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CONDENSED BRIDGEHEAD NITROGEN HETEROCYCLIC SYSTEMS : SYNTHESIS AND BIOACTIVITY OF IMIDAZO [2, 1-*b*] -1, 3, 4 – THIADIAZOLO [2,3-*c*] - s -TRIAZOLES, *s*-TRIAZOLO[3,4-*b*]-1,3,4-THLADIAZOLO [3,2-*b*] IMIDAZO[4,5-*b*] QUINOXALINE AND *bis*-(*s*-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLO[3,2-*b*][IMIDAZO[4,5-*b*] CYCLOHEXANE]-5*a*,6*a*-DIENE)

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ABSTRACT
Condensation of 4-amino-3-n-butyl-5-mercapto-*s*-triazole **1** with cyanogen bromide gives 6-amino-3-n-butyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole **2** which on condensation with chloranil yields 3,9-di-n-butyl-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo [3,2-*b*] [imidazo [4, 5-*b*] cyclohexane]-5a, 6a-diene) **3.** 3-n-butyl-*s*-triazolo [3,4-*b*]-1, 3,4-thiadiazolo [3,2-*b*]imidazo [4, 5-*b*]quinoxaline **4** is obtained by a similar condensation of 2 with 2,3-dichloroquinoxaline. The reaction of 2 with α -haloketones followed by bromination affords 7-aryl-3-n-butyl-imidazo [2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles**5** and their 6-bromo analogues **6** respectively. The antibacterial and antifungal activities of some of the compounds have also been evaluated.

KEYWORDS
4-amino-5-n-butyl-5-mercapto-*s*-triazole ; 6-amino-3-n-butyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole ; 3,9-di-n-butyl -6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo [3,2-*b*] [imidazo [4, 5-*b*] cyclohexane]-5a, 6a-diene); 3-n-butyl -*s*-triazolo [3,4-*b*]-1, 3,4-thiadiazolo [3,2-*b*]imidazo [4, 5-*b*]quinoxaline ; 7-aryl-3-n-butyl -imidazo [2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles

INTRODUCTION
Imidazole compounds exhibit antibacterial[i], antiinflammatory[ii], hypertensive and anticonvulsive[iii] activities whereas *s*-triazole system displays diuretic and natriuretic activities[iv]. Our earlier work on the synthesis of bridgehead nitrogen heterocyclic systems[v-xiii] and the applications of imidazoles as anthelmintics[xiv] and nematocides[xv] stimulated considerable interest in exploring the possible synthesis of potential condensed heterocyclic systems in which a biologically active thiadiazole nucleus is fused to two other biologically active imidazole/imidazoquinoxaline and s-triazole moieties, resulting in the synthesis of 3,9-di-n-butyl-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo [3,2-*b*] [imidazo [4, 5-*b*] cyclohexane]-5a, 6a-diene) **3.** 3-n-butyl -*s*-triazolo [3,4-*b*]-1, 3,4-thiadiazolo [3,2-*b*]imidazo [4, 5-*b*]quinoxaline**4** and 7-aryl-3-n-butylimidazo [2, 1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-

triazoles**5.** We report in this paper, the synthesis of some interesting heterocyclic systems derived from 4-amino-3-n-butyl-5-mercapto--*s*-triazole and the associated biological activities.

