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Synthesis and anti-*Helicobacter pylori* activity of 5-(nitroaryl)-1,3,4-thiadiazoles with certain sulfur containing alkyl side chain

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Abstract—A series of 5-(nitroaryl)-1,3,4-thiadiazoles bearing certain sulfur containing alkyl side chain similar to pendent residue in tinidazole molecule were synthesized and evaluated against *Helicobacter pylori* using disk diffusion method. The synthesized compounds were also evaluated for their antibacterial, antifungal and cytotoxic effects. Study of the structure–activity relationships of this series of compounds indicated that both the structure of the nitroaryl unit and the pendent group on 2-position of 1,3,4-thiadiazole ring dramatically impact the anti-*H. pylori* activity. While compound **7a** containing 2-[2-(ethylsulfonyl)ethylthio]-side chain from nitrothiophene series was the most potent compound tested against clinical isolates of *H. pylori*, however, nitroimidazoles **6c** and **7c** were found to be more promising compounds because of their respectable anti-*H. pylori* activity besides less cytotoxic effects.

The pathogenic bacterium, *Helicobacter pylori*, infect half of the human population and is one of the genetically most diverse bacterial species known. Moreover, *H. pylori* is now a well-recognized cause of chronic active gastritis, peptic ulcer disease, gastric carcinoma, and mucosa-associated lymphoid tissue (MALT)-type gastric carcinoma, and its eradication is strongly recommended for patients with these diseases.[1,2]

Current treatment for *H. pylori* infections includes an anti-secretory agent plus two or more of the following antibiotics: amoxicillin, clarithromycin, nitroimidazoles, tetracycline, and levofloxacin.[3] Strains displaying primary resistance to nitroimidazoles and clarithromycin are being reported with increasing frequency throughout the world. Together with noncompliance, antibiotic resistance is a major cause of treatment failure in patients with these infections.[4,5] For this reason, there is a need for a safe and effective treatment with a compound having an excellent anti-*H. pylori* activity.

Nitroheterocyclic compounds such as nitroimidazoles, nitrofurans, and nitrothiophenes are being extensively used in therapy against amoebic and anaerobic infections.[6] Although metronidazole has been frequently used in treatment regimens for *H. pylori* infection, but other nitroheterocyclic drugs such as tinidazole and furazolidone (Fig. 1) have been used in place of metronidazole to treat *H. pylori* with varying degrees of success.[7] Moreover, the antimicrobial property of 1,3,4-thiadiazole derivatives is well documented and their attachment with other heterocycles often ameliorates the bioresponses

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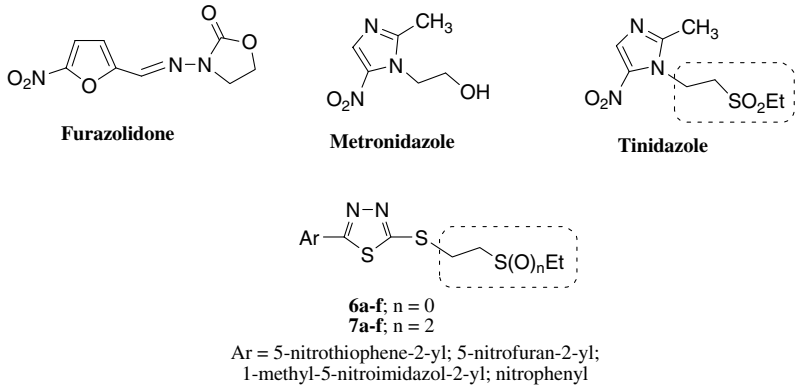

Figure 1. Structures of some nitroheterocycle antimicrobials used in the treatment of *H. pylori* infection and designed 2-[2-(ethylthio)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles **6a**–**f** and 2-[2-(ethylsulfonyl)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles **7a**–**f** as new anti-*H. pylori* agents.

depending on the type of substituent and position of attachment.[8] In view of the antimicrobial property of the above pharmacophores, it was envisaged that the combined effect of both nitroaryl and 1,3,4-thiadiazole entities would result in increased antimicrobial activity. We have previously reported the synthesis of some novel and biologically active 5-(nitroaryl)-1,3,4-thiadiazoles.[9–12] In continuation of our work on bioactive 5-(nitroaryl)-1,3,4-thiadiazoles and looking at the importance of ethylsulfonylethyl side chain in tinidazole molecule, it was thought that it would be worthwhile to design and synthesize 5-(nitroaryl)-1,3,4-thiadiazoles containing ethylsulfonylethyl or ethylthioethyl side chain to generate a series of new 5-(nitroaryl)-1,3,4-thiadiazole derivatives (**6a**–**f** and **7a**–**f**) and screen them for potential anti-*Helicobacter pylori* activity (Fig. 1).

