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Synthesis, spectral characterization and biological studies on new benzothiazoles as antimicrobial agents

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Abstract

A series of 2-[2,4-bis(aryl/alkylamino)thiazol-5-oyl]benzothiazole derivatives were synthesized from 1-aryl-3-(N,N'-diarylamidino)thioureas and 2-(2-bromoacetyl)benzothiazole with triethylamine. Their structures were established on the basis of IR,^{1}H NMR, ^{13}C NMR and mass spectral analyses. All the synthesized compounds were screened for their antibacterial and antifungal potential. All the compounds showed significant activity against the microorganisms tested.

Keywords: benzothiazole, triethylamine, antibacterialactivity, antifungal activity

Introduction

It is well-known fact that infectious microorganisms, i.e. bacteria and fungi, cause serious diseases and responsible for nearly one-half of the deaths in India. Marine Organisms are known to contain several pharmacologically active compounds [13]. A few marine natural products or their synthetic analogs are in clinical use or at various stages of drug development. Many alkaloids are derived from marine organisms such as sponges, coelenterates, tunicates (ascuiduians), bryosoans, red algae and symbiotic bacteria. Many of them have been reported to have antitumor (Aiello *et al*; 2008) [1], antimicrobial (sareen *et al*; 2006) [9], antileishmaial (Delmas *et al*, 2004) [2], anticonvalsant (Ugale *et al*, 2012) [11], antidiabetic (pattan *et al*, 2005) [8], and anti-inflammatory (Venkatesh and pandeya, 2009) activities [12]. In the light of literature survey, these compounds posses benzothiazole unit having a useful pharmacophore moiety and exhibit anti-cancer, anti-inflammatory, anti-bacterial, anti fungal, anti-tubercular, and anti oxidant activities [4]. For this study we have prepared novel derivatives of bis aryl aminothiazol oyl benzothiazoles 3 a-h (see Table 3). In addition, the benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities [5]. Due to their importance in pharmaceutical utilities, the synthesis of various benzothiazole derivatives is of considerable interests. All the synthesized compounds were screened for their antibacterial and anti fungal activities.

2. Experimental

2.1 Material and methods

The reagents and solvents used were of AR grade. All chemicals were purchased from merck specialities pvt. Ltd. and Himedia. Laboratories pvt. Ltd.

The spectra were recorded on JEOL DRX 300 or DPX 300 NMR spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using argon/ xenon, 6 kV, Ma as the FAB gas and m-nitro-benzyl alcohol as the matrix) for FAB mass spectra and Nicolet 400D FTIR spectrometer. Melting points were uncorrected. Elemental analysis was done at the Central Drug Research Institute, India.

2.2 General procedure for the synthesis of 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles 3a-h

The reaction sequences employed for the synthesis of title compounds are shown in Fig 1. 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles 3a-h were prepared accordind to the following method (Abbs Fen Reji *et al*., 2009).

