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Synthesis and biological activity of 5-nitrofuran-containing (1,3,4-thiadiazol-2-yl)piperazine moieties as a new type of anti-*Helicobacter pylori* heterocycles

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Abstract: In order to find new and potent drug candidates for the treatment of *Helicobacter pylori* infections, in this study attention was focused on the synthesis and anti-*H. pylori* activity of a series of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazoles containing piperazinyl functionality at the C-2 position of the 1,3,4--thiadiazole ring. The synthesis of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2--yl]piperazine derivatives **3a**–**h** and pyrrolidine derivative **3i** was achieved with a versatile and efficient synthetic route *via* 2-chloro-5-(5-nitrofuran-2-yl)-1,3,4--thiadiazole. The inhibitory activity of the new derivatives **3a**–**i** against twenty clinical *H. pylori* strains was evaluated by the disc diffusion method and compared with the commercially available standard drug metronidazole. Resulting biological data indicated that most compounds exhibited strong inhibitory activity even at doses lower than 2 μg/disc (average zone of inhibition >20 mm) while metronidazole had little or no growth inhibition at this dose. Compound **3c** containing the *N*-benzoylpiperazin-1-yl moiety showed the most potent inhibitory activity.

Keywords: synthesis; 1,3,4-thiadiazole; 5-nitrofuran; antibacterial activity; *Helicobacter pylori*.

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INTRODUCTION

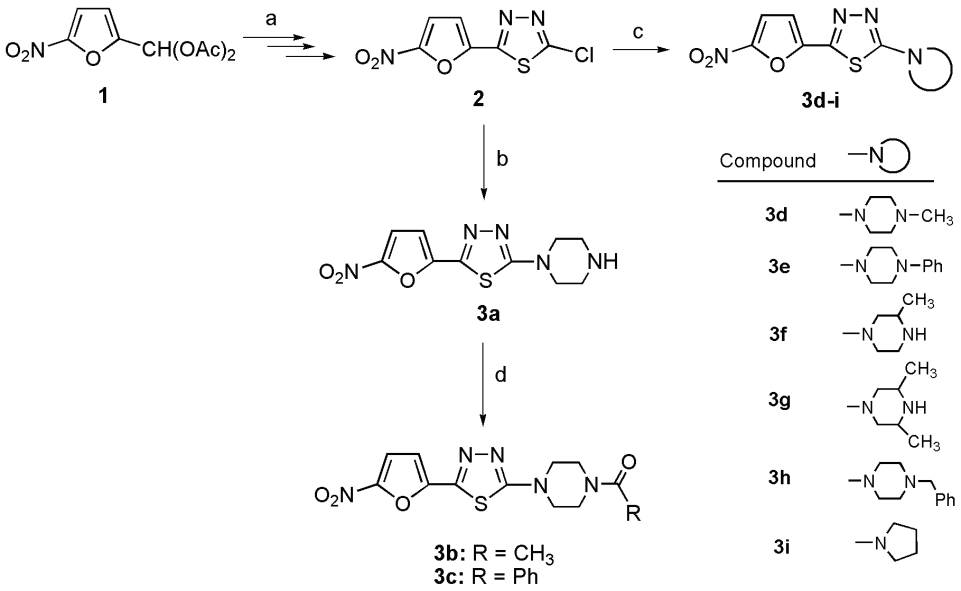
Helicobacter pylori is considered the major causative bacterium responsible in gastric ulcer, and other gastro-duodenal inflammatory symptoms and complications.[1] Eradication of these pathogens leads to a significant reduction of gastric ulcers, which may also lead to the prevention of mucosa associated lymphoid tissue (MALT) malignancies.[2] Several regimens are arranged under dual, triple and quadruple therapy aiming at higher treatment and eradication rates. The most effective treatment regimens include a combination of antibiotics (beta--lactams, macrolides and quinolones), bactericidal agents (bismuth salts) and antiprotozoal agents (metronidazole).[3,4] The most significant risk factor in the treatment protocols are the emergence of resistant strains.[5] The pattern of local prevalence of antimicrobial resistant strains varies in different regions of the world. There are reports on the activity of furazolidone (a nitrofuran analog) on *H. pylori* strains resistant to metronidazole (a nitroimidazole analog) in Iran and neighboring countries.[6] Thus, the search for new types of nitroheterocyclic compounds, including nitrofurans, is an attractive therapeutic target to find new and potent drug candidates for the treatment of *H. pylori* infections.

