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Synthesis and Antimicrobial Activity of Arylazopyrazole Pyrimidone Clubbed Heterocyclic Compounds

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Abstract: Ethyl-3-oxo-2-(2-(4-sulfamoylphenyl)hydrazono) butanoate (2) on condensation with 6-methyl-2-oxo-4-subsituted phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (3a-e) to gave 4-(2-(3-methyl-1-(6-methyl-2-oxo-4-subsituted phenyl-1,2,3,4-tetrahydro pyrimidine -5-carbonyl)-5-oxo-1H-pyrazol-4(5H)-ylidene) hydrazine) benzene sulfonamide (4a-e), which on reaction with benzaldehyde gives 4-(2-(1-(4-([1,1'-biphenyl]-4-yl)-3-(hydroxyl (phenyl) aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)hydrazinyl) benzenesulfonamide(5a-e).The structures of all these compounds (4a-e) were recognized by analytical and spectral studies. The synthesized compounds were evaluated for their antimicrobial activity against various bacteria and fungi.

Keywords: Sulphadrug, Pyrazole and Antimicrobial Activity

I. INTRODUCTION

Sulpha drugs are bacteriostatic and are also referred to as antibacterial. The sulphonamides are synthetic antimicrobial agents with a wide spectrum encompassing most Gram-positive and many Gram-negative organisms.[1-3]
The heterocyclic compound, pyrimidinones shows various antimicrobial, hypnotic, antiviral, sedative, antineoplastic, anticonvulsant, analgesic and anti-inflammatory. [4-9]The nitrogen containing pyrazole and its derivatives is show application in medicinal chemistry like antibactiral,antifungal,analgesic, anti-inflammatory, antipyretic, antiparasitic and antimalarial.[10-14] The arylazopyrazoles are generally prepared by combination of aryl-azo-ethyl actoacetate derivatives and hydrazine derivatives, which shows biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties.[15-17] These heterocyclic systems find wide use in medicine, agriculture and industry. Merging of both of arylazopyrazole and pyrimidone moieties into one molecule may enhance the drug activity to some extent, or may class of drug. Thus the objective of the present work is to explore new derivatives of pyrimidone containing arylazopyrazole of sulfa drug. The present communication comprises such concepts. So the whole synthetic approach is shown in scheme-1.

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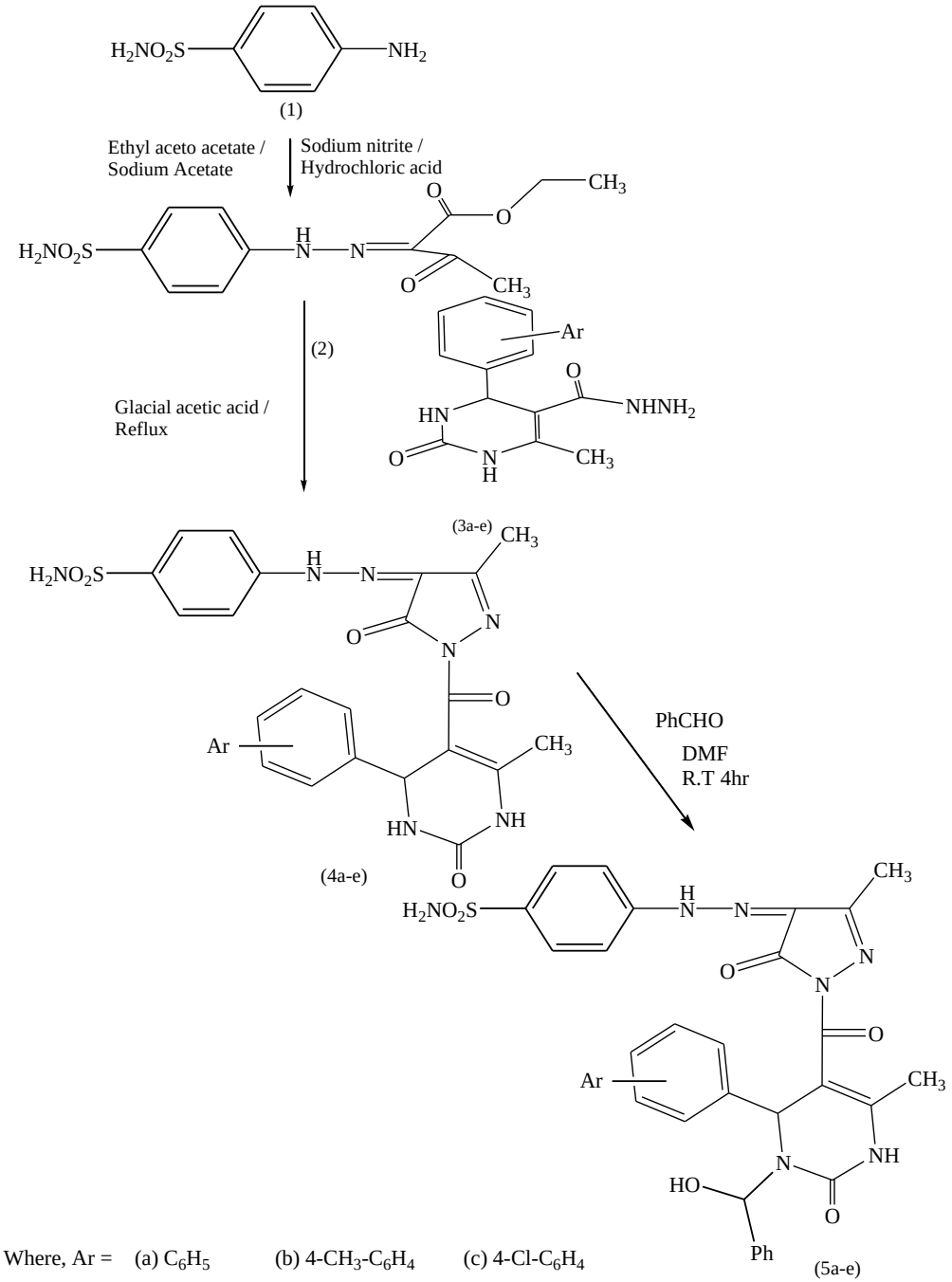

