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ORIGINAL RESEARCH

Effect of chiral polyhydrochromenes on cannabinoid system

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Abstract
A set of chiral polyhydrochromenes was synthesized by clay-catalyzed reactions of monoterpenoids (−)-isopulegol, (+)-neoisopulegol and (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **5** with aromatic and heteroaromatic aldehydes. These compounds resemble in structure phytocannabinoids, some of them demonstrated analgesic activity in vivo. Polyhydrochromenes containing amino groups were obtained through the interaction of (−)-isopulegol with 5-hydroxymethylfurfural, followed by substitution of hydroxy-group with bromine and further reaction with amines. The ability of all synthesized compounds to influence the endocannabinoid system was studied for the first time. Although the polyhydrochromenes did not significantly bind to CB_1 and CB_2 cannabinoid receptors and did not inhibit MAGL activity at the concentration of 10 μM, isopulegol derivative **2i** containing 3-bromothiophene substituent inhibited FAAH activity with an IC_{50} value of 7.6 μM. Thus, this compound may increase endocannabinoid system activity.

Keywords CB_1 · CB_2 · Anandamide · Fatty acid amide hydrolase (FAAH) · Monoacylglycerol lipase (MAGL) · Isopulegol · Aldehyde

Introduction

The endocannabinoid system consists of two type of G-protein coupled receptors (CB_1 and CB_2) and a group of neuromodulatory lipids derived from arachidonic acid, anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG) (Aghazadeh Tabrizi et al. 2016). Endocannabinoid levels are controlled by the hydrolytic activity of fatty acid amide hydrolase (FAAH) for AEA and monoacylglycerol lipase (MAGL) for 2-AG (Makriyannis 2014). Cannabinoid receptors are involved in the regulation of nausea, obesity, pain, anxiety, depression, and neurodegenerative disorders (Khurana et al. 2017).

The most known exocannabinoid ligands are phytocannabinoids. Cannabidiol and Δ^9-tetrahydrocannabinol (Fig. 1) isolated from *Cannabis* and combining monoterpenoid fragment with *para*-menthane structure and aromatic ring are the most abundant phytocannabinoids with pronounced biological effects (Woodhams et al. 2017; Dos Santos et al. 2015; Javid et al. 2016). In particular, pronounced analgesic effect of phytocannabinoids attracts special attention due to their ability to control neuropathic pain (King et al. 2017; Walter et al. 2016). Earlier we have found that several heterocyclic compounds **1** and **2** (Fig. 1) also containing *para*-menthane and aromatic moieties and synthesized by interaction of monoterpenoid alcohols with aldehydes possess high analgesic activity in vivo along with low acute toxicity (Mikhalchenko et al. 2013; Il'Ina et al. 2014; Pavlova et al. 2015; Pavlova et al. 2016; Nazimova et al. 2016; Pavlova et al. 2017). For compound **1a**, it was shown the

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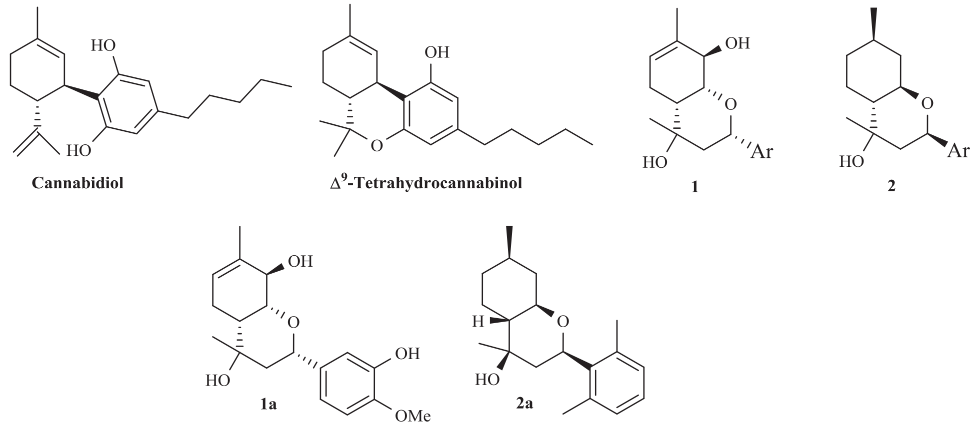
Fig. 1 Structures of cannabinoids and compounds **1** and **2**



loss of analgesic effect in presence of the selective CB_1 receptor antagonist rimonabant (Pavlova et al. 2017). It means that the endocannabinoid system may be involved in the mechanism of action of this compound. At the same time, the ability of these compounds to effect cannabinoid system was not studied yet. The only published data concern competition binding of a small set of dimethyl-substituted compounds of type **2** with CB_1 and CB_2 cannabinoid receptor subtypes (Slater et al. 2018). Among these compounds, only **2a** was marginally active against these receptors with ~20% displacement of radioligand at 10 μM concentration.

The goal of this work is to study whether compounds of types **1** and **2** having different substituents at aromatic/heteroaromatic ring can interact with cannabinoid system.

Results and discussion

Chemistry

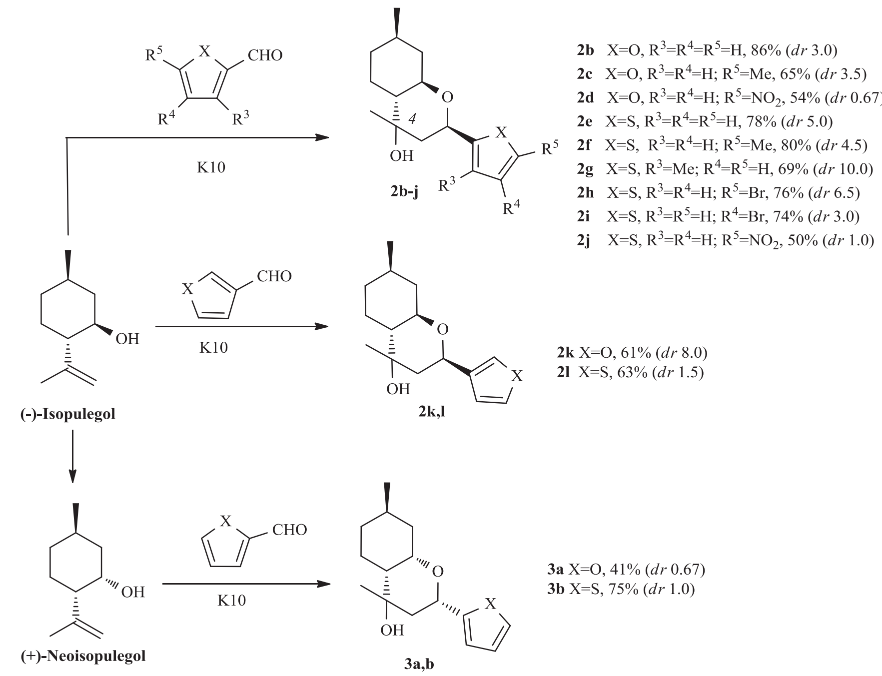
Compounds of types **1** and **2** can be synthesized by acid-catalyzed interaction of monoterpenoids with aldehydes (Patrusheva et al. 2018). Although different catalysts, including $TsOH/SiO_2$ (Macedo et al. 2010), $BF_3{\cdot}Et_2O$ (Bondalapati et al. 2011), $Sc(OTf)_3$ (Yadav et al. 2010), I_2 (Silva and Quintiliano 2009), and zeolites (Stekrova et al. 2015) can be applied for these transformations, the most often catalysts used are clays (Baishya et al. 2013; Stekrova et al. 2015; Timofeeva et al. 2015; Timofeeva et al. 2016; Sidorenko et al. 2018a; Sidorenko et al. 2018b). Earlier, we obtained a set of compounds **2b–l** by clay K10 catalyzed reactions of (−)-isopulegol with heteroaromatic aldehydes (Scheme 1) (Nazimova et al. 2016; Nazimova et al. 2017). These octahydrochromene derivatives with heteroaromatic substituents demonstrated high analgesic activity in vivo. Compounds **3a, b** were synthesized by (+)-neoisopulegol reactions with corresponding aldehydes (Nazimova et al. 2016). The products were formed as a mixture of diastereomers at C-4.

It was found recently that the use of $BF_3{\cdot}Et_2O/H_2O$ system for reaction of monoterpenoid alcohols with aldehydes led to formation of fluorine containing compounds **4** along with compounds of type **2** (Scheme 2) (Mikhalchenko et al. 2016; Patrusheva et al. 2016). Thus, compounds **2m** and **4a** were obtained by the reaction of (−)-isopulegol with 3,4,5-trimethoxybenzaldehyde (Mikhalchenko et al. 2016). In addition to these compounds, in this work fluorine containing compounds **4b–f**, as well as hydroxyl containing analogues **2n–p** were synthesized.

Acid-catalyzed reactions of isopulegol with aromatic/heteroaromatic aldehydes allow one to obtain octahydrochromenes with various substituents in the aromatic ring excluding amine-containing substituent. To synthesize these compounds, three step approaches has been elaborated in the current work (Scheme 3). At first step, compound **2q** was synthesized by clay catalyzed reaction of (−)-isopulegol with 5-hydroxymethylfurfural obtained from fructose in accordance with (Tian et al. 2013). The individual stereoisomer (*R*)-**2q** and mixture of (*R*)-**2q** and (*S*)-**2q** (*dr* 1.0) were isolated by column chromatography. Then, bromide **2r** was synthesized by the reaction of (*R*)-**2q** or mixture **2q** with PBr_3. This compound appeared to be unstable at room temperature and was involved in the reaction with a set of secondary amines without separation, giving amine-containing compounds **2s–v**.

The last group of monoterpenoid based compounds was synthesized from diol **5**, obtained in three stages from (−)-verbenone in accordance with (Il'ina et al. 2007). Clay catalyzed reaction of monoterpenoid **5** with a set aldehydes led to formation of compound **1a** and its analogues **1b–e** (Scheme 4).

Thus, large set of chiral octahydrochromenes belonging to four structural types, **1**, **2**, **3** and **4**, has been synthesized from monoterpenoid alcohols (−)-isopulegol, (+)-neoisopulegol and compound **5**.



Scheme 1 Synthesis of **2b**-**l** and **3a**, **b**; *dr* is the 4*R*/4*S* diastereomers ratio (Nazimova et al. 2016)

Biology

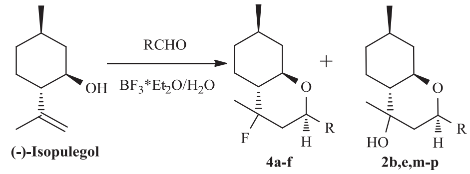
The ability of substituted polyhydrochromenes **1**–**4** to bind to CB_1 and CB_2 receptors was studied with a radioactivity-based binding assay. The experiments were performed using membrane preparations overexpressing $h$$CB_1$ and $h$$CB_2$ using [^{3}H]CP55,940 as a competitive ligand as previously reported (Chicca et al. 2017). While the classic CB_1 receptor agonist (*R*)-WIN55,212-2 (Showalter et al. 1996) decreased [^{3}H]CP55,940 signal to 10%, all tested chromenes did not significantly bind to CB_1 receptor at the screening concentration of 10 µM (Fig. 2).

