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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, structural characterization, antimicrobial and antifungal activity of substituted 6-fluorobenzo[*d*]thiazole amides

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Abstract A series of novel 1-[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted phenyl amides was synthesized by the condensation reaction of (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine with substituted benzoyl chlorides under mild conditions. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra, elemental analyses and in three cases also by single-crystal X-ray diffraction techniques. The optical activities were confirmed by optical rotation measurements. All the synthesized compounds were screened for antibacterial and antifungal activity against a variety of bacterial and fungal strains. Some of the compounds reveal antibacterial and antifungal activity comparable or slightly better to that of chloramphenicol, cefoperazone and amphotericin B used as medicinal standards.

Keywords Fluorinated benzothiazole derivates · Substituted benzoyl chloride · Antimicrobial activity · Antifungal activity

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Introduction

Benzothiazoles are group of heterocyclic moieties found in a plethora of natural compounds both of terrestrial or marine origin and play an important role in living systems (Gunawardana *et al*., 1988, 1992; Turan-Zitouni *et al*., 2003). These compounds reveal interesting biocidal activities against a wide range of bacteria (Bondock *et al*., 2010), viruses (Nagarajan *et al*., 2003), helminths (Sarkar *et al*., 2008), fungi (Reuveni, 2003) and last but not least some tumor cell lines (Lion *et al*., 2006; Sekar *et al*., 2010). Molecular skeleton of these compounds can serve as a unique and versatile playground for further synthetic modification and thus also for an experimental drug design. The studies of structure–activity relationships interestingly reveal that a slight variation of the structure of substituent group at C-2 position commonly results in significant change of its biological activity (Pejchal *et al*., 2011a, b; Imramovsky *et al*., 2013).

(*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethanamine, as a representative of above-mentioned group of compounds, is the fundamental scaffold for antimicrobial treatment (Patel and Rathod, 2006), herbicides, plant desiccants and defoliants compounds (Hamprecht *et al*., 1999). Similar compounds with adjacent substitution, such as isopropyl[(*S*)-1-[(*R*)-1-(6-flourobenzothiazolel-2-yl)ethylcarbamoyl]-2-methylpropyl] carbamate (Scheme 1), is reported as commercially used fungicide (benthiavalicarb isopropyl or KIF 230) highly effective for controlling the oomycete fungal pathogen *Plasmopara viticola*, which causes downy mildew in grapevines (Sarkar *et al*., 2008). The aims of this study are the preparation and complete characterization of novel amide derivates of compound **3** and an investigation of its fundamental biological activities (Schemes 2, 3).

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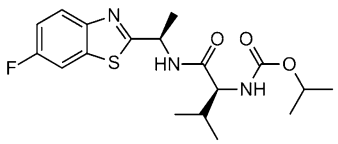
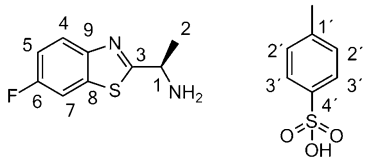
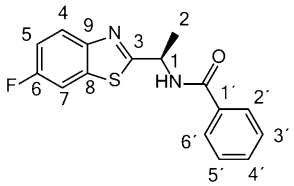


Scheme 1 Commercially available fungicide benthiavalicarb isopropyl



Scheme 2 Proton numbering for assignment of ^{1}H NMR shifts (compound **2**)

Scheme 3 Proton numbering for assignment of ^{1}H NMR shifts (compounds **3a**–**m**)



Experimental

All reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Merck, Acros Organics). Phosgene was purchased from Synthesia (Pardubice, Czech Republic). Reactions were monitored by thin-layer chromatography plates coated with 0.2-mm silica gel 60 F_{254} (Merck). TLC plates were visualized by the UV irradiation (254 nm). All melting points were determined on Melting Point B-545 apparatus (Buchi, Germany) and are uncorrected. Infrared spectra (ZnSe ATR experiments) were recorded on a FT-IR spectrometer (PerkinElmer, USA) in the range of 600–4000 cm^{-1}. The NMR spectra were measured in DMSO-*d6* solutions at ambient temperature on a Bruker Advance III 400 (400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 376.5 MHz for ^{19}F). Coupling constants are presented in Hz. Proton chemical shifts in DMSO-d6 are related to the middle of the solvent multiplet ($\delta = 2.50$). ^{13}C NMR spectra were measured using APT pulse sequence. Carbon chemical shifts are referenced to the middle of the solvent's multiplet ($\delta = 39.5$ in DMSO-d6). The optical rotation was measured on a PerkinElmer 341 instrument, and concentration c is given in g/100 mL. Elemental analysis (C, H, N) was performed on an automatic microanalyzer CE Instruments EA 1110 CHN elemental analyzer (Fisons Instruments).

Desired compounds (4*R*)-4-methyl-1,3-oxazolidine-2,5-dione **1** and (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine *p*-toluenesulfonic salt **2** were synthesized by reported method (Hijikata, 2003; Pejchal *et al.*, 2011a). The structures of the intermediates were confirmed by ^{1}H NMR, ^{13}C NMR and melting point.

Characterization of synthesized compound (R)-4-methyloxazolidine-2,5-dione (1)

This compound was obtained by reaction of D-alanine with phosgene. It was obtained as white solid; Yield: 83 %; m.p. 89–90 °C ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.01$ (s, 1H, N*H*), 4.47 (q, 1H, $^{3}J = 7.2$ Hz, C*H*), 1.33 (d, 3H, $^{3}J = 7.2$ Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100.62 MHz) $\delta = 172.5$ (COO), 151.8 (CONH), 52.9 (CH), 16.8 (CH_3).

Characterization of synthesized compound (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate (2)

This compound was obtained by reaction of (*R*)-4-methyloxazolidine-2,5-dione with 2-amino-6-fluorobenzothiazole. It was obtained as white solid; Yield: 81 %; m.p. 241–242 °C ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 8.74$ (s, 2H, NH_2), 8.12 (dd, 1H, $^{4}J = 2.4$ Hz, $^{3}J_{F\text{-}H} = 8.4$ Hz, H-7), 8.09 (dd, 1H, $^{3}J = 9.2$ Hz, $^{4}J_{F\text{-}H} = 4.8$ Hz, H-4), 7.48 (d, 2H, $^{3}J = 8.0$ Hz, H-2′), 7.37 (dt, 1H, $^{4}J = 2.4$ Hz, $^{3}J = 9.2$ Hz, $^{3}J_{F\text{-}H} = 9.2$ Hz, H-5), 7.10 (d, 2H, $^{3}J = 8.0$ Hz, H-3′), 5.01 (quint, 1H, $^{3}J = 6.8$ Hz, H-3), 2.28 (s, 3H, CH_3), 1.66 (d, 3H, $^{3}J = 6.8$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 169.1$ (C, d, $^{4}J_{F\text{-}C} = 3.4$ Hz, C-9), 159.9 (C, d, $^{1}J_{F\text{-}C} = 243.5$ Hz, C-6), 148.8 (C, C-3), 144.9 (C, C-4′), 138.5 (C, C-1′), 136.4 (C, d, $^{3}J_{F\text{-}C} = 11.9$ Hz, C-8), 128.5 (CH, C-2′), 125.7 (CH, C-3′), 124.3 (CH, d, $^{3}J_{F\text{-}C} = 9.6$ Hz, C-4), 115.5 (CH, d, $^{2}J_{F\text{-}C} = 24.9$ Hz, C-5), 109.0 (CH, d, $^{2}J_{F\text{-}C} = 27.4$ Hz, C-7), 48.4 (CH, C-1), 20.9 (CH_3), 19.9 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -115.21$. Anal. Calcd. for $C_{16}H_{17}FN_2O_3S_2$ (368.44): C, 52.16; H, 4.65; N, 7.60. Found: C, 52.00; H, 4.82; N, 17.51.

