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Condensed bridgehead nitrogen heterocyclic systems: Synthesis and bioactivity of 2,3-dihydrothiazolo[3',2' : 2,3]-*as*-triazino[5,6-*b*] indole, 2,3-dihydro-4*H*-[1,3]thiazino[3',2' : 2,3]-*as*-triazino[5,6-*b*]indole and quinoxalino[2',3' : 4,5]thiazolo[3,2-*b*]indolo[2,3-*e*]-*as*-triazine and their isomeric systems

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2,3-Dihydro-8-isopropyl-5*H*-*as*-triazino[5,6-*b*]indole-3-thione **2** on condensation with 1,2-dibromoethane, 1-3-dibromopropane and 2,3-dichloroquinoxaline gives the cyclized products, 7-isopropyl-2,3-dihydrothiazolo[3',2':2,3]-*as*-triazino[5,6-*b*] indole **3**, 2,3-dihydro-8-isopropyl-4*H*-[1,3]thiazino[3',2':2,3]-*as*-triazino[5,6-*b*]indole **4** and 9-isopropylquinoxalino[2',3' : 4,5]thiazolo[3,2-*b*]indolo[2,3-*e*]-*as*-triazine **5**, respectively and not the angular isomers, 7-isopropyl-2,3-dihydro[2',3':3,4]-*as*-triazino[5,6-*b*]indole **6**, 8-isopropyl-1*H*-2,3-dihydro[1,3]thiazino[2',3':3,4]-*as*-triazino[5,6-*b*]indole **7** and 3-isopropylquinoxalino [2',3':4,5]thiazolo[2,3-*c*]indolo[2,3-*e*]-*as*-triazine **8**. The unequivocal synthesis of the latter **6, 7** and **8** has been accomplished by reaction of 5-isopropylisatin-3-thiosemicarbazone **1** with 1,2-dibromoethane, 1,3-dibromopropane and 2,3-dichloroquinoxaline, respectively. The bioactivity of the synthesized compounds have also been evaluated.

In continuation of our earlier studies[1-8] on the orientation of cyclization in the reaction of unsymmetrical mercaptoazoles with bifunctional compounds, we report herein the results of our study on the reaction of unsymmetrical azine (mercaptoindolotriazine) with alkyl halides and 2,3-dichloroquinoxaline and the associated bioactivity.

Condensation of 2,3-dihydro-8-isopropyl-5*H*-*as*-triazino[5,6-*b*]indole-3-thione **2** [obtained by the reaction of 5-isopropylisatin with thiosemicarbazide followed by the cyclization of the intermediate 5-isopropylisatin-3-thiosemicarbazone **1** with alkali] with 1,2-dibromoethane was likely to give 7-isopropyl-2,3-dihydrothiazolo[3',2' : 2,3]-*as*-triazino-[5,6-*b*] indole **3** or 7-isopropyl-2,3-dihydrothiazolo-[2',3' : 3,4]-*as*-triazino[5,6-*b*]indole **6** or both depending on the mode of cyclization. However, the reaction of **2** with 1,2-dibromoethane gave a single product (TLC) to which the structure **3** and not **6** was assigned, as the product was not identical with an authentic sample of **6** obtained by the reaction of **1** with 1,2-dibromoethane. The amide carbonyl (-NH-C=O) absorption at 1685 cm^{-1} present in I was found absent in the IR spectrum of the product obtained by the reaction of **1** with 1,2-dibromoethane. This corroborated the cyclic structure of **6**. The structures **3** and **6** were further supported by their ^{1}HNMR spectral data (vide Experimental).

Similarly, the condensation of **2** with 1,3-dibromopropane and 2,3-dichloroquinoxaline yielded 2,3-dihydro-8-isopropyl-4*H*-[1,3] thiazino [3',2' : 2,3]-*as*-triazino[5,6-*b*]indole **4** and 9-isopropylquinoxalino[2',3':4,5]thiazolo[3,2-*b*]indolo[2,3-*e*]-*as*-triazine **5**, respectively as they were not found to be identical with their authentic angular isomers **7** and **8** obtained from **1** by similar treatment with 1,3-dibromopropane and 2,3-dichloroquinoxaline, respectively (**Scheme I**).

