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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 6,7-BIS[3-(4-SUBSTITUTED PHENYL)-4-OXO-THIAZOLIDIN-2-YLIDENE AMINO]QUINOXALINE-2,3 (1*H*,4*H*)-DIONES

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ABSTRACT

6,7-Diaminoquinoxaline-2,3(1*H*,4*H*)-dione **(1)** on treatment with substituted aromatic iso-thiocyanate yielded 6,7-bis[3'-aryl thiocarbamido]-quinoxaline-2,3(1*H*,4*H*)-diones **(2a-e),** which on cyclisation with monochloroacetic acid in presence of anhydrous sodium acetate and glacial acetic acid afforded 6,7-bis[3-(4-substitutedphenyl)-4-oxothiazolidin-2-ylideneamino]quinoxaline-2,3 (1*H*, 4*H*)-diones **(3a-e)**. The constitution of the synthesized compounds is supported by IR, ^{1}H NMR, Mass and elemental analysis. The compounds were subjected to preliminary *in vitro* evaluation for antibacterial activity against various Gram-positive bacterial strains *Staphyllococus aureus*, *Bacillus cereus* and Gram-negative strain *Pseudomonas aeuroginosa,*

Key words: Synthesis, Quinoxaline-2,3(1*H*,4*H*)-diones, Antibacterial activity

INTRODUCTION

In continuation of earlier work on quinoxaline-2,3-dione derivatives, in present work, we report the synthesis and antibacterial activity of 6,7-bis[3-(4-substitutedphenyl)-4-oxothiazolidin-2-ylideneamino]quinoxaline-2,3(1*H*,4*H*)-diones.

Quinoxalines and their heterocyclic products are one of the interesting systems reported in literature. It is well documented that quinoxaline derivatives possess antimicrobial[1], antifungal[2], tuberculostatic[3,4], antiviral[5] and anticancer[6,7] activities. Literature also reveals that N-alkyl/substituted phenyl/ heteroaryl thiocarbamides possess a broad spectrum of activity. They have specific bactericidal[8], fungicidal[9], anthelmentic[10], and anti-tumor[11] activity. Moreover, 2-imino-4-thiazolidinone derivatives find their applications as bacteriostatic[12], fungicidal[13], anticonvulsant[14] and anti-tumor agents[15].

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Keeping in view the clinical significance of quinoxalines, 2-imino-4-thiazolidinones and substituted thiocarbamides in present work, we report the synthesis and antibacterial activity of 6,7-bis[3-(4-substitutedphenyl)-4-oxothiazolidin-2-ylideneamino]quinoxaline-2,3(1*H*,4*H*)-diones.

EXPERIMENTAL

All the melting points of the synthesized compounds were recorded in open capillary tube using liquid paraffin bath and are uncorrected. IR spectra (cm^{-1}) were recorded in KBr disc on Perkin Elmer RXI-FTIR system. The ^1H NMR spectra were recorded on Bruker AC-300F NMR spectrometer (300MHz) using $CDCl_3$ / DMSO-d_6 as solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were obtained by Jeol SX 102/DA-6000 mass spectrometer. All the compounds gave satisfactory elemental analysis and the purity of synthesized compound was checked by thin layer chromatography.

The reaction sequence leading to formation of title compounds is outlined in **Scheme 1**. The title compounds **(3a-e)** have been synthesized by cyclization of 6,7-bis[3'-aryl thiocarbamido]-quinoxaline-2,3 (1*H*,4*H*)-diones **(2a-e)** with monochloro acetic acid in presence of anhydrous sodium acetate and glacial acetic acid. 6,7-Bis[3'-aryl thiocarb amido]-quinoxaline-2, 3 (1*H*, 4*H*)-diones have been synthesized by the reaction between 6,7-diaminoquinoxaline-2, 3(1*H*, 4*H*)-dione and substituted aromatic isothiocyanates in methanol.

The structures of the synthesized compounds were determined by IR, ^1H NMR, Mass and elemental analysis. The physical data and antibacterial activity data of compounds **(2a-e)** and **(3a-e)** are recorded in Tables 1 and 2, respectively.

