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Synthesis and antibacterial activity of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indoles

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Abstract—A series of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indole derivatives have been synthesized and tested against the Gram positive and Gram negative strains of bacteria namely *Staphylococcus aureus* (MTCCB 737), *Salmonella typhi* (MTCCB 733), *Pseudomonas aeruginosa* (MTCCB 741), *Streptomyces thermonitrificans* (MTCCB 1824) and *Escherichia coli* (MTCCB 1652). All synthesized compounds showed mild to moderate activity. However, compounds **4d**–**f** were found to have potent activity against pathogenic bacteria used in the study. Their MIC ranged from 3.75 to 60 μg/disc. In vitro toxicity tests demonstrated that toxicity of **4d**–**f** was not significantly different than that of gentamycin. However, at higher concentration (1000–4000 μg/ml) difference was highly significant.

Since the introduction of penicillin in the 1940s, antibiotics have a history of success in controlling morbidity due to infectious diseases. But, as a consequence of frequent use, bacterial resistance to known classes of antibiotics has become a severe global problem in recent years and presents a continuous clinical challenge.[1–3] Resistance can result from modification of an antibacterial target or from functional bypassing of that target, or it can be contingent on impermeability, efflux or enzymatic inactivation of the drug.[4] There are serious concerns that untreatable pathogens may develop at an alarming rate in the near future. Strategies to address this challenge include the design of improved versions of antibacterial classes already in clinical use and the use of drug combinations. The application of these strategies can be quite successful, but a high risk of rapid resistance development remains. Thus, an urgent need for new potent classes of antibiotics with novel modes of action persists.

Pyrazino [1,2-*a*] indoles have attracted a great deal of attention due to their therapeutic uses as serotonin antagonist,[5] thrombolytic,[6] in cardiovascular diseases,[7] antidepressant, anxiolitics,[8] central nervous system depressants,[9] anticonvulsants,[10] antihistaminic,[11] protein kinase C inhibitors,[12] 5-HT_{2A},[13] 5-HT_{2C}[13,14] and selective imidazoline I_2 receptor ligands.[15] The antibacterial activity of the indole derivatives has not been much studied. One report shows the activity of pyrazinoate towards resistant *Mycobacterium tuberculosis*.[16] Some triazino [5,6-*b*] indoles have been reported to have antifungal properties.[17]

2-(3-Methyl-1*H*-indol-1-yl) ethylamine **2** was obtained by the reaction of 3-methylindole **1** with 2-chloroethylamine hydrochloride in CH_3CN in the presence of NaOH and Bu_4NHSO_4 by reported procedures.[18] Key benzotriazolyl intermediate 2-(1*H*-1,2,3,4-benzotriazol-1-ylmethyl)-10-methyl-1,2,3,4-tetrahydropyrazino [1,2-*a*] indole **5** and nucleophilic substituted derivative **6a**,**b** and compounds **7**–**9** were obtained according to our