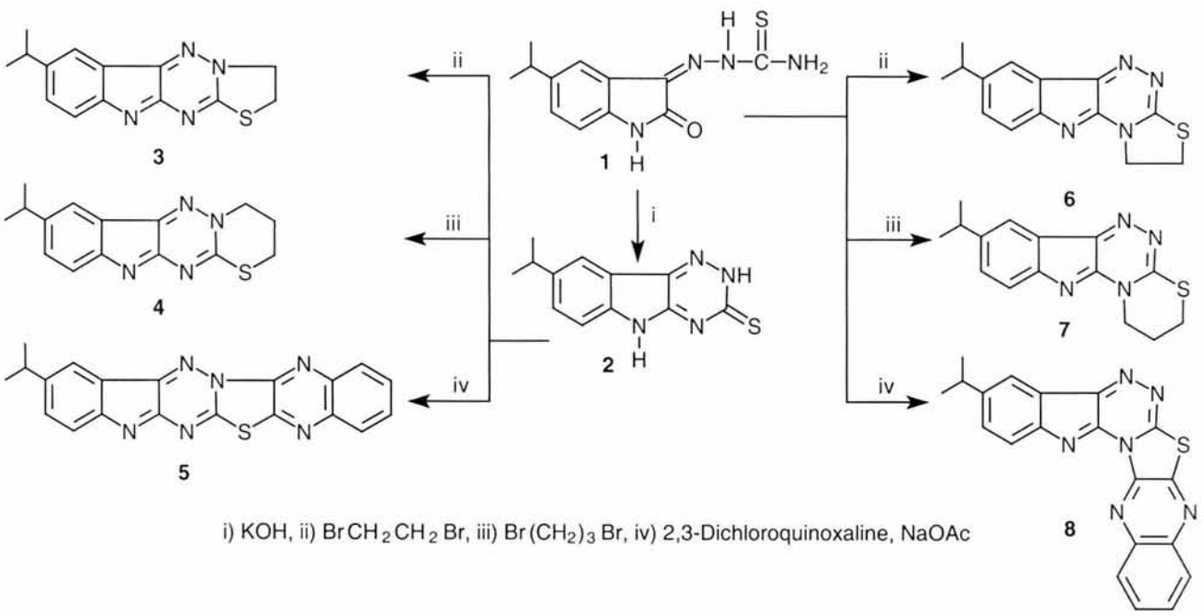
Bioactivity

The compounds **3**, **4**, **5**, **6**, **7** and **8** were evaluated for their antibacterial activity against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and the fungus C*andida albicans* by neat samples and serial plate dilution method[9].

All the six compounds showed activity against *S. aureus* and C. *albicans* when treated as neat samples and may be used for local application in the form of powder or ointment provided further studies indicate the absence of toxicity following local application.

Experimental Section

TLC was run on silica gel G plates using acetone : benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr) (ν_{max} in cm^{-1}) and ^{1}HNMR ($CDCl_3$)



Scheme I

spectra (δ, ppm, downfield from TMS) were recorded on Hitachi-215 and Varian-200MHz spectrometers respectively.

5-Isopropylisatin-3-thiosemicarbazone 1. The compound **1** was prepared by heating for half an hour, a mixture of 5-isopropylisatin and thiosemicarbazide in water and glacial acetic acid (instead of aqueous potassium carbonate) following the method of Ghladych *et al.*[10], yield 1.75 g (66.79%), m.p 245°C (Found: C, 54.69; H, 5.30; N, 21.52; S, 12.34. $C_{12}H_{14}N_4SO$ requires C, 54.96; H, 5.34; N, 21.37; S, 12.21%); IR: 830, 870 (1,2,4–trisubstituted benzene ring), 1130 (C=S), 1625 (C=N), 1685 (C=O), 3210, 3320, 3440 (NH, NH_2).

