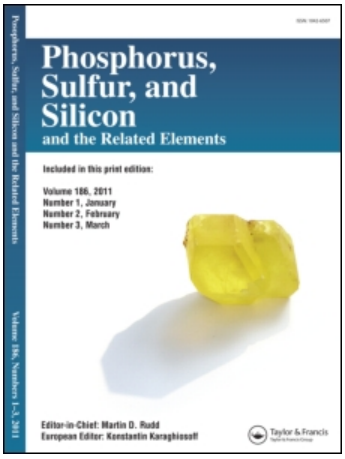

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Synthesis and Biological Activity of 3-[4*H*-(1,2,4)-Triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione

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Synthesis and Biological Activity of 3-[4*H*-(1,2,4)-Triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione

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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 (2a–h) in good yield. Rearrangement of compounds (2a–h) with benzoyl isothiocyanate / 4-chloro-benzoyl isothiocyanate / 2,4-dichloro-benzoyl isothiocyanate yields corresponding 1,3,5-oxadiazine derivatives (3). Structural elucidation of these compounds was based on elementary analysis and spectral data studies. The newly synthesized compounds were evaluated for their antibacterial activities.

Keywords 4-Amino-1,2,4-triazole; antibacterial activity; 1,3,5-oxadiazine

INTRODUCTION

4-Amino-1,2,4-triazole[1] and their condensed products[2–5] are the starting materials for the synthesis of a wide variety of heterocyclic derivatives, which are of great importance in medicinal chemistry.[6–8] Many reports of the synthesis of N-arylideneamino-1,2,4-triazole derivatives are currently known.[9–11] These compounds display diverse biological activity, including antibacterial, antifungicidal, analgesic, and anti-inflammatory activity.[12–14] These heterocyclic systems find wide use in medicine, agriculture, and industry. The 1,3,5-oxadiazine derivatives can be synthesized by 1,4-cycloaddition of benzoyl isothiocyanate with a Schiff's base.[15,16] 1,3,5-Oxadiazine derivatives act as a herbicides, which was reported by Japanese scientists.[17] The microwave-assisted synthesis of 1,3,5-oxadiazine derivatives has been attempted

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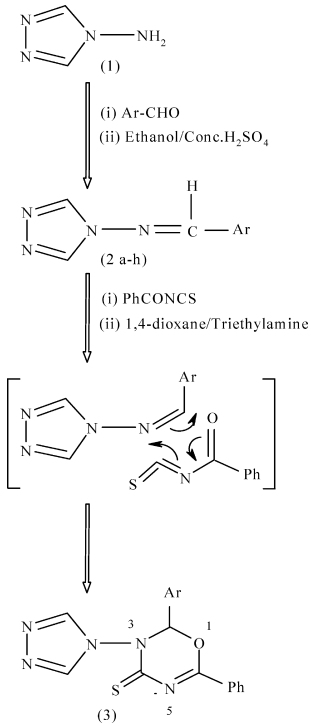
successfully.[18] 1,3,5-oxadiazine derivatives are employed as an additive in textile finishing or cleaning.[19] 1,3,5-Oxadiazine derivatives are also reported as pesticides or fungicides.[20] Recently, the coumarin ring containing 1,3,5-oxadiazine has been reported.[21] Hence, the present communication comprises the synthesis of 3-[4*H*-(1,2,4)-triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione (**3**) and is shown in Scheme 1.



SCHEME 1 Where Ar = (a) C_6H_5, (b) 4-OH-C_6H_4, (c) 2-OH-C_6H_4, (d) 4-OCH_3-C_6H_4, (e) 4-OH-3-OCH_3-C_6H_3, (f) 4-Cl-C_6H_4, (g) 2-NO_2-C_6H_4, (h) 5-Br-2-OH-C_6H_3. Ph = (x) C_6H_5, (y) 4-chloro-C_6H_4, (z) 2,4-di chloro-C_6H_3.

