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Supplementary Data

Naphtahlene and 2,3-dihydrobenzo[b][1,4]dioxin Derivatives With Extended Side Chains as New Scaffolds of CB_2 Selective Ligands

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Experimental

Chemistry

All starting materials, reactants and solvents were obtained from Sigma–Aldrich and were used without further purification. Melting points were determined on Buchi B-540 Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Advance 300 MHz spectrometer using $CDCl_3$ or CD_3OD or DMSO-d_6 as a solvent; chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS; multiplicities are abbreviated as: s: singlet; d: doublet; q: quartet; m: multiplet; dd: doublet of doublet; ddd: doublet of doublet of doublet, dt: doublet of triplet. HR-ESI mass spectra were recorded on Bruker microTOF-Q II instrument. Column chromatography was performed using Biotage flash chromatography system with columns packed with KP-Sil, 60A, 32-63 µM. Reaction progress was monitored by TLC performed on pre-coated silica gel plates (ALUGRAM SILG/UV254) and detection of the components was made by UV light (254 nm).

General procedure for the synthesis of 3-(2-Aryl)-prop-2-enal (2a-c):

To the arylaldehyde (19 mmol) in a flask cooled in a salt ice bath acetaldehyde (24 mL) was added with stirring. A clear solution formed, to which potassium hydroxide (0.26 g, 4.6 mmol) dissolved in methanol (1.3 mL) was added dropwise, keeping the temperature of the reaction mixture at 0–5 ^{o}C. Stirring was continued for 2 h. At the end of the period the temperature was allowed to rise until it reached room temperature. Acetic anhydride (10 mL) was then added and the mixture was heated to 100 ^{o}C for 30 min. The reaction mixture was then poured into a

flask containing water (72 mL) and concentrated hydrochloric acid (9.6 mL) was added, heated to 100 °C and stirred for 20 min. The reaction mixture was then cooled to 0 °C and the precipitate formed was filtered off, washed with water, dried under vacuum in the presence of P_2O_5 and KOH, and purified by column chromatography.

3-Naphthalen-2-yl-propenal (2a)[11]

Yellow solid; yield: 42%; mp: 124-126 °C; ^{1}H NMR ($CDCl_3$) δ 9.79 (d, *J* = 7.7 Hz, 1H), 8.02 (s, 1H), 7.95 – 7.85 (m, 3H), 7.70 (dd, *J* = 17.1, 8.8 Hz, 2H), 7.60 – 7.54 (m, 2H), 6.86 (dd, *J* = 15.9, 7.7 Hz, 1H).

3-(9H-Fluoren-3-yl)-propenal (2b)

White solid; yield: 40%; mp: 81-83 °C, ^{1}H NMR ($CDCl_3$) δ 9.75 (d, *J* = 7.7 Hz, 1H), 7.84 (dd, *J* = 15.1, 9.3 Hz, 3H), 7.65 – 7.54 (m, 3H), 7.42 (ddd, *J* = 15.3, 7.2, 1.3 Hz, 2H), 6.79 (dd, *J* = 15.9, 7.7 Hz, 1H), 3.98 (s, 2H).

3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-propenal (2c)[12]

Yellow resin; yield: 33%; mp: 62-64 °C; ^{1}H NMR ($CDCl_3$) δ 9.65 (d, *J* = 7.7 Hz, 1H), 7.13 – 6.52 (m, 5H), 4.30 (qd, *J* = 4.2, 3.6, 1.8 Hz, 4H).

General procedure for the synthesis 5-(2-Aryl)-penta-2,4-dienoic acid methyl ester (3a-c):

To a solution of trimethylphosphonoacetate (0.881mmol) in dry THF (6ml) at 0 °C was added dropwise KHDMS (0.5M in toluene) (0.911 mmol) during 10 min. this mixture was stirred for 1h at 0 °C and then cooled at -78 °C. A solution of the prop-2-enal derivative (0.294 mmol) in THF

(4ml) was added dropwise at this temperature to the mixture. This mixture was stirred during 30 min at -78 ^{o}C and then the ice bath was removed and the reaction mixture was allowed to warm while stirring for an additional 45 min after which it was poured into water and ethylacetate. After separation, the aqueous layer was extracted with ethyl acetate (x3). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was then purified using column chromatography.

5-Naphthalen-2-yl-penta-2,4-dienoic acid methyl ester (3a)[1]

Yellow resin; yield: 81%; ^{1}H NMR ($CDCl_3$) δ 7.82 (dd, *J* = 7.7, 2.5 Hz, 4H), 7.65 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.11 – 6.90 (m, 2H), 6.04 (d, *J* = 15.3 Hz, 1H), 3.79 (s, 3H).

5-(9H-Fluoren-3-yl)-penta-2,4-dienoic acid methyl ester (3b)

White solid; yield: 42%; mp: 125-127 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.83 – 7.73 (m, 2H), 7.67 (s, 1H), 7.58 – 7.44 (m, 3H), 7.41 – 7.28 (m, 3H), 6.98 (s, 1H), 6.01 (dd, *J* = 14.9, 2.2 Hz, 1H), 3.92 (s, 2H), 3.78 (s, 3H). HR-ESI-MS m/z Calcd for $C_{19}H_{16}NaO_2$ ($M+Na^{+}$): 299.1043, Found: 299.1034.

5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-penta-2,4-dienoic acid methyl ester (3c)

Brown resin; yield: 37%; ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.97 (dt, *J* = 8.2, 2.0 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.78 – 6.66 (m, 2H), 5.94 (d, *J* = 15.3 Hz, 1H), 4.30 – 4.24 (m, 4H), 3.76 (s, 3H).

4.4. General procedure for the synthesis of 5-(2-Aryl)-penta-2,4-dienoic acid (4a-c):

Each ester (1.0 mmol) was refluxed in a methanolic/aqueous sodium hydroxide solution (0.1 M, 3 equiv) for 3 h. Then the reaction mixture was allowed to get room temperature, made acidic (pH 3-4) by adding diluted HCl, and finally extracted with ethyl acetate. The organic layer was dried and the solvent evaporated to yield the crude acid, which was thoroughly dried under vacuum before being subjected to the successive reaction without further manipulation.

5-Naphthalen-2-yl-penta-2,4-dienoic acid (4a)[2]

White solid; yield: 78%; mp: 179-181 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, *J* = 9.7, 3.3 Hz, 4H), 7.58 (dd, *J* = 4.9, 0.5 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.11 – 7.02 (m, 2H), 6.05 (d, *J* = 14.7 Hz, 1H).

5-(9H-Fluoren-3-yl)-penta-2,4-dienoic acid (4b)

White solid; yield: 91%; mp: 163-165 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 7.97 – 7.89 (m, 2H), 7.82 (s, 1H), 7.61 (dd, *J* = 7.8, 2.3 Hz, 2H), 7.45 – 7.31 (m, 3H), 7.26 – 7.10 (m, 2H), 6.02 (d, *J* = 15.1 Hz, 1H), 3.96 (s, 2H). HR-ESI-MS m/z Calcd for $C_{18}H_{14}O_2$: 262.0994, Found: 262.0951.

5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-penta-2,4-dienoic acid (4c)

White solid; yield: 85%; mp: 157-159 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.97 (dt, *J* = 8.2, 2.0 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.78 – 6.66 (m, 2H), 5.94 (d, *J* = 15.3 Hz, 1H), 4.30 – 4.24 (m, 4H).

General procedure for the synthesis of 5-(2-Aryl)-penta-2,4-dienoic acid amide (5a-b, 6a-c, 7a-c):

Each acid (1.0 mmol) is stirred with HATU (1.5 mmol) and diisopropylethylamine (1.5 mmol) in anhydrous dimethyl formamide for 30 minutes in an ice bath (0^{o}C). To the same solution, the respective amine (1.5 mmol) was added and mixture was left to room temperature and continuous stirring overnight. The reaction mixture was diluted with ethyl acetate and the organic layer was then washed with 1N HCl, brine, dried and evaporated under pressure and the residue was purified by column chromatography on silica gel.