General experimental procedure and characterization data of prepared amides compounds 3a–3m

To the mixture of toluene (70 mL) and water (30 mL) was added sulfonate salt of (*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethanamine **2** (5.0 mmol) as a gray powder and substituted aroyl chloride (7.5 mmol). Solution of sodium hydroxide was added dropwise to the reaction mixture to change pH to 9–10 (approx. 4.5 g of 10 % solution). Reaction mixture was stirred 5 h at room temperature. The pH was maintained on 9–10 with addition of sodium hydroxide solution. Reaction mixture was heated to 70 °C.

Toluene layer was separated and concentrated by vacuum distillation. Distillation residue was cooled down to 0–5 °C. The precipitate was collected by filtration.

Characterization of synthesized compounds 3a–m

*N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]benzamide (**3a**)*

This compound was prepared by reaction of benzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 84.0 %; m.p. 163–164 °C; $[\alpha]_D^{20}$ +48.7 (c 1, acetone); IR (ATR) ν_{max} 3255, 1530 (NH of CONH), 1645 (CO of CONH), 1455, 1348, 1329, 1198, 859, 821 cm^{-1}; ^1H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.32$ (1H, d, $^3J = 7.5$ Hz, N*H*), 7.99 (1H, dd, $^3J = 8.8$ Hz, $^4J_{F\text{-}H} = 5.2$ Hz, H-4), 7.96 (3H, m, H-7, H-2′), 7.60–7.50 (3H, m, H-3′, H-4′), 7.36 (1H, dt, $^4J = 2.6$ Hz, $^3J = 9.1$ Hz, $^3J_{F\text{-}H} = 9.1$ Hz, H-5), 5.54 (1H, quint, $^3J = 7.2$ Hz, H-1), 1.71 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 176.1$ (C, d, $^4J_{F\text{-}C} = 3.3$ Hz, C-9), 166.4 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 242.1$ Hz, C-6), 149.7 (C, d, $^5J_{F\text{-}C} = 1.4$ Hz, C-3), 135.8 (C, d, $^3J_{F\text{-}C} = 11.3$ Hz, C-8), 133.8 (C, C-1′), 131.7 (CH, C-4′), 128.4 (CH, C-3′, C-5′), 127.5 (2CH, C-2′, C-6′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.7$ Hz, C-4), 114.5 (CH, d, $^2J_{F\text{-}C} = 24.7$ Hz, C-5), 108.5 (CH, d, $^2J_{F\text{-}C} = 27.1$ Hz, C-7), 48.0 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.6$; Anal. Calcd. for $C_{16}H_{13}FN_2OS$ (300.35): C, 63.98; H, 4.36; N, 9.33; S, 10.68. Found: C, 64.08; H, 4.28; N, 9.38; S, 10.58.

*2-Chloro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3b**)*

This compound was prepared by reaction of 2-chloro benzoylchloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 86 %; m.p. 168–170 °C; $[\alpha]_D^{20}$ +66.7 (c 1, acetone); IR (ATR)ν_{max} 3237, 1534 (NH of CONH), 1628 (CO of CONH), 1453, 1330, 1329, 866, 810, 730 cm^{-1}; ^1H NMR (DMSO-d_6, 400.13 MHz): $\delta =$ (1H, d, $^3J = 7.7$ Hz, N*H*), 8.03 (1H, dd, $^4J = 2.6$ Hz, $^3J_{F\text{-}H} = 8.9$ Hz, H-7); 8.00 (1H, dd, $^3J = 8.9$ Hz, $^4J_{F\text{-}H} = 5.1$ Hz, H-4), 7.56–7.43 (4H, m, H-3′–H-6′), 7.38 (1H, dt, $^4J = 2.7$ Hz, $^3J(^1H, ^1H) = 9.1$ Hz, $^3J_{F\text{-}H} = 9.1$ Hz, H-5), 5.47 (1H, quint, $^3J = 7.2$ Hz, H-1); 1.66 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.4$ (C, d, $^4J_{F\text{-}C} = 3.0$ Hz, C-9), 166.3 (C=O), 159.6 (C, d, $^1J_{F\text{-}C} = 241.0$ Hz, C-6), 149.7 (C, d, $^5J_{F\text{-}C} = 1.4$ Hz, C-3), 136.2 (C, C-2′), 135.8 (C, d, $^3J_{F\text{-}C} = 12.0$ Hz, C-8), 131.1 (CH, C-4′), 130.0 (CH, C-1′), 129.7 (CH, C-3′), 128.9 (CH, C-6′), 127.2 (CH, C-5′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.6$ Hz, C-4), 114.6 (CH, d, $^2J_{F\text{-}C} = 24.8$ Hz, C-5), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.2$ Hz, C-7), 47.9 (CH, C-1), 19.9 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.5$; Anal. Calcd. for $C_{16}H_{12}ClFN_2OS$ (334.80): C, 57.40; H, 3.61; N, 8.37; S, 9.58. Found: C, 57.55; H, 3.67; N, 8.28; S, 9.38.

*3-Chloro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3c**)*

This compound was prepared by reaction of 3-chlorobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 88 %; m.p. 174–176 °C; $[\alpha]_D^{20}$ +67.5 (c 1, acetone); IR (ATR) ν_{max} 3240, 1537 (NH of CONH), 1644 (CO of CONH), 1456, 1332, 824, 763, 708 cm^{-1}; ^1H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.44$ (1H, d, $^3J = 7.5$ Hz, N*H*), 7.97 (3H, m, H-4, H-7, H-2′), 7.89 (1H, d, $^3J = 7.8$ Hz, H-6′), 7.65 (1H, d, $^3J = 7.6$ Hz, H-4′), 7.56 (1H, t, $^3J = 8.0$ Hz, H-5′), 7.37 (1H, dt, $^4J = 2.6$ Hz, $^3J = 9.1$ Hz, $^3J_{F\text{-}H} = 9.1$ Hz, H-5), 5.51 (1H, quint, $^3J = 7.2$ Hz, H-1), 1.70 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.6$ (C, d, $^4J_{F\text{-}C} = 3.2$ Hz, C-9), 165.6 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 243.0$ Hz, C-6), 149.7 (C, d, $^5J_{F\text{-}C} = 1.3$ Hz, C-3), 135.8 (C, d, $^3J_{F\text{-}C} = 12.1$ Hz, C-8), 135.7 (C, C-1′), 133.3 (C, C-3′), 131.5 (CH, C-4′), 130.5 (CH, C-5′), 127.2 (CH, C-6′), 126.4 (CH, C-2′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.6$ Hz, C-4), 114.6 (CH, d, $^2J_{F\text{-}C} = 24.7$ Hz, C-5), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.1$ Hz, C-7), 48.2 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.5$; Anal. Calcd. $C_{16}H_{12}ClFN_2OS$ (334.80): C, 57.40; H, 3.61; N, 8.37; S, 9.58. Found: C, 57.52; H, 3.72; N, 8.28; S, 9.42.

