

Development of highly affine and selective fluorinated cannabinoid receptor type 2 ligands

Moldovan, R.-P.; Hausmann, K.; Deuther-Conrad, W.; Brust, P.;

Originally published:

April 2017

ACS Medicinal Chemistry Letters (2017), 566-571

DOI: <https://doi.org/10.1021/acsmedchemlett.7b00129>

Perma-Link to Publication Repository of HZDR:

<https://www.hzdr.de/publications/Publ-24953>

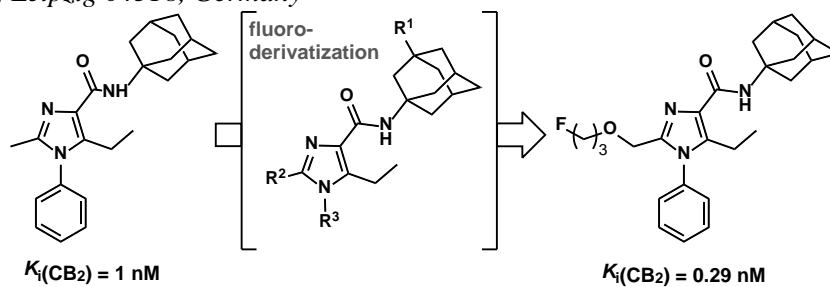
Release of the secondary publication
on the basis of the German Copyright Law § 38 Section 4.

Graphical Abstract

Development of highly affine and selective fluorinated cannabinoid receptor type 2 ligands

Leave this area blank for abstract info.

Rareș-Petru Moldovan*, Kristin Hausmann, Winnie Deuther-Conrad, Peter Brust
*Helmholtz-Zentrum Dresden-Rossendorf e. V., Institute of Radiopharmaceutical Cancer Research,
Permoserstrasse 15, Leipzig 04318, Germany*



Development of highly affine and selective fluorinated cannabinoid receptor type 2 ligands

Rareş-Petru Moldovan *, Kristin Hausmann, Winnie Deuther-Conrad, Peter Brust

Helmholtz-Zentrum Dresden-Rossendorf e. V., Institute of Radiopharmaceutical Cancer Research, Permoserstr. 15, Leipzig 04318, Germany

Abstract:

CB₂ receptors are involved in various pathological processes and the visualization of the expression level alteration with a non-invasive technique like PET is of high interest. In this work we focused on the introduction of the fluorine atom by modifying at various positions the structure of the highly affine and selective CB₂ ligand *N*-(adamantan-1-yl)-5-ethyl-2-methyl-1-phenyl-1H-imidazole-4-carboxamide (**5**, $K_i(\text{CB}_2) = 1 \text{ nM}$, $K_i(\text{CB}_1) > 10,000 \text{ nM}$). The highest CB₂ binding affinity was obtained by derivatization of the imidazole 2-position. This study allowed the identification of compound **15** as one of the most potent ($K_i(\text{CB}_2) = 0.29 \text{ nM}$) and selective ($\text{CB}_1/\text{CB}_2 > \text{xx}$), CB₂ ligand discovered so far, eligible for the development of an [¹⁸F]-PET radiotracer.

Keywords: Cannabinoid receptor type 2, Imidazole, Binding affinity, Fluorine, Positron emission tomography

1. Introduction

Cannabis sativa and its extracts have been used for centuries as therapeutic agent and recreational use.¹⁻³ The isolation and structure elucidation of the main psychoactive constituent, (–)-*trans*- Δ^9 -tetrahydrocannabinol (THC) by Mechoulam and co-workers⁴ led to the identification of the endocannabinoid system which is formed out of the cannabinoid receptors and their modulatory lipids.⁵ Two types of cannabinoid receptors have been well characterized so far namely cannabinoid receptors type 1 (CB₁)⁶ and cannabinoid receptors type 2 (CB₂)⁷. Further receptors are proposed to belong to the cannabinoid family like GPR55 and GPR18 however the research on this subtypes is at early stage.^{8, 9} The relatively low protein sequence similarity of these two G-protein coupled receptors types (44%) enables the development of selective drugs for specific targeting in pathologic conditions. The CB₁ receptors are located at the neurons and their activation is responsible for the psychotropic effect of the THC.¹⁰ Recently, the crystal structure of the CB₁ receptors has been reported facilitating future molecular modeling based SAR drug discovery and structure optimization studies for this receptor subtype.¹¹ On the contrary, the CB₂ receptors are mainly located peripheral, non-psychotropic,¹³ and are involved in regulation of several diseases related to immune system,^{14, 15} inflammation, neuropathic pain¹³ and cancer.¹⁶⁻¹⁹ CB₂ receptors have also been identified in the brain but at low levels.²⁰⁻²² It is unclear which physiological role does the CB₂ receptor play in healthy brain however it has been shown to be involved in basic neuronal transmission.^{23, 24} Studies of the signaling pathways in mouse brain cortex, showed distinct activation of G_α protein subunit when using various CB₂ ligands suggesting different binding mode.^{25, 26} The CB₂ receptors are able to form heteromers with other receptors including CB₁ (mainly post-synaptic) leading to new functionalities and therefore new signaling paths.²⁷ In pathological conditions, the up-regulation of the CB₂ receptors has been reported in association with inflammatory processes, neurodegeneration²⁸ and apoptosis in several cancer cell lines.^{29, 30} Moreover, the neuroprotective role of the CB₂ receptors was demonstrated upon induced mild traumatic brain injury by using a CB₂ antagonist.³¹

In the past decades the development of selective CB₂ receptor ligands was topic of countless publications.^{10, 32-35} However, despite the high number of ligands specifically developed for this target, only a minor number of compounds were considered for clinical trials and none of them is currently approved for human use.²⁷ The predominantly disfavored pharmacological properties of CB₂ ligands are dictated by the hydrophobic nature of the cannabinoid receptors to favorably recognize the highly lipophilic compounds. Unlike THC which is freely passing the BBB, most of the lipophilic substances are not penetrating brain and show high nonspecific binding to fat tissue.³⁶ Profiling studies were performed for the identification of CB₂ receptors ligands with the best molecular pharmacology for studying the CB₂ receptors.³⁷ As a result, despite the promising therapeutic and diagnostic potential of targeting CB₂ receptors,^{28, 35, 38-40} the development of ligands with enhanced neuropharmacological properties remains a challenging task.⁴¹

The medicinal chemistry of the CB₂ receptor ligands is summarized in several reviews and compresses various structural motifs.^{28, 35, 38-40} Beside the classical THC (**1**) derived cannabinoid ligands,⁴¹ *N*-alkylindole-3-carboxamide is one of the most popular building block of cannabinoid receptor ligands and efforts to develop CB₂ receptor selective proved to be fruitful as proven by compound **2** (A-796260)⁴² in Figure 1.⁴³⁻⁴⁷ The quinoline is also a widely used scaffold in the medicinal chemistry of CB₂ receptors and representatively

* Corresponding author. Rareş-Petru Moldovan Tel.: +49-341-234-179-4634; fax: +49-341-234-179-4699; e-mail: r.moldovan@hzdr.de

exemplified in Figure 1 by compound **3** (JTE-907).⁴⁸⁻⁵⁴ Unlike indoles, the quinoline type ligands generally possess high selectivity towards the CB₂ receptors. In the past years, several [¹¹C] and [¹⁸F] labeled radioligands have been developed for this scaffold^{50, 55-59} including [¹¹C]NE40, the first and only CB₂ radioligand which has been tested in human subject to date.⁶⁰⁻⁶² More recently, a novel series of pyrrole and thiophene derived compounds has been reported, some of which with high affinity and selectivity for the CB₂ receptors as exemplified by compound **4** ($K_i(\text{CB}_2) = 2.15 \text{ nM}$).⁶³ Consequently, the imaging properties of an ¹¹C-labeled analog of **4** have been investigated by *in vitro* and *in vivo* autoradiography and PET studies by Haider and co-workers.⁶⁴

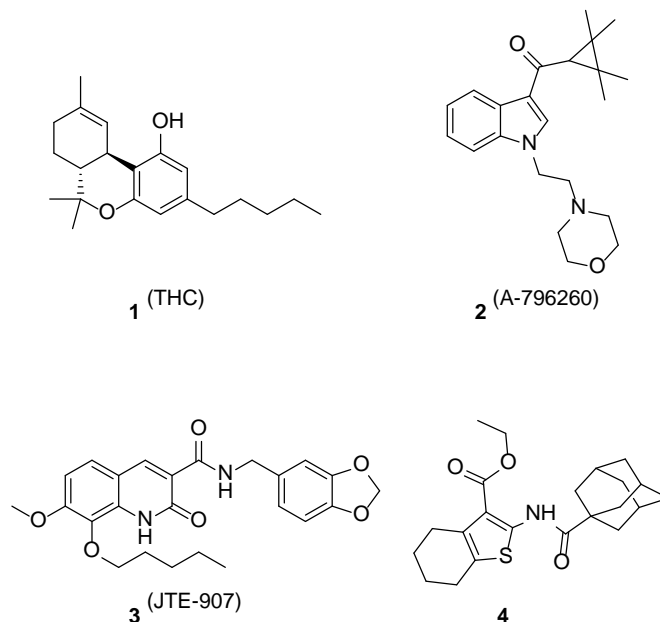


Figure 1. The structure of THC and three representative CB₂ ligands.^{41, 48, 42, 63}

Our previous efforts to develop fluorinated CB₂ receptor (radio)ligands used oxazoles, thiazole and indole as scaffolds.⁶⁵⁻⁶⁹ Recently, we reported the development of a highly affine and selective [¹⁸F]-labeled CB₂ radiotracer ($K_i(\text{CB}_2) = 0.4 \text{ nM}$, $K_i(\text{CB}_1) = 380 \text{ nM}$) and proved its applicability in a mouse model of neuroinflammation,⁶⁸ however, this radioligand suffers from low metabolic stability *in vivo*. For future vantage points we redirected our focus on the structure of the highly affine and selective *N*-(adamantan-1-yl)-5-ethyl-2-methyl-1-phenyl-1*H*-imidazole-4-carboxamide (**5**, Figure 2).⁷⁰ Compound **5** was reported by Lange and co-workers⁷⁰ as a result of a thorough SAR study and its suitable pharmacological properties have been highlighted (e.g.: CB₁/CB₂ >10000, MW = 349, LogP_{HPLC} = 3.5, PSA = 47)³⁶.

