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Synthesis, structural study and antimicrobial screening of bridgehead nitrogen containing 1,8-bis-thiadiazino-triazolyl-octanes

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ABSTRACT

A facile synthesis of 1,8-bis-[5,6-diaryl-[1,3,4]-thiadiazino-(3,4-c)-[1,2,4]-triazol-5-yl]-octanes have been carried out by reacting 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane with substituted benzoins in presence of potassium hydroxide. The required 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane was synthesized by reacting sebacic acid dihydrazide with carbondisulphide and potassium hydroxide followed by the addition of hydrazine hydrate. The parent compound sebacic acid dihydrazide was prepared by refluxing the mixture of sebacic acid and thionyl chloride followed by the addition of hydrazine hydrate. The constitution of synthesized compounds has been delineated on the basis of chemical transformation, elemental analysis, equivalent weight determination and IR, ^{1}H-NMR, mass spectral studies. The title compounds have been screened for their antimicrobial activity against gram-positive as well as gram-negative microorganisms.

Keywords: Synthesis, antimicrobial screening, 1,8-bis-thiadiazino-triazolyl-octanes.

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]. Thiadiazino-triazoles 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, we report herein the synthesis, structural study and antimicrobial screening of bridgehead nitrogen containing substituted 1,8-bis-thiadiazino-triazolyl-octanes.

MATERIALS AND METHODS

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 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. 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".

The parent compound sebacic acid dihydrazide (**1**) was prepared by refluxing the mixture of sebacic acid (0.01 mole) and thionyl chloride (0.02 mole) for 20 min. followed by the addition of hydrazine hydrate (0.02 mole). The reaction mixture was cooled and basified with dilute ammonium hydroxide solution to afford a free base. It was crystallized from aqueous ethanol, (**1**) (80%), m.p. 214^{0}C.

Synthesis of 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane (2).
The compound 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane (**2**) was prepared by the interaction of sebacic acid dihydrazide (**1**) (0.01 mole) with carbondisulphide (0.02 mole) and potassium hydroxide (0.6 N, 5 mL) followed by the dropwise addition of hydrazine hydrate (0.02 mole) with constant stirring. The stirring was continued for 30 min. at room temperature. The reaction mixture was cooled and poured in distilled water when a pale pink coloured precipitate was obtained. It was crystallized from aqueous ethanol, (**2**) (70%), m.p. 205^{0}C.

Synthesis of 1,8-bis-(5,6-diphenyl-[1,3,4]-thiadiazino-(3,4-c)-[1,2,4]-triazol-5-yl)-octane (4a).
The mixture of 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane (**2**) (0.01 mole) and 2-hydroxy-1,2-diphenyl-ethanone (benzoin) (0.02 mole) in KOH (0.02 mole) was refluxed in 15 mL ethanol for 1.5 hr. The reaction mixture was cooled and poured in distilled water when a light pink coloured precipitate was obtained. It was crystallized from aqueous ethanol and identified as 1,8-bis-(5,6-diphenyl-[1,3,4]-thiadiazino-(3,4-c)-[1,2,4]-triazol-5-yl)-octane (**4a**) (80%), m.p. 246°C. (Found: C, 69.11; H, 4.99; N, 15.99; S, 8.99. Calcd. for $C_{40}H_{38}N_8S_2$: C, 69.16; H, 5.47; N, 16.13; S, 9.22%); ν_{max} 1597 (C=N), 1335 (C-N), 1207 (N-N), 692 cm^{-1} (C-S); δ ($CDCl_3$+DMSO-d_6) 7.23-7.99 (20H, m, Ar-H), 2.17 (2H, s, S-CH), 1.63 (16H, bs, -CH_2); m/z 403 (M^+-2(C_6H_5)C_4N_4HS), 291 (M^+-(CH_2)$_8$.2(C_6H_5)C_4N_4HS) [18,19]. This reaction was extended to synthesize other compounds (**4b,c**): (**4b**) (70%), m.p.253^{0}C (Found: C, 57.49; H, 4.03; N, 13.33; S, 7.33. Calcd. for $C_{40}H_{34}N_8S_2Cl_4$: C, 57.69; H, 4.08; N, 13.46; S, 7.69%); ν_{max} 1597 (C=N), 1335 (C-N), 1207 (N-N), 660 cm^{-1} (C-S); δ ($CDCl_3$+DMSO-d_6) 7.04-7.79 (16H, m, Ar-H), 1.69 (2H, s, S-CH), 1.25 (16H, bs, -CH_2); m/z 472 (M^+-2(C_6H_4Cl)C_4N_4HS), 360 (M^+-(CH_2)$_8$.2(C_6H_4Cl)C_4N_4HS); (**4c**) (70%), m.p. 249^{0}C (Found: C, 63.20; H, 4.78; N, 14.66; S, 8.22. Calcd. for $C_{40}H_{38}N_8O_4S_2$: C, 63.32; H, 5.01; N, 14.77; S, 8.44%).

