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Synthesis of [*N*, *N*′-Bis(5-benzoyl-4-phenylthiazol-2-yl)-*N*, *N*′-bisbenzyl]ethane-1, 2-diamines

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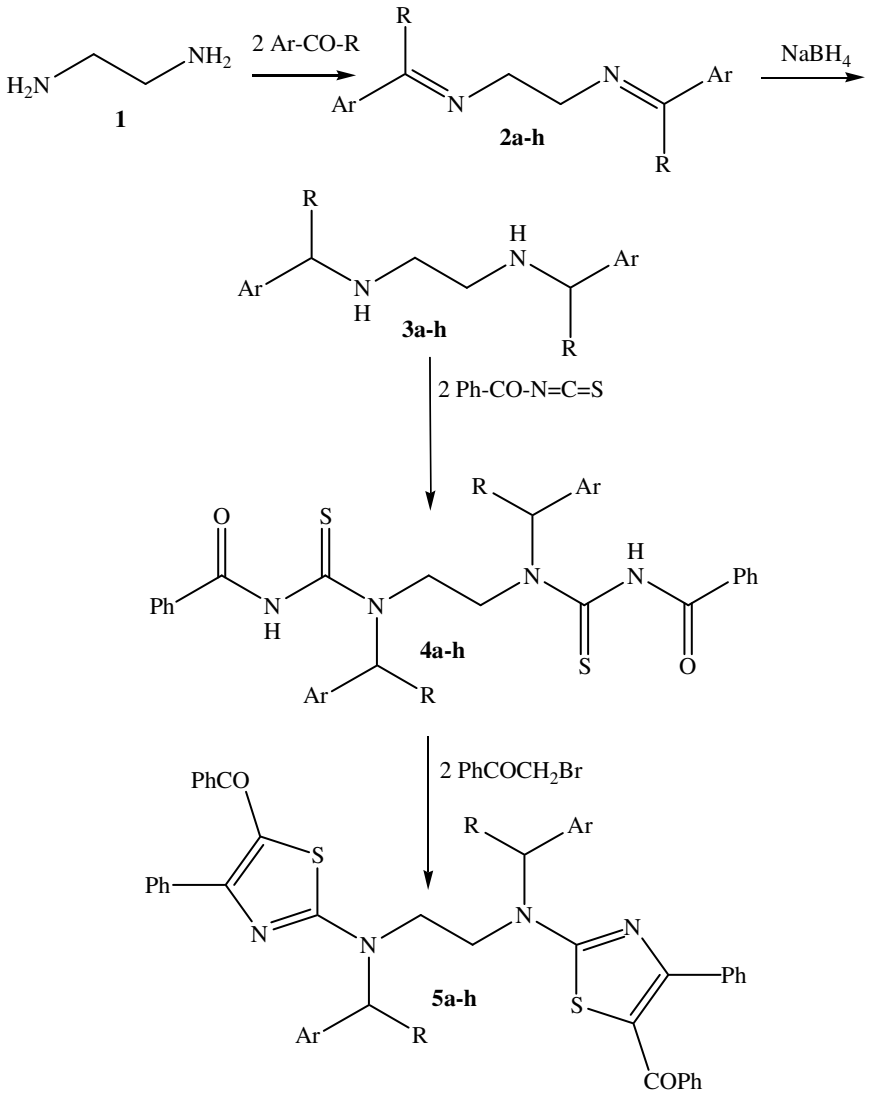
Synthesis of [*N,N*′-bis(*N*-benzoylthiocarbamoyl)-*N,N*′-bis(benzyl)]ethane-1,2-diamines **4a-h**, their cyclization to [*N,N*′-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N*′--bisbenzyl]ethane-1,2-diamines **5a-h** by reaction with phenacyl bromide and the results of antibacterial activity assay of **4a-h** and **5a-h** are reported.

