

Synthesis and antimicrobial activity of 4-(5-ARYL-2-FUROYL)morpholines and 4-[(5-ARYL-2-FURYL)carbonothioyl]morpholines

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Abstract

By the reaction of furan-2-carboxylic acids and furfural with diazonium salts **1a-j** the arylfuran-2-carboxylic acids **4a-e** and 5-aryl-furan-2-carbaldehydes **5a-f** were synthesized. Acids **4a-e** were transformed into appropriated acylchlorides **6a-e** and were used for preparation of 4-(5-aryl-2-furoyl)morpholines **7a-e**. 4-[(5-Aryl-2-furyl)carbonothioyl]morpholines **8a-f** were prepared from aldehydes **5a-f** by using Willgerodt-Kindler reaction. The structures of the obtained compounds were confirmed by ¹H NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures. The antimicrobial activities of synthesized compounds **7a-e** and **8a-f** were investigated and the compounds with high activity against *C. neoformans* ATCC 208821 were identified.

Keywords

antimicrobial activity, 4-(5-aryl-2-furoyl)morpholines, 4-[(5-aryl-2-furyl)carbonothioyl]morpholines

Introduction

The development of methods of combinatorial synthesis of heterocyclic compounds and their biological evaluation are important points in organic and medical chemistry. In our previous work we have developed methods of synthesis of furan (Obushak et al. 2008; Gorak et al. 2009), pyrazole (Matiichuk et al. 2008), thiazole (Tsyalkovsky et al. 2005; Zimenkovskii et al. 2006; Ostapiuk et al. 2012;

Chaban et al. 2019a) and triazole (Pokhodylo et al. 2009a) derivatives based on using of diazonium salt as starting reagents. Some condensed molecules were also prepared (Pokhodylo et al. 2009b; Zubkov et al. 2010; Klenina et al. 2013, 2017; Chaban et al. 2014, 2016, 2017, 2018, 2019b, c; Zelisko et al. 2015). Arendiazonium salts are obtained from available aromatic amines.

In this article we described the synthesis and antimicrobial evaluation of morfolides and thiomorfolides of

5-arylfuran-2-carboxylic acids. It should be noticed that 5-aryl-2-furamides possessing various types of biological and pharmacological activities such as anticancer (Cui et al. 2010), anti-inflammatory (Kort et al. 2008) and antihyperalgesic (Yogeeswari et al. 2011). These compounds were investigated as agents for treatment of infectious diseases that are caused by microorganisms like *Mycobacterium tuberculosis* (Jeankumar et al. 2012) and *Trypanosoma brucei* (Urich et al. 2014; Manda et al. 2014) parasites, having additionally in mind the lack of information on the biological properties of 5-phenylfuran-2-carbothioamide.

Experimental part

Materials and methods

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying. All the melting points were determined in an open capillary and are uncorrected. ¹H-spectra were recorded on a Varian Mercury 400 (400 MHz for ¹H) instrument with TMS or deuterated solvent as an internal reference. Satisfactory elemental analyses were obtained for new compounds (C±0.17, H±0.21, N±0.19).

Chemistry

General procedure of preparation 4-(5-aryl-2-furoyl) morpholines (7a-e). A solution of acyl chlorides 0.005 mol in 20 mL dioxane and morpholine (0.001 mol) were stirred at room temperature for 1 hour. Next the mixture was poured in 50ml of water. The resulting solid was filtered, washed with water, dried, and crystallized with ethanol-DMFA.

4-[5-(4-Fluorophenyl)-2-furoyl]morpholine (7a). Yield 85%; m.p. = 116–117 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.87–7.77 (m, 2H, ArH), 7.32 (t, J 8.8 Hz, 2H, ArH), 7.13 (d, J 3.6 Hz, 1H, 3-H_{Fur}), 7.09 (d, J 3.6 Hz, 1H, 4-H_{Fur}), 3.73 (brs, 4H, (CH₂)₂N), 3.66 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₄FNO₃: C, 65.45; H, 5.13; N, 5.09. Found: C, 65.58; H, 5.17; N, 5.14.

4-[5-(4-Nitrophenyl)-2-furoyl]morpholine (7b). Yield 82%; m.p. = 191–192 °C. ¹H NMR (400 MHz, DMSO-d₆) d 8.31 (d, J 7.6 Hz, 2H, ArH), 8.02 (d, J 7.6 Hz, 2H, ArH), 7.44 (d, J 3.2 Hz, 1H, 3-H_{Fur}), 7.21 (d, J 3.2 Hz, 1H, 4-H_{Fur}), 3.74 (brs, 4H, (CH₂)₂N), 3.67 (br s, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₄N₂O₅: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.51; H, 4.63; N, 9.33.