4-Amino-3-n-butyl-5-mercapto-*s*-triazole **1** on condensation with cyanogen bromide afforded 6-amino-3-n-butyl-*s*-triazolo [3,4-*b*]-1,3, 4-thiadiazole **2.** The structural assignment of **2** was supported by IR &^{1}HNMR spectral data (vide Experimental). Condensationof **2**with chloranil gave a compound which was assigned the structure **3** on the basis of spectral data. The appearance of absorption band at 1650cm^{-1} is in good agreement with system **3.** Condensation of **2** with 2,3-dichloroquinoxaline furnished **4,** another bridgehead heterocyclic system. The structural assignment of **4** was supported by spectral data and elemental analysis (vide Experimental). Condensation of **2** with α-haloketones furnished 7-aryl-3-n-butylimidazo [2, 1-*b*] - 1,3,4-thiadiazolo[2,3-*c*]-s-triazoles**5 (Scheme-1).** Lack of absorption band in the IR spectra of **5** in the region 1670-1700cm^{-1} showed the absence of a carbonyl group, thereby suggesting a cyclic structure for **5.** The appearance of a signal at δ7.52(1H, s, C_6-H) in the ^{1}HNMR spectrumof **5a**(R=Br)corroborated the cyclic structure. Bromination of **5** yielded 6-bromo derivative and the structural assignment was confirmed by the disappearance of signal atδ7.52due to the C_6-H proton.

ANTIMICROBIAL ACTIVITY

The compounds **4, 5a**(R=Br) and **6a**(R=Br)were evaluated for their antimicrobial activity against the gram-positive *Staphylococcus aureus,* the gram-negative *Escherichia coli*and *Pseudomonas aeruginosa* and the fungus *Candida albicans*by neat samples and serial plate dilution method[xvi].

The minimum inhibitory concentration (MIC) of **5a**(R=Br) and**6a**(R=Br) against *C. albicans*was found to be 125μg/ml and 62.5 μg/ml respectively. The compounds **4, 5a** and **6a** were found to be active against *E.coli, S. aureus* and *P.aeruginosa,* when tested 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 AND RESULTS

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBrin cm^{-1})and ^{1}HNMR spectra(Chemical shift in δ , ppm) were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively.

4-amino-3-n-butyl-5-mercapto-*s*-triazole 1

A mixture of thiocarbohydrazide(10.6g) and n- pentanoic acid (30ml) was refluxed for 4 hr. The reaction mixture was cooled to room temperature and excess pentanoic acid distilled off under reduced pressure. The residual mixture was recrystallized from ethanol as colourless crystals, yield 75 % ,m.p. 190°C (Found : C, 42.14; H, 7.21; N, 37.27;S,18.37%. $C_6H_{12}N_4S$ requires C, 41.86; H,6.96;N,32.55; S,18.60%); IR : 1520 (C-Nstretching), 1600,1610 (C=C and C=N), 2600 (S-H stretching), 3185,3220(N-H,NH_2 group).

6-Amino-3-n-butyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole 2.

A mixture of **1** (5.0g, .029 mole) and cyanogen bromide (6.10g, 0.058 mole) in absolute ethanol (75ml) was heated under reflux on a water bath for 6 hours, cooled to room temp. andneutralized with K_2CO_3 solution. The solid thus separated out was filtered and recrystallized from ethanol, m.p.175°C, yield 3.5g(61.18%). (Found : C, 42.84; H, 5.67; N, 35.24; S, 16.42%. $C_7H_{11}N_5S$ requires C, 42.63; H, 5.58; N, 35.53; S, 16.24%); IR :1515 (C-N stretching), 1625 (N-H in plane bending), 3240, 3280 (N-H stretching).

3,9-Di-n-butyl-6,14-dioxo-*bis*-(*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]-imidazo[4,5-*b*]cyclohexane]-5a,6a-diene) 3

A solution of compd. **2** (1.0g, .005 mole) in aceticacid (40ml) was added to a solution of chloranil (0.61g, .0025 mole) and anhyd. sodium acetate (0.41g, .005 mole) in gl. acetic acid (20ml). The reaction mixture was heated under reflux for 3 hr. The mixture was cooled, the solid thus separated out was filtered and washed thoroughly with water & recrystallized from ethanol m.p.>250°C , yield .300g (18%),. (Found : C, 48.38; H, 3.72; N, 28.57; S, 13.24%. $C_{20}H_{18}N_{10}S_2O_2$ requires C, 48.58; H, 3.64; N, 28.34; S, 12.95%); IR :1525 (C-N stretching), 1590, 1610, 1620 (C=C and C=N), 1655 (C=O), 3030 (aromatic C-H stretching).

