



Synthesis and biological activity of thiazolidinone containing heterocyclic compound

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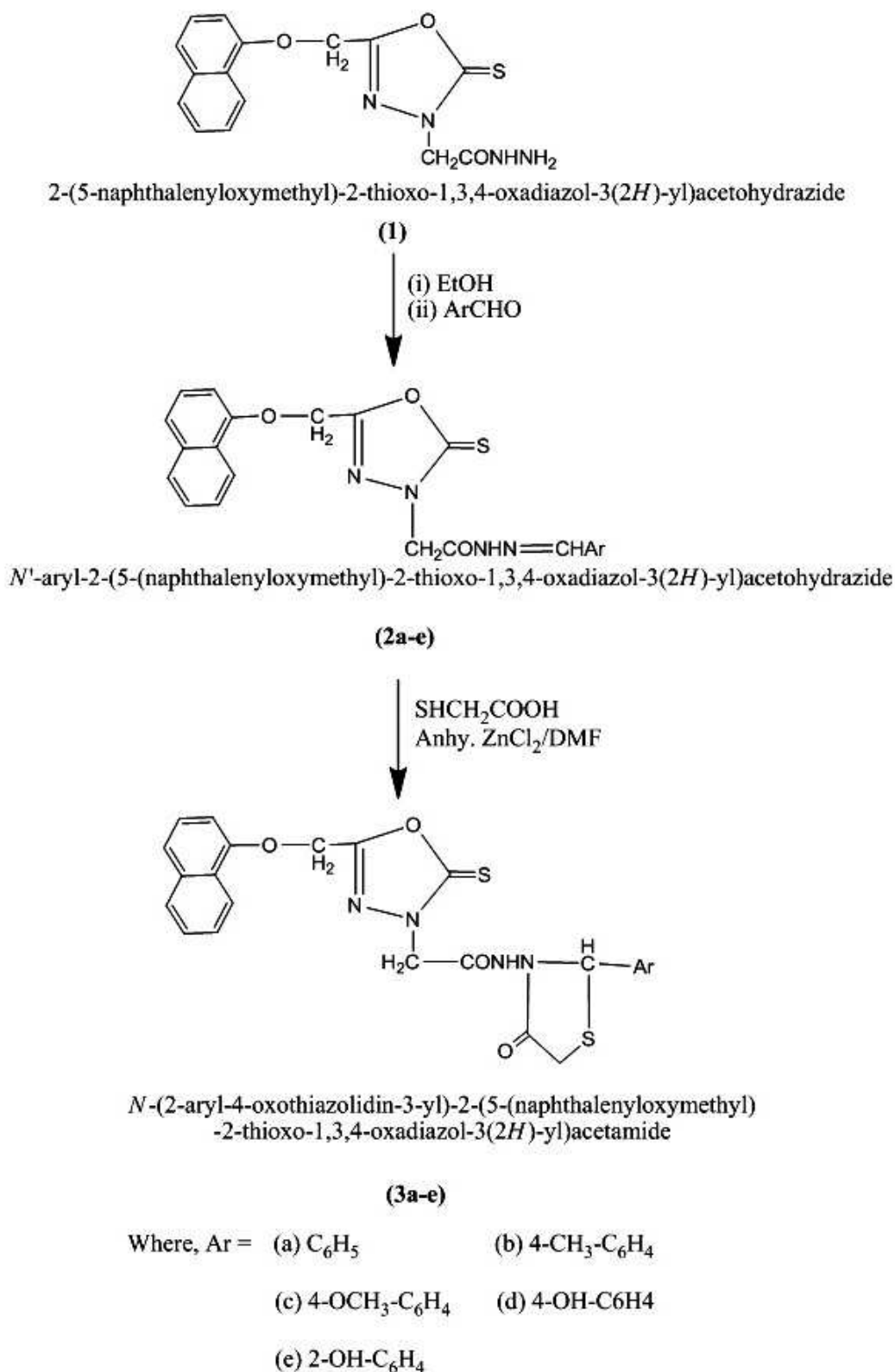
ABSTRACT

2-(5-(Naphthalenyloxymethyl)-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-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e) in good yields. Cyclocondensation of compounds (2a-e) with thioglycolic acid yields *N*-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide (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.

Key words: acetohydrazide, thiazolidine, antibacterial activity.

INTRODUCTION

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungal, analgesic, anti-inflammatory properties [1-15]. These heterocyclic systems find wide use in medicine, agriculture and industry. 4-Thiazolidinones and its arylidene compounds give good pharmacological properties [16-20]. 4-Thiazolidinones are also known to exhibit antitubercular [21], antibacterial [22], antifungal [23] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone and hydrazide 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 phenoxy oxadiazole hydrazide containing thiazolidinone moiety. Hence the present communication comprises the synthesis of *N*-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide (3a-e). The synthetic approach is shown in scheme-1.



Scheme-1

EXPERIMENTAL SECTION

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 ¹H NMR and ¹³C 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 N-aryl-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (**2a-e**)

General procedure: – An equimolecular mixture of 2-(5-(naphthalenyloxymethyl)-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 1-2 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation of N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide (**3a-e**)

General procedure: A mixture N'-aryl-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) aceto hydrazide (**2a-e**) (0.01 mole) in THF (30ML) and mercapto acetic acid (thioglycolic acid) (0.01 mole) with a pinch of anhydrous ZnCl₂ was refluxed for 12 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: chloroform (8:2; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 4-thiazolidinones(**2a-e**), which were obtained in 50-65% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

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 **2c**, **2d**, **3c** and **3d** were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Table -3.