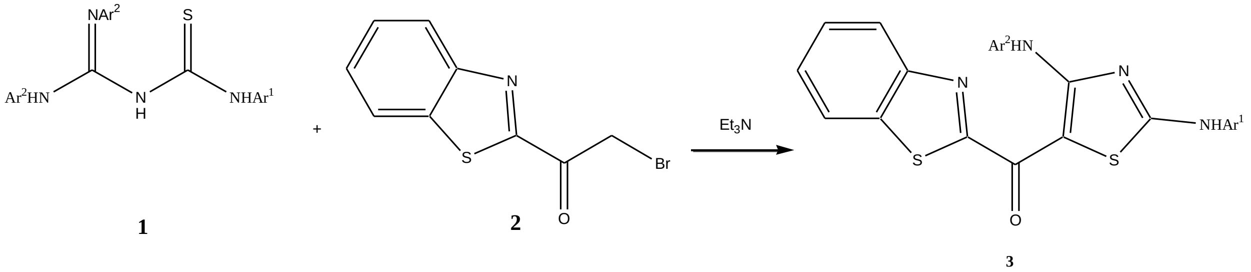

Fig 1: synthetic route of molecules 3

A solution of 1-aryl-3-(N,N’-diarylamidino)thiourea (1 mmol) in DMF (2Ml) was added to a solution of 2-(2-bromoacetyl)benzothiazole **2 (**0.254g, 1m mol), which was prepared from 2-(1-hydroxyethyl)benzothiazole (Sawhney and singh, [10]1970; Gupta *et al*, 1980[3]; Joshua and Rajasekharan,[7] 1974; Hunter, [6] 1925a,b, 1926) in DMF (2ml). The reaction mixture was stirred well and triethylamine (0.15 ml, 1mmol) was added. The reaction mixture was warmed at 35-40◦c for 10min. It was then cooled and poured into ice-cold water with constant stirring. A yellowish orange precipitate thus obtained was filtered, washed with water and dried. The crude product was crystallized from methanol: water (2:1) and then from benzene: petroleum ether (1:1) to give a yellowish orange crystalline solid.

2.3 2-[2,4-bis(phenylamino)thiazol-5-oyl]benzothiazole 3a

This was prepared and purified as per the above mentioned procedure. Yield 65%, m.p. 235-38◦C Analysis: Found: C,64.31; H, 3.85; N, 13.25%; Calc. for $C_{23}H_{16}N_4OS_2$ (428.52): C64.46; H, 3.76; N, 13.08%; IR(KBr)cm^{-1} : 3433, 3272, 3198, 3048, 1626, 1600, 1562, 1485, 1445, 1414, 1324, 1268, 912, 757, 690 ; ^{1}H NMR: (300 MHz, DMSO-d6) δ 7.11-7.23 (m, 2H, 2ArH); 7.38-7.50 (m, 4H, 4ArH); 7.53-7.72 (m, 4H, H-5, H-6, 2ArH); 7.77 (d, 8.1Hz, 2H, 2ArH); 8.12 (d, 7.8Hz, 1H, H-4); 8.23 (d, 7.8Hz, 1H, H-7); 11.85 (s, 1H, NH). ^{13}C NMR; (75 MHz, DMSO-d6) δ; 91.1, 119.7, 120.1, 122.8, 123.7, 123.9, 124.3, 126.8, 127.0, 129.0, 135.9, 138.7, 138.9, 152.8, 163.6, 169.6, 170, 6, 172.1; FABMS: 429(MH$^+$).

2.4 2-(2-chloroamino-4-phenylaminothiazol-5-oyl) benzothiazole 3b

This was prepared and purified as per the above mentioned procedure. Yield 70%, m.p. 265-67◦C Analysis: Found: C,52.243; H, 2.643; N, 14.65%; Calc. for $C_{17}H_{11}ClN_4OS_2$ (386.91): C,52.774; H, 2.8714; N, 14.484%; IR(KBr)cm^{-1} :3441, 3133, 2359, 1640, 1549, 1401, 703, 663, 393; ^{1}H NMR: (300MHz, CdCl$_3$) δ ; 8.251 (s, 1H); 7.440-7.207 (m, 10H); 7.957 (s, 1H).

2.5 2-(2-methylamino-4-phenylaminothiazol-5-oyl) benzothiazole 3c

This was prepared and purified as per the above mentioned procedure. Yield 68%, m.p. 241-43◦ CAnalysis: Found: C, 58.543;H,3.786;N,15.123%;Calc.for$C_{18}H_{14}N_4OS_2$(366.49):C5 8.990;H,3.858;N,15.2900%;IR(KBr)cm^{-1}: 3331, 3007, 2856, 2923, 1807, 1740, 1649, 1589, 1500, 1461, 1355, 1266, 1182, 1165, 1081, 1048, 998, 914, 880, 763, 730, 702 ; ^{1}H NMR: (300MHz, CdCl$_3$) δ; 8.108 (s, 2H); 7.531 (s, 1H); 7.321 (d, J= 7.2Hz, 3H); 7.066 (d, J= 7.8Hz, 3H); 2.928 (s, 3H); 2.529 (t, J= 1.8Hz, 2H).

