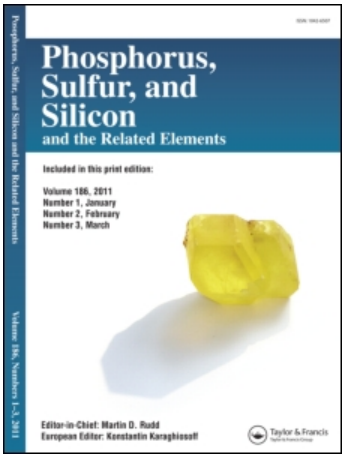

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Synthesis and Biological Activity of 3-[4*H*-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones

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Synthesis and Biological Activity of 3-[4*H*-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones

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4-Amino-1,2,4-triazole (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 4-(arylidene-amino)-4H-[1,2,4]-triazole (2 a–h) in good yields. Cyclocondensation of compounds (2 a–h) with thioglycolic acid yields 3-[4H-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones (3 a–h). The structures of these compounds were established on the basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords 4-Amino-1,2,4-triazole; antibacterial activity; thiazolidinone

INTRODUCTION

4-Amino-1,2,4-triazoles and their condensed products[1–3] are the starting materials for the synthesis of a wide variety of heterocyclic derivatives, which are of great importance in medicinal chemistry.[4–6] Many reports of the synthesis of N-arylideneamino-1,2,4-triazole derivatives are currently known.[7–9] These compounds display diverse biological activity, including antibacterial, antifungicidal, analgesic, anti-inflammatory activity.[10–12] These heterocyclic systems find wide use in medicine, agriculture, and industry. 4-thiazolidinones[13–15] give good pharmacological properties.[16] 4-thiazolidinones are known to exhibit antitubercular,[17] antibacterial,[18] antifungal,[19] and anticonvulsant activities; therefore, we wanted to determine if merging thiazolidinone and triazole moieties would enhance the drug activity of these compounds to some extent, or whether they might possess some of the abovementioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of triazole

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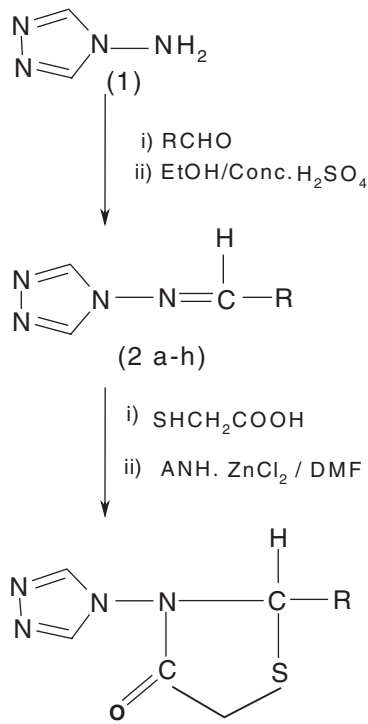

Where, R = (a) C_6H_5 (e) 4-OH-3-OCH_3-C_6H_3
(b) 4-OH-C_6H_4 (f) 4-Cl-C_6H_4
(c) 2-OH-C_6H_4 (g) 2-NO_2-C_6H_4
(d) 4-OCH_3-C_6H_4 (h) 5-Br-2-OH-C_6H_3

SCHEME 1

containing thiazolidinone moiety. Hence, the present communication comprises the synthesis of 3-[4*H*-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones. The reaction is shown in Scheme 1, and the characterization is shown in Tables II and III.

BIOLOGICAL SCREENING

Antibacterial Activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis and staphylococcus aureus*)

TABLE I Analytical and Spectral Data of Compounds (2a–h)

Compd.	Molecular formula (mol.wt.)	Yield	MM.pP.°C	Elemental analysis %C Found	%C Calcd.	%H Found	%H Calcd.	%N Found	%N Calcd.	^{1}H NMR (δ, ppm) Ar—H	—CH=N	—OH	—OCH_3
2a	$C_9H_8N_4$ (172.2)	90	134	62.60	62.72	4.55	4.65	32.45	32.52	7.5–7.7 (m, 5H)	9.5–9.7(t)	—	—
2b	$C_9H_8N_4O$ (188.2)	80	140	57.30	57.39	4.20	4.25	29.75	29.76	7.5–7.8 (m, 4H)	9.5–10.2(t)	5.1(s)	—
2c	$C_9H_8N_4O$ (188.2)	83	132	57.32	57.39	4.20	4.25	29.75	29.76	7.5–7.8 (m, 4H)	9.5–10.2(t)	5.3(s)	—
2d	$C_{10}H_{10}N_4O$ (202)	88	164	59.35	59.41	4.88	4.95	27.70	27.72	7.5–7.8 (m, 4H)	9.5–9.8(t)	-	3.9(s)
2e	$C_{10}H_{10}N_4O_2$ (218)	77	178	55.00	55.05	4.55	4.59	25.65	25.69	7.5–7.7 (t, 3H)	9.5–9.7(t)	5.2(s)	3.7(s)
2f	$C_9H_8N_4Cl$ (206.65)	75	185	52.25	52.26	3.85	3.87	27.05	27.10	7.5–7.8 (m, 4H)	9.5–9.9(t)	—	—
2g	$C_9H_7N_5O_2$ (217.20)	78	122	49.70	49.72	3.20	3.22	32.20	32.23	7.5–7.8 (m, 4H)	9.5–9.85(t)	—	—
2h	$C_9H_7N_4OBr$ (267.10)	81	145	40.40	40.43	2.60	2.62	20.95	20.97	7.5–7.8 (t, 3H)	9.5–9.75(t)	5.3(s)	—

