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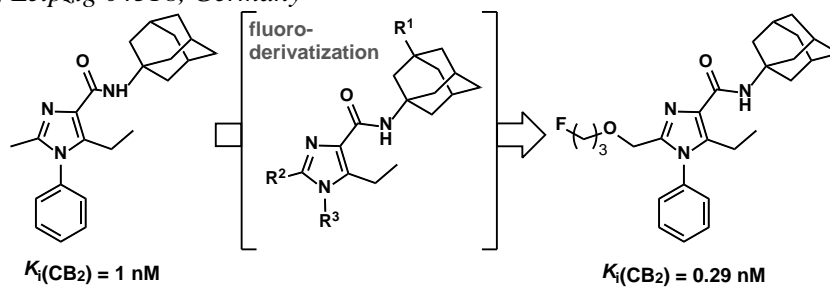
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## Graphical Abstract

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

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## Abstract:

CB<sub>2</sub> 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 CB<sub>2</sub> 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 CB<sub>2</sub> 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 ( $\text{CB}_1/\text{CB}_2 > \text{xx}$ ), CB<sub>2</sub> ligand discovered so far, eligible for the development of an [<sup>18</sup>F]-PET radiotracer.

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

## 1. Introduction

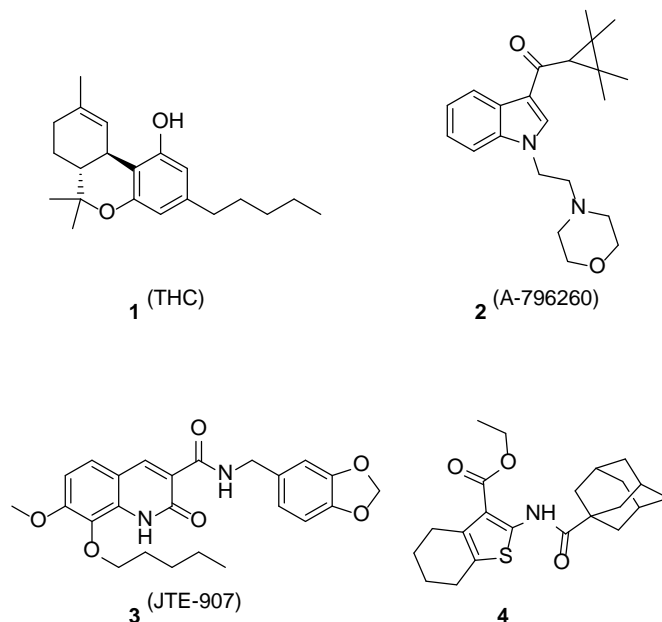
*Cannabis sativa* and its extracts have been used for centuries as therapeutic agent and recreational use.<sup>1-3</sup> The isolation and structure elucidation of the main psychoactive constituent, (–)-*trans*- $\Delta^9$ -tetrahydrocannabinol (THC) by Mechoulam and co-workers<sup>4</sup> led to the identification of the endocannabinoid system which is formed out of the cannabinoid receptors and their modulatory lipids.<sup>5</sup> Two types of cannabinoid receptors have been well characterized so far namely cannabinoid receptors type 1 (CB<sub>1</sub>)<sup>6</sup> and cannabinoid receptors type 2 (CB<sub>2</sub>)<sup>7</sup>. Further receptors are proposed to belong to the cannabinoid family like GPR55 and GPR18 however the research on this subtypes is at early stage.<sup>8, 9</sup> 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 CB<sub>1</sub> receptors are located at the neurons and their activation is responsible for the psychotropic effect of the THC.<sup>10</sup> Recently, the crystal structure of the CB<sub>1</sub> receptors has been reported facilitating future molecular modeling based SAR drug discovery and structure optimization studies for this receptor subtype.<sup>11</sup> On the contrary, the CB<sub>2</sub> receptors are mainly located peripheral, non-psychotropic,<sup>13</sup> and are involved in regulation of several diseases related to immune system,<sup>14, 15</sup> inflammation, neuropathic pain<sup>13</sup> and cancer.<sup>16-19</sup> CB<sub>2</sub> receptors have also been identified in the brain but at low levels.<sup>20-22</sup> It is unclear which physiological role does the CB<sub>2</sub> receptor play in healthy brain however it has been shown to be involved in basic neuronal transmission.<sup>23, 24</sup> Studies of the signaling pathways in mouse brain cortex, showed distinct activation of G<sub>α</sub> protein subunit when using various CB<sub>2</sub> ligands suggesting different binding mode.<sup>25, 26</sup> The CB<sub>2</sub> receptors are able to form heteromers with other receptors including CB<sub>1</sub> (mainly post-synaptic) leading to new functionalities and therefore new signaling paths.<sup>27</sup> In pathological conditions, the up-regulation of the CB<sub>2</sub> receptors has been reported in association with inflammatory processes, neurodegeneration<sup>28</sup> and apoptosis in several cancer cell lines.<sup>29, 30</sup> Moreover, the neuroprotective role of the CB<sub>2</sub> receptors was demonstrated upon induced mild traumatic brain injury by using a CB<sub>2</sub> antagonist.<sup>31</sup>

