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Short communication

Synthesis and biological evaluation of some thiazolidinone derivatives of steroid as antibacterial agents

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ABSTRACT

Steroidal thiazolidinone derivatives were prepared by the multi-step reactions of steroid. It is prepared from steroidal thiosemicarbazones with ethyl bromoacetate in dioxane. Steroidal thiosemicarbazones were prepared by the reaction of thiosemicarbazide with steroidal ketones. The structures of these compounds were elucidated by IR, ^{1}H NMR, Fab mass spectrometries and their purities were confirmed by elemental analyses. The antibacterial activity of these compounds was evaluated by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria and then the minimum inhibitory concentration (MIC) of compounds was determined. The results showed that steroidal thiazolidinone derivatives are better in inhibiting the growth as compared to steroidal thiosemicarbazone derivatives of both types of the bacteria (Gram-positive and Gram-negative). Compounds **7** and **8** are better antibacterial agents as compared to standard drug Amoxicillin.

1. Introduction

The treatment of infectious diseases still remains an important and challenging problem. Despite search of novel antimicrobial agents is a field of current and growing interest. Many compounds have been synthesized with this aim, their clinical use has been limited by their relatively high risk of toxicity, bacterial resistance and/or pharmacokinetic deficiencies. A major research emphasis to counter this growing problem is the development of antimicrobials structurally unrelated to the existing molecules. One possibility to achieve this goal is the combination of a steroid molecule with structural elements possessing appropriate biological activities [1–3]. In addition, considerable attention has been focused on substituted thiosemicarbazone derivatives due to their interesting biological activity. Compounds with a thiosemicarbazone structure are known to possess tranquilizing, muscle relaxant, psychoanaleptic, hypnotic, ulcerogenic, antidepressant, antibacterial, antifungal and analgesic anti-inflammatory properties [4–11]. Steroidal thiosemicarbazones dramatically increase the diversity of certain biological properties [12–14]. The presence of thiazolidinone moiety in the structure of several naturally occurring molecules with important antibiotic, immunosuppressive and antitumor activities has been known for several years [15–18]. The aminothiazole ring system has found application in drug development for the treatment of HIV-infection, hypertension and inflammation [19]. Several thiazolidinone derivatives have been shown to exhibit excellent bactericidal [20] fungicidal [21,22] and anthelmintic [23] activities. Recently thiazolidinones have been synthesized and screened for possible antimicrobial activities [24,25]. Thiazolidinone as evident from the literature, it was noted that lot of research has been carried out on thiazolidinone derivatives have been antibacterial but no work has been done on steroidal (cholesterol) derivatives screening on bacterial. In this paper the steroidal thiazolidinone derivatives have been synthesized by the reaction of steroidal thiosemicarbazones and ethyl bromoacetate in dioxane. The activities of these compounds were screened *in vitro* against bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Salmonella typhimurium* and *Escherichia coli*.

2. Results and discussion

Thiosemicarbazones prepared by condensing the steroidal ketones with cyclopentyl thiosemicarbazide in the presence of catalytic amount of conc. HCl gave yield 63–69%. 3β-acetoxycholest-6-one [26], 3β-chloro-cholest-6-one [27], 5α-cholest-6-one [28] were prepared according to the published methods. The thiosemicarbazone derivatives were used as starting material for the preparation of thiazolidinone derivatives. The thiazolidinone derivatives were synthesized by the literature procedure [29] as indicated in Scheme 1. Thiosemicarbazones were refluxed with ethyl bromoacetate in dioxan for 12 h and after that solvent was removed under reduced pressure and crystallization was done in ethanol. All the compounds were soluble in DMSO and ethanol. The

