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Preparation and Antimicrobial Studies of Oxadiazine Containing Heterocyclic Compounds

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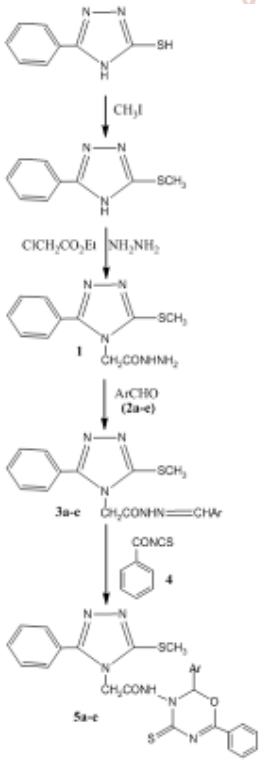
ABSTRACT

The triazole derivative say 2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetohydrazide (1) was prepared. Various Schiff bases (3a-e) of 1 were prepared by reacting with various benzaldehyde derivatives (2a-e). All the 3a-e compounds condensed with benzoyl isothiocyanate (4) to afford N-(2-aryl-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetamide derivatives(5a-e). All the synthesized compounds characterized spectroscopically and tested for antimicrobial activity.

KEYWORDS*: oxadiazine, triazole, antibacterial activity and antifungal activities*

INTRODUCTION

The present research paper comprises the novel heterocyclic compounds which contains oxadiazine and triazole. Triazole derivatives have been found to possess various pharmacological activities, such as, antiinflammatory, analgesics, antipyretic and antifungal, anticonvulsant, antitumor, antiviral and analgesic activities. [1-5]Another heterocyclic compound says, 1,3,4-oxadiazole moiety can also give biological activity as 1,3,4-oxadiazole derivatives have also biological activity[6-8].The arylidine derivatives of N'-arylidene-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetohydrazide (3a-e) were prepared and condensed with benzoyl isothiocyanate considering with the potential pharmaceutical activity of these derivatives. All the final products N-(2-aryl-6-phenyl-4-thioxo-2H-1,3,5-oxadiazin-3(4H)-yl)-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetamide derivatives (5a-e) were characterized duly. The synthetic route is as follow.



Where Ar=C_6H_5,4-ClC_6H_4,4-BrC_6H_4,4-FC_6H_4,4-$NO_2C_6H_4$

EXPERIMENTAL

Materials

All chemicals used were of laboratory grade. 2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetohydrazide (1) prepared by reported research work.[9]

Measurement

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.

Preparation of N'-arylidene-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetohydrazide (3a-e)

An equimolecular mixture of 2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl) acetohydrazide (1), and the various aromatic aldehydes (2a-h) in ethyl alcohol was refluxed for 2-3 hrs. The solid separated was collected by filtration, dried and recrystallized. The yields, melting points and other characterization data of these compounds are given in Table-1.

Preparation of N-(2-aryl-6-phenyl-4-thioxo-2H-1,3)-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetamide derivatives(5a-e)

A solution of **(3a-e)** in glacial acetic acid was stirred with benzoyl isothiocyanate (4) for 7-8 hours at 75-80°C. The

solvent was removed under reduced pressure, and the residue was diluted with water. It was extracted with ether, washed with saturated bicarbonate solution, water, brine solution and dried. The solvent was removed and the crude product was purified by recrystallization from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -2.