In the past decades the development of selective CB<sub>2</sub> receptor ligands was topic of countless publications.<sup>10, 32-35</sup> 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.<sup>27</sup> The predominantly disfavored pharmacological properties of CB<sub>2</sub> 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.<sup>36</sup> Profiling studies were performed for the identification of CB<sub>2</sub> receptors ligands with the best molecular pharmacology for studying the CB<sub>2</sub> receptors.<sup>37</sup> As a result, despite the promising therapeutic and diagnostic potential of targeting CB<sub>2</sub> receptors,<sup>28, 35, 38-40</sup> the development of ligands with enhanced neuropharmacological properties remains a challenging task.<sup>41</sup>

The medicinal chemistry of the CB<sub>2</sub> receptor ligands is summarized in several reviews and compresses various structural motifs.<sup>28, 35, 38-40</sup> Beside the classical THC (**1**) derived cannabinoid ligands,<sup>41</sup> *N*-alkylindole-3-carboxamide is one of the most popular building block of cannabinoid receptor ligands and efforts to develop CB<sub>2</sub> receptor selective proved to be fruitful as proven by compound **2** (A-796260)<sup>42</sup> in Figure 1.<sup>43-47</sup> The quinoline is also a widely used scaffold in the medicinal chemistry of CB<sub>2</sub> receptors and representatively

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exemplified in Figure 1 by compound **3** (JTE-907).<sup>48-54</sup> Unlike indoles, the quinoline type ligands generally possess high selectivity towards the CB<sub>2</sub> receptors. In the past years, several [<sup>11</sup>C] and [<sup>18</sup>F] labeled radioligands have been developed for this scaffold<sup>50, 55-59</sup> including [<sup>11</sup>C]NE40, the first and only CB<sub>2</sub> radioligand which has been tested in human subject to date.<sup>60-62</sup> More recently, a novel series of pyrrole and thiophene derived compounds has been reported, some of which with high affinity and selectivity for the CB<sub>2</sub> receptors as exemplified by compound **4** ( $K_i(\text{CB}_2) = 2.15 \text{ nM}$ ).<sup>63</sup> Consequently, the imaging properties of an <sup>11</sup>C-labeled analog of **4** have been investigated by *in vitro* and *in vivo* autoradiography and PET studies by Haider and co-workers.<sup>64</sup>



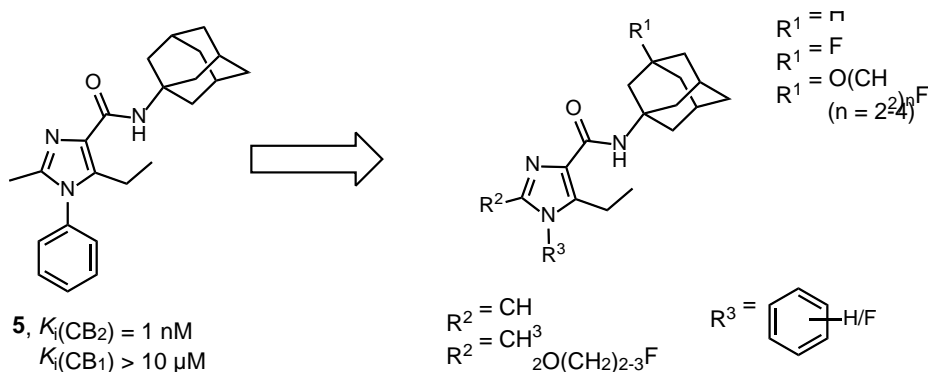
**Figure 1.** The structure of THC and three representative CB<sub>2</sub> ligands.<sup>41, 48, 42, 63</sup>