3-n-butyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo [4,5-*b*]quinoxaline 4

A solution of **2**(.800g,.004 mole), 2,3-dichloroquinoxaline (0.80g, .004 mole) and anhydrous sodium acetate (0.32g, .004 mole) in absolute ethanol (50 ml) was heated for reflux for 6 hr. The reaction mixture was concentrated and cooled. The solid thus separated was filtered off, dried and recrystallized from ethanolm.p. 145°C, yield0.35 g (26.71 %). (Found : C, 55.57; H, 3.91; N ,30.28 ; S, 9.72%. $C_{15}H_{13}N_7S$ requires C, 55.72; H, 4.02; N, 30.34; S, 9.90%); IR : 750 (1,2 -disubstituted benzene ring), 1520 (C-N stretching), 1610, 1620 (C=C and C=N); ^{1}HNMR ($CDCl_3$) : 0.93(3H, s, -CH_3 protons), 1.18-1.39 (4H, m, protons of two methylene grps of the unit CH_3-($\underline{CH_2}$)$_2$-CH_2- moiety), 2.6 (2H, t(J=6.0 Hz), protons of methylene grp adj. to triazole ring), 7.7-8.09 (4H,m, proton of quinoxaline ring).

7-(p-bromophenyl)-3-n-butylimidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles 5a(R=Br)

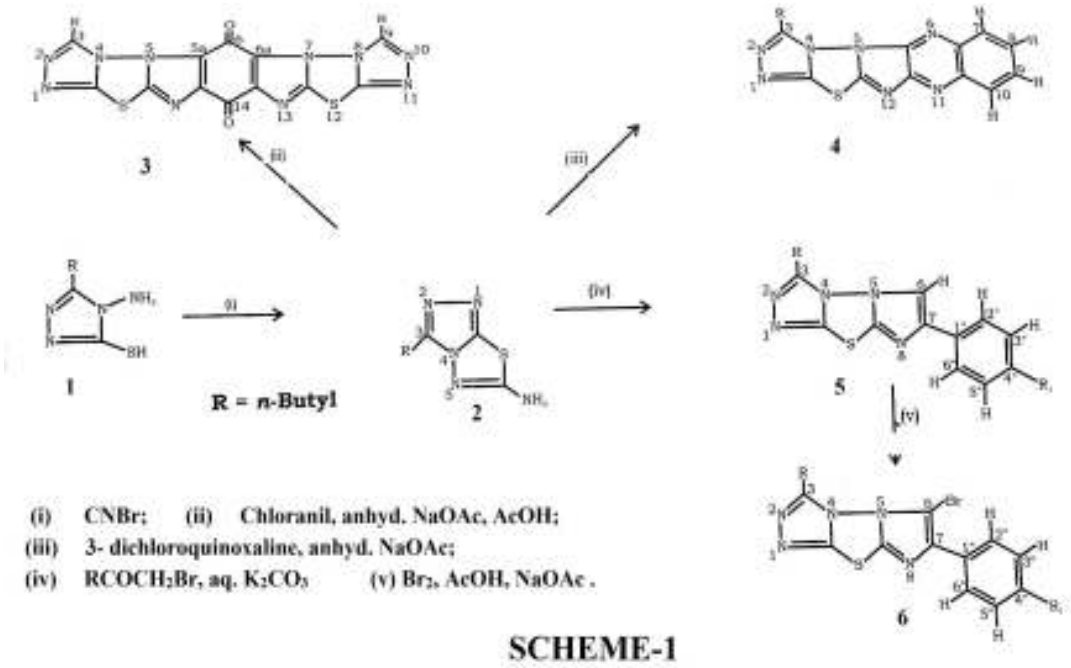
A mixture of **2**(1.0g, .005 mole), *p*-bromophenacyl bromide (1.39g, .005 mole) inanhyd. ethanol(50 ml) was heated under refluxfor 6 hours and cooled to room temperature, decant off excess of alcohol and neutralized with aq. K_2CO_3 solution. The solid thus separated was filtered and recrystallized from ethanol, m.p. >250°C,yield .600g (31.57%). (Found: C, 47.66; H, 3.68; N, 18.44; S, 8.38%. $C_{15}H_{14}N_5SBr$ requires C, 47.87; H, 3.72; N, 18.61; S, 8.51%); IR : 820 (1,4-disubstituted benzene ring), 1530 (C-N stretching), 1620 (C=C and C=N), 3030 (aromatic C-H stretching); ^{1}HNMR ($CDCl_3$) :1.13(3H,t(J=6.0 Hz),-CH_3 protons), 1.2-1.85 (4H,m, protons of the two methylene grps of the unit (CH_3-($\underline{CH_2}$)$_2$-CH_2-), 2.96 (2H, t (J=8.0 Hz), protons of the methylene grp. adj. to triazole ring), 7.52(1H,s,C_6-H), 6.36 (2H,d(J=8.0 Hz), H-3' & H-5'),8.68 (2H,d(J=8.0 Hz),H-2' & H-6').