2, 3-Dihydro-8-isopropyl-5*H*-*as*-triazino [5, 6-*b*]indole-3-thione 2. It was obtained from base catalyzed cyclization of 5-isopropylisatin-3-thiosemicarbazone **2** according to method of Vishnu *et al.*[11], yield 9.25 g (75.81%), m.p.>250°C (Found : C, 59.18, H, 4.96; N, 22.69, S, 13.19. $C_{12}H_{12}N_4S$ requires C, 59.02; H, 4.92; N, 22.95; S, 13.11%); IR : 825, 880 (1,2,4-trisubstituted benzene ring), 1135 (C=S), 1560 (C-N stretching), 1620 (C=N), and 3320 (N-H).

7-Isopropyl-2,3-dihydrothiazolo[3',2':2,3]-*as*-triazino[5,6-*b*]indole 3. A mixture of **2** (1.22 g, 0.005 mole) and 1,2-dibromoethane (0.94 g, 0.005 mole) in a mixture of DMF (25 mL) and absolute alcohol (25 mL) was refluxed on a heating mantle for 4 hr. The mixture was cooled and neutralised with ammonium hydroxide solution. The solid, thus obtained was filtered, washed well with water and crystallised from ethanol as brown coloured crystals, yield 0.81 g (60.48%), m.p. 235°C (Found : C, 62.35; H, 5.24; N, 20.49; S, 11.70. $C_{14}H_{14}N_4S$ requires C, 62.22; H, 5.19; N, 20.74; S, 11.85%); IR: 840, 865 (1,2,4-trisubstituted benzene ring), 1565 (C–N stretching), 1620 (C=N); ^{1}H NMR ($CDCl_3$) : 1.32 (6H, d, *J*=7.5Hz, CH_3 protons of isopropyl group), 3.03 (1H, septet, methine protons of isopropyl group), 3.65 (2H, t, *J*=6.7Hz, SCH_2), 4.82 (2H, t, *J*=7.5Hz, NCH_2), 7.40 (1H, d, *J*=8.8 Hz, C_8-H), 7.68 (1H, d, *J*=8.8Hz, C_9-H),7.88 (1H, s, C_6-H).

2,3-Dihydro-8-isopropyl-4*H*-[1,3]thiazino[3',2' : 2,3]-*as*-triazino[5,6-*b*]indole 4. Condensation of **2** (1.22 g, 0.005 mole) with 1,3-dibromopropane (1.01 g, 0.005mole) in a mixture of DMF (25 mL) and absolute alcohol (20 mL), following the above procedure furnished **4** as yellow coloured crystals; yield 0.9 g (63.38%), m.p. 225°C (Found : C, 63.20; H, 5.55; N, 19.85; S, 11.06. $C_{15}H_{16}N_4S$ requires C, 63.38; H, 5.63; N, 19.72; S, 11.27%); IR : 880, 835 (1,2,4-trisubstituted benzene ring), 1620 (C=N); ^{1}H NMR ($CDCl_3$): 1.32 (6H, d, *J* = 7.5 Hz, CH_3 protons of isopropyl group), 3.02 (1H, septet, methine proton of isopropyl group), 3.25 (2H, t, *J*=6.7Hz, SCH_2), 4.45 (2H, t, *J*=6.0Hz, NCH_2), 2.44-2.6 (2H, m, C_3-

methylene protons), 7.60 (1H, d, J=7.0Hz, C_9-H), 7.70 (1H, d, J=7.0 Hz, C_{10}-H), 7.89 (1H, s, C_7-H).

9-Isopropylquinoxalino[2',3' : 4,5]thiazolo[3,2-*b*]indolo[2,3-*e*]-*as*-triazine 5. A mixture of **2** (1.22 g, 0.005mole), 2,3-dichloroquinoxaline (0.995 g, 0.005 mole) and anhydrous sodium acetate (0.82 g, 0.01mole) in a mixture of DMF (25 mL) and absolute alcohol (20 mL) was refluxed for 4 hr, then cooled and poured into ice-cold water. The resulting brown solid was filtered, washed well with water and crystallised from ethanol as brown coloured crystals, yield 1.4 g (75.67%), m.p. 235°C (Found : C, 64.72; H, 3.73; N, 22.84; S, 8.94. $C_{20}H_{14}N_6S$ requires C, 64.86; H, 3.78; N, 22.70; S, 8.65%); IR : 755, 830, 880 (1,2-di- and 1,2,4-trisubstituted benzene rings), 1600, 1620 (C=N); ^{1}H NMR (DMSO-d_6) : 1.25 (6H, d, J=5.5Hz, CH_3 protons of isopropyl group), 4.52 (1H, septet, methine protons of isopropyl group), 7.0-8.4 (7H, m, Ar-H).