*4-Chloro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3d**)*

This compound was prepared by reaction of 4-chlorobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 87 %; m.p. 193–194 °C; $[\alpha]_D^{20}$ +64.2 (c 1, acetone); IR (ATR) ν_{max} 3265, 1534 (NH of CONH), 1641 (CO of CONH), 1456, 1333, 1252, 1196, 1015, 843, 704, 680 cm^{-1}; ^1H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.39$ (1H, d, $^3J = 7.3$ Hz, N*H*), 8.01 – 7.94 (4H, m, H-4, H-7, H-2′, H-6′), 7.59 (2H, d, $^3J = 8.6$ Hz, H-3′, H-5′), 7.36 (1H, dt, $^4J = 2.6$ Hz, $^3J = 9.1$ Hz, $^3J_{F\text{-}H} = 9.1$ Hz, H-5), 5.52 (1H, quint, $^3J = 7.2$ Hz, H-1), 1.70 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.7$ (C, d, $^4J_{F\text{-}C} = 3.2$ Hz, C-9), 165.3 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 240.8$ Hz, C-6), 149.7 (C, d, $^5J_{F\text{-}C} = 1.6$ Hz, C-3), 136.6 (C, C-4), 135.7 (C, d, $^3J_{F\text{-}C} = 11.7$ Hz, C-8), 132.5 (C, C-1′), 129.5 (2CH, C-2′, C-6′), 128.5 (2CH, C-3′,

C-5′), 123.7 (CH, d, $^{3}J_{F\text{-}C} = 9.5$ Hz, C-4), 114.5 (CH, d, $^{2}J_{F\text{-}C} = 24.7$ Hz, C-5), 108.6 (CH, d, $^{2}J_{F\text{-}C} = 27.1$ Hz, C-7), 48.1 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.5$; Anal. Calcd. $C_{16}H_{12}ClFN_2OS$ (334.80): C, 57.40; H, 3.61; N, 8.37; S, 9.58. Found: C, 57.51; H, 3.78; N, 8.25; S, 9.44.

*3-Fluoro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3e**)*

This compound was prepared by reaction of 3-fluorobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 85 %; m.p. 157–159 °C; $[\alpha]_D^{20}$ +58.4 (c 1, acetone); IR (ATR) ν_{max} 3258, 1533 (NH of CONH), 1640 (CO of CONH), 1456, 1335, 1014, 825 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.40$ (1H, d, $^{3}J = 7.5$ Hz, N*H*), 8.00 (1H, dd, $^{3}J = 8.9$ Hz, $^{4}J_{F\text{-}H} = 4.9$ Hz, H-4), 7.96 (1H, dd, $^{4}J = 2.6$ Hz, $^{3}J_{F\text{-}H} = 8.8$ Hz, H-7), 7.80 (1H, dd, $^{4}J = 2.5$ Hz, $^{3}J_{F\text{-}H} = 8.8$ Hz, H-2′), 7.74 (1H, m, H-6′), 7.58 (1H, m, H-5′), 7.44 (1H, dt, $^{4}J = 2.5$ Hz, $^{3}J = 9.1$ Hz, $^{3}J_{F\text{-}H} = 9.1$ Hz, H-4′), 7.37 (1H, dt, $^{4}J = 2.6$ Hz, $^{3}J = 9.2$ Hz, $^{3}J_{F\text{-}H} = 9.2$ Hz, H-5), 5.52 (1H, quint, $^{3}J = 7.2$ Hz, H-1), 1.70 (3H, d, $^{3}J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): δ 175.7 (C, d, $^{4}J_{F\text{-}C} = 3.2$ Hz, C-9), 165.0 (C, d, $^{4}J_{F\text{-}C} = 2.5$ Hz, C = O), 162.0 (C, d, $^{1}J_{F\text{-}C} = 244.6$ Hz, C-3′), 159.5 (C, d, $^{1}J_{F\text{-}C} = 242.1$ Hz, C-6), 149.7 (C, d, $^{5}J_{F\text{-}C} = 1.4$ Hz, C-3), 136.0 (C, d, $^{3}J_{F\text{-}C} = 6.7$ Hz, C-1′), 135.7 (C, d, $^{3}J_{F\text{-}C} = 11.8$ Hz, C-8), 130.6 (CH, d, $^{3}J_{F\text{-}C} = 8.0$ Hz, C-5′), 123.8 (CH, d, $^{3}J_{F\text{-}C} = 9.6$ Hz, C-4), 123.7 (CH, d, $^{4}J_{F\text{-}C} = 2.9$ Hz, C-6′), 118.6 (CH, d, $^{2}J_{F\text{-}C} = 21.1$ Hz, C-4′), 114.6 (CH, d, $^{2}J_{F\text{-}C} = 24.7$ Hz, C-5), 114.3 (CH, d, $^{2}J_{F\text{-}C} = 22.8$ Hz, C-2′), 108.6 (CH, d, $^{2}J_{F\text{-}C} = 27.1$ Hz, C-7), 48.1 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -112.6, -116.5$; Anal. Calcd. $C_{16}H_{12}F_2N_2OS$ (318.34): C, 60.37; H, 3.80; N, 8.80; S, 10.07. Found: C, 60.45; H, 3.68; N, 8.92; S, 10.18.

*2-Methoxy-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3f**)*

This compound was prepared by reaction of 2-methoxybenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 85 %; m.p. 91–92 °C; $[\alpha]_D^{20}$ +52.5 (c 1, acetone); IR (ATR) ν_{max} 3257, 1527 (NH of CONH), 1640 (CO of CONH), 1458, 1248, 1012, 821, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.00$ (1H, d, $^{3}J = 7.7$ Hz, N*H*), 8.00 (1H, dd, $^{3}J = 8.9$ Hz, $^{4}J_{F\text{-}H} = 4.9$ Hz, H-4), 7.98 (1H, dd, $^{4}J = 2.6$ Hz, $^{3}J_{F\text{-}H} = 8.9$ Hz, H-7), 7.71 (1H, dd, $^{3}J = 7.5$ Hz, $^{4}J = 1.8$ Hz H-5′), 7.51 (1H, m, H-4′), 7.37 (1H, dt, $^{4}J = 2.6$ Hz, $^{3}J = 9.2$ Hz, $^{3}J_{F\text{-}H} = 9.2$ Hz, H-5), 7.17 (1H, d, $^{3}J = 8.2$ Hz, H-3′), 7.01 (1H, m, H-5′), 5.51 (1H, quint, $^{3}J = 7,2$ Hz, H-1), 3.93 (3H, s, O-C*H*$_3$), 1.68 (3H, d, $^{3}J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): δ 175.9 (C, d, $^{4}J_{F\text{-}C} = 3.1$ Hz, C-9), 165.3 (C=O), 159.5 (C, d, $^{1}J_{F\text{-}C} = 242.2$ Hz, C-6), 157.0 (C, C-2′), 149.7 (C, d, $^{5}J_{F\text{-}C} = 1.6$ Hz, C-3), 135.9 (C, d, $^{3}J_{F\text{-}C} = 11.5$ Hz, C-8), 132.5 (CH, C-4′), 130.2 (CH, C-6′), 123.7 (CH, d, $^{3}J_{F\text{-}C} = 9.5$ Hz, C-4), 123.1 (C, C-1′), 120.5 (CH, C-5′), 114.5 (CH, d, $^{2}J_{F\text{-}C} = 24.9$ Hz, C-5), 112.1 (CH, C-3′), 108.6 (CH, d, $^{2}J_{F\text{-}C} = 27.1$ Hz, C-7), 56.0 (OCH_3), 47.9 (CH, C-1), 20.3 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.6$; Anal. Calcd. $C_{17}H_{15}FN_2O_2S$ (330.38): C, 61.80; H, 4.58; N, 8.48; S, 9.71. Found: C, 61.66; H, 4.68; N, 8.29; S, 9.64.