Recently, as part of an ongoing research program to find new and potent drug candidates for the treatment of *H. pylori* infection, attention was focused on the synthesis and anti-*H. pylori* activity of a series of 5-(nitroaryl)-1,3,4-thiadiazoles.[7–11] With this point of view and the potent biological activity of 2-(5--nitrofuran-2-yl)-1,3,4-thiadiazoles, the synthetic strategy is now focused on the introduction of a cyclic amine functionality at the C-2 position of the 1,3,4-thiadiazole ring. Accordingly, it was decided to synthesize and evaluate a series of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine derivatives.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine derivatives **3a**–**h** and the pyrrolidine derivative **3i** was achieved employing a versatile and efficient synthetic route *via* 2-chloro-5-(5-nitrofuran-2-yl)-1,3,4--thiadiazole (**2**) (Scheme 1). The intermediate **2** was prepared from commercially available 5-nitrofurfurylidene diacetate (**1**) according to previously described methods.[12,13] Nucleophilic substitution of the chloro- compound **2** with (un)substituted piperazines in refluxing ethanol afforded compounds **3a** and **3d**–**h** in good yields. Similarly, the reaction of compound **2** with pyrrolidine in refluxing ethanol yielded compound **3i**. *N*-Acetylation of the unsubstituted piperazine derivative **3a** with acetic anhydride produced compounds **3b**. Reaction of piperazine derivative **3a** with benzoyl chloride in benzene/pyridine afforded the *N*-benzoyl piperazine derivative **3c**.



Scheme 1. Synthesis of compounds **3a**–**i**. a) Ref. 11: *i*) thiosemicarbazide, EtOH, reflux, 1h; *ii*) $NH_4Fe(SO_4)_2 \cdot 12H_2O$, H_2O, reflux, 16 h; *iii*) $NaNO_2$, HCl, Cu, 0 °C→r.t, 3 h; b) piperazine, EtOH, reflux, 3h; c) substituted piperazine or pyrrolidine, EtOH, reflux, 2–3 h; d) acetic anhydride, acetic acid, reflux, 20 min, r.t, 12 h; or benzoyl chloride, benzene, pyridine, 24 h.

Analytic and spectral characterization

The structures of compounds **3a**–**i** were confirmed using IR, ^{1}H-NMR and mass spectrometry.

*1-[5-(5-Nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3a**)*. Yield: 73 %; m.p.: 214–216 °C; Anal. Calcd. for $C_{10}H_{11}N_5O_3S$: C, 42.70; H, 3.94; N, 24.90 %. Found: C, 42.77; H, 3.80; N, 25.06 %. IR (KBr, cm^{-1}): 3431 (N–H), 1551 and 1347 (NO_2). ^{1}H-NMR (80 MHz. $CDCl_3$, δ / ppm): 7.85 (1H, *d*, 4-H furan, *J* = = 4.0 Hz), 7.42 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.82–3.30 (5H, *m*, $2CH_2$ and NH piperazine), 3.19–2.99 (4H, *m*, piperazine). MS (*m*/z, %): 281 (M^+, 10), 225 (10), 82 (18), 69 (71), 67 (100).

*1-Acetyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3b**)*. Yield: 66 %; m.p.: 221–223 °C; Anal. Calcd. for $C_{12}H_{13}N_5O_4S$: C, 44.58; H, 4.05; N, 21.66 %. Found: C, 44.55; H, 3.88; N, 21.53 %. IR (KBr, cm^{-1}): 1664 (C=O), 1556 and 1352 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, δ / ppm): 7.41 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.2 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.95–3.45 (8H, *m*, piperazine), 2.17 (3H, *s*, CH_3). MS (*m*/*z*, %): 323 (M^+, 10), 165 (12), 239 (12), 110 (19), 100 (23), 237 (25), 224 (35), 53 (100).