Antibacterial activity

All the synthesized compounds **(2a-e)** and **(3a-e)** were screened *in vitro* for their antibacterial activity against Gram positive bacterial strains *Staphylococcus aureus* and *Bacillus cereus*, Gram negative bacterial strain *Pseudomonas aeruginosa* at concentrations 20 to 80 μg/mL by well diffusion method using DMF as solvent control and nutrient agar was employed as culture media. After 24 hours of incubation at

37ºC, the zones of inhibition were measured in mm. The activity was compared with known antibiotic Ciprofloxacin and the data are represented in Table 2. All the compounds showed moderate activity against Gram positive strains while weak to

moderate activity was observed against Gram negative strain at higher concentrations. Compounds **(2b)** and **(3e)** showed highest activity against *B. cereus*. However, the activities of the tested compounds were less than that of standard antibacterial agent used.

Synthesis of 6,7-bis[3'-phenylthiocarbamido]-quinoxaline-2,3(1*H*,4*H*)-dione (2a)

A mixture of 6,7-diaminoquinoxaline-2,3(1*H*,4*H*)-dione (0.01 mole) and phenyl isothiocyanate (0.02 mole) in methanol (50 mL) was refluxed on a water bath for 3 hours. The reaction was monitored by TLC using benzene-acetone (3 : 1) as eluent. After completion of reaction, the reaction mixture was then cooled, and the separated crystalline solids was filtered, dried and recrystallized from ethanol / acetic acid mixture to give pure **(2a).**

Similarly, the other compounds of the series were prepared and the physical data are given in Table 1.

Table 1. Physical and chemical data of compounds (2a-e) and (3a-e)

Comp.	R	M.P. (ºC)	Yield (%)	Molecular formula	Mol. weight	N (%) found (Calcd.)	S (%) found (Calcd.)
(2a)	H-	326	70	$C_{22}H_{18}N_6O_2S_2$	463	18.17 (18.20)	13.86 (13.88)
(2b)	Cl-	278	68	$C_{22}H_{16}N_6O_2S_2$	531	15.81 (15.89)	12.07 (12.11)
(2c)	Br-	190	72	$C_{22}H_{16}Br_2N_6O_2S_2$	620	13.55 (13.58)	10.34 (10.32)
(2d)	H_3C-	264	76	$C_{24}H_{22}N_6O_2S_2$	491	17.13 (17.21)	13.07 (13.09)
(2e)	CH_3O-	307	65	$C_{24}H_{22}N_6O_4S_2$	523	16.08 (16.13)	12.27 (12.31)
(3a)	H-	294	72	$C_{26}H_{18}N_6O_4S_2$	543	15.49 (15.51)	11.82 (11.90)
(3b)	Cl-	187	70	$C_{26}H_{16}N_6O_4S_2$	611	13.74 (13.81)	10.49 (10.44)
(3c)	Br-	216	68	$C_{26}H_{16}Br_2N_6O_4S_2$	700	12.00 (12.05)	09.16 (9.19)

Comp.	R	M.P. (ºC)	Yield (%)	Molecular formula	Mol. weight	N (%) found (Calcd.)	S (%) found (Calcd.)
(3d)	CH_3-	214	72	$C_{28}H_{22}N_6O_4S_2$	571	14.73 (14.76)	11.24 (11.30)
(3e)	CH_3O-	191	70	$C_{28}H_{22}N_6O_6S_2$	603	13.95 (14.01)	10.64 (10.69)

(2a) IR (KBr) cm^{-1}: 1255 (C=S), 1602 (C=C Ar), 1699 (CO-NH), 3030 (C-H str.), 3188(NH str.); ^{1}H NMR (DMSO): δ 2.50 (impurity in DMSO), 3.34 (s, 4H, -NH- thiocarb amidle), 6.90 – 7.56 (m, 12H, Ar-H), 9.85 (s, 2H, -NH-CO-quinoxaline ring); MS m/z (%) : 103 (5.2), 117 (10.2), 194 (15.7), 195 (5.2), 196 (2.6), 227 (5.2), 241 (5.2), 268 (21), 344 (10.5), 376 (5.2), 391 (100; base peak), 404 (10.5), 420 (15.7), 434 (10.5), 447 (15.7), 463 (10.5; M^+).

