Optimization of pharmacokinetic properties by modification of a carbazole-based cannabinoid receptor subtype 2 (CB_2) ligand

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Abstract

Recently, the development of the fluorinated PET tracer [^{18}F]**1a** for imaging of CB_2 receptors in the central nervous system was reported. [^{18}F]**1a** showed high CB_2 affinity and selectivity over the CB_1 subtype, but rapid biotransformation in mice. In addition to the amide hydrolysis, oxidative *N*-dealkylation and carbazole oxidation were postulated as main metabolic pathways. Based on these results, novel carbazole derivatives with additional 6-substituents (**23a**, **24a**), modified hydrogenation state (**26a**) and enlarged fluoroalkyl substituent (**13a**, **13b**) were synthesized and pharmacologically evaluated. The key step in the synthesis of substituted carbazoles **23a**, **24a** and **26a** was a Fischer indole synthesis. Nucleophilic substitution of tosylated lactate **5** by carbazole anion

provided the fluoroisopropyl derivatives **13a** and **13b**. Partial hydrogenation of the aromatic carbazole system (**26a**) was not tolerated by the CB_2 receptor. A methylsulfonyl moiety in 6-position (**24a**) led to considerably reduced CB_2 affinity, whereas a 6-methoxy moiety (**23a**) was well tolerated. An additional methyl moiety in the fluoroethyl side chain of **1a** resulted in fluoroisopropyl derivatives **13** with unchanged high CB_2 affinity and CB_2 : CB_1 selectivity. Compared with the fluoroethyl derivative **1a**, the carbazole *N*-atom of the fluoroisopropyl derivative **13a** ($K_i(CB_2)$ = 2.9 nM) is better shielded against the attack of CYP enzymes as formation of N-oxides was not observed and *N*-dealkylation took place to a less amount.

Key words

Cannabinoid CB_2 receptor ligands; carbazole; fluoroisopropyl side chain; Fischer indole synthesis; structure affinity relationships, selectivity; metabolic stability; identification of metabolites, PET

1. Introduction

The first medical use of *Cannabis sativa* L. for the treatment of rheumatic pain, constipation and malaria, as well as the toxic effects, were reported in one of the oldest pharmacopeia, the *pen-ts'ao chin*g [1]. It is assumed that this book was written in the first century A.D. based on oral traditions from the years around 2700 B.C. [2]. However, cannabis did not find a broad medical application in the western world until the midst 19th century, as reflected by the first medical conference on Cannabis in 1860, organized by the Ohio State Medical Society. The preliminary peak of the medical use was reached at the end of the 19th century, however, in the first decades

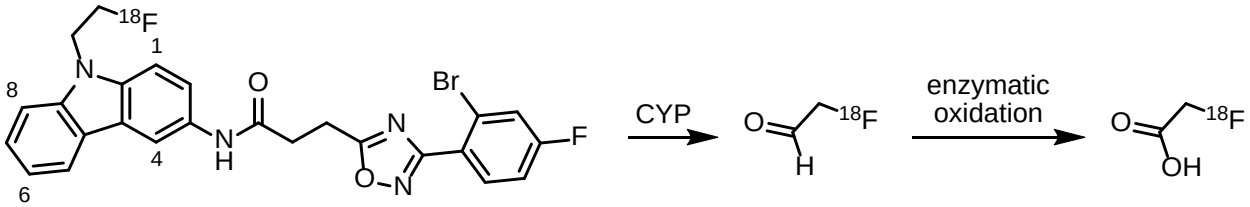
of the 20th century, the use decreased again due to political reasons and the development of new synthetic drugs such as acetylsalicylic acid and barbiturates [2].

In 1964, the isolation and characterization of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) stimulated the discovery of the endogenous cannabinoid (endocannabinoid) system in the following decades. After cloning of the cannabinoid receptor subtypes CB_1 [3] and CB_2 [4] in the early 1990s, it was possible to develop selective compounds for CB_1 and CB_2 receptors, respectively. Both CB receptor subtypes belong to the class of $G_{i/o}$ protein-coupled receptors (GPCR) and show an amino acid sequence homology of 44 % [5], but differ primarily in their expression pattern. The CB_1 receptor is one of the most common GPCR of the central nervous system (CNS) and is present in all four brain regions (cerebrum, diencephalon, cerebellum, brainstem) [6]. In these regions the CB_1 receptor plays an important modulating role for the release of other excitatory and inhibitory neurotransmitters (e.g. GABA) [7], especially in the synapses of neurons. The psychoactive side effects of THC, such as dysphoria and concentration disorders, are also attributed to activation of the CB_1 receptor.

In contrast, the expression of the CB_2 receptor in the CNS under normal conditions is rather low. However, the expression of the CB_2 receptor can be increased up to 100-fold under inflammatory conditions (neuroinflammation) [8]. In many test systems, it could be shown that activation of the CB_2 receptor reduces the release of numerous inflammatory mediators, such as IL-1, IL-6 and tumor necrosis factor α (TNF α), as well as increases the release of anti-inflammatory factors (e.g. IL-10), thus resulting in an overall anti-inflammatory effect [9]. Therefore, the CB_2 receptor is regarded as a potential target for drugs directed for the treatement of many neuroimmunological and neurodegenerative diseases including depression, schizophrenia, Alzheimer's

disease, multiple sclerosis, amyotrophic lateral sclerosis, down syndrome, and Huntington's disease [9],[10],[11],[12],[13].

The positron emission tomography (PET) is an imaging modality that enables visualization and quantification of receptors under healthy and pathological conditions. The site of bound radiochemically labeled compound is visualized *in vivo* by the simultaneous detection of two gamma photons. The preferably used radioisotope is ^{18}F, which has a half-life of 110 min compared to ^{11}C with a half-life of 20 min [14].



[^{18}F]**1a**
K_i (hCB$_2$) = 2.3 nM
K_i (hCB$_1$) > 1 µM

[^{18}F]**2**

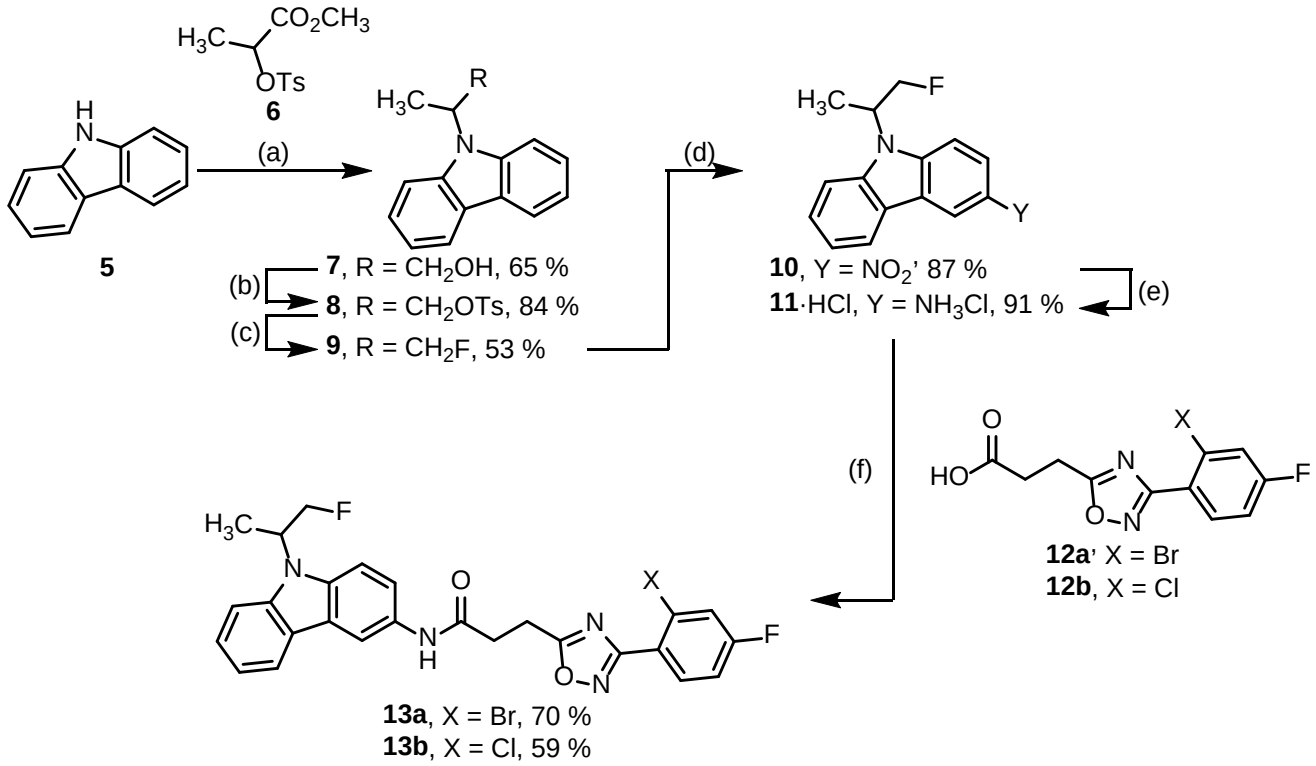
[^{18}F]**3**

Figure 1. Postulated biotransformation of [^{18}F]**1a**.

In 2013, we described the synthesis, radiosynthesis and biological evaluation of the CB_2 receptor PET tracer [^{18}F]**1a** containing a (phenyl-oxadiazolyl)propionamide scaffold [15],[16]. The ligand showed a high CB_2 affinity (K_i (hCB_2) = 2.3 nM), excellent selectivity over the CB_1 receptor (ca. 500-fold), penetration into the brain and low tendency to loose [^{18}F]fluoride *in vivo*. On the other hand, **1a** showed some disadvantages like a rapid metabolism and relatively high lipophilicity (log$D_{7.4}$ = 3.82 – 4.21, recorded by HPLC). During *in vivo* experiments, a very polar radiometabolite was detected by radio-HPLC. It was postulated that [^{18}F]fluoroacetic acid [^{18}F]**3** was formed by oxidative cleavage of the [^{18}F]fluoroethyl moiety at the carbazole system (Figure 1). In this work, we aim to synthesize fluorinated CB_2 receptor ligands with a sterically more demanding fluoroisopropyl residue in 9-position of the carbazole system to inhibit oxidative degradation by CYP enzymes. Moreover, different substituents in 6-position

of the carbazole scaffold of **1a** should be introduced to inhibit metabolic oxidation at 6-position, reduce the lipophilicity and modulate the electron density in the aromatic system.