4-[5-(2,5-Dichlorophenyl)-2-furoyl]morpholine (7c). Yield 91%; m.p. = 105–106 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.83 (d, J 2.0 Hz, 1H, 6-HArH), 7.63 (d, J 8.8 Hz, 1H, 3-HArH), 7.48 (dd, J 8.6, 2.4 Hz, 1H, 4-HArH), 7.30 (d, J 3.6 Hz, 1H, 3-H_{Fur}), 7.18 (d, J 3.6 Hz, 1H, 4-H_{Fur}), 3.72 (brs, 4H, (CH₂)₂N), 3.66 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₃Cl₂NO₃: C, 55.24; H, 4.02; N, 4.29. Found: C, 55.12; H, 3.97; N, 4.32.

4-[5-(2,6-Dichlorophenyl)-2-furoyl]morpholine (7d). Yield 87%; m.p. = 103–104 °C. ¹H NMR (400 MHz, DM-

SO-d₆) d 7.83 (d, J 2.3 Hz, 1H), 7.62 (d, J 8.6 Hz, 1H), 7.48 (dd, J 8.6, 2.4 Hz, 1H), 7.30 (d, J 3.6 Hz, 1H, 3-H_{Fur}), 7.17 (d, J 3.6 Hz, 1H, 4-H_{Fur}), 3.72 (brs, 4H, (CH₂)₂N), 3.66 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₃Cl₂NO₃: C, 55.24; H, 4.02; N, 4.29. Found: C, 55.11; H, 3.96; N, 4.21.

4-[5-(4-Chloro-2-nitrophenyl)-2-furoyl]morpholine (7e). Yield 93%; m.p. = 135–136 °C. ¹H NMR (400 MHz, DMSO-d₆) d 8.18 (s, 1H, 3-HArH), 7.96 (d, J 8.8 Hz, 1H, 5-HArH), 7.87 (d, J 8.4 Hz, 1H, 6-H ArH), 7.19 (d, J 3.2 Hz, 1H, 3-H_{Fur}), 7.17 (d, J 3.2 Hz, 1H, 4-H_{Fur}), 3.63 (br s, 8H, 4'CH₂). Anal. Calculated for C₁₅H₁₃ClN₂O₅: C, 53.50; H, 3.89; N, 8.32. Found: C, 53.39; H, 3.84; N, 8.37.

General procedure of preparation 4-[(5-aryl-2-furyl)carbonothioyl]-morpholines (8a-f). A mixture of 0.01 mol of arylfurfurals 6, 0.013 mol of morpholine, and 0.32 g (0.01 mol) of fine powder of sulfur in 20 ml of DMF was stirred at 100 °C for 6 hours. The cooled reaction mixture was diluted with water (100 ml) and the precipitate which was separated was filtered off and recrystallized with ethanol-DMFA.

4-[[5-(4-Isopropylphenyl)-2-furyl]carbonothioyl]morpholine (8a). Yield 65%; m.p. = 65–66 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.69 (d, J 7.6 Hz, 2H, ArH), 7.34 (d, J 7.6 Hz, 2H, ArH), 7.15 (d, J 2.0 Hz, 1H, 3-H_{Fur}), 7.03 (d, J 2.0 Hz, 1H, 4-H_{Fur}), 4.14 (brs, 4H, (CH₂)₂N), 3.75 (brs, 4H, (CH₂)₂O), 2.92 (septet, J 6.8 Hz, 1H, CHMe₂), 1.21 (d, J 6.8 Hz, 6H, CH(CH₃)₂). Anal. Calculated for C₁₈H₂₁NO₂S: C, 68.54; H, 6.71; N, 4.44; S, 10.16. Found: C, 68.67; H, 6.79; N, 4.51; S, 10.22.

4-[[5-(2-Fluorophenyl)-2-furyl]carbonothioyl]morpholine (8b). Yield 73%; m.p. = 89–90 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.82 (dt, J 8.0, 1.6 Hz, 1H, ArH), 7.42–7.34 (m, 1H, ArH), 7.33–7.20 (m, 2H, ArH), 7.14 (d, J 3.6 Hz, 1H, 3-H_{Fur}), 6.91 (t, J 3.6 Hz, 1H, 4-H_{Fur}), 4.17 (brs, 4H, (CH₂)₂N), 3.79 (br s, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₄FNO₂S: C, 61.84; H, 4.84; N, 4.81; S, 11.01. Found: C, 61.72; H, 4.78; N, 4.88; S, 10.92.