Where, Ar = (a) C_6H_5 (b) 4-CH_3-C_6H_4 (c) 4-Cl-C_6H_4

(d) 4-NO_2-C_6H_4 (e) 4-OH-C_6H_4

SCHEME-I

II. EXPERIMENTAL

The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer. ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Purity of compound was checked by TLC on silica gel plates and the spots were visualized by UV lamp. 6-methyl-2-oxo-4-subsitutedphenyl-1,2,3,4-tetrahydro pyrimidine-5-carbo hydrazide (3a-e) were synthesis by reported method.[18] The yields, melting points and other characterization data of these compounds are given in Table -1.

Synthesis of 4-(2-(3-methyl-1-(6-methyl-2-oxo-4-subsituted phenyl-1,2,3,4-tetrahydro pyrimidine -5-carbonyl)-5-oxo-1H-pyrazol-4(5H)-ylidene) hydrazinyl) benzene sulfonamide (4a-e)

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A mixture of ethyl-3-oxo-2-(2-(4-sulfamoylphenyl)hydrazono)butanoate (2) and 6-methyl-2-oxo-4-subsitutedphenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (3a-e)[19,20]were mixed with glacial acetic acid and then refluxed for appropriate time. Then cooled and resulting solid was filtered off dried and crystallized from alcohol. The yields, melting points and other characterization data of these compounds are given in Table -2.

Synthesis of 4-(2-(1-(4-([1,1'-biphenyl]-4-yl)-3-(hydroxy(phenyl)aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carbonyl)-3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)hydrazinyl)benzenesulfonamide (5a-e)

In a round bottom flask a solution of 4-(2-(3-methyl-1-(6-methyl-2-oxo-4-subsitutedphenyl-1,2,3,4-tetrahydro pyrimidine -5-carbonyl)-5-oxo-1H-pyrazol-4(5H)-ylidene) hydrazinyl) benzene sulfonamide (4a-e) (0.10mmol) and benzaldehyde (0.020mmol) in DMF(50ml) was taken and stirred by placing on magnetic stirrer at room temperature for 4 hours. The product was checked by TLC. The mixture was poured on crashed ice. The precipitates falled out. Filtered, Washed and air-dried. Repurified by ethanol. The yield was 65%. The details are given in Table-3.

Table-1 Physical and Analytical Data of the Compounds Synthesized (3a-e)

Comp. No.	Molecular Formula (Mol.wt.)	LC-MS Data	M.P.* ˚C	Yield %	Elemental Analysis					
					C%		H%		N%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{12}H_{14}N_4O_2$ (246)	248	135-137	78	58.53	58.5	5.73	5.7	22.75	22.7
3b	$C_{13}H_{16}N_4O_2$ (260)	263	142-144	82	59.99	59.9	6.20	6.1	21.52	21.5
3c	$C_{12}H_{13}N_4O_2Cl$ (280)	295	130-132	76	51.34	51.3	4.67	4.6	19.96	19.9
3d	$C_{12}H_{13}N_5O_4$ (291)	306	124-126	80	49.48	49.48	4.50	4.4	24.04	24.0
3e	$C_{13}H_{16}N_4O_3$ (276)	280	120-121	69	56.51	56.4	5.84	5.8	20.28	20.2