*1-Benzoyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3c**)*. Yield: 63 %, m.p.: 225–227 °C; Anal. Calcd. for $C_{17}H_{15}N_5O_4S$: C, 52.98; H, 3.92; N,

18.17 %. Found: C, 53.08; H, 3.90; N, 18.11 %. IR (KBr, cm^{-1}): 1639 (C=O), 1555 and 1362 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, δ / ppm): 7.42 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.24 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 7.30–7.10 (5H, *m*, phenyl), 3.95–3.65 (8H, *m*, piperazine). MS (*m*/*z*, %): 385 (M^+, 5), 236 (10), 148 (10), 166 (20), 77 (63), 105 (100).

*1-Methyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3d**)*. Yield: 46 %; m.p.: 199–202 °C; Anal. Calcd. for $C_{11}H_{13}N_5O_3S$: C, 44.74; H, 4.44; N, 23.71 %. Found: C, 44.80; H, 4.27; N, 23.70 %. IR (KBr, cm^{-1}): 1551 and 1352 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$,) *δ* / ppm): 7.45 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.15 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.80–3.55 (4H, *m*, piperazine), 2.65–2.48 (4H, *m*, piperazine), 2.35 (3H, *s*, N–Me piperazine). MS (*m*/*z*, %): 295 (M^+, 10), 83 (42), 68 (100).

*1-[5-(5-Nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]-4-phenylpiperazine (**3e**)*. Yield: 42 %; m.p.: 202–205 °C (dec); Anal. Calcd. for $C_{16}H_{15}N_5O_3S$: C, 53.77; H, 4.23; N, 19.60 %. Found: C, 53.94; H, 4.26; N, 19.44 %. IR (KBr, cm^{-1}): 1555 and 1357 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, *δ* / ppm): 7.45 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.4–7.2 (5H, *m*, phenyl), 6.98 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.94––3.73 (4H, *m*, piperazine), 3.45–3.29 (4H, *m*, piperazine). MS (*m*/*z*, %): 357 (M^+, 8), 77 (6), 161 (9), 143 (22), 102 (60), 132 (100).

*3-Methyl-1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3f**)*. Yield: 52 %; m.p.: 124–125 °C; Anal. Calcd. for $C_{11}H_{13}N_5O_3S$: C, 44.74; H, 4.44; N, 23.71 %. Found: C, 44.67; H, 4.30; N, 23.64 %. IR (KBr, cm^{-1}): 3421 (N–H), 1556 and 1349 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, *δ* / ppm): 7.42 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.15 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 4.05–3.75 (5H, *m*, $2CH_2$ and NH piperazine), 3.28–2.85 (3H, *m*, CH_2 and CH piperazine), 1.16 (3H, *d*, CH_3, *J* = 5.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$, *δ* / ppm): 19.3, 45.1, 50.1, 50.5, 57.2, 124.7, 128.8, 140.5, 149.5, 151.6, 172.6. MS (*m*/*z*, %): 295 (M^+, 8), 83 (22), 70 (100).

*3,5-Dimethyl-1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3g**)*. Yield: 30 %; m.p.: 126–129 °C; Anal. Calcd. for $C_{12}H_{15}N_5O_3S$: C, 46.59; H, 4.89; N, 22.64 %. Found: C, 46.60; H, 5.03; N, 22.71 %. IR (KBr, cm^{-1}): 3431 (N–H), 1549 and 1347 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, *δ* / ppm): 7.40 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.47 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 4.05–3.75 (2H, *m*, 2CH piperazine), 3.15–2.75 (5H, *m*, $2CH_2$ and NH piperazine), 1.16 (6H, *d*, $2CH_3$, *J* = 5.8 Hz,). ^{13}C-NMR (125 MHz, $CDCl_3$, *δ* / ppm): 19.2, 50.2, 56.6, 102.3, 113.8, 145.5, 148.5, 153.1, 172.8. MS (*m*/*z*, %): 309 (M^+, 7), 252 (7), 223 (7), 130 (8), 95 (15), 84 (42), 81 (90) ,70 (100).