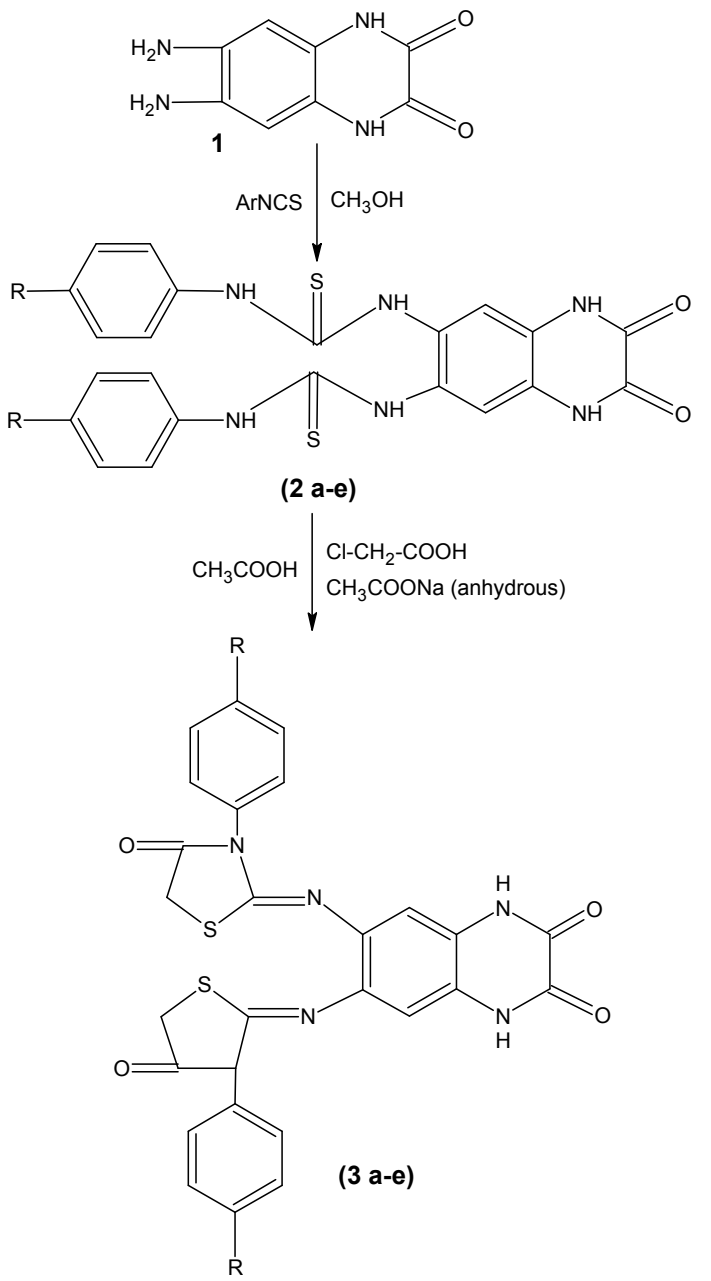
(2b) IR (KBr) cm^{-1}: 1276 (C=S), 1596 (C=C Ar), 1701 (CO-NH), 3049 (C-H str.), 3234 (NH str.);^{1}H NMR (DMSO): δ 2.50 (impurity in DMSO), 3.34 (s, 4H, -NH-thiocarbamidle), 7.25 – 7.96 (m, 10H, Ar-H), 9.92 (s, 2H, -NH-CO-quinoxaline ring); MS m/z (%) : 201 (49), 202 (100; base peak), 203 (28), 204 (38), 218(06), 242 (06), 226 (03), 294 (11), 312 (7), 368 (33), 396 (7), 426 (11), 448 (20), 498 (7), 511 (18), 531 (21;M^+).

Synthesis of 6,7-bis[4-oxo-3-phenylthiazolidin-2-ylideneamino] quinoxaline -2, 3 (1*H*, 4*H*) - dione (3a): Compound 6,7-Bis[3'-phenylthiocarbamido]-quinoxaline-2,3(1*H*,4*H*)-dione (0.01 mole), monochloroacetic acid (0.022 mole) and anhydrous sodium acetate (0.03 mole) were mixed with glacial acetic acid (50 mL) and the reaction mixture was refluxed for a period of 5 hours, during which it gave a clear solution. After cooling it was poured in ice-cold water. The solid precipitated was filtered, washed with cold water and recrystallized from acetic acid to get pure **(3a).**

Similarly, the other compounds of the series were prepared and the physical data are given in Table 1.