Our synthetic route to target compounds **6a**–**f** and **7a**–**f** is shown in Fig. 2. The key intermediate 2-chloro-5-(nitroaryl)-1,3,4-thiadiazole **4** was prepared from commercially available 5-nitroarylcarboxaldehyde diacetate or nitroarylcarboxaldehyde according to the previously described methods.[9–11] The reaction of **4** with thiourea in refluxing ethanol afforded the 5-(nitroaryl)-1,3,4-thiadiazole-2-thiol **5**.[12,13] Treatment of **5** with 2-(ethylthio)ethyl chloride or 2-(ethylsulfonyl)ethyl chloride in the presence of potassium hydroxide afforded desired target compounds **6a**–**f** and **7a**–**f**, respectively.[14,15]

The synthesized compounds **6a**–**f** and **7a**–**f** were assessed against different species of Gram-positive (*Staphylococcus aureus* ATCC 6538p and *Staphylococcus epidermidis* ATCC 12228) and Gram-negative bacteria (*Escherichia coli* ATCC 8739 and *Klebsiella pneumoniae* ATCC 10031) and against various strains of pathogenic fungi (*Candida albicans* PTCC 5027, *Saccharomyces cerevisiae* PTCC 5177, *Microsporum gypseum* PTCC 5070 and *Aspergillus niger* PTCC 5012) using a conventional agar dilution method.[16,17] The data obtained against all the assayed species were in the 32 to >64 μg/mL range. From these results it was possible to submit all the synthesized compounds for subsequent screening toward *H. pylori*.

The anti-*H. pylori* activity of synthesized compounds was evaluated by comparing the inhibition zone diameters determined by the paper disk diffusion bioassay along with commercially available antibacterials, metronidazole and amoxicillin. Each compound with various concentrations was loaded on standard disks and the latter were placed on Mueller–Hinton agar plate, earlier inoculated with bacterial suspension. Following incubation for 3–5 days at 37 °C, the inhibition zone around each disk was recorded. All tests were performed in triplicate and the antibacterial activity was expressed as the mean of inhibition diameters (mm) produced by title compounds.[18] The antibacterial activity was classified as follows: strong response, zone diameter >20 mm; moderate response, zone diameter 16–20 mm; weak response, zone diameter 11–15 mm; and little or no response, zone diameter <10 mm.

Preliminarily, compounds **6a**–**f** and **7a**–**f** were evaluated against both metronidazole sensitive and metronidazole resistant *H. pylori* strains at three concentrations (8, 16, and 32 μg/disk) and the results are shown in Table 1.

Table 1 reveals that all nitroheteroaryl derivatives (**6a**–**c** and **7a**–**c**) showed remarkable antimicrobial activity against both metronidazole-sensitive and metronidazole-resistant *H. pylori* strains at concentrations of 8, 16, and 32 μg/disk (inhibition zone diameter >20 mm). While nitrophenyl analogs (**6d**–**f** and **7d**–**f**) had no respectable inhibitory activity at concentrations of 8–32 μg/disk with the exception of 4-nitrophenyl derivatives **6f** and **7f**, the 4-nitrophenyl analog **7f** showed strong inhibitory activity but less than nitroheteroaryl derivatives at similar concentrations.

In view of the results obtained with nitroheteroaryl derivatives (**6a**–**c** and **7a**–**c**), we proceeded to survey the antibacterial potential of these compounds against a broader panel of *H. pylori*. For this purpose, the antibacterial activities of selected compounds (**6a**–**c** and **7a**–**c**) at concentrations of 32, 16, 8, 4, 2, 1, and 0.5 μg/disk were assessed against twenty clinical isolates of *H. pylori*.[19] The averages of inhibition zone diameters (in mm) of title compound in comparison to metronidazole and amoxicillin are presented in Table 2.

Table 2 reveals that all selected compounds show high activity against clinical isolates of *H. pylori* in compar-