2. Synthesis

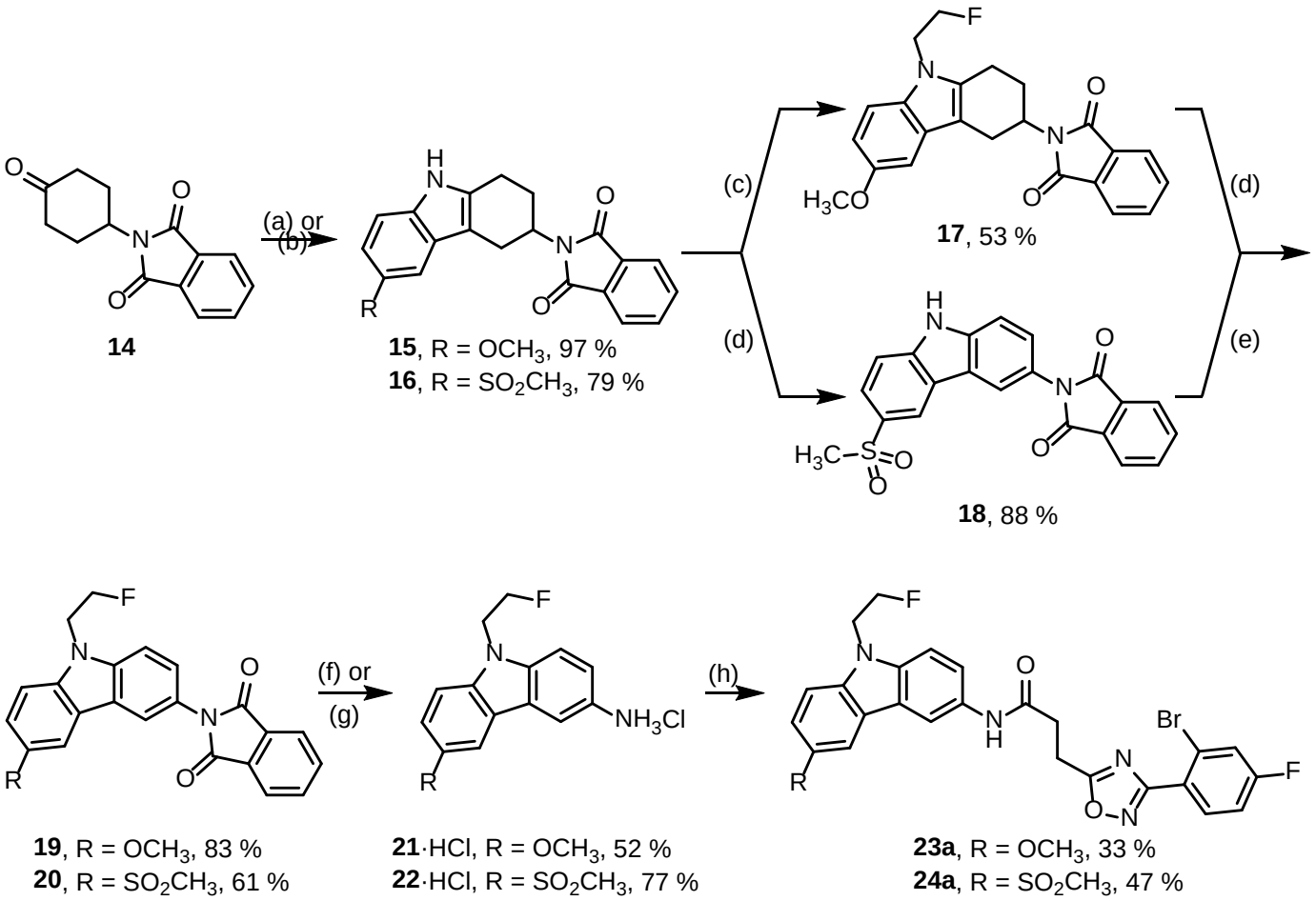


Scheme 1. Reagents and reaction conditions: (a) 1. NaH, DMF, rt → 110 °C; 2. $LiAlH_4$, THF, rt → reflux. (b) tosyl chloride, NEt_3, pyridine, CH_2Cl_2, rt. (c) TBAF·$3H_2O$, 60 °C. (d) HNO_3 65 %, CH_2Cl_2, 0 °C. (e) 1. H_2, Pd/C 10 %, THF, 1 bar, rt; 2. HCl in Et_2O. (f) COMU®, EtN*i*Pr_2, THF, rt.

For the synthesis of CB_2 ligands **13** with fluoroisopropyl side chain racemic, methyl lactate **4** was tosylated [17] and the product **6** was reacted with deprotonated carbazole **5**. Subsequent reduction of the ester with $LiAlH_4$ afforded alcohol **7** in 65 % yield. Treatment of **7** with tosyl chloride under basic conditions yielded tosylate **8**, which was reacted with TBAF·$3H_2O$ in a nucleophilic substitution under solvent-free conditions. Fluoroisopropylcarbazole **9** was nitrated with nitric acid 65 % at 0 °C. Hydrogenation

of **10** catalyzed by Pd/C provided the primary aromatic amine **11**, which was precipitated as HCl salt **11**·HCl. In the last step, carbazolamine·HCl **11**·HCl was acylated with carboxylic acids **12a** and **12b** in the presence of COMU® to yield amides **13a** and **13b** (Scheme 1). The 1,2,4-oxadiazol building blocks **11** and **12** were obtained by NH_2OH addition to 2-bromo- and 2-chloro-4-fluorobenzonitrile followed by acylation with succinic anhydride [15], [18], [19].

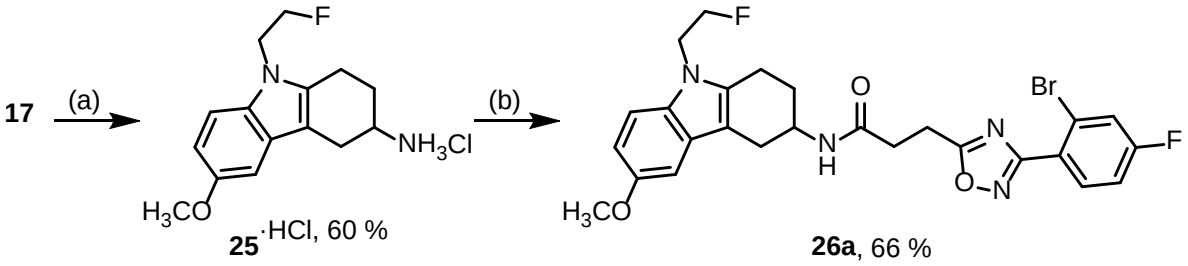
The Craig plot [20] was used for the selection of suitable substituents in 6-position. A methoxy group was selected as an electron-donating substituent and a methylsulfonyl moiety as a polar electron-withdrawing substituent. Moreover, the two substituents are sterically more demanding and possess additional H-bond acceptors.



Scheme 2. Reagents and reaction conditions: (a) 4-methoxyphenylhydrazine hydrochloride, EtOH, reflux. (b) 4-(methylsulfonyl)phenylhydrazine, AcOH, reflux. (c) NaH, DMF, $TsOCH_2CH_2F$, 0 °C → 95 °C. (d) DDQ, THF, reflux. (e) Cs_2CO_3, DMF, $TsOCH_2CH_2F$, 0 °C → rt. (f) 1. **19**, $H_2N\text{-}NH_2\cdot H_2O$, EtOH, reflux; 2. HCl in Et_2O. (g) 1. **20**, $H_2N\text{-}NH_2\cdot H_2O$, EtOH, CH_2Cl_2, 40 °C; 2. HCl in Et_2O. (h) **12a**, COMU®, $EtN(iPr)_2$, THF, rt.

To obtain carbazoles with a substituent in 6-position, 4-methoxy- and 4-(methylsulfonyl)phenylhydrazine were reacted with cyclohexanone derivative **14** in a Fischer indole synthesis [21]. The required 4-methylsulfonylphenylhydrazine was synthesized by nucleophilic aromatic substitution of 4-chlorophenyl methyl sulfone with hydrazine according to the literature [22]. Tetrahydrocarbazole **15** was alkylated with fluoroethyl tosylate and DDQ was used for the oxidation to afford the carbazole **19**. For the synthesis of carbazole **20** the aromatization was carried out first and afterwards

the fluoroethyl moiety was introduced using Cs_2CO_3 instead of NaH. Hydrazinolysis of the phthalimides **19** and **20** led to the primary amines **21** and **22**, which were acylated with propionic acid **12a** to obtain amides **23a** and **24a** (Scheme 2).



25·HCl, 60 %

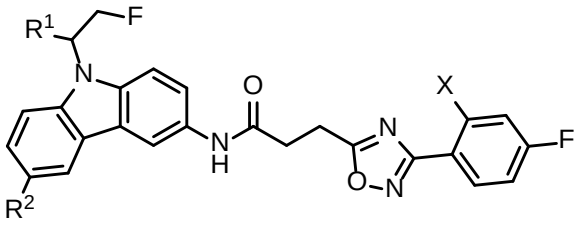
26a, 66 %

Scheme 3. Reagents and reaction conditions: (a) 1. $H_2N\text{-}NH_2\cdot H_2O$, EtOH, reflux; 2. HCl in Et_2O. (b) **12a**, COMU®, Et*i*Pr_2, THF, rt.

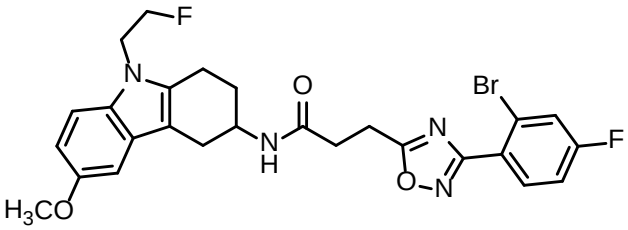
Furthermore, the tetrahydrocarbazole **26a** was synthesized to determine the effects of the less planar scaffold on CB_2 affinity. Therefore, tetrahydrocarbazole **17** was subjected to hydrazinolysis and **25**·HCl was coupled with propionic acid **12a** to yield amide **26a** (Scheme 3).

3. Receptor affinity

Table 1. CB_1 and CB_2 receptor affinity of fluorosiopropyl derivatives **13**, compounds **23** and **24** with a substituent in 6-position and tetrahydrocarbazole derivative **26a**.



13,**23a**,**24a**



26a

compd	R^1	R^2	X	K_i (hCB_2) ± SEM [nM][a)]	displacement (hCB_1)[b)]
1a	H	H	Br	2.9 ± 0.4	22 %[c)]
13a	CH_3	H	Br	2.9 ± 0.4	12 %
13b	CH_3	H	Cl	1.5 ± 0.1	10 %
23a	H	OCH_3	Br	56 ± 7	3 %
24a	H	SO_2CH_3	Br	1137 ± 124	8 %
26a				1 %[b)]	10 %
CP 55,940				8.4 ± 0.2	9.3 ± 0.1
WIN 55,212-2				8.6 ± 0.2	8.7 ± 0.2
HU 210				9.8 ± 0.04	9.6 ± 0.1

[a)] The reported K_i-values are mean values of three independent experiments (n = 3).

[b)] Due to the low hCB_1 affinity, only the radioligand displacement at a test compound concentration of 1 µM is given. Mean value of two independent experiments (n = 2).

[c)] Mean value of four experiments (n = 4).

The fluoroisopropyl derivatives **13a** and **13b** show similar high CB_2 affinity as the fluoroethyl derivative **1a**. Also, the affinity of both compounds to the CB_1 receptor is very low indicating high selectivity over the CB_1 receptor.

Compared to a proton, the 6-methoxy group of **23a** has a similar polarity, but is sterically more demanding, possesses an additional H-bond acceptor and increases the electron density of the carbazole system. With a K_i value of 56 nM, the CB_2 affinity of **23a** is by 19-fold decreased compared to the lead compound **1a**. In contrast, the methylsulfonyl group is a very polar substituent, possesses two additional H-bond acceptors, decreases the electron density in the carbazole system and is sterically much more demanding than a proton. Compared to the lead compound **1a**, the CB_2 affinity of sulfone **24a** is 400-fold decreased.

Due to the sp^3-hybridized C-atoms in 1- to 4-position, tetrahydrocarbazole **26a** is no longer planar, which is not tolerated by the CB_2 receptor. At a test compound concentration of 1 µM, the tetrahydrocarbazole **26a** could only displace 1 % of the radioligand. Obviously, the K_i value is greater than 1 µM.

4. Metabolism studies of 13a

In vivo studies of [^{18}F]**1a** in mice revealed low metabolic stability as only 35 % of intact radiotracer [^{18}F]**1a** were detected 60 min after injection [15]. Furthermore, the *in vitro* stability over time was determined by incubation with mouse liver microsomes and metabolite structures were identified in our lab using LC-MS-MS [23]. After an incubation time of 90 min, 69.8 ± 0.5 % (SEM) of **1a** remained intact. The hydrolysis of the amide bond was identified as major clearance pathway, which was also reported and described in *in vivo* experiments with rats and mice [15], [19]. In addition, the oxidative *N*-dealkylation of the carbazole-*N*-atom **1a** was postulated, resulting in a loss of the F-atom of the potential positron emitter. Therefore, the effect of an additional methyl moiety in α-position to the tertiary amine (**13a**) on the metabolism was investigated.

Fluoroisopropylcarbazole **13a** was incubated with mouse liver microsomes or mouse plasma. The resulting samples were analyzed using LC-qToF-MS, which allowed identification of metabolites through exact masses and fragmentation experiments.