4-[[5-(4-Bromophenyl)-2-furyl]carbonothioyl]morpholine (8c). Yield 82%; m.p. = 142–143 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.72 (d, J 8.4 Hz, 2H, ArH), 7.66 (d, J 8.4 Hz, 2H, ArH), 7.17 (d, J 3.2 Hz, 1H, 3-H_{Fur}), 7.14 (d, J 3.6 Hz, 1H, 4-H_{Fur}), 4.14 (brs, 4H, (CH₂)₂N), 3.75 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₄BrNO₂S: C, 51.15; H, 4.01; N, 3.98; S, 9.10. Found: C, 51.02; H, 3.96; N, 4.05; S, 9.16.

4-[[5-(2,6-Dichlorophenyl)-2-furyl]carbonothioyl]morpholine (8d). Yield 69%; m.p. = 120–121 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.68–7.61 (m, 2H, ArH), 7.58–7.51 (m, 1H, ArH), 7.18 (d, J 2.8 Hz, 1H, 3-H_{Fur}), 6.84 (d, J 2.8 Hz, 1H, 4-H_{Fur}), 4.22 (brs, 2H, CH₂N), 3.95 (brs, 2H, CH₂N), 3.72 (br s, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₃Cl₂NO₂S: C, 52.64; H, 3.83; N, 4.09; S, 9.37. Found: C, 52.51; H, 3.77; N, 4.14; S, 9.45.

4-[[5-(3,5-Dichlorophenyl)-2-furyl]carbonothioyl]morpholine (8e). Yield 75%; m.p. = 238–239 °C. ¹H NMR (400 MHz, DMSO-d₆) d 7.80 (s, 2H, ArH), 7.59 (s, 1H, ArH), 7.35 (d, J 2.8 Hz, 1H, 3-H_{Fur}), 7.13 (d, J 2.8 Hz, 1H, 4-H_{Fur}), 4.23 (brs, 2H, CH₂N), 4.01 (brs, 2H, CH₂N), 3.74 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₃Cl₂NO₂S: C, 52.64; H, 3.83; N, 4.09; S, 9.37. Found: C, 52.69; H, 3.89; N, 4.01; S, 9.46.

4-[[5-(2-Chloro-4-nitrophenyl)-2-furyl]carbonothioyl]morpholine (8f). Yield 81%; m.p. = 142–143 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.40 (s, 1H, 3-HArH), 8.28 (d, *J* 8.8 Hz, 1H, 5-HArH), 8.11 (d, *J* 8.8 Hz, 1H, 6-HArH), 7.52 (d, *J* 2.8 Hz, 1H, 3-H_{Fur}), 7.19 (d, *J* 2.8 Hz, 1H, 4-H_{Fur}), 4.27 (brs, 2H, CH₂N), 3.99 (brs, 2H, CH₂N), 3.75 (brs, 4H, (CH₂)₂O). Anal. Calculated for C₁₅H₁₃ClN₂O₄S: C, 51.07; H, 3.71; N, 7.94; S, 9.09. Found: C, 51.16; H, 3.79; N, 7.82; S, 9.17.

Microbiology

Antibacterial data collection to signify bacterial strains and growth conditions. Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD600), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each of them, using the negative control (media only) and positive control (bacteria without inhibitors) at the same time as references.

Antifungal data collection. Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD530), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each of them, using the negative control (media only) and positive control (bacteria without inhibitors) at the same time as references.

Inhibition. Percentage growth inhibition of an individual sample is based on Negative controls (media only) and positive controls (bacterial/fungal media without