5-Naphthalen-2-yl-penta-2,4-dienoic acid (2-hydroxy-ethyl)-amide (5a)

Yellow powder; yield: 48%; mp: 155-157 ^{o}C, ^{1}H NMR ($CDCl_3$) δ 7.87 – 7.75 (m, 4H), 7.64 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.53 – 7.41 (m, 3H), 7.09 – 7.02 (m, 1H), 6.97 (dd, *J* = 15.7, 10.1 Hz, 1H), 6.03 (d, *J* = 14.8 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.56 (dd, *J* = 10.0, 5.8 Hz, 2H). HR-ESI-MS m/z Calcd for $C_{17}H_{17}NNaO_2$ ($M+Na^+$): 290.1151, Found: 290.1151.

5-(9H-Fluoren-3-yl)-penta-2,4-dienoic acid (2-hydroxy-ethyl)-amide (5b)

Yellow resin; yield: 50%; ^{1}H NMR ($CDCl_3$) δ 7.76 (t, *J* = 8.2 Hz, 2H), 7.67 – 7.63 (m, 1H), 7.58 – 7.28 (m, 6H), 6.96 – 6.90 (m, 1H), 5.99 (d, *J* = 14.8 Hz, 1H), 3.91 (s, 2H), 3.83 – 3.76 (m, 2H), 3.59 – 3.50 (m, 2H). HR-ESI-MS m/z Calcd for $C_{20}H_{19}NNaO_2$ ($M+Na^+$): 328.1308, Found: 328.1306**.**

5-Naphthalen-2-yl-penta-2,4-dienoic acid cyclopropylamide (6a)

Brown powder; yield: 40%; mp: 164-166 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz), 7.63 (dd, *J* = 10.4, 2.6 Hz), 7.47 (ddd, *J* = 17.8, 8.8, 7.8 Hz), 7.04 (d, *J* = 15.5 Hz), 7.00 – 6.88 (m), 5.92 (d, *J* =

14.8 Hz), 5.62 (s), 2.89 – 2.79 (m), 0.84 (q, *J* = 6.7 Hz), 0.69 – 0.53 (m). HR-ESI-MS m/z Calcd for $C_{18}H_{17}NNaO$ ($M+Na^+$): 286.1202, Found: 286.1200.

5-(9H-Fluoren-3-yl)-penta-2,4-dienoic acid cyclopropylamide (6b)

Yellow crystals; yield: 55%; mp: 187-189 ^oC; ^1H NMR ($CDCl_3$) δ 7.81 – 7.71 (m, 2H), 7.64 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.28 (m, 4H), 7.01 – 6.86 (m, 2H), 5.89 (d, *J* = 14.9 Hz, 1H), 5.61 (s, 1H), 3.91 (s, 2H), 2.89 – 2.78 (m, 1H), 0.84 (q, *J* = 6.7 Hz, 2H), 0.61 – 0.51 (m, 2H). HR-ESI-MS m/z Calcd for $C_{21}H_{19}NNaO$ ($M+Na^+$): 324.1359, Found: 324.1359.

5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-penta-2,4-dienoic acid cyclopropylamide (6c)

Yellow powder; yield: 40%; mp: 177-179 ^oC; ^1H NMR ($CDCl_3$) δ 7.35 (dd, *J* = 14.9, 10.2 Hz, 1H), 7.02 – 6.90 (m, 2H), 6.84 – 6.76 (m, 1H), 6.76 – 6.58 (m, 2H), 5.84 (d, *J* = 14.8 Hz, 1H), 5.65 (s, 1H), 4.26 (s, 4H), 2.82 (dq, *J* = 7.3, 3.7 Hz, 1H), 0.81 (td, *J* = 7.1, 5.1 Hz, 2H), 0.61 – 0.48 (m, 2H). HR-ESI-MS m/z Calcd for $C_{16}H_{18}NO_3$ ($M+H^+$): 272.1281, Found: 272.1281.

(5-Naphthalen-2-yl-penta-2,4-dienoylamino)-acetic acid ethyl ester (7a)

Yellow powder; yield: 75%; mp: 154-156 ^oC; ^1H NMR ($CDCl_3$) δ 7.80 (d, *J* = 9.1 Hz, 4H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.47 (dt, *J* = 9.2, 8.3 Hz, 3H), 7.06 (d, *J* = 15.5 Hz, 1H), 6.97 (dd, *J* = 14.7, 9.3 Hz, 1H), 6.07 (d, *J* = 15.0 Hz, 1H), 4.25 (dd, *J* = 14.2, 7.1 Hz, 2H), 4.16 (d, *J* = 5.1 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{19}H_{19}NNaO_3$ ($M+Na^+$): 332.1257, Found: 322.1258

(5-9H-Fluoren-3-yl-penta-2,4-dienoylamino)-acetic acid ethyl ester (7b)

Yellow powder; yield: 49%; mp: 177-179 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.76 (t, *J* = 8.2 Hz, 2H), 7.67 – 7.28 (m, 6H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.06 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.16 (d, *J* = 5.0 Hz, 2H), 3.94 – 3.88 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{22}H_{21}NNaO_3$: 370.1414, Found: 370.1417.

(5-2,3-Dihydro-benzo[1,4]dioxin-6-yl-penta-2,4-dienoylamino)-acetic acid ethyl ester (7c)

Yellow powder; yield: 40%; mp: 157-159 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.37 (ddd, *J* = 14.9, 9.5, 0.8 Hz, 1H), 7.00 – 6.89 (m, 2H), 6.86 – 6.77 (m, 1H), 6.76 – 6.60 (m, 2H), 5.97 (d, *J* = 14.8 Hz, 1H), 4.32 – 4.17 (m, 6H), 4.13 (d, *J* = 5.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{17}H_{19}NNaO_5$ ($M+Na^+$): 340.1155, Found: 340.1160.

General procedure for the synthesis 6-(Aryloxy)-hexanoic acid ethyl ester: (9a-b)

A mixture of phenolic compound (5.0 mmol), anhydrous potassium carbonate (2.5 mmol), and potassium fluoride (5.0 mmol) in dry acetone was refluxed under nitrogen atmosphere and continuously stirred for half hour, and then a solution of the corresponding bromoalkylethyl ester (5.0 mmol) in dry acetone was added, refluxing for another 48-72 h and checking the reaction by TLC. Afterward the reaction mixture was concentrated, diluted with water, and extracted with chloroform. The extracts were collected, dried, and evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel.

6-(Naphthalen-2-yloxy)-hexanoic acid ethyl ester (9a)

Brown oil; yield: 70%; ^{1}H NMR ($CDCl_3$) δ 7.78 – 7.67 (m, 3H), 7.42 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.16 – 7.11 (m, 2H), 4.19-4.06 (m, 4H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.81 – 1.69 (m, 2H), 1.64-1.56 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

6-(Naphthalen-1-yloxy)-hexanoic acid ethyl ester (9b)

Brown oil; yield: 80%; ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.78 (dd, *J* = 6.2, 3.2 Hz, 1H), 7.52 – 7.30 (m, 4H), 6.78 (d, *J* = 7.2 Hz, 1H), 4.19 – 4.06 (m, 4H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.02 – 1.88 (m, 2H), 1.76 (dt, *J* = 14.9, 7.3 Hz, 2H), 1.63 (ddd, *J* = 15.8, 8.8, 3.8 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

General procedure for the synthesis 6-(Aryloxy)-hexanoic acid (2-hydroxy-ethyl)-amide (10a-b)

Each ester (0.150 g) was dissolved, under nitrogen atmosphere and stirring, in ethanolamine (4 mL) and warmed at 120-130 °C for 4-6 h. The resulting mixture was diluted with water and extracted with chloroform, the extracts were washed with a solution of ammonium chloride, dried, evaporated, and the raw material was purified by column chromatography on silica gel.

