Indian Journal of Heterocyclic Chemistry
Vol. 27 - Number 03 (Jul-Sep 2017) 269-274

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

Synthesis, Characterization and Antifungal Activity of 2-(Substituted-phenyl)-3-bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl amino-5-*H*-4-thiazolidinone Derivatives

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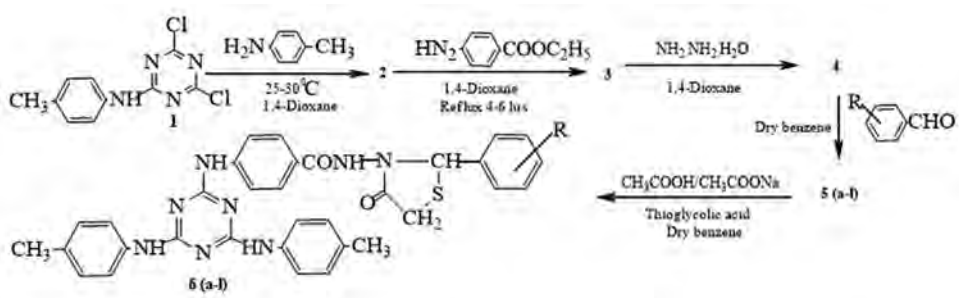
ABSTRACT A series of 4-thiazolidinone derivatives (**6a-l**) bearing s-triazine moiety has been prepared by the condensation of Schiff bases bis-2,4(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl-substituted-benzylhydrazones (**5a-l**) with thioglycolic acid. The structures of synthesized compounds have been characterized by infrared and ^{1}H nuclear magnetic resonance spectral data and elemental analyses. The synthesized compounds **(6a-l)** have been screened *in vitro* against *Aspergillus niger, Aspergillus flavus, Trichoderma viride, Candida albicans,* and *Fusarium oxysporum* for their antifungal activities.



KEYWORDS Antifungal activity, 4-Thiazolidinone, s-Triazine, Schiff base.

INTRODUCTION

Antibiotics are substances produced by one microorganism and kill or prevent the growth of another microorganism. The term antibiotic in today's common usage is used to refer the drug that attempts to rid your body of a microbial infection. Antimicrobials not only just include antibiotics but also synthetically formed compounds as well.

Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) a valuable dyestuff intermediate is obtained industrially by the vapor-phase polymerization of cyanogens chloride on charcoal with very reactive chlorine atoms and can be displaced readily by nucleophilic reagents.[1]

The literature survey reveals that 4-thiazolidinones bearing triazine moieties have a vast medicinal importance. This ring system is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[2] 4-thiazolidinones a saturated form of thiazole ring with carbonyl group on fourth carbon have been considered as a magic moiety

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or wonder nucleus which possesses almost all types of biological activities[3] such as anti-HIV,[4] anticonvulsant,[5] anticancer,[6] antitubercular,[7] cardioprotective,[8] anti-inflammatory,[9] antidiabetic[10] and antimicrobial.[11]

Thiazolidinones serve as backbone in the synthesis of various heterocyclic compounds. The presence of >C=N group is responsible for various biological activities[12-14] and can be altered depending on the type of substituents present on 4-thiazolidinones. Many of these compounds have been found to display from moderate to good biological activities[15] on screening for antibacterial and anti-tubercular activities.

The significance of this class of compounds encouraged us to continue investigations toward the antifungal activity evaluation of some thiazolidinones bearing triazine moiety.