In the case of CB_2 receptor, five compounds (**1a**, **2b**, **2k**, **4a**, and **4d**) marginally interacted with the receptor leading to a 15–25% displacement of the [^{3}H]CP55,940 (Fig. 3). Compounds **2b** and **2k** are furan-containing analogues of recently studied chromenol **2a** (Slater et al. 2018), which demonstrated similar activity. Compounds **4a** and **4d** contain fluorine atom, their counterparts with hydroxy group **2m** and **2p** were not active. Note, that just for compound **1a** it was shown the loss of analgesic effect in vivo in presence of rimonabant (Pavlova et al. 2017).

As all tested compounds did not show significant interaction with CB receptors at 10 µM concentration, we also studied their ability to influence AEA and 2-AG hydrolysis.

FAAH is primarily responsible for AEA degradation and indirectly involved in AEA uptake (Chicca et al. 2012; Nicolussi et al. 2014; Chicca et al. 2017), thus its inhibition leads to increasing endocannabinoid system activity. FAAH activity was measured using U937 cell homogenate in the presence of test compounds (10 µM) as previously reported (Chicca et al. 2017). We found, that isopulegol derivative **2i** containing 3-bromothiophene substituent inhibited FAAH activity with an IC_{50} value (50% inhibiting concentration) of 7.6 ± 1.5 µM (Fig. 4a). In agreement with the inhibition of FAAH, compound **2i** also inhibited AEA uptake in living U937 cells with an IC_{50} value of 15.1 ± 2.1 µM (Fig. 4b). None of the other compounds inhibited FAAH activity or AEA uptake at the concentration of 10 µM (Suppl. Figs 1 and 2). Note, that high in vivo analgesic activity of compound **2i** in acetic acid-induced writhing test (10 mg/kg dose, mice) was recently reported (Nazimova et al. 2016). It is known, that FAAH inhibition attenuates neuropathic pain (Jhaveri et al. 2006) and gastric ulceration (Naidu et al. 2009) in rodents. Thus, the analgesic effect of **2i** may be caused, at least partly, by FAAH inhibition. The potent and selective AEA uptake inhibitor WOBE437 (Chicca et al. 2017) exerted analgesic and anti-inflammatory effects at the dose of 10 mg/kg in a model of chronic inflammation in BALB/C mice (monoarthitis of the knee) (Reynoso-Moreno et al. 2018). At the same time, structurally similar compounds **2e** and **2h** also demonstrated an analgesic effect (Nazimova et al. 2016), do not influence cannabinoid system, which implies the existence of other mechanisms of action.

2-AG activity is terminated by enzymatic hydrolysis primarily mediated by MAGL and MAGL inhibitors produce antinociceptive effects (Kinsey et al. 2013; Aghazadeh Tabrizi et al. 2018). None of our compounds showed a significant inhibition of MAGL activity at the concentration



4a, 2m R=3,4,5-(3MeO)C_6H_2, **4a** 76% (*dr* 0.29), **2m** 15% (*dr* 5.0) (Mikhalchenko et al. 2016)
4b, 2n R=C_6H_5, (*S*)-**4b** 70%, **2n** 20% (*dr* 0.22)
4c, 2o R=4-NO_2-C_6H_4, (*S*)-**4c** 60%, **2o** 25% (*dr* 1.5)
4d, 2p R=cyclohexyl, **4d** 60% (*dr* 2.0), (*S*)-**2p** 15%
4e, 2b R=fur-2-yl, **4e** 70% (*dr* 7.3), **2b** 20% (*dr* 0.5)
4f, 2e R=thiophen-2-yl, **4f** 60% (*dr* 3.5), **2e** 30% (*dr* 0.29)

Scheme 2 Synthesis of **2b, e, m–p** and **4a–f**; *dr* is 4*S*/4*R* the diastereomers ratio

of 10 µM, unlike the classic MAGL inhibitor JZL184 (Kinsey et al. 2013), which was used as a positive control (Suppl. Fig. 3).

Conclusion

Large set of chiral hydrochromenes was synthesized by clay-catalyzed reactions of monoterpenoids (−)-isopulegol, (+)-neoisopulegol and (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **5** with aromatic and heteroaromatic aldehydes. It is known that some of these compounds possess analgesic activity with possible involvement of cannabinoid system. Amine-containing derivatives were obtained through the interaction of (−)-isopulegol with 5-hydroxymethylfurfural, followed by substitution of hydroxy-group with bromine and further reaction with amines.

The ability of all synthesized compounds to influence the endocannabinoid system was studied for the first time. We found, that all these chromene derivatives do not bind to CB_1 receptor at the concentration of 10 µM concentration. Five compounds (**1a**, **2b**, **2k**, **4a**, and **4d**) marginally interact at the same concentration with CB_2 receptor leading to 15–25% displacement of the radioligand. Moreover, all tested compounds do not affect MAGL activity. At the same time, isopulegol derivative **2i** containing 3-bromothiophene substituent inhibits FAAH activity with an IC_{50} value of 7.6 µM, and thus may increase endocannabinoid system activity. Taking into account that FAAH inhibition attenuates various types of pain, it can be assumed that earlier found analgesic effect of **2i** may be caused, at least partly, by FAAH inhibition.

Materials and methods

Chemistry

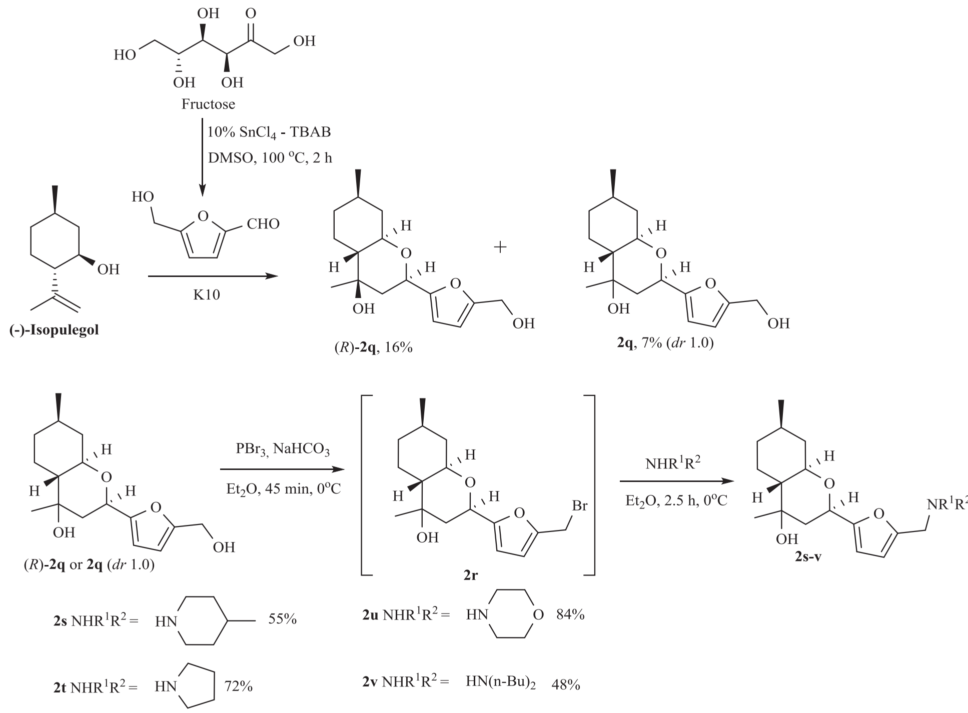
All commercially available compounds and solvents were reagent grade and were used without further treatment unless otherwise noted. As the catalyst, we used montmorillonite K10 clay (*Aldrich*). The clay was calcinated at 105°C for 3 h immediately before use. CH_2Cl_2 was passed through calcined Al_2O_3. (–)-Isopulegol ($[\alpha]_D^{31} = -21$ (*c* 0.4, $CHCl_3$)) was purchased from Aldrich. (+)-Neoisopulegol $[\alpha]_D^{30,6} = +29$ (*c* 0.498, C_6H_{14}) was synthesized according to (Chavan et al. 1993) from (–)-isopulegol (*Aldrich*), the content of the main substance was not less than 98.0%. (1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **5** ($[\alpha]_D^{30,6} = -49.1$ (*c* 0.26, $CHCl_3$)) was synthesized according to (Il'ina et al. 2007) from (–)-verbenone (*Aldrich*), the content of the main substance was not less than 98.0%.

Column chromatography: silica gel (SiO_2; 60–200 µ; *Macherey-Nagel*); hexane/EtOAc 100:0 → 0:100. GC/MS (purity control and products analysis): Agilent 7890A with a quadrupole mass spectrometer Agilent 5975C as a detector, HP-5MS quartz column, 30,000 × 0.25 mm, He (1 atm) as carrier gas. Optical rotation: *polAAr 3005* spectrometer, $CHCl_3$ soln. HR-MS: *DFS-Thermo-Scientific* spectrometer in a full scan mode (15–500 *m/z*, 70 eV electron-impact ionization, direct sample introduction). ^1H and ^{13}C NMR: *Bruker DRX-500* apparatus at 500.13 MHz (^1H) and 125.76 MHz (^{13}C) and *Bruker* Avance-III 600 apparatus at 600.30 MHz (^1H) and 150.95 MHz (^{13}C) in $CDCl_3$ or $CDCl_3/CD_3OD$; chemical shifts δ in ppm rel. to residual $CHCl_3$ (δ (H) 7.24, δ (C) 76.90 ppm), *J* in Hz; structure determinations by analyzing the ^1H NMR spectra, including ^1H–^1H double resonance spectra and ^1H–^1H 2D homonuclear correlation (COSY, NOESY); J-modulated ^{13}C NMR spectra (JMOD), and ^{13}C–^1H 2D heteronuclear correlation with one-bond and long-range spin-spin coupling constants (C–H COSY, $^1J(C,H) = 135$ Hz; HSQC, $^1J(C,H) = 145$ Hz; COLOC, $^{2,3}J(C,H) = 10$ Hz; HMBC, $^{2,3}J(C,H) = 7$ Hz). All the target compounds reported in this paper have the purity of at least 95%. Please note that numeration of atoms in the compounds (see SI) is given for assigning the signals in the NMR spectra and does not coincide with that for the names according to the nomenclature of compounds.

Spectral and analytical studies were carried out at the Collective Chemical Service Center of the Siberian Branch of the Russian Academy of Sciences.

Compounds **2a–l** were obtained from (–)-isopulegol and corresponding aldehydes in the presence of montmorillonite K10 according to the described procedures (Nazimova et al. 2016) in the following yields: **2b** (86%, *dr* 3.0), **2c** (65%, *dr*

Scheme 3 Synthesis of **2q** and **2s–v**; *dr* is 4*R*/4*S* the diastereomers ratio



3.5), **2d** (54%, *dr* 0.67), **2e** (78%, *dr* 5.0), **2f** (80%, *dr* 4.5), **2g** (69%, *dr* 10.0), **2h** (76%, *dr* 6.5), **2i** (74%, *dr* 3.0), **2j** (50%, *dr* 1.0), **2k** (61%, *dr* 8.0), **2l** (63%, *dr* 1.5).

Compounds **3a**, **3b** were obtained from (+)-neoisopulegol and corresponding aldehydes in the presence of montmorillonite K10 according to the described procedures (Nazimova et al. 2016) in the following yields: **3a** (41%, *dr* 0.67), **3b** (75%, *dr* 1.0).

