Synthesis and Antimicrobial Activity of Pyrazolone-Thioxopyrimidone Clubbed Heterocyclic Compounds

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ABSTRACT
Ethyl 3-oxo-2-(2-(4-(N-thiazol-2-ylsulfamoyl) phenyl) hydrazono)butanoate (1) on condensation with 4-(4-alkyl phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5- carbohydrazide (2a-e) to afford 2-(1-(4-(4-alkyl phenyl)-6-methyl-2-thioxo-1,2,3,4- tetrahydro pyrimidine-5-carbonyl) -3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)-N-(thiazol-2- yl) hydrazine sulfonamide (3a-e). On reaction (3a-e) with 1,2-dibromoethane yield 2-(1-(7-(4-alkyl phenyl)-5-methyl-3,7,8,8a-tetrahydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonyl)-3- methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)-N-(thiazol-2-yl)hydrazinesulfonamide(4a-e).The structures of all the compounds series (3a-e) and (4a-e) were characterized analytically. The compounds were also monitored for anti microbial activity.

***Key words**:* Pyrazole, aryl hydrazo pyrazole, pyrimidone, antimicrobial activity and spectral studies.

I INTRODUCTION

Literature reviewed on pyrimidine derivatives here a wide range of pharmaceutical activities like antipyratics, antimicrobial, anticonvulsant, anti-TB, anti neoplastic and antiviral activities. [1-8] Pyrimidine rings are present in natural prickets (as drugs) to found in nature and present in various natural drugs to synthetic drugs. Sulphur containing heterocyclic compounds are acknowledged as good antibacterial drugs.[10-12] hence in present paper we cubbing of sulfa drug, aryl hydrazo pyrazole and pyrimidone moieties into one molecule may have good medicinal property. The present communication deals with the synthetic approach shown in Fig 1.

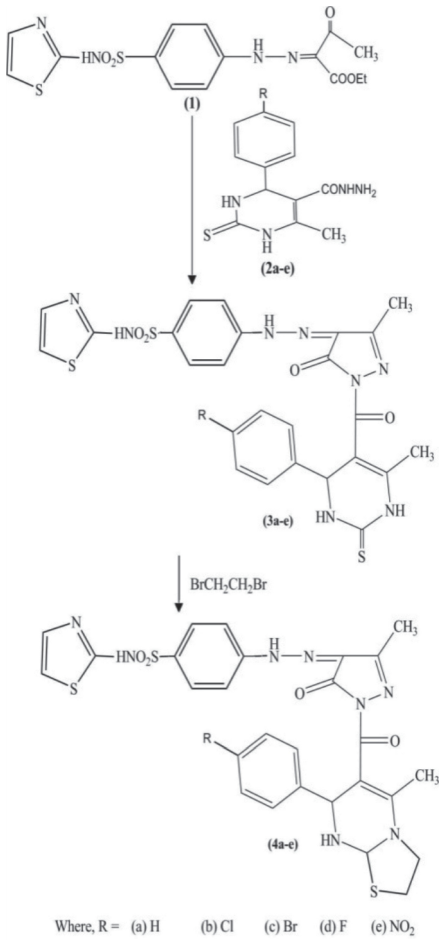

Fig. 1 Synthetic Approach

II EXPERIMENTAL

Ethyl 3-oxo-2-(2-(4-(N-thiazol-2-ylsulfamoyl)phenyl)hydrazono)butanoate(1) and 4-(4-alkyl phenyl)-6-methyl-2- thioxo-1,2,3,4-tetrahydro pyrimidine-5- carbohydrazide (2a-e) were synthesis by reported method.[11,13,14] All other reagents were used of laboratory grade.

The IR spectra of all compounds were taken in fused KBr pellets by using FTIR Spectrophotometer. H1 NMR spectral signals were recorded on Bruker (400MHz) spectrophotometer. LC-MS of few derivatives were scanned on branded instruments. All the compounds were checked for their purity by TLC. The analytical data of all derivatives are furnished in Tables 1 and 2.

The antibacterial activity of both the series of compounds (3a-e) and (4a-e) were studied against gram +Ve and
–Ve bacteria shown in Table-3. The activity was measured at a conc, 50µg/ml by agar- cup plate method.[15] The percentage inhibition of growth of bacteria by the compounds is shown in Table-3.