RESULTS AND DISCUSSION

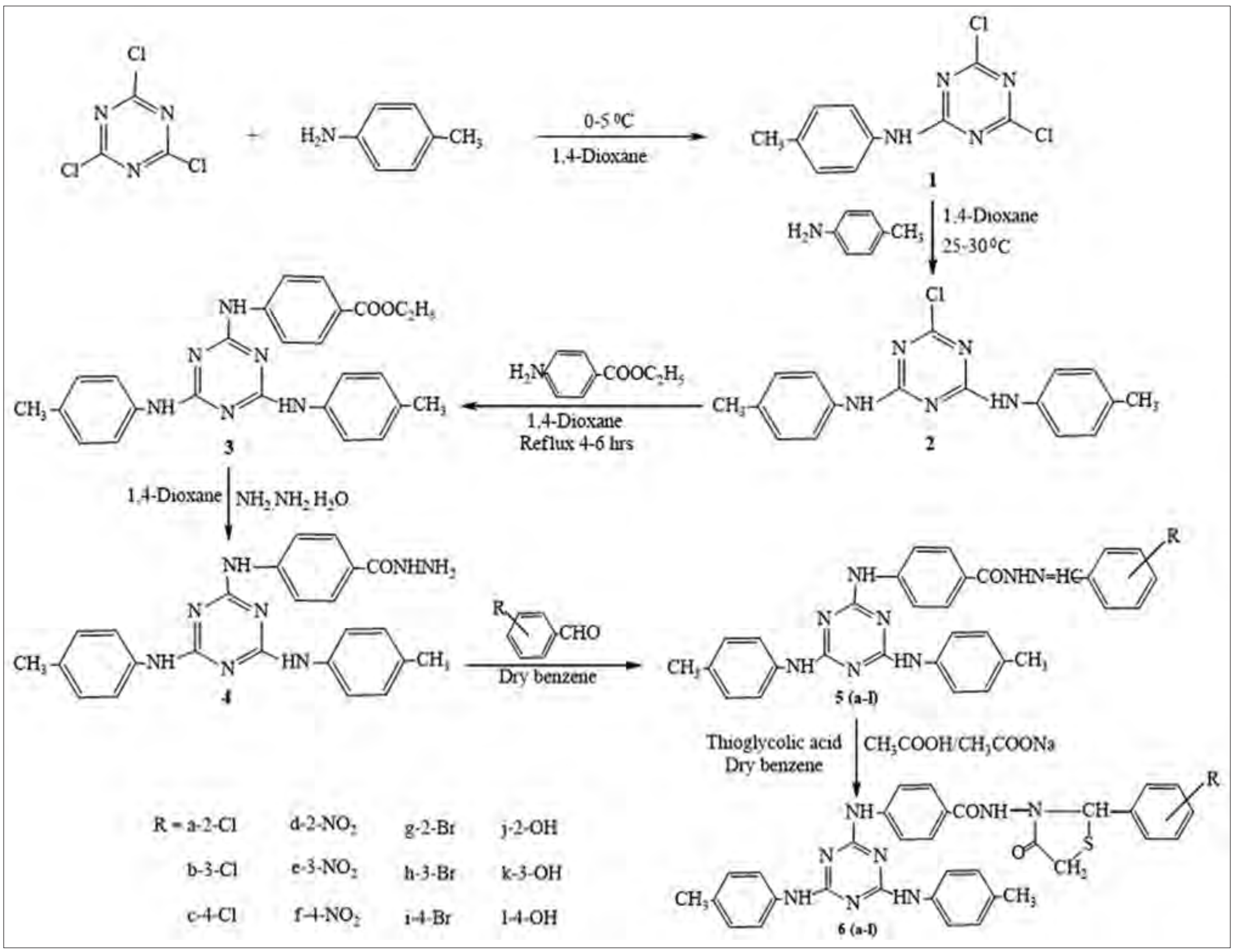
The reaction sequence for the synthesis of 3-((4,6-bis(p-tolylamino)-1,3,5-triazin-2-yl)amino)-N-(2-(4-substituted-phenyl)-4-oxothiazolidin-3-yl)benzamides **(6a-l)** has been depicted in **Scheme 1**.

Bis-2,4(4'-methylphenylamino)-s-triazine (**2**) was prepared by the reaction of cyanuric chloride and *p*-toluidine in 1,4-dioxane in two steps. The compound **2** was treated with ethyl *p*-aminobenzoate in 1,4-dioxane to give bis-2,4-(4-methylphenylamino)-s-triazine-6-yl-aminoethylbenzoate **(3)**. The compound **4** was prepared by the reaction of compound **3** with hydrazine hydrate. The compound **4** was condensed with various aromatic aldehydes to give Schiff bases **(5a-l)**, which on treatment with thioglycolic acid gave substituted-4-thiazolidinones **(6a-l)**. The structure of synthesized compounds was characterized by infrared (IR) and ^{1}H nuclear magnetic resonance (NMR) spectral data and elemental analyses. The physical and elemental analytical data of **(6a-l)** are summarized in **Table 1.**

Antifungal activity

The synthesized compounds have been screened for their antifungal activities using filter paper disc-diffusion plate method.[16-19] The testing was carried out at a concentration of 50 ppm and 100 ppm against fungal strains, namely, *Aspergillus niger, Aspergillus flavus, Trichoderma viride, Candida albicans*, and *Fusarium oxysporum* taking Nystatin as standard drug. Most of the compounds showed moderate activity 15-20 mm against different fungal strains (**Table 2**).