TABLE II Analytical and Spectral Data of Compounds (3a–h)

Compd.	Molecular formula (mol.wt.)	Yield	M.p.^{0}C	Elemental analysis %C Found (calcd.)	% H Found (calcd.)	%N Found (calcd.)	%S Found (calcd.)	^{1}H NMR (δ, ppm) =CH_2 of ring	C_2-H	Ar—H	—CH=N	—OH	—OCH_3
3a	$C_{11}H_{10}N_4OS$ (246.32)	63	143	53.55 (53.58)	4.03 (4.06)	22.71 (22.73)	13.00 (13.00)	3.27 (S,2H)	5.92 (S,1H)	7.5–7.7 (m, 5H)	9.5–9.7(d)	—	—
3b	$C_{11}H_{10}N_4O_2S$ (262.32)	65	149	50.30 (50.32)	3.80 (3.81)	21.30 (21.35)	12.20 (12.20)	3.38 (S,2H)	5.80 (S,1H)	7.5–7.8 (m, 4H)	9.5–10.2(d)	5.1(s)	—
3c	$C_{11}H_{10}N_4O_2S$ (262.32)	58	158	50.28 (50.32)	3.80 (3.81)	21.30 (21.35)	12.18 (12.20)	4.18 (S,2H)	5.82 (S,1H)	7.5–7.8 (m, 4H)	9.5–10.2(d)	5.3(s)	—
3d	$C_{12}H_{12}N_4O_2S$ (276.12)	68	134	52.10 (52.15)	4.28 (4.35)	20.25 (20.28)	11.50 (11.59)	3.30 (S,2H)	5.90 (S,1H)	7.5–7.7 (m, 4H)	9.5–9.8(d)	—	3.9(s)
3e	$C_{12}H_{12}N_4O_3S$ (292.12)	57	170	49.10 (49.29)	4.10 (4.11)	19.15 (19.17)	10.90 (10.95)	4.10 (S,2H)	5.92 (S,1H)	7.5–7.8 (t, 3H)	9.5–9.7(d)	5.2(s)	3.7(s)
3f	$C_{11}H_{10}N_4OSCl$ (280.77)	48	183	46.85 (47.01)	3.55 (3.56)	19.90 (19.95)	11.35 (11.40)	4.18 (S,2H)	5.85 (S,1H)	7.5–7.8 (m, 4H)	9.5–9.9(d)	—	—
3g	$C_{11}H_9N_5O_3S$ (291.32)	54	156	45.20 (45.31)	3.00 (3.09)	24.00 (24.03)	10.90 (10.98)	3.60 (S,2H)	5.92 (S,1H)	7.5-7.8 (m, 4H)	9.5–9.85(d)	—	—
3h	$C_{11}H_9N_4O_2SBr$ (341.22)	63	194	38.70 (38.68)	2.61 (2.64)	16.40 (16.41)	9.28 (9.38)	3.75 (S,2H)	5.90 (S,1H)	7.5-7.7 (t, 3H)	9.5–9.75(d)	5.3(s)	—

TABLE III Antibacterial Activity of Compounds (3a–h)

	Zone of inhibition				
	Gram +ve		Gram –ve		
Compounds	*Bacillus subtilis*	*Staphylococcus aureus*	*Klebsiella promioe*	*Salmonella typhi*	*E. coli*
3a	55	56	48	45	65
3b	43	65	57	54	69
3c	45	65	70	42	84
3d	72	78	75	82	86
3e	64	60	42	63	40
3f	81	72	70	85	68
3g	83	70	68	78	75
3h	68	56	62	66	58
Tetracycline	83	57	72	80	75

and gram-negative bacteria (*E.coli, salmonella typhi, and klebsiella promioe*) at a concentration of 50 μg/ml by agar cup plate method. Methanol system was used as control in this method. Under similar conditions, using tetracycline as a standard for comparison, we carried out a control experiment. The area of inhibition of zone measured in cm. Compound 3d, 3f, and 3g were found more active against the above microbes. Other compounds found to be less or moderate active than tetracycline (Table III).