2. Results and discussion

2.1. Chemistry

The aim of the present work is the synthesis of a fluorinated CB₂ ligand based on the structure of compound **5** (Figure 2) as preliminary work for the development of a novel ¹⁸F-labeled radiotracer for imaging of the cerebral CB₂ receptors with PET. For this, its (fluoro)derivatization was questioned. The newly synthesized derivatives should retain the high CB₂ affinity and selectivity of the lead compound **5** and should contain a fluorine atom at a position which allows a facile incorporation of the ¹⁸F. Previous SAR studies performed on various CB₂ ligands,⁶⁵ including the work which led to the identification of **5**⁷⁰ highlighted the need of a lipophilic (eg. tetramethylcyclopropyl, myrtaanyl or adamantyl)^{47, 52, 71} subunit as pharmacophore.⁷² However, recent studies showed the possibility to hydroxylate adamantane 3-position without loss of affinity towards the CB₂ receptors^{57, 64} opening for us the possibility to fluoroalkoxylate this position of the molecule. On the other side, the phenyl subunit has been less explored and its ability to tolerate fluoroalkylation needs to be investigated especially due to the robustness and metabolic stability of aryl fluorides.^{73, 74} In parallel we decided to introduce fluorine also at the imidazole-2-position (Figure 2) and check the influence on the CB₂ receptor binding affinity.

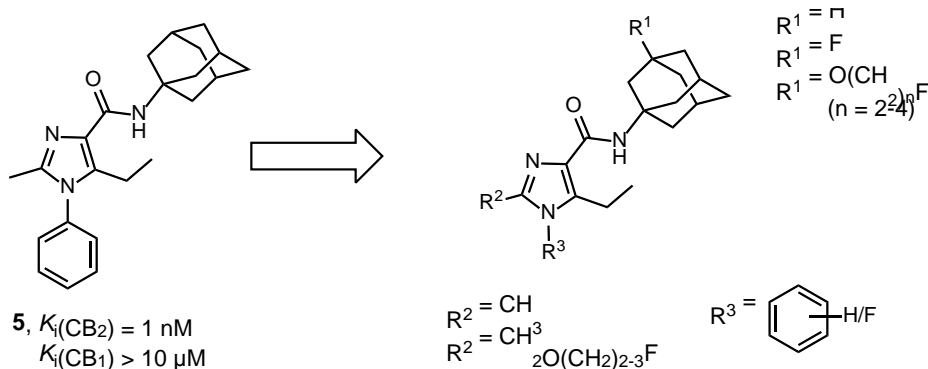
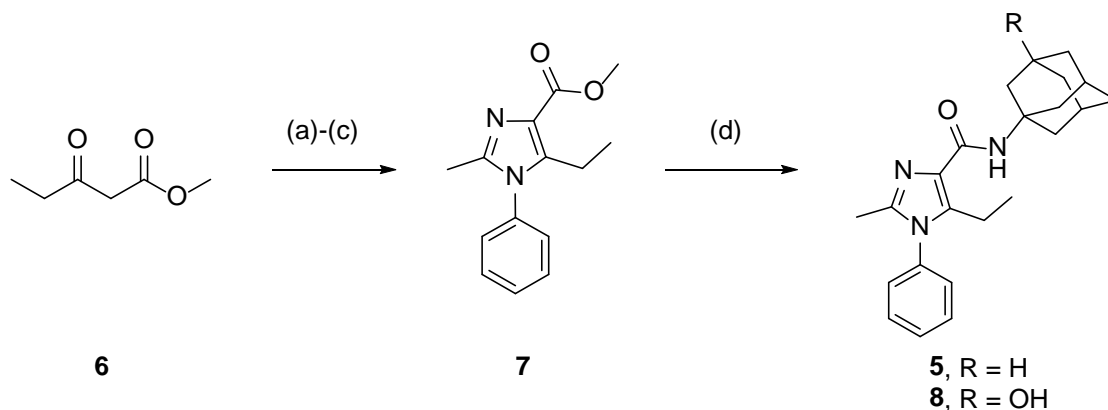
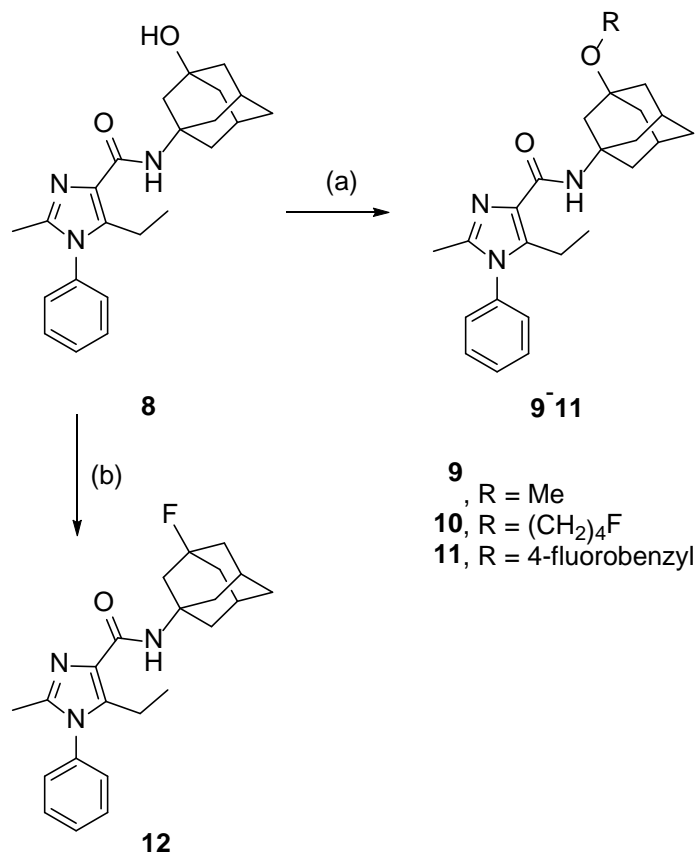


Figure 2. Lead compound **5** and conceptual design of fluorinated derivatives.

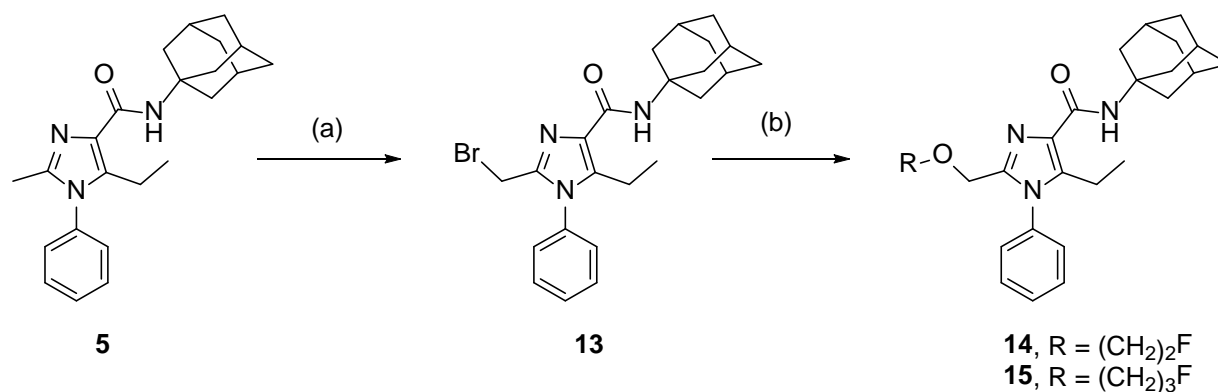
The synthesis of the lead compound **5** and its hydroxyadamantane derivative **8** was performed as described and depicted in Scheme 1 starting from the commercially available methyl 3-oxopentanoate (**6**).⁷⁰ Nitration of **6** gave the respective oxime which was further acetylated with acetic anhydride under catalytic (Pd/C-H₂) reductive reactions conditions, followed by condensation with aniline in presence of TFA at elevated temperature and concluded with cycloaromatization to imidazole **7**. Ester hydrolysis followed by Castro's reagent (BOP)⁷⁵ mediated amide bond formation with adamantane or 3-aminoadamantan-1-ol as coupling partner delivered compounds **5** and **8** respectively (Scheme 1). With large amounts of **8** in our hands various reactions conditions were tested to etherify the alcohol the adamantane subunit. First, compound **8** was reacted with excess of MeI under deprotonative reaction conditions (NaH) in DMF to give **9** in 14% yield after 22 hours at room temperature. Large amounts **8** remained unreacted. The reaction yield could not be enhanced by increasing the reaction time or the temperature. Attempts to synthesize a fluoroethoxy or a fluoropropoxy analogue by reacting the alcohol **8** with various electrophiles (eg. 1-fluor-2-iodoethane, 1-fluoro-3-iodopropane, and the corresponding mesylates and triflates) in presence of a base (NaH up to 5 equiv) failed in delivering the desired ether presumably due to the low nucleophilicity of the bulky alcohol combined with the volatility and instability of the nucleophiles at elevated temperature. We were however able to synthesize the 1-fluorobutoxy derivative **10** in 19% yield by using 10 equiv of 1-fluoro-4-bromobutane at 80 °C for 22 hours and also the benzylether **11** (Scheme 2). Furthermore, the DAST promoted fluorodeoxygenation of **8** was performed to give **12** in nearly quantitative yield.^{58, 76} At this point it is worthwhile to be mentioned that a "classical" (S_N2) radiofluorination procedure would not be applicable for the radiosynthesis of [¹⁸F]-**12** and other methods would need to be developed.⁷⁷



Scheme 1. Reagents and conditions: (a) NaNO₂, AcOH/H₂O, 0 °C to rt., 2 h (77%); (b) H₂, Pd/C, Ac₂O, AcOH 1 atm., rt., 20 h (quantitative); (c) aniline, TFA, butyronitrile, 117 °C., 1.5 h (24%); (d) i. LiOH, H₂O/MeOH 70 °C, 5 h; ii. 1M HCl, rt.; iii. 1-adamantylamine for **5** and 3-amino-1-hydroxyadamantane for **8**, BOP, Et₃N, DCM (30% over two steps).⁷⁰