RESULTS AND DISCUSSION

The structures of 4-(arylidene-amino)-4*H*-[1,2,4]-triazoles (**2a–h**) were confirmed by elemental analysis and IR spectra showing absorption bands at 1620–1640 cm^{-1} (C=N), ~1040 cm^{-1} (N—N of triazole), 3250–3300 cm^{-1} (C—H of triazole and C—H of arylidene), 3030–3080 cm^{-1} (C—H of Ar), 1475–1525 cm^{-1} (C=C of Ar), 1575–1625 cm^{-1} (C—C of Ar), and additional peaks appear due to the 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), 1310–1340 and 1490–1560 cm^{-1} ($—NO_2$), ~1075 cm^{-1} (C—Br). All spectra comprise the expected NMR signals, including 9.5–10.2 (t, 2H of CH=N of triazole and 1H of CH=N of arylidene), 7.5–7.8 (m, aromatic proton), whereas the additional signals appear due to substitution in the aromatic ring with signals at 5.1–5.3 (s, H of —OH) and 3.7–3.9 (s, H of $—OCH_3$). The C, H, N analysis and ^{1}H NMR data of all compounds are presented in Table I.

The structures assigned to 3-[4*H*-(1,2,4)-triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione (**3**) 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 oxadiazine), 1350 cm^{-1} (C=S of oxadiazine), 1300 cm^{-1} (C—O—C of oxadiazine). All the compounds show the expected NMR signals for different kinds of protons at their respective positions, which are same as in (2a–h) with additional NMR signals: 4.3 (s, C_2—H of oxadiazine), which confirmed the structures of oxadiazine derivatives. The C, H, N, S analysis and ^{1}H NMR data of all compounds are presented in Tables II, III, and IV.

An examination of data reveals that the elemental contents are consistent with the predicted structure (**3**) shown in Scheme 1. The IR and NMR data also confirm the assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS data of selected samples. The LC-MS of selected samples 3ax and 3fx give molecular ion peaks (m/z) at 337 and 370, respectively. These values correspond to their molecular weights.

The antibacterial activity of series (**3**) 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 activity of these compounds with ampicillin (standard) shows that these compounds have almost similar activity.

BIOLOGICAL SCREENING

Antibacterial Activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, and *Klebsiella pneumoniae*) at a concentration of 50 μg/ML by the agar cup plate method. A methanol system was used as control in this method. Under similar conditions, ampicillin was used as a standard drug for comparison. The area of inhibition zone is measured in centimeters. Compounds 3fy, 3fz, and 3hz were found to be more active against the

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

Compd.	Molecular formula (mol. wt.)	Yield	mp (°C)	Elemental analysis % C Found (Calcd.)	% H Found (Calcd.)	% N Found (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) (where Ph = C_6H_5 in Scheme 1)

Compd.	Molecular formula (Mol.wt.)	Yield	mp (°C)	Elemental analysis % C Found (Calcd.)	% H Found (Calcd.)	% N Found (Calcd.)	% S Found (Calcd.)	^{1}H NMR (δ , ppm) C_2—H of Oxadiazine	Ar—H	—CH═N of triazole	—OH	—OCH_3
3ax	$C_{17}H_{13}N_5OS$ (335.4)	65	145	60.73 (60.82)	3.85 (3.88)	20.83 (20.87)	9.47 (9.54)	4.3(s)	7.5–7.7 (m, 5H)	9.5–9.7 (d)	—	—
3bx	$C_{17}H_{13}N_5O_2S$ (351.4)	67	151	57.88 (58.05)	3.57 (3.70)	19.85 (19.92)	9.08 (9.11)	4.3(s)	7.5–7.8 (m, 4H)	9.5–10.2 (d)	5.1 (s)	—
3cx	$C_{17}H_{13}N_5O_2S$ (351.4)	60	160	58.15 (58.05)	3.75 (3.70)	20.00 (19.92)	9.31 (9.11)	4.2(s)	7.5–7.8 (m, 4H)	9.5–10.2 (d)	5.3 (s)	—
3dx	$C_{18}H_{15}N_5O_2S$ (365.2)	70	137	59.12 (59.15)	4.08 (4.11)	19.15 (19.17)	8.73 (8.76)	4.4(s)	7.5–7.7 (m, 4H)	9.5–9.8 (d)	—	3.9 (s)
3ex	$C_{18}H_{15}N_5O_3S$ (381.2)	58	173	56.50 (56.66)	3.88 (3.93)	18.30 (18.36)	8.33 (8.40)	4.3(s)	7.5–7.8 (t, 3H)	9.5–9.7 (d)	5.2 (s)	3.7 (s)
3fx	$C_{17}H_{12}N_5OSCl$ (369.85)	50	188	55.10 (55.16)	3.20 (3.24)	18.87 (18.93)	8.61 (8.65)	4.3(s)	7.5–7.8 (m, 4H)	9.5–9.9 (d)	—	—
3gx	$C_{17}H_{12}N_6O_3S$ (380.4)	56	202	53.24 (53.63)	3.05 (3.15)	21.93 (22.08)	8.36 (8.41)	4.2(s)	7.5–7.8 (m, 4H)	9.5–9.85 (d)	—	—
3hx	$C_{17}H_{12}N_5O_2SBr$ (430.3)	64	196	47.40 (47.41)	2.77 (2.79)	16.14 (16.27)	7.42 (7.44)	4.3(s)	7.5–7.7 (t, 3H)	9.5–9.75 (d)	5.3 (s)	—