*1-Benzyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3h**)*. Yield: 50 %; m.p.: 151–154 °C (dec); Anal. Calcd. for $C_{17}H_{17}N_5O_3S$: C, 54.97; H, 4.61; N, 18.86 %. Found: C, 55.04; H, 4.69; N, 18.72 %. IR (KBr, cm^{-1}): 1547 and 1352 (NO_2). ^{1}H-NMR (80 MHz, $CDCl_3$, *δ* / ppm): 7.44 (1H, *d*, 4-H furan,

J = 4.0 Hz), 7.40–7.20 (5H, *m*, phenyl), 7.14 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.80–3.49 (6H, *m*, piperazine and CH_2–Ph), 2.75–2.40 (4H, *m*, piperazine). ^{13}C--NMR (125 MHz, $CDCl_3$, δ / ppm): 50.1, 51.9, 62.8, 124.8, 127.4, 128.4, 128.7, 129.1, 137.3, 140.4, 149.7, 151.6, 172.4. MS (*m*/*z*, %): 371 (M^+, 8), 166 (8), 159 (20), 132 (20), 55 (24), 146 (70), 89 (80), 91 (100).

*2-(5-Nitrofuran-2-yl)-5-pyrrolidin-1-yl-1,3,4-thiadiazole (**3i**)*. Yield: 58 %; m.p.: 247–249 °C; Anal. Calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.11; H, 3.79; N, 21.04 %. Found: C, 45.50; H, 3.61; N, 21.00 %. IR (KBr, cm^{-1}): 1541 and 1349 (NO_2); ^{1}H-NMR (80 MHz, , δ / ppm): 7.40 (1H, *d*, 4-H furan, *J* = 4.0 Hz), 7.15 (1H, *d*, 3-H furan, *J* = 4.0 Hz), 3.88–3.38 (4H, *m*, pyrrolidine), 2.35–1.93 (4H, *m*, pyrrolidine). ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 25.7, 51.1, 109.9, 113.9, 144.5, 148.9, 153.1, 169.1. MS (*m*/*z*, %): 266 (M^+, 50), 147 (6), 132 (15), 237 (15), 114 (30), 192 (39), 100 (39), 70 (100).

Anti-Helicobacter pylori *activity*

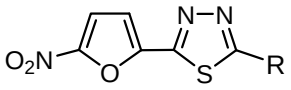
The growth inhibitory activity of the nitrofuran derivatives **3a**–**i** against *H. pylori* was evaluated using the paper disc diffusion method.[14,15] The diameters of the inhibition zone of title compounds were compared with the commercially available antibacterial metronidazole. Different doses of the compounds were loaded on standard discs (6 mm diameter), which were then placed on a Muller––Hinton agar plate, previously inoculated with bacterial suspension. After incubation for 3–5 days at 37 °C, the inhibition zone around each disc was recorded. All tests were performed in triplicate and the antibacterial activity is given as the mean of inhibition diameters (mm) produced by the title compounds. The compounds **3a**–**i** were initially evaluated against three *H. pylori* strains at a high dose of 32 μg/disc and the results are summarized in Table I. Generally, the antibacterial activity of compounds can be 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. The results given in Table I revealed that all the synthesized nitrofuran analogs **3a**–**i**, exhibited strong antimicrobial activity against *H. pylori* strains at a dose of 32 μg/disc (inhibition zone diameter >20 mm).

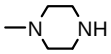
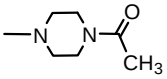
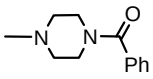
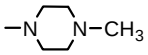
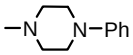
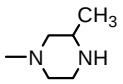
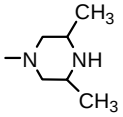
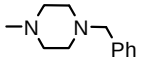
Due to the strong inhibitory activity of compounds **3a**–**i** at 32 μg/disc, all compounds were further tested at the doses lower than 32 μg/disc against a broader panel of *H. pylori* strains (twenty clinical isolates). The antibacterial activities of the target compounds at doses of 16, 8, 4, 2, 1, 0.5 and 0.25 μg/disc against 20 clinical isolates of *H. pylori* are given in Table II as the average diameters of the inhibition zones.

The inhibition zone diameters of compounds at different doses indicate that all compounds exhibit higher inhibitory activity against the clinical isolates of *H. pylori* compared to the standard drug, metronidazole. The inhibition zone dia-

meters of all compounds were on average more than 20 mm at 8 μg/disc, which is greater than that of metronidazole. Compounds **3a**–**d** showed strong growth inhibitory activity at doses of 4 and 2 μg/disc, while metronidazole had very weak activity at these doses. The *N*-benzoylpiperazine derivative **3c** had strong activity even at 0.5 μg/disc (inhibition zone = 20 mm). The inhibition zone diameters at the lowest dose (0.25 μg/disc), indicated that the *N*-acetyl and *N*-benzoyl compounds (**3b** and **3c**, respectively) still had a weak growth inhibition while the remaining compounds showed little or no activity at this dose.

