50.32 50.20	3.22 3.20	36.13 36.15	66	228	DMF/H_2O
VII	$C_{19}H_{13}N_9O_3$ 415	54.94 55.00	3.13 3.20	30.36 30.42	63	195	EtOH
VIIIa	$C_{13}H_{10}N_8SO$ 326	47.85 47.80	3.07 3.10	34.35 34.40	70	175	MeOH
VIIIb	$C_{16}H_{14}N_8O$ 334	57.48 57.40	4.19 4.00	33.53 33.61	55	240	Benzene
IXa	$C_{13}H_{10}N_8SO$ 326	47.85 47.90	3.07 3.11	34.35 34.41	59	200	EtOH
IXb	$C_{16}H_{14}N_8SO$ 366	52.46 52.39	3.82 3.88	30.60 30.56	65	233	EtOH
Xa	$C_{13}H_{10}N_8O_2$ 310	50.32 50.40	3.22 3.32	36.13 36.20	56	190	Anisole
Xb	$C_{16}H_{14}N_8O_2$ 350	54.86 55.10	4.00 3.80	32.00 32.12	60	220	Ethanol
XIa	$C_{16}H_{12}N_8SO_4$ 412	46.60 46.69	2.91 3.10	27.18 27.20	75	290	Benzene
XIb	$C_{19}H_{16}N_8SO_4$ 452	50.44 50.49	3.54 3.48	24.78 24.80	66	240	MeOH
XII	$C_{13}H_8N_6SO_2$ 312	50.00 50.22	2.56 2.48	26.92 26.80	55	210	DMF/H_2O
XIII	$C_{13}H_{10}N_8SO$ 326	47.85 47.88	3.07 3.10	34.35 34.40	70	170	EtOH
XIV	$C_{15}H_{10}N_8SO$ 350	51.43 51.36	2.86 2.79	32.00 32.13	70	240	EtOH
XV	$C_{18}H_{13}N_6SOCl$ 424.5	50.88 50.77	3.06 3.15	19.79 19.82	62	200	AcOH
XVI	$C_{20}H_{17}N_7SO_3$ 435	55.17 55.20	3.91 3.80	22.53 22.59	65	230	MeOH
XVII	$C_{12}H_8N_6O$ 252	57.14 56.89	3.17 3.20	33.33 33.53	68	290	AcOH

acetic acid was heated under reflux for 3 hr, cooled and poured onto ice. The resulting solid was crystallized to give IVa,b.

Synthesis of 2,5-dihydro-6-(4',5'-dihydro-4'-oxo-1'-phenylpyrazolo[3,4-d]pyrimidi-n-5`-yl)-1,2,4-triazine-3(4H)-one (V).

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TABLE 2: Spectral data of the new compounds