RESULTS AND DISCUSSION

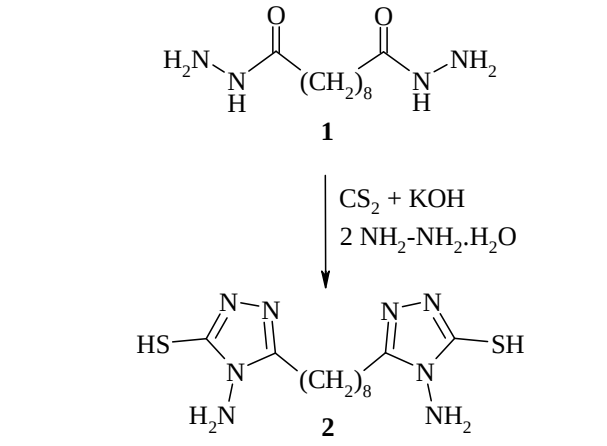
The parent compound sebacic acid dihydrazide (**1**) was prepared by refluxing the mixture of sebacic acid (0.01 mole) and thionyl chloride (0.02 mole) for 20 min. followed by the addition of hydrazine hydrate (0.02 mole) and basification with dilute ammonium hydroxide.

The compound 1,8-bis-(3-mercapto-4-amino-[1,2,4]-triazol-5-yl)-octane (**2**) was prepared by the interaction of sebacic acid dihydrazide (**1**) (0.01 mole) with carbondisulphide (0.02 mole) and potassium hydroxide (0.6 N, 5 mL) followed by the dropwise addition of hydrazine hydrate (0.02 mole) with constant stirring (**Scheme 1**).

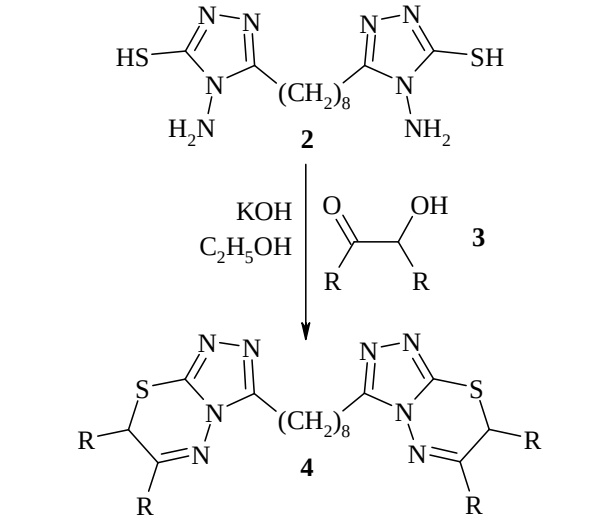
The compound (**2**) was transformed into 1,8-bis-(5,6-diaryl-[1,3,4]-thiadiazino-(3,4-c)-[1,2,4]-triazol-5-yl)-octanes (**4a-c**) by condensing it with substituted benzoins (**3a-c**) (0.02 mole) in presence of KOH (0.02 mole) using ethanol as a solvent for 1.5 hr. The reaction mixture was cooled and poured in distilled water. The resulting precipitate was crystallized from aqueous ethanol (**Scheme 2**).

Antimicrobial activity
The synthesized compounds (**4a-c**) were screened for their antibacterial activity using cup plate diffusion method [20,21]. 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 (**4a**) and (**4c**) were highly active against *S. aureus* and moderately active against *S. typhi* and *B. subtilis*. Most of the compounds were found inactive against *E. coli* (**Table 1**). To determine minimum inhibitory concentration (MIC), the serial dilution technique [22] was followed using nutrient broth medium. The MIC values of compounds (**4a**) and (**4c**), were determined against *S. aureus*, which were found to be 76 and 82 µg ml^{-1} respectively.



(Scheme 1)



(Scheme 2)

Table 1 - Antimicrobial activity of compounds 4a-c.

Compounds	Antibacterial activity				
	E. coli	*S. aureus*	*S. typhi*	*B. subtilis*	*A. aerogenes*
4a	–	+++	++	++	–
4b	+	–	–	++	++
4c	–	+++	++	++	++

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

CONCLUSION

In present work, synthesis of 1,8-bis-(5,6-diaryl-[1,3,4]-thiadiazino-(3,4-c)-[1,2,4]-triazol-5-yl)-octanes (**4a-c**) have been reported. The methods applied for the syntheses are quite simple, efficient and completed within a short period of time with high percent yield. Antimicrobial screening of these compounds revealed that, most of the compounds have better antibacterial activities.

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