From the results, it is clear that compounds tested showed variable toxicity against different fungal strains. This variation in toxicity can be attributed to different structures and



Scheme 1

Table 1: Physical and elemental analysis data of compounds (6a-l)

Compound	Molecular formula	M. wt.	Yields %	m.p. (ºC)	Elemental analysis					
					C %		H %		N %	
					Calcd	Found	Calcd	Found	Calcd	Found
6a	$C_{33}H_{29}N_8O_2ClS$	637.145	72	146	62.12	62.11	4.58	4.56	17.58	17.55
6b	$C_{33}H_{29}N_8O_2ClS$	637.145	76	146	62.12	62.10	4.58	4.56	17.58	17.56
6c	$C_{33}H_{29}N_8O_2ClS$	637.145	74	146	62.12	62.09	4.58	4.55	17.58	17.55
6d	$C_{33}H_{29}N_9O_4S$	647.682	68	142	61.10	61.08	4.5	4.3	19.46	19.43
6e	$C_{33}H_{29}N_9O_4S$	647.682	69	142	61.10	61.09	4.5	4.3	19.46	19.44
6f	$C_{33}H_{29}N_9O_4S$	647.682	78	142	61.10	61.08	4.5	4.4	19.46	19.4
6g	$C_{33}H_{29}N_8O_2BrS$	681.595	75	147	58.15	58.13	4.28	4.25	16.44	16.42
6h	$C_{33}H_{29}N_8O_2BrS$	681.595	71	147	58.15	58.12	4.28	4.25	16.44	16.41
6i	$C_{33}H_{29}N_8O_2BrS$	681.595	73	147	58.15	58.12	4.28	4.25	16.44	16.41
6j	$C_{33}H_{30}N_8O_3S$	618.693	77	129	64.06	64.03	4.88	4.86	18.11	18.09
6k	$C_{33}H_{30}N_8O_3S$	618.693	71	129	64.06	64.04	4.88	4.87	18.11	18.09
6l	$C_{33}H_{30}N_8O_3S$	618.693	78	129	64.06	64.03	4.88	4.86	18.11	18.08

Table 2: Antifungal activities of compounds (6a-l)

Compound	Concentration (ppm)									
	A. niger		*A. flavus*		*T. viride*		*C. albicans*		*F. oxysporum*	
	50	100	50	100	50	100	50	100	50	100
6a	+++	++++	+++	++++	++	+++	+	++	+++	++++
6b	+++	++	++	+++	++	+++	++	+++	+++	++++
6c	+++	+++	++++	+++	+	+++	+++	+++	+++	++
6d	++	++	+	+	+	++	+	++	-	-
6e	++	+++	++	+++	++	+++	++	+++	++	+++
6f	++	+++	++	++	+++	+++	+++	++	+++	++
6g	-	+	+	+	+	++	-	-	+	++
6h	++	+++	++	+++	++	+++	++	+++	++	+++
6i	++	+++	++	+++	++	+++	++	+++	++	+++
6j	++	+++	+	++	+	++	++	+++	++	+++
6k	++	+++	++	+++	+++	+++	++++	++	++++	+++
6l	++	+++	++	+++	++	+++	++	+++	++	+++
Std.	+++	++++	++++	++++	+++	++++	+++	++++	+++	++++

