Supporting Information

for

Synthesis and antimicrobial activity of 1H-1,2,3-triazole and carboxylate analogues of metronidazole

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Experimental section and copies of NMR spectra
Contents

Experimental section

Copies of $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR and HRMS spectra of compounds
Experimental section

General

All experiments were carried out in dry reaction vessels under dry nitrogen atmosphere. All reagents were obtained from Sigma-Aldrich, Germany. Silica gel for column chromatography were of 100–200 mesh, Solvents were purified by following standard procedures. Optical rotations were measured using the sodium D line on a polarimeter. Thin-layer chromatography (TLC) was carried using silica gel F254 pre-coated plates. UV-light and I2 stain were used to visualize the spots. The 1H and 13C NMR spectra were recorded on NMR spectrometer (Bruker: 600 MHz for 1H, 150 MHz for 13C and 564 MHz for 19F) using CDCl3 as a solvent. The high-resolution electrospray ionization mass spectra (HRESIMS) were recorded on an Agilent 6530 LC Q-TOF instrument. Organic extracts and solutions of pure compounds were dried over anhydrous MgSO4. For X-ray measurements, single crystal of 3, 5c, 7b, were mounted on a MiTeGen loop with grease and examined on a Bruker D8 Venture APEX diffractometer equipped with Photon 100 CCD area detector at 296 (2) K using graphite-monochromated MoKα radiation(λ = 0.71073Å). Data was collected using the APEX-II software [1], integrated using SAINT [2], and corrected for absorption using a multi-scan approach (SADABS) [3]. The structure was elucidated using intrinsic phasing (SHELXT) [4]. Final cell constants were determined from full least squares refinement of all observed reflections. All non-H atoms were located from subsequent difference maps and refined anisotropically with SHELXL-2016 [4] using full least squares refinement against F2. H-atoms were added at calculated positions and refined with a riding model. The structure has been deposited with the CCDC (CSD deposition number = 2063128-2063130).

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl 4-methylbenzenesulfonate (2)

To a solution of metronidazole (1, 0.8 g, 3.07 mmol) in dry DCM (25.0 mL), triethylamine (0.86 mL, 6.15 mmol) was added at 0 ºC. Then tosyl chloride (0.650 g, 3.38 mmol) was added over 2 h and catalytic amount of DMAP (0.038 g, 0.30 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. Then the reaction mixture was treated with aqueous 1 N HCl (10 mL) and extracted with DCM (3 × 30 mL). The organic layer was washed with saturated NaHCO3 (15 mL) and water (15 mL). The combined organic phases were dried over
anhydrous MgSO₄ and concentrated under reduced pressure. Flash chromatography of the crude product afforded metronidazoletosylate 2 [5] (1.197 g, 96%) as a yellow colour solid; m.p. 141-143 °C; ¹H NMR (600 MHz, chloroform-d) δ 7.71 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.46 (t, J = 4.9 Hz, 2H), 4.29 (t, J = 4.8 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 3H); ¹³C NMR (150 MHz, chloroform-d) δ 151.5, 145.6, 133.1, 131.5, 130.0, 127.5, 67.6, 45.3, 39.2, 21.5, 14.4; HRMS (ESI⁺): Found (M+H⁺): 326.0714 C₁₃H₁₆N₃O₅S required 326.0716.

1-(2-Azidoethyl)-2-methyl-5-nitro-1H-imidazole (3)

A stirred mixture of metronidazoletosylate 2 (1.000 g, 2.41 mmol) and sodium azide (0.472 g, 7.25 mmol) in DMF (30 mL) was heated for 3 h at 70 °C, cooled and then treated with ice–water (200 mL). The mixture was extracted with diethyl ether (2 × 150 mL) and the combined extracts were washed successively with water (2 × 30 mL) and brine (1 × 20 mL), dried over anhydrous MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography to yield the title product metroazide 3 [6] as a dark brown colour solid (0.536 g, 88%). m.p. 122-124 °C; ¹H NMR (600 MHz, chloroform-d) δ 7.93 (s, 1H), 4.40 (t, J = 5.5 Hz, 2H), 3.74 (t, J = 5.6 Hz, 2H), 2.50 (s, 3H); ¹³C NMR (150 MHz, chloroform-d) δ 151.3, 133.4, 50.9, 45.5, 14.5; HRMS (ESI⁺): Found (M+H⁺): 197.0740 C₆H₉N₆O₂ required 197.0737.