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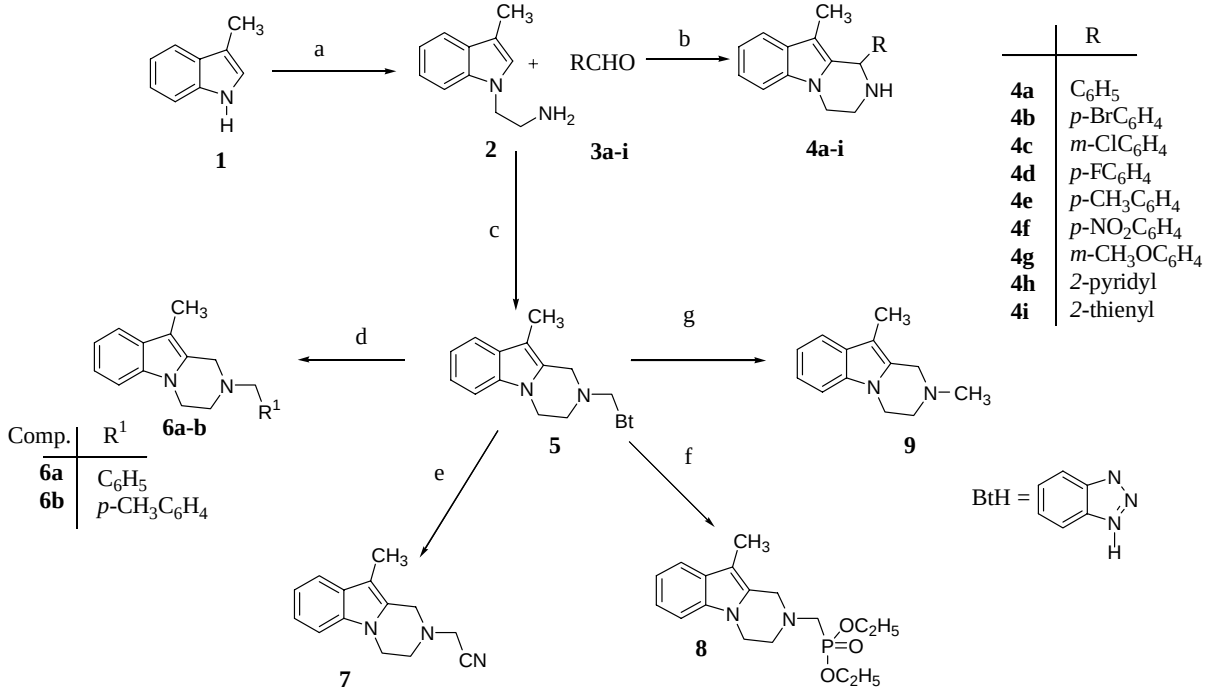
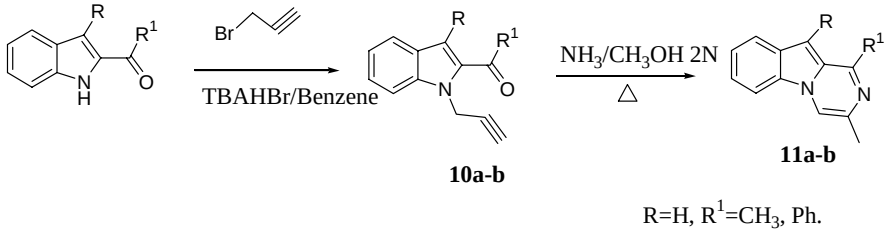
published procedure.[18] 1-Substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indoles **4a**–**i** were obtained as a racemic mixture in high yields by the reaction of 2-(3-methyl-1*H*-indol-1-yl) ethylamine **2b** with benzotriazole and aldehydes **3a**–**i** in the presence of catalytic amount of $AlCl_3$ in CH_2Cl_2 (Scheme 1).[19] The structures of new compounds **4c** and **4g** are clearly supported by their ^1H, ^{13}C NMR spectra and microanalysis.[20] The ^1H NMR spectra showed NC*H*-pyrazino singlet signal for **4a**–**i** at ~5.3 ppm. Presence of exchangeable N*H*-pyrazino was confirmed by deuterium exchange. 1,3-Dimethylpyrazino [1,2-*a*] indole **11a** and 3-methyl-1-phenyl-pyrazino [1,2-*a*] indole **11b** were prepared by the reaction of 1-propargyl-2-acetylindole **10a** and 1-propargyl-2-benzoylindole **10b** in dry ammonia and methanol (Scheme 2).[21] 1-Propargyl-2-acetylindole **10a** and 1-propargyl-2-benzoylindole **10b** were synthesized by standard procedure[22] starting from 2-acetyl-1*H*-indole[23] and 2-benzoyl-1*H*-indole.[24]

The in vitro antibacterial activity was tested by disc diffusion method[25] using pathogenic strains of *Staphylococcus aureus*, *Salmonella typhi*, *Streptomyces thermonitrificans*, *Pseudomonas aeruginosa* and *Escherichia coli*. The experimental[27] result of antibacterial activity indicated a variable degree of efficacy of the compounds against different strains of bacteria (Table 1). Compound **4a** showed strong activity against *P. aeruginosa* (MIC 3.75 μg/disc); however, it did not show any effect on other strains of bacteria even up to a concentration of 60.00 μg/disc. Similarly the **4c** was effective against *P. aeruginosa* and *S. thermonitrificans* only, the MIC being 3.75 and 15.00 μg/disc, respectively. Significant activity was observed with **4d**–**4f** against all the bacterial strains used in the study and their MIC ranged from 7.50 to 60.00 μg/disc. Other compounds appeared to be broad spectrum, as they showed mild to moderate effect on most of the strains, although the compound with pyrazinoate moiety was shown earlier to inhibit the growth of *M. tuberculosis* at a concentration of 0.5–32 μg/ml. However, pyrazino [1,2-*a*] indoles have not been investigated. We, for the first time, synthesized substituted pyrazino [1,2-*a*] indoles and tested for the antimicrobial properties. The activity of the compound



Scheme 1. Synthesis of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indoles. Reagents and conditions: (a) $ClCH_2CH_2NH_2HCl$, NaOH, TBAHS, CH_3CN, reflux, 36 h; (b) benzotriazole, dichloromethane, catalytic $AlCl_3$, 25 °C, 85–96%; (c) benzotriazole, HCHO (2 equiv), 25 °C stirring; (d) R^1MgX, THF, reflux; (e) NaCN, DMSO, 25 °C, 36 h; (f) $P(OEt)_3$, $ZnBr_2$, DCM, 25 °C, 24 h; (g) $NaBH_4$, THF, reflux,12 h.



Scheme 2. Reaction conditions: molar ratio indole **10a–b**, 1/2 M NH_3 in MeOH = 1:20, sealed tube.