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Synthesis and biological studies of triazole-thiazolidinone containing compounds

Tejas C. Shah and Vipul P. Prajapati

Sheth M. N. Science College, Patan

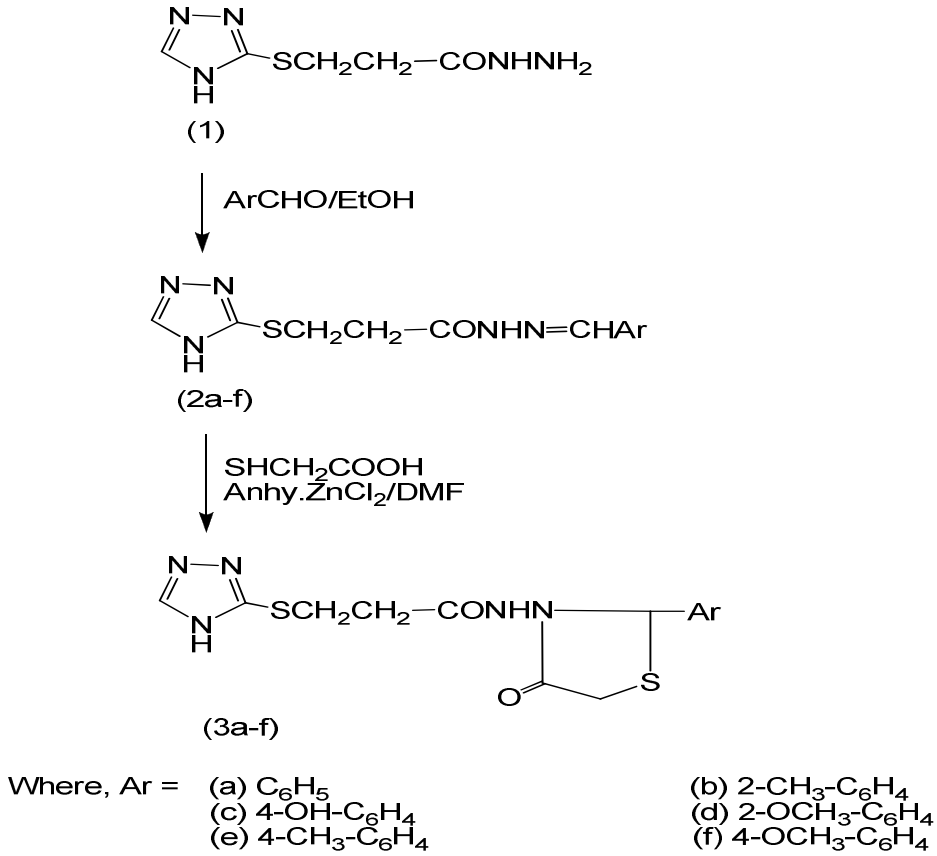
ABSTRACT

3-(4H-1, 2, 4-triazol-3-ylthio)propane hydrazide(1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 3-(4H-1,2,4-triazol-3-ylthio)-N'-arylidene propane hydrazide(2a-f) in good yields. Cyclo condensation of compounds (4a-f) with thioglycolic acid yields 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f). 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: 3-(4H-1, 2, 4-triazol-3-ylthio)propane hydrazide, thiazolidine, antibacterial activity.

INTRODUCTION

During the last few decades, considerable attention has been devoted to synthesis of 1,2,4-triazole derivatives possessing such comprehensive bioactivities as antibacterial, antifungal [1-3], antimycobacterial [4], anti-inflammatory [5], analgesic [6], anticancer [7], antihypertensive [8], anticonvulsant [9], antiviral [10], antidepressant [11], antiasthmatic [12], diuretic [13] and hypoglycemic [14] activities. Several compounds containing 1, 2, 4-triazole rings are well known commercial drugs. For example, Fluconazole [15] is used as an antimicrobial drug. Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [16-18]. 4-Thiazolidinones and its arylidene compounds give good pharmacological properties [19-23]. 4-thiazolidinones are also known to exhibit antitubercular [24], antibacterial [25], antifungal [26] 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 triazole containing thiazolidinone moiety. Hence the present communication comprises the synthesis of 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide. The synthetic approach is shown in scheme-1.



SCHEME - 1

MATERIALS AND METHODS

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* 3-(4H-1, 2, 4-triazol-3-ylthio)-N'-arylidene propane hydrazide (2a-f)**

A mixture of 3-(4H-1 ,2, 4-triazol-3-ylthio)propane hydrazide (1) and the aromatic aldehydes (a-f) in ethyl alcohol was refluxed on a water bath for 1.5 hrs. The solid separated was collected by filtration, dried and recrystallized from ethyl alcohol. The yields, melting points and other characterization data of these compounds are given in Table -1.