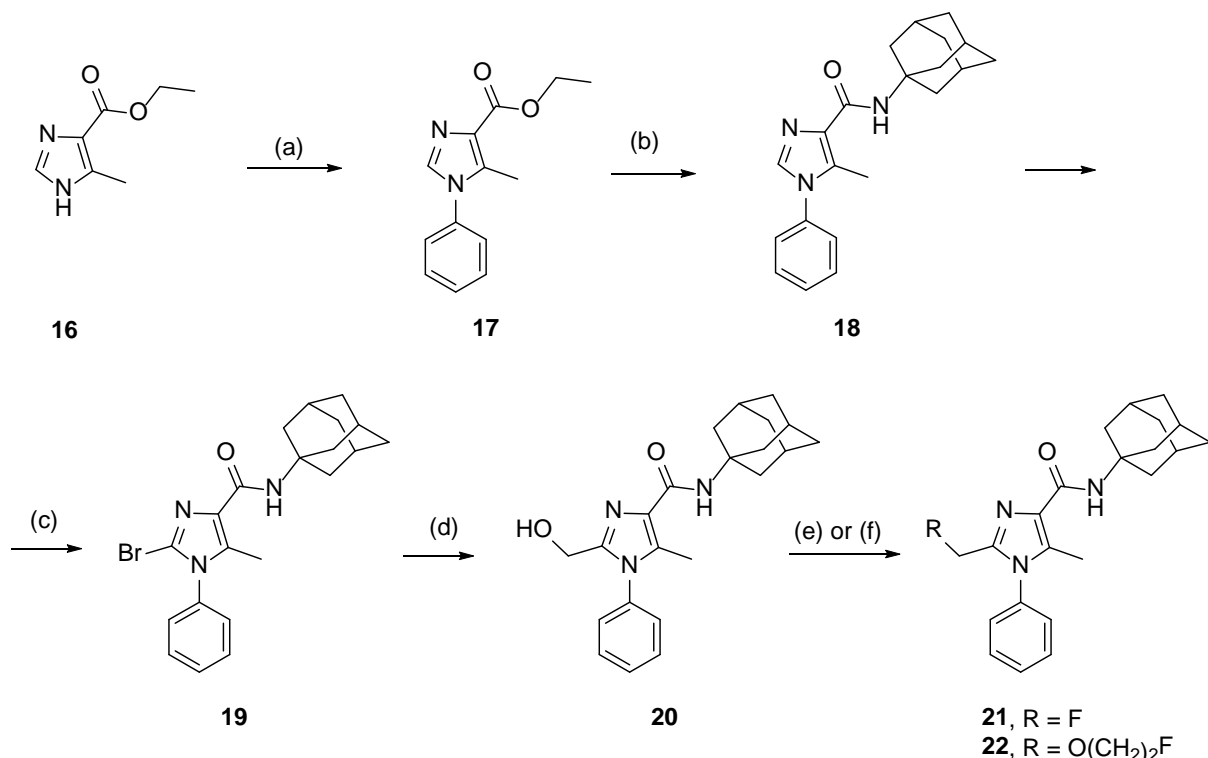


Scheme 2. Reagents and conditions: (a) RX, NaH, DMF (**9**, 14%; **10**, 19%; **11**, 42%); (b) DAST, DCM, -78 °C to rt., (>90%).



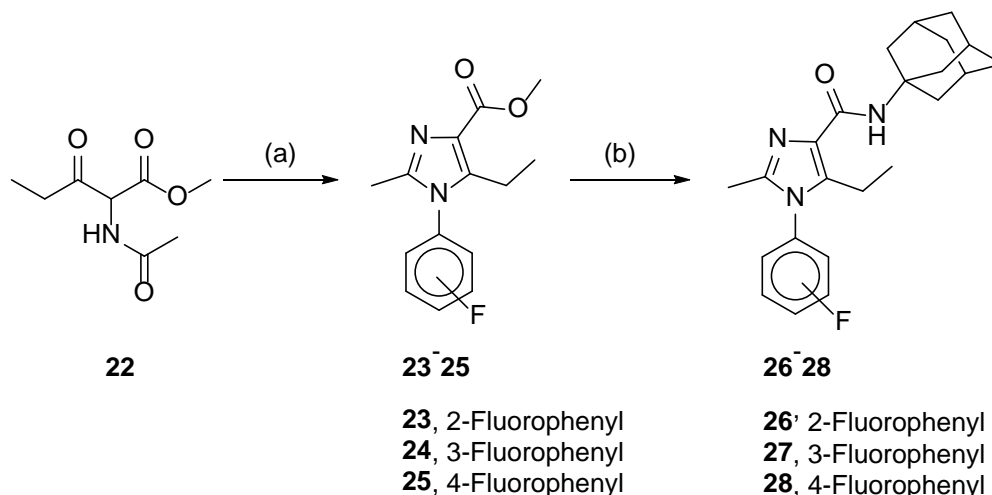
Scheme 3. Reagents and conditions: (a) NBS, AIBN, CCl₄, 77 °C, 6 h (32%); (b) R-OH, Cs₂CO₃, MeCN, 40 °C, 60 min (>90%).

It has previously been shown that both methyl and ethyl substituents are well tolerated at the imidazole 2-position without altering the binding affinity towards CB₂ receptors and therefore, we redirected our attention at this position in our efforts to introduce the fluorine atom. Treatment of **5** with NBS under radical reactions conditions employing AIBN delivered a complex reaction mixture from which we were hardly able to isolate **13** in 32% yield. The low yield and the difficult purification can be explained by the competitive high reactivity of the imidazole-5-ethyl group. Treatment of **13** with 2-fluoroethanol and 3-fluoropropanol in presence of Cs₂CO₃, smoothly gave ethers **14** and **15** respectively. Encouraged by these preliminary results, we decided to develop an alternative, more efficient method for the functionalization of imidazole at the 2-position. For this, we designed the 2-bromoimidazole key intermediate **19** starting from the commercially available **16**. In the first step, Chan-Lam coupling^{78, 79} resulted in formation of **17** (24% yield, together with its regioisomer, 34% yield, structure not shown in Scheme 4), which was then coupled with 1-adamantylamine to the amide **18**, and further selectively brominated with NBS at the second position to give **19**. Grignard reaction, using DMF as quencher formed the respective aldehyde which was smoothly reduced by NaBH₄ in presence of MeOH to give alcohol **20**. Compound **20** was converted by the DAST mediated fluorodeoxygenation into the fluoromethyl derivative **21** in good yield and *via* Williamson ether synthesis⁸⁰ into the fluoroethoxy derivative **22**.



Scheme 4. Reagents and conditions: (a) C₆H₇BO₂, CuI (cat.) EtOH/H₂O, 85 °C, 60 h (**17** 24%, regioisomer 34%); (b) 1-adamantylamine, AlMe₃, DCM, 35 °C (40%) (c) NBS, MeCN, rt., 4 h (85%); (d) i. LDA, THF, -78 °C, 30 min, ii. DMF, -78 °C to rt., iii. NaBH₄, MeOH, 0 °C, 30 min (30% over two steps); (e) DAST, DCM, -78 °C 30 min, **21**, 91 %; (f) 1-bromo-2-fluoroethane, DMF, NaH, **22**, 83%.

To further explore the structure of the lead compound **5**, the impact of the introduction of a fluorine atom at the phenyl ring on the CB₁/CB₂ binding affinities was to be studied. Therefore, the three regioisomers **26**, **27** and **28** were synthesized by using the corresponding fluoroanilines (*o*-, *m*-, and *p*-, respectively) as source of fluorine *via* a two-step synthesis sequence starting from **22**. Weinreb amidation employing AlMe₃⁸¹ delivered the fluoroaryl derivatives **26-28** in moderate yield (Scheme 5, 4-7% over two steps).



Scheme 5. Reagents and conditions: (a) fluoroaniline, TFA, butyronitrile, 117 °C., 1.5 h (**23**, 12% yield; **24**, 15% yield; **25**, 18% yield); (b) 1-adamantylamine, AlMe₃, DCM, 35 °C, 22 h (**26**, 31 % yield; **27**, 47% yield; **28**, 33% yield).

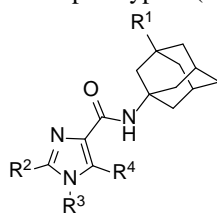
2.2. *In vitro* binding affinity

All the herein reported compounds were tested *in vitro* for binding affinity towards the CB₂ and CB₁ receptors according to a protocol well established in our labs.⁶⁵ For the CB₂ assay, [³H]WIN55.212-2 was used as competitive radioligand ($K_D = 2.1$ nM) and increasing concentrations of our compounds (100 pM to 10 μM) using CHO cells stably transfected with the human CB₂ (Prof Paul L. Prather, University Arkansas for Medical Sciences, Little Rock, USA). The non-specific binding was determined by using 10 μM WIN55.212-2. The CB₁ binding affinity determinations were performed with hCB₁-CHO obtained from Euroscreen, Gosselies, Belgium and [³H]CP55.40 as comparative radioligand.⁶⁵

As shown in Table 1 the hydroxylation at the adamantane subunit led to a drastic drop of affinity towards CB₂ receptors proving the need of a lipophilic partial structure at this site of the molecule (compound **8**, $K_i = 101$ nM). Methoxylation at this position led to a slight increase in affinity whereas butoxylation nearly restored the binding affinity to the low nanomolar range of the starting compound **5**. The implementation of the 4-fluorobenzyl as substituent at this position further improved the binding affinity towards the CB₂ receptors. Surprisingly the 3-fluoroadamantane derivative **12** slightly surpassed the low nanomolar affinity of the lead molecule with a binding affinity of 1 nM.

The three fluorophenyl regioisomers (**26**, **27** and **28** respectively) possess high CB₂ affinity ($K_i(\text{CB}_2) < 10$ nM) and CB₁/CB₂ selectivity (>1000) revealing a moderate influence of the phenyl ring on the ligand binding mode to the CB₂ receptors. Investigations performed at the imidazole-2-position expelled a drastic CB₂ binding affinity drop of compound **18** displaying the distinct need of a substituent at this position of the molecule. Accordingly, the imidazole-2-fluoromethyl derivative **21** correlated with the low nanomolar CB₂ receptor affinity of the lead compound **5**. The introduction of an ether function and simultaneous chain elongation at this position did not considerably alter the binding affinity as demonstrated by the imidazole-2-fluoroethoxylated compounds **14** and **22**. Notably, the use of a fluoropropoxy ether at this part of the molecule expulped to subnanomolar level (0.29 nM, Table 1) the binding affinity towards the CB₂ receptors. It is worthwhile to indicate that for all the herein reported derivatives the CB₁ receptor affinity remained constantly low (> 1μM).

Table 1. Binding affinity (K_i) at the human cannabinoid receptor type 2 (CB₂) receptor.