Compound	Spectral data
I	IR: ν/cm^{-1}: 2980 (CH aliphatic),1710 (C=O$_{ester}$),1640 (C=O $_{pyrimidinone}$), 1610-1600 (C=N, C=C), ^{1}H NMR (DMSO-d$_6$), δ: 1.25 (t,3H, OCH$_2$CH$_3$), 4.3 (q,2H, OCH$_2$CH$_3$), 7.3-8.2 (m, 5H, Ar-H), 8.61(s, 1H, CH pyrazole), 8.72 (s, 1H, CH pyrimidinone)
II	IR: ν/cm^{-1}:3340, 3268(NH, NH$_2$), 2980(CH $_{aliphatic}$), 1675 -1640 (C=O), 1610-1585 (C=N, C=C), ^{1}H NMR (DMSO-d$_6$), δ: 3.4 (bs, 2H, NH$_2$), 7.30-8.25 (m, 5H, Ar-H), 8.61 (s, 1H, CH pyrazole), 8.72 (s, 1H, CH pyrimidinone), 10.00 (bs, 1H, N-H hydrazide)
IIIa	IR: ν/cm^{-1}: 2990-2930 (CH $_{aliphatic}$), 1760 (2C=O$_{N-CO}$), 1635 (C=O $_{pyrimidinone}$), 1610-1585 (C=N, C=C). ^{1}H NMR (DMSO-d$_6$), δ: 2.1 (s, 3H, CH$_3$), 7.18-8.26 (m, 5H, Ar-H), 8.61 (s, 1H, CH pyrazole), 8.72 (s, 1H, CH pyrimidinone), 10.80 (bs, 2H, NHC=O)
IIId	IR: ν/cm^{-1}: 2950-2930 (CH $_{aliphatic}$), 1740 (2C=O$_{N-CO}$), 1630 (C=O $_{pyrimidinone}$), 1610-1585 (C=N, C=C). ^{1}H NMR (DMSO-d$_6$), δ: 2.1 (s, 3H, CH$_3$), 7.18-8.26 (m, 9H, Ar-H), 8.61(s, 1H, CH pyrazole), 8.72(s, 1H, CH pyrimidinone), 10.80 (bs, 2H, NHC=O)
IIIe	IR: ν/cm^{-1}: 3370, 3260, 3170(NH$_2$, N-H) 2970(CH $_{aliphatic}$), 2650(S-H)), 1630(C=O pyrimidinone), 1610-1585(C=N, C=C), 1165, 1278 (NHC=S) ^{1}H NMR (DMSO-d$_6$), δ: 7.18-8.26(m, 13H, Ar-H, C-H pyrazole, NH$_2$C=S), 8.61 (s, 1H, CH pyrazole), 8.72 (s, 1H, CH pyrimidinone), 9.41 (bs, 1H, NHC=S), 10.80 (bs, 1H, NHC=O)
IVa	IR: ν/cm^{-1}: 3180 (NH) 2980 (CH aliphatic), 1630 (C=O $_{pyrimidinone}$), 1610-1590 (C=N, C=C). ^{1}H NMR (DMSO-d$_6$), δ: 2.4 (s,3H, CH$_3$),7.3-8.2(m, 5H, Ar-H), 8.6(s, 1H, CH $_{pyrazole}$), 8.7(s, 1H, CH $_{pyrimidinone}$), 9.2(s, 1H, NH)
V	IR: ν/cm^{-1}: 3220 (NH), 2980 (CH aliphatic), 1630 (C=O $_{pyrimidinone}$), 1610-1585 (C=N, C=C). ^{1}H NMR (DMSO-d$_6$), δ: 7.3-8.2 (m, 5H, Ar-H), 8.6 (s, 1H, CH $_{pyrazole}$), 8.7 (s, 1H, CH $_{pyrimidinone}$), 10.5 (s, 2H, nH)
VII	IR: ν/cm^{-1}: 3220(NH), 2980 (CH aliphatic), 1690(C=O $_{triazinone}$)1630 (C=O $_{pyrimidinone}$), 1610-1585(C? N, C? C). ^{1}H NMR (DMSO-d$_6$), δ: 7.3-8.2(m, 9H, Ar-H), 8.6(s, 1H, CH $_{pyrazole}$), 8.7(s, 1H, CH $_{pyrimidinone}$), 10.5(s, 2H, NH)
VIIIa	IR: ν/cm^{-1}: 3300 - 3150 (NH and NH$_2$), 2980 (CH aliphati), 1630 (C=O $_{pyrimidinone}$), 1610-1590(C=N, C=C), ^{1}H NMR(DMSO-d$_6$), δ:3.4(bs, 2H, NH$_2$), 7.30-8.25(m, 5H, Ar-H), 8.61(s,1H, CH pyrazole),8.72(s,1H,CH pyrimidinone),10.00(bs,1H, NH).
IXa	IR: ν/cm^{-1}:3290 (NH$_2$),2980(CH aliphatic), 1700-1630 (C=O), 1610-1590 (C=N, C=C), 1150 (C-S). ^{1}H NMR(DMSO-d$_6$), δ: 4.4(s, 2H,CH$_2$), 5.8 (s,2H,NH$_2$), 7.30-8.25(m, 5H, Ar-H), 8.61(s, 1H, CH pyrazole), 8.72(s, 1H, CH pyrimidinone), 12.1 (s,1H,NH).
XIV	IR: ν/cm^{-1}: 2980(CH $_{aliphatic}$), 1635(C=O $_{pyrimidinone}$), 1610-1585 (C=N, C=C), ^{1}H NMR (DMSO-d$_6$), δ: 3.48-3.56(dd, 1H, C5-H $_{thiadiazino}$), 4.19-4.25 (d, 2H, C6-H $_{thiadiazino}$), 7.1-8.2(m, 5H, Ar-H), 8.6(s, 1H, C3-H$_{pyrazole}$) and 8.7(s, 1H, C6-H$_{pyrimidinone}$).
XVII	IR: ν/cm^{-1}: 3220 (NH),2980(CH aliphatic), 1690(C=O $_{triazolo}$), 1610-1585 (C=N, C=C), ^{1}H NMR (DMSO-d$_6$), δ:7.3-8.2 (m, 5H, Ar-H), 8.6(s, 1H, CH$_{pyrazole}$), 8.7 (s, 1H, CH$_{pyrimidinone}$), 12.5 (s,1H,NH).