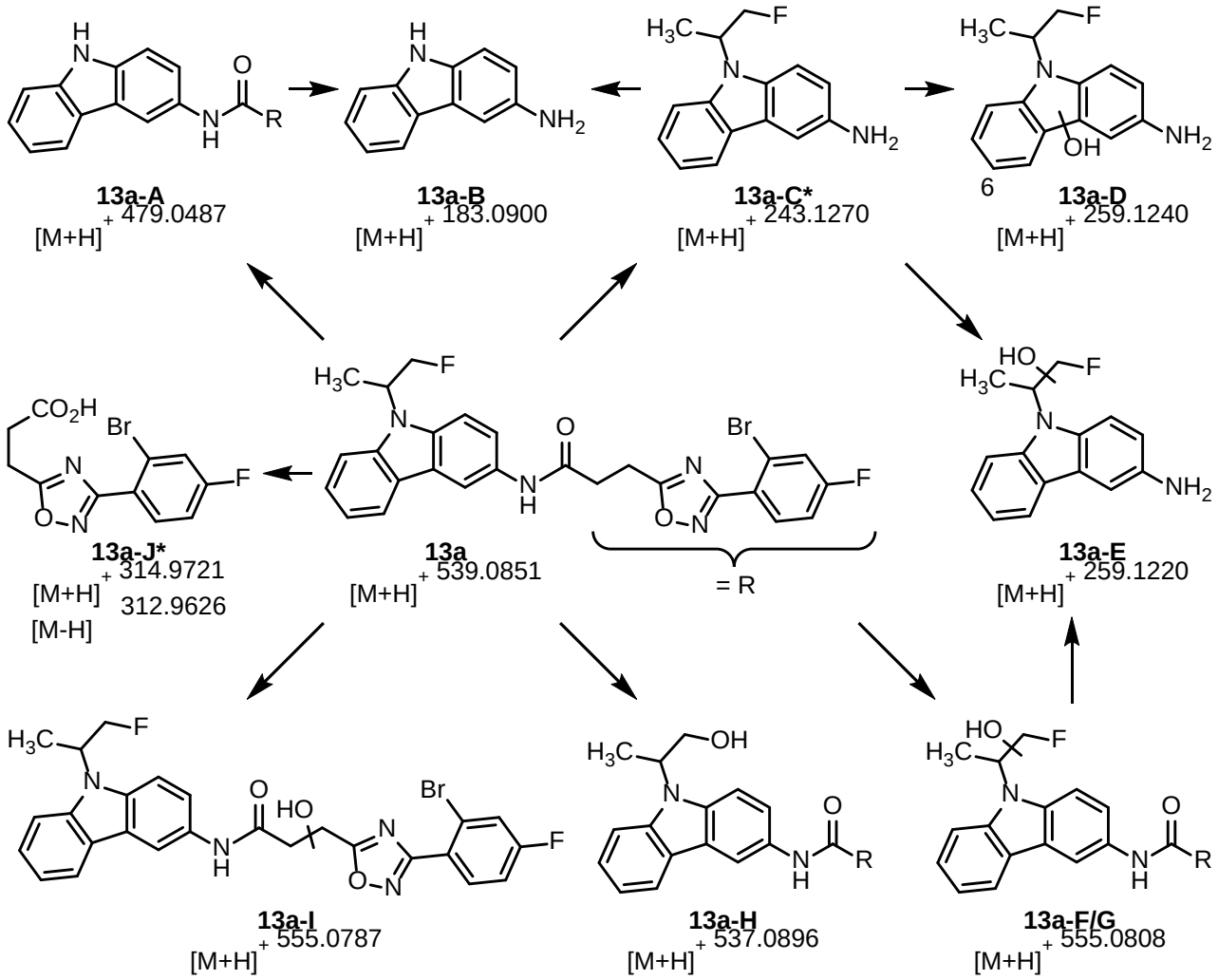


Figure 2. Proposed structures of metabolites identified 90 min after incubation of **13a** with mouse liver microsomes and NADPH. * The marked metabolites were also formed without NADPH and in murine blood serum.

In total, ten metabolites of compound **13a** were detected (Figure 2). Oxidative *N*-dealkylation led to metabolite **13a-A**, and following amide-hydrolysis to primary aromatic amine **13a-B**. This metabolite could also be formed by hydrolysis of the parent compound **13a** and subsequent *N*-dealkylation of **13a-C**. Two additional primary aromatic amines **13a-D** and **13a-E** resulted from hydroxylation of **13a-C**. The exact

position of the OH moiety at the carbazole ring of metabolite **13a-D** is unknown. However, the 6-position is most likely bearing the hydroxy moiety. Moreover, the two metabolites **13a-F** and **13a-G**, hydroxylated in the fluoroisopropyl side chain, could be detected (t_R = 11.82 min and 12.14 min), which possess almost the same fragmentation pattern (see supporting information, chapter 2). Therefore, it is assumed, that the hydroxy groups are attached to the terminal alkyl moieties of the isopropyl side chain, since a hydroxy moiety at the C-atom in the middle would lead to an unstable hemiaminal. Metabolite **13a-H** was obtained by defluorination. Although this metabolite was formed in minor amounts, the F-atom of the potential positron emitter is lost. In contrast to the identified metabolites of **1a** [23], formation of a carbazole *N*-oxide was not observed. It is assumed that the sterically demanding fluoroisopropyl moiety is shielding the carbazole N-atom from oxidative attack by CYP enzymes. The fragmentation pattern of metabolite **13a-I** bearing the OH moiety at the trimethylene spacer connecting the carbazole and 1,2,4-oxadiazole rings is given in Figure 3.

Since fragmentation of metabolite **13a-I** led to a carbazole fragment (*m/z* 243.1305) without OH-moiety, which is formed by cleavage of the amide bond, hydroxylation of the carbazole and fluoroisopropyl substructures was excluded. (Figure 3) Fragment *m/z* 285.9750 proved hydroxylation of the phenyloxadiazolylpropyl part of the molecule. Furthermore, fragment *m/z* 214.9611 with a diazirine ring excluded hydroxylation of the phenyl ring, and thus confirmed the position of the OH group in the trimethylene linker. Diazirine derivatives, resulting from 1,2,4-oxadiazole fragmentation under electron impact ionization conditions, have already been described by Pihlaja *et al.* [24].

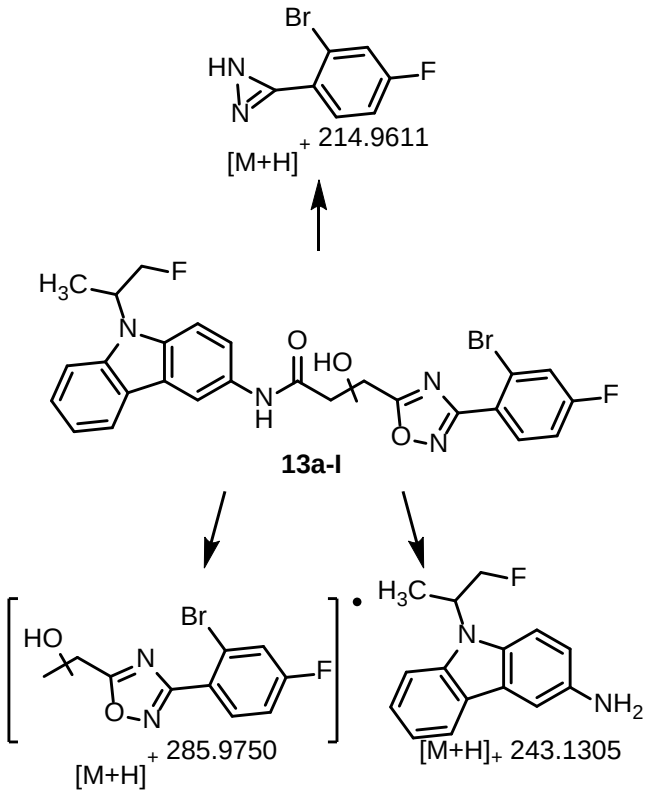


Figure 3. Fragmentation of metabolite **13a-I**.

In order to show the effect of the additional methyl moiety of the fluoroisopropyl derivative **13a** on oxidative *N*-dealkylation the fluoroethyl and fluoroisopropyl derivatives **1a** and **13a** were incubated under the same conditions with mouse liver microsome preparations and NADPH. The extracted ion chromatograms (EICs) of the resulting *N*-unsubstituted carbazole **13a-A** (= **1a-A**) are compared in Figure 4. According to the EICs, the additional methyl moiety reduced oxidative *N*-dealkylation of **13a** approximately by two-thirds after 90 min in comparison with the oxidative *N*-dealkylation of the fluoroethyl moiety.

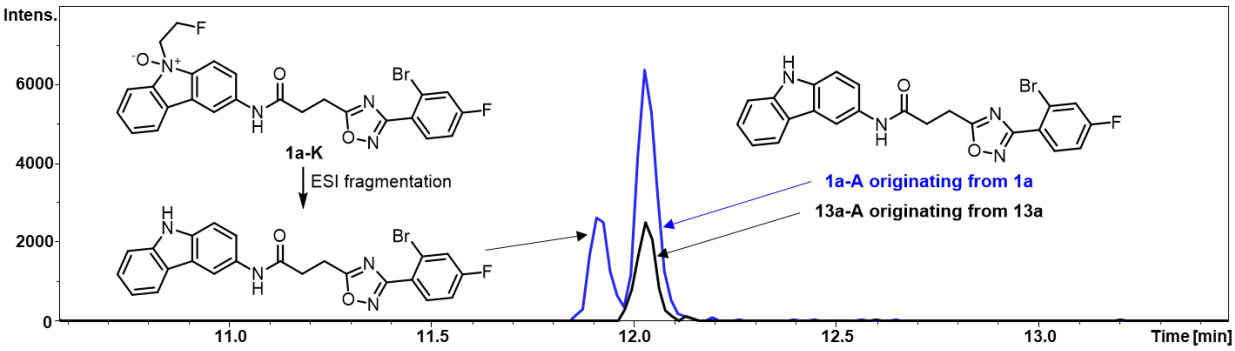


Figure 4. EICs *m/z* 479.0513 for the incubations of **1a** and **13a** with mouse liver microsomes and NADPH. The left blue peak resulted from the in-source fragmentation of metabolite **1a-K** [23].

5. Conclusion

In order to inhibit *N*-dealkylation and oxidation of the *N*-substituted carbazole moiety of the potent CB_2 agonist **1a** (K_i (hCB_2) = 2.9 nM) novel ligands with a modified carbazole substitution pattern were synthesized. The key step of the synthesis of CB_2 ligands with modified substituents in 6-position or with a partly hydrogenated carbazole scaffold was a Fischer indole synthesis with *N*-protected 4-aminocyclohexanone **14** and substituted phenylhydrazines. Whereas a methylsulfonyl moiety in 6-position of the carbazole system (**24a**) was not tolerated by the CB_2 receptor, the methoxy derivative **23a** showed considerable CB_2 affinity (K_i = 56 nM). Partial hydrogenation of the carbazole to form a tetrahydrocarbazole system (**26a**) led to complete loss of CB_2 affinity indicating that a planar aromatic ring system is essential to achieve strong interactions with the CB_2 receptor. Introduction of an additional methyl moiety into the fluoroethyl side chain of **1a** resulted in the fluoroisopropyl derivatives **13a** (K_i (hCB_2) = 2.9 nM) and **13b** (K_i (hCB_2) = 1.5 nM) with almost the same CB_2 affinity and selectivity over the CB_1 subtype. Investigation of the *in vitro* metabolism of the fluoroisopropyl derivative **13a** with murine microsomes and subsequent LC-MS-MS analysis revealed ten metabolites in small amounts. In comparison to **1a** [23], formation

of an *N*-oxide was not observed and the extent of oxidative *N*-dealkylation was reduced to one third. In can be concluded that the additional methyl moiety of the fluoroisopropyl derivatives **13** does not reduce CB_2 affinity, but is able to shield the carbazole *N*-atom from oxidative attack by microsomal CYP enzymes. Thus, the fluoroisopropyl moiety represents a promising substituent for the development of carbazole-based PET tracers for the selective imaging of CB_2 receptors in the CNS.

6. Experimental

6.1 Chemistry, General Methods

Oxygen and moisture sensitive reactions were carried out under nitrogen, dried with silica gel with moisture indicator (orange gel, Merck) and in dry glassware (Schlenk flask or Schlenk tube). Temperatures were controlled with dry ice/acetone (-78 °C), ice/water (0 °C), Cryostat (Julabo FT 901 or Huber TC100E-F), magnetic stirrer MR 3001 K (Heidolph) or RCT CL (IKA®), together with temperature controller EKT HeiCon (Heidolph) or VT-5 (VWR) and PEG or silicone bath. All solvents were of analytical grade quality. Demineralized water was used. THF was distilled from sodium/benzophenone. Methanol was distilled from magnesium methanolate. CH_3CN and ethanol abs. were dried with molecular sieves (3 Å); DMF, ethyl acetate and toluene were dried with molecular sieves (4 Å). Thin layer chromatography (tlc): tlc silica gel 60 F_{254} on aluminum sheets (Merck). Flash chromatography (fc): Silica gel 60, 40–63 µm (Merck); parentheses include: diameter of the column (ø), length of the stationary phase (l), fraction size (v) and eluent. Melting point: Melting point system MP50 (Mettler Toledo), open capillary, uncorrected. MS: MicroTOFQII mass spectrometer (Bruker Daltonics); deviations of the found exact masses from the calculated exact masses were 5 ppm or less; the data were analyzed with DataAnalysis (Bruker). NMR: NMR spectra were recorded on Agilent DD2 400 MHz

and 600 MHz spectrometers; chemical shifts (δ) are reported in parts per million (ppm) against the reference substance tetramethylsilane and calculated using the solvent residual peak of the undeuterated solvent. IR: FT/IR IRAffinity-1 IR spectrometer (Shimadzu) using ATR technique.

6.2 HPLC method for the determination of the purity

Equipment 1: Pump: L-7100, degasser: L-7614, autosampler: L-7200, UV detector: L-7400, interface: D-7000, data transfer: D-line, data acquisition: HSM-Software (all from LaChrom, Merck Hitachi); Equipment 2: Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (Thermo Fisher Scientific); column: LiChropher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized water with 0.05 % (V/V) trifluoroacetic acid, B: acetonitrile with 0.05 % (V/V) trifluoroacetic acid; gradient elution (% A): 0 - 4 min: 90 %; 4 - 29 min: gradient from 90 % to 0 %; 29 - 31 min: 0 %; 31 - 31.5min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %.