** Uncorrected*

Table-2 Physical and Analytical Data of the Compounds Synthesized (4a-e)

Comp. No.	Molecular Formula	LC-MS Data	M.P.* ˚C	Yield %	Elemental Analysis							
					C%		H%		N%		S%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	$C_{22}H_{21}N_7O_5S$ (495)	502	192-194	62	53.33	53.3	4.27	4.2	19.79	19.7	6.47	6.4
4b	$C_{23}H_{23}N_7O_5S$ (509)	512	197-199	65	54.22	54.2	4.55	4.5	19.24	19.2	6.29	6.2
4c	$C_{22}H_{20}N_7O_5SCl$ (529)	536	198-201	60	49.86	49.8	3.80	3.7	18.50	18.4	6.05	6.0
4d	$C_{22}H_{20}N_8O_7S$ (540)	558	191-193	63	48.89	48.8	3.73	3.7	20.73	20.7	5.93	5.9
4e	$C_{23}H_{23}N_7O_6S$ (525)	528	195-198	67	52.56	52.5	4.41	4.4	18.66	18.6	6.10	6.0

** Uncorrected*

Table-3 Physical and Analytical Data of the Compounds Synthesized (5a-e) as per reported method [21]

Comp. No.	Molecular Formula	LC-MS Data	M.P.* ˚C	Yield %	Elemental Analysis							
					C%		H%		N%		S%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	$C_{29}H_{27}N_7O_6S$ (601)	614	196-198	60	57.90	57.8	4.49	4.4	16.30	16.2	5.32	5.3
5b	$C_{30}H_{29}N_7O_6S$ (615)	627	202-203	59	58.53	58.5	4.71	4.7	15.93	15.9	5.20	5.1
5c	$C_{29}H_{26}N_7O_6SCl$ (635)	650	204-205	57	54.80	54.8	4.09	4.0	15.43	15.4	5.03	5.0
5d	$C_{29}H_{26}N_8O_8S$ (646)	666	214-215	61	53.86	53.8	4.02	4.0	17.33	17.3	4.95	4.9
5e	$C_{30}H_{29}N_7O_7S$ (631)	649	208-209	64	57.05	57.0	4.59	4.5	15.53	15.5	5.07	5.0

** Uncorrected*

III. BIOLOGICAL SCREENING

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Antibacterial activities: Antibacterial activities of prepared compounds were studied against gram-positive Bacteria and gram-negative Bacteria at a concentration of 50µg/ml by agar cup plate method.[22] Methanol system was used as control in this method. Under similar conditions, using tetracycline as a standard for comparison The percentage area of inhibition of measured. Compounds **5e** and **4e** were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline. (Table -4)

Table-4 Antibacterial Activity of Compounds (4a-e) and (5a-e)

Comp. No.	Zone of Inhibition(mm)				
	Gram +ve		*Gram -ve*		
	Bacillus Subtilis	***Staphylococcus aureus***	***Kllebsiella promioe***	***Salmonella Typhl***	***E.coil***
4a	58	43	58	46	58
4b	54	48	62	58	60
4c	57	47	73	45	59
4d	69	44	78	64	62
4e	70	50	81	72	66
5a	60	44	60	47	59
5b	55	49	63	59	61
5c	59	49	74	46	62
5d	70	47	80	66	63
5e	72	51	82	74	69
Tetracycline	79	55	87	76	72

Antifungal activity: The fungicidal activity of prepared compounds **(5a-e)** and **(4a-e)** was studied at 1000 ppm concentration in vitro plant pathogenic organisms listed in Table-4. The antifungal activities of all the samples were measured on each of these plant pathogenic strains on potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 gms, dextrose 20gms, agar 20 gms and water 1 litre five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120° C for 15 min. at 15 atm pressure. These medium were poured into sterile Petiri plate and the organisms were inoculated after cooling the Petri plate. The percentage inhabitation for fungi was calculated after 5 days using the formula given below.

Percentage of inhibition = 100(X-Y) / X

Where, X: Area of colony in control plate
Y: Area of colony in test plate
The fungicidal activity all compounds **(5a-e)** and **(4a-e)** are shown in Table-5.