Compound	R ¹	R ²	R ³	R ⁴	$K_i(\text{CB}_2)$ [nM] ^a	$K_i(\text{CB}_1)$ [nM]
5	H	Me	Phenyl	Et	2.98 ± 0.33 (1.03 ± 0.2) ^b	>1000
8	OH	Me	Phenyl	Et	101 ± 18.5	>1000
9	OMe	Me	Phenyl	Et	69.3 ± 15.7	>10000

10	O(CH ₂) ₄ F	Me	Phenyl	Et	13.9 ±1.8	>10000
11	4-Fluorobenzyl ether	Me	Phenyl	Et	7.44 ±1	NA
12	F	Me	Phenyl	Et	1.0 ±0.2	32620
26	H	Me	2-Fluorophenyl	Et	5.56 ±0.28	>10000
27	H	Me	3-Fluorophenyl	Et	3.41 ±0.18	>10000
28	H	Me	4-Fluorophenyl	Et	10.2 ±0.2	>10000
14	H	CH ₂ O(CH ₂) ₂ F	Phenyl	Et	1.1 ±0.2	7600
15	H	CH ₂ O(CH ₂) ₃ F	Phenyl	Et	0.29 ±0.02	NA
18	H	H	Phenyl	Me	201 ±16.5	>10000
21	H	CH ₂ F	Phenyl	Me	4.16 ±3.5	5000
22	H	CH ₂ O(CH ₂) ₂ F	Phenyl	Me	3.45 ±0.6	9200

^aValues are means ± standard deviations of two to three experiments run in triplicate.

^b K_i of compound **5** as reported in ⁷⁰.

3. Conclusion

In summary, a novel series of CB₂ fluorinated 1-aryl-imidazole-4-yl-carboxamide ligands has been synthesized by varying the 1-aryl subunit, the imidazole 2-position, and the adamantane. First *in vitro* investigations revealed a moderate tolerability of an ether function at the adamantane subunit with a binding affinity towards CB₂ receptors in good correlation with the size of the ether group. On the other hand the introduction of the fluorine at the phenyl ring has a only a minor impact on the CB₂ binding affinity, however the introduction of an ¹⁸F atom at this position might be challenging due to the unfavorable electron density for an S_N2 radiofluorination. Thus, the implementation of more suitable surrogates at this position (e.g. 2-fluoropyridine) needs to be considered. The most suitable position for fluoroderivatization was discovered to be the imidazole position-2. As a result, the 2-(3-fluoropropoxy)methyl-1H-imidazole derivative **15** was identified with the sub-nanomolar binding affinity of 0.29 nM combined with an excellent selectivity against the CB₁ receptor subtype (CB₁/CB₂>1000). We are currently in the development process of an ¹⁸F PET tracer based on this compound.

4. Experimental

4.1. Chemistry

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen or argon. All chemicals and reagents were purchased from commercially available sources and used without further purification. Thin layer chromatography (TLC): Silica gel 60 F254 plates (Merck KGaA, Darmstadt, Germany). Flash chromatography (fc): Silica gel 60, 40-64 μm (Merck). Room temperature (rt.) was 21 °C. MS: MAT GCQ (Thermo Finnigan MAT GmbH, Bremen, Germany). ¹H, ¹³C and ¹⁹F NMR spectra were recorded on VARIAN "MERCURY plus" (300 MHz for ¹H NMR, 75 MHz for ¹³C NMR, 282 MHz for ¹⁹F NMR) and VARIAN "MERCURY plus" and BRUKER DRX-400 (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR, 377 MHz for ¹⁹F NMR); δ in ppm related to tetramethylsilane; coupling constants (*J*) are given with 0.1 Hz resolution. Multiplicities of NMR signals are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets). ESI/Ion trap mass spectra (LRMS) were recorded with a Bruker Esquire 3000 plus instrument (Billerica, MA, USA). High resolution mass spectra were recorded on an FT-ICR APEX II spectrometer (Bruker Daltonics; Bruker Corporation, Billerica, MA, USA) using electrospray ionization (ESI) in positive ion mode.

4.1.1. General procedure 1

The respective fluoroaniline (3 mmol, 1.5 equiv) and trifluoroacetic acid (3 mmol, 1.5 equiv) were added to a solution of **22** (2 mmol, 1.0 equiv) in 5 mL butyronitrile and the reaction mixture was refluxed for 2 h. After evaporation of the solvent the resulting residue was taken up in dichloromethane (15 ml) and washed with an aq. K₂CO₃ sol. (2 x 15 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel.

4.1.2. General procedure 2

The corresponding carboxylic acid (1 mmol, 1 equiv), Et₃N (3 mmol, 3 equiv) and BOP (1.3 mmol, 1.3 equiv) were added to a suspension of the the corresponding adamantane amine (1 mmol, 1 equiv) in 5 mL DCM at 0 °C, and the mixture was stirred at room temperature for 20 hours. The reaction was quenched by addition of 2 mL water followed by a 10 mL aq. saturated sol. of NaHCO₃ and 15 mL EA. The phases were separated and the aqueous phase was washed with 2x10 mL EA. The combined organic fractions were washed with 20 mL brine, dried over MgSO₄ and concentrated by rotary evaporation. The obtained residue was purified by column chromatography on silica.

4.1.3. General procedure 3

NaH (60% in mineral oil, 2 mmol, 2 equiv) was added to a sol. of alcohol **8** (1 mmol, 1 equiv), in 0.5 mL DMF, and the mixture was stirred for 5 minutes at room temperature. Thereafter the alkylating agent RX (5 mmol, 5 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of H₂O (2 mL), followed by 15 mL aq. saturated sol. NaHCO₃ and 20 mL EA while stirring. The phases were separated, the organic phase was washed with 20 mL EA and the combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica.

4.1.4. General procedure 4

Al(CH₃)₃ (2 M solution in heptane, 0.2 mmol, 1.3 equiv) was added to a solution of 1-adamantylamine (0.2 mmol, 1.3 equiv) in anhydrous dichloromethane (1.8 ml) and the reaction mixture was magnetically stirred for 10 min at room temperature. The corresponding methylester (0.16 mmol, 1.0 equiv) was then added and the mixture was stirred at 35 °C for 22 h, poured into an aq. NaHCO₃ sol. (10 ml) and stirred for 30 min at room temperature. After filtration over celite, the solution was extracted with dichloromethane (2 x 15 ml). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuum. Purification was performed by flash chromatography on silica gel.

4.1.5. 5-Ethyl-N-(3-hydroxyadamantan-1-yl)-2-methyl-1-phenyl-1H-imidazol-4-carboxamid (**8**)

Compound **8** was obtained by *General procedure 2*, yield 68%, white solid; R_f = 0.16 (EA); ¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 7.53 – 7.50 (m, 3H), 7.23 – 7.15 (m, 2H), 7.04 (s, 1H), 2.79 (q, J = 7.5 Hz, 2H), 2.19 – 1.99 (m, 9H), 1.85 – 1.45 (m, 8H), 0.97 (t, J = 7.4 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 163.2, 143.0, 139.0, 135.8, 129.7, 129.4, 127.7, 69.3, 53.9, 49.5, 44.2, 40.6, 35.0, 30.7, 17.6, 14.0, 13.6; MS (ESI+): m/z (%) = 380.2, calcd. 380.2 for C₂₃H₂₉N₃O₂ [M+H]⁺.

4.1.6. 5-Ethyl-N-(3-methoxyadamantan-1-yl)-2-methyl-1-phenyl-1H-imidazol-4-carboxamid (**9**)

Compound **9** was obtained by *General procedure 3*, yield 25%, white solid; R_f = 0.36 (EA); ¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 7.56 – 7.54 (m, 3H), 7.26 – 7.19 (m, 2H), 7.07 (s, 1H), 3.29 (s, 3H), 2.82 (q, J = 7.4 Hz, 2H), 2.20 – 2.06 (m, 9H), 1.77 – 1.48 (m, 8H), 1.00 (t, J = 7.4 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 163.1, 143.0, 138.9, 135.8, 129.7, 129.4, 127.7, 73.1, 53.8, 48.2, 44.6, 40.8, 40.3, 35.4, 30.4, 29.7, 17.6, 14.0, 13.6; HRMS (ESI+): m/z (%) = 394.2487, calcd. 394.5297 for C₂₄H₃₁N₃O₂ [M+H]⁺.

4.1.7. 5-Ethyl-N-(3-(4-fluorobutoxy)adamantan-1-yl)-2-methyl-1-phenyl-1-H-imidazole-4-carboxamide (**10**)

Compound **10** was obtained by *General procedure 3*, yield 19%, pale yellow solid; R_f = 0.67 (EA); ¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 7.48 – 7.46 (m, 3H), 7.14 – 7.11 (m, 2H), 4.39 (dt, J = 47.3, J = 6.1 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 2.74 (q, J = 7.4 Hz, 2H), 2.31 – 1.92 (m, 12H), 1.82 – 1.40 (m, 12H), 0.91 (t, J = 7.4 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) = 142.9, 129.8, 129.6, 127.6, 85.2, 83.1, 72.9, 59.4, 54.0, 45.2, 40.8, 40.8, 35.4, 30.5, 29.7, 27.6, 27.3, 26.3, 26.2, 17.6, 14.0; HRMS (ESI+): m/z (%) = 454.2850, calcd. 454.2864 for C₂₇H₃₆FN₃O₂ [M+H]⁺.

4.1.8. 5-Ethyl-N-(3-((4-fluorobenzyl)oxy)adamantan-1-yl)-2-methyl-1-phenyl-1H-imidazole-4-carboxamide (**11**)

Compound **11** was obtained by *General procedure 3*, yield 38%, white solid; R_f = 0.55 (EA/PE 1:1); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.70 – 7.50 (m, 3H), 7.33 (dd, J = 8.5, 5.6 Hz, 2H), 7.26 – 7.18 (m, 2H), 7.02 (t, J = 8.8 Hz, 2H), 4.52 (s, 2H), 2.83 (q, J = 7.4 Hz, 2H), 2.46 – 1.46 (m, 17H), 1.01 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 160.8, 143.0, 135.5, 129.9, 129.1 (d, J = 8.1 Hz), 127.6, 115.0 (d, J = 21.3 Hz), 73.9, 62.0, 45.2, 40.9 (d, J = 7.7 Hz), 35.4, 30.5, 17.6, 13.9; HRMS (ESI+): m/z (%) = 488.2714, calcd. 488.2713 for C₃₀H₃₅FN₃O₂⁺ [M+H]⁺.

