Concise synthesis of potential 4-hydroxy-5-fluoropentyl side-chain metabolites of four synthetic cannabinoids

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General procedures
Organic solvents were concentrated under reduced pressure in a rotary evaporator (LABOROTA 4000, Heidolph) at 30 to 60 °C. Microwave irradiation was performed using an Initiator 60 EXP Microwave System (Biotage). TLC (SUPELCO, Silica gel on TLC Al foils, 0.75 mL/g pore volume, F254) was carried out using UV-light (CAMAG, 254 nm) and/or PAA-dip (acetic acid: H2SO4: p-anisaldehyde 50:1:0.5) for visualization. Silica gel (Merck Grade 9385, high purity grade, pore size: 60 Å, particle size: 0.037–0.063 mm) was used for flash column chromatography. HPLC-MS was performed on a Gilson system (Pump: Gilson gradient pump 322; UV/VIS detector (215 nm): Gilson 155; MS detector: Thermo Finnigan Surveyor MSQ; Gilson Fraction Collector FC204) with mobile phases (Organic: 90:10 MeCN:H2O with 10 mM ammonium acetate; Aqueous: 95:5 H2O:MeCN with 10 mM ammonium acetate), one column for analytical runs (Waters XSELECT phenyl-hexyl, 2.5 µm, 50 x 4.6 mm) and one column for preparative analysis (Waters XBridge C18, 5 µm, 100 x 19 mm). Purity was analyzed on an Agilent 1220 infinity LC system with a Poroshell 120 EC-C18 2.7 µm, 100 x 3 mm column. Detection by UV at 210 nm. NMR-spectra were recorded on a Varian instrument (1H-NMR: 300 MHz/500 MHz, 13C-NMR: 75.4 MHz/125 MHz and 19F-NMR: 282.2 MHz). Chemical shifts were assigned with the solvent peak as a reference according to earlier described definitions.

Compound synthesis
General procedure for opening of epoxides: Method A: Compounds 3 or 7b (1 equiv.) was dissolved in anhydrous THF (1 mL) or toluene (2.2 mL) together with TBAF (4-6 equiv.) solid, which had been dried using toluene and methanol to remove the water from TBAF·3H2O until no loss of mass could be observed, in a microwave vial. The reaction mixtures were heated using microwave irradiation at 165 °C for 45-60 min. The reaction mixture was diluted with water and extracted with EtOAc three times. The organic layers were combined, concentrated and purified by flash column chromatography and preparative HPLC to afford compounds 4 and 8b in 49% and 43% yield respectively.

Method B: The mixture of 7a, 7b or 7c (1 equiv.) and 1M TBAF (4-4.5 equiv.) in THF was heated at 70 -80 °C for 4 -16 hours. The work-up and purification procedure was the same as that described in Method A. The product of 8a, 8b or 8c was achieved in 40%, 86% and 40% yield respectively.
**N-(adamantan-1-yl)-1H-indole-3-carboxamide (2)**

To a stirred solution of 1H-indole-3-carboxylic acid 1 (150.0 mg, 0.93 mmol) in THF (15 mL), adamantan-1-amine hydrochloride (262.0 mg, 1.40 mmol), TBTU (448.2 mg, 1.40 mmol) and TEA (389.4 µL, 2.79 mmol) were added. The temperature was increased to 70 °C until completion of reaction (17 h) indicated by TLC. The reaction mixture was quenched with water (10 mL) followed by extraction with EtOAc (3 x 10 mL). The organic phases were combined and evaporated under reduced pressure and purified using flash column chromatography (EtOAc:Toluene, 1:1) to give 2 (186.0 mg, 68%). 1H-NMR (300 MHz, CD3OD) δ: 8.02-7.95 (m, 1H), 7.82 (s, 1H), 7.42-7.35 (m, 1H), 7.18-7.08 (m, 2H), 2.20-2.14 (m, 6 H), 2.13-2.08 (m, 3 H), 1.80-1.72 (m, 6 H). 13C-NMR (75.4 MHz, CD3OD) δ: 168.0, 138.1, 128.9, 127.0, 123.3, 121.8, 121.4, 113.1, 112.8, 53.1, 42.8, 37.6, 31.1.