Compounds **4a** and **2m** were obtained from (–)-isopulegol and 3,4,5-trimethoxybenzaldehyde in the presence of $BF_3{\cdot}Et_2O/H_2O$ system according to the described procedures (Mikhalchenko et al. 2016) in the following yields: **4a** (76%, *dr* 0.29), **2m** (15%, *dr* 5.0).

Compound **1a** (29%, *dr* 5.0) was obtained from diol **5** and 3-hydroxy-4-methoxybenzaldehyde in the presence of montmorillonite K10 according to the described procedures (Il'ina et al. 2011).

Compounds **1c**, **1e** were obtained from diol **5** and corresponding aldehydes in the presence of montmorillonite K10 according to the described procedures (Pavlova et al. 2016) in the following yields: **1c** (42%, *dr* 3.3), **1e** (54%, *dr* 2.8).

General procedure 1 for compounds 2n–e and 4b–f synthesis (GP 1)

(–)-Isopulegol (2.4 mmol) and aldehyde (2.9 mmol) were dissolved in CH_2Cl_2 (5 ml) and cooled to 2 °C. Then water (17.8 mmol) was added to the $BF_3{\cdot}Et_2O$ (3.6 mmol) solution in CH_2Cl_2 (5 ml) under vigorous stirring. Resulting cloudy solution of $BF_3{\cdot}Et_2O$ was added dropwise to the mixture of aldehyde and (–)-isopulegol, and then the reaction mixture was stirred for required time period at 2 °C. Then 10% $NaHCO_3$ solution was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Reaction mixture was separated on a SiO_2 column (hexane/EtOAc 100:0–0:100 as eluent).

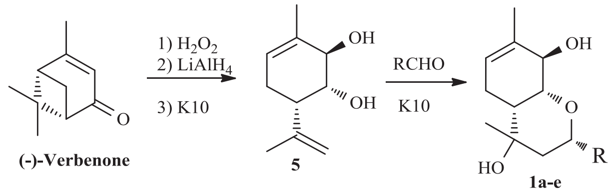
General procedure 2 for compounds 2s–v synthesis (GP 2)

The mixture of **2q** (3 eqv.), PBr_3 (1 eqv.) and $NaHCO_3$ (4 eqv.) in 5 ml Et_2O was stirred at 0 °C for 45 min. Then an appropriate amine (21 eqv.) was added and mixture was stirred at 0 °C for 2.5 h. The residue was filtered off, the solvent was distilled off, and the reaction mixture was separated on a SiO_2 column (hexane/EtOAc 100:0–0:100 as eluent).

General procedure 3 for compounds 1b, 1d synthesis (GP 3)

The solution of diol **2** and an appropriate aldehyde in CH_2Cl_2 (10 ml) was added to a suspension of K10 in CH_2Cl_2 (10 ml). The solvent was distilled off. The mixture was stored at r.t. for the required period of time. Then ethyl acetate (10 ml) was added. The catalyst was filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column (hexane/EtOAc 100:0–0:100 as eluent).

Scheme 4 Synthesis of **1a–e**; *dr* is the 4*S*/4*R* diastereomers ratio



1a R=3-(HO),4-(MeO)C_6H_3, 29% (*dr* 5.0) (Il'ina et al. 2011)
1b R=fur-2-yl, 63% (*dr* 1.0)
1c R=thiophen-2-yl, 42% (*dr* 3.3) (Pavlova et al. 2016)
1d R=fur-3-yl, 65%, (*dr* 1.4)
1e R=5-methylfur-2-yl 58% (*dr* 1.5)

(2R,4S,4aR,7R,8aR)-4-Fluoro-4,7-dimethyl-2-phenyloctahydro-2H-chromene 4b and (2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-phenyloctahydro-2H-chromen-4-ol 2n

Compound (*S*)-**4b** (0.475 g, 70%) and **2n** (0.135 g, 20%, *dr* 0.22) were obtained from (–)-isopulegol and benzaldehyde according to the *GP1*. Compound (*R*)-**4b** formed only in trace amounts. The reaction was carried out for 120 min. The ^{1}H and ^{13}C NMR spectra of **2n** correspond to the literature data (Yadav et al. 2010).

(*S*)-4b NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89–0.99 (m, 1H, H_a-8), 0.95 (d, 3H, $J_{18,9} = 6.6$, Me-18), 1.06–1.15 (m, 1H, H_a-10), 1.17–1.36 (m, 2H, H_a-6, H_a-7), 1.35 (d, 3H, $^3J_{17,F} = 21.4$, Me-17), 1.46–1.58 (m, 1H, H_a-9), 1.72 (ddd, 1H, $^3J_{4a,F} = 39.4$, $J_{4a,4e} = 14.2$, $J_{4a,3a} = 11.8$, H_a-4), 1.73–1.79 (m, 1H, H_e-8), 1.90 (dm, 1H, $J_{7e,7a} = 13.1$, the others $J < 3.5$ Hz, H_e-7), 2.03 (dm, 1H, $J_{10e,10a} = 12.2$, the others $J < 4.5$ Hz, H_e-10), 2.09 (ddd, 1H, $J_{4e,4a} = 14.2$, $^3J_{4e,F} = 9.6$, $J_{4e,3a} = 2.4$, H_e-4), 3.56–3.62 (m, 1H, H_a-1), 4.77 (dd, 1H, $J_{3a,4a} = 11.8$, $J_{3a,4e} = 2.4$, H_a-3), 7.22–7.26 (m, 1H, H-14), 7.29–7.37 (m, 4H, H-12, H-13, H-15, H-16). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 75.71 (d, C-1), 74.64 (d, C-3), 45.77 (t, $^2J = 21.4$, C-4), 93.36 (s, $^1J = 171.5$, C-5), 48.48 (d, $^2J = 20.3$, C-6), 22.42 (t, $^3J = 2.0$, C-7), 34.36 (t, C-8), 31.11 (d C-9), 41.16 (t, C-10), 142.30 (s, C-11), 125.79 (d, C-12, C-16), 128.25 (d, C-13, C-15), 127.27 (d, C-14), 24.20 (q, $^2J = 24.9$, C-17), 22.12 (q, C-18). $[\alpha]_D^{25.3} = 58.3$ (*c* 0.33, $CHCl_3$). HR-MS: *m/z* calcd. for $C_{15}H_{20}O_4$: 264.1356. Found: 264.1358.

(2R,4S,4aR,7R,8aR)-4-Fluoro-4,7-dimethyl-2-(4-nitrophenyl)octahydro-2H-chromene (S)-4c and (2R,4S(R),4aR,7R,8aR)-4,7-dimethyl-2-(4-nitrophenyl)octahydro-2H-chromen-4-ol 2o

Compounds (*S*)-**4c** (0.480 g, 60%) and **2o** (0.198 g, 25%, *dr* 1.5) were obtained from (–)-isopulegol and 4-nitrobenzaldehyde according to the *GP1*. The reaction was carried out for 120 min.

(*S*)-4c NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88–0.98 (m, 1H, H_a-8), 0.94 (d, 3H, $J_{18,9} = 6.6$, Me-18), 1.11 (dddd, 1H, $J_{10a,10e} \approx J_{10a,1a} \approx J_{10a,9a} = 12.2$, $J_{10a,F} = 1.5$, H_a-10), 1.16–1.34 (m, 2H, H_a-6, H_a-7), 1.34 (d, 3H, $^3J_{17,F} = 21.5$, Me-17), 1.46–1.57 (m, 1H, H_a-9), 1.61 (ddd, 1H, $^3J_{4a,F} = 38.6$, $J_{4a,4e} = 14.2$, $J_{4a,3a} = 11.8$, H_a-4), 1.76 (dm, 1H, $J_{8e,8a} = 13.2$, the others $J < 3.5$ Hz, H_e-8), 1.86–1.92 (m, 1H, H_e-7), 2.01 (dm, 1H, $J_{10e,10a} = 12.2$, the others $J < 4.5$ Hz, H_e-10), 2.10 (ddd, 1H, $J_{4e,4a} = 14.2$, $^3J_{4e,F} = 9.3$, $J_{4e,3a} = 2.4$, H_e-4), 3.55–3.62 (m, 1H, H_a-1), 4.86 (dd, 1H, $J_{3a,4a} = 11.8$, $J_{3a,4e} = 2.4$, H_a-3), 7.50 (br.d, 2H, $J_{12,13} = J_{16,15} = 8.9$, H-12, H-16), 8.16 (br.d, 2H, $J_{13,12} = J_{15,16} = 8.9$, H-13, H-15). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 75.77 (d, C-1), 73.64 (d, C-3), 45.64 (t, $^2J = 21.5$, C-4), 93.01 (s, $^1J = 172.3$, C-5), 48.33 (d, $^2J = 20.1$, C-6), 22.34 (t, $^3J = 2.6$, C-7), 34.23 (t, C-8), 31.05 (d, C-9), 40.97 (t, C-10), 149.78 (s, C-11), 126.35 (d, C-12, C-16), 123.47 (d, C-13, C-15), 147.07 (c, C-14), 24.07 (q, $^2J = 24.8$, C-17), 22.06 (q, C-18). $[\alpha]_D^{25.3} = 56.4$ (*c* 0.47, $CHCl_3$). HRMS: *m/z* calcd. for $C_{17}H_{22}O_3NF$: 307.1578. Found: 307.1580.

The NMR spectra were recorded for the mixture (*S*)-2o and (*R*)-2o isomers (1:0.70)

(*S*)-2o NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88–0.98 (m, 1H, H_a-8), 0.93 (d, 3H, $J_{18,9} = 6.6$, Me-18), 1.06–1.21 (m, 3H, H_a-7, H_a-6, H_a-10), 1.22 (c, 3H, Me-17), 1.42–1.54 (m, 1H, H_a-9), 1.57 (dd, 1H, $J_{4a,4e} = 13.8$, $J_{4a,3a} = 11.7$, H_a-4), 1.71–1.77 (m, 1H, H_e-8), 1.80–1.85 (m, 1H, H_e-7), 1.85 (dd, 1H, $J_{4e,4a} = 13.8$, $J_{4e,3a} = 2.4$, H_e-4), 1.96–2.03 (m, 1H, H_e-10), 3.56–3.61 (m, 1H, H_a-1), 4.89 (dd, 1H, $J_{3a,4a} = 11.7$, $J_{3a,4e} = 2.4$, H_a-3), 7.50 (br.d, 2H, $J_{12,13} = J_{16,15} = 8.8$, H-12, H-16), 8.15 (br.d, 2H, $J_{13,12} = J_{15,16} = 8.8$, H-13, H-15). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 75.47 (d, C-1), 73.64 (d, C-3), 47.99 (t, C-4), 69.22 (s, C-5), 49.23 (d, C-6), 22.37 (t, C-7), 34.24 (t, C-8), 31.14 (d, C-9), 41.09 (t, C-10), 150.51 (s, C-11), 126.41 (d, C-12, C-16), 123.41 (d, C-13, C-15), 146.88 (c, C-14), 28.08 (q, C-17), 22.10 (q, C-18). HRMS: *m/z* calcd. for $C_{17}H_{23}O_4N$: 305.1622. Found: 305.1618.