(3a) IR (KBr) cm^{-1}: 1485 (C=C, Ar.), 1541 (C=O), 1602 (C=N), 3026 (C-H str.), 3390 (NH, str.); ^{1}H NMR (DMSO): δ 2.50 (impurity in DMSO), 3.34 (s, 4H, -CH_2 thiazolidine ring), 6.90–7.56 (m, 12H, Ar-H), 9.85 (s, 2H, -NH-CO-quinoxaline ring); MS m/z (%) : 104 (8.5), 118 (8.5), 194 (5.7), 227 (2.8), 239 (2.8), 254 (2.8), 268 (91.4), 269

(100; base peak), 282 (2.8), 296 (2.8), 311 (1.4), 324 (1.4), 338 (2.8), 352 (2.8), 378 (2.8), 392 (14.2), 405 (28.8), 422 (20), 498 (1.4), 511 (2.8), 542 (2.8), 543 (5.7 ; M^+),



Scheme 1

(3b) IR (KBr) cm^{-1}:1502 (C=C Ar.), 1544 (C=O), 1589 (C=N), 3010 (C-H str.), 3195 (NH str.) ; ^1H NMR (DMSO):δ 2.50 (impurity in DMSO), 3.34 (s, 4H, -CH_2 thiazolidine ring), 7.36-7.58 (m, 10H, Ar-H), 9.72 (s, 2H, -NH-CO-quinoxaline ring); MS m/z (%) : 296 (10), 311 (10.5), 332 (12), 378 (16), 396 (5), 412(18), 466 (10), 482 (100; base peak), 524 (24), 576 (10), 611 (33; M^+).

RESULTS AND DISCUSSION

Table 2 shows the *in vitro* antibacterial activity data, all the compounds showed moderate to high activity against *Staphylococcus aureus* and *Bacillus cereus* while weak to moderate activity was observed against *Pseudomonas aureginosa*. The compounds **(2b)** and **(3e)** were highly active against *Bacillus cereus*, compound **(2b)** was highly active whereas compounds **(2e)**, **(2c)** and **(2a)** were moderately active against *Staphylococcus aureus***,** compounds **(2b)** and **(3e)** was moderately active against *Pseudomonas aureginosa,* while the rest of the compounds displayed weak activity against all organisms. However, the activities of the tested compounds are less than that of standard antibacterial agent used.

Table 2. Antibacterial activity of compounds (2a-e) and (3a-e)

Compound	Concentration (μg /mL)	*S. aureus*	*B. cereus*	*P. aeruginosa*
		Zone of inhibition (mm)		
(2a)	20	14	13	--
	40	15	16	--
	60	16	16	9
	80	17	17	12
(2b)	20	15	15	--
	40	19	17	--
	60	19	15	12
	80	24	19	16
(2c)	20	14	15	--
	40	15	15	--

Cont…

Compound	Concentration (μg /mL)	*S. aureus*	*B. cereus*	*P. aeruginosa*
		Zone of inhibition (mm)		
	60	14	17	12
	80	18	18	14
(2d)	20	12	10	--
	40	13	12	--
	60	15	15	11
	80	16	16	13
(2e)	20	12	9	--
	40	10	16	--
	60	14	16	12
	80	18	18	14
(3a)	20	8	--	--
	40	11	10	--
	60	12	13	9
	80	13	15	10
(3b)	20	--	--	--
	40	--	9	--
	60	10	10	9
	80	16	12	8
(3c)	20	11	9	--
	40	11	14	--
	60	12	17	10
	80	14	18	12
(3d)	20	9	9	--
	40	11	12	--
	60	13	13	10

Cont…

Compound	Concentration (μg /mL)	*S. aureus*	*B. cereus*	*P. aeruginosa*
		Zone of inhibition (mm)		
(3e)	80	14	14	11
	20	10	10	--
	40	11	15	--
	60	12	16	12
Ciprofloxacin	80	15	21	15
	20	21	23	20
	80	25	26	24
***DMF* (control)**		--	--	--

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