Report of Work Done for Minor Research Project

UGC approval Letter No.: F.No. 47-152/12(WRO)

Title of the Research Project:
"Synthesis of novel Pyrimidine derivatives and Their Biological Activities"

Principal Investigator: H J SHAH

Name of College: K K Shah Jarodwala Maninagar Science, Ahmedabad

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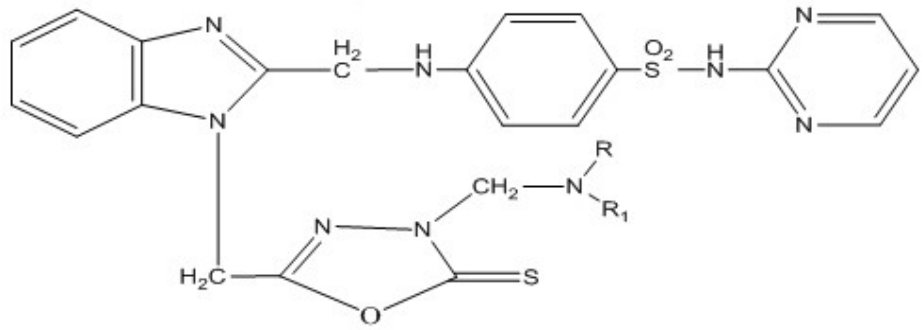
INTRODUCTION:

Pyrimidine is a six member heterocyclic compounds with two nitrogen atoms at 1,3 position. Oxadiazole are five member heterocyclic compounds with two nitrogen atoms and one oxygen atom. Depending on the position of hetero atoms they are named as 1,2,3;1,2,4;1,2,5 and 1,3,4-oxadiazole.Substituted 1,3,4-oxadiazole are the heterocyclic compounds that have been found to exhibit diverse biological activities. The heterocyclic compounds, especially nitrogen-containing heterocycles with a sulfur atom are an important class of compounds in medicinal chemistry.[1-4] Hydrazinolysis of esters is the conventional method for preparing acyl hydrazides [5-7]. In current era, the research on hydrazides and its derivatives are carried out due to their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [8-10]. Other heterocyclic compounds says, oxadiazoles and their condensed products play a vital role in medicinal chemistry and exhibit diverse biological activities such as antibacterial, antifungal, anti-inflammatory, analgesic and anticancer activity[11-15]. Hence, it was thought of interest to combine Sulfapyrimidine containing benzimidazole with oxadiazole moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. the current study

covers the study of 4-((1-((4-((dialkylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (4a-e).



4-((1-((4-((dialkylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)methylamino)-*N*-(pyrimidin-2-yl)benzenesulfonamide **(4a-e)**

Where,

	4a	**4b**	**4c**	**4d**	**4e**
R	CH_3	CH_3	Et	Et	Ph
R1	CH_3	Et	Et	Ph	Ph

MATERIALS AND METHODS

Materials:

Sulfapyrimidine prepared by reported method. [16] 4-((1H-benzo[d]imidazol-2-yl)methyl amino)-N-(pyrimidin-2-yl)benzene sulfonamide (1) was prepared by method reported [17].

Novel heterocyclic compound namely, 4-((1-((4-((dialkylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide(4a-e) have been prepared by mannich reaction, a N-(pyrimidin-2-yl)-4-((1-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino) benzenesulfonamide(3) react with formaldehyde and

different secondary amines. The compound (3) prepared from 4-((1-(2-hydrazinyl-2-oxoethyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzenesulfonamide (2) with CS_2/KOH**.** 4-((1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzene sulfonamide(1) react with chloro acetic acid and hydrazine hydrate gives compound (2).All the structures of novel synthesized compounds were established on basis of analytical and spectral data. The newly synthesized compounds were studied for their antibacterial and antifungal activities.