6.3 Synthetic procedures

*6.3.1 2-(Carbazol-9-yl)propan-1-ol (**7**) [25]*

Preparation of this compound is described in the literature [25] following a different synthesis route.

Under N_2 atmosphere, carbazole (**5**, 1.79 g, 11 mmol, 1 eq.) was dissolved in dry DMF (54 mL). NaH (60 % dispersion in Paraffin Oil, 0.99 g, 25 mmol, 2.3 eq.) was added and the mixture was stirred for 30 min. After the dropwise addition of tosylate **6** (6.38 g, 25 mmol, 2.3 eq.), the reaction mixture was stirred at 110 °C for 43 h. Water (10 mL) and a saturated Na_2CO_3 solution (40 mL) were added and the mixture was extracted

with ethyl acetate (200 mL). The organic layer was washed with water (2 x 50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. $LiAlH_4$ (1.63 g, 42 mmol, 4 eq.) was suspended in dry THF (130 mL) and the ester dissolved in THF (20 mL) was added over 15 min. The mixture was heated at reflux for 16 h before it was quenched with a NaOH solution (1M, 10 mL) and water (40 mL). Insoluble impurities were removed by filtration and washed with ethyl acetate (200 mL). The organic layer was separated from the aqueous layer and washed with brine (50 mL). Afterwards, the ethyl acetate layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc with a gradient (ø = 5 cm, l = 18 cm, v = 60 mL, cyclohexane/ethyl acetate 85:15, 70:30, R_f = 0.35 (cyclohexane/ethyl acetate 7:3)). Beige solid, mp 117 °C, yield 1.56 g (65 %). Purity (HPLC): 98.6 % (t_R = 20.4 min). $C_{15}H_{15}NO$ (225.3 g/mol). Exact mass (APCI): m/z = 226.1224 (calcd. 226.1226 for $C_{15}H_{16}NO$ [$M+H^+$]). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 1.59 (d, *J* = 7.2 Hz, 3H, CH_3), 3.85 - 3.90 (m, 1H, C*H*$_2$OH), 4.00 - 4.06 (m, 1H, C*H*$_2$OH), 4.88 - 4.95 (m, 2H, NC*H*, CH_2O*H*), 7.17 (t, *J* = 7.4 Hz, 2H, 3-H, 6-H), 7.40 (t, *J* = 7.7 Hz, 2H, 2-H, 7-H), 7.65 (d, *J* = 8.3 Hz, 2H, 1-H, 8-H), 8.14 (d, *J* = 7.7 Hz, 2H, 4-H, 5-H). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 15.8 (1C, CH_3), 53.3 (1C, NCH), 63.3 (1C, *C*H_2OH), 111.1 (2C, C-1, C-8), 118.8 (2C, C-3, C-6), 120.5 (2C, C-4, C-5), 123.0 (2C, C-4a, C-4b), 125.8 (2C, C-2, C-7), 140.1 (2C, C-8a, C-9a). FTIR (neat): ṽ (cm^{-1}) = 3325 (m, O-H), 3062 (w, C-H, arom), 2877 (w, C-H, aliph), 1593 (s, C-C, arom).

*6.3.2 2-(Carbazol-9-yl)propyl 4-methylbenzenesulfonate (**8**)*

Under N_2 atmosphere, tosyl chloride (2.55 g, 13 mmol, 2 eq.) was dissolved in dry CH_2Cl_2 (30 mL), dry pyridine (10 mL) and triethylamine (1.4 mL, 10 mmol, 1.5 eq.). Carbazole derivative **7** (1.50 g, 6.7 mmol, 1 eq.) dissolved in dry CH_2Cl_2 (10 mL) was

added dropwise over 10 min. The reaction mixture was stirred at room temperature for 17 h followed by evaporation to dryness in vacuo. The residue was dissolved in HCl (1 M, 20 mL) and the solvent was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with a saturated Na_2CO_3 solution (20 mL), which was extracted with CH_2Cl_2 (2 x 20 mL). After drying (Na_2SO_4), the combined CH_2Cl_2 layers were concentrated under reduced pressure. The residue was purified by fc (Ø = 4 cm, l = 18 cm, v = 30 mL, cyclohexane/ethyl acetate 90:10, R_f = 0.39 (cyclohexane/ethyl acetate 8:2)). Colorless solid, mp 93 °C, yield 2.14 g (84 %). Purity (HPLC): 99.7 % (t_R = 24.5 min). $C_{22}H_{21}NO_3S$ (379.5 g/mol). Exact mass (APCI): m/z = 380.1310 (calcd. 380.1315 for $C_{22}H_{22}NO_3S$ $[M+H^+]$). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 1.57 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 2.29 (s, 3H, Ar-CH_3), 4.45 (dd, *J* = 10.7/4.1 Hz, 1H, CH_2), 4.70 (dd, *J* = 10.7/9.6 Hz, 1H, CH_2), 5.18 - 5.25 (m, 1H, NCH), 7.03 (d, *J* = 8.4 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.18 (t, *J* = 7.5 Hz, 2H, 3-H_{carb}, 6-H_{carb}), 7.21 (d, *J* = 8.3 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.34 (t, *J* = 7.6 Hz, 2H, 2-H_{carb}, 7-H_{carb}), 7.51 (d, *J* = 8.3 Hz, 2H, 1-H_{carb}, 8-H_{carb}), 8.11 (d, *J* = 7.7 Hz, 2H, 4-H_{carb}, 5-H_{carb}). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 14.7 (1C, CH*C*H_3), 21.1 (1C, Ar-CH_3), 49.2 (1C, NCH), 70.4 (1C, CH_2), 110.2 (2C, C-1$_{carb}$, C-8$_{carb}$), 118.8 (2C, C-3$_{carb}$, C-6$_{carb}$), 120.1 (2C, C-4$_{carb}$, C-5$_{carb}$), 122.6 (2C, C-4a$_{carb}$, C-4b$_{carb}$), 125.5 (2C, C-2$_{carb}$, C-7$_{carb}$), 126.8 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 129.6 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 131.3 (1C, C-1$_{phenyl}$), 139.0 (2C, C-8a$_{carb}$, C-9a$_{carb}$), 144.5 (1C, C-4$_{phenyl}$). FTIR (neat): ṽ (cm^{-1}) = 2943 (w, C-H, aliph), 1597 (w, C-C, arom), 1354 (s, SO_3), 1165 (s, SO_3).

*6.3.3 9-(1-Fluoropropan-2-yl)carbazole (**9**)*

TBAF·3H_2O (2.71 g, 8.6 mmol, 2.2 eq.) was added to tosylate **8** (1.48 g, 3.9 mmol, 1 eq.) and the mixture was stirred at 60 °C for 23 h. After addition of ethyl acetate (80 mL), the organic layer was washed with water (2 x 40 mL) and brine (40 mL), dried

(Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø = 4 cm, l = 16 cm, v = 30 mL, cyclohexane/ethyl acetate 99:1, R_f = 0.65 (cyclohexane/ethyl acetate 8:2)). Colorless solid, mp 82 - 83 °C, yield 0.472 g (53 %). Purity (HPLC): 96.4 % (t_R = 23.0 min). $C_{15}H_{14}FN$ (227.3 g/mol). Exact mass (APCI): m/z = 228.1185 (calcd. 228.1183 for $C_{15}H_{15}FN$ $[M+H^+]$). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.78 (dd, *J* = 7.2/1.5 Hz, 3H, CH_3), 4.84 (ddd, *J* = 33.2/9.0/5.8 Hz, 1H, CH_2F), 4.96 (ddd, *J* = 33.7/9.0/5.8 Hz, 1H, CH_2F), 5.05 - 5.19 (m, 1H, NCH), 7.25 (ddd, *J* = 7.9/6.9/1.2 Hz, 2H, 3-H, 6-H), 7.45 (ddd, *J* = 8.3/6.9/1.2 Hz, 2H, 2-H, 7-H), 7.49 (dt, *J* = 8.2/1.0 Hz, 2H, 1-H, 8-H), 8.11 (dt, *J* = 7.8/0.9 Hz, 2H, 4-H, 5-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 14.9 (d, *J* = 5.0 Hz, CH_3), 50.9 (d, *J* = 21.8 Hz, 1C, NCH), 84.3 (d, *J* = 175.0 Hz, 1C, CH_2F), 109.9 (2C, C-1, C-8), 119.3 (2C, C-3, C-6), 120.5 (2C, C-4, C-5), 123.7 (2C, C-4a, C-4b), 125.8 (2C, C-2, C-7), 139.8 (2C, C-8a, C-9a). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 3059 (w, C-H, arom), 2951 (w, C-H, aliph), 1593 (m, C-C, arom).

*6.3.4 9-(1-Fluoropropan-2-yl)-3-nitrocarbazole (**10**)*

Fluoroisopropylcarbazole **9** (0.537 g, 2.4 mmol, 1 eq.) was dissolved in CH_2Cl_2 (12 mL) and cooled down to 0 °C. HNO_3 65 % (250 µL, 3.6 mmol, 1.5 eq.) was added and the solution was stirred at 0 °C for 4 h. Afterwards, the reaction mixture was diluted with water (5 mL), neutralized with a saturated $NaHCO_3$ solution and the aqueous layer was diluted with water to 10 mL. After evaporation of CH_2Cl_2 in vacuo, the aqueous layer was extracted with ethyl acetate (1 x 20 mL, 2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The residue was purified by fc (Ø = 3 cm, l = 15 cm, v = 20 mL, cyclohexane/ethyl acetate 30:70, R_f = 0.60 (cyclohexane/ethyl acetate 6:4)). Yellow solid, mp 192 - 193 °C, yield 0.561 g (87 %). Purity (HPLC): 98.6 % (t_R = 22.6 min). $C_{15}H_{13}FN_2O_2$ (272.3 g/mol). Exact mass (APCI): m/z = 273.1047 (calcd. 273.1034 for $C_{15}H_{14}FN_2O_2$ $[M+H^+]$). ^1H NMR (400 MHz,

DMSO-D_6): δ (ppm) = 1.67 (dd, *J* = 7.2/0.9 Hz, 3H, CH_3), 4.86 (ddd, *J* = 45.7/10.0/4.2 Hz, 1H, CH_2F), 5.08 (ddd, *J* = 48.3/9.8/8.7 Hz, 1H, CH_2F), 5.34 - 5.52 (m, 1H, NCH), 7.32 - 7.37 (m, 1H, 6-H), 7.56 (ddd, *J* = 8.4/7.2/1.3 Hz, 1H, 7-H), 7.85 (d, *J* = 8.4 Hz, 1H, 8-H), 7.91 (d, *J* = 9.2 Hz, 1H, 1-H), 8.31 (dd, *J* = 9.2/2.4 Hz, 1H, 2-H), 8.43 (d, *J* = 7.8 Hz, 1H, 5-H), 9.18 (d, *J* = 2.2 Hz, 1H, 4-H). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 13.9 (d, *J* = 6.9 Hz, 1C, CH_3), 51.1 (d, *J* = 19.3 Hz, 1C, NCH), 83.6 (d, *J* = 170.5 Hz, 1C, CH_2F), 110.7 (1C, C-1), 111.6 (1C, C-8), 117.1 (1C, C-4), 120.7 (1C, C-6), 121.1 (1C, C-2), 121.5 (1C, C-5), 122.5 (1C, C-4a), 122.7 (1C, C-4b), 127.4 (1C, C-7), 140.1 (1C, C-3), 140.7 (1C, C-8a), 143.0 (1C, C-9a). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 2966 (w, C-H, aliph), 1593 (w, C-C, arom), 1508 (m, C-C, arom), 1315 (s, NO_2).

*6.3.5 9-(1-Fluoropropan-2-yl)carbazol-3-ammonium chloride (**11**·HCl)*

Under N_2 atmosphere, nitrocarbazole **10** (0.528 g, 1.9 mmol, 1 eq.) was dissolved in dry THF (52 mL). Pd/C 10 % (80 mg) was added and the mixture was stirred for 24 h under H_2 atmosphere (balloon). After filtration through Celite®, the mixture was concentrated under reduced pressure and the residue was dissolved in Et_2O. A solution of HCl in Et_2O (2 M, 1.0 mL, 2.0 mmol, 1.03 eq.) was added dropwise until the salt **11**·HCl precipitated completely. The precipitate was filtered off, washed with cold Et_2O and dried under reduced pressure. R_f = 0.52 (cyclohexane/ethyl acetate 3:7). Grey solid, mp 220 - 240 °C (decomposition), yield 0.492 g (91 %). Purity (HPLC): 97.9 % (t_R = 15.4 min). $C_{15}H_{16}ClFN_2$ (278.8 g/mol). Exact mass (APCI): m/z = 243.1283 (calcd. 243.1292 for $C_{15}H_{16}FN_2$ [M+H^+]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 1.64 (d, *J* = 6.9 Hz, 3H, CH_3), 4.84 (ddd, *J* = 45.8/9.9/4.4 Hz, 1H, CH_2F), 5.05 (dt, *J* = 48.3/9.1 Hz, 1H, CH_2F), 5.27 - 5.43 (m, 1H, NCH), 7.25 (t, *J* = 7.4 Hz, 1H, 6-H), 7.41 - 7.56 (m, 2H, 2-H, 7-H), 7.77 (d, *J* = 8.3 Hz, 1H, 8-H), 7.84 (d, *J* = 8.8 Hz, 1H, 1-H), 8.15 (d, *J* = 2.2 Hz, 1H, 4-H), 8.20 (d, *J* = 7.7 Hz, 1H, 5-H), 10.45 (s, 3H, -NH_3^+).