TABLE I. *In vitro* antibacterial activity of compounds **3a**–**i** at 32 μg/disc against *H. pylori* using the disc diffusion method



Compound	R	Inhibition zone diameter[a], mm (range)
3a		50 (44–60)
3b		45.3 (45–48)
3c		42.6 (44–47)
3d		48.6 (47–51)
3e		23 (19–33)
3f		42 (42–44)
3g		41 (40–46)
3h		28 (25–31)
3i		46 (46–48)

[a]The anti-*Helicobacter pylori* activity was determined by the paper disc diffusion bioassay. All tests were performed in triplicate and the antibacterial activity is expressed as the mean of the inhibition diameters produced by the title compounds

The comparison of inhibition zone diameters produced by title compounds revealed that substitution of piperazine moiety by *N*-phenyl, *N*-benzyl, 3-methyl and 3,5-dimethyl diminished the inhibitory activity against clinical isolates of *H. pylori*. In contrast, *N*-benzoylation of the piperazine ring increased the anti-*H.*

pylori activity. In addition, the introduction of *N*-methyl or *N*-acetyl groups on the piperazine ring did not improve the antibacterial activity against *H. pylori*.

TABLE II. Inhibition zone diameters of compounds **3a–i** at different doses against 20 clinical *H. pylori* isolates. Antibacterial activities are expressed as the mean of inhibition zone diameters (mm). Range of inhibition zone diameters against 20 clinical *H. pylori* isolates are given in parenthesis

Compound	Concentration, μg/disc						
	0.25	0.5	1	2	4	8	16
3a	7.9 (6–10)	12.6 (6–15)	17.9 (11–30)	23.8 (14–40)	29. 6 (17–50)	33. 6 (21–57)	43.5 (28-60)
3b	11.8 (6–19)	16.7 (6–22)	19.7 (14–30)	23.1 (15–50)	29.7 (15–60)	34.8 (20–60)	40.4 (24–60)
3c	15.1 (6–20)	20.1 (11–30)	24.1 (14–30)	28.8 (11–43)	35.2 (18–49)	41.2 (20–55)	49.1 (34–60)
3d	8.2 (6–11)	14.8 (6–20)	18.1 (10–28)	22.9 (14–38)	28.2 (15–60)	34.1 (21–60)	40.6 (30–60)
3e	6.5 (6–9)	7.6 (6–10)	12.3 (6–16)	17.3 (10–30)	18.4 (11–40)	21.4 (12–40)	23.9 (15–41)
3f	6 (6)	7.1 (6–10)	8.5 (6–10)	13.0 (6–20)	19.3 (8–30)	23.1 (12–37)	30.8 (18–50)
3g	6 (6)	8.4 (6–15)	12.7 (6–16)	17.8 (15–22)	20.7 (15–25)	20.5 (15–25)	21.5 (18–25)
3h	7.7 (6–9)	11.1 (6–17)	15.2 (8–20)	19.8 (6–28)	22.6 (10–26)	23.5 (15–30)	24.8 (18–30)
3i	6.7 (6–9)	8.5 (6–12)	13.2 (6–17)	19.9 (12–26)	25.3 (18–33)	33.3 (24–39)	38.1 (26–49)
Metronidazole	6	6	9.2 (4–21)	13.1 (6–19)	16.0 (8–26)	19.8 (11–27)	24.1 (17–32)

EXPERIMENTAL

The purity of the synthesized compounds was confirmed by thin layer chromatography (TLC) using various solvents of different polarities. Merck silica gel 60 F254 plates were applied for the analytical TLC. Melting points were measured using a Kofler hot-stage apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu 470 (Shimadzu, Tokyo, Japan) spectrophotometer (potassium bromide disks). Nuclear magnetic resonance spectra were determined in $CDCl_3$ containing TMS as an internal standard using Bruker 80 or 500 spectrometers. The mass spectra were recorded on a Finnigan MAT TSQ-70 spectrometer at 70 eV. Elemental analyses were realized on a CHN-O-rapid elemental analyzer (Heraeus GmbH, Hanau, Germany) for C, H and N, and the results were within ±0.4 % of the theoretical values. All reagents were purchased from Merck and Aldrich and used as such without purification. The solvents employed in the reactions were previously distilled.