6-(Naphthalen-2-yloxy)-hexanoic acid (2-hydroxy-ethyl)-amide (10a)

Yellow powder; yield: 85%; mp: 107-109 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 – 7.67 (m, 3H), 7.42 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.15 – 7.09 (m, 2H), 5.88 (s, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.72 (dd, *J* = 9.8, 4.9 Hz, 2H), 3.42 (dd, *J* = 10.0, 5.6 Hz, 2H), 2.25 (t, *J* = 7.5 Hz,

2H), 1.93 – 1.81 (m, 2H), 1.81 – 1.69 (m, 2H), 1.24 (s, 2H). HR-ESI-MS m/z Calcd for $C_{18}H_{24}NO_3$ ($M+H^+$): 302.1761, Found: 302.1751.

6-(Naphthalen-1-yloxy)-hexanoic acid (2-hydroxy-ethyl)-amide (10b)

Brown oil; yield: 60%; ^{1}H NMR ($CDCl_3$) δ 8.30 – 8.23 (m, 1H), 7.82 – 7.76 (m, 1H), 7.52 – 7.32 (m, 4H), 6.79 (d, *J* = 7.2 Hz, 1H), 5.87 (s, 1H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.76 – 3.67 (m, 2H), 3.41 (dd, *J* = 10.3, 5.3 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.91 – 2.00 (m, 2H), 1.79 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.64 (dd, *J* = 15.6, 8.6 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 1H). HR-ESI-MS m/z Calcd for $C_{18}H_{23}NNaO_3$ ($M+Na^+$): 324.1570, Found: 324.1584.

General procedure for the synthesis 6-(Aryloxy)-hexanoic acid (11a-b)

Each ester (1.0 mmol) was refluxed in a methanolic/aqueous sodium hydroxide solution (0.1 M, 3 equiv) for 3 h. Then the reaction mixture was allowed to get room temperature, made acidic (pH 3-4) by adding diluted HCl, and finally extracted with ethyl acetate. The organic layer was dried and the solvent evaporated to yield the crude acid, which was thoroughly dried under vacuum before being subjected to the successive reaction without further manipulation.

6-(Naphthalen-2-yloxy)-hexanoic acid (11a)

White crystals; yield: 39%; mp: 92-94 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.80 – 7.67 (m, 3H), 7.46 – 7.39 (m, 1H), 7.32 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.17 – 7.10 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.82 – 1.70 (m, 2H), 1.65 – 1.57 (m, 2H).

6-(Naphthalen-1-yloxy)-hexanoic acid (11b)[3]

White powder; yield: 70%; mp: 78-80 ^{o}C**.**

4.9. General procedure for the synthesis 6-(Aryloxy)-hexanoic acid amide (12a-b, 13a-b)

Each acid (1.0 mmol) is stirred with HATU (1.5 mmol) and diisopropylethylamine (1.5 mmol) in anhydrous dimethyl formamide for 30 minutes in an ice bath (0oC). To the same solution, the respective amine (1.5 mmol) was added and mixture was left to room temperature and continuous stirring overnight. The reaction mixture was diluted with ethyl acetate and the organic layer was then washed with 1N HCl, brine, dried and evaporated under pressure and the residue was purified by column chromatography on silica gel.

6-(Naphthalen-2-yloxy)-hexanoic acid cyclopropylamide (12a)

White crystals; yield: 47%; mp: 111-113 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.81 – 7.66 (m, 3H), 7.46 – 7.39 (m, 1H), 7.35 – 7.28 (m, 1H), 7.16 – 7.08 (m, 2H), 5.57 (s, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.61 (q, *J* = 7.3 Hz, 3H), 3.10 (q, *J* = 7.3 Hz, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.60 – 1.51 (m, 2H), 0.76 (dd, *J* = 12.3, 6.9 Hz, 2H), 0.54 – 0.42 (m, 2H). HR-ESI-MS m/z Calcd for $C_{19}H_{23}NNaO_2$ ($M+Na^+$): 320.1621, Found: 320.1621.

6-(Naphthalen-1-yloxy)-hexanoic acid cyclopropylamide (12b)

Brown powder; yield: 37%; mp: 104-106 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.43 (ddd, *J* = 20.8, 12.1, 7.5 Hz, 4H), 6.79 (d, *J* = 7.1 Hz, 1H), 5.51 (s, 1H), 4.14 (t, *J* = 6.4 Hz, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.93 (dd, *J* = 14.1, 6.8 Hz, 2H), 1.76 (dt, *J* = 15.4, 7.7 Hz, 2H),

1.61 (dd, *J* = 15.4, 7.9 Hz, 2H), 1.25 (s, 1H), 0.76 (dd, *J* = 12.4, 5.6 Hz, 2H), 0.46 (t, *J* = 7.7 Hz, 2H). HR-ESI-MS m/z Calcd for $C_{19}H_{24}NO_2$ ($M+H^+$): 298.1802, Found: 298.1963.

6-(Naphthalen-2-yloxy)-hexanoylamino]-acetic acid ethyl ester (13a)

Brown resin; yield: 80%; ^{1}H NMR ($CDCl_3$) δ 7.78 – 7.69 (m, 3H), 7.46 – 7.39 (m, 1H), 7.36 – 7.28 (m, 1H), 7.16 – 7.10 (m, 2H), 5.95 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.05 (m, 2H), 4.04 (d, *J* = 5.1 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.77 (dt, *J* = 15.0, 7.3 Hz, 2H), 1.60 (d, *J* = 2.4 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{20}H_{26}NO_4$ ($M+H^+$): 344.1856, Found: 344.1867.

[6-(Naphthalen-1-yloxy)-hexanoylamino]-acetic acid ethyl ester (13b)

Brown powder; yield: 30%; mp: 69-71 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.30 – 8.23 (m, 1H), 7.81 – 7.75 (m, 1H), 7.51 – 7.43 (m, 2H), 7.42 – 7.31 (m, 2H), 6.79 (dd, *J* = 7.2, 1.3 Hz, 1H), 5.94 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 8.0, 4.5 Hz, 2H), 4.03 (d, *J* = 5.1 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.90 (m, 2H), 1.86 – 1.73 (m, 2H), 1.64 (ddd, *J* = 12.8, 7.4, 4.2 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{20}H_{25}NNaO_4$ ($M+Na^+$): 366.1676, Found: 366.1689.

General procedure for the synthesis of 5-(aryloxy/thio)-pentanenitrile (15a-d)

A mixture of the naphthol or naphthalene thiol derivative (3 mmol), 5-bromovaleronitrile (3 mmol) and K2CO3 (3.6 mmol) in anhydrous dimethylformamide (DMF, 100 ml) was stirred at 80oC for 2 h. After cooling to room temperature, the reaction mixture was poured into ice water with vigorous stirring. The resulting suspension was extracted with EtOAc (2x100 ml); the organic extract was washed with water (3x100ml) and brine, dried over anhydrous Na2SO4, and

evaporated to give the desired product in a high yield (~87%), that was used without further purification.

5-(Naphthalen-2-yloxy)-pentanenitrile (15a)

Brown resin; yield: 87%; ^{1}H NMR ($CDCl_3$) δ 7.77 (dt, *J* = 8.9, 6.4 Hz, 3H), 7.46 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.36 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.19 – 7.09 (m, 2H), 4.16 (t, *J* = 5.6 Hz, 2H), 2.50 (t, *J* = 6.8 Hz, 2H), 2.11 – 1.90 (m, 4H).