2.6 2-(2-methoxyamino-4-phenylaminothiazol-5-oyl) benzothiazole 3d

This was prepared and purified as per the above mentioned procedure. Yield 65%, m.p. 236-38◦C Analysis: Found: C,58.543;H,3.786;N,15.123%; Calc. for $C_{18}H_{14}N_4O_2S_2$ (366.498): C58.990;H,3.858;N,15.2900% ;IR(KBr)cm^{-1}:3424, 3132, 2358, 1617, 1562, 1490, 1401, 1211, 1087, 1020, 819, 756, 724, 501; ^{1}H NMR: (300MHz, CdCl$_3$) δ : 7.392.7.348 (m, 1H); 7.260 (s, 1H); 7.16 (d, J= 6.3Hz, 1H); 3.627-3.578 (m, 1H); 1.584-1.510 (m, 2H) ; 1.369-1.295 (m, 2H); 0.916 (t, J= 5.4Hz, 3H).

2.7 2-(2-ethoxyamino-4-phenylaminothiazol-5-oyl) benzothiazole 3e

This was prepared and purified as per the above mentioned procedure. Yield 70%, m.p. 257-59◦C Analysis: Found: C,57.342; H, 4.065; N, 14.322%; Calc. for $C_{19}H_{15}N_4O_2S_2$ (396.52): C57.551; H, 4.0753;N,14.1326%;IR(KBr)cm^{-1}:3063, 2985, 2923, 2851, 2773, 2555, 2376, 2170, 2114, 1902, 1874, 1835, 1740, 1690, 1606, 1506, 1439, 1411, 1299, 1249, 1171, 1120, 1048, 919, 825, 802, 763, 707 ; ^{1}H NMR: (300MHz, CdCl$_3$) δ: 7.418-6.855 (m, 13H); 4.047-3.978 (m, 1H); 1.435-1.377 (m, 2H).

2.8 2-(2-ethylamino-4-phenylaminothiazol-5-oyl) benzothiazole 3f

This was prepared and purified as per the above mentioned procedure. Yield 70%, m.p. 248-50◦C Analysis: Found: C,59.543; H, 4.121; N, 14.564%; Calc. for $C_{19}H_{16}N_4OS_2$ (380): C59.971; H, 4.246;N,14.726%;IR(KBr)cm^{-1} : 3382, 3137, 1613, 1494, 1401, 1223, 752, 693; ^{1}H NMR: (300MHz, CdCl$_3$) δ: 7.400 (d, J= 6.3Hz, 1H); 7.362-7.327 (m, 7H); 7.270 (d, J= 6.3Hz, 2H); 1.157 (t, J= 3.3Hz, 1H); 3.680-3.630 (m, 2H); 3.365-3.297 (m, 1H); FABMS:380(MH$^+$).

2.9 2-(2-butylamino-4-phenylaminothiazol-5-oyl) benzothiazole 3g

This was prepared and purified as per the above mentioned procedure. Yield 65%, m.p. 255-56◦C Analysis: Found: C, 60.765; H, 4.564; N, 14.212% ; Calc.for $C_{20}H_{18}N_4OS_2$ (394.5): C,60.883;H,4.607;N,14.726 %IR(KBr)cm^{-1} :3456, 3129, 1633, 1401, 533 ;^{1}HNMR:(300MHz,CdCl$_3$) δ : 8.14 (t, J= 11.4 Hz, 1 H); 7.993 (d, J= 8.1Hz, 1 H); 7.659 (d, J= 8.1 Hz, 1 H); 7.674-7.509 (m, 3 H); 7.487-7.254 (m, 5 H); 7.122 (d, J= 8.4 Hz, 1 H); 1.393 (d, J= 6.3 Hz, 2 H); 1.242-1.167 (m, 4 H); 1.095 (d, J= 6.6 Hz, 1 H); 0.967-0.850 (m, 1 H).