4.1.9. 5-Ethyl-N-(3-fluoroadamantan-1-yl)-2-methyl-1-phenyl-1H-imidazole-4-carboxamide (**12**)

DAST (33μL, 0.25 mmol, 1.5 equiv) was added to a –78 °C cold solution of **8** (65 mg, 0.16 mmol, 1 equiv) in 2 mL dry DCM. The reaction was allowed to warm up to rt. after which 10 mL H₂O was added and the mixture was washed 2x10 mL DCM. The combined organic solutions were dried over sodium sulfate and the volatiles were eliminated under reduced pressure. The resulting residue was subject of column chromatography purification on silica gel (EA/PE 2:8) to give **12** as white solid (83% yield). R_f = 0.12 (EA/PE 1:4); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.66 – 7.43 (m, 3H), 7.26 – 7.16 (m, 2H), 7.12 (s, 1H), 2.80 (q, J = 7.4 Hz, 2H), 2.45 – 2.26 (m, 4H), 2.15 (s, 3H), 2.11 (s, 4H), 2.02 – 1.79 (m, 4H), 1.72 – 1.47 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 163.0, 143.0, 139.1, 135.7, 129.7, 129.4, 127.6, 93.5, 91.6, 54.4 (d, J = 12.1 Hz), 46.7 (d, J = 18.5 Hz), 41.8 (d, J = 17.4 Hz), 40.4, 34.8, 31.1 (d, J = 10.3 Hz), 17.6, 13.9, 13.5; HRMS (ESI+): m/z (%) = 382.2293, calcd. 382.2295 for C₂₃H₂₉FN₃O⁺ [M+H]⁺.

4.1.10. Methyl-5-ethyl-1-(2-fluorophenyl)-2-methyl-1-H-imidazole-4-carboxylate (**23**)

Compound **23** was obtained by *General procedure 3*, yield 31%, beige solid; R_f = 0.63 (EA/PE 1:1); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.56 – 7.39 (m, 1H), 7.36 – 6.82 (m, 4H), 2.73 (ddq, J = 20.7, 13.6, 6.8 Hz, 2H), 2.35 – 1.90 (m, 11H), 1.78 – 1.50 (m, 7H), 0.91 (t, J = 7.5 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm) = 143.4, 129.9, 125.3, 117.4, 42.0, 36.7, 29.9, 29.7, 17.7, 13.8; HRMS (ESI+): m/z (%) = 382.2292, calcd. 382.2289 for C₂₃H₂₈FN₃O [M+H]⁺.

4.1.11. N-(Adamantan-1-yl)-5-ethyl-1-(3-fluorophenyl)-2-methyl-1H-imidazol-4-carboxamid (**27**)

Compound **27** was obtained by *General procedure 3*, yield 47%, beige solid; R_f = 0.63 (EA/PE 1:1); ¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 7.57 - 7.46 (m, 1H), 7.29 - 7.18 (m, 1H), 7.03 – 6.92 (m, 3H), 2.82 (q, J = 7.5 Hz, 2H), 2.27 - 2.05 (m, 12H), 1.84 - 1.62 (m,

6H), 0.98 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ (ppm) = 164.7, 161.4, 142.8, 138.8, 131.3, 131.2, 123.8, 123.8, 117.1, 116.8, 115.7, 115.35, 51.7, 42.0, 36.7, 29.8, 29.7, 17.7, 14.2, 13.6; HRMS (ESI+): m/z (%) = 382.2288, calcd. 382.2289 for $\text{C}_{23}\text{H}_{28}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$.

4.1.12. *N*-(Adamantan-1-yl)-5-ethyl-1-(4-fluorophenyl)-2-methyl-1*H*-imidazole-4-carboxamide (**28**)

Compound **28** was obtained by General procedure 3, yield 33%, beige solid; $R_f = 0.63$ (EA/PE 1:1); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.19 – 7.07 (m, 4H), 7.00 – 6.83 (m, 1H), 2.73 (q, $J = 7.4$ Hz, 2H), 2.17 – 1.98 (m, 12H), 1.76 – 1.56 (m, 6H), 0.91 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm) = 164.2, 161.7, 143.1, 139.0, 129.7, 129.6, 117.2, 116.9, 51.7, 42.0, 36.7, 29.8, 29.7, 17.7, 14.2, 13.6. HRMS (ESI+): m/z (%) = 382.2286, calcd. 382.2289 for $\text{C}_{23}\text{H}_{28}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$.

4.1.13. *N*-(Adamantan-1-yl)-2-(bromomethyl)-5-ethyl-1-phenyl-1*H*-imidazole-4-carboxamide (**13**)

NBS (161 mg, 0.9 mmol, 1.1 equiv) and AIBN (13 mg, 0.90 mmol, 0.1 equiv) was added to a solution of **5** (300 mg, 0.82 mmol, 1 equiv) in 5 mL CCl_4 at room temperature and the mixture was refluxed for 6 h. Upon cooling, NaHCO_3 sat. aq. sol. (10 mL) was added and the solution was extracted with DCM (2x10 mL). The combined organic layers were dried over Na_2SO_4 , concentrated under reduced pressure and the resulting residue was subject to flash chromatography purification (silica, EA/PE 1:9 to EA/PE 1:4), to give **13** (110 mg, 0.24 mmol, 30%) as tan white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.72 – 7.58 (m, 3H), 7.38 – 7.32 (m, 2H), 7.05 (s, 1H), 4.29 (s, 2H), 2.95 – 2.74 (m, 2H), 2.32 – 2.05 (m, 9H), 1.74 (q, $J = 12.3$ Hz, 6H), 1.03 (t, $J = 7.5$ Hz, 3H).

4.1.14. *N*-(Adamantan-1-yl)-5-ethyl-2-((2-fluoroethoxy)methyl)-1-phenyl-1*H*-imidazole-4-carboxamide (**14**)

2-Fluoroethanol (13 μL , 0.2 mmol, 2 equiv) was added to a solution of **13** (44 mg, 0.1 mmol, 1 equiv) and Cs_2CO_3 (65 mg, 0.2 mmol, 2 equiv) in 2 mL MeCN and the reaction mixture was warmed to 45 °C for 60 min. Upon completion, the reaction was quenched by addition of NaHCO_3 sat. aq. sol. (5 mL) and the resulting mixture was extracted with DCM (2x5 mL). The combined organics were dried over Na_2SO_4 and the product (**14**, 30 mg, 0.7 mmol, 72% yield) was obtained by flash chromatography (EA/PE 2:8). $R_f = 0.18$ (EA/PE 1:4); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.49 – 7.39 (m, 3H), 7.32 – 7.22 (m, 2H), 7.10 (s, 1H), 4.57 – 4.19 (m, 4H), 3.76 – 3.43 (m, 2H), 2.84 (q, $J = 7.5$ Hz, 2H), 2.25 – 2.00 (m, 9H), 1.80 – 1.61 (m, 6H), 1.00 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ (ppm) = 162.6, 142.0, 140.2, 129.5, 129.5, 127.8, 110.0, 82.6 (d, $J = 169.7$ Hz), 69.4 (d, $J = 19.8$ Hz), 41.7, 36.4, 29.6, 29.6, 17.5, 13.8; HRMS (ESI+): m/z (%) = 426.2557, calcd. 426.2557 for $\text{C}_{25}\text{H}_{34}\text{FN}_3\text{O}_2^+$ $[\text{M}+\text{H}]^+$.

4.1.15. *N*-(Adamantan-1-yl)-5-ethyl-2-((3-fluoropropoxy)methyl)-1-phenyl-1*H*-imidazole-4-carboxamide (**15**)

3-Fluoropropanol (16 μL , 0.2 mmol, 2 equiv) was added to a solution of **13** (44 mg, 0.1 mmol, 1 equiv) and Cs_2CO_3 (65 mg, 0.2 mmol, 2 equiv) in 2 mL MeCN and the reaction mixture was warmed to 45 °C for 60 min. Upon completion, the reaction was quenched by addition of NaHCO_3 sat. aq. sol. (5 mL) and the resulting mixture was extracted with DCM (2x5 mL). The combined organics were dried over Na_2SO_4 and the product (**15**, 30 mg, 0.7 mmol, 69% yield) was obtained by flash chromatography (EA/PE 2:8). $R_f = 0.18$ (EA/PE 1:4); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.49 – 7.39 (m, Hz, 3H), 7.45 – 7.23 (m, 2H), 7.11 (s, 1H), 4.56 – 4.15 (m, 4H), 3.57 – 3.33 (m, 2H), 2.84 (q, $J = 7.4$ Hz, 2H), 2.24 – 2.00 (m, 9H), 1.90 (dd, $J = 12.1, 6.1$ Hz, 2H), 1.75 – 1.67 (m, 6H), 1.00 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ (ppm) = 162.6, 141.99, 140.23, 129.56, 129.50, 127.82, 109.99, 82.63 (d, $J = 169.7$ Hz), 69.38 (d, $J = 19.8$ Hz), 41.79, 36.48, 29.67, 29.61, 17.53, 13.88; HRMS (ESI+): m/z (%) = 440.2713, calcd. 440.2713 for $\text{C}_{26}\text{H}_{35}\text{FN}_3\text{O}_2^+$ $[\text{M}+\text{H}]^+$.

4.1.16. Ethyl-5-methyl-1-phenyl-1*H*-imidazole-4-carboxylate (**17**)

Phenyl boronic acid (3.16 g, 25.92 mmol, 1.6 equiv) and CuI (308 mg, 0.81 mmol, 0.10 equiv) were added to a solution of ethyl-5-methyl-1*H*-imidazole-4-carboxylate **16** (2.50 g, 16.2 mmol, 1.0 equiv) in ethanol/water (100 ml, 1/1 (v/v)) and the mixture was stirred at 85°C for 60 h. After cooling to room temperature the solvent was evaporated in vacuum. The two regioisomers were separated by flash chromatography (EA/PE 1:1 to EA) to give **17** (0.90 g, 3.89 mmol, 24%) as beige solid. $R_f = 0.48$ (EA); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) = 7.59 (s, 1H), 7.56 – 7.43 (m, 3H), 7.31 – 7.24 (m, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 2.46 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H).