4.10.2. 5-(Naphthalen-2-ylsulfanyl)-pentanenitrile (15b)

Yellowish-brown soild; yield: 85%; mp: 75-77 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.82 – 7.70 (m, 4H), 7.52 – 7.39 (m, 3H), 3.10 – 3.02 (m, 2H), 2.40 – 2.33 (m, 2H), 1.89 – 1.81 (m, 4H).

4.10.3. 5-(Naphthalen-1-yloxy)-pentanenitrile (15c)

Brown resin; yield: 83.3%; ^{1}H NMR ($CDCl_3$) δ 8.26 – 8.20 (m, 1H), 7.84 – 7.77 (m, 1H), 7.53 – 7.33 (m, 4H), 6.80 (d, *J* = 7.4 Hz, 1H), 4.20 (t, *J* = 5.6 Hz, 2H), 2.51 (t, *J* = 6.9 Hz, 2H), 2.17 – 1.94 (m, 4H).

4.10.4. 5-(Benzo[1,3]dioxol-5-yloxy)-pentanenitrile (15d)

Brown oil; yield: 84%; ^{1}H NMR ($CDCl_3$) δ 6.67 (ddd, *J* = 15.4, 8.4, 0.7 Hz, 1H), 6.49 – 6.39 (m, 1H), 6.34 – 6.21 (m, 1H), 5.91 (dd, *J* = 1.9, 1.0 Hz, 2H), 3.93 (t, *J* = 5.3 Hz, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 1.99 – 1.75 (m, 4H).

4.11. General procedure for the synthesis of 5-(aryloxy/thio)-pentylamine (16a-d):

To an ice-cold suspension of $LiAlH_4$ (3.98 mmol) in Et_2O (10 mL) was added a solution of the nitrile (1.99 mmol) in Et_2O (10 mL). The gray suspension was stirred for 1 h at 0 ^oC and for an additional 4.5 h at room temperature. After cooling to 0 ^oC, a NaOH solution (10 mL, 1 N) was added followed by the addition of water (20 mL). The aqueous layer was extracted with Et_2O (3x50 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated to dryness.

5-(Naphthalen-2-yloxy)-pentylamine (16a)

Yellow oil; yield: 50%; ^1H NMR ($CDCl_3$) δ 7.81 – 7.66 (m, 3H), 7.43 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.32 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.17 – 7.10 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.82 – 2.69 (m, 2H), 1.94 – 1.81 (m, 2H), 1.62 – 1.52 (m, 4H).

5-(Naphthalen-2-ylsulfanyl)-pentylamine (16b)

Yellowish-brown oil; yield: 57%; ^1H NMR ($CDCl_3$) δ 7.82 – 7.70 (m, 4H), 7.52 – 7.39 (m, 3H), 3.10 – 3.02 (m, 2H), 2.69-2.77 (m, 2H), 2.36 – 2.29 (m, 2H), 1.89 – 1.81 (m, 4H).

5-(Naphthalen-1-yloxy)-pentylamine (16c)

Brown oil; yield: 67.8%; ^1H NMR ($CDCl_3$) δ 8.31 – 8.24 (m, 1H), 7.82 – 7.75 (m, 1H), 7.52 – 7.43 (m, 2H), 7.43 – 7.32 (m, 2H), 6.80 (dd, *J* = 7.2, 1.3 Hz, 1H), 4.15 (t, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 6.6 Hz, 2H), 1.96 (p, *J* = 6.6 Hz, 2H), 1.63 – 1.56 (m, 4H).

5-(Benzo[1,3]dioxol-5-yloxy)-pentylamine (16d)

Yellow oil; yield: 70.6%; ^{1}H NMR ($CDCl_3$) δ 6.67 (dd, *J* = 15.0, 8.4 Hz, 1H), 6.45 (dd, *J* = 21.5, 2.5 Hz, 1H), 6.27 (ddd, *J* = 22.3, 8.4, 2.5 Hz, 1H), 5.90 (s, 2H), 3.88 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 1.76 (dt, *J* = 13.1, 6.5 Hz, 4H), 1.50 (dd, *J* = 7.3, 3.6 Hz, 2H).

General procedure for the synthesis of Ethanesulfonic acid [5-(aryloxy/thio)-pentyl]-amide (17a-d)

Ethanesulfonyl chloride (0.721 mmol) was dissolved in a biphasic mixture of EtOAc (15 ml) and saturated Na_2CO_3 (10 ml). The requisite amine (3 equiv) was added to the reaction, and the mixture was stirred for 4 h. The organic phase was removed, washed with 3N HCl (3x50 mL) and brine (30 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the corresponding product, which was purified by column chromatography.

Ethanesulfonic acid [5-(naphthalen-2-yloxy)-pentyl]-amide (17a)

White crystalline powder; yield: 71%; mp: 89-91 ^{o}C, ^{1}H NMR ($CDCl_3$) δ 7.83 – 7.69 (m, 3H), 7.49 – 7.41 (m, 1H), 7.35 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 3.19 (q, *J* = 6.6 Hz, 2H), 3.06 (q, *J* = 7.4 Hz, 2H), 1.88 (s, 2H), 1.71 – 1.60 (m, 2H), 1.39 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 2H). HR-ESI-MS m/z Calcd for $C_{17}H_{24}NO_3S$ ($M+H^+$): 322.1471, Found: 322.1472.

Ethanesulfonic acid [5-(naphthalen-2-ylsulfanyl)-pentyl]-amide (17b)

Yellowish-brown crystals; yield: 67%; mp: 73-75 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.82 – 7.70 (m, 4H), 7.51 – 7.38 (m, 3H), 3.11 (dd, *J* = 13.0, 6.6 Hz, 2H), 3.06 – 2.96 (m, 4H), 1.72 (dt, *J* = 14.1, 7.3 Hz, 2H),

1.34 (t, *J* = 7.4 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{17}H_{24}NO_2S_2$ ($M+H^+$): 338.1243, Found: 338.1237.

Ethanesulfonic acid [5-(naphthalen-1-yloxy)-pentyl]-amide (17c)

Brown oil; yield: 98%; ^1H NMR ($CDCl_3$) δ 8.29 – 8.22 (m, 1H), 7.83 – 7.75 (m, 1H), 7.53 – 7.44 (m, 2H), 7.41 (s, 1H), 7.40 – 7.32 (m, 1H), 6.80 (dd, *J* = 7.3, 1.0 Hz, 1H), 4.16 (t, *J* = 6.1 Hz, 2H), 3.18 (q, *J* = 6.6 Hz, 2H), 3.03 (q, *J* = 7.4 Hz, 2H), 2.02 – 1.91 (m, 2H), 1.76 – 1.61 (m, 4H), 1.35 (t, *J* = 7.4 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{34}H_{46}N_2NaO_6S_2$ ($2M+Na^+$): 665.2689, Found: 665.2690.

Ethanesulfonic acid [5-(benzo[1,3]dioxol-5-yloxy)-pentyl]-amide (17d)

White solid; yield: 70%; mp: 77-79 ^oC; ^1H NMR ($CDCl_3$) δ 6.71 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.32 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.92 (s, 2H), 3.90 (t, *J* = 6.2 Hz, 2H), 3.16 (dd, *J* = 13.3, 6.7 Hz, 2H), 3.06 (q, *J* = 7.4 Hz, 2H), 1.86 – 1.57 (m, 6H), 1.39 (t, *J* = 7.4 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{14}H_{22}NO_5S$ ($M+H^+$): 316.1213, Found: 316.1217.

General procedure for the synthesis of 1-Ethyl-3-[5-(aryloxy/thio)-pentyl]-urea (18a-d)

To a solution of an amine (0.75 mmol) in toluene (5 ml) was added ethylisocyanate (0.75 mmol). This reaction mixture was stirred at room temperature until completion (TLC monitoring). The resultant suspension was filtered, and the residue was purified by column chromatography.