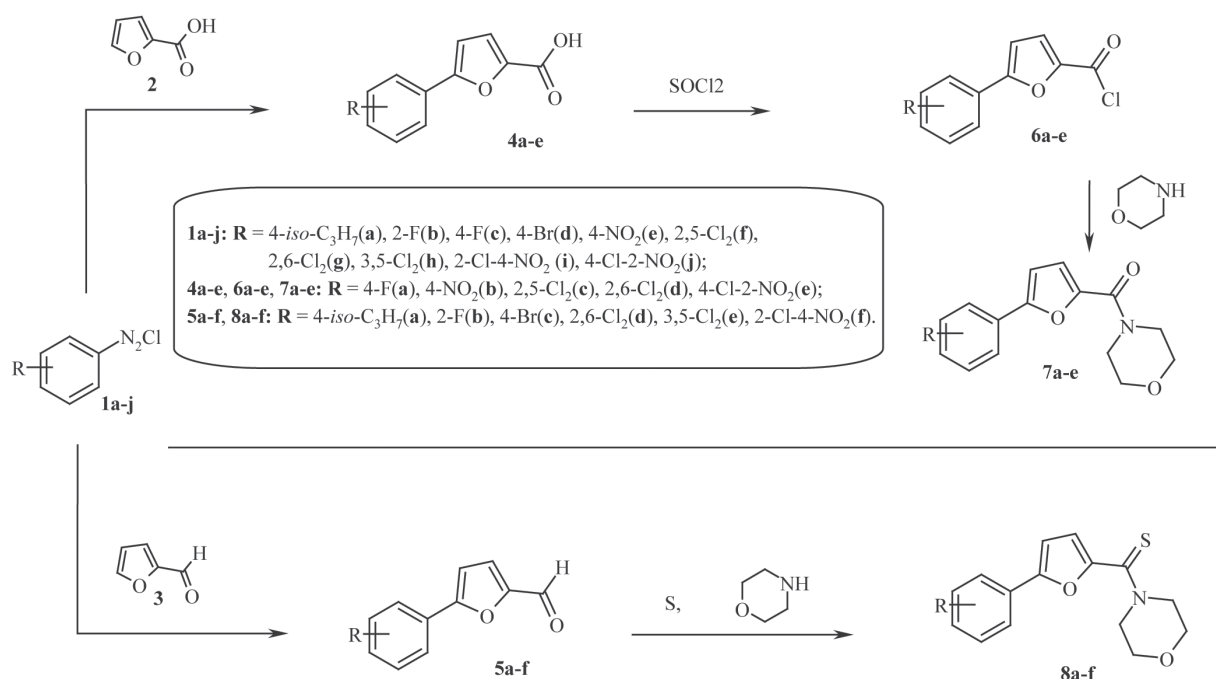
inhibitors). Negative inhibition values indicate that the growth rate (or OD600) is higher compared to the Negative Control (Bacteria/fungi only, set to 0% inhibition). The growth rates for all bacteria and fungi has a variation of -/+ 10%, which is within the reported normal distribution of bacterial/fungal growth (<https://www.co-add.org>).

Results and discussion

Chemistry

Our synthesis started from aromatic diazonium salts 1a–j and furan-2-carboxylic acids 2 or furfural 3. At first stage furan compounds undergo acylation in Meerwein reaction condition (Obushak et al. 2008) according methods described in literature (Gorak et al. 2009). As a result 5-aryl-furan-2-carboxylic acids 4a–e and 5-arylfuran-2-carbaldehydes 5a–f were synthesized. To prepare target morfolides the acids 4a–e were transformed into appropriated acylchlorides 6a–e. They were used in acylation of morfoline. The reaction was performed in dioxane at the room temperature. Thiomorfolides 8a–f were prepared by using Wilgerodt-Kindler reaction according to the procedure which was described in scheme (Fedorovich et al. 2007).

The structures of prepared compounds were confirmed by ¹H NMR spectroscopy and elemental analysis. ¹H NMR spectral data of compounds 7a–e and 8a–f revealed supporting evidence to identify their structures. The two singlet signals belonging to morfoline protons in compounds 7a–e were detected at 3.72–3.74 and 3.66–3.67 ppm respectively. But the chemical shift of the CH₂NCH₂ protons of morfoline ring in compounds 8a–f were detected in the range of 3.75–4.01 and 4.14–4.27 ppm as two singlet peaks. This means that the rotation around the C(S)-N bonds is restricted.



Scheme. Synthesis of 4-(5-aryl-2-furoyl)morpholines and 4-[(5-aryl-2-furyl)carbonothioyl]morpholines.

Table 1. Antimicrobial activity compounds 7a–e and 8a–f.