The antifungal activity of both the series of compounds (3a-e) and (4a-e) were measured at 1000ppm concentration in vitro Plant pathogen shown in Table-4 have been selected for study.[16]

Synthesis of 2-(1-(4-(4-alkyl phenyl)-6- methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carbonyl)-3-methyl-5-oxo- 1H-pyrazol-4(5H)-ylidene)-N-(thiazol-2- yl)hydrazine sulfonamide (3a-e)

Ethyl 3-oxo-2-(2-(4-(N-thiazol-2-ylsulfamoyl)phenyl)hydrazono)butanoate (1)and 4-(4-alkylphenyl)-6-methyl-2- thioxo-1,2,3,4-tetrahydropyrimidine-5- carbohydrazide (2a-e) were mixed at stoichiometric ratio with CH_3COOH (glacial) and then refluxed for 9-10 hrs. The resultant was filtered, washes with water and then dry ether and crystallized from ethanol. Finally, the characteristics of these novel heterocyclic derivatives are presented Table -1.

Synthesis of 2-(1-(7-(4-alkylphenyl)-5- methyl-3,7,88,8a-tetrahydro-2H- thiazolo[3,2-a] pyrimidine-6-carbonyl)- 3-methyl-5-oxo-1H-pyrazol-4(5H)- ylidene)-N-(thiazol-2-yl)hydrazine sulfonamide (4a-e)

In a round bottom flask each of (3a-e) (10mmol) and 1,2-dibromoethane (20mmol) in 1,4-dioxane (20ml) was refluxed for 5 hrs. The resulting solution kept at room temperature. The product is in form of salt filtered, it was then treated with saturated sodium bicarbonate solution than by rectified spirit. The product was checked by TLC frequently. The details given in Table-2.

III RESULTS AND DISCUSSIONS

The ethyl 3-oxo-2-(2-(4-(N-thiazol- 2-yl sulfamoyl) phenyl) hydrazono) butanoate(1) react with 4-(4-alkyl phenyl)

-6-methyl-2- thioxo-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (2a-e) to give 2-(1-(4-(4- alkyl phenyl)-6-methyl-2- thioxo-1,2,3,4- tetrahydro pyrimidine-5- carbonyl)-3- methyl-5-oxo-1H-pyrazol- 4(5H)-ylidene)- N-(thiazol-2-yl) hydrazinesulfonamide (3a- e), which gives 2-(1-(7-(4-alkylphenyl)-5- methyl- 3,7,8,8a-tetrahydro-2H-thiazolo[3,2- a]pyrimidine-6-carbonyl)-3- methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)- N- (thiazol-2-yl)hydrazine sulfonamide (4a-e) on reaction with 1,2-tetracyclin bromoethane.

The Molecular frameworks of **(3a-e)** were assigned by C,H,N values and FTIR spectral features giving medium bands at 3030cm^{-1}(aromatic C-H band), 3330 and 3155 cm^{-1}(NH), 1620-1630cm^{-1}(C=N), 1680 cm^{-1}(CO), 2950, 1370cm^{-1}(-CH_3,CH_2),680(C-S), 1160(SO_2),1695- 1750 cm^{-1} (Carbonyl), 1070(thioketone), 1555,1375(-Nitro group), H1 NMR data in δppm : 9.95-11.9(S,4H,NH group), 2.52- 2.60(S, 6H, of 2CH_3), 5.42(S,1H,CH), 6.80-7.40(CS) (s,7H,ArH). The elemental content of all these heterocyclic derivatives were illustrated in Table-1.

The FTIR of **(4a-e)** were 3030- 3080 cm^{-1}(Alkane of aromatic), 3330cm^{-1} (aromatic CH band), 1620-1630cm^{-1}(C=N), 1680cm^{-1}(CO),2950,1370cm^{-1}(-CH_3,CH_2), 680(C-S),1160(SO_2),1695-1750cm^{-1} (Carbonyl),1080(-Cl),1555,1375(-NO_2), 1070(C-Br),1150 (C-F). H1 NMR signals at δppm:10.1-11.9(s,3H,NH), 2.52-2.60(s,6H,Methyl group),5.42(s,1Hof =CH),6.80-7.40(s,7H,ArH), 5.20 (s,1H of =CH), 2.46-3.12(t,4H of 2=CH_2). The elemental (C,H,N) analysis of all these heterocyclic compounds are illustrated in Table -2.