1-Ethyl-3-[5-(naphthalen-2-yloxy)-pentyl]-urea (18a)

White powder; yield: 97%; mp: 128-130 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.78 – 7.69 (m, 3H), 7.46 – 7.39 (m, 1H), 7.36 – 7.29 (m, 1H), 7.16 – 7.10 (m, 2H), 4.11 (dt, *J* = 12.8, 6.8 Hz, 4H), 3.21 (dt, *J* = 9.3, 6.5 Hz, 4H), 1.93 – 1.82 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{18}H_{24}N_2NaO_2$ ($M+Na^+$): 323.1730, Found: 323.1726.

1-Ethyl-3-[5-(naphthalen-2-ylsulfanyl)-pentyl]-urea (18b)

White solid; yield: 60%; mp: 107-109 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.81 – 7.70 (m, 4H), 7.50 – 7.38 (m, 3H), 4.18 – 4.04 (m, 2H), 3.22 – 3.14 (m, 4H), 3.07 – 2.98 (m, 2H), 1.76 – 1.69 (m, 2H), 1.54 – 1.48 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{18}H_{25}N_2OS$ ($M+H^+$): 317.1682, Found: 317.1683.

1-Ethyl-3-[5-(naphthalen-1-yloxy)-pentyl]-urea (18c)

Brown powder; yield: 55%; mp: 89-91 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.25 – 8.15 (m, 1H), 7.73 (dt, *J* = 7.1, 2.0 Hz, 1H), 7.48 – 7.23 (m, 4H), 6.73 (d, *J* = 7.2 Hz, 1H), 4.26 – 4.01 (m, 4H), 3.23 – 3.04 (m, 4H), 2.86 (dd, *J* = 21.2, 1.7 Hz, 2H), 1.95 – 1.82 (m, 2H), 1.06 (td, *J* = 7.4, 2.0 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{18}H_{24}N_2NaO_2$ ($M+Na^+$): 323.1730, Found: 323.1729.

1-[5-(Benzo[1,3]dioxol-5-yloxy)-pentyl]-3-ethyl-urea (18d)

White solid; yield: 64%; mp: 142-144 ^{o}C, ^{1}H NMR (CD_3OD) δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.26 (s, 2H), 5.28 (t, *J* = 6.3 Hz, 2H), 4.57 – 4.48 (m, 4H), 3.15 (dt, *J* = 13.3, 6.7 Hz, 2H), 2.90 (dt, *J* = 9.8, 4.4 Hz, 4H), 2.48 (t, *J* = 7.2 Hz, 3H). HR-ESI-MS m/z Calcd for $C_{15}H_{23}N_2O_4$ ($M+H^+$): 295.1652, Found: 295.1650.

General procedure for the synthesis of [5-(Aryloxy/thio)-pentyl]-urea (19c-d)

A mixture of the amine (1 mmol) is stirred with potassium isocyanate (1.5 mmol) and ammonium chloride (0.14 mmol) in dimethyl formamide, at room temperature for 4 hr. The reaction mixture is evaporated under pressure and water added (10ml). The syrup is left to stir for 2hr and the resulting precipitate was filtered, washed with water and recrystallised from water.

[5-(Naphthalen-1-yloxy)-pentyl]-urea (19c)

Brown powder; yield: 96%; mp: 111-113 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.30 – 8.23 (m, 1H), 7.82 – 7.76 (m, 1H), 7.52 – 7.43 (m, 2H), 7.43 – 7.32 (m, 2H), 6.79 (dd, *J* = 7.3, 1.3 Hz, 1H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.28 – 3.17 (m, 2H), 1.95 (q, *J* = 6.6, 5.9 Hz, 2H), 1.63 (p, *J* = 3.6 Hz, 4H). HR-ESI-MS m/z Calcd for $C_{16}H_{21}N_2O_2$: 273.1598, Found: 273.1774

[5-(Benzo[1,3]dioxol-5-yloxy)-pentyl]-urea (19d)

White solid; yield: 63%; mp: 162-164 ^{o}C; ^{1}H NMR (CD_3OD) δ 6.70 (d, *J* = 8.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.35 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 3.91 (t, *J* = 6.3 Hz, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 1.77 (dt, *J* = 13.4, 6.6 Hz, 2H), 1.61 – 1.45 (m, 4H). HR-ESI-MS m/z Calcd for $C_{13}H_{19}N_2O_4$ ($M+H^+$): 267.1339, Found: 267.1338.

1. Molecular Modeling part

Multiple XED-based field templates model

This technology was applied in this work only to interpret the activity of some of the already-synthesised ligands in the shadow of the field similarity with known selective ligands. However, it is also worth noting that it can be used for further optimization by structural modification of the ligands to maximize field similarity to the reference ligands.

Extended Electron distribution based field pharmacophores can describe ligands better than feature based pharmacophores.[4] The main advantage of the field template over traditional pharmacophore methods is that the field patterns are calculated directly from the structure of a conformation.[5] It relies on representing all the steric and electrostatic features of a conformation in an analogue manner. For example, the field points near a hydrogen bonding group are not constant for every molecule and will vary according to the steric restrictions around this group and the nature of the substituents that are attached to the molecule (donating or withdrawing groups). As a result, field templates encode more information than traditional pharmacophore features. Moreover, XED force field can account for less common interactions like C-H hydrogen bonding, pi-pi stacking, cation-pi interactions.[5]

The field technology was used here by creating field templates that represent different classes of selective CB2 ligands that in turn can be used either in screening and/or SAR interpretation of ligands.

First, we adopted the categorization carried out by Yang and coworkers[6]and used 54 different ligands belonging to different categories to create the field templates (Figure S2-S10).

In effect, 54 field templates were created where each field template corresponds to the bioactive conformation of one of the ligands in these different categories. In order to achieve this, Field templater was used in order to create a detailed 3D hypothesis for binding using five reference CB2-selective ligands .[7]

After that the 54 ligands were aligned using field align against the field template which represents the 5 reference compounds (Figure S1). After that, the aligned ligands which are supposed to assume the bioactive conformation were used as reference ligand templates for activity interpretation.

As mentioned in the manuscript, the design of our new chemical scaffolds was partly based on the structure of previously discovered CB2 ligands that were reported by our group. Of these, compound XI ((E)-6-Naphthalen-2-yl-4-oxohex-5-enoic acid ethanolamide) showed a log (SI) of 1 where SI is calculated as Ki (CB1)/Ki (CB2) and Ki (CB1) was >10,000 and Ki (CB2) was 1000 nM.[8]

The model was first used to interpret the activity of this compound since it doesn't belong to a specific class of ligands. Thus, the compound was profiled against the 54 field templates which were generated in step two. The compound showed maximum similarity against F29 (Figure S6) where, the total similarity was 0.7. F29 code name is MDA75 and has a log (SI) of 1.37, where Ki (CB1) is >10,000 nM and Ki (CB2) is 422 nM. F29 It is a selective CB2 agonist that was recently discovered.[9] The field similarity (Figure 1 in the main manuscript) of our compound to MDA7 may interpret the activity of such compound on CB2.

In an attempt to interpret the activity of some of the newly synthesized active CB2 ligands, compound 18b was also shown to have a high field similarity against MDA7. This is correlated with the results of the biological evaluation which showed a log (SI) of 1.3 where Ki (CB1) is >10,000 nM and Ki (CB2) is approximately 500 nM (almost half that of the previously discovered compound, XI).

