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Synthesis, Characterization and Biological Study of Novel Pyrrole Derivatives

Mishra RR[1*], Vyas KB[2] and Nimavat KS[3]

[1]*M/S Shree Tirupati Industries, Palanpur (Gujarat) India.*

[2]*Sheth L. H. Science College, Mansa, Gujarat, India.*

[3]*Government Science College, Gandhinagar, Gujarat, India.*

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ABSTRACT

A facile condensation of aromatic aldehydes with 2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1) was give the corresponding N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e) in good yield. Cyclo condensation of compounds (2a-e) with maleic anhydride yields 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

KEYWORDS

2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide, pyrrole, antibacterial and antifungal activities.

INTRODUCTION

The heterocyclic systems find wide use in medicine, agriculture and industry. One of the other compounds says, oxadiazoles and their condensed products play a vital role in medicinal chemistry [1-3]. Pyrrole and its arylidene compounds give good pharmacological properties [4-10]. Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [11-20]. Hence, it was thought of interest to merge both of pyrrole and oxadiazole moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of oxadiazole containing pyrrole moiety.

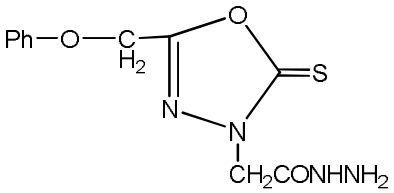
***Address for Correspondence:**
Rakesh R. Mishra
A-45, Narmada Nagari Section-3,
Opposite Gorwa ITI College,
Gorwa Sahyog, Vadodara- 390016, Gujarat.
E-Mail Id: rakeshmishra17@gmail.com

Hence the current communication covers the study of 1-(4-(1H-naphtho[1,8-de][1,2,3]triazin-1-ylsulfonyl)phenyl)-2-aryl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid. The synthetic approach is shown in scheme-1.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

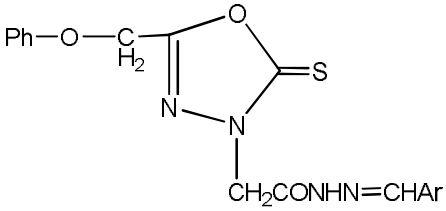
Preparation of N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (2a-e):– An equimolecular mixture of 2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (1) (0.01mole) and the aromatic aldehydes (a-e) in ethanol (15ml) was refluxed on a water bath for 1.5-3 hrs. The solid separated was collected by filtration, dried and



2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(1)

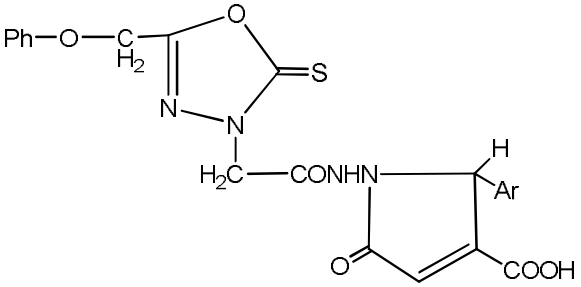
Ar-CHO/Ethanol



N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetohydrazide

(2a-e)

maleic anhydride



2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2*H*)-yl)acetamido)-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid

(3a-e)

Where Ar = (a) C_6H_5, (b) 4-CH_3-C_6H_4, (c) 2-OH-C_6H_4,

(d) 4-OH-C_6H_4, (e) 4-OCH_3-C_6H_4

Scheme 1

recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e):- A mixture of N'-aryl-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (2a-e) (0.01 mole) and Maleic anhydride (0.01mole) in chloroform

(50ml) was refluxed for 4.5-6 hrs. The reaction mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was recrystallized from ethanol to give 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e), which were obtained in 66-83% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