Our previous efforts to develop fluorinated CB<sub>2</sub> receptor (radio)ligands used oxazoles, thiazole and indole as scaffolds.<sup>65-69</sup> Recently, we reported the development of a highly affine and selective [<sup>18</sup>F]-labeled CB<sub>2</sub> 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,<sup>68</sup> 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).<sup>70</sup> Compound **5** was reported by Lange and co-workers<sup>70</sup> as a result of a thorough SAR study and its suitable pharmacological properties have been highlighted (e.g.: CB<sub>1</sub>/CB<sub>2</sub> >10000, MW = 349, LogP<sub>HPLC</sub> = 3.5, PSA = 47)<sup>36</sup>.

## 2. Results and discussion

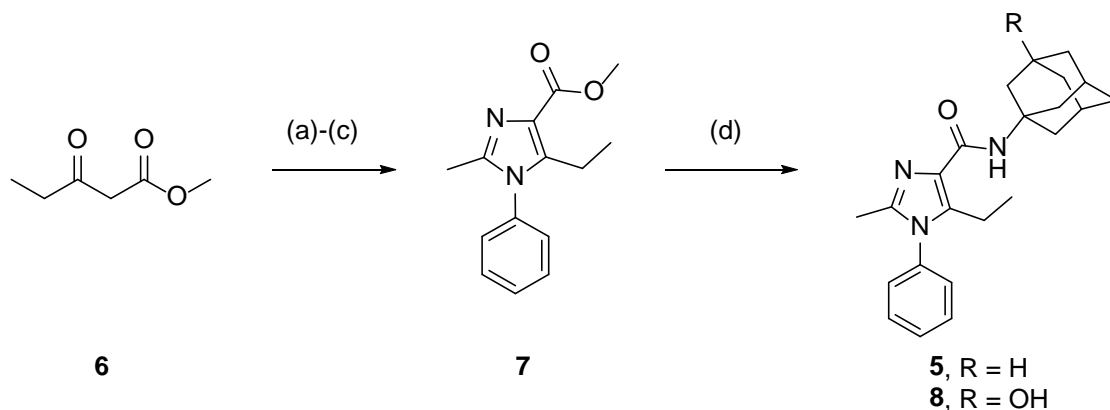
### 2.1. Chemistry

The aim of the present work is the synthesis of a fluorinated CB<sub>2</sub> ligand based on the structure of compound **5** (Figure 2) as preliminary work for the development of a novel <sup>18</sup>F-labeled radiotracer for imaging of the cerebral CB<sub>2</sub> receptors with PET. For this, its (fluoro)derivatization was questioned. The newly synthesized derivatives should retain the high CB<sub>2</sub> affinity and selectivity of the lead compound **5** and should contain a fluorine atom at a position which allows a facile incorporation of the <sup>18</sup>F. Previous SAR studies performed on various CB<sub>2</sub> ligands,<sup>65</sup> including the work which led to the identification of **5**<sup>70</sup> highlighted the need of a lipophilic (eg. tetramethylcyclopropyl, myrtaanyl or adamantyl)<sup>47, 52, 71</sup> subunit as pharmacophore.<sup>72</sup> However, recent studies showed the possibility to hydroxylate adamantane 3-position without loss of affinity towards the CB<sub>2</sub> receptors<sup>57, 64</sup> 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.<sup>73, 74</sup> In parallel we decided to introduce fluorine also at the imidazole-2-position (Figure 2) and check the influence on the CB<sub>2</sub> receptor binding affinity.