TABLE III Analytical and Spectral Data of Compounds (3a–h) (Where Ph = 4-Chloro-C_6H_4 in Scheme 1)

Compd.	Molecular formula (mol. wt.)	Yield	mp (°C)	Elemental analysis % C Found (Calcd.)	% H Found (Calcd.)	% N Found (Calcd.)	% S Found (Calcd.)	^{1}H NMR (δ, ppm) C_2—H of Oxadiazine	Ar—H	—CH=N of triazole	—OH	—OCH_3
3ay	$C_{17}H_{12}N_5OSCl$ (370.85)	60	141	54.75 (55.00)	3.74 (3.24)	18.24 (18.88)	8.62 (8.63)	4.3(s)	7.5–7.8 (m, 5H)	9.5–9.9 (d)	—	—
3by	$C_{17}H_{12}N_5O_2SCl$ (386.85)	57	148	53.24 (52.73)	3.37 (3.10)	18.04 (18.10)	8.27 (8.27)	4.3(s)	7.5–7.7 (m, 4H)	9.5–10.2 (d)	5.1 (s)	—
3cy	$C_{17}H_{12}N_5O_2SCl$ (386.85)	52	139	53.21 (52.73)	3.36 (3.10)	18.06 (18.10)	8.25 (8.27)	4.2(s)	7.5–7.8 (m, 4H)	9.5–10 (d)	5.2 (s)	—
3dy	$C_{18}H_{14}N_5O_2SCl$ (400.65)	63	171	54.05 (53.91)	3.24 (3.50)	17.23 (17.47)	7.98 (8.00)	4.3(s)	7.5–7.7 (m, 4H)	9.5–9.8 (d)	—	3.9 (s)
3ey	$C_{18}H_{14}N_5O_3SCl$ (416.65)	52	185	52.28 (51.84)	3.53 (3.36)	16.64 (16.80)	7.62 (7.68)	4.3(s)	7.5–7.7 (t, 3H)	9.5–9.7 (d)	5.3 (s)	3.8 (s)
3fy	$C_{17}H_{11}N_5OSCl_2$ (405.3)	48	192	50.30 (50.33)	2.94 (2.71)	17.13 (17.27)	7.88 (7.90)	4.3(s)	7.5–7.8 (m, 4H)	9.5–9.9 (d)	—	—
3gy	$C_{17}H_{11}N_6O_3SCl$ (415.85)	54	130	50.03 (49.06)	3.05 (2.65)	19.86 (20.2)	7.67 (7.70)	4.3(s)	7.5–7.8 (m, 4H)	9.5–9.8 (d)	—	—
3hy	$C_{17}H_{11}N_5O_2SClBr$ (465.75)	53	153	43.95 (43.80)	2.83 (2.36)	14.93 (15.03)	6.78 (6.87)	4.2(s)	7.5–7.7 (t, 3H)	9.5–9.7 (d)	5.3 (s)	—

TABLE IV Analytical and Spectral Data of Compounds (3a–h) (where Ph = 2,4-Di Chloro-C_6H_3 in Scheme 1)