RESULTS AND DISCUSSION

It was observed that 2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N'-aryl-2-(5-(phenoxy methyl) -2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (2a-e). The structures of (2a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 1628-1645(C=N), 3020-3080 cm^{-1}(C-H, of Ar.), 1720-1750cm^{-1} (-CO), 2815-2850 cm^{-1} (-OCH_3),3450-3485cm^{-1}(-OH),2950,1370cm^{-1} (-CH_3), 1185 (C=S),1620(C=N ring),765(C-O-C ring).^{1}H NMR : 6.9–8.1(m, 10H, Ar-H), 11.80 (s,1H, CONH), 8.4(s,1H,N=CH),4.1(s,1H,CH_2),2.62(s,1H,CH_2), 2b; 2.4(s,3H,CH_3), 2c;11.20 (s,1H, OH), 2d;11.20(s,1H,OH), 2e; 3.90 (3H,s,OCH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 2-aryl-5-oxo-1-(2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamido)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (3a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1720 cm^{-1} (C=O of pyrrole ring), 3040-3058 cm^{-1}(C-H, of Ar.),3450-3550 cm^{-1}(-OH),1660-1670 cm^{-1} (-CO of -COOH), 1628-1645 cm^{-1} (C=N), 2815-2850 cm^{-1} (-OCH_3), 1185 (C=S),1620(C=N ring), 765(C-O-C ring). ^{1}H NMR: 6.9–8.1(m, 10H, Ar-H), 11.80 (s,1H, CONH), 4.72(1H,s, C_2H of the ring), 5.19(1H,s,C_4H),12.96(1H,s)(-COOH), 4.1(s,1H,CH_2),2.62(s,1H,CH_2), 3b; 2.1 (3H, s, CH_3), 3c;11.20 (s,1H, OH), 3d;11.20(s,1H,OH), 3e; 3.90 (3H,s,OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

The examination of elemental analytical data reveals 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 final structure of all compounds is confirmed by LC-MS. LC-MS data of Samples 3b and 3e gives the molecular ion peak (m/z) at 495 and 509 respectively. These values are corresponds to their molecular weight.

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) 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. Compounds 3d and 3e were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Table -3.

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activities of all the compounds (3a-e) were measured on each of these plant pathogenic strains on a potato

Table 1: Analytical Data and Elemental Analysis of Compounds (2a-e)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P. ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{18}H_{16}N_4O_3S$ (368)	87	235	58.6	58.68	4.3	4.38	15.2	15.21	8.6	8.70
2b	$C_{19}H_{18}N_4O_3S$ (382)	79	243	59.6	59.67	4.7	4.74	14.6	14.65	8.3	8.38
2c	$C_{18}H_{16}N_4O_4S$ (384)	78	238	56.2	56.24	4.1	4.20	14.5	14.57	8.3	8.34
2d	$C_{18}H_{16}N_4O_4S$ (384)	83	236	56.2	56.24	4.1	4.20	14.5	14.57	8.3	8.34
2e	$C_{19}H_{18}N_4O_4S$ (398)	80	242	57.2	57.27	4.5	4.55	14.0	14.06	8.0	8.05

Table 2: Analytical Data and Elemental Analysis of Compounds (3a-e)

Compd.	Molecular formula (Mol. wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{22}H_{18}N_4O_6S$ (466)	489	67	215-217	56.64	56.65	3.87	3.89	12.00	12.01	6.85	6.87
3b	$C_{23}H_{20}N_4O_6S$ (480)	495	65	221-222	57.47	57.49	4.18	4.20	11.64	11.66	6.66	6.67
3c	$C_{22}H_{18}N_4O_7S$ (482)	498	69	216-218	54.76	54.77	3.75	3.76	11.60	11.61	6.63	6.65
3d	$C_{22}H_{18}N_4O_7S$ (482)	496	66	223-225	54.75	54.77	3.76	3.76	11.59	11.61	6.64	6.65
3e	$C_{23}H_{20}N_4O_7S$ (496)	509	67	220-221	55.62	55.64	4.05	4.06	11.26	11.28	6.45	6.46

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 (3a-e) is shown in Table-4.

Table 3: Antibacterial Activity of Compounds (3a-e)

Compounds	**Gram +Ve**		**Gram -Ve**	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E.coli***
3a	53	49	66	60
3b	54	50	68	61
3c	56	51	58	69
3d	64	56	71	74
3e	66	58	74	76
Tetracycline	68	60	77	80

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

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Fusarium oxyporium***	***Botrydepladia Thiobromine***	***Aspergillus Niger***
3a	56	59	62	58	59
3b	55	61	63	56	57
3c	60	58	65	58	56
3d	64	68	68	74	62
3e	68	67	69	71	64

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