General procedure for the synthesis of 1-[5-(5-nitrofuran-2-yl)-1,3,4 thiadiazol-2-yl]piperazine derivatives

To a mixture of 2-chloro-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole (**2,** 231 mg, 1.0 mmol) in ethanol (15 ml), appropriate substituted piperazine (1.0 mmol) was added and refluxed for 3 h.

The completion of reaction was monitored by TLC. After cooling, the separated solid was filtered off and re-crystallized from ethanol.

*Synthesis of 1-acetyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3b**)*

Acetic anhydride (3 ml) was added to a mixture of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3a**, 280 mg, 1.0 mmol) in acetic acid (12.5 ml) and refluxed for 20 min. The mixture was stirred at room temperature overnight and then poured in to ice-water. The yellow precipitate was separated and washed with water and crystallized from ethanol to give pure compound **3b**.

*Synthesis of 1-benzoyl-4-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine (**3c**)*

Benzoyl chloride (70.5 mg, 0.5 mmol) was added under stirring to a suspension of 1-[5--(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl] piperazine (**3a**, 140 mg, 0.5 mmol) in benzene (1 ml) and pyridine (0.5 ml) at 0–5 °C and then, the reaction mixture was stirred at room temperature for 24 h. After evaporation of solvents under reduced pressure, the residue was washed with water and crystallized from ethanol to give compound **3c**.

*Synthesis of 2-(5-nitrofuran-2-yl)-5-pyrrolidin-1-yl-1,3,4-thiadiazole (**3i**)*

A mixture of 2-chloro-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole (**2**, 231 mg, 1.0 mmol) and pyrrolidine (70 mg, 1.0 mmol) in ethanol (10 ml) was refluxed for 1 h. After completion of the reaction, the orange precipitate was filtered and crystallized from ethanol.

CONCLUSIONS

In this study, attention was focused on the synthesis and anti-*Helicobacter pylori* activity of a series of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazoles containing a piperazinyl functionality at the C-2 position of the 1,3,4-thiadiazole ring. The synthesis of the 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]piperazine derivatives **3a**–**h** and the pyrrolidine derivative **3i** was achieved using a versatile and efficient synthetic route *via* 2-chloro-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole. Based on the resulting biological data, compound **3c** containing the *N*-benzoyl-piperazin-1-yl moiety showed the most potent inhibitory activity against *H. pylori* strains. The potent activity and straightforward synthesis of these nitrofurans suggest that they are potential candidates for the development of new anti-*H. pylori* agents.

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ИЗВОД

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ 5-НИТРОФУРАНА, КОЈИ САДРЖЕ (1,3,4-ТИАДИАЗОЛ-2-ИЛ)ПИПЕРАЗИНСКУ СТРУКТУРУ, КАО НОВИ ТИП АНТИ-*Helicobacter pylori* ХЕТЕРОЦИКЛА

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У циљу проналажења новог ефикасног лека за лечење од инфекција изазваних *Helicobacter pylori* нашу пажњу усмерили смо према синтези и испитивању анти-*H. pylori* активности серије 5-(5-нитрофуран-2-ил)-1,3,4-тиадиазола који садрже пиперазинилни структурни фрагмент у положају C-2 1,3,4-тијадиазолског прстена. Синтеза деривата 1-[5-(5-нитрофуран-2-ил)-1,3,4-тиадиазол-2-ил]пиперазина **3a**–**h** и пиролидинског деривата **3i** постигнута је преко интермедијера 2-хлор-5-(5-нитрофуран-2-ил)-1,3,4-тиадиазола. Користећи диск-дифузиону методу испитана је инхибиторна активност нових деривата **3a**–**i** према двадесет клиничких сојева *H. pylori* и извршено је поређење добијених резултата са резултатима активности метронидазола, комерцијалног стандарда. Добијени резултати показују да већина једињења показује јаку инхибиторну активност чак и при дозама мањим од 2 μg/диск (просечна зона инхибиције је >20 mm), док метронидазол показује малу инхибицију или потпуно одсуство инхибиције при истим дозама. Највећу инхибицију показује једињење **3c** које садржи *N*-бензоилпиперазин-1-ил фрагмент.

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