**2-(3-bromopropyl)oxirane**

2-(3-bromopropyl)oxirane is commercially available. However, it can be synthesized as described below. To a stirred solution of 5-bromopent-1-ene (238 µL, 2.01 mmol) in DCM (8 mL) at rt, m-CPBA (520 mg, 3.01 mmol) was added slowly. After completion of reaction (3h) indicated by 1H-NMR, the solution was quenched with saturated NaHSO3 (5 mL) followed by extraction with DCM (3 x 10 mL). The combined organic phases were washed with NaHCO3 (6 x 15 mL) and dried with MgSO4 followed by evaporation under reduced pressure to give 2-(3-bromopropyl)oxirane (260.7 mg, 79%). 1H-NMR (300 MHz, CDCl3) δ: 3.53-3.41 (m, 2H), 2.94 (dtd, J = 6.7, 4.1, 2.7 Hz, 1H), 2.80-2.75 (m, 1H), 2.51 (dd, J = 4.9, 2.7 Hz, 1H), 2.11-1.96 (m, 2H), 1.82 (dddd, J = 13.4, 8.8, 6.2, 4.5 Hz, 1H), 1.67-1.56 (m, 1H).

**N-(adamantan-1-yl)-1-(3-(oxiran-2-yl)propyl)-1H-indole-3-carboxamide (3)**

To a stirred solution of 2 (260.8 mg, 0.89 mmol) in THF (10 mL) at 0 °C, t-BuOK (178.9 mg, 1.59 mmol) was added. After 15 minutes 2-(3-bromopropyl)oxirane (292.0 mg, 1.77 mmol) was added and the temperature was gradually increased to rt. After completion of reaction indicated by TLC (22 h) the mixture was quenched with H2O (10 mL) followed by extraction with EtOAc (3 x 10 mL). The combined organic layers were evaporated under reduced pressure and purified with flash column chromatography (EtOAc:n-heptane, 4:1) to give 3 (241.2 mg, 0.64 mmol, 72%). 1H-NMR (300 MHz, CDCl3): δ 7.91-7.84 (m, 1H), 7.68 (s, 1H), 7.39-7.32 (m, 1H), 7.30-7.19 (m, 2H), 5.75 (broad s, 1 H), 4.34-4.06 (m, 2H), 2.90 (dtd, J = 6.8, 4.0, 2.7 Hz, 1H), 2.73 (dd, J = 4.9, 3.9 Hz, 1H), 2.44 (dd, J = 4.9, 2.7 Hz, 1H), 2.20-2.12 (m, 10H), 2.07-1.93 (m, 2H), 1.81-1.63 (m, 7H), 1.46-1.32 (m, 1H). 13C-NMR (75.4 MHz, CDCl3): δ 164.6, 136.6, 131.5, 125.4, 122.5, 121.4, 120.1, 112.5, 110.3, 52.3, 51.8, 46.8, 46.4, 42.3, 36.6, 29.7, 29.6, 26.7.

**N-(adamantan-1-yl)-1-(5-fluoro-4-hydroxypentyl)-1H-indole-3-carboxamide (4)**
The title compound was synthesized according to Method A of the general procedure for opening of epoxides using 3 (39.0 mg, 0.10 mmol), TBAF (186.6 mg, 0.59 mmol) and dry THF (1 mL) in a Biotage 0.5-2.0 mL conical vial under microwave irradiation at 165 °C for 60 minutes. The mixture was analyzed by LC-MS showing 85% conversion. The solution was diluted with EtOAc (10 mL) and washed with water (3 x 10 mL) followed by concentration of the organic phase under reduced pressure. The crude product was purified with flash column chromatography (EtOAc:toluene, 3:1) and LC-PREP (20%-100%) to give 4 (20.0 mg, 49%).

(1H-indol-3-yl)(4-methylnaphthalen-1-yl)methanone (6a)

Indole 5 (820 mg, 7 mmol) was dissolved in dry DCM (20 mL). To the solution ZrCl₄ (1628 mg, 7 mmol) and synthesized 4-methyl-1-naphthoyl chloride was added and the resulting reaction mixture was left to react for 8 hours under nitrogen and kept at 0 °C. Subsequently the reaction was quenched by the addition of water (20 mL), the water phase was then extracted using DCM (3 x 20 mL). The combined organic layers were concentrated under reduced pressure before the resulting residue was chromatographed on silica using a mobile phase system of EtOAc:n-heptane (3:2) followed by a second column using a mobile phase system of EtOAc:n-heptane (1:2). The fractions containing 6a were collected and concentrated under reduced pressure to afford 6 (500 mg, 33%). Product was identified by correct mass (LC-MS) and by the presence of the signal at 195.5 ppm (MeOD) in the 13C-NMR.