General procedure for synthesis of 1H-1,2,3-triazole derivatives of metronidazole (5a–i)

To a solution of metroazide 3 (1.0 equiv) and different alkyne derivatives 4a-i (1.2 equiv) in acetonitrile (10 mL), CuI (2.0 equiv) and triethylamine (3.0 equiv) were added at room temperature, and the mixture was stirred for 3 h. The reaction mixture was diluted with EtOAc (20 mL), 10 mL of aqueous NH₄Cl was added and, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layer was washed with brine solution, dried over anhydrous MgSO₄, and concentrated in vacuo to obtain a crude residue that was purified by flash chromatography to obtain desired metronidazole 1H-1,2,3-triazole derivatives (5a–i) (85-94%).

1-(2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl)-4-phenyl-1H-1,2,3-triazole (5a)

Pale yellow colour solid [7]; Yield = 85%; m.p. 221-223 °C; ¹H NMR (600 MHz, chloroform-d) δ 8.01 (s, 1H), 7.77 – 7.67 (m, 2H), 7.44 (s, 1H), 7.40 (t, J = 7.5
1-(2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl)-4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (5b)

Light brown colour solid; Yield = 90%; m.p. 230–232 °C; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.61 (s, 1H), 8.07 (brs, 1H), 7.98 (d, \(J = 8.0\) Hz, 2H), 7.78 (d, \(J = 8.0\) Hz, 2H), 4.91 (t, \(J = 5.4\) Hz, 2H), 4.79 (t, \(J = 5.5\) Hz, 2H), 1.94 (s, 3H); \(^{13}\)C NMR (150 MHz, DMSO-\(d_6\)) \(\delta\) 151.5, 145.2, 138.6, 134.3, 133.3, 128.3, 128.1, 125.9, 125.6, 123.5, 49.0, 46.0, 12.9; \(^{19}\)F NMR (564 MHz, DMSO-\(d_6\)) \(\delta\) -61.19; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 367.1134 \(C_{15}H_{14}F_3N_6O_2\) required 367.1132.

4-(4-Fluorophenyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole (5c)

Light green colour solid; Yield = 92%; m.p. 224–226 °C; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.13 (s, 1H), 7.99 (brs, 1H), 7.67 (t, \(J = 6.7\) Hz, 2H), 7.05 (d, \(J = 8.6\) Hz, 2H), 4.81 (s, 2H), 4.74 (s, 2H), 1.86 (s, 3H); \(^{13}\)C NMR (150 MHz, DMSO-\(d_6\)) \(\delta\) 163.1, 161.5, 146.5, 133.4, 127.5, 127.4, 127.0, 121.9, 115.9, 115.7, 49.3, 46.7, 13.5; \(^{19}\)F NMR (564 MHz, DMSO-\(d_6\)) \(\delta\) -113.59; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 317.1141 \(C_{14}H_{14}FN_6O_2\) required 317.1143.

Methyl 1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole-4-carboxylate (5d)

Pale yellow colour solid [7]; Yield = 86%; m.p. 212-214 °C; \(^1\)H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 7.99 (s, 1H), 7.84 (s, 1H), 4.86 (t, \(J = 5.6\) Hz, 2H), 4.82 (d, \(J = 5.6\) Hz, 2H), 3.92 (s, 3H), 2.03 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d\)) \(\delta\) 160.4, 151.0, 140.5, 133.9, 128.2, 52.3, 49.8, 46.1, 29.6, 13.5; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 281.0997 \(C_{10}H_{13}N_6O_4\) required 281.0994.