Keywords: Bisthiazole, antibacterial activity

The concept of the multivalent mode of docking interaction involving one ligand binding simultaneously to more than one binding domains on the biomacromolecule has been the basis of a new trend in drug discovery lately. In a recent review[1] many examples of enhanced bioactivity of dimeric drug molecules, such as yohimbine and vitamin D homodimers, antiasthmatic salmetrol heterodimer, capable of multivalent binding have been cited. Nature also resorts to such multiple binding interactions to increase the overall strength of interactions between a ligand and its receptor. Compounds bearing more than one thiazole units also exhibit significant biological activities. We noted that, though a few reports exist on the synthesis of 5,5′-bisthiazoles[2] and 2,2′-bithiazoles,[3] the synthesis of bis-2-amino-5-ketothiazoles are much less investigated. Further, the aminothiazole moiety is a more biocompatible and better lipophilic, but a less acidic bioisosteric replacement for a phenol group. It is a valuable pharmacophore unit, present in many recent examples of bioactive compounds including thrombotic[4] and bacterial DNA-gyrase[5] inhibitors that are potentially useful in cardiac and cancer treatments. Hence, we have now sought to access homodimeric diaminoketothiazoles based on monomeric 2,4-diaminoketothiazoles, the cytotoxicity of which we have reported recently[6]. Thus, prompted by the several recent reports on biologically active bisheterocycles[7]including bisthiazoles [8] and by our interest in the synthesis of biologically active 2-aminothiazoles[9], we now report the synthesis of bis-2-amino-5-ketothiazoles. With our interest in the development of a viable access to bis-2-amino-5-ketothiazoles that consisted of two thiazole units linked together by a short bridge, we reasoned that such a bisthiazole system may be obtained in a multistep transformation starting from a bisacylthiourea. Thus, *N,N*′-dibenzylethane-1,2-diamines **3a-h**, accessed by the reduction of the Schiff's bases **2a-h** prepared from ethane-1,2-diamine **1** and araldehydes, were reacted with benzoyl isothiocyanate to obtain hitherto unreported bisacylthioureas **4a-h** (**Scheme I**).

The reaction of a typical example **4a** with a halomethyl reagent in a [4+1] ring construction approach to bisthiazoles was first investigated. As the first example, [*N,N*′-bis(*N,N*′-benzoylthiocarbamoyl)-*N,N*′-bisbenzyl]ethane-1,2-diamine **4a** was reacted with phenacyl bromide in 1:2 molar ratio in acetone. The reaction afforded a product **5a** with molecular composition $C_{48}H_{38}N_4O_2S_2$ from elemental analysis. In its IR spectrum, there were no bands assignable to N-H groups. Further, in the place of the strong $\nu_{C=O}$



2-5a: Ar = C_6H_5, R = H; **2-5b**: Ar = 2-HOC_6H_4, R = H;
2-5c: Ar = 4-$MeOC_6H_4$, R = H; **2-5d**: Ar = 4-MeC_6H_4, R = H;
2-5e: Ar = 4-$Me_2NC_6H_4$, R = H; **2-5f**: Ar = C_6H_5, R = Me;
2-5g: Ar = 4-ClC_6H_4, R = Me; **2-5h**: Ar = 4-$MeOC_6H_4$, R = Me

Scheme I

band at 1635 cm^{-1} seen in the precursor bisthiourea **4a**, the product obtained **5a** exhibited only a moderately strong νC=O band at 1600 cm^{-1}. The ^1H NMR spectrum of the product **5a** showed a set of three multiplets in the region δ 7.05-7.45, which together accounted for thirty hydrogens, thereby indicating the incorporation of six phenyl rings in the product. The ^1H NMR spectrum also showed a four-hydrogen singlet at δ 4.71, which suggested the presence of two benzylic groups. Another such singlet at δ 3.88 further indicated the presence of a -NCH_2-CH_2N- group. The FAB MS of **5a** showed a MH^+ peak at *m/z* 767 fragment ions at *m/z* 91 and 105 indicating the presence of benzyl and benzoyl units in the molecule**.** On the basis of these evidences, the product is considered to be *N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bisbenzyl]ethane-1,2-diamine **5a**. A similar reaction sequence was adopted to prepare seven other examples of such bisthiazoles **5b-h**.

