Heterocyclic Letters
Vol. 6| No.1|149-153| Nov-Jan| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

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-THIADIAZOLO [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]-5a,6a-DIENE)

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ABSTRACT
Condensation of 4-amino-5-mercapto-3-(*p*-nitrophenyl)-*s*-triazole**1** with cyanogen bromide gives 6-amino-3-(*p*-nitrophenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole **2** which on condensation with chloranil yields 3,9-di-(*p*-nitrophenyl)-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-(*p*-nitrophenyl)-*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** withα-haloketones followed by bromination affords 7-aryl-3-(*p*-nitrophenyl)-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-mercapto-3-(*p*-nitrophenyl)-*s*-triazole**,**6-amino-3-(*p*-nitrophenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole **,** 3,9-di-(*p*-nitrophenyl)-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-(*p*-nitrophenyl)-*s*-triazolo [3,4-*b*]-1, 3,4-thiadiazolo [3,2-*b*]imidazo [4, 5-*b*]quinoxaline,7-aryl-3-(*p*-nitrophenyl)-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 novel bridgehead nitrogen heterocyclic systems[v-xiii] and the applications of imidazoles as anthelmintics[xiv] and nematocides[xv] stimulated considerable interest in exploring the possible synthesisof potential condensed heterocyclic systems in which a biologically active thiadiazole nucleus is fused to two other biologically activeimidazole/imidazoquinoxaline and s-triazole moieties, resulting in the synthesis of 3,9-di-(*p*-nitrophenyl)-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-(*p*-nitrophenyl)-*s*-triazolo [3,4-*b*]-1,3,4-thiadiazolo [3,2-*b*]imidazo [4,5-*b*]quinoxaline**4** and 7-aryl-3-(*p*-nitrophenyl)-imidazo [2, 1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole**5.** We report in this paper, the synthesis of some interesting heterocyclic systems derived from 4-amino-5-mercapto-3-(*p*-nitrophenyl)-*s*-triazole and the associated

biological activities.

The required compound 4-amino-5-mercapto-3-(p-nitrophenyl)-*s*-triazole**1** was prepared in excellent yield following the method of Dhaka *etal*[xvi]. Condensation of **1** with cyanogen bromide afforded 6-amino-3-(*p*-nitrophenyl)-*s*-triazolo [3,4-*b*]-1,3,4-thiadiazole **2.** The structural assignment of **2** was supported by spectral data (vide experimental). The reaction of **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.** 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-(*p*-nitrophenyl)-imidazo[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 δ7.21(1H, s, C_6-H) in the ^{1}HNMR spectrumof **5a**(R=Cl) corroborated the cyclic structure. Bromination of **5** yielded 6-bromo derivative and the structural assignment was confirmed by the disappearance of signal at δ7.21due to the C_6-H proton.

ANTIMICROBIAL ACTIVITY

The compounds **4, 5a**(R=Cl) and **6a**(R=Cl)were evaluated fortheir 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[xvii].

The minimum inhibitory concentration (MIC) of **5a**(R=Cl) and**6a**(R=Cl) against *C. albicans*was found to be 125μg/ml and 62.5 μg/ml respectively. The compounds **4, 5a**(R=Cl) and **6a**(R=Cl) 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 (KBr) (ν_{max}in cm^{-1}) and^{1}HNMR ($CDCl_3$/DMSO-d_6) (δ, ppmdownfield from TMS) spectra were recorded on a Hitachi-215 and Varian VXR-200 MHz spectro-meters respectively.

3-(p-nitrophenyl)-4-amino-5-mercapto-*s*-triazole 1

It was prepared from p-nitrobenzoyl hydrazide according to the method of Dhaka *etal*[xvi] in 77.8% yield, m.p. >250°C (Found: C, 40.31; H, 2.72; N, 29.37; S, 13.78%. $C_8H_7N_5S0_2$ requires C, 40.50; H, 2.95; N, 29.53; S, 13.50%); IR: 840 (1,4-disubstituted benzene ring), 1355, 1540 (NO_2 group), 1510 (C-Nstretching), 1620 (C=N stretching), 1630 (N-H in plane bending), 2600 (S-H stretching), 3040 (aromatic C-H stretching), 3240, 3420 (N-H stretching).