A suspension of IIIb(1g) in ethanol(50ml) with liq ammonia(10ml) and ammonium acetate(2g) was refluxed for 4hr. The excess solvent was removed and diluted with cold water and the resulting solid mass was crystallized to give V.

Synthesis of dihydro-1,2,4,5-tetrazine derivatives VI and VII

A mixture of IIIc and/or IIId (0.01mol) and hydrazine hydrate (0.02mol) in ethanol was heated under reflux for 4hr, cooled and poured onto ice. The solid obtained was crystallized to give VI and/or VII.

Acidic cyclization of IIIe,f : formation of VIIIa,b

A mixture of IIIe and/or IIIg (1g) and conc. H_2SO_4 (10ml) was stirred for 2hr at room temp. The reaction mixture was poured onto ice and the residue was washed with cold water and purified to give VIIIa,b.

Basic cyclization of IIIe,f : formation of IXa,b

A mixture of IIIe,f (0.01mol) and aq.sodium hydroxide (10%, 50ml) was refluxed for 3hr. The reaction mixture was acidified with dil HCI and the solid obtained was filtered and crystallized to give IXa,b.

Oxidative cyclization of IIIe,f formation of Xa,b

A mixture of IIIe.f (0.01mol) and mercuric oxide (1 g) in methanol (20ml) washeated under reflux for 3 hr. The reaction mixture was filtered hot and filtrate poured onto ice. The resulting solid was crystallized to give Xa,b.

1, 3-Disubstituted-2-thioxo-5-dihydropyrimidin-4,6 dione (XIa,b)

A mixture of equimolar amounts of IIIe,f , malonic acid and acetyl chloride was heated at 80-120° for 2 hr. The cold reaction mixture was treated with methanol to give XIa,b.

2-Mercapto-5-substituted-1,3,4-oxadiazole (XII)

A mixture of II (0.01mol), CS_2 (5ml), KOH (5g in 20 ml H_2O) and ethanol (50ml) was refluxed for 4 hr, cooled, poured into ice cold aq HCl. The solid obtained was filtered and recrystallized to give XII.

Synthesis of N-amino-3-mercapto-5-substituted s-triazole (XIII)

A mixture of XII (0.01mol) and hydrazine hydrate (0.01mol) in ethanol (50ml) was heated under reflux for 3hr then cooled and diluted with cold water. The solid obtained was recrystallized to give XIII.

6-H-1,3,4-thiadiazino-[2,3-c] [1,2,4]triazole derivative (XIV)

A mixture of equimolar amounts of XIII, chloro acetaldehyde diethylacetal in sodium ethylate was refluxed for 2hr, cooled and poured into ice cold aq HCl. The solid thus obtained was crystallized to give XIV.

Chlorination oi IIIg: formation of XV

A mixture of IIIg(0.01mol) and $POCl_3$(0.02mol) was refluxed for 1 hr. cooled and poured onto ice with stirring. The solid obtained was filtered and crystallized to give XV

Reaction of XV with ethanolamine : formation of XVI

A mixture of XV (0.01mol) and ethanolamine (0.01mol) in acetic anhydride-dyridine (1:1,20ml) was heated under reflux for 4 hr, cooled and poured into ice cold aq HCI with stirring. The resultant solid was crystallized to give XVI.

Characterisation data of newly synthesised compounds are recorded in TABLE 1.

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