To assess the bioactivity of the bisthioureas **4a-h** and the bisthiazoles **5a-h**, these were screened for their antibacterial activity against nine bacterial strains: *Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Salomo-*

Table I — Antibacterial activity of the bisthioureas **4a-h** and bisthiazoles **5a-h**

Compd	Bacterial strain[@] *vs* Activity[#]								
	I	II	III	IV	V	VI	VII	VIII	IX
4a	8	7	7	8	8	10	7	8	10
4b	9	9	9	6	7	6	6	7	8
4c	6	NA	NA	8	NA	7	NA	6	6
4d	6	8	8	7	8	NA	6	NA	NA
4e	7	9	9	7	9	NA	7	NA	8
4f	6	11	11	6	6	NA	6	7	7
4g	NA	11	11	6	7	7	6	7	7
4h	6	11	11	NA	NA	NA	6	7	6
5a	8	8	8	7	7	11	NA	8	8
5b	8	7	10	7	7	7	6	NA	9
5c	6	9	NA	8	6	NA	NA	NA	8
5d	7	9	6	7	NA	NA	NA	6	9
5e	6	6	NA	7	NA	NA	6	NA	7
5f	9	9	10	7	9	NA	NA	6	8
5g	10	9	11	8	9	NA	8	NA	7
5h	NA	12	7	7	8	7	NA	6	7
Streptomycin	16	17	15	15	14	11	20	16	11

[@] *Serratia marcescens* I, *Escherichia coli* II, *Klebsiella pneumoniae* III, *Proteus vulgaris* IV, *Salomonella typhi* V, *Pseudomonas aerugenosa* VI, *Pseudomonas flurescens* VII, *Staphylococcus aureus* VIII, *Bacillus subtilis* IX. NA: No activity

[#] Values are diameter of zone of inhibition (mm) and average of three replicates.

nella typhi, Pseudomonas aerugenosa, Pseudomonas flurescens, Staphylococcus aureus, and Bacillus subtilis using Kirby-Baur method[10]. The bisthioureas and bisthiazoles however showed only moderate antibacterial activity (**Table 1**).

Experimental Section

Melting points are uncorrected and were determined in an open capillary method using an immersion-bath of silicone oil. The IR spectra were recorded on a AVATAR 330 FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on JEOL DRX 300 or DPX 300 and Perkin-Elmer R-32 NMR spectrometers. JEOL SX 102 and DA-6000 mass spectrometers (using Argon/Xenon as the FAB gas and *m*-nitrobenzyl alcohol as the matrix) were used to record the FAB Mass spectra. All new compounds gave satisfactory C, H and N analysis (SAIF, Kochi or CDRI, Lucknow).

Preparation of [*N,N′*-bis(N-benzoylthiocarbamoyl)-*N,N′*-bis(benzyl)]ethane-1,2-diamines 4a-h

To a stirred solution of benzoyl chloride (0.01 mole, 1.2 mL) and tetra-*n*-butylammonium bromide (TBAB, 0.2 g) in benzene (10 mL), aqueous potassium thiocyanate solution (11 mL, 33%) was added drop wise and the mixture was further stirred for 30 min. The aqueous layer was removed by a Pasteur pipet and the benzene layer was dried with anhy. calcium chloride and decanted. Subsequently, *N,N′*-bis(benzyl)ethane-1,2-diamine (0.005 mole) in benzene (5 mL) was added to the above solution of benzoyl isothiocyanate during 2 hr under stirring. The reaction-mixture was then diluted with petroleum ether (3-5 mL). The colourless [*N,N′*-bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(benzyl)]ethane-1,2-diamines **4a-h** so obtained was washed with petroleum ether and crystallized from ethanol-water or DMF-water mixtures.

[*N,N′*-Bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(benzyl)]ethane-1,2-diamine **4a***:* (75%), m.p. 140-42ºC; IR (KBr): 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 90 MHz): 3.69, 4.17, 4.60, 4.93, 5.45 (m, 8H, 4CH$_2$), 6.8-8.1 (m, 20H, ArH); FAB MS *m/z* 567 (MH$^+$); Calcd. for $C_{32}H_{30}N_4O_2S_2$: C, 67.81; H, 5.33; N, 9.88. Found: C, 67.70; H, 5.29; N, 9.78%.

[*N,N′*-Bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(2-hydroxybenzyl)]ethane-1,2-diamine **4b**: (71%), m.p. 175-78ºC; IR (KBr): 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 90 MHz): 3.80, 4.20, 4.57, 4.77, 5.22 (m, 8H), 6.4-8.1 (m, 18H, ArH), 9.6 (s, 2H, ArOH), 9.8 (broad, 2 NH); FAB MS *m/z* 599 (MH$^+$); Calcd. for $C_{32}H_{30}N_4O_4S_2$: C, 64.18; H, 5.05; N, 9.35. Found: C, 64.02 ; H, 5.10 ; N, 9.29%.