4.1.17. *N*-(Adamantan-1-yl)-5-methyl-1-phenyl-1*H*-imidazole-4-carboxamide (**18**)

Compound **18** was obtained according to *General Procedure 3*, 40% yield, beige solid. $R_f = 0.75$ (EA); $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ (ppm) = 7.49 – 7.39 (m, 3H), 7.38 (s, 1H), 7.24 – 7.14 (m, 2H), 6.95 (s, 1H), 2.42 (s, 3H), 2.12 – 2.01 (m, 9H), 1.72 – 1.58 (m, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm) = 162.8, 135.4, 134.5, 132.5, 132.2, 129.7, 129.1, 126.0, 51.6, 41.8, 36.5, 29.5, 10.2; HRMS (ESI+): m/z (%) = 336.2075, calcd. 336.2075 for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$.

4.1.18. *N*-(Adamantan-1-yl)-2-bromo-5-methyl-1-phenyl-1*H*-imidazole-4-carboxamide (**19**)

N-bromosuccinimide (291 mg, 1.6 mmol, 1.1 equiv) was added in one portion to a solution of **18** (500 mg, 1.5 mmol, 1.0 equiv) in MeCN (8 mL) and the reaction mixture was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was taken up in EA (10 ml) and washed with an aq. NaHCO_3 -sol. (15 ml). The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. Purification by flash chromatography on silica gel (EA/PE 1:5) yielded **19** (519 mg, 1.3 mmol, 85%) as a beige solid. $R_f = 0.52$ (EA/PE 1:3); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.62 – 7.48 (m, 3H), 7.24 – 7.15 (m, 2H), 6.92 (s, 1H), 2.38 (s, 3H), 2.13 (d, $J = 13.0$ Hz, 9H), 1.81 – 1.63 (m, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm) = 162.2, 136.0, 135.3, 133.1, 130.1, 129.9, 128.1, 118.0, 52.0, 42.0, 36.7, 29.7, 11.3; HRMS (ESI+): m/z (%) = 414.1170, calcd 414.1175 for $\text{C}_{21}\text{H}_{24}\text{BrN}_3\text{O}$ $[\text{M}+\text{H}]^+$.

4.1.19. *N*-(Adamantan-1-yl)-2-(hydroxymethyl)-5-methyl-1-phenyl-1*H*-imidazole-4-carboxamide (**20**)

LDA (2M in THF, 1 mL, 2 mmol, 2 equiv) was added to a –78 °C cold solution of **19** (400 mg, 1 mmol, 1 equiv) in 5 mL THF, and the reaction mixture was maintained at this temperature for 30 min after which DMF (300 μL , 9.6 mmol, 10 equiv) was added. The cooling bath was removed and the mixture was allowed to react for one hour at room temperature after which a saturated aq. sol. of NH_4Cl (10 mL) and DCM (10 mL) were added. The phases were separated and the aqueous phase was extracted once with DCM. The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was subject to flash chromatography purification on silica gel (EA/PE 1:9; $R_f = 0.3$). The aldehyde was obtained as white solid (100 mg, 0.3 mmol 30%).

NaBH₄ (7 mg, 0.2 mmol, 1 equiv) was added to a 0 °C cold MeOH (2 mL) solution of aldehyde (70 mg, 0.2 mmol, 1 equiv), and the mixture was stirred for 30 min at 0 °C. The reaction was quenched by addition of NH₄Cl (5 mL) and the whole was extracted twice with 5 mL DCM. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Compound **20** (70 mg, 0.2 mmol, 1 equiv) was obtained as white solid and used without further purification in the next step. R_f = 0.3 (EA/PE 1:1); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.72 – 7.43 (m, 3H), 7.42 – 7.14 (m, 2H), 7.03 (s, 1H), 4.46 (s, 2H), 3.33 (s, 1H), 2.39 (s, 3H), 2.26 – 2.00 (m, 9H), 1.86 – 1.56 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 162.7, 145.4, 134.6, 134.0, 130.4, 129.7, 129.6, 127.4, 56.3, 51.7, 41.8, 36.5, 29.5, 10.4.

4.1.20. *N*-(Adamantan-1-yl)-2-(fluoromethyl)-5-methyl-1-phenyl-1H-imidazole-4-carboxamide (**21**)

DAST (18 μL, 0.13 mmol, 1 equiv) was added to a –78 °C cold solution of **21** (50 mg, 0.13 mmol, 1 equiv) in dry DCM (2 mL) and the mixture was stirred at this temperature for 30 min. Aq. NaHCO₃ sol. (5 mL) was then added for quenching and the reaction was extracted once with DCM (5 mL). The organic solution was dried over sodium sulfate and concentrated under reduced pressure. The product was purified by flash chromatography (silica, EA/PE 1:4), and obtained as white solid (45 mg, 0.11 mmol, 91%). R_f = 0.15 (EA/PE 1:4); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.72 – 7.43 (m, 3H), 7.39 – 7.23 (m, 2H), 7.08 (s, 1H), 5.14 (d, *J* = 48.9 Hz, 2H), 2.42 (d, *J* = 2.1 Hz, 3H), 2.30 – 2.03 (m, 9H), 1.88 – 1.63 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 162.6, 140.4 (d, *J* = 19.5 Hz), 134.7 (d, *J* = 51.5 Hz), 131.6, 129.8 (d, *J* = 4.1 Hz), 127.5, 74.8 (d, *J* = 167.0 Hz), 51.7, 41.8, 36.5, 29.5, 10.6; HRMS (ESI+): *m/z* (%) = 390.1952, calcd. 390.1958 for C₂₂H₂₆FN₃NaO⁺ [M+Na]⁺.

4.1.21. *N*-(adamantan-1-yl)-2-((2-fluoroethoxy)methyl)-5-methyl-1-phenyl-1H-imidazole-4-carboxamide (**22**)

Compound **22** was obtained according to *General procedure 3* as white solid, 83% yield. R_f = 0.65 (EA/PE 1:1); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.60 – 7.47 (m, 3H), 7.36 – 7.26 (m, 2H), 7.06 (s, 1H), 4.59 – 4.39 (m, 2H), 4.36 (s, 2H), 3.75 – 3.52 (m, 2H), 2.39 (s, 3H), 2.16 (d, *J* = 19.4 Hz, 9H), 1.81 – 1.66 (m, 6H), 0.89 (dt, *J* = 10.5, 6.4 Hz, 3H), ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 163.1, 142.1, 134.9, 134.3, 129.5, 129.3, 127.6, 83.5, 81.8, 69.3 (d, *J* = 19.8 Hz), 64.3, 51.6, 41.8, 36.5, 29.6 (d, *J* = 13.3 Hz), 22.7, 14.1, 10.6; HRMS (ESI+): *m/z* (%) = 412.2390, calcd. 412.2400 for C₂₄H₃₁FN₃O₂⁺ [M+H]⁺.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Rareș-Petru Moldovan and Kristin Hausmann conceived and performed the chemical syntheses. Winnie Deuther-Conrad and Peter Brust planned and performed the radioligand binding studies.

Acknowledgments

We thank Mrs. Tina Spalholz for help with radioligand binding studies. We thank the staff of the Institute of Analytical Chemistry, Department of Chemistry and Mineralogy of the University of Leipzig, for the MS and NMR spectra.

Supplementary Materials

¹H NMR spectra of compounds **5**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **21**, **22**, **26**, **27** and **28**.

References and notes

- Hanus, L. O.; Meyer, S. M.; Munoz, E.; Tagliatela-Scafati, O.; Appendino, G. Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* **2016**.
- Zdrojewicz, Z.; Pypno, D.; Cabala, K.; Bugaj, B.; Waracki, M. Potential applications of marijuana and cannabinoids in medicine. *Polski Merkuriusz Lekarski* **2014**, *37*, 248-52.
- Russo, E. B. Beyond cannabis: plants and the endocannabinoid system. *Trends Pharmacol. Sci.* **2016**, *37*, 594-605.
- Gaoni, Y.; Mechoulam, R. Isolation, structure, and partial synthesis of an active constituent of Hashish. *J. Am. Chem. Soc.* **1964**, *86*, 1646-1647.
- Reggio, P. H. Endocannabinoid Binding to the Cannabinoid Receptors: What Is Known and What Remains Unknown. *Curr. Med. Chem.* **2010**, *17*, 1468-1486.
- Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561-564.
- Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61-65.
- Begg, M.; Pacher, P.; Batkai, S.; Osei-Hyiaman, D.; Offertaler, L.; Mo, F. M.; Liu, J.; Kunos, G. Evidence for novel cannabinoid receptors. *Pharmacology & therapeutics* **2005**, *106*, 133-45.
- Brown, A. J. Novel cannabinoid receptors. *Br. J. Pharmacol.* **2007**, *152*, 567-575.
- Yang, P.; Wang, L.; Xie, X. Q. Latest advances in novel cannabinoid CB₂ ligands for drug abuse and their therapeutic potential. *Future. Med. Chem.* **2012**, *4*, 187-204.
- Hua, T.; Vemuri, K.; Pu, M.; Qu, L.; Han, G. W.; Wu, Y.; Zhao, S.; Shui, W.; Li, S.; Korde, A.; Laprairie, R. B.; Stahl, E. L.; Ho, J. H.; Zvonok, N.; Zhou, H.; Kufareva, I.; Wu, B.; Zhao, Q.; Hanson, M. A.; Bohn, L. M.; Makriyannis, A.; Stevens, R. C.; Liu, Z. J. Crystal structure of the human cannabinoid receptor CB₁. *Cell* **2016**, *167*, 750-762.e14.
- Shao, Z.; Yin, J.; Chapman, K.; Grzemska, M.; Clark, L.; Wang, J.; Rosenbaum, D. M. High-resolution crystal structure of the human CB₁ cannabinoid receptor. *Nature* **2016**, doi: 10.1038/nature20613.
- Malan, T. P., Jr.; Ibrahim, M. M.; Lai, J.; Vanderah, T. W.; Makriyannis, A.; Porreca, F. CB₂ cannabinoid receptor agonists: pain relief without psychoactive effects? *Current opinion in pharmacology* **2003**, *3*, 62-7.
- Leleu-Chavain, N.; Desreumaux, P.; Chavatte, P.; Millet, R. Therapeutic potential of CB₂ receptors in immune-related diseases. *Curr. Mol. Pharmacol.* **2013**, *6*, 183-203.