^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 13.9 (d, *J* = 6.9 Hz, 1C, CH_3), 50.5 (d, *J* = 19.4 Hz, 1C, NCH), 83.6 (d, *J* = 170.4 Hz, 1C, CH_2F), 110.9 (1C, C-8), 111.4 (1C, C-1), 114.7 (1C, C-4), 119.4 (1C, C-6), 120.5 (1C, C-5), 120.6 (1C, C-2), 121.9 (1C, C-4b), 122.8 (1C, C-4a), 123.1 (1C, C-3), 126.5 (1C, C-7), 138.5 (1C, C-9a), 140.1 (1C, C-8a). FTIR (neat): ṽ (cm^{-1}) = 3452 (w, N-H), 2854 (m, C-H, aliph).

*6.3.6 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-[9-(1-fluoropropan-2-yl)carbazol-3-yl]propanamide (**13a**)*

Under N_2 atmosphere, *N*-ethyl-*N*,*N*-diisopropylamine (0.14 mL, 0.83 mmol, 3 eq.) and COMU® (155 mg, 0.36 mmol, 1.3 eq.) were added to a solution of carboxylic acid **12a** (96 mg, 0.31 mmol, 1.1 eq.) in dry THF (3 mL). After the reaction mixture had been stirred at room temperature for 50 min, carbazolamine hydrochloride **11**·HCl (78 mg, 0.28 mmol, 1 eq.) was added and stirring was continued for 24 h. Afterwards, all volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The organic solvent was washed with water (2 x 10 mL) and brine (50 mL). After drying (Na_2SO_4), the organic layer was concentrated in vacuo. The residue was purified by fc with a gradient (ø = 2 cm, l = 15 cm, v = 10 mL, cyclohexane/ethyl acetate/triethylamine 70:30:1, 65:35:1, R_f = 0.64 (cyclohexane/ethyl acetate 4:6)). Yellowish solid, mp 147 - 148 °C, yield 105 mg (70 %). Purity (HPLC): 96.5 % (t_R = 23.8 min). $C_{26}H_{21}BrF_2N_4O_2$ (539.4 g/mol). Exact mass (APCI): m/z = 539.0895 (calcd. 539.0889 for $C_{26}H_{22}{}^{79}BrF_2N_4O_2$ [M+H^+]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 1.61 (d, *J* = 6.4 Hz, 3H, CH_3), 2.99 (t, *J* = 6.9 Hz, 2H, CH_2CH_2CONH), 3.36 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CONH), 4.82 (ddd, *J* = 46.0/9.7/4.4 Hz, 1H, CH_2F), 5.02 (dt, *J* = 48.2/9.0 Hz, 1H, CH_2F), 5.16 - 5.34 (m, 1H, NCH), 7.17 (t, *J* = 7.4 Hz, 1H, 6-H_{carb}), 7.36 - 7.48 (m, 2H, 7-H_{carb}, 5-H_{phenyl}), 7.51 (dd, *J* = 8.9/1.9 Hz, 1H, 2-H_{carb}), 7.65 (d, *J* = 8.7 Hz, 1H, 1-H_{carb}), 7.68 (d, *J* = 8.5 Hz, 1H, 8-H_{carb}), 7.82 (dd, *J* = 8.6/2.5

Hz, 1H, 3-H_{phenyl}), 7.88 (dd, *J* = 8.7/6.1 Hz, 1H, 6-H_{phenyl}), 8.04 (d, *J* = 7.6 Hz, 1H, 5-H_{carb}), 8.41 (d, *J* = 1.7 Hz, 1H, 4-H_{carb}), 10.15 (s, 1H, CON*H*). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 14.0 (d, *J* = 6.8 Hz, 1C, CH_3), 21.8 (1C, *C*$H_2$$CH_2$CONH), 32.0 (1C, CH_2*C*H_2CONH), 50.3 (d, *J* = 19.6 Hz, 1C, NCH), 83.7 (d, *J* = 170.4 Hz, 1C, CH_2F), 110.5 (2C, C-1_{carb}, C-8_{carb}), 110.8 (1C, C-4_{carb}), 115.5 (d, *J* = 21.6 Hz, 1C, C-5_{phenyl}), 118.7 (1C, C-2_{carb}), 118.7 (1C, C-6_{carb}), 120.0 (1C, C-5_{carb}), 121.4 (d, *J* = 25.1 Hz, 1C, C-3_{phenyl}), 122.1 (d, *J* = 10.2 Hz, 1C, C-2_{phenyl}), 122.4 (2C, C-$4a_{carb}$, C-$4b_{carb}$), 124.4 (d, *J* = 3.5 Hz, 1C, C-1_{phenyl}), 125.7 (1C, C-7_{carb}), 131.2 (1C, C-3_{carb}), 133.6 (d, *J* = 9.4 Hz, 1C, C-6_{phenyl}), 135.9 (1C, C-$9a_{carb}$), 140.0 (1C, C-$8a_{carb}$), 162.8 (d, *J* = 253.2 Hz, 1C, C-4_{phenyl}), 166.6 (1C, C-$3_{oxadiazole}$), 168.5 (1C, C=O), 179.6 (1C, C-$5_{oxadiazole}$). FTIR (neat): ṽ (cm^{-1}) = 3279 (w, NH), 2924 (w, C-H, aliph), 1643 (m, C=O), 1593 (m, C-C, arom), 1550 (m, C-C, arom).

*6.3.7 3-[3-(2-Chloro-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-[9-(1-fluoropropan-2-yl)carbazol-3-yl]propanamide (**13b**)*

Under N_2 atmosphere, *N*-ethyl-*N*,*N*-diisopropylamine (0.16 mL, 0.91 mmol, 3 eq.) and COMU® (169 mg, 0.39 mmol, 1.3 eq.) were added to a solution of carboxylic acid **12b** (90 mg, 0.33 mmol, 1.1 eq.) in dry THF (3 mL). After the reaction mixture had been stirred at room temperature for 30 min, carbazolamine hydrochloride **11**·HCl (85 mg, 0.30 mmol, 1 eq.) was added and stirring was continued for 24 h. Afterwards, all volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with NaOH solution (1 M, 10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø = 2 cm, l = 15 cm, v = 10 mL, cyclohexane/ethyl acetate 70:30, R_f = 0.64 (cyclohexane/ethyl acetate 4:6)). Beige solid, mp 157 - 159 °C, yield 88 mg (59 %). Purity (HPLC): 98.2 % (t_R = 23.3 min). $C_{26}H_{21}ClF_2N_4O_2$ (494.9 g/mol).

Exact mass (APCI): m/z = 495.1393 (calcd. 495.1394 for $C_{26}H_{22}{}^{35}ClF_2N_4O_2$ [M+H$^+$]). ^{1}H NMR (600 MHz, DMSO-D$_6$): δ (ppm) = 1.61 (d, *J* = 6.9 Hz, 3H, CH_3), 3.00 (t, *J* = 6.9 Hz, 2H, $CH_2C\mathit{H_2}CONH$), 3.36 (t, *J* = 6.9 Hz, 2H, $C\mathit{H_2}CH_2CONH$), 4.81 (ddd, *J* = 45.9/9.8/4.4 Hz, 1H, CH_2F), 5.02 (dt, *J* = 48.1/9.0 Hz, 1H, CH_2F), 5.19 - 5.30 (m, 1H, NCH), 7.17 (t, *J* = 7.4 Hz, 1H, 6-H$_{carb}$), 7.38 - 7.44 (m, 2H, 3-H$_{phenyl}$, 7-H$_{carb}$), 7.51 (dd, *J* = 8.8/1.6 Hz, 1H, 2-H$_{carb}$), 7.63 - 7.70 (m, 3H, 1-H$_{carb}$, 8-H$_{carb}$, 5-H$_{phenyl}$), 7.97 (dd, *J* = 8.6/6.2 Hz, 1H, 6-H$_{phenyl}$), 8.04 (d, *J* = 7.7 Hz, 1H, 5-H$_{carb}$), 8.41 (d, *J* = 1.3 Hz, 1H, 4-H$_{carb}$), 10.15 (s, 1H, CON*H*). ^{13}C NMR (151 MHz, DMSO-D$_6$): δ (ppm) = 14.0 (d, *J* = 6.7 Hz, 1C, CH_3), 21.8 (1C, $\mathit{C}H_2CH_2CONH$), 32.0 (1C, $CH_2\mathit{C}H_2CONH$), 50.3 (d, *J* = 19.6 Hz, 1C, NCH), 83.7 (d, *J* = 170.4 Hz, 1C, CH_2F), 110.5 (2C, C-1$_{carb}$, C-8$_{carb}$), 110.8 (1C, C-4$_{carb}$), 115.2 (d, *J* = 21.7 Hz, 1C, C-3$_{phenyl}$), 118.4 (d, *J* = 25.5 Hz, 1C, C-5$_{phenyl}$), 118.7 (1C, C-2$_{carb}$), 118.7 (1C, C-6$_{carb}$), 120.0 (1C, C-5$_{carb}$), 122.3 (d, *J* = 3.4 Hz, 1C, C-1$_{phenyl}$), 122.4 (2C, C-4a$_{carb}$, C-4b$_{carb}$), 125.7 (1C, C-7$_{carb}$), 131.2 (1C, C-3$_{carb}$), 133.4 (d, *J* = 9.7 Hz, 1C, C-6$_{phenyl}$), 133.5 (d, *J* = 11.1 Hz, 1C, C-2$_{phenyl}$), 135.9 (1C, C-9a$_{carb}$), 139.9 (1C, C-8a$_{carb}$), 163.0 (d, *J* = 252.5 Hz, 1C, C-4$_{phenyl}$), 165.7 (1C, C-3$_{oxadiazole}$), 168.6 (1C, C=O), 179.6 (1C, C-5$_{oxadiazole}$). FTIR (neat): ṽ (cm^{-1}) = 3282 (w, NH), 2927 (w, C-H, aliph), 1639 (m, C=O), 1593 (m, C-C, arom), 1550 (m, C-C, arom).

*6.3.8 N-(6-Methoxy-1,2,3,4-tetrahydrocarbazol-3-yl)phthalimide (**15**) [21]*

A solution of *N*-(4-oxocyclohexyl)phthalimide (**14**, 5.00 g, 21 mmol, 1 eq.) and 4-methoxyphenylhydrazine hydrochloride (3.59 g, 21 mmol, 1 eq.) in dry ethanol (100 mL) was heated at reflux for 2.5 h. After cooling down to room temperature, the precipitate was filtrated off and washed with ethanol 96 % (3 x 10 mL). The solid was dried under reduced pressure and freeze-dried overnight. R_f = 0.66 (cyclohexane/ethyl acetate/dimethylethylamine 5:5:0.2). Colorless solid, mp 222 - 223 °C, yield 6.88 g (97 %). Purity (HPLC): 84.1 % (t_R = 22.2 min). $C_{21}H_{18}N_2O_3$ (346.4 g/mol). Exact mass

(APCI): m/z = 347.1389 (calcd. 347.1390 for $C_{21}H_{19}N_2O_3$ [M+H$^+$]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 2.03 - 2.11 (m, 1H, 2-H), 2.67 (tt, *J* = 12.3/ 6.4 Hz, 1H, 2-H), 2.80 - 2.98 (m, 3H, 1-CH_2, 4-H), 3.20 - 3.28 (m, 1H, 4-H), 3.71 (s, 3H, OCH_3), 4.43 - 4.52 (m, 1H, 3-H), 6.65 (dd, *J* = 8.7/2.4 Hz, 1H, 7-H), 6.82 (d, *J* = 2.4 Hz, 1H, 5-H), 7.15 (d, *J* = 8.7 Hz, 1H, 8-H), 7.84 - 7.91 (m, 4H, 4-H_{phth}, 5-H_{phth}, 6-H_{phth}, 7-H_{phth}), 10.61 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 22.6 (1C, C-1), 24.7 (1C, C-4), 26.5 (1C, C-2), 47.8 (1C, C-3), 55.3 (1C, OCH_3), 99.7 (1C, C-5), 106.3 (1C, C-4a), 109.9 (1C, C-7), 111.2 (1C, C-8), 123.0 (2C, C-4_{phth}, C-7_{phth}), 127.2 (1C, C-4b), 131.3 (1C, C-8a), 131.5 (2C, C-$3a_{phth}$, C-$7a_{phth}$), 134.2 (1C, C-9a), 134.4 (2C, C-5_{phth}, C-6_{phth}), 153.0 (1C, C-6), 167.9 (2C, C=O). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 3425 (w, N-H), 3379 (w, C-H, arom), 2924 (w, C-H, aliph), 1697 (s, C=O), 1597 (w, C-C, arom).