Table:-1 Analytical Data and Elemental Analysis of Compounds (3a-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.
3a	$C_{18}H_{17}N_5OS$ (351)	77	197-199	61.5	61.52	4.8	4.88	19.9	19.93	9.1	9.12
3b	$C_{18}H_{16}N_5OSCl$ (385)	72	205-206	56.0	56.03	4.1	4.18	18.1	18.15	8.3	8.31
3c	$C_{18}H_{16}N_5OSBr$ (429)	70	214-216	50.2	50.24	3.7	3.75	16.2	16.27	7.4	7.45
3d	$C_{18}H_{16}N_5OSF$ (369)	68	219-221	58.5	58.52	4.3	4.37	18.9	18.96	8.6	8.68
3e	$C_{18}H_{16}N_6O_3S$ (396)	69	208-210	54.5	54.54	4.0	4.07	21.1	21.20	8.0	8.09

* Uncorrected LC-MS data of 3c-435,3e-408

Table:-2 Analytical Data and Elemental Analysis of Compounds (5a-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.
5a	$C_{26}H_{22}N_6O_2S_2$ (514)	72	262-263	60.0	60.08	4.3	4.31	16.3	16.33	12.4	12.46
5b	$C_{26}H_{21}N_6O_2S_2Cl$ (548.5)	68	254-255	56.8	56.87	3.8	3.86	15.3	15.31	11.6	11.68
5c	$C_{26}H_{21}N_6O_2S_2Br$ (592)	72	249-251	52.6	52.61	3.5	3.57	14.1	14.16	5.3	5.39
5d	$C_{26}H_{21}N_6O_2S_2F$ (532)	66	257-259	58.6	58.63	3.9	3.97	15.7	15.78	12.0	12.04
5e	$C_{26}H_{21}N_7O_4S_2$ (559)	69	260-261	55.7	55.80	3.7	3.78	17.5	17.52	11.4	11.46

* Uncorrected LC-MS data of 5a-521,5d-539

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 [10-12]. 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 3b and 5b were found more toxic for microbes. All compounds found to be less or moderate active shown in Tables -3.

Table:-3 Antibacterial Activity of Compounds (3a-e) and (5a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3a	45	59	56	64
3b	53	73	66	76
3c	52	72	63	73
3d	48	65	61	70
3e	49	62	58	66
4a	46	61	57	64
4b	54	74	67	77
4c	54	72	64	76
4d	49	65	62	71
4e	49	64	60	67

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro[10-12]. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum*. The antifungal activity of all the compounds (3a-e) and (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 fungicidal activity displayed by various compounds (3a-e) and (4a-e) is shown in Tables-4.

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

Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum
3a	57	51	55	55
3b	70	70	65	62
3c	69	67	69	64
3d	65	65	56	57
3e	59	54	57	59
4a	58	52	57	57
4b	70	72	66	63
4c	68	68	63	63
4d	67	67	57	58
4e	60	55	58	60

RESULTS AND DISCUSSION

The IR spectra of 5 N'-arylidene-2-(3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-yl)acetohydrazide (3a-e) showing an absorption bands at 1720-1740cm^{-1} (C=O), 730cm^{-1} (C-S-C), 3040-3080cm^{-1} (C-H, of Ar.), 1630(C=N ring),1080(-Cl),1555, 1375(-NO_2), 710(C-Br), 1255(C-F),1625cm^{-1} (-C=CH-Ar). ^{1}H NMR: 8.42 (1H, s,-CH), 7.50-8.30(9H, m,Ar-H), 4.84(2H,s,CH_2),2.61(3H,s,CH_3).The C, H, N, S analysis data of all compounds are presented in Table-1.

The IR spectra of (5a-e) are almost resemble those of the corresponding (3a-e),1720-1740cm^{-1} (C=O), 730cm^{-1} (C-S-C), 3040-3080cm^{-1} (C-H, of Ar.), 1630-1620(C=N ring),1080(-Cl),1555, 1375(-NO_2), 710(C-Br), 1255(C-F), 1185(C=S). ^{1}H NMR: 7.35-8.30 (14H, m,Ar-H), 8.42(1H, s,-CH), 4.84(2H,s,CH_2),2.61(3H,s,CH_3),5.68(1H,s,CH).The C, H, N, S analysis data of all compounds are presented in Table-2. LC-MS of selected samples 3c and 5d show the peak respectely at 435 and 539 which assign the molecular weight of compound,

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.

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