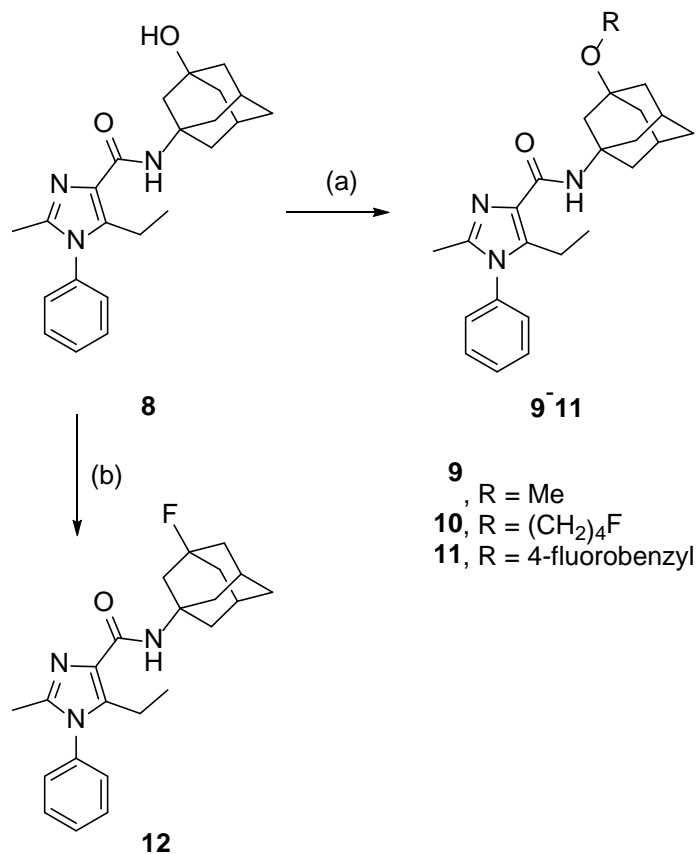


**Figure 2.** Lead compound **5** and conceptual design of fluorinated derivatives.

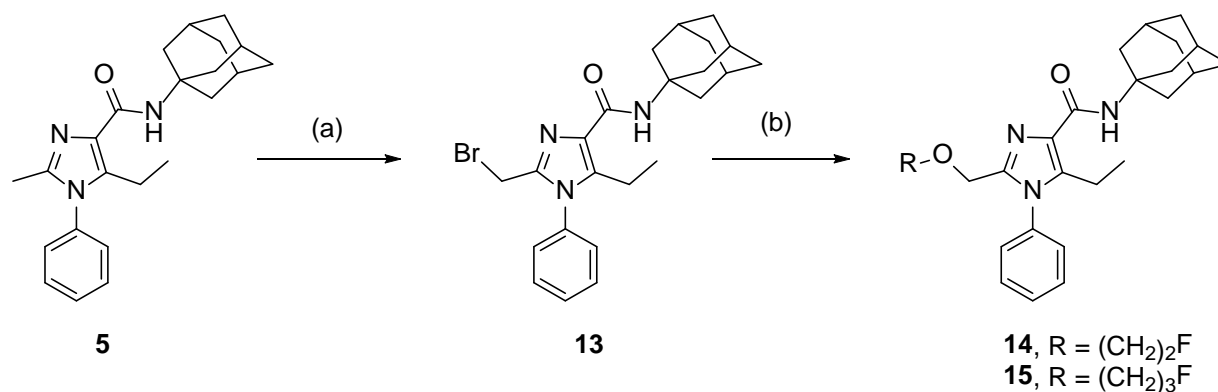
The synthesis of the lead compound **5** and its hydroxyadamantane derivative **8** was performed as described and depicted in Scheme 1 starting from the commercially available methyl 3-oxopentanoate (**6**).<sup>70</sup> Nitration of **6** gave the respective oxime which was further acetylated with acetic anhydride under catalytic (Pd/C-H<sub>2</sub>) 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)<sup>75</sup> mediated amide bond formation with adamantine 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-fluoro-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.<sup>58, 76</sup> At this point it is worthwhile to be mentioned that a "classical" (S<sub>N</sub>2) radiofluorination procedure would not be applicable for the radiosynthesis of [<sup>18</sup>F]-**12** and other methods would need to be developed.<sup>77</sup>



**Scheme 1.** Reagents and conditions: (a) NaNO<sub>2</sub>, AcOH/H<sub>2</sub>O, 0 °C to rt., 2 h (77%); (b) H<sub>2</sub>, Pd/C, Ac<sub>2</sub>O, AcOH 1 atm., rt., 20 h (quantitative); (c) aniline, TFA, butyronitrile, 117 °C., 1.5 h (24%); (d) i. LiOH, H<sub>2</sub>O/MeOH 70 °C, 5 h; ii. 1M HCl, rt.; iii. 1-adamantylamine for **5** and 3-amino-1-hydroxyadamantane for **8**, BOP, Et<sub>3</sub>N, DCM (30% over two steps).<sup>70</sup>