Compound	<i>S. aureus</i> ATCC 43300	<i>E. coli</i> ATCC ATCC 25922	<i>K. pneumoniae</i> ATCC 700603	<i>P. aeruginosa</i> ATCC 27853	<i>A. baumannii</i> ATCC 19606	<i>C. albicans</i> ATCC 90028	<i>C. neoformans</i> ATCC 208821
7a	50.3; 54.9	0.0; 1.4	3.8; 9.0	-4.9; -7.7	13.1; 2.9	4.1; 5.8	-14.1; -8.7
7b	13.1; 34.9	1.5; 4.8	-0.1; 15.3	-1.1; 4.1	1.8; 3.5	3.9; 7.3	85.1; 96.2
7c	27.6; 31.6	2.1; 4.6	-4.8; 9.9	-0.9; 2.0	2.6; 5.9	1.4; 4.6	55.9; 57.5
7d	-18.5; -7.3	6.1; 9.0	-1.6; 1.4	2.8; 3.1	-13.1; 13.6	18.5; 7.2	30.7; 33.8
7e	-12.8; 2.1	-1.6; 0.4	11.9; 9.0	4.0; 6.0	-0.2; -9.3	3.2; 3.4	24.6; 26.8
8a	30.0; 30.3	0.7; 1.8	4.7; 6.3	-7.8; 0.6	-10.3; 3.6	13.7; 15.3	96.9; 98.2
8b	12.7; 9.8	0.5; 1.0	10.1; 6.2	-2.6; 2.7	10.9; 21.7	35.7; 59.0	52.0; 63.8
8c	11.6; 6.7	-4.0; -5.2	0.5; 8.0	-3.3; -5.1	4.7; 5.0	5.0; 6.7	100.7; 95.2
8d	0.8; 1.4	2.0; 2.5	11.5; 3.4	-2.0; -2.6	20.0; 9.6	-1.2; 0.9	-11.9; -4.3
8e	2.0; 8.0	2.3; 2.3	3.6; 4.3	-2.0; 2.9	10.1; 6.0	12.8; 18.5	-21.9; -31.2
8f	-10.4; -11.4	-5.4; -8.3	-6.7; -6.9	-1.8; -3.6	-11.4; -11.7	1.2; 5.4	-12.0; -12.7

Biology

The antimicrobial screening was performed by CO-ADD (the Community for Antimicrobial Drug Discovery) funded by the Wellcome Trust (UK) and the University of Queensland (Australia) (<https://www.co-add.org>). The growth inhibition was measured against five bacterial strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*) and two fungal strains (*Candida albicans* and *Cryptococcus neoformans*). The standard concentration employed for screening was 32 mg/ml in DMSO. The observed *in vitro* antimicrobial activities of our synthesized products 7a–e and 8a–f are tabulated in Table 1.

In most cases the tested compounds 7a–e and 8a–g displayed a low antimicrobial activity *in vitro* when screened on the tested microorganisms. But compounds 7a, 7c and 8a have shown weak to medium antibacterial activity against gram-positive bacteria *Staphylococcus aureus* ATCC 43300 with range of GP= 27.6–54.9% and 7b, 8a and 8c high activity against fungi *Cryptococcus neoformans* ATCC 208821 (GP=85.1–100.7%). For compounds 7b, 8a and 8c MIC and cytotoxicity to Human embryonic kidney and Human red blood cells were also investigated. They demonstrated significant activity (MIC = 4–16ug/ml) and low cytotoxicity to Human embryonic kidney and Human red blood cells. In all cases HkCC₅₀ and HmHC₁₀ were above >32 ug/ml. The selectivity indexes were also calculated. They were above 2 for tested compounds (Table 2).

A retrospective antimicrobial activity results analysis of the subjects 4-(5-aryl-2-furoyl)morpholines and 4-[(5-aryl-2-furyl)carbonothioyl] morpholines allowed

Table 2. Antimicrobial activity and cytotoxicity to Human embryonic kidney cells and 7b and 8a,c (ug/mL).

Compound	MIC	HkCC ₅₀	HmHC ₁₀	SI = HC ₁₀ /MIC
7b	8; 8	>32; >32	>32; >32	>4; >4
8a	4; 4	>32; >32	>32; >32	>8; >8
8c	16; 16	>32; >32	>32; >32	>2; >2

us to distinguish the following chemical optimization vectors. Test compounds exhibit different activity, which is determined by the nature of the substituent. The resulting 4-(5-aryl-2-furoyl)morpholines (7a–e) have no high antimicrobial activity. however, compound 7b has high antifungal activity which allows us to conclude the pharmacophore properties of the nitro group in 2-furoylmorpholines moiety. 4-[(5-Aryl-2-furyl)carbonothioyl] morpholines (8a–f) exhibits relatively not very high antimicrobial activity. However, compounds 8a and 8c were found to have high antifungal activity. The results obtained demonstrate that the antimicrobial effect of the synthesized compounds is probably due to the contribution of morpholine nucleus and a number of structural fragments that are pharmacophore for the class heterocycles and the type of pharmacological activity.

Conclusions

In our work, we presented an efficient synthesis and antimicrobial activity evaluation of some 4-(5-aryl-2-furoyl)morpholines and 4-[(5-aryl-2-furyl)carbonothioyl] morpholines. First, antimicrobial activity was detected among the compounds tasted. Further optimization of the structure to improve their activities is currently in progress.

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