*2-Methyl-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3g**)*

This compound was prepared by reaction of 2-methylbenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 86 %; m.p. 161–163 °C; $[\alpha]_D^{20}$ +78.1 (c 1, acetone); IR (ATR) ν_{max} 3243, 1532 (NH of CONH), 1640 (CO of CONH), 1456, 1329, 1200, 1012, 810, 725 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.22$ (1H, d, $^{3}J = 7.6$ Hz, N*H*), 8.00 (2H, m, H-4, H-7), 7.44 – 7.27 (5H, m, H-5, H-3′–H-6′), 5.47 (1H, quint, $^{3}J = 7.2$ Hz, H-1), 3.40 (3H, s, C*H*$_3$); 1.66 (3H, d, $^{3}J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 176.0$ (C, d, $^{4}J_{F\text{-}C} = 3.1$ Hz, C-9), 169.0 (C=O), 159.5 (C, d, $^{1}J_{F\text{-}C} = 242.1$ Hz, C-6), 149.7 (C, d, $^{5}J_{F\text{-}C} = 1.4$ Hz, C-3), 136.3 (C, C-2′), 135.8 (C, d, $^{3}J_{F\text{-}C} = 11.7$ Hz, C-8), 135.5 (C, C-1′), 130.5 (CH, C-4′), 129.7 (CH, C-3′), 127.2 (CH, C-5′), 125.6 (CH, C-6′), 123.7 (CH, d, $^{3}J_{F\text{-}C} = 9.5$ Hz, C-4), 114.5 (CH, d, $^{2}J_{F\text{-}C} = 24.7$ Hz, C-5), 108.6 (CH, d, $^{2}J_{F\text{-}C} = 27.2$ Hz, C-7), 47.8 (CH, C-1), 19.9 (CH_3, C-2), 19.5 (CH_3); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.5$; Anal. Calcd. $C_{17}H_{15}FN_2OS$ (314.38): C, 64.95; H, 4.81; N, 8.91; S, 10.20. Found: C, 65.06; H, 4.78; N, 8.79; S, 10.28.

*4-Methyl-3-nitro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3h**)*

This compound was prepared by reaction of 3-nitro-4-methylbenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 87 %; m.p. 162–163 °C; $[\alpha]_D^{20}$ +38.5 (c 1, acetone); IR (ATR) ν_{max} 3256, 1525 (NH of CONH), 1638 (CO of CONH), 1456, 1335, 1198, 1020, 818 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.58$ (1H, d, $^{3}J = 7.6$ Hz, N*H*), 8.57 (1H, d, $^{4}J = 1.7$ Hz, H-2′), 8.17

(1H, dd, $^3J = 7.9$ Hz, $^4J = 1.5$ Hz, H-5′), 8.00 (1H, dd, $^3J = 9.0$ Hz, $^4J_{F\text{-}H} = 4.9$ Hz, H-4), 7.95 (1H, dd, $^4J = 2.3$ Hz, $^3J_{F\text{-}H} = 8.8$ Hz, H-7), 7.65 (1H, d, $^3J = 8.1$ Hz, H-6′), 7.36 (1H, dt, $^4J = 2.6$ Hz, $^3J = 9.2$ Hz, $^3J_{F\text{-}H} = 9.2$ Hz, H-5), 5.54 (1H, quint, $^3J = 7.2$ Hz, H-1), 2.58 (3H, s, C$\underline{H_3}$), 1.71 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.4$ (C, d, $^4J_{F\text{-}C} = 3.1$ Hz, C-9), 164.2 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 242.3$ Hz, C-6), 149.7 (C, d, $^5J_{F\text{-}C} = 1.3$ Hz, C3), 148.8 (C, C-3′), 136.6 (C, C-4′), 135.7 (C, d, $^3J_{F\text{-}C} = 11.5$ Hz, C-8), 133.2 (CH, C-6′), 132.6 (C, C-1′), 132.1 (CH, C-5′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.6$ Hz, C-4), 123.4 (CH, C-2′), 114.6 (CH, d, $^2J_{F\text{-}C} = 24.8$ Hz, C-5), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.2$ Hz, C-7), 48.2 (CH, C-1), 19.8 (CH_3, C-2), 19.7 (CH_3); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.4$; Anal. Calcd. $C_{17}H_{14}FN_3O_3S$ (359.37): C, 56.82; H, 3.93; N, 11.69; S, 8.92. Found: C, 56.68; H, 4.05; N, 11.52; S, 8.84.

*N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]furan-2-carboxamide (**3i**)*

This compound was prepared by reaction of 3-nitro-4-methylbenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 85 %; m.p. 136–137 °C; $[\alpha]_D^{20}$ +28.7 (c 1, acetone); IR (ATR) ν_{max} 3266, 1532 (NH of CONH), 1633 (CO of CONH), 1456, 1348, 1012, 815 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.23$ (1H, d, $^3J = 7.7$ Hz, N*H*), 7.99 (1H, dd, $^3J = 8.9$ Hz, $^4J_{F\text{-}H} = 4.9$ Hz, H-4), 7.95 (1H, dd, $^4J = 2.6$ Hz, $^3J_{F\text{-}H} = 8.8$ Hz, H-7), 7.90 (1H, m, H-3′), 7.36 (1H, dt, $^4J = 2.6$ Hz, $^3J = 9.1$ Hz, $^3J_{F\text{-}H} = 9.1$ Hz, H-5), 7.25 (1H, m, H-5′), 6.67 (1H, m, H-4′), 5,47 (1H, quint, $^3J = 7.2$ Hz, H-1), 1,68 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.6$ (C, d, $^4J_{F\text{-}C} = 3.2$ Hz, C-9), 159.5 (C, d, $^1J_{F\text{-}C} = 242.4$ Hz, C-6), 157.6 (C=O), 149.7 (C, d, $^5J_{F\text{-}C} = 1.7$ Hz C-3), 147.3 (C, C-1′), 145.6 (CH, C-3′), 135.8 (C, d, $^3J_{F\text{-}C} = 11.3$ Hz, C-8), 123.8 (CH, d, $^3J_{F\text{-}C} = 9.5$ Hz, C-4), 114.6 (CH, d, $^2J_{F\text{-}C} = 24.8$ Hz, C-5), 114.4 (CH, C-5′), 112.0 (CH, C-4′), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.2$ Hz, C-7), 47.3 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.6$; Anal. Calcd. $C_{14}H_{11}FN_2O_2S$ (290.31): C, 57.92; H, 3.82; N, 9.65; S, 11.04. Found: C, 58.08; H, 3.88; N, 9.75; S, 10.95.

*3,5-Dinitro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]benzamide (**3j**)*

This compound was prepared by reaction of 3,5-dinitrobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 85 %; m.p. 224–225 °C; $[\alpha]_D^{20}$ +34.7 (c 1, acetone); IR (ATR) ν_{max} 3283, 1527 (NH of CONH), 1644 (CO of CONH), 1456, 1343, 1306, 1092, 816 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 10.01$ (1H, d, $^3J = 7.3$ Hz, N*H*), 9.14 (2H, d, $^4J = 2.1$ Hz, H-2′, H-6′), 8.99 (1H, t, $^4J = 2.1$ Hz, H-4′), 8.00 (1H, dd, $^3J = 9.0$ Hz, $^4J_{F\text{-}H} = 4.9$ Hz, H-4), 7.96 (1H, dd, $^4J = 2.7$ Hz, $^3J_{F\text{-}H} = 8.8$ Hz, H-7), 7.36 (1H, dt, $^4J = 2.7$ Hz, $^3J = 9.0$ Hz, $^3J_{F\text{-}H} = 9.0$ Hz, H-5), 5.59 (1H, quint, $^3J = 7.2$ Hz, H-1), 1.74 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.4$ (C, d, $^4J_{F\text{-}C} = 3.1$ Hz, C-9), 162.2 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 242.1$ Hz, C-6), 149.5 (C, d, $^5J_{F\text{-}C} = 1.4$ Hz, C-3), 148.3 (2C, C-3′, C-5′), 136.1 (C, C-1′), 135.7 (C, d, $^3J_{F\text{-}C} = 11.7$ Hz, C-8), 127.8 (2CH, C-2′, C-6′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.5$ Hz, C-4), 121.3 (CH, C-4′), 114.7 (CH, d, $^2J_{F\text{-}C} = 24.8$ Hz, C-5), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.2$ Hz, C-7), 48.5 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.3$; Anal. Calcd. $C_{16}H_{11}FN_4O_5S$ (390.35): C, 49.23; H, 2.84; N, 14.35; S, 8.21. Found: C, 49.20; H, 2.75; N, 14.52; S, 8.12.