4-(4-Bromophenyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole (5e)

Colour less solid; Yield = 89%; m.p. 235-237 °C; \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.48 (s, 1H), 8.05 (s, 1H), 7.71 (d, \(J = 8.1\) Hz, 2H), 7.64 (d, \(J = 8.1\) Hz, 2H), 4.87
(t, \(J = 5.5\) Hz, 2H), 4.75 (t, \(J = 5.6\) Hz, 2H), 1.92 (s, 3H); \(^{13}\)C NMR (150 MHz, DMSO-\(d_6\)) \(\delta\) 151.2, 145.5, 138.4, 133.3, 131.9, 129.6, 127.1, 122.6, 121.0, 49.0, 46.0, 12.9; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 377.0360 \(C_{14}H_{14}BrN_6O_2\) required 377.0362. Found (M+H\(^+\)): 379.0344 \(C_{14}H_{14}BrN_6O_2\) required 379.0341.

4-(1-(2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)aniline (5f)

Light brown colour solid; Yield = 87%; m.p. 240-242 °C; \(^1\)H NMR (600 MHz, chloroform-\(d_6\)) \(\delta\) 7.98 (s, 1H), 7.53 – 7.47 (m, 2H), 7.28 (d, \(J = 1.3\) Hz, 1H), 6.70 – 6.67 (m, 2H), 4.78 (s, 4H), 3.79 (s, 2H), 1.96 (d, \(J = 1.3\) Hz, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d_6\)) \(\delta\) 151.4, 148.9, 146.9, 133.8, 133.5, 128.6, 127.0, 120.0, 119.0, 115.1, 114.8, 49.5, 46.5, 13.3; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 314.1364 \(C_{14}H_{16}N_7O_2\) required 314.1367.

1-(2-(4-(2,4-difluorophenyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole (5g)

Colourless solid [7]; Yield = 90%; m.p. 228-230 °C; \(^1\)H NMR (600 MHz, chloroform-\(d_6\)) \(\delta\) 8.36 (s, 1H), 8.07 (s, 1H), 7.63 (d, \(J = 7.7\) Hz, 2H), 4.84 (t, \(J = 5.4\) Hz, 2H), 4.81 (d, \(J = 4.8\) Hz, 2H), 1.92 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d_6\)) \(\delta\) 160.1, 160.0, 151.2, 147.2, 141.2, 133.8, 133.6, 132.3, 128.8, 122.9, 112.2, 49.6, 46.4, 13.4; \(^{19}\)F NMR (564 MHz, chloroform-\(d_6\)) \(\delta\) -110.74, -109.34; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 313.1422 \(C_{15}H_{17}F_2N_6O_2\) required 313.1419.

4-(2,4-difluorophenyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole (5h)

Pale yellow colour solid; Yield = 94%; m.p. 236-238 °C; \(^1\)H NMR (600 MHz, chloroform-\(d_6\)) \(\delta\) 8.36 (s, 1H), 8.07 (s, 1H), 7.63 (d, \(J = 7.7\) Hz, 2H), 4.84 (t, \(J = 5.4\) Hz, 2H), 4.81 (d, \(J = 4.8\) Hz, 2H), 1.92 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d_6\)) \(\delta\) 160.1, 160.0, 151.2, 147.2, 141.2, 133.8, 133.6, 132.3, 128.8, 122.9, 112.2, 49.6, 46.4, 13.4; \(^{19}\)F NMR (564 MHz, chloroform-\(d_6\)) \(\delta\) -110.74, -109.34; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 335.1056 \(C_{14}H_{13}F_3N_6O_2\) required 335.1058.