*6.3.9 N-[6-(Methylsulfonyl)-1,2,3,4-tetrahydrocarbazol-3-yl]phthalimide (**16**)*

A solution of *N*-(4-oxocyclohexyl)phthalimide (**14**, 3.53 g, 15 mmol, 1 eq.) and 4-(methylsulfonyl)phenylhydrazine (2.70 g, 15 mmol, 1 eq.) in glacial acetic acid (110 mL) was heated at reflux for 47 h. The mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (200 mL). Afterwards, the organic layer was washed with water (2 x 70 mL) and brine (70 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc with a gradient (ø = 6 cm, l = 13 cm, v = 60 mL, cyclohexane/CH_2Cl_2 60:40, 50:50, 30:70, 0:100, CH_2Cl_2/methanol 100:10, R_f = 0.51 (cyclohexane/ethyl acetate/formic acid 3:7:0.2)). Pale yellow solid, mp 282 - 284 °C, yield 4.50 g (79 %). Purity (HPLC): 86.6 % (t_R = 19.6 min). $C_{21}H_{18}N_2O_4S$ (394.5 g/mol). Exact mass (APCI): m/z = 395.1072 (calcd. 395.1060 for $C_{21}H_{19}N_2O_4S$ [M+H$^+$]). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 2.11 (d, *J* = 12.3 Hz, 1H, 2-H), 2.64 - 2.74 (m, 1H, 2-H), 2.92 - 3.01 (m, 3H, 1-CH_2, 4-H), 3.12 (s, 3H, CH_3), 3.29 - 3.33 (m, 1H, 4-H), 4.47 - 4.54 (m, 1H, 3-H), 7.49 (d, *J* =

8.6 Hz, 1H, 8-H), 7.56 (dd, *J* = 8.6/1.4 Hz, 1H, 7-H), 7.84 - 7.93 (m, 5H, 5-H, 4-H_{phth}, 5-H_{phth}, 6-H_{phth}, 7-H_{phth}), 11.45 (s, 1H, NH). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 22.5 (1C, C-1), 24.2 (1C, C-4), 26.2 (1C, C-2), 44.6 (1C, CH_3), 47.4 (1C, C-3), 108.3 (1C, C-4a), 111.2 (1C, C-8), 117.3 (1C, C-5), 118.9 (1C, C-7), 123.0 (2C, C-4_{phth}, C-7_{phth}), 126.3 (1C, C-4b), 130.7 (1C, C-6), 131.5 (2C, C-$3a_{phth}$, C-$7a_{phth}$), 134.5 (2C, C-5_{phth}, C-6_{phth}), 136.8 (1C, C-9a), 138.5 (1C, C-8a), 167.9 (2C, C=O). FTIR (neat): ṽ (cm^{-1}) = 3348 (m, N-H), 2939 (w, C-H, aliph), 1697 (s, C=O), 1620 (w, C-C, arom), 1130 (s, SO_2).

*6.3.10 N-[9-(2-Fluoroethyl)-6-methoxy-1,2,3,4-tetrahydrocarbazol-3-yl]phthalimide (**17**)*

Under N_2 atmosphere, tetrahydrocarbazole **15** (3.00 g, 8.7 mmol, 1 eq.) was dissolved in dry DMF (43 mL) and NaH (60 % dispersion in Paraffin Oil, 0.866 g, 18 mmol, 2.5 eq.) was added at 0 °C. After stirring at 0 °C for 30 min, fluoroethyl tosylate (2.46 g, 11 mmol, 1.3 eq.) was added slowly to the reaction mixture. The mixture was heated at 95 °C for 2.5 h. Water (5 mL) was added, the reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (300 mL). The organic layer was washed with saturated Na_2CO_3 solution (2 x 100 mL) and water (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. R_f = 0.67 (cyclohexane/ethyl acetate/dimethylethylamine 6:4:0.2). Pale yellow solid, mp 150 -190 °C (decomposition), yield 1.81 g (53 %). Purity (HPLC): 99.2 % (t_R = 23.3 min). $C_{23}H_{21}FN_2O_3$ (392.4 g/mol). Exact mass (APCI): m/z = 393.1606 (calcd. 393.1609 for $C_{23}H_{22}FN_2O_3$ [M+H^+]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 2.08 - 2.18 (m, 1H, 2-H), 2.66 (tt, *J* = 12.2/ 7.2 Hz, 1H, 2-H), 2.81 - 3.01 (m, 3H, 1-CH_2, 4-H), 3.25 (t, *J* = 13.0 Hz, 1H, 4-H), 3.72 (s, 3H, OCH_3), 4.31 - 4.51 (m, 3H, C*H*$_2$$CH_2$F, 3-H), 4.65 (dt, *J* = 47.5/4.3 Hz, 2H, CH_2F), 6.72 (dd, *J* = 8.8/2.2 Hz, 1H, 7-H), 6.86 (d, *J* = 2.1 Hz, 1H,

5-H), 7.31 (d, *J* = 8.8 Hz, 1H, 8-H), 7.83 - 7.93 (m, 4H, 4-H_{phth}, 5-H_{phth}, 6-H_{phth}, 7-H_{phth}). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 21.5 (1C, C-1), 24.6 (1C, C-4), 26.3 (1C, C-2), 43.0 (d, *J* = 20.3 Hz, 1C, *C*$H_2$$CH_2$F), 47.6 (1C, C-3), 55.3 (1C, OCH_3), 82.9 (d, *J* = 167.5 Hz, 1C, CH_2F), 99.9 (1C, C-5), 106.6 (1C, C-4a), 110.1 (2C, C-7, C-8), 123.0 (2C, C-4$_{phth}$, C-7$_{phth}$), 126.8 (1C, C-4b), 131.5 (2C, C-3a$_{phth}$, C-7a$_{phth}$), 131.7 (1C, C-8a), 134.5 (2C, C-5$_{phth}$, C-6$_{phth}$), 135.2 (1C, C-9a), 153.4 (1C, C-6), 167.9 (2C, C=O). FTIR (neat): ṽ (cm^{-1}) = 2931 (w, C-H, aliph), 1701 (s, C=O), 1589 (w, C-C, arom).

*6.3.11 N-[6-(Methylsulfonyl)carbazol-3-yl]phthalimide (**18**)*

Tetrahydrocarbazole **16** (2.00 g, 5.1 mmol, 1 eq.) was dissolved in THF (40 mL) and DDQ (2.88 g, 13 mmol, 2.5 eq.) was added to the solution. The reaction mixture was heated at reflux for 3 h. After removing the solvent under reduced pressure, the residue was filtered, washed with water (350 mL), dried under reduced pressure and freeze-dried overnight. R_f = 0.45 (cyclohexane/ethyl acetate/formic acid 4:6:0.2). Pale yellow solid, mp > 300 °C, yield 1.75 g (88 %). Purity (HPLC): 75.9 % (t_R = 18.7 min). $C_{21}H_{14}N_2O_4S$ (390.4 g/mol). Exact mass (APCI): m/z = 391.0735 (calcd. 391.0747 for $C_{21}H_{15}N_2O_4S$ [M+H$^+$]). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 3.24 (s, 3H, CH_3), 7.55 (dd, *J* = 8.5/1.9 Hz, 1H, 2-H), 7.72 (d, *J* = 8.5 Hz, 1H, 1-H), 7.75 (d, *J* = 8.6 Hz, 1H, 8-H), 7.93 - 7.95 (m, 3H, 7-H, 5-H_{phth}, 6-H_{phth}), 8.00 - 8.02 (m, 2H, 4-H_{phth}, 7-H_{phth}), 8.37 (d, *J* = 1.7 Hz, 1H, 4-H), 8.74 (d, *J* = 1.8 Hz, 1H, 5-H), 12.09 (s, 1H, NH). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 44.5 (1C, CH_3), 111.8 (1C, C-1), 111.8 (1C, C-8), 120.5 (1C, C-4), 120.6 (1C, C-5), 121.9 (1C, C-4b), 122.1 (1C, C-3), 123.4 (2C, C-4$_{phth}$, C-7$_{phth}$), 124.0 (1C, C-4a), 124.5 (1C, C-7), 126.6 (1C, C-2), 131.2 (1C, C-6), 131.6 (2C, C-3a$_{phth}$, C-7a$_{phth}$), 134.8 (2C, C-5$_{phth}$, C-6$_{phth}$), 140.0 (1C, C-9a), 142.7 (1C, C-8a), 167.6 (2C, C=O). FTIR (neat): ṽ (cm^{-1}) = 3352 (m, N-H), 2920 (w, C-H, aliph), 1705 (s, C=O), 1604 (w, C-C, arom), 1134 (s, SO_2).

*6.3.12 N-[9-(2-Fluoroethyl)-6-methoxycarbazol-3-yl]phthalimide (**19**)*

Tetrahydrocarbazole **17** (1.40 g, 3.6 mmol, 1 eq.) was dissolved in THF (28 mL) and DDQ (2.02 g, 8.9 mmol, 2.5 eq.) was added to the solution. The reaction mixture was heated at reflux for 2 h. After evaporation of the solvent under reduced pressure, the residue was filtered and washed with ethyl acetate (250 mL) and CH_2Cl_2 (70 mL). The solvents were evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (200 mL). Afterwards, the organic layer was washed with a saturated Na_2CO_3 solution (70 mL), a saturated NH_4Cl solution (70 mL), water (2 x 70 mL) and brine (70 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting product was used without further purification. R_f = 0.44 (cyclohexane/ethyl acetate/dimethylethylamine 5:5:0.2). Dark yellow solid, mp 222 °C, yield 1.15 g (83 %). $C_{23}H_{17}FN_2O_3$ (388.4 g/mol). Compound was purified by fc with a gradient (Ø = 2 cm, l = 14 cm, v = 10 mL, cyclohexane/ethyl acetate/dimethylethylamine 80:20:1, 75:25:1, 60:40:1) leading to a purity (HPLC) of 96.9 % (t_R = 21.4 min). Exact mass (APCI): m/z = 389.1284 (calcd. 389.1296 for $C_{23}H_{18}FN_2O_3$ $[M+H^+]$). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 3.85 (s, 3H, OCH_3), 4.72 - 4.86 (m, 4H, CH_2CH_2F), 7.14 (dd, *J* = 8.9/2.5 Hz, 1H, 7-H), 7.46 (dd, *J* = 8.7/2.0 Hz, 1H, 2-H), 7.60 (d, *J* = 8.9 Hz, 1H, 8-H), 7.71 (d, *J* = 8.7 Hz, 1H, 1-H), 7.73 (d, *J* = 2.4 Hz, 1H, 5-H), 7.91 - 7.95 (m, 2H, 5-H_{phth}, 6-H_{phth}), 7.98 - 8.02 (m, 2H, 4-H_{phth}, 7-H_{phth}), 8.20 (d, *J* = 1.9 Hz, 1H, 4-H). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 43.1 (d, *J* = 20.1 Hz, 1C, CH_2CH_2F), 55.6 (1C, OCH_3), 82.7 (d, *J* = 167.7 Hz, 1C, CH_2F), 103.2 (1C, C-5), 109.7 (1C, C-1), 110.7 (1C, C-8), 115.4 (1C, C-7), 119.9 (1C, C-4), 122.1 (1C, C-4a), 122.3 (1C, C-4b), 122.7 (1C, C-3), 123.4 (2C, C-4_{phth}, C-7_{phth}), 125.2 (1C, C-2), 131.6 (2C, C-$3a_{phth}$, C-$7a_{phth}$), 134.7 (2C, C-5_{phth}, C-6_{phth}), 135.6 (1C, C-8a),

140.1 (1C, C-9a), 153.6 (1C, C-6), 167.7 (2C, C=O). FTIR (neat): ṽ (cm^{-1}) = 2924 (w, C-H, aliph), 1716 (s, C=O).