*4-Nitro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]benzamide (**3k**)*

This compound was prepared by reaction of 4-nitrobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 86 %; m.p. 217–218 °C; $[\alpha]_D^{20}$ +48.7 (c 1, acetone); IR (ATR) ν_{max} 3284, 1529 (NH of CONH), 1641 (CO of CONH), 1456, 1342, 1310, 825 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.65$ (1H, d, $^3J = 7.4$ Hz, N*H*), 8.36 (2H, d, $^3J = 8.8$ Hz, H-3′, H5′), 8.16 (2H, d, $^3J = 8.8$ Hz, H-2′, H-6′), 8.00 (1H, dd, $^3J = 9.0$ Hz, $^4J_{F\text{-}H} = 5.0$ Hz, H-4), 7.96 (1H, dd, $^4J = 2.7$ Hz, $^3J_{F\text{-}H} = 8.8$ Hz, H-7), 7.36 (1H, dt, $^4J = 2.7$ Hz, $^3J = 9.0$ Hz, $^3J_{F\text{-}H} = 9.0$ Hz, H-5), 5.54 (1H, quint, $^3J = 7.2$ Hz, H-1), 1.71 (3H, d, $^3J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.3$ (C, d, $^4J_{F\text{-}C} = 3.1$ Hz, C-9), 164.8 (C=O), 159.5 (C, d, $^1J_{F\text{-}C} = 242.4$ Hz, C-6), 149.6 (C, d, $^5J_{F\text{-}C} = 1.3$ Hz, C-3), 149.3 (C, C-4′), 139.3 (C, C-1′), 135.7 (C, d, $^3J_{F\text{-}C} = 11.8$ Hz, C-8), 129.1 (2CH, C-2′, C-6′), 123.7 (CH, d, $^3J_{F\text{-}C} = 9.5$ Hz, C-4), 123.7 (CH, C-3′, C-5′), 114.7 (CH, d, $^2J_{F\text{-}C} = 24.5$ Hz, C-5), 108.6 (CH, d, $^2J_{F\text{-}C} = 27.2$ Hz, C-7), 48.3 (CH, C-1), 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.4$; Anal. Calcd. $C_{16}H_{12}FN_3O_3S$ (345.35): C, 55.65; H, 3.50; N, 12.17; S, 9.28. Found: C, 55.78; H, 3.55; N, 12.12; S, 9.18.

*2-Chloro-4-nitro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]benzamide (**3l**)*

This compound was prepared by reaction of 2-chloro-4-nitrobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 88 %; m.p. 156–158 °C; $[\alpha]_D^{20}$ +41.7

(c 1, acetone); IR (ATR) ν_{max} 3282, 1539 (NH of CONH), 1644 (CO of CONH), 1456, 1373, 857, 822 cm-1; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.68$ (1H, d, $^{3}J = 7.7$ Hz, N*H*), 8.39 (1H, d, $^{4}J = 2.2$ Hz, H-3′), 8.30 (1H, dd, $^{3}J = 8.4$ Hz, $^{4}J = 2.2$ Hz, H-5′), 8.02 (2H, m, H-4, H-7), 7.78 (1H, d, $^{3}J = 8.4$ Hz, H-6′), 7.39 (1H, dt, $^{4}J = 2.6$ Hz, $^{3}J = 9.1$ Hz, $^{3}J_{F\text{-}H} = 9.1$ Hz, H-5), 5.50 (1H, quint, $^{3}J = 7.2$ Hz, H-1), 1.67 (3H, d, $^{3}J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 174.6$ (C, d, $^{4}J_{F\text{-}C} = 3.0$ Hz, C-9), 164.8 (C=O), 159.5 (C, d, $^{1}J_{F\text{-}C} = 242.0$ Hz, C-6), 149.6 (C, d, $^{5}J_{F\text{-}C} = 1.3$ Hz, C-3), 148.4 (C, C-4′), 141.8 (C, C1′), 135.8 (C, d, $^{3}J_{F\text{-}C} = 11.8$ Hz, C-8), 131.2 (C, C-2′), 130.0 (CH, C-6′), 124.7 (CH, C-3′), 123.9 (CH, d, $^{3}J_{F\text{-}C} = 9.4$ Hz, C-4), 122.5 (CH, C-5′), 114.7 (CH, d, $^{2}J_{F\text{-}C} = 25.1$ Hz, C-5), 108.6 (CH, d, $^{2}J_{F\text{-}C} = 27.2$ Hz, C-7), 48.0 (CH, C-1), 19.9 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.3$; Anal. Calcd. $C_{16}H_{11}ClFN_3O_3S$ (379.79): C, 50.60; H, 2.92; N, 11.06; S, 8.44. Found: C, 50.78; H, 2.85; N, 11.12; S, 8.38.

*4-Chloro-3-nitro-N-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]benzamide (**3m**)*

This compound was prepared by reaction of 4-chloro-3-nitrobenzoyl chloride with (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate. It was obtained as white solid; Yield 86 %; m.p. 161–162 °C; $[\alpha]_D^{20}$ +44.3 (c 1, acetone); IR (ATR) ν_{max} 3263, 1527 (NH of CONH), 1636 (CO of CONH), 1456, 1341, 1010, 843, 693 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400.13 MHz): $\delta = 9.67$ (1H, d, $^{3}J = 7.5$ Hz, N*H*), 8.62 (1H, d, $^{4}J = 2.1$ Hz, H-2′), 8.23 (1H, dd, $^{3}J = 8.4$ Hz, $^{4}J = 2.1$ Hz, H-6′), 8.00 (1H, dd, $^{3}J = 8.9$ Hz, $^{4}J_{F\text{-}H} = 4.9$ Hz, H-4), 8.02 (2H, m, H-7, H-5′), 7.37 (1H, dt, $^{4}J = 2.7$ Hz, $^{3}J = 9.1$ Hz, $^{3}J_{F\text{-}H} = 9.1$ Hz, H-5), 5.53 (1H, quint, $^{3}J = 7.2$ Hz, H-1), 1.70 (3H, d, $^{3}J = 7.2$ Hz, H-2); ^{13}C NMR (DMSO-d_6, 100.62 MHz): $\delta = 175.0$ (C, d, $^{4}J_{F\text{-}C} = 3.1$ Hz, C-9), 163.3 (C=O), 159.5 (C, d, $^{1}J_{F\text{-}C} = 242.4$ Hz, C-6), 149.6 (C, d, $^{5}J_{F\text{-}C} = 1.7$ Hz, C-3), 147.3 (C, C-3′), 135.7 (C, d, $^{3}J_{F\text{-}C} = 11.7$ Hz, C-8), 133.6 (C, C-1′), 132.7 (CH, C-6′), 132.2 (CH, C-5′), 128.4 (C, C-4′), 124.7 (CH, C-2′), 123.8 (CH, d, $^{3}J_{F\text{-}C} = 9.6$ Hz, C-4), 114.7 (CH, d, $^{2}J_{F\text{-}C} = 24.9$ Hz, C-5), 108.7 (CH, d, $^{2}J_{F\text{-}C} = 27.2$ Hz, C-7), 48.3 (CH, C-1, 19.8 (CH_3, C-2); ^{19}F NMR (DMSO-d_6, 376.46 MHz): $\delta = -116.4$; Anal. Calcd. $C_{16}H_{11}ClFN_3O_3S$ (379.79) C, 50.60; H, 2.92; N, 11.06; S, 8.44. Found: C, 50.74; H, 2.88; N, 11.15; S, 8.35.