4-(4-methoxyphenyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole (5i)

Pale yellow colour solid; Yield = 94%; m.p. 236-238 °C; \(^1\)H NMR (600 MHz, chloroform-\(d_6\)) \(\delta\) 8.36 (s, 1H), 8.07 (s, 1H), 7.63 (d, \(J = 7.7\) Hz, 2H), 4.84 (t, \(J = 5.4\) Hz, 2H), 4.81 (d, \(J = 4.8\) Hz, 2H), 1.92 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d_6\)) \(\delta\) 160.1, 160.0, 151.2, 147.2, 141.2, 133.8, 133.6, 132.3, 128.8, 122.9, 112.2, 49.6, 46.4, 13.4; \(^{19}\)F NMR (564 MHz, chloroform-\(d_6\)) \(\delta\) -110.74, -109.34; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 335.1056 \(C_{14}H_{13}F_3N_6O_2\) required 335.1058.
= 8.4 Hz, 2H), 4.84 (t, \(J = 4.8\) Hz, 2H), 4.74 (t, \(J = 5.4\) Hz, 2H), 3.76 (s, 3H), 1.90 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d\)) \(\delta\) 159.6, 159.1, 146.5, 134.0, 133.2, 128.4, 126.5, 123.0, 121.3, 114.3, 55.2, 48.8, 46.2, 13.0; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 329.1341 \(\text{C}_{15}\text{H}_{17}\text{N}_{6}\text{O}_{3}\) required 329.1338.

**General procedure for synthesis of metronidazole carboxylate derivatives (7a–e)**

To a mixture of metronidazole 1 (1.0 equiv), different substituted acid chlorides 6a–e (1.2 equiv), in the presence of pyridine (1.2 equiv) and catalytic amount of DMAP was added to dry DCM (10.0 mL). The reaction was heated at room temperature with stirring under a nitrogen atmosphere for 4–5 h. Then the reaction mixture was treated with aqueous 1 N HCl (2 \(\times\) 10 mL) and extracted with DCM (3 \(\times\) 30 mL). The organic layer was washed with saturated NaHCO\(_3\) (15 mL) and water (15 mL). The combined organic phases were dried over anhydrous MgSO\(_4\). The solvent was removed under vacuum, and the crude product was purified by silica gel column chromatography (eluting with EtOAc/hexane, 8:2) to give metronidazole carboxylate derivatives (7a–e) (86–93%).

**2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate (7a)**

White solid; Yield = 86%; m.p. 187-189 °C; \(^{1}\)H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 7.93 (s, 1H), 7.89 – 7.85 (m, 2H), 7.54 (td, \(J = 7.5, 1.4\) Hz, 1H), 7.42 – 7.38 (m, 2H), 4.69 – 4.66 (m, 2H), 4.65 – 4.63 (m, 2H), 2.44 (d, \(J = 1.1\) Hz, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d\)) \(\delta\) 166.0, 150.8, 133.6, 133.2, 129.5, 128.9, 128.6, 62.8, 45.2, 14.3; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 276.0834 \(\text{C}_{13}\text{H}_{14}\text{N}_{3}\text{O}_{4}\) required 276.0836.

**2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl 4-nitrobenzoate (7b)**

Light yellow colour solid [8]; Yield = 91%; m.p. 214-216 °C; \(^{1}\)H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 8.26 (d, \(J = 8.5\) Hz, 2H), 8.07 (d, \(J = 8.5\) Hz, 2H), 7.95 (s, 1H), 4.73 (d, \(J = 4.9\) Hz, 2H), 4.71 (d, \(J = 4.9\) Hz, 2H), 2.48 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d\)) \(\delta\) 164.1, 150.8, 133.4, 133.1, 130.8, 123.8, 63.58, 44.9, 14.2; HRMS (ESI\(^+\)): Found (M+H\(^+\)): 321.0844 \(\text{C}_{13}\text{H}_{13}\text{N}_{4}\text{O}_{6}\) required 321.0842.