6-Amino-3-(*p*-nitrophenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole 2.

A mixture of **1** (7.0g, .029 mole), cyanogen bromide (6.2g, 0.058 mole) in absolute ethanol (50ml) was heated under reflux on a water bath for 6 hours. Distilled off excess of ethanol. Cooled and neutralized with aq. K_2CO_3 solution. Solid thus separated out was filtered and recrystallized from ethanol, yield 5.0 g (64.68%), m.p.240°C. (Found: C, 41.47; H, 2.09; N, 32.29; S, 12.49. $C_9H_6N_6SO_2$ requires C, 41.22; H, 2.29; N, 32.06; S, 12.21%); IR: 835 (1, 4-disubstituted benzene ring), 1355, 1530 (Nitro group), 1520 (C-N stretching), 1620 (C=C and C=N), 1625 (N-H in plane bending), 3030 (aromatic C-H stretching), 3280, 3440 (N-H stretching).

3,9-Di-(*p*-nitrophenyl)-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, .0038 mole), chloranil (.465g, .0019 mole), anhyd. sodium acetate (.48g, .0038 mole) in glacial aceticacid (30ml) was refluxed for 3 hr on heating mantle. The reaction mixture was half concentrated, cooled. Solid thus separated out was filtered and recrystallised from alcohol, yield .600g (25.21%), m.p.>250°C. (Found: C, 46.37; H, 1.57; N, 26.73; S, 10.58%. $C_{24}H_8N_{12}S_2O_6$ requires C, 46.15; H, 1.28; N, 26.92; S, 10.25%); IR : 840 (1,4-disubstituted benzene ring), 1355, 1535 (Nitro group), 1520 (C-N stretching), 1610, 1620 (C=C and C=N), 1660 (C=O), 3040 (aromatic C-H stretching); ^{1}HNMR ($CDCl_3$+DMSO-d_6) : 7.6-8.3 (8H, m, aromaticprotons).

3-(*p*-nitrophenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazolo[3,2-*b*]imidazo [4,5-*b*]quinoxaline 4

A mixture of **2**(1.0g, .0038 mole), 2,3-dichloroquinoxaline (0.759g, .0038 mole), anhydrous sodium acetate (0.311g, .0038 mole) in absolute alcohol was refluxed for 6 hr on steam bath. Distilled off excess of alcohol. Solid thus separated out was filtered and recrystallized with alcohol, yield .500g (33.78%), m.p.>250°C. (Found: C, 52.32; H, 2.31; N 28.64; S, 8.51%. $C_{17}H_8N_8SO_2$ requires C, 52.57; H, 2.06; N, 28.86; S, 8.24%); IR : 755, 835 (1,2 and 1,4-disubstituted benzene ring), 1520 (C-N stretching), 1600, 1610 (C=C and C=N); ^{1}HNMR ($CDCl_3$+DMSO-d_6) : 7.65-8.10 (4H, m, aromatic protons).

3-(*p*-nitrophenyl)-7-(*p*-chlorophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole 5a(R=Cl)

A mixture of compound **2**(1.0g, .0038 mole), *p*-chlorophenacyl bromide (.891g, .0038 mole) in absolute alcohol (25ml) was refluxedfor 6 hours on steam bath. Decant off excess of alcohol. Cooled and neutralized with aq. K_2CO_3 solution. Solid thus separated was filtered and recrystallized from alcohol, yield .500g(33.11%), m.p. 230°C. (Found: C, 51.29; H, 2.51; N, 21.35; S, 8.32%. $C_{17}H_9N_6SO_2Cl$ requires C, 51.45; H, 2.26; N, 21.18; S, 8.07%); IR : 835, 840 (1,4-disubstituted benzene ring), 1340, 1530 (Nitro group), 1525 (C-N stretching), 1610,1625 (C=C and C=N), 3030 (aromatic C-H stretching); ^{1}HNMR ($CDCl_3$+DMSO-d_6) : 7.21(1H, s, C_6-H), 7.2-8.18 (8H, m, aromatic protons).

A similar procedure was adopted for the synthesis of compound **5b**(R=Br), the characterization data of which is given in Table 1.