(*R*)-2o NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88–0.99 (m, 1H, H_a-8), 0.94 (d, 3H, $J_{18,9} = 6.6$, Me-18), 1.00–1.08 (m, 1H, H_a-7), 1.11–1.18 (m, 1H, H_a-10), 1.28–1.33 (m, 1H, H_a-6,), 1.30 (c, 3H, Me-17), 1.42–1.54 (m, 1H, H_a-9), 1.64 (br.dd, 1H, $J_{4a,4e} = 12.8$, $J_{4a,3a} = 12.0$, H_a-4), 1.71–1.77 (m, 1H, H_e-8), 1.92 (dd, 1H, $J_{4e,4a} = 12.8$, $J_{4e,3a} = 2.3$, H_e-4), 1.91–1.96 (m, 1H, H_e-7), 1.96–2.03 (m, 1H, H_e-10),

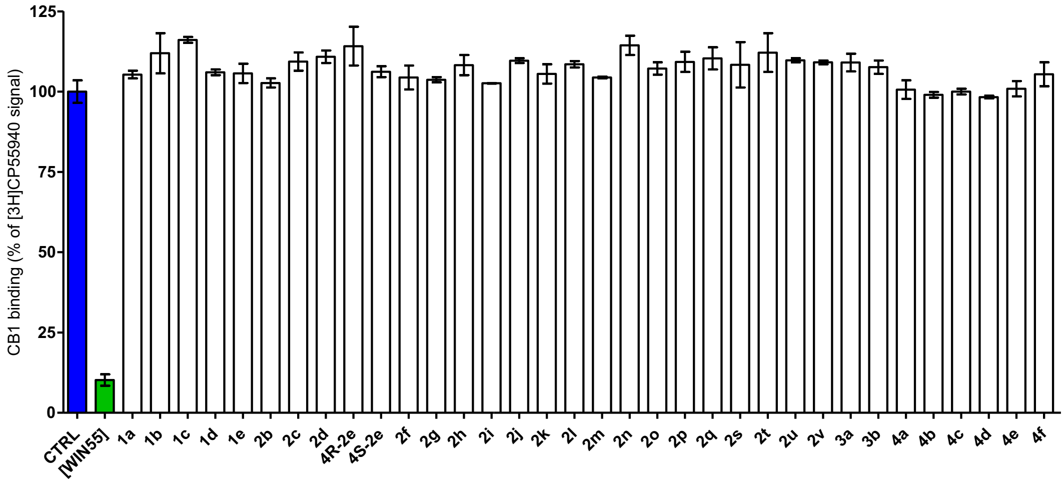


Fig. 2 CB_1 receptor binding in CHO membranes (WIN55,212 and compounds, 10 μM)

3.28 (ddd, 1H, $J_{1a,6a}$ ≈ $J_{1a,10a}$ = 10.5, $J_{1a,10e}$ = 4.2, H_a-1), 4.53 (dd, 1H, $J_{3a,4a}$ = 12.0, $J_{3a,4e}$ = 2.3, H_a-3), 7.49 (br.d, 2H, $J_{12,13}$ = $J_{16,15}$ = 8.8, H-12, H-16), 8.16 (br.d, 2H, $J_{13,12}$ = $J_{15,16}$ = 8.8, H-13, H-15). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 77.41 (d, C-1), 75.55 (d, C-3), 50.08 (t, C-4), 70.62 (s, C-5), 51.82 (d, C-6), 22.86 (t, C-7), 34.18 (t, C-8), 31.30 (d, C-9), 41.26 (t, C-10), 149.62 (s, C-11), 126.42 (d, C-12, C-16), 123.49 (d, C-13, C-15), 147.04 (c, C-14), 21.16 (q, C-17), 22.05 (q, C-18). HRMS: *m/z* calcd. for $C_{17}H_{23}O_4N$: 305.1622. Found: 305.1618.

(2R,4S(R),4aR,7R,8aR)-2-Cyclohexyl-4-fluoro-4,7-dimethyloctahydro-2H-chromene 4d and (2R,4S,4aR,7R,8aR)-2-cyclohexyl-4,7-dimethyloctahydro-2H-chromen-4-ol 2p

Compounds **4d** (0.417 g, 60%, *dr* 2.0) and (*S*)-**2p** (0.105 g, 15%) were obtained from (–)-isopulegol and cyclohexanecarbaldehyde according to the *GP1*. The reaction was carried out for 120 min. The ^{1}H and ^{13}C NMR spectra of **2p** correspond to the literature data (Yadav et al. 2010).

The NMR spectra were recorded for the mixture (*S*)-**4d** and (*R*)-**4d** isomers (1:0.5). The most signals NMR ^{1}H of these two isomers overlapped (are the same), separately we managed to observe some signals only.

(*S*)-4d NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (d, 3H, $J_{18,9}$ = 6.6, Me-18), 1.29 (d, 3H, $^3J_{17,F}$ = 21.5, Me-17), 3.27–3.33 (m, 1H, H_a-1), 3.38 (ddd, 1H, $J_{3a,4a}$ = 11.7, $J_{3a,11}$ = 6.8, $J_{3a,4e}$ = 2.0, H_a-3), the remaining proton signals are overlapping multiplets at 0.81–1.50, 1.57–1.74, and 1.78–1.96 ppm. NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 75.21 (d, C-1), 76.61 (d, C-3), 40.72 (t, ^2J = 21.6, C-4), 93.43 (s, ^1J = 170.8, C-5), 48.85 (d, ^2J = 20.3, C-6), 22.41 (t, ^3J = 2.8, C-7), 34.37 (t, C-8), 31.09 (d, C-9), 41.20 (t, C-10), 42.49 (d, C-11), 28.34 and 29.04 (2t, C-12, C-16), 25.99, 26.08 and 26.48 (3t, C-13, C-14, C-15), 24.51 (q, ^2J = 25.2, C-17), 22.10 (q, C-18). HRMS: *m/z* calcd. for $C_{17}H_{28}OF$: 267.2119. Found: 267.2112.

(*R*)-4d NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (d, 3H, $J_{18,9}$ = 6.6, Me-18), 1.29 (d, 3H, $^3J_{17,F}$ = 23.4, Me-17), 2.95 (ddd, 1H, $J_{1a,10a}$ ≈ $J_{1a,6a}$ ≈ 10.5, $J_{1a,10e}$ = 4.3, H_a-1), 3.02 (br.dd, 1H, $J_{3a,4a}$ = 11.8, $J_{3a,11}$ = 6.2, H_a-3), the remaining proton signals are overlapping multiplets at 0.81–1.50, 1.57–1.74, and 1.78–1.96 ppm. NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 76.91 (d, ^3J = 9.8, C-1), 78.91 (d, ^3J = 11.1, C-3), 42.41 (t, ^2J = 19.6, C-4), 95.55 (s, ^1J = 171.7, C-5), 50.25 (d, ^2J = 19.1, C-6), 23.19 (t, C-7), 33.98 (t, C-8), 31.24 (d, C-9), 41.32 (t, C-10), 42.59 (d, C-11), 29.05 and 28.50 (2t, C-12, C-16), 25.99, 26.07 and 26.45 (3t, C-13, C-14, C-15), 19.58 (q, ^2J = 26.2, C-17), 22.05 (q, C-18). HRMS: *m/z* calcd. for $C_{17}H_{28}OF$: 267.2119. Found: 267.2112.

(2R,4S(R),4aR,7R,8aR)-4-Fluoro-2-(furan-2-yl)-4,7-dimethyloctahydro-2H-chromene 4e

Compounds **4e** (0.417 g, 70%, *dr* 7.3) and **2b** (0.105 g, 20%, *dr* 0.5) were obtained from (–)-isopulegol and furan-2-carbaldehyde according to the *GP1*. The reaction was carried out for 120 min. The ^{1}H and ^{13}C NMR spectra of **2b** correspond to the literature data (Nazimova et al. 2016).

The NMR spectra were recorded for the mixture (*S*)-4e and (*R*)-4e isomers (1:0.1)

(*S*)-4e NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85–0.95 (m, 1H, H_a-8), 0.91 (d, 3H, $J_{16,9}$ = 6.6, Me-16), 1.05 (dddd, 1H, $J_{10a,10e}$ = $J_{10a,1a}$ = $J_{10a,9a}$ = 12.2, $J_{10a,F}$ = 1.5,

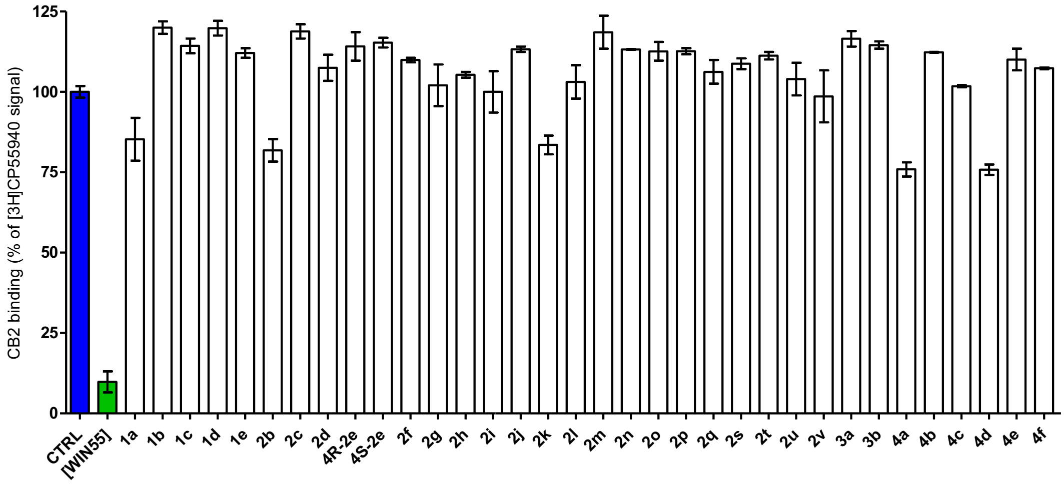


Fig. 3 CB_2 binding in CHO membranes (WIN and compounds, 10 μM)

H_a-10), 1.16–1.36 (m, 2H, H_a-6, H_a-7), 1.36 (d, 3H, $^3J_{15,F}$ = 21.4, Me-15), 1.43–1.55 (m, 1H, H_a-9), 1.69–1.76 (m, 1H, H_e-8), 1.84–1.90 (m, 1H, H_e-7), 1.95–2.10 (m, 3H, 2H-4, H_e-10), 3.52–3.59 (m, 1H, H_a-1), 4.77-4.84 (m, 1H, H_a-3), 6.24 (ddd, 1H, $J_{14,13} = 3.3$, $J_{14,12} = 0.9$, $J_{14,3a} = 0.7$, H-14), 6.29 (dd, 1H, $J_{13,14} = 3.3$, $J_{13,12} = 1.8$, H-13), 7.35 (dd, 1H, $J_{12,13} = 1.8$, $J_{12,14} = 0.9$, H-12). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 75.71 (d, C-1), 68.21 (d, C-3), 41.43 (t, $^2J = 21.9$, C-4), 93.04 (s, $^1J = 171.7$, C-5), 48.29 (d, $^2J = 20.3$, C-6), 22.36 (t, $^3J = 2.6$, C-7), 34.21 (t, C-8), 31.06 (d, C-9), 40.92 (t, C-10), 154.10 (s, C-11), 142.13 (d, C-12), 109.91 (d, C-13), 106.73 (d, C-14), 24.14 (q, ^2J = 24.8, C-15), 21.03 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{21}O_2F$: 252.1520. Found: 252.1517.