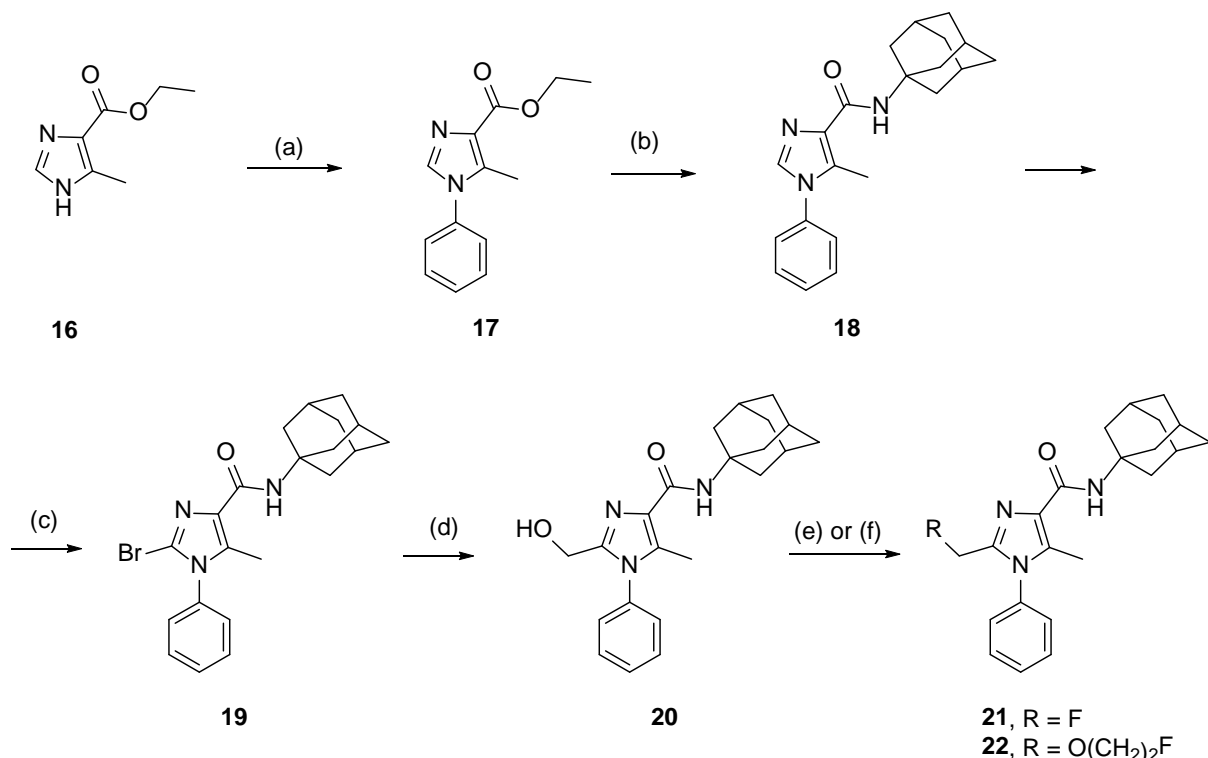


**Scheme 2.** Reagents and conditions: (a) RX, NaH, DMF (**9**, 14%; **10**, 19%; **11**, 42%); (b) DAST, DCM, -78 °C to rt., (>90%).



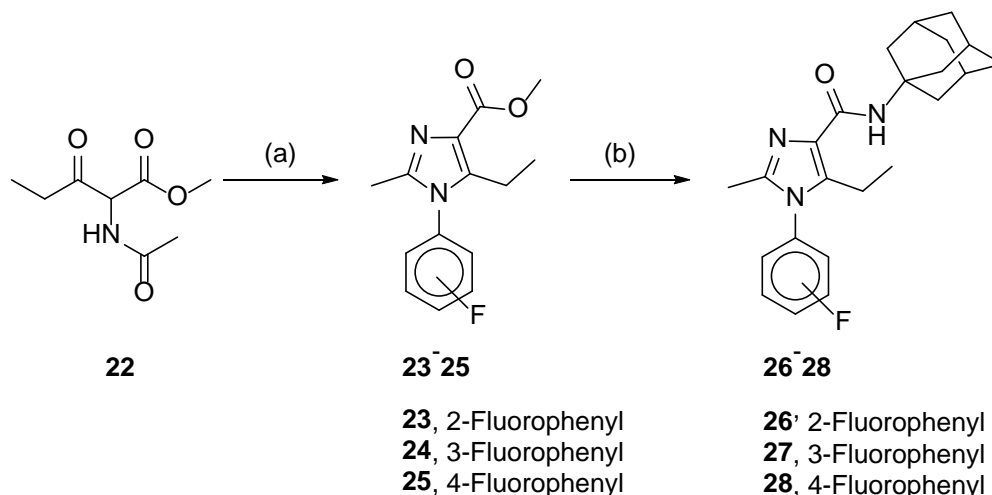
**Scheme 3.** Reagents and conditions: (a) NBS, AIBN, CCl<sub>4</sub>, 77 °C, 6 h (32%); (b) R-OH, Cs<sub>2</sub>CO<sub>3</sub>, MeCN, 40 °C, 60 min (>90%).