Similarly 7-(p-chlorophenyl)-3-n-butyl-imidazo[1,2-*d*]-*s*-triazolo[3,4-b]- 1,3,4-thiadiazole **5b** (R= Cl) was prepared havingm.p. 220°C, yield0.500 g (29.76 %). (Found : C, 54.58; H, 4.19; N ,21.37 ; S, 9.83%. $C_{15}H_{14}N_5SCl$ requires C, 54.29; H, 4.22; N, 21.11; S, 9.65%); IR :830 (1,4 -disubstituted benzene ring), 1515 (C-N stretching), 1600, 1620 (C=C and C=N), 3020 (aromatic C-H stretching).

6-bromo-7-(*p*-bromophenyl)-3-n-butylimidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles 6a (R=Br)

To a well-stirred solution of **5a** (1.3g, .0034 mole) and anhyd. sodium acetate (0.55g, .0068 mole) in gl. acetic acid (30m1), bromine (1.08g, .0068 mole) was added dropwise with constant stirring. The stirring was continued for 30 minutes. The reaction mixture was cooled and then poured onto crushed ice. The precipitate thus obtained was filtered off, dried & recrystallized from gl. acetic acid, , m.p. 220°C, yield .225g (18.59%). (Found :C,39.28; H,2.78; N,15.51; S, 6.87. $C_{15}H_{13}N_5SBr_2$requires C, 39.56; H, 2.85; N, 15.38; S, 7.03%); IR : 840 (1,4-disubstituted benzene ring), 1520 (C-N stretching), 1590,1625 (C=C and C=N), 3030 (aromatic C-H stretching); ^{1}HNMR ($CDCl_3$): :1.13(3H, t , -CH_3 protons), 1.25-1.82 (4H,m, protons of the two methylene grps of (CH_3-(CH_2)$_2$-CH_2- moiety), 2.94 (2H, t (J=8.0 Hz), protons of the methylene grp. adj. to triazole ring), 7.86(2H, d(J=8.0 Hz), H-3' & H-5'),8.02 (2H, d (J=8.0 Hz),H-2' & H-6').

Similarly 6-bromo-7-(*p*-chlorophenyl)-3-n-butylimidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazoles**6b** (R=Cl) was prepared having m.p. 250°C, yield .200g (16.26%). (Found:C,43.59 ; H, 3.22 ; N,16.84 ; S, 7.67% . $C_{15}H_{13}N_5SBrCl$ requires C, 43.84; H, 3.16; N, 17.05; S, 7.79%); IR: 835 (1,4-disubstituted benzene ring), 1530 (C-N stretching), 1600,1620 (C=C and C=N), 3030 (aromatic C-H stretching).



SCHEME-1

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