7-Isopropyl-2,3-dihydrothiazolo[2',3' : 3, 4]-*as*-triazino [5,6-*b*]indole 6. A mixture of **1** (1.31 g, 0.005mole) and 1,2-dibromoethane (0.94 g, 0.005mole) in a mixture of absolute ethanol (25 mL) and DMF (25 mL) was refluxed on a heating mantle for 4 hr, cooled and neutralised with ammonium hydroxide solution. The solid, thus obtained was filtered, washed well with water and crystallised from aq. DMF to give yellow coloured crystals, yield 1.1 g (81.48%), m.p. 244°C (Found : C, 62.08; H, 5.27; N, 20.94; S, 11.78. $C_{14}H_{14}N_4S$ requires C, 62.22; H, 5.19; N, 20.74; S, 11.85%]; IR : 840, 865 (1,2,4-trisubstituted benzene ring), 1565 (C-N stretching), 1620 (C=N); ^{1}H NMR ($CDCl_3$): 1.34 (6H, d, J=7.5Hz, CH_3 protons of isopropyl group), 3.0 (1H, septet, methine protons of isopropyl group), 3.67 (2H, t, J=7.0Hz, SCH_2), 4.85 (2H, t, J=7.5Hz, NCH_2), 7.4 (1H, d, J=8.5Hz, C_8-H), 7.7 (1H, d, J=8.5 Hz, C_9-H), 7.9 (1H, s, C_6-H).

8-Isopropyl-1*H*-2,3-dihydro[1,3]thiazino[2',3' : 3,4]-*as*-triazino[5,6-*b*]indole 7. Condensation of **1** (1.31 g, 0.005mole) and 1,3-dibromopropane (1.01 g, 0.005mole) in anhydrous ethanol (25 mL) and DMF (25 mL) following the above procedure yielded reddish-yellow coloured crystals (aq.DMF); yield 1.2 g (84.5%), m.p. >270°C (Found : C, 63.22; H, 5.71; N, 19.85; S, 11.06. $C_{15}H_{16}N_4S$ requires C, 63.38; H, 5.63; N, 19.72; S, 11.27%); IR : 840, 875 (1,2,4-trisubstituted benzene ring), 1570 (C-N stretching), 1600, 1620 (C=N); ^{1}H NMR (DMSO-d_6): 1.28 (6H, d, J=7.0Hz), CH_3 protons of isopropyl group), 2.86 (1H, septet, methine protons of isopropyl group), 3.0 (2H, t, J=6.7Hz, SCH_2),4.52 (2H, t, J=6.7Hz, NCH_2), 2.40-4.40 (2H, m, C_3-methylene protons), 6.6-8.20 (3H, m, Ar-H).

3-Isopropylquinoxalino[2',3' : 4,5]thiazolo[2,3-*c*]indolo[2,3-*e*]-*as*-triazine 8. A mixture of **1** (1.31 g, 0.005 mole), 2,3-dichloroquinoxaline (0.995 g, 0.005mole) and anhydrous sodium acetate (0.82 g, 0.01mole) in absolute ethanol (25 mL) and DMF (25 mL) was refluxed on a heating mantle for 4 hr, then cooled and poured into ice-cold water. The resulting yellow solid was washed thoroughly with water and crystallised from ethanol to give yellow crystals yield 1.4 g (75.67%), m.p. >270°C (Found: C,64.58; H, 3.72; N, 22.86; S, 8.91. $C_{20}H_{14}N_6S$ requires C, 64.86; H, 3.78; N, 22.70; S, 8.65%); IR : 755, 835, 880 (1,2-disubstituted and 1,2,4-trisubstituted benzene rings), 1625 (C=N); ^{1}H NMR ($CDCl_3$) : 1.27 (6H, d, J=6.6Hz, CH_3 protons of isopropyl group), 2.92 (1H, septet, methine protons of isopropyl group), 6.52-7.94 (7H, m, Ar-H).

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