[*N,N′*-Bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(4-methoxybenzyl)]ethane-1,2-diamine **4c***:* (76%), m.p. 173-75ºC, IR (KBr): 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 90 MHz): 3.73 (m, 8H, 2MeO+2H), 4.10, 4.47, 4.83, 5.23 (m, 6H), 6.5-8.1 (m, 18H, ArH); FAB MS *m/z* 627 (MH$^+$); Calcd. for $C_{34}H_{34}N_4O_4S_2$: C, 65.14; H, 5.46; N, 8.93. Found: C, 65.02 ; H, 5.43; N, 8.88 %.

[*N,N′*-Bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(4-methylbenzyl)]ethane-1,2-diamine 4d*:* (85%), m.p. 168-70ºC, IR (KBr): 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$, 90 MHz): 2.31 (s, 6H, CH$_3$), 3.73, 4.13, 4.50, 4.90, 5.30 (m, 8H), 6.8-8.1 (m, 18H, ArH); FAB MS *m/z* 595, (MH$^+$); Calcd. for $C_{34}H_{34}N_4O_2S_2$: C, 68.65; H, 5.76; N, 9.42. Found: C, 68.59; H, 5.75; N, 9. 49%.

[*N,N′*-Bis(*N*-benzoylthiocarbamoyl)-*N,N′*-bis(4-dimethylaminobenzyl)]ethane-1,2-diamine **4e***:* (82%), m.p.175-77ºC, IR (KBr): 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 90 MHz): 2.87 (s, 12H, NMe$_2$), 3.73, 4.13, 4.37, 4.77, 5.13 (m, 8H), 6.8-8.0 (m, 18H, ArH); FAB MS *m/z* 653 (MH$^+$); Calcd. for $C_{36}H_{40}N_6O_2S_2$: C, 66.22; H, 6.17; N, 12.87. Found: C, 66.09; H, 6.19; N, 12.86%.

[*N,N′*-bis(5-benzoylthiocarbamoyl)-*N,N′*-bis(1-phenylethyl)]ethane-1,2-diamine **4f**: (74%), m.p.178-81ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.63 (m, 6H, CH_3), 3.57-4.10(m, 6H), 7.1-8.2 (m, 20H); FAB MS *m/z* 595 (MH^+); analysis calcd. for $C_{34}H_{34}N_4O_2S_2$: C, 68.65; H, 5.76; N, 9.42. Found: C, 68.55; H, 5.69; N, 9.79%.

[*N,N′*-bis(5-benzoylthiocarbamoyl)-*N,N′*-bis[1-(4-chlorophenyl)ethyl]]ethane-1,2-diamine **4g**: (72%), m.p.220-22ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.60 (m, 6H, CH_3), 4.0-4.13 (m, 6H), 7.1-7.9 (m, 18H), 9.0 (b, 2NH); FAB MS *m/z* 663 (MH^+); Calcd. for $C_{34}H_{32}Cl_2N_4O_2S_2$: C, 61.52; H, 5.20; N, 8.44. Found: C, 61.40; H, 5.17; N, 8.40%.

[*N,N′*-bis(5-benzoylthiocarbamoyl)-*N,N′*-bis[1-(4-methoxyphenyl)ethyl]]ethane-1,2-diamine 4h: (62%), m.p.176-8ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.63 (m, 6H, CH_3), 3.73-3.93 (m, 12H), 6.7-7.9 (m, 18H); FAB MS *m/z* 655 (MH^+); Calcd. for $C_{36}H_{38}N_4O_4S_2$: C, 66.02; H, 5.84; N, 8.55. Found: C, 65.91; H, 5.82; N, 8.64%.

Preparation of [*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis(benzyl)]ethane-1,2-diamine 5a-h