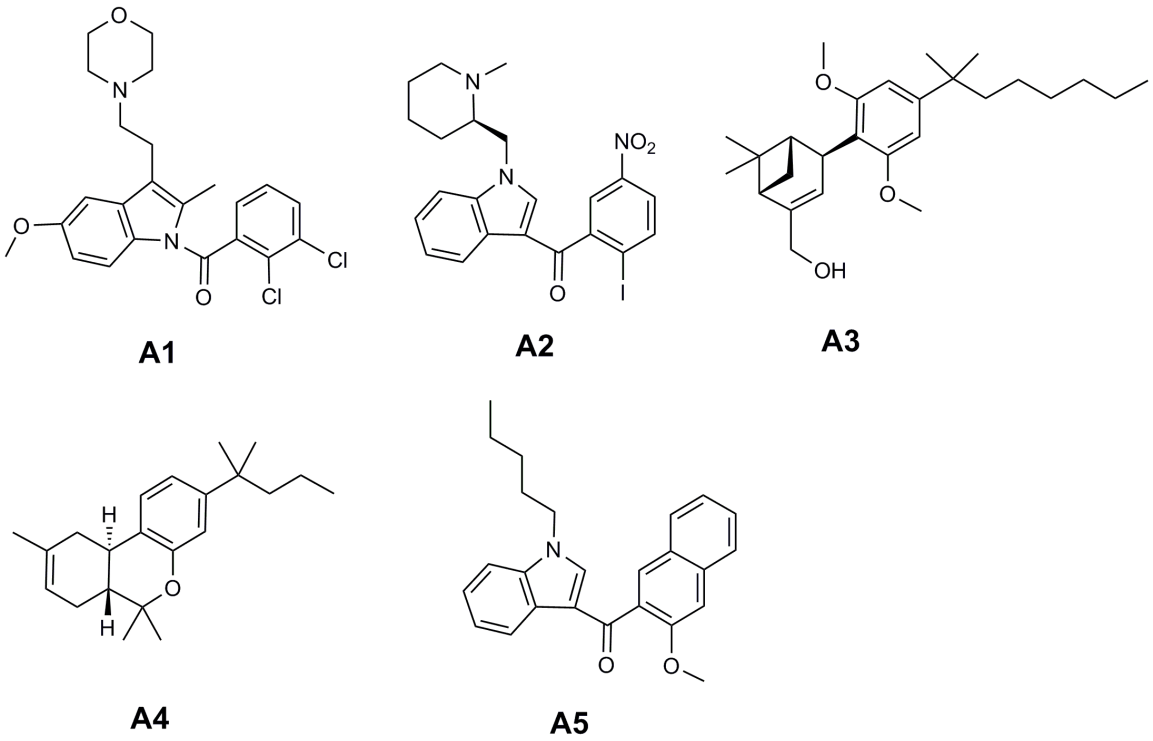


Figure S 1: The five reference compounds that were representing selective CB2 ligands. Adopted from Markt et al.[10]

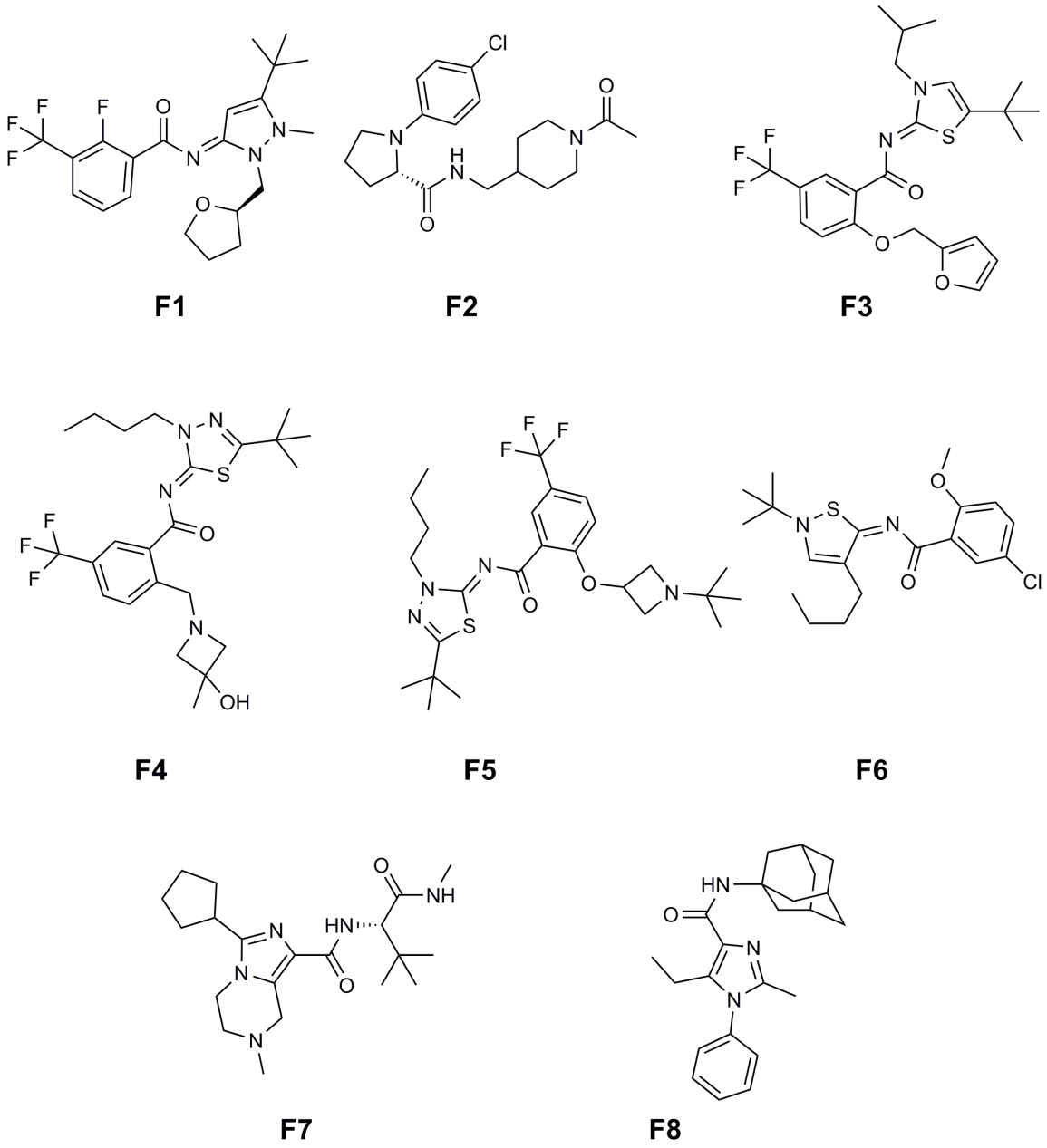


Figure S2: References representing pyrazole, pyrollidine,thiazole,isothiazole and imidazole derivatives