Compd.	Molecular formula (mol. wt.)	Yield	mp (°C)	Elemental Analysis % C Found (Calcd.)	% H Found (Calcd.)	% N Found (Calcd.)	% S Found (Calcd.)	^{1}H NMR (δ , ppm) C_2—H of Oxadiazine	Ar—H	—CH═N of triazole	—OH	—OCH_3
3az	$C_{17}H_{11}N_5OSCl_2$ (406.28)	58	146	49.84 (50.21)	3.04 (2.71)	17.13 (17.23)	7.83 (7.88)	4.3(s)	7.5–7.7 (m, 5H)	9.5–9.7 (d)	—	—
3bz	$C_{17}H_{11}N_5O_2SCl_2$ (422.28)	60	152	48.23 (48.31)	3.08 (2.60)	16.47 (16.58)	7.53 (7.58)	4.2(s)	7.5–7.8 (m, 4H)	9.5–10.2 (d)	5.1 (s)	—
3cz	$C_{17}H_{11}N_5O_2SCl_2$ (422.28)	54	144	48.27 (48.31)	3.05 (2.60)	16.46 (16.58)	7.55 (7.58)	4.3(s)	7.5–7.7 (m, 4H)	9.5–10.2 (d)	5.3 (s)	—
3dz	$C_{18}H_{13}N_5O_2SCl_2$ (436.08)	67	176	50.13 (49.53)	3.00 (2.98)	15.85 (16.05)	7.33 (7.34)	4.4(s)	7.5–7.7 (m, 4H)	9.5–9.7 (d)	—	3.8 (s)
3ez	$C_{18}H_{13}N_5O_3SCl_2$ (452.08)	47	190	48.03 (47.78)	3.10 (2.88)	15.32 (15.48)	7.03 (7.08)	4.3(s)	7.5–7.8 (t, 3H)	9.5–9.8 (d)	5.2 (s)	3.7 (s)
3fz	$C_{17}H_{10}N_5OSCl_3$ (440.73)	45	198	46.75 (46.29)	2.33 (2.27)	15.63 (15.88)	7.25 (7.26)	4.2(s)	7.5–7.7 (m, 4H)	9.5–9.7 (d)	—	—
3gz	$C_{17}H_{10}N_6O_3SCl_2$ (451.28)	50	135	45.28 (45.20)	2.28 (2.22)	18.73 (18.61)	7.10 (7.09)	4.3(s)	7.5–7.8 (m, 4H)	9.5–9.75 (d)	—	—
3hz	$C_{17}H_{10}N_5O_2SCl_2Br$ (501.18)	57	158	41.20 (40.70)	2.13 (2.00)	13.87 (13.97)	6.35 (6.38)	4.3(s)	7.5–7.7 (t, 3H)	9.5–9.85 (d)	5.3 (s)	—

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

	Zone of inhibition				
	Gram +Ve		Gram –Ve		
Compounds	*Bacillus subtilis*	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Salmonella typhi*	*Escherichia coli*
3ax	05	06	04	06	08
3bx	09	08	06	08	12
3cx	10	09	07	09	13
3dx	07	06	05	07	09
3ex	11	10	08	10	12
3fx	15	13	09	14	15
3gx	12	11	09	12	13
3hx	14	12	10	13	14
3ay	07	05	04	02	02
3by	07	08	06	04	07
3cy	09	09	07	05	09
3dy	07	06	05	03	03
3ey	15	11	09	07	10
3fy	17	15	13	12	14
3gy	17	12	10	09	12
3hy	15	13	12	11	13
3az	05	07	05	04	06
3bz	09	11	11	08	09
3cz	12	12	10	09	07
3dz	10	09	07	05	04
3ez	12	13	11	10	09
3fz	19	21	14	13	18
3gz	16	15	12	11	10
3hz	18	19	13	14	16
Ampicillin	19	15	20	21	17

above microbes. Other compounds were found to be less or moderately active compared to ampicillin (Table V).

CONCLUSION

The synthesis of compounds 3-[4*H*-(1,2,4)-triazolyl]-2,6-diaryl-1,3,5-oxadiazine-4-thione (**3**) has been done successfully. Both the moieties 1,2,4-triazole and 1,3,5-oxadiazine have important applications in medicinal use; the compounds (**3**) produced may 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 Brucker 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 (2a–h)

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 in a water bath for 1–2 h. The solid that 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]-2,6-diaryl-1,3,5-oxadiazine-4-thione (3)

A mixture of 4-(arylidene-amino)-4*H*-[1,2,4]-triazole (2a–h) (0.01 mol), benzoyl isothiocyanate[22] (0.01 mol), and triethyl amine (three drops) in 1,4-dioxane (20 mL) was refluxed for 2 h. The separated solid that formed upon dilution with water (20 mL) was filtered, dried, and recrystallized from xylene to give yellow crystals of product (**3**). All the compounds were characterized by analytical and spectral data (Tables II, III, and IV).

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