All the characteristic shown in table 1 and 2 suggest that the data are agree with the structural features shown in Scheme-1. The LC-MS of few samples indicate the peak of M^+ ion which assigned +VE molecular weight. All these features assigned the structures of 3a-e and 4a-e.

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds **3e** and **4e** found more toxic for gram-+Ve and gram- -Ve bacteria.

Table-1
Characterization of Compounds (3a-e)

No.	M.F.	Yield % age	M.P.* °C	Elemental Analysis % age							
				C		H		N		S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{19}H_{18}N_8O_4S_3$ (518)	62	213-215	44.00	43.9	3.50	3.4	21.61	21.68	18.55	18.5
3b	$C_{19}H_{17}N_8O_4S_3Cl$ (553)	65	219-220	41.26	41.2	3.10	3.0	20.26	20.2	17.39	17.3
3c	$C_{19}H_{17}N_8O_4S_3Br$ (597)	59	232-234	38.19	38.1	2.87	2.8	18.75	18.7	16.10	16.0
3d	$C_{19}H_{17}N_8O_4S_3F$ (536)	65	227-228	42.53	42.5	3.19	3.1	20.88	20.8	17.93	17.9
3e	$C_{19}H_{17}N_9O_6S_3$ (563)	63	235-236	40.49	40.4	3.04	3.0	22.37	22.3	17.07	17.0

***** *Uncorrected* LC-MS peak value of 3a:568
3d: 553

Table-2
Characteristic of Compounds (4a-e)

No.	M.F.	Yield % age	M.P.* °C	Elemental Analysis % age							
				C		H		N		S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	$C_{21}H_{22}N_8O_4S_3$ (546)	69	233-235	46.17	46.1	4.06	4.0	20.50	20.7	17.60	17.5
4b	$C_{21}H_{21}N_8O_4S_3Cl$ (580.35)	67	246-248	43.41	43.4	3.64	3.6	19.28	19.2	16.55	16.5
4c	$C_{21}H_{21}N_8O_4S_3Br$ (624)	65	243-245	40.32	40.3	3.38	3.3	17.91	17.9	15.38	15.3
4d	$C_{21}H_{21}N_8O_4S_3F$ (564)	62	240-242	44.67	44.6	3.75	3.7	19.85	19.8	17.04	17.0
4e	$C_{21}H_{21}N_9O_6S_3$ (531)	66	238-239	42.63	42.6	3.58	3.5	21.31	21.3	16.26	16.2

***** *Uncorrected* LC-MS data for 4b:594, 4e: 545

Table-3
Antibacterial Activity of Compounds (3a-e) and (4a-e)

No.	Zone of inhibition (mm)				
	Gram +ve		*Gram –ve*		
	Bacillus Subtilis	***Staphylococcus aureus***	***Kllebsiella promioe***	***Salmonella Typhl***	***E.coil***
3a	55	42	60	52	56
3b	66	48	68	60	64
3c	59	44	65	49	57
3d	64	45	66	58	61
3e	70	51	78	69	65
4a	59	43	62	55	58
4b	68	50	71	62	67
4c	63	50	69	52	59
4d	68	48	69	63	63
4e	73	52	81	73	68
Tetracycline	79	55	87	76	72

Table-4
Antifungal Properties of present heterocyclic derivatives

% age inhibition of the growth of fungus (at 1000 ppm)				
Comp. No.	***Botrydepladia Thiobromine***	***Nigrosspora Sp.***	***Penicillium Expansum***	***Rhizopus Nigricuns***
3a	64	67	64	63
3b	75	72	70	71
3c	59	63	64	66
3d	70	69	68	67
3e	77	79	76	78
4a	67	69	66	67
4b	78	74	72	74
4c	61	66	67	69
4d	72	71	70	70
4e	81	83	79	80

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