Crystallographic details

The X-ray data for colorless crystals of compounds **3b, 3f** and **3i** were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius Kappa CCD diffractometer with MoKα radiation ($\lambda = 0.71073$ Å), a graphite monochromator and the φ and χ scan mode. Data reductions were performed with DENZO-SMN (Otwinowski and Minor, 1997). The absorption was corrected by integration methods (Ahmed *et al*., 1970). Structures were solved by direct methods (Sir92) (Altomare *et al*., 1993) and refined by full matrix least square based on *F2* (SHELXL97) (Sheldrick, 1997). Hydrogen atoms were mostly localized on a difference Fourier map; however, to ensure uniformity of the treatment of the crystal, all hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors Hiso(H) = 1.2 Ueq (pivot atom) or of 1.5 Ueq for the methyl moiety with C–H = 0.96, 0.98 and 0.93 Å for methyl, methine and hydrogen atoms in the aromatic rings, respectively. Selected crystallographic data for compounds **3b, 3f** and **3i** are presented in Table 3. Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 1018178, CCDC 1018179, CCDC 1018180). Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Evaluation of antimicrobial activity

The newly synthesized compounds were screened for their antibacterial activity against a range of gram-positive bacterial strains *S. aureus* (CCM 422), *S. aureus* (CCM 4223), *S. epidermidis* (CCM 4418) and *E. faecalis* (CCM 4224), and gram-negative bacterial strains *E. coli* (CCM 3954), *E. cloacae* (CCM 1903), *P. mirabilis* (CCM 7188) and *P. aeruginosa* (CCM 3955). Nutrient broth was prepared using 9 mL of Muller–Hinton agar (70191 Fluka) and 1 mL of each dilution tested compounds prepared in sterile dry test tubes. The mixture was immediately poured into a sterile Petri dish with a diameter of 10 cm. A twofold serial dilution of the compounds and the reference drug were dissolved in DMSO. Tested compounds were taken at different concentrations (200, 100, 50, 25, 12.5 and 6.25 μg/mL) for minimum inhibitory concentration (MIC). Hundred-microliter microbial suspension of 3×10^6 cfu/mL density was streaked on the nutrient agar medium after solidification. The Petri dishes were incubated at 37 °C for 48 h. The MIC was the lowest concentration of the tested compound that resulted in no visible growth of the organisms. To ensure that the solvent had no effect on bacterial growth, a control test was also performed with test medium supplemented with DMSO at same dilutions as used in the experiment. Antifungal activity was evaluated against *C. albicans* (CCM 8311), *C. glabrata* (CCM

8270) and *C. tropicalis* (CCM 8268) in Sabouraud's dextrose agar medium (S3306 Fluka). Preparation of nutrient broth, dilution and application were carried out using the some procedure as for antimicrobial testing. The Petri dishes were incubated at 30 °C for 48 h.

Result and discussion

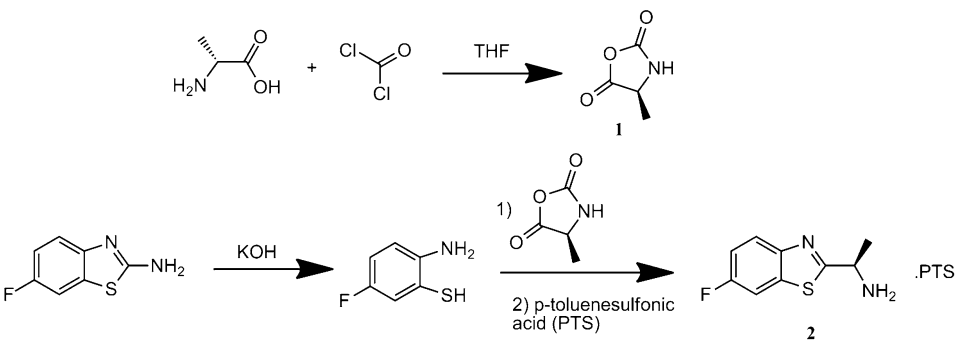
Chemistry

The starting compound (*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethanamine **2** was prepared as the corresponding *p*-toluenesulfonate salt (PTS) according to Scheme 4 (Hijikata, 2003; Pejchal *et al*., 2011a). (4*R*)-4-Methyl-1,3-oxazolidine-2,5-dione **1** was prepared by reaction of D-alanine with phosgene in THF according reported method (Blacklock *et al*., 1988); (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine *p*-toluenesulfonic salt **2** was prepared by three-step process (Scheme 4). Compound **1** reacted with water solution of potassium hydroxide in the first step to give **2**-aminobenzothiol potassium salt, which reacted with compound **1** in the second step to give hydrochloride of **2**. Product **2** *p*-toluenesulfonic salt was prepared by reaction of hydrochloride of **2** with *p*-toluenesulfonic acid in water. The synthesis of substituted 6-fluorobenzo[*d*]thiazole amides **3a**–**m** was carried out according to Scheme 5. The desired compounds **3a**–**m** were synthesized in mixture toluene–water, where the starting (*R*)-1-(6-fluorobenzo[*d*]thiazol-2-yl)ethanamine liberated from its *p*-toluene sulfonate salt subsequently reacts with corresponding aroyl chlorides in reaction mixture using an aqueous solution of sodium hydroxide. Reaction of substituted aroyl chlorides with in situ liberated amine (from **2**) form target molecules **3a**–**m** (Scheme 5). Toluene layer was warmed to 70 °C in order to dissolve product formed. Products were precipitated by cooling of the separated and concentrated toluene solution. Products were isolated by filtration in high yields 80 %–90 %. Compounds **3a**–**m** were characterized by melting points, IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra and elemental analyses (CHN). The optical activities were confirmed by optical rotation measurements. The structures of compounds **3b**, **3f** and **3i** were determined by single-crystal X-ray diffraction. The IR spectral peaks of compounds **3a**–**m** were recognized for C=O of CONH from 1628 to 1645 and NH of CONH from 1525 to 1539 and from 3237 to 3284 cm^{-1}.^{1}H NMR spectra of compounds **3a**–**m** showed the presence CONH amide proton peaks as doublets due to coupling to CH group. The signal for CH group bound to amide function appears as a quintet due to the interaction with CH_3 group and CONH protons. The assignment and numbering of ^{1}H NMR shifts are illustrated in Schemes 4 and 5 and given in experimental section. The ^{13}C NMR spectra display two peaks in the alkyl region indicating the presence of the CH_3–CH– group. Other seven peaks appearing as doublets (split by coupling with ^{19}F nuclei) were found in the aromatic part of spectra and assigned to substituted benzothiazole group. The rest of signals in the aromatic part are due to substituted phenyl groups. The optical rotation measurements were performed in acetone ($c = 1$).