[*N,N′*-bis(N-benzoylthiocarbamoyl)-*N,N′*-bis(benzyl)]ethane-1,2-diamines **4a-h** (0.05 mole) and phenacyl bromide (0.1 mole, 0.2 g) in acetone (3 mL) were refluxed for 5 hr and the reaction-mixture was kept aside for 2 hr. Light yellow crystals of [*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis(benzyl)-ethane-1,2-diamines **5a-h** separated which were filtered and dried. The crude sample was recrystallised from ethanol-water or DMF-water mixtures.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(benzyl)]ethane-1,2-diamine **5a**: (74%), m.p.200-03ºC ,IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 4H, CH_2-CH_2), 4.71 (s, 4H,CH_2Ar), 7.05-7.45 (m, 30H, ArH); FAB MS *m/z* 767 (MH^+); Calc. for $C_{48}H_{38}N_4O_2S_2$: C, 75.16; H, 4.99; N, 7.30. Found: C, 75.05; H, 4.93; N, 7.26%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(2-hydroxybenzyl)]ethane-1,2-diamine 5b: (75%) m.p. 179-81ºC IR (KBr): 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 4H, CH_2-CH_2), 4.65 (s, 4H, CH_2Ar), 6.7-7.5 (m, 28H, ArH); FAB MS m/z 799 (MH^+); Calcd. for $C_{48}H_{38}N_4O_4S_2$: C, 72.15; H, 4.79; N, 7.01. Found: C, 72.08; H, 4.73 ; N, 7.07%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(4-methoxybenzyl)]ethane-1,2-diamine **5c**: (70%) m.p. 180-82ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 6H, OCH_3), 3.83 (s, 4H, CH_2-CH_2), 4.55 (s, 4H, CH_2Ar), 6.78-7.85 (m, 28H, ArH). FAB MS *m/z* 827 (MH^+); Calcd. for $C_{50}H_{42}N_4O_4S_2$: C, 72.61; H, 5.11; N, 6.77. Found: C, 72.46; H, 5.08; N, 6.78%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(4-methylbenzyl)]ethane-1,2-diamine **5d**: (87%) m.p. 190-93ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30(s, 6H, CH_3), 3.91 (s, 4H, CH_2-CH_2). 4.60 (s, 4H, CH_2Ar), 6.72-7.43 (m, 28H, ArH); FAB MS *m/z* 795 (MH^+); Calcd. for $C_{50}H_{42}N_4O_2S_2$: C, 75.53; H, 5.32; N, 7.04. Found: C, 75.40; H, 5.29; N, 7.07%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(4-dimethyaminolbenzyl)]ethane-1,2-diamine 5e*:* (76%) m.p. 264-66ºC, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.92 (s, 12H, NMe_2), 3.81 (s, 4H, CH_2-CH_2), 4.51 (s, 4H, CH_2Ar), 6.7-7.5 (m, 28H, ArH); FAB MS *m/z* 853 (MH^+); Calcd. for $C_{52}H_{48}N_6O_2S_2$: C, 73.20; H, 5.67; N, 9.85. Found: C,73.12; H, 5.64; N, 9.89%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-(1-phenylethyl)]ethane-1,2-diamine **5f**: (77%) m.p. 225-28°C, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.70 (d, 6H, CH_3), 3.81 (s, 4H, CH_2-CH_2), 5.03 (q, 2H, CH), 6.7-7.5(m, 30H, ArH); FAB MS *m/z* 795 (MH^+); Calcd. for $C_{50}H_{42}N_4O_2S_2$: C, 75.52; H, 5.29; N, 7.05. Found: C, 75.39 ; H, 5.24; N, 7.07%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-[1(4-chlorophenyl)ethyl]]ethane-1,2-diamine **5g**: (72%) m.p. 155-56°C, IR (KBr): 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.65 (d, 6H, CH_3), 4.12 (s, 4H, CH_2-CH_2), 4.80 (q, 2H, CH), 6.4-7.5 (m, 28H, ArH). FAB MS *m/z* 863 (MH^+); Calc. for $C_{50}H_{40}Cl_2N_4O_2S_2$: C, 69.51; H, 4.66; N, 6.48. Found: C, 69.40; H, 4.64; N, 6.49%.

[*N,N′*-bis(5-benzoyl-4-phenylthiazol-2-yl)-*N,N′*-bis-[1(4-methoxyphenyl)ethyl]]ethane-1,2-diamine **5h**: (70%) m.p. 180-81°C, IR (KBr): 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.78 (d, 6H, CH_3), 3.67 (s, 4H, CH_2-CH_2), 3.81 (s,6H, OCH_3), 5.12 (q, 2H, CH), 6.51-7.44 (m, 28H, ArH); FAB MS *m/z* 855 (MH^+); Calc. for $C_{52}H_{46}N_4O_4S_2$: C, 72.99; H, 5.42; N, 6.55. Found: C, 72.82; H, 5.38; N, 6.49%.

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