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 CB<sub>2</sub> 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 Cs<sub>2</sub>CO<sub>3</sub>, 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<sup>78, 79</sup> 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 NaBH<sub>4</sub> 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 synthesis<sup>80</sup> into the fluoroethoxy derivative **22**.



**Scheme 4.** Reagents and conditions: (a) C<sub>6</sub>H<sub>7</sub>BO<sub>2</sub>, CuI (cat.) EtOH/H<sub>2</sub>O, 85 °C, 60 h (**17** 24%, regioisomer 34%); (b) 1-adamantylamine, AlMe<sub>3</sub>, 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. NaBH<sub>4</sub>, 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 CB<sub>1</sub>/CB<sub>2</sub> 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 AlMe<sub>3</sub><sup>81</sup> 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, AlMe<sub>3</sub>, DCM, 35 °C, 22 h (**26**, 31 % yield; **27**, 47% yield; **28**, 33% yield).

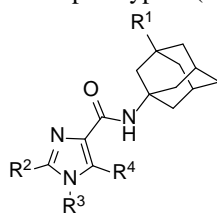
## 2.2. *In vitro* binding affinity

All the herein reported compounds were tested *in vitro* for binding affinity towards the CB<sub>2</sub> and CB<sub>1</sub> receptors according to a protocol well established in our labs.<sup>65</sup> For the CB<sub>2</sub> assay, [<sup>3</sup>H]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 CB<sub>2</sub> (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 CB<sub>1</sub> binding affinity determinations were performed with hCB<sub>1</sub>-CHO obtained from Euroscreen, Gosselies, Belgium and [<sup>3</sup>H]CP55.40 as comparative radioligand.<sup>65</sup>

As shown in Table 1 the hydroxylation at the adamantane subunit led to a drastic drop of affinity towards CB<sub>2</sub> 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 CB<sub>2</sub> 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 CB<sub>2</sub> affinity ( $K_i(\text{CB}_2) < 10$  nM) and CB<sub>1</sub>/CB<sub>2</sub> selectivity (>1000) revealing a moderate influence of the phenyl ring on the ligand binding mode to the CB<sub>2</sub> receptors. Investigations performed at the imidazole-2-position expelled a drastic CB<sub>2</sub> 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 CB<sub>2</sub> 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 CB<sub>2</sub> receptors. It is worthwhile to indicate that for all the herein reported derivatives the CB<sub>1</sub> receptor affinity remained constantly low (> 1μM).

**Table 1.** Binding affinity ( $K_i$ ) at the human cannabinoid receptor type 2 (CB<sub>2</sub>) receptor.



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

10	O(CH <sub>2</sub> ) <sub>4</sub> 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 <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> F	Phenyl	Et	1.1 ± 0.2	7600
15	H	CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub> F	Phenyl	Et	0.29 ± 0.02	NA
18	H	H	Phenyl	Me	201 ± 16.5	>10000
21	H	CH <sub>2</sub> F	Phenyl	Me	4.16 ± 3.5	5000
22	H	CH <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> F	Phenyl	Me	3.45 ± 0.6	9200

<sup>a</sup>Values are means ± standard deviations of two to three experiments run in triplicate.

<sup>b</sup>K<sub>i</sub> of compound **5** as reported in <sup>70</sup>.