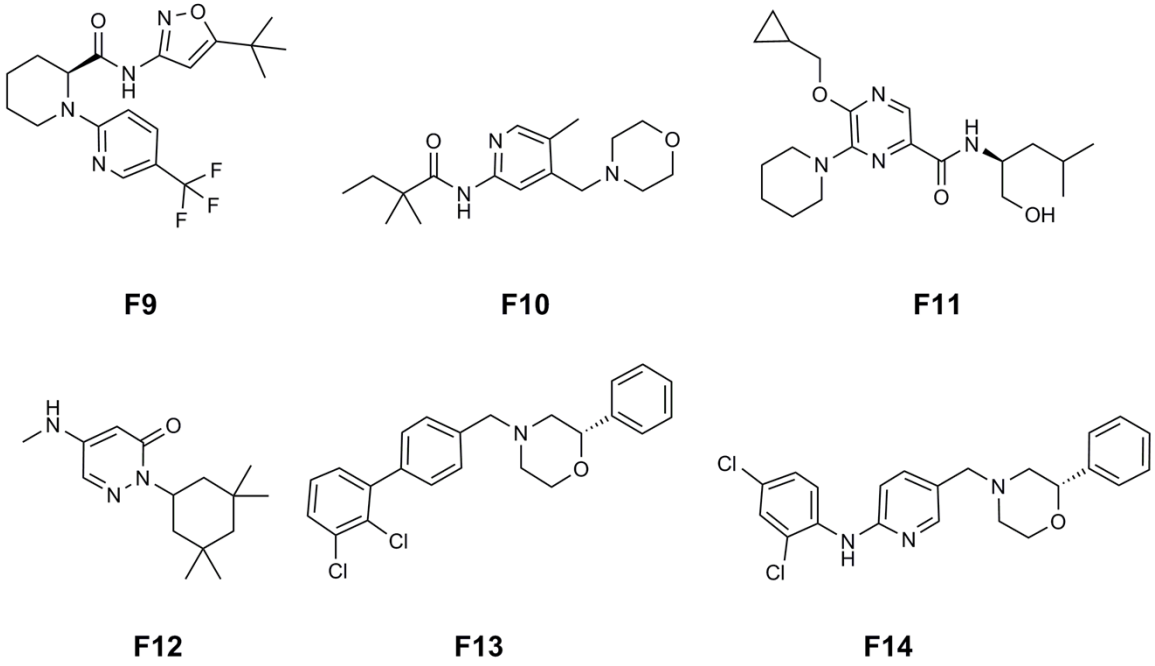


Figure S3: References representing pyridine, pyrazine,pyridazine and morpholine derivatives

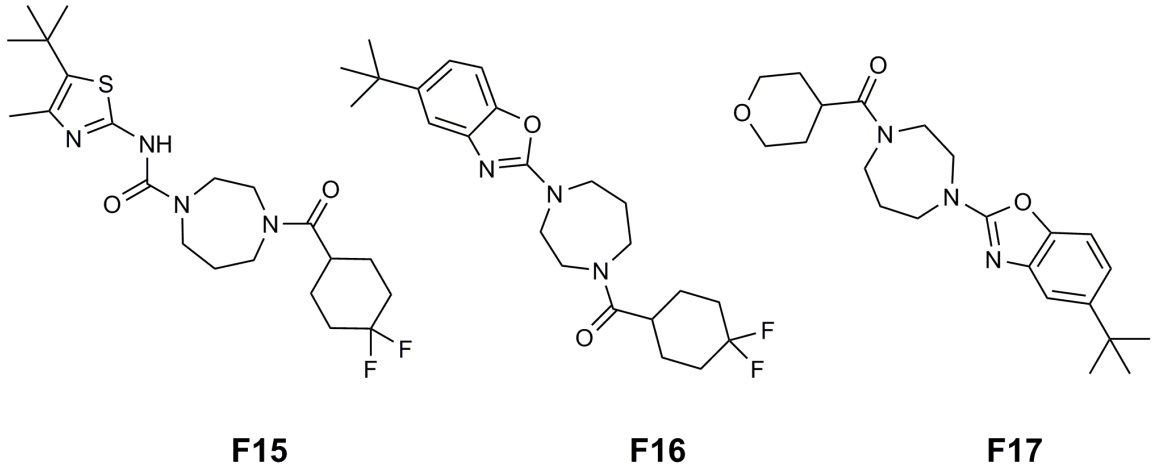


Figure S4: References representing diazepane derivatives

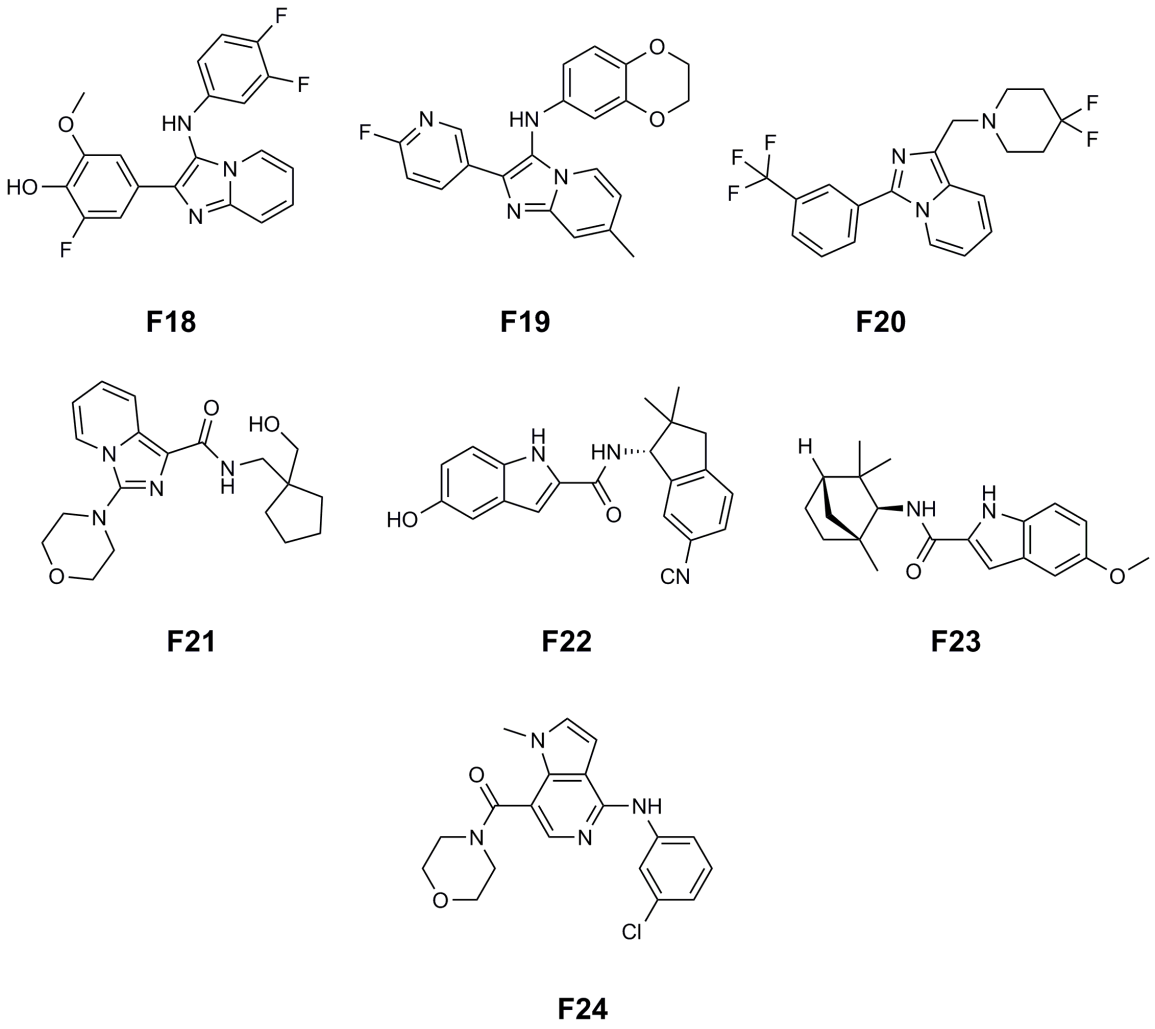
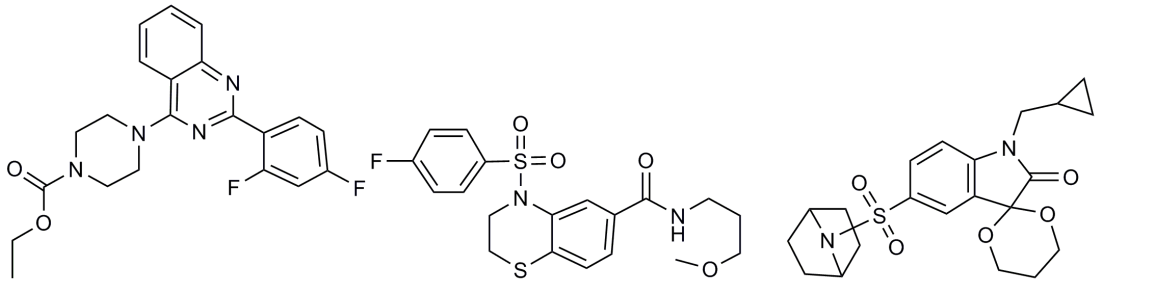
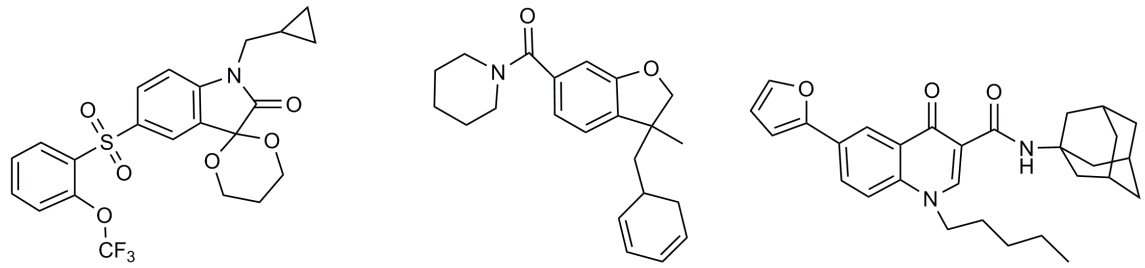


