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NOVEL SYNTHESIS OF BIOLOGICALLY ACTIVE BRIDGEHEAD NITROGEN CONTAINING BIS-TRIAZOLO-THIADIAZINES

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Abstract: *A novel synthesis of 1,4-bis-(6,7-di-[substituted]-phenyl-5H-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazin-3-yl)-benzenes have been carried out by reacting 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene with substituted benzoins in presence of potassium hydroxide. The required 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene was synthesized by treating terephthalic acid dihydrazide with carbondisulphide and potassium hydroxide followed by the addition of hydrazine hydrate. Title compounds were acetylated to afford bis-acetyl/triacetyl derivatives. Structures of all synthesized compounds were established on the basis of IR, ^{1}H-NMR, mass spectral studies and by chemical transformation, elemental analysis and equivalent weight determination. Title compounds have been screened for biological activity against gram-positive as well as gram-negative microorganisms.*

Keywords: *Synthesis, antimicrobial screening, bis-triazolo-thiadiazines.*

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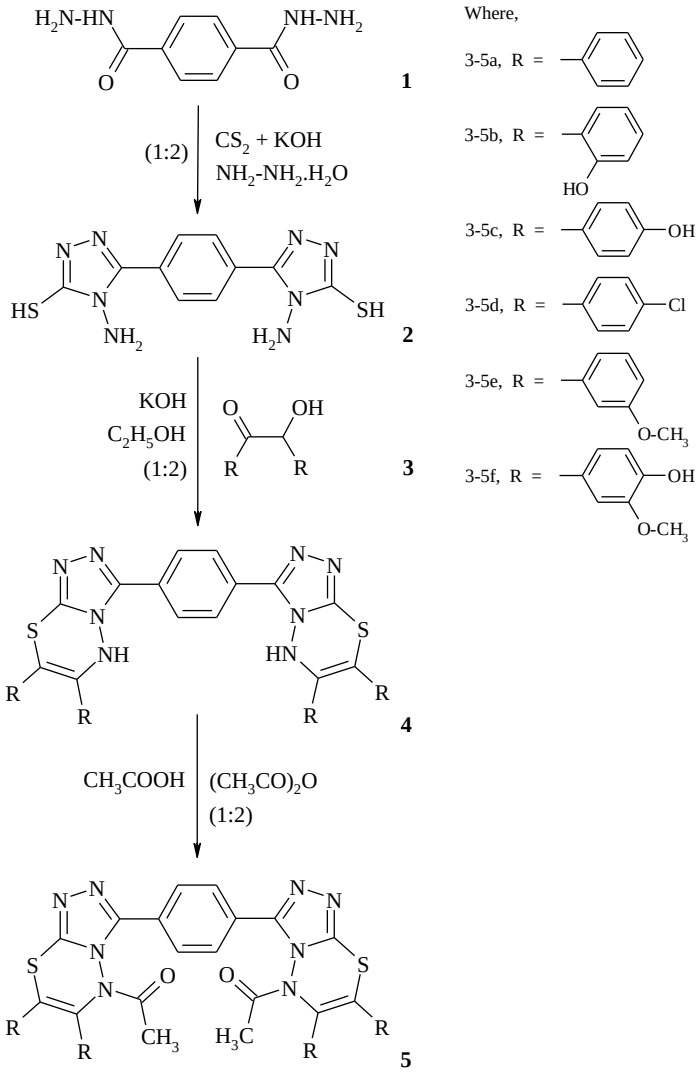
INTRODUCTION

The heterocyclic compounds and especially those containing sulphur and nitrogen atoms possess a wide variety of biological activities[1,2]. Therapeutic effect of 1,2,4-triazole and 1,2,4-triazole-3-one containing compounds have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis and hypertension[3,4]. 1,2,4-triazoles fused with 1,3,4-thiadiazines are found to possess diverse applications in the field of medicine[5,6]. Triazolo-thiadiazines are reported to show a broad spectrum of pharmacologicallly important properties like antifungal[7], antibacterial[8], antiviral[9], anthelmentic[10], antitumor[11], anti-inflammatory[12], antituberculor[13], diuretics[14], anticancer[15] and hypoglycaemic agents[16]. These two fused systems are reported to possess significant CNS depressant, herbicidal, anthelmintic activities and have been widely used in pharmaceutical and agrochemical industry[17]. In view of these findings about the utility of fused heterocyclic compounds in various fields and as a part of wider programme to provide alternative routes for the synthesis of 5 and 6 membered heterocyclic compounds[18-20], we report herein the synthesis of bis-(substituted)-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiadiazines.