*6.3.13 N-[9-(2-Fluoroethyl)-6-(methylsulfonyl)carbazol-3-yl]phthalimide (**20**)*

Under N_2 atmosphere, carbazole derivative **18** (1.10 g, 2.8 mmol, 1 eq.) was dissolved in dry DMF (25 mL). Cs_2CO_3 (1.84 g, 5.6 mmol, 2 eq.) was added at 0 °C. After stirring at 0 °C for 30 min, fluoroethyl tosylate (0.738 g, 3.4 mmol, 1.2 eq.) was added slowly to the reaction mixture. Stirring was continued for 18 h at room temperature. Afterwards, the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (200 mL) and the solution was washed with water (3 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc with a gradient (ø = 3 cm, l = 20 cm, v = 30 mL, cyclohexane/CH_2Cl_2 60:40, 50:50, 30:70, 15:85, 0:100, CH_2Cl_2/methanol 100:0.5, cyclohexane/CH_2Cl_2/ dimethylethylamine 30:70:1, 15:85:0, R_f = 0.60 (cyclohexane/ethyl acetate/ dimethylethylamine 1:9:0.2)). Pale yellow solid, mp 289 - 292 °C, yield 0.756 g (61 %). Purity (HPLC): 96.0 % (t_R = 20.0 min). $C_{23}H_{17}FN_2O_4S$ (436.5 g/mol). Exact mass (APCI): m/z = 437.0965 (calcd. 437.0966 for $C_{23}H_{18}FN_2O_4S$ $[M+H^+]$). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 3.26 (s, 3H, CH_3), 4.78 - 4.97 (m, 4H, CH_2CH_2F), 7.63 (dd, *J* = 8.7/2.0 Hz, 1H, 2-H), 7.89 (d, *J* = 8.8 Hz, 1H, 1-H), 7.92 - 7.97 (m, 3H, 8-H, 5-H_{phth}, 6-H_{phth}), 7.99 - 8.05 (m, 3H, 7-H, 4-H_{phth}, 7-H_{phth}), 8.43 (d, *J* = 2.0 Hz, 1H, 4-H), 8.78 (d, *J* = 1.8 Hz, 1H, 5-H). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 43.4 (d, *J* = 19.9 Hz, 1C, CH_2CH_2F), 44.4 (1C, CH_3), 83.1 (d, *J* = 163.3 Hz, 1C, CH_2F), 110.6 (1C, C-8), 110.7 (1C, C-1), 120.5 (1C, C-4), 120.5 (1C, C-8), 121.6 (1C, C-4b), 121.9 (1C, C-4a), 123.4 (2C, C-4$_{phth}$, C-7$_{phth}$), 124.5 (1C, C-3), 124.7 (1C, C-7), 126.7 (1C, C-2), 131.6 (2C, C-3a$_{phth}$, C-7a$_{phth}$), 131.7 (1C, C-6), 134.8 (2C, C-5$_{phth}$, C-6$_{phth}$), 140.4 (1C, C-9a),

143.1 (1C, C-8a), 167.5 (2C, C=O). FTIR (neat): ṽ (cm^{-1}) = 2935 (w, C-H, aliph), 1712 (s, C=O), 1597 (w, C-C, arom), 1138 (s, SO_2).

*6.3.14 9-(2-Fluoroethyl)-6-methoxycarabzol-3-ammonium chloride (**21**·HCl)*

Hydrazine monohydrate (0.36 mL, 7.3 mmol, 3 eq.) was added to a solution of phthalimide **19** (0.947 g, 2.4 mmol, 1 eq.) in ethanol 96 % (25 mL). The reaction mixture was heated at reflux for 2.25 h. After cooling down to room temperature, the solution was filtered, the residue was washed with ethanol 96 % followed by evaporation of the solvent. The residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with NaOH solution (1 M, 30 mL), water (30 mL) and brine (30 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was dissolved in Et_2O, filtered and the product was precipitated by the addition of a solution of HCl in Et_2O (2 M, 1.2 mL, 2.4 mmol, 1 eq.). The product was filtered off, washed with Et_2O (10 mL) and dried under reduced pressure. R_f = 0.50 (cyclohexane/ethyl acetate/dimethylethylamine 3:7:0.2). Grey solid, mp 180 - 210 °C (decomposition), yield 0.373 g (52 %). Purity (HPLC): 88.9 % (t_R = 14.7 min). $C_{15}H_{16}ClFN_2O$ (294.8 g/mol). Exact mass (APCI): m/z = 259.1242 (calcd. 259.1241 for $C_{15}H_{16}FN_2O$ [$M+H^+$]). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 3.87 (s, 3H, OCH_3), 4.59 - 4.91 (m, 4H, CH_2CH_2F), 7.15 (dd, *J* = 8.9/2.5 Hz, 1H, 7-H), 7.45 (dd, *J* = 8.7/2.2 Hz, 1H, 2-H), 7.59 (d, *J* = 8.9 Hz, 1H, 8-H), 7.70 (d, *J* = 8.7 Hz, 1H, 1-H), 7.76 (d, *J* = 2.5 Hz, 1H, 5-H), 8.12 (d, *J* = 2.1 Hz, 1H, 4-H), 10.41 (s, 3H, $-NH_3^+$). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 43.1 (d, *J* = 20.0 Hz, 1C, CH_2CH_2F), 55.7 (1C, OCH_3), 82.6 (d, *J* = 167.7 Hz, 1C, CH_2F), 103.3 (1C, C-5), 110.5 (1C, C-1), 110.8 (1C, C-8), 114.9 (1C, C-4), 115.9 (1C, C-7), 120.5 (1C, C-2), 121.9 (1C, C-4b), 122.2 (1C, C-4a), 122.6 (1C, C-3), 135.8 (1C, C-8a), 139.8 (1C, C-9a), 153.7 (1C, C-6). FTIR (neat): ṽ (cm^{-1}) = 2858 (w, C-H, aliph), 1562 (w, C-C, arom).

*6.3.15 9-(2-Fluoroethyl)-6-(methylsulfonyl)carbazol-3-ammonium chloride (**22**·HCl)*

CH_2Cl_2 (15 mL) and hydrazine monohydrate (32 µL, 0.65 mmol, 2 eq.) were added to a stirred suspension of phthalimide **20** (0.143 g, 0.33 mmol, 1 eq.) in ethanol 96 % (3 mL). The mixture was heated at 40 °C for 20 h. After the mixture was cooled down to room temperature, phthalhydrazide was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and the solution was washed with NaOH solution (1 M, 3 x 10 mL), water (10 mL) and brine (10 mL). Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave a residue, which was dissolved in THF (10 mL) and precipitated with a solution of HCl in Et_2O (2 M, 0.16 mL, 0.33 mmol, 1 eq.). After filtration, the product was washed with Et_2O (3 x 2 mL) and dried under reduced pressure. R_f = 0.33 (ethyl acetate/dimethylethylamine 10:0.2). Colorless solid, mp 205 - 250 °C (decomposition), yield 86 mg (77 %). Purity (HPLC): 98.5 % (t_R = 12.5 min). $C_{15}H_{16}ClFN_2O_2S$ (342.8 g/mol). Exact mass (APCI): m/z = 307.0908 (calcd. 307.0911 for $C_{15}H_{16}FN_2O_2S$ $[M+H^+]$). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) = 3.27 (s, 3H, CH_3), 4.76 - 4.91 (m, 4H, CH_2CH_2F), 7.56 (dd, *J* = 8.7/2.1 Hz, 1H, 2-H), 7.85 (d, *J* = 8.7 Hz, 1H, 1-H), 7.92 (d, *J* = 8.7 Hz, 1H, 8-H), 8.02 (dd, *J* = 8.7/1.8 Hz, 1H, 7-H), 8.31 (d, *J* = 1.9 Hz, 1H, 4-H), 8.83 (d, *J* = 1.9 Hz, 1H, 5-H), 10.34 (s, 3H, $-NH_3^+$). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 43.4 (d, *J* = 20.0 Hz, 1C, CH_2CH_2F), 44.4 (1C, CH_3), 82.5 (d, *J* = 167.6 Hz, 1C, CH_2F), 110.7 (1C, C-8), 111.4 (1C, C-1), 115.2 (1C, C-4), 120.8 (1C, C-4b), 121.3 (1C, C-5), 121.9 (1C, C-2), 122.2 (1C, C-4a), 124.9 (1C, C-7), 125.0 (1C, C-3), 131.7 (1C, C-6), 140.0 (1C, C-9a), 143.1 (1C, C-8a). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 2804 (w, C-H, aliph), 1597 (w, C-C, arom), 1103 (s, SO_2).

*6.3.16 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-[9-(2-fluoroethyl)-6-methoxycarbazol-3-yl]propanamide (**23a**)*

Under N_2 atmosphere, *N*-ethyl-*N*,*N*-diisopropylamine (0.11 mL, 0.65 mmol, 3 eq.) and COMU® (120 mg, 0.28 mmol, 1.3 eq.) were added to a solution of carboxylic acid **12a** (75 mg, 0.24 mmol, 1.1 eq.) in dry THF (3 mL). After the reaction mixture was stirred at room temperature for 30 min, carbazolamine hydrochloride **21**·HCl (64 mg, 0.22 mmol, 1 eq.) was added and stirring was continued for 23 h. All volatiles were removed under reduced pressure and the residue was suspended in ethyl acetate (5 mL) and water (5 mL). Afterwards, the suspension was filtered and the residue was washed with water (10 mL), ethyl acetate (4 mL), ethanol 96 % (4 mL) and CH_2Cl_2 (4 mL). The product was dried under reduced pressure and freeze-dried overnight. R_f = 0.44 (cyclohexane/ethyl acetate/formic acid 5:5:0.2). Colorless solid, mp 191 °C, yield 39 mg (33 %). Purity (HPLC): 96.9 % (t_R = 23.0 min). $C_{26}H_{21}BrF_2N_4O_3$ (555.4 g/mol). Exact mass (APCI): m/z = 555.0842 (calcd. 555.0838 for $C_{26}H_{22}{}^{79}BrF_2N_4O_3$ [M+H$^+$]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 2.99 (t, *J* = 6.9 Hz, 2H, CH_2CH_2CONH), 3.36 - 3.38 (m, 2H, CH_2CH_2CONH), 3.85 (s, 3H, OCH_3), 4.60 - 4.82 (m, 4H, CH_2CH_2F), 7.07 (dd, *J* = 8.8/2.5 Hz, 1H, 7-H_{carb}), 7.42 - 7.48 (m, 2H, 2-H_{carb}, 5-H_{phenyl}), 7.49 - 7.52 (m, 2H, 1-H_{carb}, 8-H_{carb}), 7.58 (d, *J* = 2.4 Hz, 1H, 5-H_{carb}), 7.83 (dd, *J* = 8.6/2.6 Hz, 1H, 3-H_{phenyl}), 7.89 (dd, *J* = 8.8/6.1 Hz, 1H, 6-H_{phenyl}), 8.43 (d, *J* = 1.7 Hz, 1H, 4-H_{carb}), 10.12 (s, 1H, CONH). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 21.8 (1C, CH_2CH_2CONH), 31.9 (1C, CH_2CH_2CONH), 43.0 (d, *J* = 20.2 Hz, 1C, CH_2CH_2F), 55.6 (1C, OCH_3), 82.6 (d, *J* = 167.8 Hz, 1C, CH_2F), 102.7 (1C, C-5_{carb}), 109.4 (1C, C-1_{carb}), 110.4 (1C, C-8_{carb}), 111.1 (1C, C-4_{carb}), 115.0 (1C, C-7_{carb}), 115.5 (d, *J* = 21.6 Hz, 1C, C-5_{phenyl}), 118.8 (1C, C-2_{carb}), 121.4 (d, *J* = 25.0 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 122.1 (d, *J* = 10.0 Hz, 1C, C-2_{phenyl}), 122.4 (1C, C-$4b_{carb}$), 124.4 (d, *J* = 3.4 Hz, 1C, C-1_{phenyl}), 130.8 (1C, C-3_{carb}), 133.6 (d, *J* = 9.4 Hz, 1C, C-

6_{phenyl}), 135.6 (1C, C-$8a_{carb}$), 137.3 (1C, C-$9a_{carb}$), 153.2 (1C, C-6_{carb}), 162.8 (d, *J* = 253.3 Hz, 1C, C-4_{phenyl}), 166.5 (1C, C-$3_{oxadiazole}$), 168.5 (1C, C=O), 179.6 (1C, C-$5_{oxadiazole}$). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 3263 (w, N-H), 2931 (w, C-H, aliph), 1643 (s, C=O).