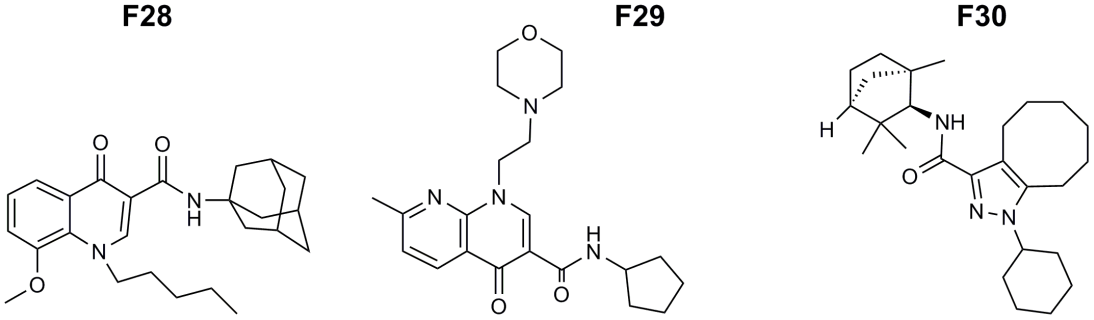
Figure S5: References representing imidazopyridine, indole and azaindole derivatives



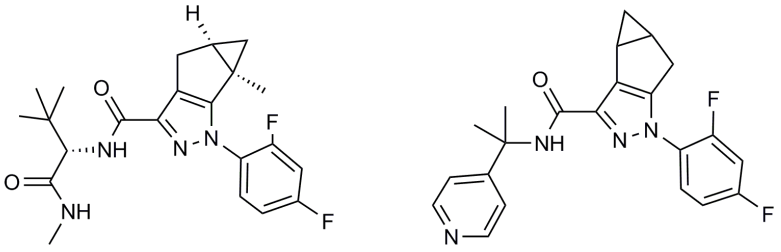
F25 F26 F27



F28 F29 F30

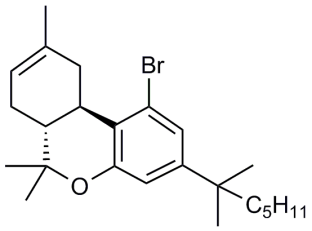


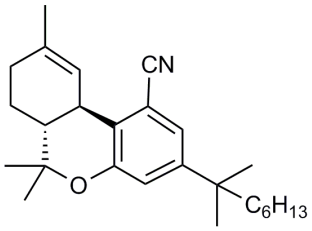
F31 F32 F33



F34 F35

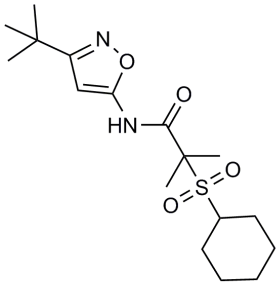
Figure S6: References representing benzo-fused, pyrazole-fused and pyridine-fused derivatives

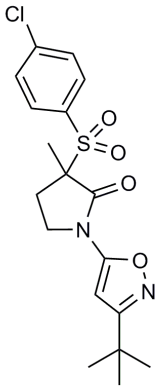


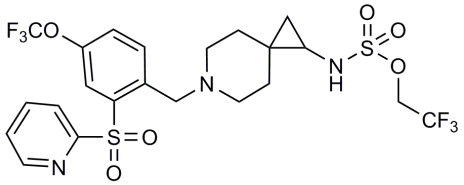


F36 **F37**

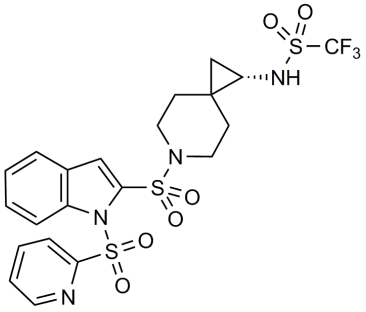
Figure S7: References representing tetrhydrocannabinol derivatives





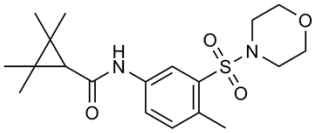


F38 **F39** **F40**

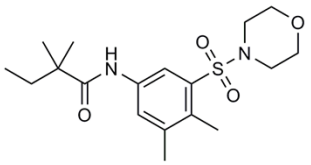


F41

Figure S8: References representing sulfone derivatives



F42



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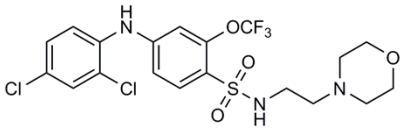

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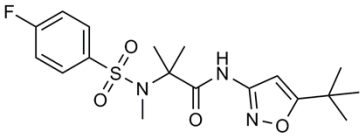
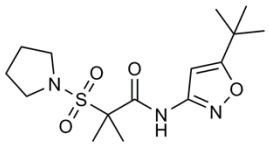
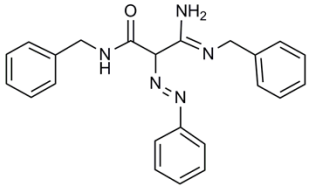


F45

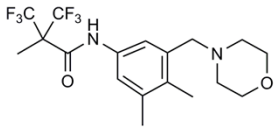


F46

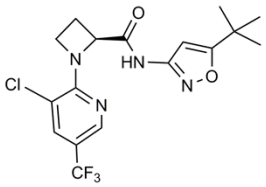
Figure S9: References representing sulfonamides derivatives



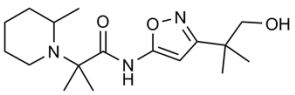
F47



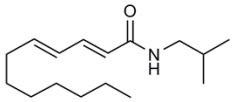
F48



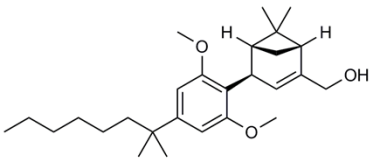
F49



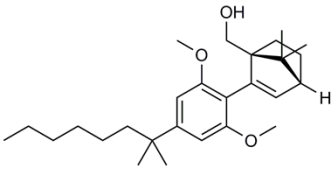
F50



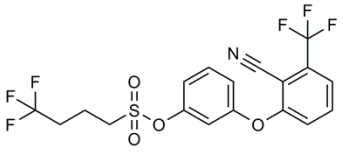
F51



F52



F53



F54

Figure S 10: References representing other miscellaneous scaffolds

Biological testing

All the synthesized compounds were screened in a competitive binding experiment in parallel with as previously described.[11]

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