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ORIGINAL ARTICLE

# Synthesis of novel steroidal oxazolo quinoxaline as antibacterial agents

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**Abstract** Steroidal [oxazolo(4,5-b)quinoxaline-2-yl-hydrazone] derivative **(7a–9a) (7b–9b)** were prepared by the multi-step reactions of steroid. It is prepared via the reaction of steroidal semicarbazones with 2,3-dichloroquinoxaline at 80 °C in ethanol. The structures of the compounds were evident by IR, $^1$H NMR and mass spectrometry 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 compounds **(7a, 7b, 8a, 8b)** are better antibacterial agent as compared with the standard drug amoxicillin.



## 1. Introduction

Infections such as food poisoning, rheumatic, salmonellosis and diarrhea caused by multidrug-resistant Gram-positive and Gram-negative pathogens such as *Staphylococcus aureus, Streptolococcus Pyogenes, Salmonella typhimurium and Escherichia coli* (Avilffe, 1997). These pathogens are responsible for significant morbidity and mortality in both the hospital (Pfaller et al., 1999) and community settings (Abi-Hanna et al., 2000; Collignon, 1999; Merlino et al., 2000). Million of people in the subtropical regions of the world are infected and 20,000 deaths every year due to these parasitic bacterial infections. Amoxicillin, norfloxacin, ciprofloxacin are the principal drugs of choice in the treatment of bacterial infection since they are effective against extra intestinal and intestinal wall infection (Johnson, 1993), the leading drug, has been shown to be both mutagenic effect in bacteria and carcinogenic to rodents (Alauddin and Smith 1962). These are also showing severe side effects (nausea, metallic taste, dizziness, hypertension, etc.) as well as resistance have been reported (Parihar and Ramana 2004). The ideal treatment for this disease does not, therefore, exist and new agents are required. Oxadiazolines constitute an important class of heterocyclic compounds and widely utilized as a useful synthetic material in drug research (Merlani et al., 2004). The study of quinoxaline and

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oxazolo quinoxaline derivatives have become of much interest in recent years on account of their antibacterial, antiviral, anticancer antifungal, antihelmintic and insecticidal activities (Abid and Azam 2006). In this paper the steroidal oxazoloquinoxaline **(7a–9a) (7b–9b)** has been synthesized by the condensation of the steroidal semicarbazone with 2,3-dichloroquinoxaline in ethanol.

## 2. Experimental

### *2.1. Materials and methods*

The entire chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by precoated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). All melting points were measured with a capillary apparatus and are uncorrected. All the compounds were routinely checked by IR, $^1$H NMR and mass spectrometry. IR spectra were recorded in KBr on a Perkin–Elmer model 1620 FTIR spectrophotometer. $^1$H NMR spectra were recorded at ambient temperature using a Brucker spectroscopin DPX-600 MHz spectrophotometer in DMSO. The following abbreviations were used to indicate the peak multiplicity s – singlet, d – doublet, t – triplet, m – multiple. FAB mass spectra were recorded on a JEOL SX102 mass spectrometer using Argon/Xenon (6 kV, 10 mB gas. Column chromatography was performed on silica gel (100–200 mesh). Anhydrous sodium sulfate was used as a drying agent for the organic phase. All the steroidal ketone derivatives were prepared according to published method (Millurn and Truter, 1956; Anagnostopoulos and Fieser 1954; Backer and Squire 1948).

### *2.2. General method for the preparation of steroidal semicarbazones*

To a solution of steroidal ketones (5.19 mM) in ethanol (50 ml) was added a mixture of semicarbazide hydrochloride (5.19 mM) and sodium acetate (3.0 g) in ethanol (20 ml). The reaction mixture was refluxed for 2 h on a steam bath and cooled. The separated solid was filtered, washed with water and recrystallized from methanol to give compounds steroidal semicarbazones.

### *2.3. General method for the preparation of oxazolo qunoxalines*

A mixture of steroidal semicarbazones (0.01 M) and 2,3-dicholoro quinoxaline (0.01 M) in anhydrous ethanol (15 ml), was refluxed for 24 hr. Progress of reaction was monitored by TLC After completion of the reaction solvent was removed under reduced pressure and residue thus obtained was purified by column chromatography (10:90, diethyl ether:petroleum ether) and further crystallized from the appropriate solvents.

#### *2.3.1. 3β-Acetoxycholest-5-en-7-[oxazolo (4,5-b) quinoxaline] (**7a**)*

Brown solid (DMSO); yield: 65%; m.p. 168 °C; IR $\nu_{max}$ cm$^{-1}$; 3422 (N–H), 2932 (C–H aliphatic), 1568 (C═N), 1622 (C═C), 1152 (C–N), 1243 (C–O); $^1$H NMR (DMSO-$d_6$)/ppm: 8.46 (s, 1H, N–H), 7.20–7.80 (m, 4H, aromatic), 5.24 (s, 1H, C6–H), 4.6 (br m, $w_{1/2}$ = 17 Hz, C3α axial), 2.08 (s, 3H, $OCOCH_3$), 1.14 (C10, $CH_3$), 0.74 (C13, $CH_3$), 0.92 and 0.84 for other methyl proton; mass spectra ($M^+$); at *m*/*z* 626, 579 (M−AcO), 513 (M-side chain), 456 (M−$C_9H_4N_3O$), 441 (M−$C_9H_5N_4O$). Anal. calc. for ($C_{38}H_{51}N_5O_3$); C, 72.96; H, 8.16; N, 11.2. Found: C, 72.95; H, 8.12; N,10.98.