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *penicillium expansum, Botrydepladia thiobromine, Nigrospora Sp., Trichothesium Sp., and Rhizopus nigricum*. The antifungal activity of all the compounds (3a−h) was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200 g, dextrose 20 g, agar 20 g and 1 L water. Five day old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120°C for 15 min at 15 atm pressure; the resulting product was 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:

$$\text{Percentage of inhibition} = 100(X - Y)/X, \quad (1)$$

where, X = area of colony in control plate; and Y = Area of colony in test plate.

The fungicidal activity displayed by various compounds (3a–h) is shown in Table IV.

RESULTS AND DISCUSSION

The structures of 4-(arylidene-amino)-4*H*-[1,2,4]-triazole (2a–h) were confirmed by elemental analysis and IR spectra showing absorption band at 1620–1640 cm^{-1}(C=N), ~1040 cm^{-1}(N–N of triazole), 3250–3300 cm^{-1} (C–H of Triazole), 3030–3080 cm^{-1} (C–H of Ar.), 1475–1525 cm^{-1} (C=C of Ar.), 1575–1625 cm^{-1} (C–C of Ar.), while additional peak appears due to substitution in the Aromatic ring showing absorption band at ~1230 cm^{-1} (C–O), 3450–3550 cm^{-1} (O–H), 2815–2850 cm^{-1} (C–H of $-OCH_3$), ~1095 cm^{-1} (C–Cl), 1310–1360 and 1490–1560 cm^{-1} ($-NO_2$), ~1075 cm^{-1} (C–Br). All the spectra comprises the common signals with their assignment are : t 9.5–10.2 (2H of CH=N of triazole and 1H of CH=N of arylidene), m 7.5–7.8 (aromatic proton). The additional signal appears due to substitution in aromatic ring showing common signals at 5.1–5.3 (H of –OH) and 3.7–3.9 (H of $-OCH_3$) both as singlets.

The structures assigned to 3-[4*H*-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones (3a–h) were supported by the elemental analysis and IR spectra showing same absorption bands as in (2a–h) with additional bands at 1000–1400 cm^{-1} (C–N of thiazolidinone ring), 1690 cm^{-1} (C=O of thiazolidinone ring), 680 cm^{-1} (C–S–C of thiazolidinone ring), 3075–3095 cm^{-1} (=CH_2 of thiazolidinone ring). All the compounds show the NMR signals for different kinds of protons at their respective positions which are same as in (2a–h) with additional signals with their assignment are: s 3.27–4.18 (CH_2 of thiazolidinone ring) and s 5.80–5.92 (C_2-H of thiazolidinone ring), which confirmed the structures of thiazolidinone derivatives.

The examination of the data reveals that the elemental contents are consistent with the predicted structure shown in Scheme 1. The IR and NMR data also allow a direct assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of samples 3a and 3c gave the molecular ion peaks (m/z) at 248 and 265, respectively. These values correspond to their molecular weight.

The antibacterial activity of series (3a–h) was carried out against some strains of bacteria. The results show that the prepared compounds are toxic against the bacteria. The comparison of the antibacterial

TABLE IV Antifungal Activity of Compounds (3a–h)

	Zone of inhibition at 1000 ppm (%)				
Compounds	*Penicillium expansum*	*Botrydepladia thiobromine*	*Nigrospora sp.*	*Trichothesium sp.*	*Rhizopus nigricum*
3a	75	60	72	55	53
3b	64	71	64	56	70
3c	74	73	78	68	66
3d	70	68	65	80	72
3e	55	58	73	65	68
3f	53	64	63	74	62
3g	62	73	66	62	57
3h	75	80	64	73	69

activity of these compounds with tetracycline shows that these compounds have almost similar activity.

CONCLUSION

The clubbing of 1,2,4-triazole and thiazolidinone has been done successfully into one molecule. Both the moieties have important applications in medicinal use; the produced compounds may be act as good biological compounds.

EXPERIMENTAL

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

Preparation of 4-(Arylidene-amino)-4H-[1,2,4]-triazole (2 a−h)—General Procedure

An equimolecular mixture of 4-Amino-1,2,4-triazole 1, (0.84 g, 0.01 mol), and the aromatic aldehyde (a−h) in ethanol(15 ml) and conc. H_2SO_4(0.4 ml) was refluxed on a water bath for 1−2 h. 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 I.

Preparation of 3-[4H-(1,2,4)-triazolyl]-2-aryl-1,3-thiazolidin-4-ones (3 a–h)—General Procedure

A mixture of 4-(arylidene-amino)-4*H*-[1,2,4]-triazole (2 a—h) (0.01 mol) in DMF (10 ml) and thioglycolic acid (0.87 ml, 0.0125 mol) with a pinch of anhydrous zinc chloride was refluxed for about 8–9 h. The excess solvent was removed under vacuum and residue was poured into ice-cold water and then neutralized with sodium bicarbonate solution. Solid separated was filtered and dried. The product thus obtained was purified by column chromatography over silica gel using benzene: chloroform (8:2 V/V) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol (50–60 yield%).

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