(4-methylnaphthalen-1-yl)(1-(3-oxiran-2-yl)propyl)-1H-indol-3-yl)methanone (7a)

Compound 6a (500 mg, 1.75 mmol) was dissolved in DMF/THF (1:6, 12 mL) and cooled to 0°C. To the solution t-BuOK (295 mg, 2.63 mmol) was added. The reaction mixture was left to stir for 15 minutes prior to the addition of 2-(3-bromopropyl)oxirane (433 mg, 2.63 mmol) as the reaction mixture was brought to rt and left to stir overnight. The progression of the reaction was monitored by TLC. The solvents were evaporated and water (20 mL) was added. The solution was then extracted using EtOAc (3 x 20 mL). The combined organic phases were gathered and concentrated under reduced pressure. The resulting residue was chromatographed on silica using a mobile phase of EtOAc:n-heptane (1:1) and the fractions containing compound 7 were collected and concentrated under reduced pressure to afford 7a (525 mg, 81%). ¹H-NMR (300 MHz, CDCl₃): δ 8.58-8.52 (m, 1H), 8.27 (ddd, J = 8.3, 1.5, 0.7 Hz, 1H), 8.08 (ddd, J = 8.5, 1.5, 0.7 Hz, 1H), 7.59-7.52 (m, 2H), 7.47 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.42-7.32 (m, 5H), 4.20-4.02 (m, 2H), 2.83 (ddd, J = 6.7, 3.9, 2.7 Hz, 1H), 2.77 (d, J = 0.9 Hz, 2H), 2.68 (dd, J = 4.9, 4.0 Hz, 1H), 2.36 (dd, J = 4.9, 2.7 Hz, 1H), 2.00-1.89 (m, 2H), 1.64 (ddd, J = 14.5, 7.9, 6.6, 3.9 Hz, 1H), 1.39-1.23 (m, 1H). ¹³C-NMR (75.4 MHz, CDCl₃): δ 192.2, 137.9, 137.5, 137.0, 136.7, 132.8, 130.9, 127.1, 126.6, 126.4, 126.1, 125.8, 125.3, 124.3, 123.7, 122.9, 122.8, 117.8, 110.0, 51.5, 46.6, 46.5, 29.3, 26.5, 19.8.

(1-(5-fluoro-4-hydroxypentyl)-1H-indol-3-yl)(4-methylnaphthalen-1-yl)methanone (8a)
Compound 8a was synthesized according to Method B of the general procedure for opening of epoxides using 7a (525 mg, 1.42 mmol) and 1M TBAF·THF (6 mL, 6 mmol) under conventional heating at 70 °C overnight for about 16 h. The crude product was purified by flash chromatography using a mobile phase system of EtOAc:n-heptane (1:1) followed by another column using a mobile phase system of EtOAc:toluene (1:1). The fractions containing compound 8 were gathered and purified further using LC-PREP (20%-100%) to afford 8a (220.8 mg, 40%).

(1H-indol-3-yl)(naphthalene-1-yl) methanone (6b)

To a stirred solution of indole 5 (480 mg, 4.1 mmol) in 10 mL DCE at 0 °C, the solution of 1-napthoyl chloride (600 mg, 3.15 mmol) in 10 mL DCE was added dropwise under nitrogen flow, followed by the addition of ZrCl₄ (1.1 g, 4.72 mmol). The mixture was heated to 30 °C. After completion of the reaction (20 h) it was quenched with 10 mL of water, filtered through cotton and extracted with EtOAc (2 x 40 mL) and washed with water (2 x 30 mL). The organic phase was concentrated under reduced pressure, and the crude product was dissolved in a minimum amount of acetone and pre-absorbed onto silica gel. The sample silica gel was applied to a flash column and the crude product was purified using EtOAc:n-heptane (1:1) to give compound 6b (544 mg, 64%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 8.73 (broad s, 1H), 8.52-8.46 (m, 1H), 8.17 (dd, J = 8.2, 1.6 Hz, 1H), 7.95 (dd, J = 8.3, 1.7 Hz, 1H), 7.92-7.87 (m, 1H), 7.64 (dd, J = 7.0, 1.3 Hz, 1H), 7.53–7.31 (m, 7H). ¹³C-NMR (75.4 MHz, CDCl₃) δ 193.1, 138.8, 136.8, 135.7, 133.8, 130.8, 130.2, 128.3, 127.0, 126.4, 126.1, 126.0, 125.9, 124.6, 124.1, 124.1, 122.5, 118.9, 111.9.