15. Rom, S.; Persidsky, Y. Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. *J. Neuroimmune. Pharmacol.* **2013**, *8*, 608-620.
16. Castaneto, M. S.; Gorelick, D. A.; Desrosiers, N. A.; Hartman, R. L.; Pirard, S.; Huestis, M. A. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug & Alcohol Dependence* **2014**, *144*, 12-41.
17. Ellert-Miklaszewska, A.; Ciechomska, I.; Kaminska, B. Cannabinoid signaling in glioma cells. *Adv. Exp. Med. Biol.* **2013**, *986*, 209-220.
18. Chakravarti, B.; Ravi, J.; Ganju, R. K. Cannabinoids as therapeutic agents in cancer: current status and future implications. *Oncotarget* **2014**, *5*, 5852-5872.
19. Zogopoulos, P.; Korkolopoulou, P.; Patsouris, E.; Theocharis, S. The antitumor action of cannabinoids on glioma tumorigenesis. *Histology and histopathology* **2014**.
20. Glass, M.; Faull, R. L. M.; Dragunow, M. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* **1997**, *77*, 299-318.
21. Ashton, J. C.; Friberg, D.; Darlington, C. L.; Smith, P. F. Expression of the cannabinoid CB₂ receptor in the rat cerebellum: an immunohistochemical study. *Neurosci. Lett.* **2006**, *396*, 113-116.
22. Van Sickle, M. D.; Duncan, M.; Kingsley, P. J.; Mouihate, A.; Urbani, P.; Mackie, K.; Stella, N.; Makriyannis, A.; Piomelli, D.; Davison, J. S.; Marnett, L. J.; Di Marzo, V.; Pittman, Q. J.; Patel, K. D.; Sharkey, K. A. Identification and functional characterization of brainstem cannabinoid CB₂ receptors. *Science (New York, N.Y.)* **2005**, *310*, 329-332.
23. Rogers, N. Cannabinoid receptor with an 'identity crisis' gets a second look. *Nat. Med.* **2015**, *21*, 966-967.
24. Stempel, A. V.; Stumpf, A.; Zhang, H.-Y.; Özdoğan, T.; Pannasch, U.; Theis, A.-K.; Otte, D.-M.; Wojtalla, A.; Rácz, I.; Ponomarenko, A.; Xi, Z.-X.; Zimmer, A.; Schmitz, D. Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. *Neuron* **2016**, *90*, 795-809.
25. Diez-Alarcia, R.; Ibarra-Lecue, I.; Lopez-Cardona, Á. P.; Meana, J.; Gutierrez-Adán, A.; Callado, L. F.; Agirregoitia, E.; Urigüen, L. Biased agonism of three different cannabinoid receptor agonists in mouse brain cortex. *Front. Pharmacol.* **2016**, *7*.
26. Dhopeshwarkar, A.; Mackie, K. Functional selectivity of CB₂ cannabinoid receptor ligands at a canonical and noncanonical pathway. *J. Pharmacol. Exp. Ther.* **2016**, *358*, 342-351.
27. Navarro, G.; Morales, P.; Rodríguez-Cueto, C.; Fernández-Ruiz, J.; Jagerovic, N.; Franco, R. Targeting cannabinoid CB₂ receptors in the central nervous system. Medicinal chemistry approaches with focus on neurodegenerative disorders. *Front. Neurosci.* **2016**, *10*.
28. Aso, E.; Ferrer, I. CB₂ Cannabinoid Receptor As Potential Target against Alzheimer's Disease. *Front. Neurosci.* **2016**, *10*, 243.
29. Varley, J.; Brooks, D. J.; Edison, P. Imaging neuroinflammation in Alzheimer's and other dementias: Recent advances and future directions. *Alzheimer's & Dementia* **2014**, *1*-11.
30. Giacoppo, S.; Mandolino, G.; Galuppo, M.; Bramanti, P.; Mazzone, E. Cannabinoids: new promising agents in the treatment of neurological diseases. *Molecules* **2014**, *19*, 18781-18816.
31. Bu, W.; Ren, H.; Deng, Y.; Del Mar, N.; Guley, N. M.; Moore, B. M.; Honig, M. G.; Reiner, A. Mild traumatic brain injury produces neuron loss that can be rescued by modulating microglial activation using a CB₂ receptor inverse agonist. *Front. Neurosci.* **2016**, *10*.
32. Evens, N.; Bormans, G. M. Non-invasive imaging of the type 2 cannabinoid receptor, focus on positron emission tomography. *Curr. Top. Med. Chem.* **2010**, *10*, 1527-1543.
33. Ory, D.; Celen, S.; Verbruggen, A.; Bormans, G. PET radioligands for *in vivo* visualization of neuroinflammation. *Curr. Pharm. Des.* **2014**, *20*, 5897-5913.
34. Han, S.; Thatte, J.; Buzard, D. J.; Jones, R. M. Therapeutic utility of cannabinoid receptor type 2 (CB₂) selective agonists. *J. Med. Chem.* **2013**, *56*, 8224-8256.
35. Dhopeshwarkar, A.; Mackie, K. CB₂ Cannabinoid receptors as a therapeutic target-what does the future hold? *Mol. Pharmacol.* **2014**, *86*, 430-437.
36. Pajouhesh, H.; Lenz, G. R. Medicinal Chemical Properties of Successful Central Nervous System Drugs. *NeuroRx*. **2005**, *2*, 541-553.
37. Soethoudt, M.; Grether, U.; Fingerle, J.; Grim, T. W.; Fezza, F.; de Petrocellis, L.; Ullmer, C.; Rothenhausler, B.; Perret, C.; van Gils, N.; Finlay, D.; MacDonald, C.; Chicca, A.; Gens, M. D.; Stuart, J.; de Vries, H.; Mastrangelo, N.; Xia, L.; Alachouzos, G.; Baggelaar, M. P.; Martella, A.; Mock, E. D.; Deng, H.; Heitman, L. H.; Connor, M. Cannabinoid CB₂ receptor ligand profiling reveals biased signalling and off-target activity. *Nat. Commun.* **2017**, *8*, 13958.
38. Rossi, F.; Bellini, G.; Luongo, L.; Manzo, I.; Tolone, S.; Tortora, C.; Bernardo, M. E.; Grandone, A.; Conforti, A.; Docimo, L.; Nobili, B.; Perrone, L.; Locatelli, F.; Maione, S.; Giudice, E. M. d. Cannabinoid Receptor 2 as Antiobesity Target: Inflammation, Fat Storage, and Browning Modulation. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 3469-3478.
39. Aso, E.; Ferrer, I. Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. *Front. Pharmacol.* **2014**, *5*, 37.
40. Rimplejeet, K.; Sneha, R. A.; Surjit, S. Endocannabinoid System: A Multi-Facet Therapeutic Target. *Curr. Clin. Pharmacol.* **2016**, *11*, 110-117.
41. Bow, E. W.; Rimoldi, J. M. The Structure-Function Relationships of Classical Cannabinoids: CB₁/CB₂ Modulation. *Perspect. Medicin. Chem.* **2016**, *8*, 17-39.
42. Yao, B. B.; Hsieh, G. C.; Frost, J. M.; Fan, Y.; Garrison, T. R.; Daza, A. V.; Grayson, G. K.; Zhu, C. Z.; Pai, M.; Chandran, P.; Salyers, A. K.; Wensink, E. J.; Honore, P.; Sullivan, J. P.; Dart, M. J.; Meyer, M. D. *In vitro* and *in vivo* characterization of A-796260: a selective cannabinoid CB₂ receptor agonist exhibiting analgesic activity in rodent pain models. *Brit. J. Pharmacol.* **2008**, *153*, 390-401.
43. D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M. Conformationally restrained analogs of pravadoline: nanomolar potent, enantioselective, (aminoalkyl)indole agonists of the cannabinoid receptor. *J. Med. Chem.* **1992**, *35*, 124-135.
44. Aung, M. M.; Griffin, G.; Huffman, J. W.; Wu, M.-J.; Keel, C.; Yang, B.; Showalter, V. M.; Abood, M. E.; Martin, B. R. Influence of the *N*-1 alkyl chain length of cannabimimetic indoles upon CB₁ and CB₂ receptor binding. *Drug Alcohol Depend.* **2000**, *60*, 133-140.
45. Eissenstat, M. A.; Bell, M. R.; D'Ambra, T. E.; Alexander, E. J.; Daum, S. J.; Ackerman, J. H.; Gruett, M. D.; Kumar, V.; Estep, K. G. Aminoalkylindoles: structure-activity relationships of novel cannabinoid mimetics. *J. Med. Chem.* **1995**, *38*, 3094-3105.
46. Zhang, M.-Z.; Chen, Q.; Yang, G.-F. A review on recent developments of indole-containing antiviral agents. *Eur. J. Med. Chem.* **2015**, *89*, 421-441.
47. Pasquini, S.; Mugnaini, C.; Ligresti, A.; Tafi, A.; Brogi, S.; Falciani, C.; Pedani, V.; Pesco, N.; Guida, F.; Luongo, L.; Varani, K.; Borea, P. A.; Maione, S.; Di Marzo, V.; Corelli, F. Design, synthesis, and pharmacological characterization of indol-3-ylacetamides, indol-3-ylacetamides, and indol-3-ylcarboxamides: potent and selective CB₂ cannabinoid receptor inverse agonists. *J. Med. Chem.* **2012**, *55*, 5391-5402.
48. Iwamura, H.; Suzuki, H.; Ueda, Y.; Kaya, T.; Inaba, T. *In vitro* and *in vivo* pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB₂ Receptor. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 420-425.
49. Evens, N.; Muccioli, G. G.; Houbrechts, N.; Lambert, D. M.; Verbruggen, A. M.; Van Laere, K.; Bormans, G. M. Synthesis and biological evaluation of carbon-11- and fluorine-18-labeled 2-oxoquinoline derivatives for type 2 cannabinoid receptor positron emission tomography imaging. *Nucl. Med. Biol.* **2009**, *36*, 455-465.
50. Mu, L.; Bieri, D.; Slavik, R.; Drandarov, K.; Muller, A.; Cermak, S.; Weber, M.; Schibli, R.; Kramer, S. D.; Ametamey, S. M. Radiolabeling and *in vitro/in vivo* evaluation of *N*-(1-adamantyl)-8-methoxy-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxamide as a PET probe for imaging cannabinoid type 2 receptor. *J. Neurochem.* **2013**, *126*, 616-624.
51. Mugnaini, C.; Brizzi, A.; Ligresti, A.; Allarà, M.; Lamponi, S.; Vacondio, F.; Silva, C.; Mor, M.; Di Marzo, V.; Corelli, F. Investigations on the 4-Quinolone-3-carboxylic Acid Motif. 7. Synthesis and Pharmacological Evaluation of 4-Quinolone-3-carboxamides and 4-Hydroxy-2-quinolone-3-carboxamides as High Affinity Cannabinoid Receptor 2 (CB₂R) Ligands with Improved Aqueous Solubility. *J. Med. Chem.* **2016**, *59*, 1052-1067.
52. Pasquini, S.; De Rosa, M.; Ligresti, A.; Mugnaini, C.; Brizzi, A.; Caradonna, N. P.; Cascio, M. G.; Bolognini, D.; Pertwee, R. G.; Di Marzo, V.; Corelli, F. Investigations on the 4-quinolone-3-carboxylic acid motif. 6. Synthesis and pharmacological evaluation of 7-substituted quinolone-3-carboxamide derivatives as high affinity ligands for cannabinoid receptors. *European journal of medicinal chemistry* **2012**, *58*, 30-43.