Results and Discussion

The parent compound 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene **2** was prepared by the interaction of terephthalic acid dihydrazide **1** (0.01 mole) with carbondisulphide (0.02 mole) and potassium hydroxide (2M, 10 mL) followed by the dropwise addition of hydrazine hydrate (0.02 mole) with constant stirring. It was transformed into 1,4-bis-(6,7-di-[substituted]-phenyl-5H-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazin-3-yl)-benzenes **4a-f** by condensing it with substituted benzoins **3a-f** (0.02 mole) in presence of potassium hydroxide (2M, 10 mL) using ethanol as a solvent for 1.5 hr. The reaction mixture was cooled and poured in distilled water. The resulting precipitate was crystallized from aqueous ethanol. Compounds **4a-f** on acylation with mixture acetic anhydride and glacial acetic acid afforded bis-acetyl/triacetyl derivatives **5a-f**. **(Scheme 1)**



Scheme 1

Antimicrobial activity

The synthesized compounds **4a-f** were screened for their antibacterial activity using cup plate diffusion method.[21,22] The bacterial organisms used included both gram-positive as well as gram-negative strains like *E. coli, S. aureus, S. typhi, B. subtilis* and *A. aerogenes*. Sensitivity plates were seeded with a bacterial innoculum of $1x10^6$ CIU ml^{-1} and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 µg ml^{-1}) in DMF, so that concentration of each test compound was 100 µg ml^{-1}. The zones of inhibition were recorded after incubation for 24 hr. at 37^0C, using Vernier caliper. Inhibition zone record of the compounds clearly indicated that **4b**, **4c**, **4e** and **4f** were highly active against *E. coli* and

moderately active against *S. typhi, S. aureus, A. aerogenes*. Majority of the compounds were found inactive against *B. subtilis* (**Table 1**).

To determine minimum inhibitory concentration (MIC), the serial dilution technique[23] was followed using nutrient broth medium. The MIC values of compounds **4b**, **4c**, **4e** and **4f**, were determined against *E. coli* which were found to be 80, 78, 82 and 85 µg ml^{-1} respectively.

Screening of these compounds **4a-f** having the concentration 1%, for antifungal activity using paper disc method[24] showed that **4e** and **4f** were highly active against *A. niger*, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 hr. at 37^0C (**Table 1**).

Table 1 - Antibacterial and antifungal activity of compounds 4a-f.

Compounds	Antibacterial activity					Antifungal activity
	E. coli	*S. aureus*	*S. typhi*	*B. subtilis*	*A. aerogenes*	*A. niger* (Conc. 1%)
4a	+	+	+	+	+	–
4b	++	++	++	+	++	++
4c	+	++	++	–	++	++
4d	–	+	–	–	–	+
4e	++	++	++	–	++	+++
4f	+++	++	++	+	++	+++

(–) : Inactive (12 mm and less) (+) : Weakly active (13-16 mm)
(++) : Moderately active (17-20 mm) (+++) : Highly active (21 mm and above)

Experimental

The melting points of all synthesized compounds were recorded using hot paraffin-bath and are uncorrected. Chemicals used were of AR grade. ^{1}H-NMR spectra were recorded on Bruker-DRX-600 spectrophotometer with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1} in nujol mull and as KBr pellete. Mass spectral measurements were carried out by EI method on Jeol-JMC-300 spectrometer at 70 eV. Purity of the compounds was checked on silica gel-G plates by TLC. The substituted Benzoins were prepared by the procedure described in "Vogel's text book of practical organic chemistry".

Synthesis of 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene 2.

The compound 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene **2** was prepared by the interaction of terephthalic acid dihydrazide **1** (0.01 mole) with carbondisulphide (0.02 mole) and potassium hydroxide (2M, 10 mL) followed by the dropwise addition of hydrazine hydrate (0.02 mole) with constant stirring. The stirring was continued for 30 minutes at room temperature. The reaction mixture was cooled and poured in distilled water, a white precipitate was obtained. It was washed with water and recrystallized from ethanol, **2** (80%), m.p. 214^{0}C(d). (Found: C, 39.04; H, 3.18; N, 36.64; S, 20.80. Calcd. for $C_{10}H_{10}N_8S_2$: C, 39.21; H, 3.26; N, 36.60; S, 20.91%); ν_{max} 3421, 3381 (NH), 1678 (C=N), 1291 (C-N), 1212 (N-N), 751 cm^{-1} (C-S)[25,26].

Synthesis of 1,4-bis-(6,7-diphenyl-5H-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazin-3-yl)-benzene 4a.