Table:-1 Analytical Data and Elemental Analysis of Compounds (4a-e)

Compd.	Molecular formula	Yield %	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{24}H_{25}N_9O_3S_2$	68	195	52.24	52.25	4.56	4.57	22.83	22.85	11.61	11.63
4b	$C_{25}H_{27}N_9O_3S_2$	73	189	53.06	53.08	4.79	4.81	22.27	22.29	11.32	11.34
4c	$C_{26}H_{29}N_9O_3S_2$	72	192	53.85	53.87	5.02	5.04	21.72	21.75	11.05	11.06
4d	$C_{30}H_{29}N_9O_3S_2$	68	194	57.38	57.40	4.64	4.66	20.06	20.08	10.20	10.22
4e	$C_{34}H_{29}N_9O_3S_2$	67	187	60.41	60.43	4.31	4.33	18.63	18.65	9.47	9.49

***** Uncorrected

The structures assigned to 4-((1-((4-((dialkylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)methylamino)-N-(pyrimidin-2-yl)benzene- sulfonamide (4a-e) were supported by the elemental analysis , IR and NMR spectra showing an absorption bands at 1620-1648(C=N),3020-3080cm^{-1}(C-H of Ar.), 2950,2878,1370cm^{-1}(-,CH_2),1185(C=S), 765 (C-O-C ring) 1175,1390(SO_2).^{1}HNMR: 7.21–7.68(m, 8H, Ar-H), 6.96-8.32(m,3H,PyrimidoneAr-H),4.86-4.38,4.78(s,4H,CH_2),5.64-5.78(s,2H,NH), 4a;2.17(s, 6H, CH_3), 4b;2.26(s,3H,CH_3), 1.08 (t,3H,CH_3), 2.67(q,2H,CH_2),4c;1.08(t,6H,CH_3), 2.67(q, 4H, CH_2),4d;1.08 (t,3H,CH_3),2.67 (q,2H,CH_2), 6.82–7.27(m,5H,Ar-H),4e;6.82–7.27(m, 10H, Ar-H).The C, H, N, S analysis data of all compounds are presented in Table-1.

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative bacteria (*klebsiella promioe and E.coli*) at a concentration of 50µg/ml by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in cm. The antibacterial activities of all the compounds are shown in Table-2.

Table:-2 Antibacterial Activity of Compounds (4a-e)

Compounds	Gram +Ve		Gram -Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
4a	55	49	68	62
4b	54	51	67	61
4c	57	50	59	66
4d	65	59	70	72
4e	66	58	72	73
Tetracycline	68	60	77	80

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro.Plant pathogenic organisms used were *Rhizopus nigricum, Nigrospora Sp. and Aspergillus niger*. The antifungal activities of all the compounds (4a-e) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five 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 displayed by various compounds (4a-e) is shown in Table-3.

Table:-3 Antifungal Activity of Compounds (4a-e)

Zone of Inhibition at 1000 ppm (%)			
Compounds	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Aspergillus Niger***
4a	61	66	65
4b	59	65	63
4c	65	64	62
4d	69	72	66
4e	72	70	69

RESULTS AND DISCUSSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR and NMR data also direct for assignment of the predicted structure.

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative bacteria (*klebsiella promioe and E.coli*). All compounds were found toxic for Bacteria. Compounds 4d and 4e were found more toxic , Other compounds found to be less active than tetracycline are shown in Table-2.

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Rhizopus nigricum, Nigrospora Sp. and Aspergillus niger*. The percentage inhibition for fungi was calculated after five days using the formula given. The fungicidal activity displayed by various compounds (4a-e) is shown in Table-3. Compounds 4d and 4e were found more active, other compounds found to be less or moderate active.

CONCLUSION:

The novel heterocyclic compound i.e. Oxadiazole-benzimidazole with pyrimidine fused derivatives (4a-e) were successfully synthesized. All the synthesize compounds structure were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities. Among all the synthesize compounds 4d and 4e showed more active as antibacterial and antifungal agent.

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