***Preparation of* 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f)**

A mixture 3-(4H-1, 2, 4-triazol-3-ylthio)-N'-arylidene propane hydrazide **(2a-f)** in THF and thioglycolic acid with a pinch of anhydrous $ZnCl_2$ was refluxed for 10-11hrs. 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 (7:3; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 3-(4H-1, 2, 4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f), which were obtained in 56-69% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

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 mm. Compounds 3c and 3d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3.

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

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	$C_{12}H_{13}N_5OS$ (275)	81	239-241	52.33	52.35	4.75	4.76	25.42	25.44	11.64	11.65
2b	$C_{13}H_{15}N_5OS$ (289)	85	241-243	53.94	53.96	5.21	5.23	24.18	24.20	11.06	11.08
2c	$C_{12}H_{13}N_5O_2S$ (291)	78	233-235	49.45	49.47	4.48	4.50	24.03	24.04	11.00	11.01
2d	$C_{13}H_{15}N_5O_2S$ (305)	83	229-232	51.12	51.13	4.92	4.95	22.93	22.94	10.47	10.50
2e	$C_{13}H_{15}N_5OS$ (289)	77	225-227	53.95	53.96	5.21	5.23	24.19	24.20	11.06	11.08
2f	$C_{13}H_{15}N_5O_2S$ (305)	80	228-230	51.11	51.13	4.93	4.95	22.91	22.94	10.48	10.50

***** *Uncorrected*

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

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	$C_{14}H_{15}N_5O_2S_2$ (349)	65	209-211	48.10	48.12	4.31	4.33	20.02	20.04	18.33	18.35
3b	$C_{15}H_{17}N_5O_2S_2$ (363)	62	206-208	49.56	49.57	4.69	4.71	19.25	19.27	17.62	17.64
3c	$C_{14}H_{15}N_5O_3S_2$ (365)	58	198-200	46.00	46.01	4.12	4.14	19.15	19.16	17.52	17.55
3d	$C_{15}H_{17}N_5O_3S_2$ (379)	64	189-192	47.46	47.48	4.50	4.52	18.45	18.46	16.88	16.90
3e	$C_{15}H_{17}N_5O_2S_2$ (363)	66	205-207	49.55	49.57	4.70	4.71	19.25	19.27	17.63	17.64
3f	$C_{15}H_{17}N_5O_3S_2$ (379)	62	196-198	47.46	47.48	4.51	4.52	18.44	18.46	16.89	16.90

***** *Uncorrected*

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

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	50	49	62	52
3b	54	53	56	56
3c	66	65	77	49
3d	68	67	79	78
3e	63	58	59	63
3f	65	64	71	48
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 activities of all the compounds (3a-f) 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 (3a-f) is shown in Tables-4.

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

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus niger***	***Botrydepladia thiobromine***	***Rhizopus nigricum***	***Fusarium oxyporium***
3a	59	53	61	59	65
3b	60	54	63	64	62
3c	68	69	65	63	71
3d	72	70	72	76	75
3e	67	68	64	63	60
3f	68	65	66	64	63

RESULTS AND DISCUSSION

It was observed that 3-(4H-1, 2, 4-triazol-3-ylthio)propane hydrazide(1), on condensation with various aromatic aldehydes, yields 3-(4H-1,2,4-triazol-3-ylthio)-N'-arylidene propane hydrazide(2a-f). The structures of (2a-f) 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.), 1720-1750 cm^{-1} (CO), 2815-2850 cm^{-1}(OCH_3), 2950, 1370 cm^{-1} (CH_3), 3380-3290 cm^{-1}(OH).^{1}H NMR:7.91-9.6 (6H, m, Ar-H), 3.36-2.58(4H, t, -CH_2), 8.43-8.80(1H, s, N=CH), 8.62-8.81(2H, s, NH), 2b; 2.45(3H, s, CH_3), 2c; 5.35(1H, s, OH), 2d; 3.90(3H, s, OCH_3), 2e; 5.37 (1H, s, OH), 2f; 3.92 (3H, s, OCH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 3-(4H-1,2,4-triazol-3-ylthio)-N-(4-oxo-2-arylthiazolidin-3-yl) propanamide (3a-f) were supported by the elemental analysis and IR spectra showing an absorption bands at 1690cm^{-1} (C=O of thiazolidinone ring), 718cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH), 2815-2850 cm^{-1} (OCH_3), 2950, 1370 cm^{-1} (CH_3), 3380-3290 cm^{-1} (OH).^{1}H NMR: 3.85-3.95 (2H,s,CH_2 of the ring), 5.95-5.96(1H,s,CH), 6.90-7.95 (6H,m,Ar-H), 8.20-8.22 (1H,s,CONH), 8.62-8.81(2H,s,NH), 3b; 2.48(3H,s,CH_3),2c; 5.38(1H,s,OH),3d; 3.92(3H,s, OCH_3), 3e; 5.38(1H,s, OH), 3f; 3.95 (3H, s,OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

CONCLUSION

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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