53. Pasquini, S.; Ligresti, A.; Mugnaini, C.; Semeraro, T.; Cicione, L.; De Rosa, M.; Guida, F.; Luongo, L.; De Chiaro, M.; Cascio, M. G.; Bolognini, D.; Marini, P.; Pertwee, R.; Maione, S.; Marzo, V. D.; Corelli, F. Investigations on the 4-Quinolone-3-carboxylic Acid Motif. 3. Synthesis, Structure–Affinity Relationships, and Pharmacological Characterization of 6-Substituted 4-Quinolone-3-carboxamides as Highly Selective Cannabinoid-2 Receptor Ligands. *J. Med. Chem.* **2010**, *53*, 5915-5928.
54. Turkman, N.; Shavrin, A.; Ivanov, R. A.; Rabinovich, B.; Volgin, A.; Gelovani, J. G.; Alauddin, M. M. Fluorinated cannabinoid CB₂ receptor ligands: synthesis and *in vitro* binding characteristics of 2-oxoquinoline derivatives. *Bioorg. Med. Chem.* **2011**, *19*, 5698-5707.
55. Slavik, R.; Grether, U.; Müller Herde, A.; Gobbi, L.; Fingerle, J.; Ullmer, C.; Krämer, S. D.; Schibli, R.; Mu, L.; Ametamey, S. M. Discovery of a high affinity and selective pyridine analog as a potential positron emission tomography imaging agent for cannabinoid type 2 receptor. *J. Med. Chem.* **2015**, *58*, 4266-4277.
56. Mu, L.; Slavik, R.; Müller, A.; Popaj, K.; Cermak, S.; Weber, M.; Schibli, R.; Kramer, S. D.; Ametamey, S. M. Synthesis and preliminary evaluation of a 2-oxoquinoline carboxylic acid derivative for PET imaging the cannabinoid type 2 receptor. *Pharmaceuticals* **2014**, *7*, 339-352.
57. Slavik, R.; Herde, A. M.; Bieri, D.; Weber, M.; Schibli, R.; Kramer, S. D.; Ametamey, S. M.; Mu, L. Synthesis, radiolabeling and evaluation of novel 4-oxo-quinoline derivatives as PET tracers for imaging cannabinoid type 2 receptor. *Eur. J. Med. Chem.* **2015**, *92c*, 554-564.
58. Slavik, R.; Müller Herde, A.; Haider, A.; Kramer, S. D.; Weber, M.; Schibli, R.; Ametamey, S. M.; Mu, L. Discovery of a fluorinated 4-oxo-quinoline derivative as a potential positron emission tomography radiotracer for imaging cannabinoid receptor type 2. *J. Neurochem.* **2016**.
59. Turkman, N.; Shavrin, A.; Paolillo, V.; Yeh, H. H.; Flores, L.; Soghomonian, S.; Rabinovich, B.; Volgin, A.; Gelovani, J.; Alauddin, M. Synthesis and preliminary evaluation of [¹⁸F]-labeled 2-oxoquinoline derivatives for PET imaging of cannabinoid CB₂ receptor. *Nucl. Med. Biol.* **2012**, *39*, 593-600.
60. Evens, N.; Vandeputte, C.; Coolen, C.; Janssen, P.; Sciote, R.; Baekelandt, V.; Verbruggen, A. M.; Debyser, Z.; Van Laere, K.; Bormans, G. M. Preclinical evaluation of [¹¹C]NE40, a type 2 cannabinoid receptor PET tracer. *Nucl. Med. Biol.* **2012**, *39*, 389-399.
61. Ahmad, R.; Koole, M.; Evens, N.; Serdons, K.; Verbruggen, A.; Bormans, G.; Van Laere, K. Whole-body biodistribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [¹¹C]NE40 in healthy subjects. *Mol. Imaging. Biol.* **2013**, *15*, 384-390.
62. Ahmad, R.; Postnov, A.; Bormans, G.; Versijpt, J.; Vandenbulcke, M.; Van Laere, K. Decreased *in vivo* availability of the cannabinoid type 2 receptor in Alzheimer's disease. *E. J. Nucl. Med. Mol. Imaging* **2016**, 1-9.
63. Osman, N. A.; Ligresti, A.; Klein, C. D.; Allarà, M.; Rabbito, A.; Di Marzo, V.; Abouzid, K. A.; Abadi, A. H. Discovery of novel tetrahydrobenzo[*b*]thiophene and pyrrole based scaffolds as potent and selective CB₂ receptor ligands: The structural elements controlling binding affinity, selectivity and functionality. *Eur. J. Med. Chem.* **2016**, *122*, 619-634.
64. Haider, A.; Müller Herde, A.; Slavik, R.; Weber, M.; Mugnaini, C.; Ligresti, A.; Schibli, R.; Mu, L.; Mensah Ametamey, S. Synthesis and Biological Evaluation of Thiophene-Based Cannabinoid Receptor Type 2 Radiotracers for PET Imaging. *Front. Neurosci.* **2016**, *10*.
65. Rühl, T.; Deuther-Conrad, W.; Fischer, S.; Günther, R.; Hennig, L.; Krautscheid, H.; Brust, P. Cannabinoid receptor type 2 (CB₂)-selective *N*-aryl-oxadiazolyl-propionamides: synthesis, radiolabelling, molecular modelling and biological evaluation. *Org. Med. Chem. Lett.* **2012**, *2*, 32-32.
66. Lueg, C.; Schepmann, D.; Gunther, R.; Brust, P.; Wunsch, B. Development of fluorinated CB₂ receptor agonists for PET studies. *Bioorg. Med. Chem.* **2013**, *21*, 7481-7498.
67. Teodoro, R.; Moldovan, R.-P.; Lueg, C.; Günther, R.; Donat, C. K.; Ludwig, F.-A.; Fischer, S.; Deuther-Conrad, W.; Wünsch, B.; Brust, P. Radiofluorination and biological evaluation of *N*-aryl-oxadiazolyl-propionamides as potential radioligands for PET imaging of cannabinoid CB₂ receptors. *Org. Med. Chem. Lett.* **2013**, *3*, 1-18.
68. Moldovan, R.-P.; Teodoro, R.; Gao, Y.; Deuther-Conrad, W.; Kranz, M.; Wang, Y.; Kuwabara, H.; Nakano, M.; Valentine, H.; Fischer, S.; Pomper, M. G.; Wong, D. F.; Dannals, R. F.; Brust, P.; Horti, A. G. Development of a high-affinity PET radioligand for imaging cannabinoid subtype 2 receptor. *J. Med. Chem.* **2016**, *59*, 7840-7855.
69. Moldovan, R.-P.; Deuther-Conrad, W.; Horti, A.; Brust, P. Synthesis and Preliminary Biological Evaluation of Indol-3-yl-oxoacetamides as Potent Cannabinoid Receptor Type 2 Ligands. *Molecules* **2017**, *22*, 77.
70. Lange, J. H. M.; van der Neut, M. A. W.; Wals, H. C.; Kuil, G. D.; Borst, A. J. M.; Mulder, A.; den Hartog, A. P.; Zilaout, H.; Goutier, W.; van Stuijvenberg, H. H.; van Vliet, B. J. Synthesis and SAR of novel imidazoles as potent and selective cannabinoid CB₂ receptor antagonists with high binding efficiencies. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1084-1089.
71. Yao, B. B.; Hsieh, G.; Daza, A. V.; Fan, Y.; Grayson, G. K.; Garrison, T. R.; El Kouhen, O.; Hooker, B. A.; Pai, M.; Wensink, E. J.; Salyers, A. K.; Chandran, P.; Zhu, C. Z.; Zhong, C.; Ryther, K.; Gallagher, M. E.; Chin, C. L.; Tovcimak, A. E.; Hradil, V. P.; Fox, G. B.; Dart, M. J.; Honore, P.; Meyer, M. D. Characterization of a cannabinoid CB₂ receptor-selective agonist, A-836339 [2,2,3,3-tetramethyl-cyclopropanecarboxylic acid [3-(2-methoxy-ethyl)-4,5-dimethyl-3H-thiazol-(2Z)-ylidene]-amide], using *in vitro* pharmacological assays, *in vivo* pain models, and pharmacological magnetic resonance imaging. *J. Pharmacol. Exp. Ther.* **2009**, *328*, 141-151.
72. Mella-Raipan, J.; Hernandez-Pino, S.; Morales-Verdejo, C.; Pessoa-Mahana, D. 3D-QSAR/CoMFA-based structure-affinity/selectivity relationships of aminoalkylindoles in the cannabinoid CB₁ and CB₂ receptors. *Molecules* **2014**, *19*, 2842-2861.
73. B Kevin Park; Neil R Kitteringham, a.; O'Neill, P. M. Metabolism of fluorine-containing drugs. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443-470.
74. Kuchar, M.; Mamat, C. Methods to increase the metabolic stability of ¹⁸F-radiotracers. *Molecules* **2015**, *20*, 16186-16220.
75. Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. Reactifs de couplage peptidique I (1) - l'hexafluorophosphate de benzotriazolyl *N*-oxytrisdiméthylamino phosphonium (B.O.P.). *Tetrahedron Lett.* **1975**, *16*, 1219-1222.
76. Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *40*, 574-578.
77. Brust, P.; van den Hoff, J.; Steinbach, J. Development of [¹⁸F]-labeled radiotracers for neuroreceptor imaging with positron emission tomography. *Neurosci. Bull.* **2014**, *30*, 777-811.
78. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl *C-N* bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.
79. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New *N*- and *O*-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933-2936.
80. Williamson, A. XLV. Theory of aetherification. *Philosophical Magazine Series 3* **1850**, *37*, 350-356.
81. Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. Aluminum-amine complexes for the conversion of carboxylic esters to amides. Application to the synthesis of LTD4 antagonist MK-0679. *J. Org. Chem.* **1994**, *59*, 1231-1233.