### 3. Conclusion

In summary, a novel series of CB<sub>2</sub> 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 CB<sub>2</sub> 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 CB<sub>2</sub> binding affinity, however the introduction of an <sup>18</sup>F atom at this position might be challenging due to the unfavorable electron density for an S<sub>N</sub>2 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 CB<sub>1</sub> receptor subtype (CB<sub>1</sub>/CB<sub>2</sub>>1000). We are currently in the development process of an <sup>18</sup>F 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). <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded on VARIAN "MERCURY plus" (300 MHz for <sup>1</sup>H NMR, 75 MHz for <sup>13</sup>C NMR, 282 MHz for <sup>19</sup>F NMR) and VARIAN "MERCURY plus" and BRUKER DRX-400 (400 MHz for <sup>1</sup>H NMR, 100 MHz for <sup>13</sup>C NMR, 377 MHz for <sup>19</sup>F 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. K<sub>2</sub>CO<sub>3</sub> 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), Et<sub>3</sub>N (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 NaHCO<sub>3</sub> 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 MgSO<sub>4</sub> 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 H<sub>2</sub>O (2 mL), followed by 15 mL aq. saturated sol. NaHCO<sub>3</sub> 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 MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica.

#### 4.1.4. General procedure 4

Al(CH<sub>3</sub>)<sub>3</sub> (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. NaHCO<sub>3</sub> 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<sub>f</sub> = 0.16 (EA); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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 C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>.

#### 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<sub>f</sub> = 0.36 (EA); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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 C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>.

#### 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<sub>f</sub> = 0.67 (EA); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 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 C<sub>27</sub>H<sub>36</sub>FN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>.

#### 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<sub>f</sub> = 0.55 (EA/PE 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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 C<sub>30</sub>H<sub>35</sub>FN<sub>3</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup>.

#### 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 H<sub>2</sub>O 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<sub>f</sub> = 0.12 (EA/PE 1:4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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 C<sub>23</sub>H<sub>29</sub>FN<sub>3</sub>O<sup>+</sup> [M+H]<sup>+</sup>.

#### 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<sub>f</sub> = 0.63 (EA/PE 1:1); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): 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 C<sub>23</sub>H<sub>28</sub>FN<sub>3</sub>O [M+H]<sup>+</sup>.

#### 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<sub>f</sub> = 0.63 (EA/PE 1:1); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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  $\text{CCl}_4$  at room temperature and the mixture was refluxed for 6 h. Upon cooling,  $\text{NaHCO}_3$  sat. aq. sol. (10 mL) was added and the solution was extracted with DCM (2x10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , 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,  $\text{CDCl}_3$ ):  $\delta$  (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  $\mu\text{L}$ , 0.2 mmol, 2 equiv) was added to a solution of **13** (44 mg, 0.1 mmol, 1 equiv) and  $\text{Cs}_2\text{CO}_3$  (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  $\text{NaHCO}_3$  sat. aq. sol. (5 mL) and the resulting mixture was extracted with DCM (2x5 mL). The combined organics were dried over  $\text{Na}_2\text{SO}_4$  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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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  $\mu\text{L}$ , 0.2 mmol, 2 equiv) was added to a solution of **13** (44 mg, 0.1 mmol, 1 equiv) and  $\text{Cs}_2\text{CO}_3$  (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  $\text{NaHCO}_3$  sat. aq. sol. (5 mL) and the resulting mixture was extracted with DCM (2x5 mL). The combined organics were dried over  $\text{Na}_2\text{SO}_4$  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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ )  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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.  $\text{NaHCO}_3$ -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,  $\text{CDCl}_3$ ):  $\delta$  (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,  $\text{CDCl}_3$ ):  $\delta$  (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  $\mu\text{L}$ , 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  $\text{NH}_4\text{Cl}$  (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  $\text{Na}_2\text{SO}_4$  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%).

NaBH<sub>4</sub> (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 NH<sub>4</sub>Cl (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<sub>f</sub> = 0.3 (EA/PE 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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. NaHCO<sub>3</sub> 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<sub>f</sub> = 0.15 (EA/PE 1:4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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 C<sub>22</sub>H<sub>26</sub>FN<sub>3</sub>NaO<sup>+</sup> [M+Na]<sup>+</sup>.

#### 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<sub>f</sub> = 0.65 (EA/PE 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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 C<sub>24</sub>H<sub>31</sub>FN<sub>3</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup>.

## 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.

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## Supplementary Materials

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

## References and notes

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