#### *2.3.2. 3β-Chlorocholest-5-en-7-[oxaazolo (4,5-b) quinoxaline] (**8a**)*

Dark brown solid (DMSO); yield: 85%; m.p. 188 °C; IR $\nu_{max}$ cm$^{-1}$; 3416 (N–H), 2932 (C–H aliphatic), 1558 (C═N), 1172 (C–N), 1254 (C–O); $^1$H NMR (DMSO-$d_6$)/ppm: 8.20 (s, 1H, N–H), 7.7–8.4 (m, 4H, aromatic), 5.32 (s, 1H, C6–H), 3.88 (br, m, –1H, $w_{1/2}$ = 15 Hz axial C3α-H), 1.16, (C10–$CH_3$), 0.76 (C10–$CH_3$), 0.84, 1.08 (other methyl protons); mass spectra ($M^+$) at *m*/*z* 604, 568 (M−Cl), 491 (M-side chain), 434 (M−$C_9H_4N_3O$), 419 (M−$C_9H_5N_4O$); Anal. calc. for ($C_{36}H_{48}N_5OCl$); C, 71.76; H, 7.97; N, 11.62. Found: C, 71.65; H, 7.87; N, 11.56.

#### *2.3.3. 5α-Cholest-5-en-7-[oxazolo (4,5-b) quinoxaline] (**9a**)*

Orange solid (DMSO) yield: 84%; m.p.178 °C; IR (KBr) $\nu_{max}$ cm$^{-1}$: 3442 (N–H), 2926 (C–H aliphatic), 1546 (C═N), 1128 (C–N), 1236 (C–O); $^1$H NMR (DMSO-$d_6$)/ppm: 8.12 (s, 1H, NH), 6.40–7.40 (m, 4H, aromatic), 0.68, 0.84, 1.08, 1.26 ($CH_3$–methylene proton); mass spectra ($M^+$) at *m*/*z* 568, 455 (M-Side Chain), 398 (M−$C_9H_4N_3O$), 383 (M−$C_9H_5N_4O$); Anal. calc for. ($C_{36}H_{49}N_5O$) C, 76.19; H, 8.64; N, 12.34. Found: C, 76.15; H, 8.58; N, 12.28.

#### *2.3.4. 3β-Acetoxy-5α-cholestan-6-[oxazolo (4,5-b) quinoxaline] (**7b**)*

Light orange solid. (DMSO); yield: 72%; m.p.264 °C; IR (KBr) $\nu_{max}$ cm$^{-1}$: 3426 (N–H), 2965 (C–H aliphatic), 1565 (C═N), 1155 (C–N), 1252 (C–O). $^1$H NMR (DMSO-$d_6$)/ppm: 8.40 (s, 1H, N–H), 7.50–7.90 (m, 4H, aromatic), 4.6 (br m, $w_{1/2}$ = 17 Hz, C3α axial), 2.04 (s, 3H, $OCOCH_3$), 1.20 (C10, $CH_3$), 0.68 (C13–$CH_3$), 0.92 and 0.78 for other methyl proton. Mass spectra ($M^+$) at *m*/*z* 628, 569 (M−AcO), 515 (M-side chain), 457 (M−$C_9H_4N_3O$), 443 (M−$C_9H_5N_4O$); Anal. calc. for ($C_{38}H_{53}N_5O_3$): C, 72.72; H, 8.45; N, 11.16. Found: C, 71.84; H, 8.48; N, 10.65.

#### *2.3.5. 3β-Chloro-5α-cholestan-6-[oxazolo (4,5-b) quinoxaline] (**8b**)*

Dark brown solid (DMSO); yield: 78%; m.p. 182 °C; IR (KBr) $\nu_{max}$ cm$^{-1}$: 3432 (N–H), 2942 (C–H aliphatic), 1555 (C═N), 1162 (C–N), 1265 (C–O). $^1$H NMR (DMSO-$d_6$)/ppm: 8.12 (s, 1H, N–H), 7.6–8.1 (m, 4H, aromatic), 3.88 (br, m, –1H, $w_{1/2}$ = 15 Hz axial $C_3$α–H), 1.15 ($C_{10}$–$CH_3$) 0.76 ($C_{13}$–$CH_3$), 0.86, 1.08 (other methyl proton); mass spectra ($M^+$) at *m*/*z* 606, 570 (M−Cl), 493 (M-side chain), 436 (M−$C_9H_4N_3O$), 421 (M−$C_9H_5N_4O$); Anal. calc. for ($C_{36}H_{50}N_5OCl$) C, 71.52; H, 8.27; N, 11.58. Found: C, 70.45; H, 7.65; N, 10.85.

#### *2.3.6. 5α-Cholestan-6-[oxazolo(4,5-b)quinoxaline] (**9b**)*

Red orange solid (DMSO); yield: 80%; m.p.242 °C; IR (KBr) $\nu_{max}$ cm$^{-1}$: 3438 (N–H), 2935 (C–H aliphatic), 1542 (C═N), 1144 (C–N), 1238 (C–O). $^1$H NMR (DMSO-$d_6$)/ppm: 8.06 (s, 1H, N–H), 6.80–7.50 (m, 4H, aromatic), 0.64, 0.82, 1.04, 1.24 ($CH_3$–methylene proton). Mass spectra ($M^+$) at *m*/*z* 570, 457 (M-side chain), 400 (M−$C_9H_4N_3O$), 385