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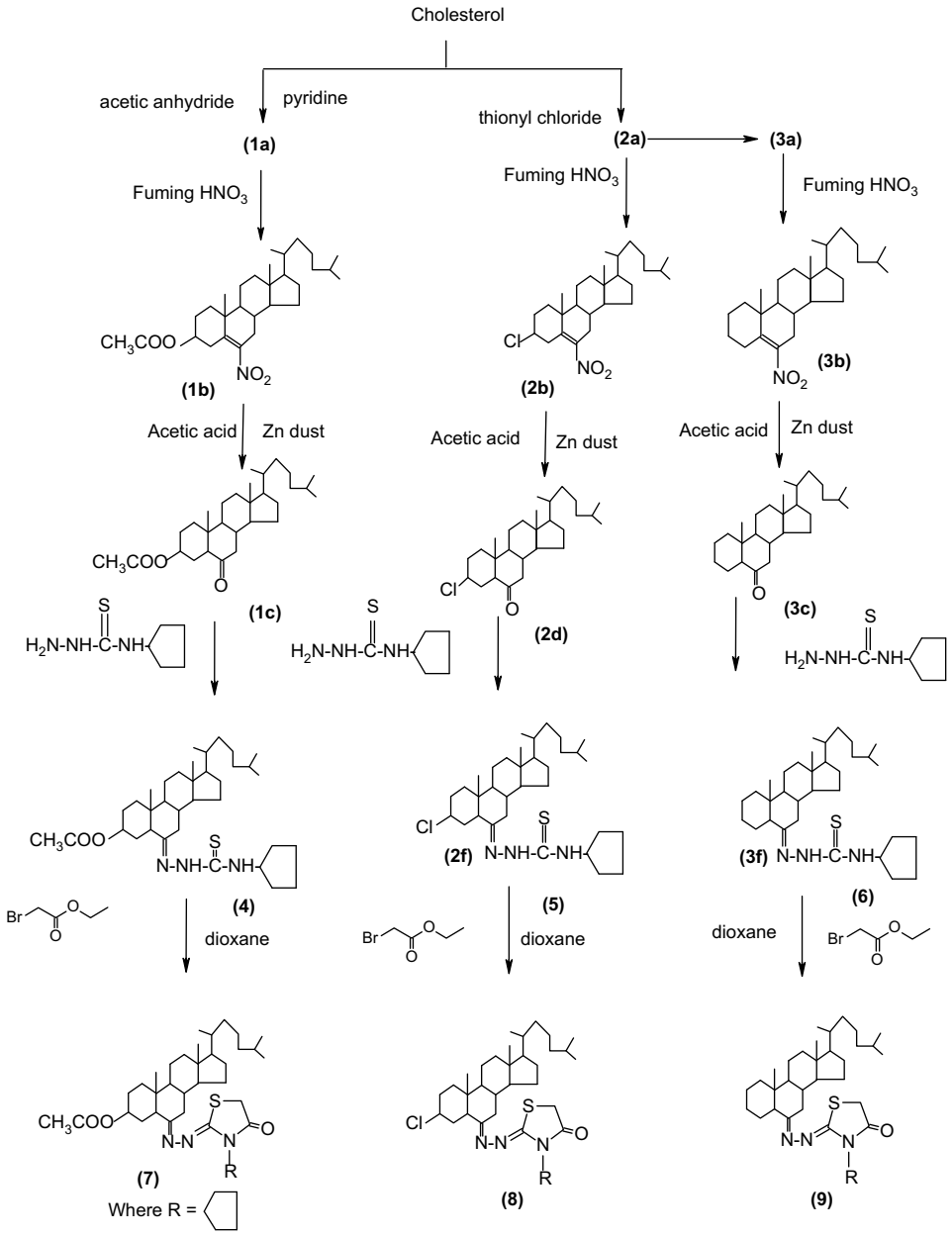

Scheme 1. Schematic diagram showing the synthesis of compounds **7**–**9**. Where compound (**1a**): 3β-acetoxycholest-5-ene, compound (**2b**): 3β-chlorocholest-5-ene, compound (**3a**): cholest-5-ene.

structures of all the compounds were established by means of their IR, ^{1}H NMR, FAB mass spectra and the elemental analyses were carried out to check the purity of the compounds.

Assignments of selected characteristic IR band positions provide significant indication for the formation of the cyclized thiazolidinone analogues of thiosemicarbazones. All the compounds showed ν (C═N) stretch at 1562–1572 cm^{-1} due to the ring closure. In addition, the absorption band at 1162–1185 cm^{-1} was attributed to the ν (C–N) stretch vibrations. The compounds showed intense bands at 624–642 cm^{-1} due to ν (C–S) stretch, which also confirm the formation of thiazole ring in all the compounds.

Further evidence for the formation of thiazolidinone compounds was obtained from the ^{1}H NMR spectra, which provide diagnostic tools for the positional elucidation of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The thiazole protons of all the compounds are shown as singlet in the range 3.80–4.21 ppm.

Characteristic peaks were observed in the mass spectra of compounds **7**–**9**, which followed the similar fragmentation pattern. The spectrum of compound **7** showed a molecular ion peak ($M^{+\bullet}$) at m/z 626, compound **8** showed a molecular ion peak ($M^{+\bullet}$) at m/z 601/603 and compound **9** showed a molecular ion peak ($M^{+\bullet}$) at m/z 569. Further fragmentation pattern of these compounds is given in the in Section 3.

2.1. Antibacterial activity

The compounds (**4**–**9**) were tested for their antibacterial activities by disc-diffusion method [30] using nutrient broth medium [contained (g/L): beef extract 3 g; peptone 5 g; pH 7.0]. The Gram-positive bacteria and Gram-negative bacteria utilized in this study consisted of *S. aureus*, *S. pyogenes*, *S. typhimurium* and *E. coli*. In the disc-diffusion method, sterile paper discs (05 mm) impregnated with compound dissolved in dimethylsulfoxide (DMSO) at