**2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl 3,5-dinitrobenzoate (7c)**

Light brown colour solid; Yield = 93%; m.p. 224-226 °C; \(^{1}\)H NMR (600 MHz, chloroform-\(d\)) \(\delta\) 9.21 (q, \(J = 1.9\) Hz, 1H), 9.03 (t, \(J = 1.6\) Hz, 2H), 7.95 (s, 1H), 4.78 (s, 4H), 2.55 (s, 3H); \(^{13}\)C NMR (150 MHz, chloroform-\(d\)) \(\delta\) 162.1, 148.7, 133.1, 132.5,
129.6, 129.3, 122.9, 122.0, 64.4, 44.7, 14.2; HRMS (ESI⁺): Found (M+H⁺): 366.0685 C₁₃H₁₂N₅O₈ required 366.0688.

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl propionate (7d)

Light green colour liquid [9]; Yield = 87%; ¹H NMR (600 MHz, chloroform-d) δ 7.87 (d, J = 1.1 Hz, 1H), 4.52 (t, J = 5.0 Hz, 2H), 4.35 – 4.32 (m, 2H), 2.44 (s, 3H), 2.20 (td, J = 7.6, 1.1 Hz, 2H), 1.01 (dd, J = 7.6, 1.2 Hz, 3H); ¹³C NMR (150 MHz, chloroform-d) δ 173.7, 150.8, 149.1, 132.8, 62.3, 45.0, 27.1, 14.1, 8.7; HRMS (ESI⁺): Found (M+H⁺): 228.0985 C₉H₁₄N₃O₄ required 228.0983.

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethyl butyrate (7e)

Colourless liquid [9]; Yield = 89%; ¹H NMR (600 MHz, chloroform-d) δ 7.96 (s, 1H), 4.60 (t, J = 5.4 Hz, 2H), 4.42 (t, J = 4.8 Hz, 2H), 2.53 (s, 3H), 2.24 (t, J = 7.2 Hz, 2H), 1.59 (q, J = 7.2 Hz, 2H), 0.90 (t, J = 7.8 Hz, 3H); ¹³C NMR (150 MHz, chloroform-d) δ 172.9, 150.7, 132.9, 62.2, 45.1, 35.7, 18.1, 14.3, 13.5; HRMS (ESI⁺): Found (M+H⁺): 242.1163 C₁₀H₁₆N₃O₄ required 242.1165.

Antimicrobial activity

The antifungal activities of the compounds were investigated as reported by Espinel-Ingrof et al. [10]. Briefly, three sterilized filter disks (0.6 cm) of each compound (1g/mL) were kept at 3 cm around the Didymella sp. plug on the surface of Potato dextrose agar (PDA) plates. The fungal plug that was taken from the actively growing edge and kept mycelial side down on the plate. The plates were incubated at 28 °C after the filter disks were transferred to the inoculated PDA plates. Metronidazole was used a positive control. The growth of each Didymella sp. was investigated by measuring the colony diameter after 7 days. The diameter (cm) of the fungal mycelium growth was measured from the center to the edge of the colony, and each group was treated three times.

Whereas, the antibacterial activities of the compounds were evaluated by culturing E. coli in nutrient broth medium as reported by Bilal et al. [11]. Compounds were added to the 12 h old culture broth of bacteria with a concentration of 1 mg/mL. Thereafter, bacteria were incubated at 37 °C for 48 h and optical density (OD) was recorded after every 12h at 600 nm by xMark™ Microplate Absorbance Spectrophotometer. While, metronidazole was used as positive control.
References