Table-5 Antifungal Activity of Compounds (4a-e) and (5a-e)

Zone of Inhibition at 1000 ppm (%)				
Comp. No.	***Botrydepladia Thiobromine***	***Nigrosspora Sp.***	***Penicillium Expansum***	***Rhizopus Nigricuns***
4a	62	73	74	54
4b	73	67	63	71
4c	56	65	55	72
4d	67	68	68	67
4e	74	80	74	76
5a	63	75	76	55
5b	75	69	66	73
5c	58	66	57	74
5d	69	69	69	69
5e	75	82	76	78

IV. RESULTS AND DISCUSSIONS

The ethyl-3-oxo-2-(2-(4-sulfamoylphenyl)hydrazono)butanoate (2) react with 6-methyl-2-oxo-4-subsitutedphenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (3a-e) to gane 4-(2-(3-methyl-1-(6-methyl-2-oxo-4-subsitutedphenyl-1,2,3,4-tetrahydro pyrimidine -5-carbonyl)-5-oxo-1H-pyrazol-4(5H)-ylidene) hydrazinyl) benzene sulfonamide (4a-e), which gives 4-(2-(1-(4-([1,1'-biphenyl]-4-yl)-3-(hydroxy(phenyl)aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonyl)-3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene) hydrazinyl) benzenesulfonamide (5a-e) on reaction with benzaldehyde.

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The structures of **(3a-e)** were confirmed by elemental analysis and IR spectra showing an absorption bands at 3500(N-H),3030-3080 cm^{-1}(C-H of Ar), 1680 cm^{-1} (CONH), 2950, 1370 cm^{-1} (-CH_3, CH_2), 1080(-Cl),1555, 1375(-NO_2),1695-1750 cm^{-1}(C=O).^{1}H NMR (400MHz , DMSO - d_6 ,δ / *ppm*) : 11.8-11.9(s,3H,NH),2.52(t,3H,CH_3), 5.42(s,1H,CH) **(3a)**: 7.23-7.37 (s,5H, ArH); **(3b)**: 1.26 (s,3H,CH_3) , 7.20-7.29 (s,4H,ArH) ; **(3c)**: 7.19-7.22(s,4H,ArH);**(3d)**:7.18-7.24(s,4H,ArH); **(3e)**: 4.21(s,3H,CH_3), 7.22-7.26(s,4H,ArH).The C, H, N analysis data of all compounds are presented in Table-1.

The IR spectra of **(4a-e)** are 1620-1630 cm^{-1}(C=N), 3030-3080 cm^{-1} (C-H of Ar.), 2960, 1370 cm^{-1} (-CH_3), 1710-1760(C=O),1380, 1160(SO_2), 1080(-Cl),1555, 1375(-NO_2), 3330 and 3155 cm^{-1}(NH) and 1585, 1548, and 1530 cm^{-1} (C=C).^{1}H NMR (400MHz , DMSO - d_6 ,δ / *ppm*): 11.8-11.9,8.4(s,3H,NH), 7.58 (s,2H,NH_2), 2.52-240(s,6H,CH_3), 5.42(s,1H, CH), 7.01-7.20(m,4H,Ar-H), **(4a)**: 7.23-7.37 (s,5H, ArH); **(4b)**: 1.26 (s,3H,CH_3) , 7.20-7.29 (s,4H,ArH) ; **(4c)**: 7.19-7.22(s,4H,ArH); **(4d)**: 7.18-7.24(s,4H,ArH); **(4e)**: 4.21(s, 3H, CH_3),7.22-7.26(s,4H,ArH).The C, H, N analysis data of all compounds are presented in Table -2.

The IR spectra of **(5a-e)** are 1620-1630 cm^{-1}(C=N),3420 cm^{-1}(OH), 3030-3080 cm^{-1} (C-H of Ar.), 2960, 1370 cm^{-1} (-CH_3), 1710-1760(C=O),1380, 1160(SO_2), 1080(-Cl),1555, 1375(-NO_2), 3330 and 3155 cm^{-1}(NH) and 1585, 1548, and 1530 cm^{-1} (C=C).^{1}H NMR (400MHz , DMSO - d_6 ,δ / *ppm*): 11.8-11.9,8.4(s,2H,NH), 7.58 (s,2H,NH_2), 2.52-240 (s,6H, CH_3), 5.42(s,1H,CH), 7.01-7.20(m,9H,Ar-H),6.67(s,1H,CH),3.72(s,1H,OH), **(5a)**: 7.23-7.37 (s,5H, ArH); **(5b)**: 1.26 (s,3H,CH_3) , 7.20-7.29 (s,4H,ArH) ; **(5c)**: 7.19-7.22(s,4H,ArH); **(5d)**: 7.18-7.24(s,4H,ArH); **(5e)**: 4.21(s, 3H, CH_3),7.22-7.26(s,4H,ArH).The C, H, N analysis data of all compounds are presented in Table -3.

The assessment of data predicts that the elemental contents are consistence with the predicted structure shown in Scheme-1.The IR data also direct for assignment of the predicted structure. The LC-MS of compounds shows the peak of M^+ ion which is consistent of molecular weight of respect sample. All these facts confirm the structures **5a-e & 4a-e**.

CONCLUSION

The examination of antibacterial activity data reveals that the compounds **4e** and **5e** found more active against the gram-positive and gram-negative bacteria.

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