Std.: Nystatin is used as standard drug, diameter of zone of inhibition in mm: The key of sign, ++++: Zone of inhibition >20 mm (strong activity), +++: Zone of inhibition >15 mm (good activity), ++: Zone of inhibition >10 mm (moderate activity), +: Zone of inhibition >5 mm (weak activity), -: Inactive, *A. niger: Aspergillus niger, A. flavus: Aspergillus flavus, T. viride: Trichoderma viride, C. albicans: Candida albicans, F. oxysporum: Fusarium oxysporum*

functional groups attached to the basic nucleus. The results of the tests as the antifungal activities indicate that when an electron-withdrawing group such as chloro, nitro, and electron-donating group like hydroxyl is attached to the phenyl ring at the 4-thiazolidinone moiety, these compounds showed very good activity against all fungal species tested. It is also clear from the results as presented in **Table 2** that in the compounds **6a, 6b, 6c, 6e,** and **6k,** the antifungal activity was increased.

EXPERIMENTAL SECTION

Materials and methods

All chemicals of analytical grade were purchased from Sigma-Aldrich and used without further purification. The melting points of compounds have been determined in an open capillary tube and are uncorrected. The completion of reactions was monitored on TLC. The IR and ^1H NMR spectra were recorded on a Shimadzu 8201 PC and AVANCE II 400 NMR spectrometer. Elemental analysis was carried out on a Carlo Elba 1108 model analyzer.

2-(4'-Methylphenylamino)-s-triazine (1)

p-Toluidine (0.01 mol) was added slowly into cyanuric chloride (0.01 mol) using 1,4-dioxane (30 ml) with stirring for 4 h at 0-5°C. Then, sodium carbonate (0.005 mol) in water (10 ml) was used drop wise to neutralize evolved HCl during the reaction. Finally, the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried, and recrystallized from 1,4-dioxane. Molecular formula (1) $C_{10}H_8Cl_2N_4$; m. p. 196°C; yield 86%; elemental analysis data found (required %) C = 47.00 (47.08), H = 3.12 (3.16), Cl = 27.76 (27.80), N = 21.91 (21.96); IR absorption frequencies in KBr (cm^{-1}) 2950 (C-H), 3105 (Ar-H), 1465 (C=N), 804 (C-N) 3366 (N-H), 1680 (C=O). ^1H NMR ($CDCl_3$, δ), 2.36 (s CH_3) 4.25 (s C-NH), 7.15 (d, C=C aromatic), 7.26 (d, C=C aromatic).

Bis-2,4-(4'-methyl-phenyl-amino)-s-triazine (2)

p-Toluidine (0.01 mol) was added slowly to compound 1 (0.01 mol) in 1,4-dioxane (35 ml) with constant stirring for 6 h at room temperature. Then, sodium carbonate (0.005 mol) dissolved in water (10 ml) was added drop wise to neutralize HCl evolved during the reaction. Finally, the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried, and recrystallized from 1,4-dioxane. Molecular formula (2) $C_{17}H_{16}ClN_5$; m. p. 179°C; yield 80%; elemental analysis data found (required %) C = 62.64 (62.67), H = 4.94 (4.95), Cl = 10.85 (10.88) N = 21.47 (21.50); IR absorption frequencies in KBr (cm^{-1}) 2950 (C-H), 3105 (Ar-H), 1465 (C=N), 804 (C-N) 3366 (N-H), 1680(C=O). ^1H NMR ($CDCl_3$, δ), 2.36 (s CH_3) 4.25 (s C-NH), 7.15 (d, C=C aromatic), 7.26 (d, C=C aromatic).

Bis-2,4-(4'-methylphenylamino)-s-triazin-6-yl-aminoethyl benzoate (3)

Ethyl *p*-aminobenzoate (0.01 mol) and compound **2 (**0.01 mol) were dissolved in 1,4-dioxane (40 ml). The reaction mixture was refluxed for 6 h, cooled, and poured into crushed ice. Then, reaction mixture was basified with aqueous solution of sodium carbonate. The solid separated out was filtered, washed with water, dried, and recrystallized from 1,4-dioxane. Molecular formula $C_{26}H_{26}N_6O_2$; m. p. 219°C; yield 78%; elemental analysis data found (required %) C = 68.60 (68.70), H = 5.66 (5.77), N = 18.39 (18.49), O = 6.84 (7.04); IR absorption frequencies in KBr (cm^{-1}) 2956 (C-H), 3102 (Ar-H), 1470 (C=N), 806 (C-N) 3362 (N-H), 1680 (C=O); ^1H NMR ($CDCl_3$, δ), 6.40 (sym. multi., 8H, $2CH_3$ subs.benzene ring), 7.45 (s, 4H, N-H sub. benzene ring) 2.38 (s, $2CH_3$, 6H), 10.01 (s, NH), 2.33 (s, CH_3), 3.04 (t, CH_2).

Bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl hydrazone (4)

A mixture of compound **3 (**0.01 mol) in 1,4-dioxane and hydrazine hydrate (0.01 mol), was refluxed on a water bath for 6 h. The product was isolated with HCl and crystallized from 1,4-dioxane. Molecular formula $C_{24}H_{24}N_8O$; m. p. 198°C; yield 79%; elemental analysis data found (required %) C = 65.34 (65.44), H = 5.49 (5.93), N = 25.34 (25.38), O = 3.53 (3.63); IR absorption frequencies in KBr (cm^{-1}), 2908 (C-H), 3056 (Ar-H), 1498 (C=N), 807 (C-N), 3356 (N-H), 1670 (C=O); ^1H NMR ($CDCl_3$, δ), 6.40 (sym. multi., 8H, $2CH_3$ subs.benzene ring), 7.45 (s, 4H, N-H sub. benzene ring) 2.38 (s, $2CH_3$, 6H), 10.01 (s, NH), 4.33 (t, NH), 4.04 (d, NH_2).

Bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl-substituted benzyl hydrazones (5)

A mixture of compound **4 (**0.01 mol) and substituted aldehyde (0.01 mol) in 1,4-dioxane (15 ml) was refluxed for 4 h. The solid product was isolated by filtration and crystallized from methanol. Molecular formula (5a) $C_{31}H_{28}N_8O$; m. p. 150°C; yield 78%; elemental analysis data found (required %) C = 70.34 (70.44), H = 5.22 (5.34), N = 21.17 (21.20), O = 2.92 (3.02); IR absorption frequencies in KBr (cm^{-1}) 2985 (C-H), 3056 (Ar-H), 3399 (N-H), 1420 (C=N), 1675 (C=O), 805 (C-N); ^1H NMR ($CDCl_3$, δ), 6.45 (Sym. multi. $2CH_3$ subs. Benzene ring 8H), 7.68 (S, 4N-H, 4H), 2.38 (s, $2CH_3$, 6H), 1.95 (s, C-H of thiazolidinone), 6.31 (sym. multi. N-H subs. benzene ring).

2-Substituted-phenyl-3-bis-2,4-(4'-methylphenylamino)-s-triazine-6-ylaminobenzoyl-amino-5-H-4-thiazolidinones (6)

Thioglycolic acid (0.01 mol) was added to compound **5 (**0.01 mol) in dry benzene (20 ml), and the mixture was refluxed for 6 h. The product was isolated from the upper organic layer by washing with water and sodium bicarbonate solution and subsequently crystallized from 1,4-dioxane. Molecular formula (6a) $C_{33}H_{29}ClN_8O_2S$; m. p. 146°C; yield 76%; elemental analysis data found (required %) C = 62.11 (62.12), H = 4.56 (4.58), Cl = 7.35 (7.25), N = 17.55 (17.58), O = 3.31 (3.22), S = 3.18 (3.20); IR absorption frequencies in KBr (cm^{-1}), 3456 (N-H, 3095 (Ar-H), 1602 (C=C), 1675 (C=O), 750 (C-S), 1306 (C=N), 802 (C-N) 675 (Ar-Cl); ^1H NMR ($CDCl_3$, δ), 6.40 (sym. multi., 8H, $2CH_3$ subs.benzene ring), 7.45 (s, 4H, N-H sub. benzene ring) 2.38 (s, $2CH_3$, 6H).

ACKNOWLEDGMENTS

One of the authors is thankful to SAIF, CDRI Lucknow, U.P., for providing ^1H NMR spectra and also thankful to head of the department of botany for assistance in performing antifungal activity screening and head of the department of Chemistry, Dr. Hari Singh Gour University, Sagar (M.P.), for providing IR spectral data and laboratory facilities.

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Received: 24 May 2017 Accepted: 06 Sep 2017