Naphthalen-1-yl(1-(3-(oxiran-2-yl)propyl)-1H-indol-3-yl) methanone (7b)

To a stirred solution of 6b (256 mg, 0.94 mmol) in DMF (10 mL) at 0 °C, 48.9 mg 60% NaH (29.3 mg, 1.22 mmol) was added at 0 °C. After 10 minutes, 2-(3-bromopropyl)oxirane (214.2 mg, 1.30 mmol) was added and the temperature was gradually increased to rt overnight. The crude mixture was evaporated under reduced pressure and purified with silica gel chromatography (EtOAc: n-heptane, 1:1 to 3:1) to give 7b (317.4 mg, 95%). ¹H-NMR (300 MHz, CDCl₃) δ: 8.53-8.46 (m, 1H), 8.18 (dd, J = 8.0, 1.8, 0.8 Hz, 1H), 7.97 (dt, J = 8.3, 1.2 Hz, 1H), 7.93-7.88 (m, 1H), 7.65 (dd, J = 7.0, 1.3 Hz, 1H), 7.56-7.42 (m, 3H), 7.41-7.33 (m, 4H), 4.24-4.06 (m, 2H), 2.86 (dd, J = 6.7, 3.9, 2.6 Hz, 1H), 2.69 (dd, J = 4.9, 3.9 Hz, 1H), 2.37 (dd, J = 4.9, 2.7 Hz, 1H), 2.05-1.93 (m, 2H), 1.74-1.61 (m, 1H), 1.41-1.29 (m, 1H). ¹³C-NMR (75.4 MHz, CDCl₃) δ 192.2, 139.2, 138.1, 137.1, 133.9, 130.9, 130.1, 128.3, 127.2, 126.9, 126.4, 126.1, 125.9, 124.7, 123.9, 123.2, 123.1, 117.9, 110.0, 51.7, 46.8, 46.7, 29.5, 26.7.

(1-(5-fluoro-4-hydroxypentyl)-1H-indol-3-yl)(naphthalene n-1-yl) methanone (8b)
Method A: The title compound was synthesized according to Method A of the general procedure for opening of epoxides using 7b (72.7 mg, 0.205 mmol), TBAF (215.3 mg, 0.823 mmol) and dry toluene (2.2 mL) in a Biotage 2.0-5.0 mL via under microwave irradiation at 165 °C for 45 minutes. The crude product was purified with LC-PREP (20%-100%), and further using flash chromatography (EtOAc:n-heptane, 1:2 to 2:1) to give compound 8b (33 mg, 43%). $^1$H-NMR (CDCl$_3$, 300 MHz) δ: 8.53-8.45 (m, 1H), 8.17 (ddd, $J = 7.6, 2.1, 0.8$ Hz, 1H), 7.94-7.82 (m, 2H), 7.60 (dd, $J = 7.0$, 1.3 Hz, 1H), 7.50-7.29 (m, 7H), 4.35-4.04 (m, 2H), 4.00 (t, $J = 7.0$ Hz, 2H), 3.76-3.61 (m, 1H), 2.62 (s, 1H), 2.00-1.69 (m, 2H), 1.39-1.27 (m, 2H). $^{13}$C-NMR (CDCl$_3$, 75.4 MHz) δ: 192.3, 138.9, 138.1, 137.0, 133.8, 130.8, 130.1, 128.3, 127.0, 126.8, 126.4, 126.0, 125.9, 124.6, 123.8, 123.0, 122.9, 117.6, 110.1, 86.6 (d, $J_{CF} = 169.3$ Hz), 69.6 (d, $J_{CF} = 19.5$ Hz), 46.9, 28.9 (d, $J_{CF} = 5.8$ Hz), 25.9. $^{19}$F-NMR (CDCl$_3$, 282.2 MHz) δ: -228.1 (td, $J_{HF} = 47.4$ Hz, 17.2 Hz).

Method B: Compound 8b was synthesized according to Method B of the general procedure for opening of epoxides using 7b (74 mg, 0.21 mmol) and 1M TBAF·THF (0.85 mL, 0.85 mmol) under conventional heating at 80 °C overnight for about 16 h. The crude product was purified by flash chromatography (EtOAc:n-heptane, 50:50 to 60:40) to give compound 8b (67 mg, 86%).