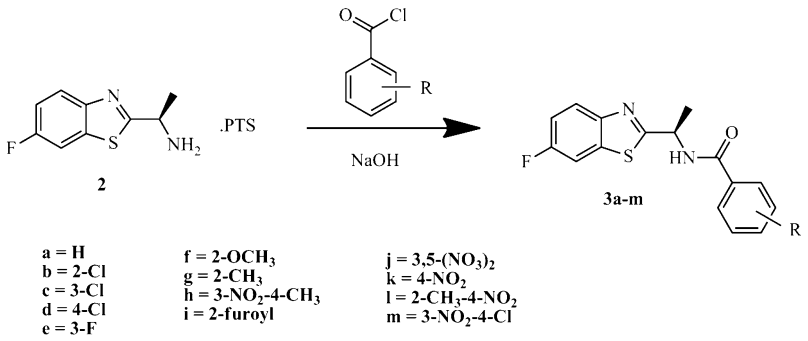
Crystallography

The benzothiazole motif is also quite popular from the point of view of high number of crystal structures (~ 1500) determined up to now, while the number of related structures to that particular work is limited to a couple of tens (Kello *et al*., 1986; Brandenburg *et al*., 1987). Taking into the account the substitution of carbon atom in the position 2 of the benzothiazole ring by a methine group or an *ipso* carbon directly connected to an aliphatic amine, only four crystal structures is selected for a direct comparison (Pindinelli *et al*., 2007; Zhang and Zhao, 2009; Pejchal *et al*., 2011; Karagiannidis *et al*., 2011). All three compounds under crystallographic investigation, **3b**, **3f** and **3i**, crystallize in the chiral $P2_1$ or $P2_12_12_1$ space groups in monoclinic or orthorhombic crystal systems as R-isomers with the central chirality at C2 atoms. In all structures, the intermolecular H-bond between the carbonyl and N–H groups form the supramolecular 2D linear wires. Moreover, in the structure of **3f**, relatively strong

Scheme 4 Synthetic route to compound **2**



Scheme 5 Synthetic route to compound **3**



intramolecular contact from N–H group to the methoxy substituent of the phenyl ring delimits the orientation of whole benzothiazole substituent and is most probably responsible for the short contact of sulfur atom and the oxygen of the carbonyl group being 3.179 (4) Å. All compounds reveal a high degree of π-electron cloud delocalization (Figs. 1, 2, 3), including the amido groups where the interatomic distances and angles are comparable to the literature parameters found for amides and peptides (Pyykkö and Atsumi, 2009a, b). In particular, in the case of the substitution pattern and interatomic distances and angles within the pendant, aminomethine group seems to be almost identical (Pejchal *et al*., 2011b).

Antimicrobial activities

All the compounds have been screened for antibacterial and antifungal activities using twofold serial dilution method (for results, see Tables 1, 2). Chloramphenicol,

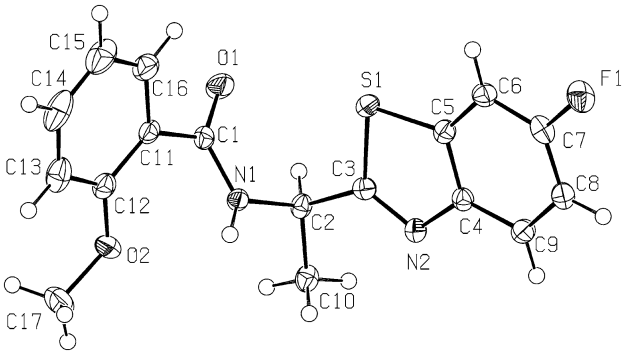


Fig. 2 Molecular structure (ORTEP 50 % probability level) of compound **3f**, only one of two independent molecules is shown. Selected interatomic distances (Å) and bond angles (°): N1 C1 1.348 (2), N1 C2 1.464 (2), O1 C1 1.232 (2), C11 C1 1.498 (3), C3 C2 1.519 (2), C10 C2 1.518 (2), N2 C3 1.284 (2), S1 C3 1.7618 (18), N2 C4 1.400 (2), S1 C5 1.7317 (19).C1 N1 C2 120.72 (14), O1 C1 N1 122.26 (16), N1 C1 C11 117.19 (15), O1 C1 C11 120.37 (16), C16 C11 C12 118.68 (17), C12 C11 C1 125.32 (16), N1 C2 C3 108.83 (14), N1 C2 C10 111.11 (14), C2 C3 S1 118.61 (12), N2 C3 C2 125.23 (16), C2 C3 S1 118.61 (12), N2 C3 S1 116.12 (14), C5 S1 C3 88.67 (9)

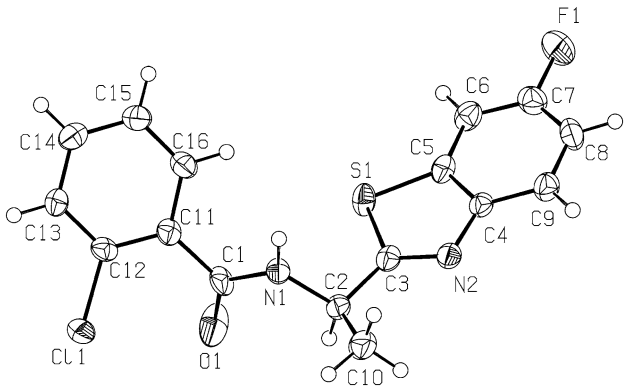


Fig. 1 Molecular structure (ORTEP 50 % probability level) of compound **3b**, only one of two independent molecules is shown. Selected interatomic distances (Å) and bond angles (°): N1 C1 1.325 (3), N1 C2 1.460 (3), C1 O1 1.227 (3), C1 C11 1.498 (4), C2 C3 1.508 (4), C2 C10 1.515 (4), N2 C3 1.296 (4), S1 C3 1.753 (3), N2 C4 1.388 (4), S1 C5 1.731 (3), C1 N1 C2 124.0 (2), O1 C1 N1 122.6 (3), N1 C1 C11 115.3 (2), O1 C1 C11 122.0 (3), C12 C11 C16 117.1 (3), C12 C11 C1 123.5 (2), N1 C2 C3 108.0 (2), N1 C2 C10 111.6 (2), C2 C3 S1 118.6 (2), N2 C3 C2 125.4 (3), C2 C3 S1 118.6 (2), N2 C3 S1 116.0 (2), C5 S1 C3 88.71 (13)

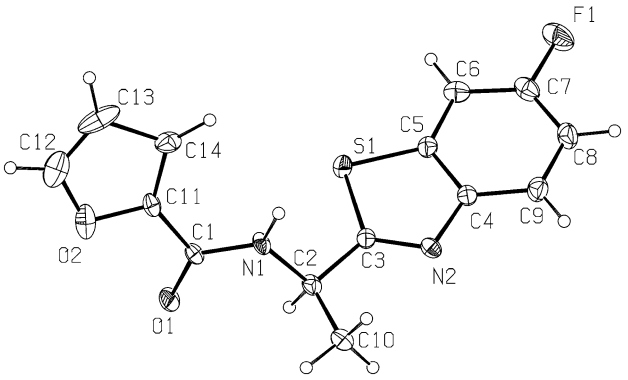


Fig. 3 Molecular structure (ORTEP 50 % probability level) of compound **3i**, only one of two independent molecules is shown. Selected interatomic distances (Å) and bond angles (°): N1 C1 1.340 (3), N1 C2 1.457 (3), O1 C1 1.231 (3), C1 C11 1.467 (4), C3 C2 1.504 (4), C2 C10 1.521 (4), N2 C3 1.301 (3), S1 C3 1.751 (3), N2 C4 1.399 (3), S1 C5 1.724 (3), C1 N1 C2 122.7 (2), O1 C1 N1 123.5 (2), N1 C1 C11 114.7 (2), O1 C1 C11 121.8 (2), C14 C11 O2 113.9 (3), C14 C11 C1 129.2 (3), O2 C11 C1 116.7 (2), N1 C2 C3 108.4 (2), N1 C2 C10 112.1 (2), C2 C3 S1 119.44 (19), N2 C3 C2 124.2 (2), C2 C3 S1 119.44 (19), N2 C3 S1 116.4 (2), C5 S1 C3 88.98 (13)

Table 1 Antimicrobial activities of the compounds **3a–m** (bacterial strains)