(*R*)-4e NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.92 (d, 3H, $J_{16,9} = 6.6$, Me-16), 1.06–1.15 (m, 1H, H_a-10), 1.39 (dd, 3H, $^3J_{15,F} = 23.2$, $J_{15,4a} = 0.8$, Me-15), 1.43–1.53 (m, 1H, H_a-9), 1.54–1.62 (m, 1H, H_a-6), 1.89–1.95 (m, 1H, H_e-7), 2.18–2.26 (m, 1H, H-4), 3.18–3.24 (m, 1H, H_a-1), 4.45 (dm, 1H, $J_{3a,4a} = 12.1$, the others $J < 2.5$ Hz, H_a-3), 6.26 (ddd, 1H, $J_{14,13} = 3.3$, $J_{14,12} = 0.9$, $J_{14,3a} = 0.7$, H-14), 6.31 (dd, 1H, $J_{13,14} = 3.3$, $J_{13,12} = 1.8$, H-13), 7.36 (dd, 1H, $J_{12,13} = 1.8$, $J_{12,14} = 0.9$, H-12), the remaining proton signals are overlapped by the signals of the main isomer (*S*)-**4e** at 0.85-0.95, 1.69–1.76 and 1.95–2.10 ppm. NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 77.43 (d, $^3J = 9.9$, C-1), 70.05 (d, $^3J = 12.7$, C-3), 43.09 (t, ^2J = 21.1, C-4), 94.51 (s, $^1J = 173.2$, C-5), 49.76 (d, $^2J = 19.5$, C-6), 23.12 (t, C-7), 33.82 (t, C-8), 31.22 (d, C-9), 41.06 (t, C-10), 153.68 (s, C-11), 142.18 (d, C-12), 109.99 (d, C-13), 106.70 (d, C-14), 19.31 (q, $^2J = 26.0$, C-15), 21.98 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{21}O_2F$: 252.1520. Found: 252.1517.

(2R,4S(R),4aR,7R,8aR)-4-Fluoro-4,7-dimethyl-2-(thiophen-2-yl)octahydro-2H-chromene 4f

Compounds **4f** (0.416 g, 60%, *dr* 3.5) and **2e** (0.205 g, 30%, *dr* 0.29) were obtained from (–)-isopulegol and thiophene-2-carbaldehyde according to the *GP1*. The reaction was carried out for 60 min. The ^{1}H and ^{13}C NMR spectra of **2e** correspond to the literature data (Nazimova et al. 2016).

The NMR spectra were recorded for the mixture (*S*)-4f and (*R*)-4f isomers (1:0.2)

(*S*)-4f NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87–0.97 (m, 1H, H_a-8), 0.93 (d, 3H, $J_{16,9} = 6.6$, Me-16), 1.04–1.12 (m, 1H, H_a-10), 1.17–1.34 (m, 2H, H_a-6, H_a-7), 1.36 (d, 3H, $^3J_{15,F} = 21.5$, Me-15), 1.44–1.55 (m, 1H, H_a-9), 1.71–1.78 (m, 1H, H_e-8), 1.86 (ddd, 1H, $^3J_{4a,F} = 39.0$, $J_{4a,4e}$ = 14.1, $J_{4a,3a} = 11.6$, H_a-4), 1.85-1.91 (m, 1H, H_e-7), 2.02 (dm, 1H, $J_{10e,10a} = 12.2$, the others $J < 4.5$ Hz, H_e-10), 2.20 (ddd, 1H, $J_{4e,4a} = 14.1$, $^3J_{4e,F} = 9.5$, $J_{4e,3a} = 2.4$, H_e-4), 3.55–3.62 (m, 1H, H_a-1), 5.01 (dd, 1H, $J_{3a,4a} = 11.6$, $J_{3a,4e}$ = 2.4, H_a-3), 6.94 (dd, 1H, $J_{13,12} = 5.0$, $J_{13,14} = 3.5$, H-13), 6.96 (ddd, 1H, $J_{14,13} = 3.5$, $J_{14,12} = 1.3$, $J_{14,3a} = 0.8$, H-14), 7.21 (dd, 1H, $J_{12,13} = 5.0$, $J_{12,14} = 1.3$, H-12). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 75.94 (d, C-1), 70.71 (d, C-3), 45.54 (t, $^2J = 21.5$, C-4), 93.23 (s, $^1J = 171.8$, C-5), 48.32 (d, $^2J = 20.3$, C-6), 22.38 (t, $^3J = 2.6$, C-7), 34.27 (t, C-8), 31.10 (d, C-9), 41.00 (t, C-10), 145.42 (s, C-11), 124.43 (d, C-12), 126.32 (d, C-13), 123.55 (d, C-14), 24.13 (q, $^2J = 24.8$, C-15), 22.07 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{21}OFS$: 268.1292. Found: 268.1288.

(*R*)-4f NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (d, 3H, $J_{16,9} = 6.6$, Me-16), 1.04–1.17 (m, 2H, H_a-7, H_a-10),

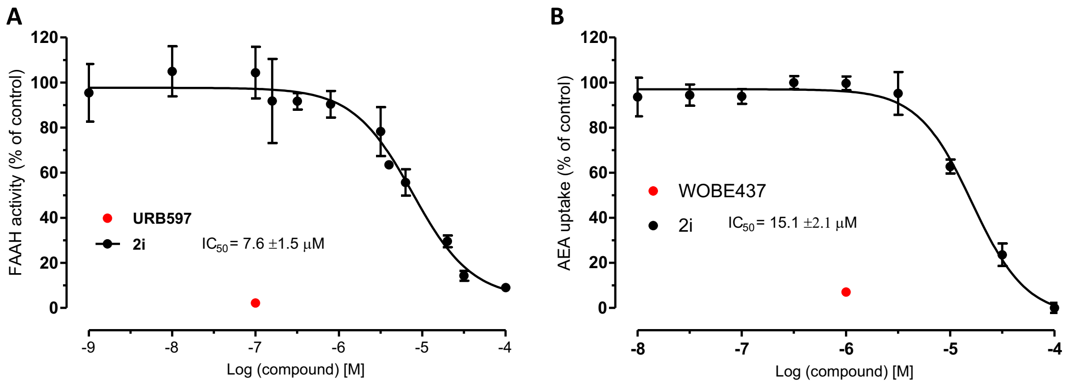


Fig. 4 **a** FAAH activity in the presence of **2i** or URB597 measured in U937 cell homogenate. t_{Inh} 15', AEA 100 nM 15', 400 rpm, 37 °C, U937 1 Mio/mL. **b** AEA uptake in the presence of **2i** or WOBE437 measured in U937 living cells. t_{Inh} 15', AEA 100 nM 15', 37 °C, U937 2 Mio/mL

1.42 (dd, 3H, $^3J_{15,F}=23.3$, $J_{15,4a}=0.8$, Me-15), 1.91–1.96 (m, 1H, H_e-7), 2.08–2.23 (m, 2H, 2H-4), 3.21–3.27 (m, 1H, H_a-1), 4.61–4.69 (m, 1H, H_a-3), 6.92–6.98 (m, 2H, H-13, H-14), 7.23 (dd, 1H, $J_{12,13}=5.0$, $J_{12,14}=1.3$, H-12), the remaining proton signals are overlapped by the signals of the main isomer (*S*)-**4f** at 0.87–1.01, 1.44–1.57, 1.70–1.78 and 1.99–2.06 ppm. NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm, $J_{C,F}$, Hz): 77.60 (d, $^3J=9.8$, C-1), 72.47 (d, $^3J=12.6$, C-3), 47.00 (t, $^2J=20.3$, C-4), 94.59 (s, $^1J=173.0$, C-5), 49.75 (d, $^2J=19.5$, C-6), 23.15 (t, C-7), 33.87 (t, C-8), 31.26 (d, C-9), 41.13 (t, C-10), 145.42 (s, C-11), 124.74 (d, C-12), 126.32 (d, C-13), 123.67 (d, C-14), 19.41 (q, $^2J=25.9$, C-15), 22.02 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{21}OFS$: 268.1292. Found: 268.1288.

5-Hydroxymethylfurfural (5-(hydroxymethyl)furan-2-carbaldehyde)

A solution of fructose (10.8 g), $SnCl_4$ (1.50 g), TBAB (1.92 g) in DMSO (60 ml) was heated at 100 °C for 2 h in air. Then, a saturated $NaHCO_3$ solution was added and product was extracted with EtOAc (6 × 20 ml). The combined organic layers was washed twice with 20 ml brine and dried over Na_2SO_4. The solvent was distilled off and of 5-(hydroxymethyl)furan-2-carbaldehyde (1.58 g, 21%) was obtained.

(2R,4R(S),4aR,7R,8aR)-2-(5-(Hydroxymethyl)furan-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol 2q

5-(Hydroxymethyl)furan-2-carbaldehyde (1.17 g) and the solution of (−)-isopulegol (1.72 g in 10 ml CH_2Cl_2) were added to the suspension of K10 clay (3 g in 20 ml CH_2Cl_2). The solvent was distilled off. The mixture was stored at r.t. for 2 h and then ethyl acetate (15 ml) was added. The catalyst was filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column to afford (*R*)-**2q** (0.502 g, 16%) and mixture of (*R*)-**2q** and (*S*)-**2q** isomers (0.218 g, 7%, *dr* 1.0).

(*S*)-2q NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84–0.93 (m, 1H, H_a-8), 0.89 (d, 3H, $J_{16,9}=6.6$, Me-16), 0.97–1.05 (m, 1H, H_a-10), 1.10–1.19 (m, 2H, H_a-6, H_a-7), 1.23 (s, 3H, Me-15), 1.39–1.47 (m, 1H, H_a-9), 1.67–1.73 (m, 1H, H_e-8), 1.79 (dd, 1H, $J_{4e,4a}=13.7$, $J_{4e,3a}=2.2$, H_e-4), 1.90 (dm, 1H, $J_{7e,7a}=13.2$, the others $J<3.5$ Hz, H_e-7), 1.92–1.97 (m, 1H, H_e-10), 1.94 (dd, 1H, $J_{4a,4e}=13.7$, $J_{4a,3a}=12.0$, H_a-4), 3.52–3.57 (m, 1H, H_a-1), 4.52 (s, 2H, 2H-17), 4.80 (dd, 1H, $J_{3a,4a}=12.0$, $J_{3a,4e}=2.2$, H_a-3), 6.15–6.18 (m, 2H, H-13, H-14). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 75.55 (d, C-1), 68.18 (d, C-3), 43.57 (t, C-4), 69.05 (s, C-5), 49.18 (d, C-6), 22.39 (t, C-7), 34.22 (t, C-8), 31.15 (d, C-9), 41.00 (t, C-10), 154.63 (s, C-11), 153.54 (d, C-12), 108.11 (d, C-13), 107.41 (d, C-14), 28.08 (q, C-15), 22.07 (q, C-16), 57.38 (t, C-17). HRMS: *m/z* calcd. for $C_{16}H_{24}O_4$: 280.1675. Found: 280.1672.