*6.3.17 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-[9-(2-fluoroethyl)-6-(methylsulfonyl)carbazol-3-yl]propanamide (**24a**)*

Under N_2 atmosphere, *N*-ethyl-*N*,*N*-diisopropylamine (91 µL, 0.53 mmol, 3 eq.) and COMU® (98 mg, 0.23 mmol, 1.3 eq.) were added to a solution of carboxylic acid **12a** (61 mg, 0.19 mmol, 1.1 eq.) in dry THF (8 mL). After the reaction mixture was stirred at room temperature for 30 min, carbazolamine hydrochloride **22**·HCl (60 mg, 0.18 mmol, 1 eq.) was added and stirring was continued for 20 h. Afterwards, all volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with NaOH solution (10 mL), water (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc with a gradient (ø = 2 cm, l = 15 cm, v = 10 mL, cyclohexane/CH_2Cl_2 40:60, 20:80, 0:100, CH_2Cl_2/methanol 100:0.5, 100:0.75, 100:1, R_f = 0.29 (cyclohexane/ethyl acetate/formic acid 4:6:0.2)). Colorless solid, mp 212 - 213 °C, yield 49 mg (47 %). Purity (HPLC): 97.6 % (t_R = 21.1 min). $C_{26}H_{21}BrF_2N_4O_4S$ (603.4 g/mol). Exact mass (APCI): m/z = 603.0508 (calcd. 603.0508 for $C_{26}H_{22}{}^{79}BrF_2N_4O_4S$ $[M+H^+]$). ^{1}H NMR (600 MHz, DMSO-D_6): δ (ppm) = 3.02 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CONH), 3.25 (s, 3H, CH_3), 3.36 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CONH), 4.74 - 4.85 (m, 4H, CH_2CH_2F), 7.45 (td, *J* = 8.5/2.6 Hz, 1H, 5-H_{phenyl}), 7.60 (dd, *J* = 8.8/1.8 Hz, 1H, 2-H_{carb}), 7.69 (d, *J* = 8.8 Hz, 1H, 1-H_{carb}), 7.80 - 7.86 (m, 2H, 8-H_{carb}, 3-H_{phenyl}), 7.89 (dd, *J* = 8.7/6.1 Hz, 1H, 6-H_{phenyl}), 7.95 (dd, *J* = 8.7/1.7 Hz, 1H, 7-H_{carb}), 8.61 (d, *J* = 1.8 Hz, 1H, 4-H_{carb}), 8.65 (d, *J* = 1.7 Hz, 1H, 5-H_{carb}), 10.25 (s, 1H, CONH). ^{13}C NMR (151 MHz, DMSO-D_6): δ (ppm) = 21.8 (1C, CH_2CH_2CONH), 32.0 (1C,

CH_2CH_2CONH), 43.3 (d, *J* = 19.9 Hz, 1C, CH_2CH_2F), 44.4 (1C, CH_3), 82.5 (d, *J* = 167.7 Hz, 1C, CH_2F), 110.2 (1C, C-8_{carb}), 110.4 (1C, C-1_{carb}), 111.2 (1C, C-4_{carb}), 115.5 (d, *J* = 21.6 Hz, 1C, C-5_{phenyl}), 119.9 (1C, C-2_{carb}), 120.1 (1C, C-5_{carb}), 121.4 (d, *J* = 25.0 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 121.8 (1C, C-$4b_{carb}$), 122.1 (d, *J* = 10.1 Hz, 1C, C-2_{phenyl}), 124.1 (1C, C-7_{carb}), 124.4 (d, *J* = 3.4 Hz, 1C, C-1_{phenyl}), 131.0 (1C, C-6_{carb}), 132.5 (1C, C-3_{carb}), 133.6 (d, *J* = 9.4 Hz, 1C, C-6_{phenyl}), 137.5 (1C, C-9a $_{carb}$), 142.9 (1C, C-$8a_{carb}$), 162.8 (d, *J* = 253.2 Hz, 1C, C-4_{phenyl}), 166.5 (1C, C-$3_{oxadiazole}$), 168.8 (1C, C=O), 179.6 (1C, C-$5_{oxadiazole}$). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 3325 (w, N-H), 2924 (w, C-H, aliph), 1678 (m, C=O), 1593 (w, C-C, arom), 1570 (m, C-C, arom), 1126 (s, SO_2).

*6.3.18 9-(2-Fluoroethyl)-6-methoxy-1,2,3,4-tetrahydrocarbazol-3-ammonium chloride (**25**·HCl)*

Hydrazine monohydrate (66 µL, 1.4 mmol, 2 eq.) was added to a solution of phthalimide **17** (268 mg, 0.68 mmol, 1 eq.) in ethanol 96 % (10 mL). The reaction mixture was heated at reflux for 2 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate (30 mL) and the organic layer was washed with NaOH solution (1 M, 20 mL). The NaOH solution was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in Et_2O and filtered followed by the addition of a solution of HCl in Et_2O (2 M, 0.34 mL, 0.68 mmol, 1.0 eq) until the salt **25**·HCl precipitated completely. The product was filtered off, washed with Et_2O (5 mL) and dried under reduced pressure. R_f = 0.35 (ethyl acetate/methanol/dimethylethylamine 7:3:0.2). Beige solid, mp 225 - 226 °C, yield 122 mg (60 %). Purity (HPLC): 96.6 % (t_R = 14.2 min). $C_{15}H_{20}ClFN_2O$ (298.8 g/mol). Exact mass (APCI): m/z = 363.1555 (calcd. 263.1554 for $C_{15}H_{20}FN_2O$ [M+H^+]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 1.86 - 1.99 (m, 1H, 2-H), 2.16 - 2.26 (m, 1H, 2-H),

2.66 (dd, *J* = 14.8/8.6 Hz, 1H, 4-H), 2.73 - 2.93 (m, 2H, 1-CH_2), 3.03 (dd, *J* = 16.6/3.3 Hz, 1H, 4-H), 3.47 (s, broad, 1H, 3-H), 3.74 (s, 3H, OCH_3), 4.33 (dt, *J* = 28.0/4.6 Hz, 2H, C*H*$_2$$CH_2F$), 4.61 (dt, *J* = 47.7/4.3 Hz, 2H, CH_2F), 6.71 (dd, *J* = 8.7/2.0 Hz, 1H, 7-H), 6.87 (d, *J* = 2.0 Hz, 1H, 5-H), 7.29 (d, *J* = 8.8 Hz, 1H, 8-H), 8.30 (s, 3H, -NH_3^+). ^{13}C NMR (101 MHz, DMSO-D_6): δ (ppm) = 19.6 (1C, C-1), 25.7 (1C, C-4), 26.6 (1C, C-2), 43.0 (d, *J* = 20.4 Hz, 1C, *C*$H_2$$CH_2F$), 46.9 (1C, C-3), 55.4 (1C, OCH_3), 82.9 (d, *J* = 167.5 Hz, 1C, CH_2F), 99.8 (1C, C-5), 104.7 (1C, C-4a), 110.2 (1C, C-8), 110.3 (1C, C-7), 126.7 (1C, C-4b), 131.7 (1C, C-8a), 134.9 (1C, C-9a), 153.5 (1C, C-6). FTIR (neat): $\tilde{\nu}$ (cm^{-1}) = 3452 (w, N-H), 2900 (m, C-H, aliph), 1589 (w, C-C, arom).

*6.3.19 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-N-[9-(2-fluoroethyl)-6-methoxy-1,2,3,4-tetrahydrocarbazol-3-yl]propanamide (**26a**)*

Under N_2 atmosphere, *N*-ethyl-*N*,*N*-diisopropylamine (0.13 mL, 0.74 mmol, 3 eq.) and COMU® (137 mg, 0.32 mmol, 1.3 eq.) were added to a solution of carboxylic acid **12a** (85 mg, 0.27 mmol, 1.1 eq.) in dry THF (3 mL). After the reaction mixture was stirred at room temperature for 30 min, tetrahydrocarbazolamine hydrochloride **25**·HCl (74 mg, 0.25 mmol, 1 eq.) was added and stirring was continued for 23 h. Afterwards, all volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with water (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by fc (Ø = 2 cm, l = 15 cm, v = 10 mL, cyclohexane/ethyl acetate 70:30, R_f = 0.38 (cyclohexane/ethyl acetate/formic acid 5:5:0.2)). Colorless solid, mp 159 °C, yield 91 mg (66 %). Purity (HPLC): 93.0 % (t_R = 22.7 min). $C_{26}H_{25}BrF_2N_4O_3$ (559.4 g/mol). Exact mass (APCI): m/z = 559.1152 (calcd. 559.1151 for $C_{26}H_{26}{}^{79}BrF_2N_4O_3$ [M+H^+]). ^{1}H NMR (400 MHz, DMSO-D_6): δ (ppm) = 1.73 - 1.85 (m, 1H, 2-H_{carb}), 1.94 - 2.03 (m, 1H, 2-H_{carb}), 2.40 - 2.48 (m, 1H, 4-H_{carb}), 2.72 (t, *J* = 7.4 Hz, 2H, CH_2C*H*$_2$CONH), 2.74

- 2.86 (m, 2H, 1-CH_{2carb}), 2.90 (dd, *J* = 15.0/5.2 Hz, 1H, 4-H_{carb}), 3.24 (t, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_2CONH$), 3.74 (s, 3H, OCH_3), 4.04 (dt, *J* = 12.0/7.2 Hz, 1H, 3-H_{carb}), 4.32 (dt, *J* = 27.8/4.1 Hz, 2H, C*H*$_2$$CH_2F$), 4.62 (dt, *J* = 47.5/4.7 Hz, 2H, CH_2F), 6.70 (dd, *J* = 8.8/2.5 Hz, 1H, 7-H_{carb}), 6.83 (d, *J* = 2.4 Hz, 1H, 5-H_{carb}), 7.27 (d, *J* = 8.8 Hz, 1H, 8-H_{carb}), 7.46 (td, *J* = 8.4/2.6 Hz, 1H, 5-H_{phenyl}), 7.84 (dd, *J* = 8.6/2.6 Hz, 1H, 3-H_{phenyl}), 7.88 (dd, *J* = 8.7/6.1 Hz, 1H, 6-H_{phenyl}), 8.15 (d, *J* = 7.6 Hz, 1H, CON*H*). ^{13}C NMR (101 MHz, DMSO-D_6): *δ* (ppm) = 20.0 (1C, C-1_{carb}), 21.9 (1C, *C*H_2CH_2CONH), 27.3 (1C, C-4_{carb}), 28.4 (1C, C-2_{carb}), 31.2 (1C, CH_2*C*H_2CONH), 42.9 (d, *J* = 20.4 Hz, 1C, *C*H_2CH_2F), 45.1 (1C, C-3_{carb}), 55.4 (1C, OCH_3), 82.9 (d, *J* = 167.6 Hz, 1C, CH_2*C*H_2F), 99.8 (1C, C-5_{carb}), 106.4 (1C, C-$4a_{carb}$), 109.9 (2C, C-7_{carb}, C-8_{carb}), 115.5 (d, *J* = 21.6 Hz, 1C, C-5_{phenyl}), 121.4 (d, *J* = 25.1 Hz, 1C, C-3_{phenyl}), 122.1 (d, *J* = 10.1 Hz, 1C, C-2_{phenyl}), 124.5 (d, *J* = 3.5 Hz, 1C, C-1_{phenyl}), 127.1 (1C, C-$4b_{carb}$), 131.6 (1C, C-$8a_{carb}$), 133.6 (d, *J* = 9.4 Hz, 1C, C-6_{phenyl}), 135.3 (1C, C-$9a_{carb}$), 153.3 (1C, C-6_{carb}), 162.8 (d, *J* = 253.3 Hz, 1C, C-4_{phenyl}), 166.5 (1C, C-$3_{oxadiazole}$), 169.4 (1C, C=O), 179,6 (1C, C-$5_{oxadiazole}$). FTIR (neat): ṽ (cm^{-1}) = 3302 (w, N-H), 2931 (w, C-H, aliph), 1635 (s, C=O).

6.4 Receptor binding studies

[^{3}H]CP55940 displacement assays were used for the determination of affinity (K_i) values of ligands for the cannabinoid CB_1 and CB_2 receptors. Membrane aliquots containing 5 µg (CHOK1hCB_1_bgal) or 1 µg (CHOK1hCB_2_bgal) of membrane protein in 100 µL assay buffer (50 mM Tris–HCl, 5 mM $MgCl_2$, 0.1 % BSA, pH 7.4) were incubated at 30 °C for 1 h, in presence of 3.5 nM [^{3}H]CP55940 (CHOK1hCB_1_bgal) or 1.5 nM [^{3}H]CP55940 (CHOK1hCB_2_bgal). Initially, 1 µM of competing ligand was used, followed by six concentrations of competing ligand (between $10^{-5.5}$ M and $10^{-10.5}$ M) when more than 50 % displacement was found at 1 µM. Non-specific binding was determined in the presence of 10 µM AM630 (CHOK1hCB2_bgal) or 10 µM

SR141716A (CHOK1hCB1_bgal). Incubation was terminated by rapid filtration through GF/C filters (Whatman International, Maidstone, UK), and followed by extensive washing using a Filtermate 96-well harvester (Perkin Elmer, Groningen, The Netherlands). Filter-bound radioactivity was determined by scintillation spectrometry using a 1450 Microbeta Wallac Trilux scintillation counter (Perkin Elmer).

Data analysis was performed by using the nonlinear regression curve fitting program GraphPad Prism 7.0 (GraphPad Software, Inc., San Diego, CA). From displacement assays, IC_{50} values were obtained by non-linear regression analysis of the displacement curves. The obtained IC_{50} values were converted into K_i values using the Cheng Prusoff equation [26] to determine the affinity of the ligands using a K_D value of [^{3}H]CP55940 of 0.93 nM at CB_2R.

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Graphical abstract