Compounds	Minimum inhibitory concentration (μg/ml)							
	Enterobacter cloacae CCM 1903	Escherichia coli CCM 3954	Proteus mirabilis CCM 7188	Pseudomonas aeruginosa CCM 3955	Enterococcus faecalis CCM 4224	Staphylococcus aureus CCM 4222	Staphylococcus aureus CCM 4223	Stahylococcus epidermidis CCM 4418
	Gram-negative			Gram-positive				
3a	50.00	>200	50.00	>200	>200	>200	>200	50.00
3b	>200	50.00	>200	>200	>200	50.00	50.00	>200
3c	>200	>200	>200	>200	>200	>200	>200	>200
3d	>200	>200	>200	>200	>200	>200	>200	>200
3e	>200	>200	>200	>200	>200	>200	>200	>200
3f	100.00	>200	50.00	>200	>200	>200	12.50	>200
3g	>200	>200	>200	100.00	>200	>200	50.00	50.00
3h	>200	100.00	>200	>200	>200	>200	>200	50.00
3i	>200	>200	>200	>200	>200	>200	>200	>200
3j	>200	>200	100.00	>200	>200	>200	>200	>200
3k	>200	>200	>200	>200	>200	>200	>200	50.00
3l	>200	>200	>200	>200	>200	>200	>200	>200
3m	>200	50.00	50.00	50.00	>200	50.00	50.00	6.25
Chloramphenicol	>200	6.25	50.00	>200	>200	6.25	>200	50.00
Cefoperazone	6.25	12.50	12.50	>200	6.25	12.50	6.25	50.00

Table 2 Antimicrobial activities of the compounds **3a–m** (fungal strains)

Compounds	Minimum inhibitory concentration (μg/ml)		
	Candida albicans CCM 8311	Candida glabrata CCM 8270	Candida tropicalis CCM 8268
3a	>200	>200	>200
3b	>200	>200	>200
3c	>200	>200	>200
3d	>200	50.00	>200
3e	25.00	50.00	100
3f	>200	>200	>200
3g	50.00	25.00	50.00
3h	50.00	>200	>200
3i	50.00	50.00	>200
3j	25.00	>200	>200
3k	>200	100.00	50.00
3l	>200	>200	>200
3m	50.00	>200	50.00
Amphotericin B	50	100	50

cefoperazone and amphotericin B were used as comparative standard drugs under the same protocol. All compounds were screened for antibacterial activity against gram-positive bacterial strains *S. aureus* (CCM 4222), *S. aureus* (CCM 4223), *S. epidermidis* (CCM 4418) and *E. faecalis* (CCM 4224), and gram-negative bacterial strains *E. coli* (CCM 3954), *E. cloacae* (CCM 1903), *P. mirabilis* (CCM 7188) and *P. aeruginosa* (CCM 3955) in Mueller–Hinton agar medium and for antifungal activity against *C. albicans* (CCM 8311), *C. glabrata* (CCM 8270) and *C. tropicalis* (CCM 8268) in Sabouraud's dextrose agar medium. Compound **3m** exhibited antibacterial activity

Table 3 Selected crystallographic data for compounds **3b, 3f** and **3i**

Compounds	**3b**	**3f**	**3i**
Empirical formula	$C_{16}H_{12}Cl\ FN_2OS$	$C_{17}H_{15}\ FN_2O_2S$	$C_{14}H_{11}\ FN_2O_2S$
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_1$	$P2_12_12_1$
a (Å)	4.8960 (2)	5.1820 (3)	4.9400 (4)
b (Å)	10.7881 (7)	11.1301 (4)	11.0531 (11)
c (Å)	14.2110 (8)	13.4580 (7)	24.3780 (11)
α (°)	90	90	90
β (°)	95.909 (5)	100.482 (5)	90
γ (°)	90	90	90
Z	2	2	4
V (Å^3)	746.62 (7)	763.25 (7)	1331.10 (18)
D_c (g cm^{-3})	1.489	1.438	1.449
Crystal size (mm)	0.35 × 0.24 × 0.10	0.58 × 018 × 0.16	0.59 × 0.27 × 0.14
Crystal shape	Block	Block	Block
μ (mm^{-1})	0.408	0.234	0.257
F (000)	344	344	600
h; k; l range	−6, 5; −14, 12; −18, 17	−6, 6; −14, 14; −17, 14	−5, 6; −14, 13; −31, 29
θ range (°)	2.37–27.49	2.39–27.50	2.02–27.00
Reflections measured	6227	6577	9993
Independent (R_{int})[a]	2870 (0.0399)	3350 (0.0305)	2935 (0.0332)
Observed [$I > 2\sigma(I)$]	2625	3184	2531
Parameters refined	199	208	181
Max/min τ (eÅ^{-3})	0.228/−0.260	0.198/0.198	0.572/−0.313
GOF[b]	1.111	1.153	1.110
R^c/wR^c	0.0373/0.0824	0.0294/0.0644	0.0464/0.1072

[a] $R_{int} = \sum\left|F_o^2 - F_{o,mean}^2\right| \Big/ \sum F_o^2$, [b] $S = \left[\sum\left(w\left(F_o^2 - F_c^2\right)^2\right) \Big/ \left(N_{diffrs} - N_{params}\right)\right]^{1/2}$, and [c] weighting scheme: $w = \left[\sigma^2\left(F_o^2\right) + (w_1P)^2 + w_2P\right]^{-1}$, where $P = \left[\max\left(F_c^2\right) + 2F_c^2\right]$, $R(F) = \Sigma||F_o| - |F_c|| / |F_o|$, and $wR(F^2) = \left[\Sigma\left(w\left(F_o^2 - F_c^2\right)^2\right) \Big/ \left(\Sigma w\left(F_o^2\right)^2\right)\right]^{1/2}$

against all bacterial strains except of *E. cloacae* (CCM 1903) and *E. faecalis* (CCM 4224). Exceptionally, high antibacterial activity has been observed for **3m** against *S. epidermidis* (CCM 4418) when compared with cefoperazone and chloramphenicol as currently used drugs. Compounds **3a** and **3f** exhibited satisfactory antibacterial activity against three strains of bacteria: *E. cloacae* (CCM 1903), *P. aeruginosa* (CCM 3955) and *S. epidermidis* (CCM 4418). On the other hand, the activity of **3b** covers another three strains: *E. coli* (CCM 3954), *S. aureus* (CCM 4222) and *S. aureus* (CCM 4223). Compounds **3h** and **3k** reveal selective and similarly high activity parameters, when compared to the standards, against *S. epidermidis* (CCM 4418) strain only. The bacterial strain *E. faecalis* (CCM 4224) seems to be resistant against all compounds tested.

All tested fungal strains can be efficiently inhibited by **3e** and **3g** in contrast to **3a**, **3b** and **3c** which exhibited no antifungal activity in the studied series. *C. albicans* as an opportunistic pathogen representing a serious threat to immunocompromised individuals deserves a special focus along with other fungal strains under investigation. As the number of immunologically weakened patients increase, opportunistic infections have become a widely recognized public health problem (Diekema *et al*., 2012). In that respect, **3m** exhibited comparable antifungal activity against *C. albicans* (CCM 8311) and *C. tropicalis* (CCM 8268) when amphotericin B is taken as a standard drug in use. Compounds **3d** and **3h** were selectively active against *C. glabrata* (CCM 8270) and *C. albicans* (CCM 8311), respectively.

The investigation of structures–activities relationships in the series of these species, based on current results, indicated that some of synthesized derivatives exhibited significant antimicrobial and antifungal activity: (1) The most active compounds in particular antibacterial and antifungal screening seem to be **3e**, **3f**, **3j** and **3m**, which is most probably caused by the presence of electron-withdrawing

nitro and fluoro substituents in *meta* positions (**3e** and **3m**) or electron-donating methyl and methoxy group in *ortho* positions of the phenyl substituent and (2) compounds having electron-withdrawing substituent in respective *ortho* or *para* positions exhibited much lower or negligible antibacterial activities. The compound **3a** containing unsubstituted phenyl group exhibited low antimicrobial, and no antifungal activity was observed.

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