2.10 2-(2-propylamino-4-phenylaminothiazol-5-oyl) benzothiazole 3h

This was prepared and purified as per the above mentioned procedure. Yield 70%, m.p. 257-59◦C Analysis: Found: C,60.234; H, 4.323; N, 13.321%; Calc. for $C_{21}H_{20}N_4OS_2$ (408.491): C,60.277; H, 4.344; N, 13.392 %;IR(KBr)cm^{-1} : 3292, 3035, 2912, 2856, 2348, 2293, 2114, 2002, 1946, 1904, 1835, 1639, 1595, 1561, 1517, 1405, 1377, 1310, 1238, 1115,1059, 908, 819,786, 758, 707; ^{1}H NMR: (300MHz, CdCl$_3$) δ : 8.14 (t, J= 11.4 Hz, 1 H); 7.993 (d, J= 8.1Hz, 1 H); 7.659 (d, J= 8.1 Hz, 1 H); 7.674-7.509 (m, 3 H); 7.487-7.254 (m, 5 H); 7.122 (d, J= 8.4 Hz, 1 H); 1.393 (d, J= 6.3 Hz, 2 H); 1.242-1.167 (m, 4 H); 1.095 (d, J= 6.6 Hz, 1 H); 0.967-0.850 (m, 1 H).

3. Biological evaluation

3.1 Antimicrobial activity

The disk diffusion test was performed using standard procedures. The inoculum suspension of each bacterial strain was swabbed on the entire surface of Mueller–Hinton agar plates (MHA, pH 7.3± 0.1, HiMedia). Sterile 6-mm filter paper disks, which were previously impregnated with the compounds (3a–h) dissolved in the solvent ethyl acetate, were aseptically placed on MHA surfaces. Sterile paper disks impregnated with 10% DMSO were used as the negative controls, whereas a disk containing Amikacin was placed in the plate as a positive control. The plates were left at ambient temperature for 15 min to allow excess prediffusion of extracts prior to incubation at 37 _C for 24 h. Diameters of inhibition zones were measured.

The newly synthesised compounds have been screened for antibacterial activity against Gram-negative Escherichia coli, Klebsiella, Pseudomona and Gram-positive Bacillus, Streptococcus, Staphyllococcus. As a reference, Amikacin G is used and a comparison of the data obtained from the study shows that almost all the new compounds now screened appeared to have remarkable antibacterial activity. And the fungal strains of Candida, Aspergillus niger and Pencillium. As a reference, Flucanazole is used and a comparison of the data obtained from the study shows that almost all the new compounds now screened appeared to have remarkable antifungal activity.

Table 1: Zones of inhibition of compounds 3a-h, standared (Amikacin) with different bacterial strains.

Compd.	**Zone of inhibition (mm)**					
	E.coli	**Klebsilla**	**Pseudomonas**	**Bacillus**	**Staphylococcus**	**Streptococnt cus**
3a	8	9	8	8	9	NA
3b	9	8	NA	9	10	NA
3c	NA	NA	NA	NA	NA	8
3d	7	10	9	9	NA	8
3e	7	NA	8	12	11	NA
3f	NA	8	8	9	8	NA
3g	9	7	9	10	10	8
3h	7	11	9	8	14	15
Amikacin (Standard)	30	18	22	20	18	20

NA- Not active

Table 2: Zones of inhibition of compounds 3a-h, standared (Flucanazole) with different fungal strains.