(*R*)-2q NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84–0.93 (m, 1H, H_a-8), 0.90 (d, 3H, $J_{16,9}=6.6$, Me-16), 0.95–1.03 (m, 1H, H_a-7), 1.04–1.10 (m, 1H, H_a-10), 1.29 (s, 3H, Me-15), 1.38–1.46 (m, 1H, H_a-9), 1.45–1.51 (m, 1H, H_a-6), 1.64–1.70 (m, 1H, H_e-8), 1.75–1.82 (m, 1H, H_e-7), 1.95–2.00 (m, 1H, H_e-10), 2.01 (dd, 1H, $J_{4e,4a}=12.4$, $J_{4e,3a}=2.4$, H_e-4), 2.08 (dd, 1H, $J_{4a,4e}=12.4$, $J_{4a,3a}=11.8$, H_a-4), 3.28–3.33 (m, 1H, H_a-1), 4.47 (dd, 1H, $J_{3a,4a}=11.8$, $J_{3a,4e}=2.4$, H_a-3), 4.54 (s, 2H, 2H-17), 6.19–6.21 (m, 2H, H-13, H-14). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 77.13 (d, C-1), 69.85 (d, C-3), 40.80 (t, C-4), 75.89 (s, C-5), 48.91 (d, C-6), 23.03 (t, C-7), 34.07 (t, C-8), 31.26 (d, C-9), 41.26 (t, C-10), 154.06 (s, C-11), 153.63 (d, C-12), 108.23 (d, C-13), 107.44 (d, C-14), 18.15 (q, C-15), 22.01 (q, C-16), 57.34 (t, C-17). HRMS: *m/z* calcd. for $C_{16}H_{24}O_4$: 280.1675. Found: 280.1672.

(2R,4R,4aR,7R,8aR)-4,7-Dimethyl-2-(5-((4-methylpiperidin-1-yl)methyl)furan-2-yl)octahydro-2H-chromen-4-ol 2s

According to the *GP2* the reaction of (*R*)-**2q** (0.191 g) and 4-methylpiperidine (0.475 g) gave compound **2s** (0.135 g, 55%).

(*R*)-2s NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85–0.94 (m, 1H, H_a-8), 0.88 (d, 3H, $J_{23,20} = 6.2$, Me-23), 0.90 (d, 3H, $J_{16,9} = 6.6$, Me-16), 0.97–1.05 (m, 1H, H_a-7), 1.06 (ddd, 1H, $J_{10a,10e} = J_{10a,9a} = 12.2$, $J_{10a,1a} = 11.1$, H_a-10), 1.20–1.32 (m, 4H, H_a-6, H-19, H-20, H-21), 1.23 (s, 3H, Me-15), 1.38–1.47 (m, 1H, H_a-9), 1.54–1.60 (m, 2H, H-19', H-21'), 1.70 (dm, 1H, $J_{8e,8a} = 12.9$, the others $J <$ 3.6 Hz, H_e-8), 1.87–2.00 (m, 6H, 2H-4, H_e-7, H_e-10, H-18, H-22), 2.81–2.88 (m, 2H, H-18', H-22'), 3.21 (ddd, 1H, $J_{1a,10a} = 11.1$, $J_{1a,6a} = 10.2$, $J_{1a,10e} = 4.3$, H_a-1), 3.45 (d, 1H, $^2J = 14.1$) and 3.50 (d, 1H, $^2J = 14.1$) –2H-17 (AB system), 4.48 (dd, 1H, $J_{3a,4a} = 9.0$, $J_{3a,4e} = 5.2$, H_a-3), 6.10 (d, 1H, $J_{13,14} = 3.2$, H-13), 6.18 (d, 1H, $J_{14,13} = 3.2$, H-14). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 77.35 (d, C-1), 70.08 (d, C-3), 45.69 (t, C-4), 70.60 (s, C-5), 51.91 (d, C-6), 22.93 (t, C-7), 34.23 (t, C-8), 31.37 (d, C-9), 41.26 (t, C-10), 153.90 (s, C-11), 151.50 (s, C-12), 109.21 (d, C-13), 106.98 (d, C-14), 21.15 (q, C-15), 22.04 (q, C-16), 55.16 (t, C-17), 53.50 and 53.36 (t, C-18, C-22), 33.98 and 33.99 (t, C-19, C-21) 30.40 (d, C-20), 21.70 (q, C-23). HRMS: *m/z* calcd. for $C_{22}H_{35}NO_3$: 361.2617. Found: 361.2612.

(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(5-(pyrrolidin-1-ylmethyl)furan-2-yl)octahydro-2H-chromen-4-ol 2t

According to the *GP2* the reaction of **2q** (0.150 g, *dr* 1.0) and pyrrolidine (0.266 g) gave compound **2t** (0.128 g, 72%, *dr* 4.0).

The NMR spectra were recorded for the mixture (*R*)-2t and (*S*)-2t isomers (1:0.25)

(*R*)-2t NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84–0.93 (m, 1H, H_a-8), 0.89 (d, 3H, $J_{16,9} = 6.5$, Me-16), 0.95–1.09 (m, 2H, H_a-7, H_a-10), 1.21 (s, 3H, Me-15), 1.26 (ddd, 1H, $J_{6a,7a} = 12.2$, $J_{6a,1a} = 10.2$, $J_{6a,7e} = 3.2$, H_a-6), 1.35–1.47 (m, 1H, H_a-9), 1.69 (dm, 1H, $J_{8e,8a} = 12.8$, the others $J < 3.5$ Hz, H_e-8), 1.72–1.77 (m, 4H, 2H-19, 2H-20), 1.87–1.99 (m, 4H, 2H-4, H_e-7, H_e-10), 2.48–2.54 (m, 4H, 2H-18, 2H-21), 3.20 (ddd, 1H, $J_{1a,10a} = 11.0$, $J_{1a,6a} = 10.2$, $J_{1a,10e} = 4.3$, H_a-1), 3.54 (d, 1H, $^2J = 14.0$) and 3.60 (d, 1H, $^2J = 14.0$) –2H-17 (AB system), 4.46 (dd, 1H, $J_{3a,4a} = 10.0$, $J_{3a,4e} = 4.3$, H_a-3), 6.08 (d, 1H, $J_{13,14} = 3.1$, H-13), 6.16 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 77.32 (d, C-1), 70.08 (d, C-3), 45.73 (t, C-4), 70.47 (s, C-5), 51.88 (d, C-6), 22.90 (t, C-7), 34.22 (t, C-8), 31.34 (d, C-9), 41.26 (t, C-10), 153.73 (s, C-11), 152.34 (s, C-12), 108.17 (d, C-13), 106.93 (d, C-14), 21.08 (q, C-15), 22.01 (q, C-16), 52.01 (t, C-17), 53.70 (t, C-18, C-21), 23.32 (t, C-19, C-20). HRMS: *m/z* calcd. for $C_{20}H_{31}NO_3$: 333.2304. Found: 333.2299.

(*S*)-2t NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (d, 3H, $J_{16,9} = 6.5$, Me-16), 1.11–1.17 (m, 1H, H_a-6), 1.22 (s, 3H, Me-15), 1.72–1.81 (m, 2H, 2H-4), 3.49–3.55 (m, 1H, H_a-1), 3.56 (d, 1H, $^2J = 14.0$) and 3.59 (d, 1H, $^2J = 14.0$) – 2H-17 (AB system), 4.79 (dd, 1H, $J_{3a,4a} = 12.0$, $J_{3a,4e} = 2.3$, H_a-3), 6.07 (d, 1H, $J_{13,14} = 3.1$, H-13), 6.14 (d, 1H, $J_{14,13} = 3.1$, H-14), the remaining proton signals are overlapped by the signals of the main isomer (*R*)-**2t** at 0.83–0.93, 0.97–1.10, 1.35–1.47, 1.66–1.77 and 2.47–2.55 ppm. NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 75.44 (d, C-1), 68.20 (d, C-3), 43.74 (t, C-4), 69.03 (s, C-5), 49.23 (d, C-6), 22.41 (t, C-7), 34.29 (t, C-8), 31.17 (d, C-9), 41.08 (t, C-10), 152.26 (s, C-12), 108.12 (d, C-13), 106.97 (d, C-14), 28.14 (q, C-15), 22.07 (q, C-16), 51.99 (t, C-17), 53.65 (t, C-18, C-21), 23.32 (t, C-19, C-20), we could not assign the signal of C-11 with certainty. HRMS: *m/z* calcd. for $C_{20}H_{31}NO_3$: 333.2304. Found: 333.2299.

(2R,4R,4aR,7R,8aR)-4,7-Dimethyl-2-(5-(morpholinomethyl)furan-2-yl)octahydro-2H-chromen-4-ol 2u

According to the *GP2* the reaction of (*R*)-**2q** (0.231 g) and morpholine (0.493 g) gave compound **2u** (0.242 g, 84%).

(*R*)-2u NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78–0.88 (m, 1H, H_a-8), 0.84 (d, 3H, $J_{16,9} = 6.6$, Me-16), 0.90–0.99 (m, 1H, H_a-7), 1.00 (ddd, 1H, $J_{10a,10e} = J_{10a,9a} = 12.2$, $J_{10a,1a} = 11.0$, H_a-10), 1.16 (s, 3H, Me-15), 1.22 (ddd, 1H, $J_{6a,7a} = 12.2$, $J_{6a,1a} = 10.2$, $J_{6a,7e} = 3.2$, H_a-6), 1.31–1.43 (m, 1H, H_a-9), 1.64 (dm, 1H, $J_{8e,8a} = 12.8$, the others $J <$ 3.5 Hz, H_e-8), 1.84–1.95 (m, 4H, 2H-4, H_e-7, H_e-10), 2.36–2.41 (m, 4H, 2H-18, 2H-21), 3.16 (ddd, 1H, $J_{1a,10a} = 11.0$, $J_{1a,6a} = 10.2$, $J_{1a,10e} = 4.3$, H_a-1), 3.40 (d, 1H, $^2J = 14.0$) and 3.44 (d, 1H, $^2J = 14.0$) –2H-17 (AB system), 3.60–3.65 (m, 4H, 2H-19, 2H-20), 4.41 (dd, 1H, $J_{3a,4a} = 10.5$, $J_{3a,4e} = 3.6$, H_a-3), 6.06 (d, 1H, $J_{13,14} = 3.2$, H-13), 6.12 (d, 1H, $J_{14,13} = 3.2$, H-14). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 77.20 (d, C-1), 69.88 (d, C-3), 45.55 (t, C-4), 70.12 (s, C-5), 51.69 (d, C-6), 22.76 (t, C-7), 34.11 (t, C-8), 31.20 (d, C-9), 41.14 (t, C-10), 154.17 (s, C-11), 150.45 (s, C-12), 109.36 (d, C-13), 106.82 (d, C-14), 20.91 (q, C-15), 21.89 (q, C-16), 55.01 (t, C-17), 52.92 (t, C-18, C-21), 66.51 (t, C-19, C-20). $[\alpha]_D^{27.3} = -7.0$ (*c* 0.74, $CHCl_3$). HRMS: *m/z* calcd. for $C_{20}H_{31}NO_4$: 349.2253. Found: 349.2248.

(2R,4R,4aR,7R,8aR)-2-(5-((Dibutylamino)methyl)furan-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol 2v

According to the *GP2* the reaction of (*R*)-**2q** (0.170 g) and dibutylamine (0.542 g) gave compound **2v** (0.112 g, 48%).