1. APEX-II, Bruker AXS, Madison, WI, USA
2. SAINT, Bruker AXS, Madison, WI, USA.
3. SADABS, Bruker AXS, Madison, USA.
4. Sheldrick. G. M. Acta Crystallogr., Sect. C: Struct. Chem. 2015, C–71, 3–8. doi:10.1107/S2053229614024218
5. Cao, J.; Liu, Y.; Zhang, L.; Du, F.; Ci, Y.; Zhang, Y.; Xiao, H.; Yao, X.; Shi, S.; Zhu, L.; Kung, H. F.; Qiao, J. J. Radioanal. Nucl. Chem. 2017, 312, 263–276. doi:10.1007/s10967-017-5210-5
6. Fernández, S.; Giglio, J.; Rey, A. M.; Cerecetto, H. Bioorg. Med. Chem. 2012, 20, 4040–4048. doi:10.1016/j.bmc.2012.05.010
7. Jarrad, A. M.; Karoli, T.; Debnath, A.; Tay, C. Y.; Huang, J. X.; Kaeslin, G.; Elliott, A. G.; Miyamoto, Y.; Ramu, S.; Kavanagh, A. M.; Zuegg, J.; Eckmann, L.; Blaskovich, M. A. T.; Cooper, M. A. Eur. J. Med. Chem. 2015, 101, 96–102. doi:10.1016/j.ejmech.2015.06.019
8. Salar, U.; Khan, K. M.; Taha, M.; Ismail, N. H.; Ali, B.; Qurat-ul-Ain, P.;erveen, S.; Ghufran, M.; Wadood, A. Eur. J. Med. Chem. 2017, 125, 1289–1299. doi:10.1016/j.ejmech.2016.11.031
9. Dubey, S.; Jain, V.; Prechti, G. B. Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. 2009, 48, 1571–1576.
10. Espinel-Ingroff, A.; Arthington-Skaggs, B.; Iqbal, N.; Ellis, D.; Pfaller, M. A.; Messer, S.; Rinaldi, M.; Fothergill, A.; Gibbs, D. L.; Wang, A. J. Clin. Microbiol. 2007, 45, 1811 LP – 1820. doi:10.1128/JCM.00134-07
11. Bilal, S.; Khan, A. L.; Shahzad, R.; Kim, Y.-H.; Imran, M.; Khan, M. J.; Al-Harrasi, A.; Kim, T. H.; Lee, I.-J. Ecotoxicol. Environ. Saf. 2018, 164, 648–658. doi:10.1016/j.ecoenv.2018.08.043
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| S40       | $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7b |
| S41       | $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7b |
| S42       | HRMS spectrum of compound 7b |
| S43       | $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7c |
| S44       | $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7c |
| S45       | HRMS spectrum of compound 7c |
| S46       | $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7d |
| S47       | $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7d |
| S48       | HRMS spectrum of compound 7d |
| S49       | $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7e |
| S50       | $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7e |
| S51       | HRMS spectrum of compound 7e |
S1: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 2

S2: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 2
S3: HRMS spectrum of compound 2

S4: ¹H-NMR spectrum (600 MHz, CDCl₃) of compound 3
S5: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 3

S6: HRMS spectrum of compound 3
S7: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5a

S8: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5a
**S9**: HRMS spectrum of compound 5a

**S10**: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5b
S11: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5b

S12: $^{19}$F-NMR spectrum (564 MHz, CDCl$_3$) of compound 5b
**S13**: HRMS spectrum of compound 5b

**S14**: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5c
S15: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5c

S16: $^{19}$F-NMR spectrum (564 MHz, CDCl$_3$) of compound 5c
S17: HRMS spectrum of compound 5c

18: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5d
S19: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5d

S20: HRMS spectrum of compound 5d
S21: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5e

S22: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5e
S23: HRMS spectrum of compound 5e

S24: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5f
S25: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5f

S26: HRMS spectrum of compound 5f
S27: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5g

S28: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5g
S29: HRMS spectrum of compound 5g

S30: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5h
S31: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5h

S32: $^{19}$F-NMR spectrum (564 MHz, CDCl$_3$) of compound 5h
S33: HRMS spectrum of compound 5h

S34: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 5i
S35: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 5i

S36: HRMS spectrum of compound 5i
S37: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7a

S38: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7a
S39: HRMS spectrum of compound 7a

S40: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7b
S41: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7b

S42: HRMS spectrum of compound 7b
S43: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7c

S44: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7c
S45: HRMS spectrum of compound 7c

S46: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7d
S47: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7d

S48: HRMS spectrum of compound 7d
S49: $^1$H-NMR spectrum (600 MHz, CDCl$_3$) of compound 7e

S50: $^{13}$C-NMR spectrum (150 MHz, CDCl$_3$) of compound 7e
S51: HRMS spectrum of compound 7e