The mixture of 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene **2** (0.01 mole) and 2-hydroxy-1,2-diphenyl-ethanone (benzoin) **3a** (0.02 mole) in KOH (2M, 10 mL) was refluxed in 15 mL ethanol for 1.5 hr. The reaction mixture was cooled and poured in distilled water, light yellow coloured precipitate was obtained. It was crystallized from aqueous ethanol and identified as 1,4-bis-(4-amino-3-mercapto-4H-[1,2,4]-triazol-5-yl)-benzene **4a** (75%), m.p. 114°C. (Found: C, 68.67; H, 3.89; N, 16.89; S, 9.66. Calcd. for $C_{38}H_{26}N_8S_2$: C, 69.30; H, 3.95; N, 17.02; S, 9.72%); ν_{max} 3379 (NH), 1594 (C=N), 1577 (C=C), 1337, 1306 (C-N), 1207 (N-N), 754 cm^{-1} (C-S); δ ($CDCl_3$+DMSO-d_6) 7.20-7.93 (24H, m, Ar-H), 5.97 (2H, s, NH); MS: m/z 504 (M^+-2C_6H_5), 433 (M^+-C_2H_5NS-(C_6H_5)$_2$), 367 (M^+-C_4HN_4S-(C_6H_5)$_2$), 350 (M^+-4C_6H_5), 291 (C_4HN_4S-(C_6H_5)$_2^+$), 225 (C_2HNS-(C_6H_5)$_2^+$), 214 (C_4HN_4S-$C_6H_5^+$), 213 (C_4N_4S-$C_6H_5^+$), 208 (C_6H_4-(C_2N_3)$_2^+$), 137 ($C_4HN_4S^+$), 136 ($C_4N_4S^+$). This reaction was extended to synthesize other compounds **4b-f**: **4b** (72%), m.p.167^{0}C (Found: C, 62.88; H, 3.51; N, 15.49; S, 8.78. Calcd. for $C_{38}H_{26}N_8O_4S_2$: C, 63.15; H, 3.60; N, 15.51; S, 8.86%); ν_{max} 3510 (OH), 3372 (NH), 1618 (C=N), 1311 (C-O), 1304 (C-N), 1222 (N-N), 758 cm^{-1} (C-S); δ ($CDCl_3$+DMSO-d_6) 8.32 (4H, s, OH), 5.88-7.76 (20H, m, Ar-H), 4.03 (2H, s, NH); **4c** (70%), m.p. 193^{0}C (Found: C, 63.02; H, 3.48; N, 15.56; S, 8.67. Calcd. for $C_{38}H_{26}N_8O_4S_2$: C, 63.15; H, 3.60; N, 15.51; S, 8.86%); **4d** (70%), m.p. 270^{0}C (Found: C, 56.81; H, 2.70; N, 13.95; S, 8.01. Calcd. for $C_{38}H_{22}N_8S_2Cl_4$: C, 57.28; H, 2.76; N, 14.07; S, 8.04%); **4e** (75%), m.p. 207^{0}C (Found: C, 63.73; H, 4.21; N, 14.32; S,8.12. Calcd. for $C_{42}H_{34}N_8O_4S_2$: C, 64.78; H, 4.37; N, 14.39; S, 8.22%); **4f** (65%), m.p. 78^{0}C (Found: C, 61.45; H, 4.04; N, 13.18; S, 7.80. Calcd. for $C_{42}H_{34}N_8O_8S_2$: C, 62.37; H, 4.20; N, 13.86; S, 7.92%).

Synthesis of 1,4-bis-(5-acetyl-6,7-diphenyl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazin-3-yl)-benzene 5a.

A mixture of 1,4-bis-(6,7-diphenyl-5H-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazin-3-yl)-benzene **4a** (0.01 mol) and acetic anhydride (0.02 mol) in glacial acetic acid (10 mL) was refluxed for 1 hr. The reaction mixture was cooled and poured in a little crushed ice with water, a cream coloured solid precipitated was crystallised from aqueous ethanol to give **5a** (65%), m.p.124^{0}C (Found: C, 66.31; H, 3.98; N, 14.89; S, 8.51. Calcd. for $C_{42}H_{30}N_8O_2S_2$: C, 67.92; H, 4.04; N, 15.09; S, 8.62%); ν_{max} 1678 (C=O), 1594 (C=N), 1578 (C=C), 1339, 1304 (C-N), 1205 (N-N), 754 cm^{-1} (C-S); δ ($CDCl_3$+DMSO-d_6) 7.19-8.19 (24H, m, Ar-H), 3.41 (6H, s, CO-CH_3). This reaction was extended to synthesize other bis-acetyl/triacetyl derivatives **5b-f** from **4b-f** respectively: **5b** (78%), m.p. 178^{0}C; **5c** (75%), m.p. 144^{0}C; **5d** (80%), m.p. 209^{0}C; **5e** (70%), m.p. 165^{0}C; **5f** (60%), m.p. 145^{0}C.

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