(*R*)-2v NMR ^{1}H (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85–0.94 (m, 1H, H_a-8), 0.87 (t, 6H, $J_{21,20} = J_{25,24} = 7.4$, Me-21, Me-25), 0.90 (d, 3H, $J_{16,9} = 6.6$, Me-16), 0.98–1.06 (m, 1H, H_a-7), 1.07 (ddd, 1H, $J_{10a,10e} = J_{10a,9a} = 12.2$, $J_{10a,1a} = 11.1$, H_a-10), 1.22–1.31 (m, 5H, H_a-6, 2H-20, 2H-24), 1.24 (s, 3H, Me-15), 1.39–1.47 (m, 5H, H_a-9, 2H-19, 2H-23), 1.71 (dm, 1H, $J_{8e,8a} = 12.8$, H_e-8), 1.89–2.01 (m, 4H, 2H-4, H_e-7, H_e-10), 2.35–2.43 (m, 4H, 2H-18, 2H-22), 3.23 (ddd, 1H, $J_{1a,10a} = 11.1$, $J_{1a,6a} = 10.2$, $J_{1a,10e} = 4.3$, H_a-1), 3.58 (d, 1H, $^{2}J = 15.3$) and 3.60 (d, 1H, $^{2}J = 15.3$) – 2H-17, 4.46 (dd, 1H, $J_{3a,4a} = 11.2$, $J_{3a,4e} = 2.8$, H_a-3), 6.07 (d, 1H, $J_{13,14} = 3.1$, H-13), 6.18 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (150 MHz, $CDCl_3$, δ, ppm): 77.33 (d, C-1), 70.11 (d, C-3), 45.73 (t, C-4), 70.61 (s, C-5), 51.92 (d, C-6), 22.93 (t, C-7), 34.23 (t, C-8), 31.37 (d, C-9), 41.28 (t, C-10), 153.48 (s, C-11), 152.37 (s, C-12), 108.65 (d, C-13), 107.01 (d, C-14), 21.13 (q, C-15), 22.05 (q, C-16), 49.99 (t, C-17), 53.43 (t, C-18, C-22), 29.02 (t, C-19, C-23), 20.54 (t, C-20, C-24), 13.95 (t, C-21, C-25). $[\alpha]_D^{27.3} = -8.2$ (*c* 0.34, $CHCl_3$). HRMS: *m/z* calcd. for $C_{24}H_{41}NO_3$: 391.3086. Found: 391.3081.

(2S,4S(R),4aR,8R,8aR)-2-(Furan-2-yl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol 1b

According to the *GP3* the reaction of diol **5** (0.30 g), furan-2-carbaldehyde (0.17 g) and montmorillonite K10 (1.0 g) for 45 min gave compound **1b** (0.268 g, 63% on converted **5**, *dr* 1.0). The conversion of the diol **5** was 90%.

NMR spectra were recorded for a mixture (*S*)-1b and (*R*)-1b (1.0: 0.75)

(*S*)-1b NMR ^{1}H (600 MHz, $CDCl_3 + CD_3OD$, δ, ppm, J/Hz): 1.48 (s, 3H, Me-15), 1.70 (br.d, 1H, $J_{4e,4a} = 13.3$, H_e-4), 1.77 (br.s, 3H, Me-16), 1.78–1.83 (m, 1H, H_a-6), 2.13–2.22 (m, 3H, H_a-4, 2H-7), 3.80 (br.t, 1H, $J_{1e,6a} \approx J_{1e,10e} \approx 2.2$, H_e-1), 3.91 (br.s, 1H, H_e-10), 4.49 (dd, 1H, $J_{3a,4a} = 12.4$, $J_{3a,4e} = 2.4$, HH_a-3), 5.60–5.63 (m, 1H, H-8), 6.26 (d, 1H, $J_{14,13} = 3.2$, HH-14), 6.29 (dd, 1H, $J_{13,14} = 3.2$, $J_{13,12} = 1.9$, H-13), 7.35 (d, 1H, $J_{12,13} = 1.9$, H-12). NMR ^{13}C (150 MHz, $CDCl_3 + CD_3OD$, δ, ppm): 77.80 (d, C-1), 70.89 (d, C-3), 38.55 (t, C-4), 70.77 (s, C-5), 38.54 (d, C-6), 22.52 (t, C-7), 124.77 (d, C-8), 131.24 (s, C-9), 70.39 (d, C-10), 153.71 (s, C-11), 142.27 (d, C-12), 110.02 (d, C-13), 107.03 (d, C-14), 26.96 (q, C-15), 20.61 (q, C-16). HR-MS: *m/z* calcd. for $C_{15}H_{20}O_4$: 264.1356. Found: 264.1358.

(*R*)-1b NMR ^{1}H (600 MHz, $CDCl_3 + CD_3OD$, δ, ppm, J/Hz): 1.27 (s, 3H, Me-15), 1.62 (br.d, 1H, $J_{4e,4a} = 14.0$, H_e-4), 1.65–1.70 (m, 1H, H_a-6), 1.77 (br.s, 3H, Me-16), 1.98–2.03 (m, 2H, H-7), 2.07 (dd, 1H, $J_{4a,4e} = 14.0$, $J_{4a,3a} = 12.0$, H_a-4), 3.92 (br.s, 1H, H_e-10), 4.23 (br.t, 1H, $J_{1e,6a} < 2.5$, H_e-1), 4.84 (dd, 1H, $J_{3a,4a} = 12.0$, $J_{3a,4e} = 2.4$, H_a-3), 5.54–5.57 (m, 1H, H-8), 6.23 (d, 1H, $J_{14,13} = 3.2$, H-14), 6.28 (dd, 1H, $J_{13,14} = 3.2$, $J_{13,12} = 1.9$, H-13), 7.34 (d, 1H, $J_{12,13} = 1.9$, H-12) NMR ^{13}C (150 MHz, $CDCl_3 + CD_3OD$, δ, ppm): 75.35 (d, C-1), 69.27 (d, C-3), 37.57 (t, C-4), 70.47 (s, C-5), 38.21 (d, C-6), 24.40 (t, C-7), 124.17 (d, C-8), 131.70 (s, C-9), 70.36 (d, C-10), 154.28 (s, C-11), 142.17 (d, C-12), 109.94 (d, C-13), 106.97 (d, C-14), 28.36 (q, C-15), 20.71 (q, C-16). HR-MS: *m/z* calcd. for $C_{15}H_{20}O_4$: 264.1356. Found: 264.1358.

(2S,4S(R),4aR,8R,8aR)-2-(Furan-3-yl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol 1d

According to the *GP3* the reaction of diol **5** (0.30 g, *dr* 1.0), furan-3-carbaldehyde (0.17 g) and montmorillonite K10 (1.0 g) for 45 min gave compound **1d** (0.243 g, 63% on converted **5**, *dr* 1.4). The conversion of the diol **5** was 78%.

(*S*)-1d NMR ^{1}H (500 MHz, $CDCl_3/CD_3OD$, δ, ppm, J/Hz): 1.41 (d, 3H, $J_{15,4a} = 0.7$, Me-15), 1.60 (ddd, 1H, $J_{4e,4a} = 13.3$, $J_{4e,3a} = 2.7$, $J_{4e,6a} = 1.2$, H_e-4), 1.72 (m, 3H, all $J \le 2.5$ Hz, Me-16), 1.72–1.77 (m, 1H, H_a-6), 1.92 (ddq, 1H, $J_{4a,4e} = 13.3$, $J_{4a,3a} = 12.1$, $J_{4a,15} = 0.7$, H_a-4), 2.04–2.10 (m, 2H, 2H-7), 3.71 (dd, 1H, $J_{1e,10e} = 2.4$, $J_{1e,6a} = 2.2$, H_e-1), 3.78 (br.s, 1H, H_e-10), 4.37 (dd, 1H, $J_{3a,4a} = 12.1$, $J_{3a,4e} = 2.7$, H_a-3), 5.53–5.57 (m, 1H, H-8), 6.32 (dd, 1H, $J_{14,13} = 1.8$, $J_{14,12} = 0.8$, H-14), 7.28 (dd, 1H, $J_{13,14} = 1.8$, $J_{13,12} = 1.5$, H-13), 7.32 (ddd, 1H, $J_{12,13} = 1.5$, $J_{12,14} = 0.8$, $J_{12,3a} = 0.6$, H-12). NMR ^{13}C (125 MHz, $CDCl_3/CD_3OD$, δ, ppm): 77.77 (d, C-1), 70.27 (d, C-3), 40.86 (t, C-4), 70.33 (s, C-5), 38.27 (d, C-6), 22.49 (t, C-7), 124.42 (d, C-8), 131.09 (s, C-9), 70.09 (d, C-10), 126.26 (s, C-11), 139.11 (d, C-12), 142.86 (d, C-13), 108.77 (d, C-14), 26.58 (q, C-15), 20.45 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{20}O_4$: 264.1356. Found: 264.1357.

NMR spectra (*R*)-1d were recorded for a mixture (*S*)-1d and (*R*)-1d (1.0:2.0)

(*R*)-1d NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.23 (s, 3H, Me-15), 1.62 (ddd, $J_{4e,4a} = 14.1$, $J_{4e,3a} = 2.6$, $J_{4e,6a} = 1.3$, H_e-4), 1.65–1.70 (m, 1H, H_a-6), 1.78 (m, 3H, all $J \le 2.5$ Hz, Me-16), 1.81 (dd, 1H, $J_{4a,4e} = 14.1$, $J_{4a,3a} = 11.8$, H_a-4), 1.92–2.01 (m, 2H, 2H-7), 3.90 (br.s, 1H, H_e-10), 4.20 (dd, 1H, $J_{1e,10e} = 2.4$, $J_{1e,6a} = 2.2$, H_e-1), 4.76 (dd, 1H, $J_{3a,4a} = 11.8$, $J_{3a,4e} = 2.6$, H_a-3), 5.53–5.56 (m, 1H, H-8), 6.35

(dd, 1H, $J_{14,13} = 1.8$, $J_{14,12} = 0.8$, H-14), 7.32 (dd, 1H, $J_{13,14} = 1.8$, $J_{13,12} = 1.5$, H-13), 7.34 (ddd, 1H, $J_{12,13} = 1.5$, $J_{12,14} = 0.8$, $J_{12,3a} = 0.5$, H-12). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 75.17 (d, C-1), 68.73 (d, C-3), 40.33 (t, C-4), 70.67 (s, C-5), 38.10 (d, C-6), 24.44 (t, C-7), 124.06 (d, C-8), 131.70 (s, C-9), 70.50 (d, C-10), 126.68 (s, C-11), 139.05 (d, C-12), 142.84 (d, C-13), 108.85 (d, C-14), 28.25 (q, C-15), 20.72 (q, C-16). HRMS: *m/z* calcd. for $C_{15}H_{20}O_4$: 264.1356. Found: 264.1357.

(2S,4S(R),4aR,8R,8aR)-4,7-dimethyl-2-(5-methylfuran-2-yl)-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol 1e

According to the *GP3* the reaction of diol **5** (0.40 g), 5-methylfuran-2-carbaldehyde (0.26 g) and montmorillonite K10 (1.3 g) for 150 min gave compounds **1e** (0.359 g, 58% on converted **5**, *dr* 1.5), (2*S*,4a*S*,8*R*,8a*R*)-7-methyl-4-methylene-2-(5-methylfuran-2-yl)-3,4,4a,5,8,8a-hexahydro-2*H*-chromen-8-ol **6** (0.025 g, 5% on converted **5**) and (2*S*,4*S*,4a*R*,8*S*,8a*R*)-4,7-dimethyl-2-(5-methylfuran-2-yl)-3,4,4a,5,8,8a-hexahydro-2H-4,8-epoxychromene **7** (0.029 g, 5% on converted **5**). The conversion of the diol **5** was 93%.