Compound	**Zone of inhibition (mm)**		
	Pencillium	**Aspergillus niger**	**Candida**
3a	9	10	12
3b	8	NA	9
3c	9	8	11
3d	NA	8	10
3e	8	NA	9
3f	9	11	8
3g	9	10	9
3h	10	11	10
Flucanazole (Standard)	14	15	15

NA- Not active

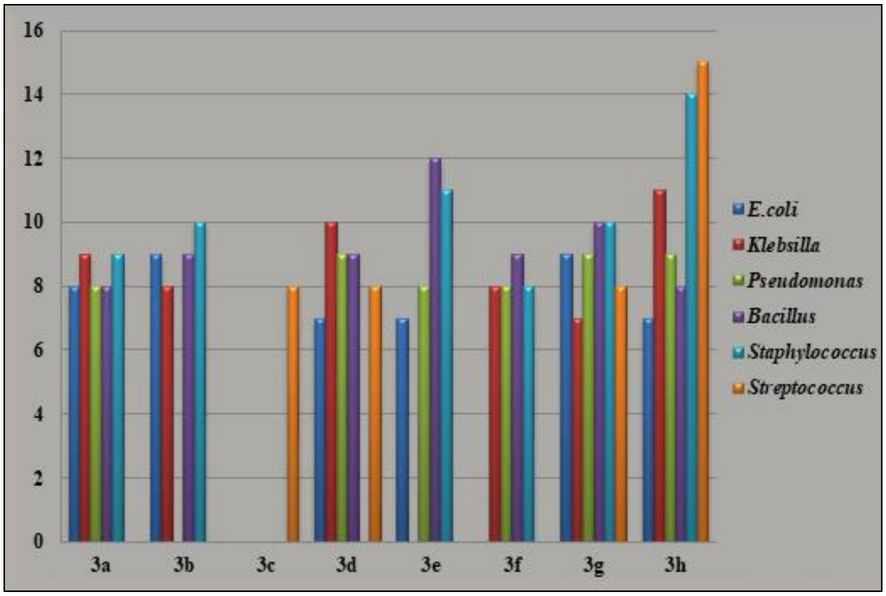

Fig 1: Bactericidal activity of compounds 3a-h

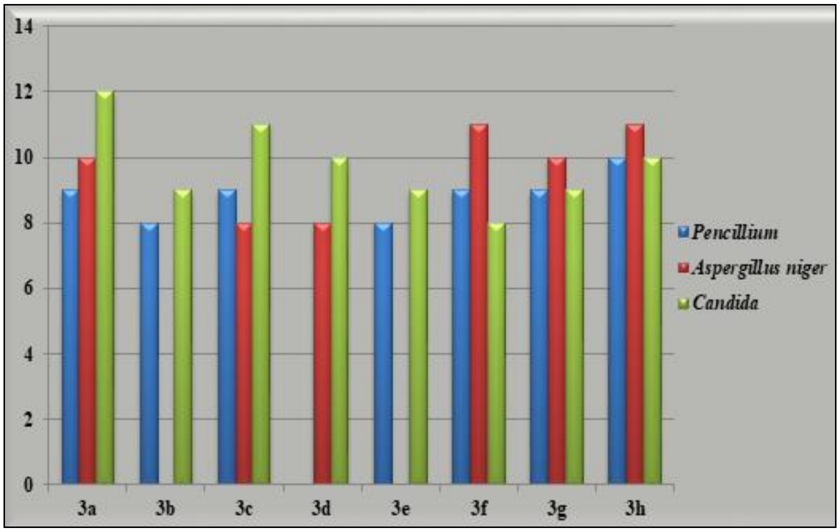

Fig 2: Fungicidal activity of compounds 3a-h

Table 3: 2-[2,4-bis(phenyl-aryl/alkylamino)thiazol-5-oyl] benzothiazole 3a-h

Compound	R
3a	phenyl
3b	4-chlorophenyl
3c	4-methylphenyl
3d	4-methoxyphenyl
3e	4-ethoxyphenyl
3f	Ethyl
3g	n-propyl
3h	n-butyl

4. Results and discussions

The structures of all compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and tested for in vitro antimicrobial activity. The antifungal screening results of these compounds are shown in Table 1 and Table 2 respectively.

From the above-mentioned results, it may be concluded that the derivatives of benzothiazoles posses moderate to potent antimicrobial activity. Compounds 3g and 3h were found to be more effective against all bacterial strains and most of the compounds were found to have moderate antifungal activity.

5. Acknowledgement

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