Table:-3 Antibacterial Activity of Compounds (**2a-e** and **3a-e**)

Compounds	Gram +Ve		Gram -Ve	
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>E.coli</i>	<i>Klebsiella promioe</i>
2a	50	51	60	45
2b	54	56	52	56
2c	60	57	57	62
2d	68	64	74	46
2e	53	55	68	60
3a	56	54	64	49
3b	55	60	55	61
3c	69	67	76	69
3d	59	62	60	67
3e	54	50	67	64
Tetracycline	55	79	74	84

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 activity of all the compounds (**2a-e**) & (**3a-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°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:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate
Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (**2a-e**) and (**3a-e**) is shown in Table-4.

Table-4 Antifungal Activity of Compounds (2a-e and 3a-e)

Compounds	Zone of Inhibition at 1000 ppm (%)				
	<i>Nigrospora Sp.</i>	<i>Aspergillus Niger</i>	<i>Botrydepladia Thiobromine</i>	<i>Rhizopus Nigricum</i>	<i>Fusarium oxysporium</i>
2a	65	64	62	54	69
2b	56	50	60	61	65
2c	68	69	70	58	73
2d	66	66	67	70	66
2e	63	60	60	74	72
3a	68	66	57	47	64
3b	59	57	62	65	65
3c	75	67	66	67	75
3d	71	66	62	70	67
3e	66	62	61	68	66

RESULTS AND DISCUSSION

It was observed that 2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)aceto hydrazide (1), on condensation with aromatic aldehydes, yields N'-aryl-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide (2a-e). The structures of (2a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1} (C-H, of Ar.), 2815-2850 cm^{-1} (-OCH₂). ¹H NMR : 6.95 – 7.91 (7H, m) (Ar - H), 11.80-11.81 (1H, s) (-CONH), 8.43-8.80 (1H, s) (-N=CH), 2b; 2.41 (3H, s) (-CH₃), 2c; 3.90 (3H, s) (-OCH₃), 2d,2e; 4.09 (2H,s) (OH). ¹³C NMR:117.9-118.1, 121.8-122.0, 128.9-129.1, 129.5-130.0, 131.2-131.5, 133.9-134.3, 159.6-160.0 (Ar-10C), 163.5-163.8(-CONH), 146.9-150.4 (-CH); 2c: 55.5-56.7 (-OCH₃); 2b: 22.5 (CH₃). The C, H, N analysis data of all compounds are presented in Table -1.

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

Compd.	Molecular formula (Mol. Wt.)	LC-MS Data	Yield	M.P.* °C	Elemental Analysis					
					%C		%H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	C ₂₂ H ₁₈ N ₄ O ₃ S (418)	435	93	242-244	63.1	63.14	4.3	4.34	13.3	13.39
2b	C ₂₃ H ₂₀ N ₄ O ₃ S (432)	456	88	232-234	63.8	63.87	4.6	4.66	12.9	12.95
2c	C ₂₃ H ₂₀ N ₄ O ₄ S (448)	462	81	234-235	61.5	61.59	4.4	4.49	12.4	12.49
2d	C ₂₂ H ₁₈ N ₄ O ₄ S (434)	453	84	241-243	60.8	60.82	4.1	4.18	12.8	12.90
2e	C ₂₂ H ₁₈ N ₄ O ₄ S (434)	452	86	226-228	60.7	60.82	4.1	4.18	12.8	12.90

* Uncorrected

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

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* °C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	C ₂₄ H ₂₀ N ₄ O ₄ S ₂ (492)	513	72	212-214	58.5	58.52	4.0	4.09	11.3	11.37	13.0	13.02
3b	C ₂₅ H ₂₂ N ₄ O ₄ S ₂ (456)	478	75	208-210	59.2	59.27	4.3	4.38	11.0	11.06	12.6	12.66
3c	C ₂₅ H ₂₂ N ₄ O ₅ S ₂ (522)	496	69	199-202	57.4	57.46	4.2	4.24	10.7	10.72	12.2	12.27
3d	C ₂₄ H ₂₀ N ₄ O ₅ S ₂ (458)	477	70	195-197	56.6	56.68	3.9	3.96	10.9	11.02	12.5	12.61
3e	C ₂₀ H ₁₈ N ₄ O ₅ S ₂ (458)	471	69	189-191	56.6	56.68	3.9	3.96	11.0	11.02	12.6	12.61

* Uncorrected

The structures assigned to N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(naphthalenyloxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl) acetamide (3a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1690 cm^{-1} (C=O of thiazolidinone ring), 718 cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095 cm^{-1} (CH₂ of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH) for (3a) compound.

¹H NMR: 3.85-3.95 (2H, s) (-CH₂ of the ring), 5.950-5.959 (1H, s) (-CH), 6.90-7.95 (10H, m) (Ar-H), 8.20-8.22 (1H, s) (-CONH), 3b; 2.43 (3H, s) (-CH₃), 3c; 3.91 (3H, s) (-OCH₃), 2d,2e; 4.09 (2H,s) (OH). ¹³C NMR:115.9-

116.2, 121.3-121.5, 126.9-127.6, 128.3-128.5, 128.9-129.2, 156.9-157.5, 168.9-169.3 (Ar-14C), 38.9-39.5 (-CH₂ of the ring), 67.8-68.3 (-CH), 164.8-165.9(-CONH), 168.9-169.9 (-CO of the ring), 3c: 56.0-56.4 (-OCH₃); 3b: 22.9 (CH₃). 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 consistent 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 all compounds are presented in Tables-1,2.

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