NMR spectra were recorded for a mixture (*S*)-1e and (*R*)-1e (1.0: 0.75)

(*S*)-1e NMR ^{1}H (500 MHz, $CDCl_3/CD_3OD$, δ, ppm, J/Hz): 1.47 (s, 3H, Me-15), 1.64 (ddd, 1H, $J_{4e,4a} = 13.3$, $J_{4e,3a} = 2.5$, $J_{4e,6a} = 1.2$, H_e-4), 1.77 (m, 3H, all $J \leq 2.5$ Hz, Me-16), 1.84 (br.t, 1H, $J_{6a,7} = 8.3$, H_a-6), 2.12–2.18 (m, 2H, 2H-7), 2.21 (dd, 1H, $J_{4a,4e} = 13.3$, $J_{4a,3a} = 12.4$, H_a-4), 2.25 (d, 3H, $J_{17,13} = 1.0$, Me-17), 3.79 (dd, 1H, $J_{1e,10e} = 2.4$, $J_{1e,6a} = 2.1$, H_e-1), 3.83 (br.s, 1H, H_e-10), 4.46 (dd, 1H, $J_{3a,4a} = 12.4$, $J_{3a,4e} = 2.5$, H_a-3), 5.59–5.63 (m, 1H, H-8), 5.90 (dq, 1H, $J_{13,14} = 3.1$, $J_{13,17} = 1.0$, H-13), 6.17 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (125 MHz, $CDCl_3/CD_3OD$, δ, ppm): 78.83 (d, C-1), 71.60 (d, C-3), 38.49 (t, C-4), 70.79 (s, C-5), 39.08 (d, C-6), 23.23 (t, C-7), 125.06 (d, C-8), 131.76 (s, C-9), 70.49 (d, C-10), 152.77 (s, C-11), 152.57 (s, C-12), 106.59 (d, C-13), 108.61 (d, C-14), 26.89 (q, C-15), 20.90 (q, C-16), 13.56 (q, C-17). HR-MS: *m/z* calcd. for $C_{16}H_{22}O_4$: 278.1513. Found: 278.1514.

(*R*)-1e NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.18 (s, 3H, Me-15), 1.53 (ddd, 1H, $J_{4e,4a} = 14.0$, $J_{4e,3a} = 2.5$, $J_{4e,6a} = 1.4$, H_e-4), 1.61 (br.t, 1H, $J_{6a,7} = 8.8$, H_a-6), 1.70 (m, 3H, all $J \leq 2.5$ Hz, Me-16), 1.89–1.96 (m, 2H, 2H-7), 1.98 (dd, 1H, $J_{4a,4e} = 14.0$, $J_{4a,3a} = 12.1$, H_a-4), 2.18 (d, 3H, $J_{17,13} = 1.0$, Me-17), 3.81 (br.s, 1H, H_e-10), 4.12 (dd, 1H, $J_{1e,10e} = 2.4$, $J_{1e,6a} = 2.1$, H_e-1), 4.70 (dd, 1H, $J_{3a,4a} = 12.1$, $J_{3a,4e} = 2.5$, H_a-3), 5.46–5.50 (m, 1H, H-8), 5.80 (dq, 1H, $J_{13,14} = 3.1$, $J_{13,17} = 1.0$, H-13), 6.05 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 75.31 (d, C-1), 69.20 (d, C-3), 37.08 (t, C-4), 69.99 (s, C-5), 37.78 (d, C-6), 24.22 (t, C-7), 123.83 (d, C-8), 131.58 (s, C-9), 69.93 (d, C-10), 152.45 (s, C-11), 151.73 (s, C-12), 105.81 (d, C-13), 107.83 (d, C-14), 27.83 (q, C-15), 20.49 (q, C-16), 13.25 (q, C-17). HR-MS: *m/z* calcd. for $C_{16}H_{22}O_4$: 278.1513. Found: 278.1514.

6 NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.79 (m, 3H, all J ≤ 2.5 Hz, Me-16), 1.93 (dddq, 1H, $J_{7e,7a} = 17.8$, $J_{7e,6a} = 6.3$, $J_{7e,8} = 5.4$, $J_{7e,16} = 1.5$, H_e-7), 2.25 (d, 3H, $J_{17,13} = 1.0$, Me-17), 2.30 (dd, 1H, $J_{4e,4a} = 14.1$, $J_{4e,3a} = 2.7$, H_e-4), 2.34 (ddm, 1H, $J_{7a,7e} = 17.8$, $J_{7a,6a} = 10.8$, H_a-7), 2.51 (ddd, 1H, $J_{6a,7a} = 10.8$, $J_{6a,7e} = 6.3$, $J_{6a,1e} = 2.1$, H_a-6), 2.79 (ddt, 1H, $J_{4a,4e} = 14.1$, $J_{4a,3a} = 12.0$, $J_{4a,15} = 2.0$, H_a-4), 3.71 (dd, 1H, $J_{1e,10e} = 2.4$, $J_{1e,6a} = 2.1$, H_e-1), 3.93 (br.s, 1H, H_e-10), 4.36 (dd, 1H, $J_{3a,4a} = 12.0$, $J_{3a,4e} = 2.7$, H_a-3), 4.80 (dd, 1H, $J_{15,4a} = 2.0$, $J_{15,15'} = 1.8$, H-15), 4.89 (dd, 1H, $J_{15',4a} = 2.0$, $J_{15',15} = 1.8$, H'-15), 5.58–5.61 (m, 1H, H-8), 5.88 (dq, 1H, $J_{13,14} = 3.1$, $J_{13,17} = 1.0$, H-13), 6.15 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 80.48 (d, C-1), 73.93 (d, C-3), 34.09 (t, C-4), 146.32 (s, C-5), 36.94 (d, C-6), 26.19 (t, C-7), 124.67 (d, C-8), 131.37 (s, C-9), 70.28 (d, C-10), 152.12 (s, C-11), 152.05 (s, C-12), 106.02 (d, C-13), 107.96 (d, C-14), 110.11 (t, C-15), 20.81 (q, C-16), 13.49 (q, C-17). HR-MS: *m/z* calcd. for $C_{16}H_{20}O_3$: 260.1407. Found: 278.1405.

7 NMR ^{1}H (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.39 (s, 3H, Me-15), 1.73 (m, 3H, all $J \leq 2.5$ Hz, Me-16), 1.78 (dd, 1H, $J_{4e,4a} = 13.0$, $J_{4e,3a} = 4.2$, H_e-4), 1.99 (dd, 1H, $J_{4a,4e} = 13.0$, $J_{4a,3a} = 11.0$, H_a-4), 2.09 (br.d, 1H, $J_{6,7} = 5.7$, H-6), 2.26 (d, 3H, $J_{17,13} = 1.0$, Me-17), 2.34 (ddm, 1H, $J_{7,7'} = 18.8$, $J_{7,6} = 5.7$, H-7), 2.51 (dm, 1H, $J_{7',7} = 18.8$, H'-7), 4.24 (br.s, 1H, H_e-10), 4.38 (br.s, 1H, H-1), 5.07 (dd, 1H, $J_{3a,4a} = 11.0$, $J_{3a,4e} = 4.2$, H_a-3), 5.12–5.16 (m, 1H, H-8), 5.87 (dq, 1H, $J_{13,14} = 3.1$, $J_{13,17} = 1.1$, H-13), 6.13 (d, 1H, $J_{14,13} = 3.1$, H-14). NMR ^{13}C (125 MHz, $CDCl_3$, δ, ppm): 80.97 (d, C-1), 67.34 (d, C-3), 42.94 (t, C-4), 83.02 (s, C-5), 45.44 (d, C-6), 28.14 (t, C-7), 120.73 (d, C-8), 139.57 (s, C-9), 80.27 (d, C-10), 152.19 (s, C-11), 152.09 (s, C-12), 105.90 (d, C-13), 108.07 (d, C-14), 21.55 (q, C-15), 20.84 (q, C-16), 13.45 (q, C-17). HR-MS: *m/z* calcd. for $C_{16}H_{20}O_3$: 260.1407. Found: 278.1405.

Biology

CB1R and CB2R binding assays

Receptor binding experiments were performed with membrane preparations as previously reported (Chicca et al. 2017). Briefly, clean membranes expressing hCB_1 or hCB_2 were resuspended in binding buffer (50 mM Tris-HCl, 2.5

mM EDTA, 5 mM $MgCl_2$, 0.5% fatty acid-free bovine serum albumin (BSA), pH 7.4) and incubated with vehicle or compounds at the concentration of 10 µM in presence of 0.5 nM of [^{3}H]CP55,940 for 90 min at 30 °C. Non-specific binding was determined in presence of 10 µM WIN55,512. After incubation, membranes were filtered through a pre-soaked 96-well microplate bonded with GF/B filters under vacuum and washed twelve times with 150 µl of ice-cold binding buffer. The filters were dried under air drier and then added with 45 µl of Microscint 20 scintillation cocktail. The radioactivity was measured using a Packard Tri-Carb 2100 TR scintillation counter. All experiments were performed at least in two independent experiments each performed in triplicate and data are reported as mean values ± SD.

FAAH and MAGL assays

FAAH and MAGL assays were performed as previously described (Chicca et al. 2017). Briefly, the assays were performed using U937 cell homogenate (100 µg) which were diluted in 200 µl of Tris-HCl 10 mM, EDTA 1 mM, pH 8 containing 0.1% fatty acid-free BSA. Compounds were added at the screening concentration of 10 µM and pre-incubated for 30 min at 37 °C under shaking (400 rpm). URB597 (0.1 µM) and JZL184 (1 µM) were used as positive controls for complete FAAH and MAGL inhibition, respectively. Then, 100 nM of AEA containing 1 nM of [ethanolamine-1-^{3}H]AEA as a tracer for FAAH or 10 µM of 2-OG containing 1 nM of [glycerol-1,2,3-^{3}H]2-OG was added to the homogenates and incubated for 15 min at 37 °C under shaking (400 rpm). The reaction was stopped by adding 400 µl of ice-cold $CHCl_3$: MeOH (1:1). Samples were vortexed and rapidly centrifuged at 16,000×*g* for 10 min at 4 °C. The aqueous phases were collected, transferred to scintillation tubes and mixed with 3 ml of Ultima Gold scintillation liquid. The radioactivity associated with the [^{3}H]glycerol formation was measured for tritium content by liquid scintillation spectroscopy. Compounds were tested in two independent experiments, each performed in triplicates and data are reported as mean values ± SD.

AEA uptake

AEA uptake inhibition was measured in U937 living cells as previously described in detail (Chicca at al. 2017). Briefly, 0.5×10^6 U937 cells per sample were diluted in 250 µl of RPMI cell culture medium without FBS. Compounds at the screening concentration of 10 µM or different concentrations of compound **2i** were pre-incubated with the cells for 15 min at 37 °C under shaking (400 rpm). A mixture of [ethanolamine-1-^{3}H]AEA (1 nM) and unlabeled AEA (final concentration of 100 nM) was added to the cells and incubated for 15 min at 37 °C under shaking (400 rpm). The uptake process was stopped by rapid filtration onto a 96-well microplate bonded with GF/C filters under vacuum and washed 3 times with 150 µl of ice-cold PBS supplemented with 1% BSA fatty acid free. The filters were dried under air drier and then added with 45 µl of Microscint 20 scintillation cocktail. The radioactivity was measured using a Packard Tri-Carb 2100 TR scintillation counter. All experiments were performed in two independent experiments each performed in triplicate and data are reported as mean values ± SD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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