![Chemical structure of 6c, 7c, and 8c](image)

(1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (6c)

To a stirred solution of indole (600 mg, 5.12 mmol) in DCM (8 mL) at 0 °C under nitrogen, ZrCl$_4$ (1789.7 mg, 7.68 mmol) was added. After 5 minutes, 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (1644.9 mg, 10.24 mmol) in DCM (3 mL) was added dropwise. The temperature was kept at 0 °C until completion of reaction (4 h) indicated by TLC. The reaction mixture was quenched with H$_2$O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H$_2$O (5 x 10 mL) and concentrated under reduced pressure. The crude product was purified with flash column chromatography (EtOAc:n-heptane, 2:3) and 6c (1050.6 mg, 85%) was isolated. $^1$H-NMR (300 MHz, CDCl$_3$) δ: 9.79 (broad s, 1H), 8.48-8.39 (m, 1H), 7.75 (d, $J = 3.0$ Hz, 1H), 7.42-7.34 (m, 1H), 1.98 (s, 1H), 1.39 (s, 6H), 1.30 (s, 6H). $^{13}$C-NMR (75.4 MHz, CDCl$_3$) δ: 196.3, 136.7, 131.5, 125.5, 123.4, 122.3, 122.1, 120.8, 111.8, 41.9, 32.0, 24.1, 17.3.

(1-(3-(oxiran-2-yl)propyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (7c)

To a stirred solution of 6c (260.7 mg, 1.08 mmol) in THF/DMF (6:1 mL) at 0 °C, t-BuOK (181.8 mg, 1.62 mmol) was added. After 15 minutes 2-(3-bromopropyl)oxirane (213.9 mg, 1.30 mmol) was added and the temperature was gradually increased to rt. After completion of reaction indicated by TLC (16 h) the mixture was quenched with H$_2$O (10 mL) followed by extraction with EtOAc (3 x 10 mL). The combined organic layers were evaporated under reduced pressure and purified with flash column chromatography (EtOAc:n-heptane, 2:3) to
give 7c (262.2 mg, 75%). 1H-NMR (300 MHz, CDCl3): δ 8.45-8.38 (m, 1H), 7.70 (s, 1H), 7.36-7.21 (m, 3H), 4.22 (td, J = 7.1, 4.2 Hz, 2H), 2.92 (dtd, J = 6.7, 3.9, 2.7 Hz, 1H), 2.75 (dd, J = 4.9, 3.9 Hz, 1H), 2.46 (dd, J = 4.9, 2.7 Hz, 1H), 2.11-1.98 (m, 2H), 1.94 (s, 1H), 1.74 (dddd, J = 14.4, 7.6, 6.8, 3.9 Hz, 1H), 1.42 (dt, J = 14.3, 7.3 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 1.310 (s, 3H), 1.306 (s, 3H). 13C-NMR (75.4 MHz, CDCl3): δ 194.7, 136.6, 133.7, 126.5, 123.0, 122.8, 122.2, 119.8, 109.6, 51.7, 46.7, 46.5, 41.7, 31.7, 29.5, 26.7, 24.1, 24.1, 17.1.

(1-(5-fluoro-4-hydroxypentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone (8c)

Compound 8c was synthesized according to Method B of the general procedure for opening of epoxides using 7c (262.2 mg, 0.81 mmol) and 1M TBAF·THF (3.24 mL, 3.24 mmol) under conventional heating at 80 °C for about 4 h. The crude product was purified with flash column chromatography (EtOAc:n-heptane, 1:1) and LC-PREP (20%-100%) to give 8c (112.3 mg, 40%).

Appendix

1H-NMR of 4
$^{13}$C-NMR of 4

![13C-NMR spectrum of 4](image1)

$^{19}$F-NMR of 4

![19F-NMR spectrum of 4](image2)
DEPT of 4

\[\begin{align*}
\uparrow &= \text{CH/CH}_3 \\
\downarrow &= \text{CH}_2
\end{align*}\]
$^{19}\text{F-NMR of 8a}$

$^{1}\text{H-NMR of 8b}$
$^{13}\text{C-NMR}$ of $8b$

$^{19}\text{F-NMR}$ of $8b$
$\text{1H-NMR of 8b (Method B, 500 MHz):}$

![1H-NMR spectrum of 8b](image1)

$\text{13C-NMR of 8b (Method B, 125 MHz):}$

![13C-NMR spectrum of 8b](image2)
$^{19}\text{F-NMR of 8b (Method B, 282.2 MHz)}$

$^{1}\text{H-NMR of 8c}$
$^{13}$C-NMR of 8c

$^{19}$F-NMR of 8c