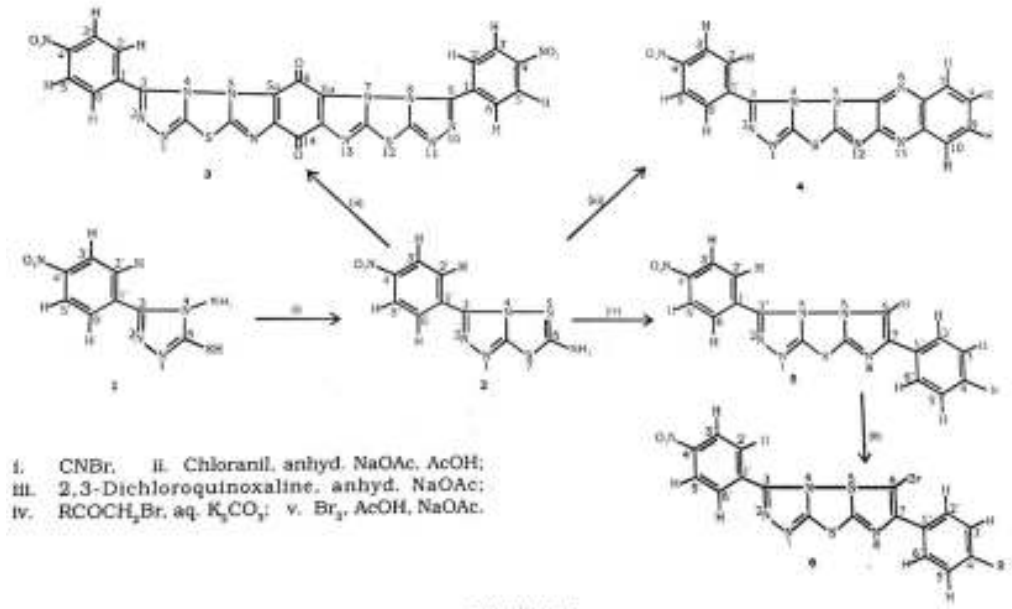
3-(*p*-nitrophenyl)-6-bromo-7-(*p*-chlorophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazolo[2,3-*c*]-*s*-triazole 6a (R=Cl)

To a well-stirred mixture of **5a** (.500g, .0012 mole) and anhyd. sodium acetate (0.196g, .0024 mole) in gl. acetic acid (30m1), bromine (.384g, .0024 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 alcohol, yield .250g (41.73%), m.p.120°C. (Found: C, 42.73; H, 1.43; N, 17.41; S, 6.54. $C_{17}H_8N_6SO_2BrCl$ requires C, 42.90; H, 1.68; N, 17.66; S, 6.72%); IR: 830, 845 (1,4-disubstituted benzene ring), 1530 (C-N stretching), 1600, 1620 (C=C and C=N), 3040 (aromatic C-H stretching); ^{1}HNMR ($CDCl_3$+DMSO-d_6) : 7.10-8.60 (8H, m, aromatic protons).

Compound **6b** (R = Br) was prepared similarly, the characterization data of which is given in **Table 1.**

Table 1: Characterization data of Compounds **5b** and **6b.**

Compd.	R	Mol. Formula	M.P. °C	Yield (%)	Found (%) (Calcd.) C	H	N	S
5b	Br	$C_{17}H_9N_6SO_2Br$	240	35.71	46.51 (46.25	2.27 2.04	19.32 19.04	7.41 7.25)
6b	Br	$C_{17}H_8N_6SO_2Br_2$	200	35.36	39.48 (39.23	1.73 1.53	16.37 16.15	6.38 6.15)



SCHEME-1

ACKNOWLEDGEMENT

The author is thankful to Dr. Jacob Klug of Ben-Gurion University of Negev, Israel for IR, NMR spectra and elemental analysis, to Dr. Saran Sudhir, Department of Pharmacology, Medical College, Rohtak for biological screening, to the authorities of Maharaja Surajmal Institute of Technology for supportive environment and to Head of the Chemistry Department, MaharshiDayanand University, Rohtak for providing laboratory facilities.

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Received on January 24, 2016.