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Development of fluorinated CB_2 receptor agonists for PET studies

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ABSTRACT

A convergent strategy was followed to modify systematically carbazole based CB_2 receptor ligands. The length of the *N*-(fluoroalkyl) group (*n* in **7**), the length of the alkanamide (*m* in **7**) and the substitution pattern of the phenyl moiety (X and Y in **7**) were varied systematically. The highest CB_2 affinity was found for the 2-fluoroethyl substituted carbazole derivative **20a** (K_i = 5.8 nM) containing the propionamide and the 2-bromo-4-fluorophenyl moiety. According to docking studies **20a** fits nicely into the binding pocket of the CB_2 receptor, but elongation of the fluoroethyl side chain leads to a different binding mode of the ligands. The high CB_2 affinity together with the high selectivity over the CB_2 subtype qualifies the fluoroethyl derivative **20a** to be developed as a PET tracer.

1. Introduction

For centuries, *Cannabis sativa* was used as a medicinal plant suppressing pain and inflammation. In the 1930s, tetrahydrocannabinol (THC) and later on more than 60 different cannabinoids were isolated and characterized.[1,2] THC and its analogs led to the identification of the endocannabinoid system consisting of the endogenous ligands anandamide (*N*-arachidonyl ethanolamine, AEA)[3] and 2-*O*-arachidonylglycerol (2-AG),[4] which are agonists of the G-protein coupled cannabinoid CB_1 and CB_2 receptors. Furthermore the enzymes, which are responsible for the biosynthesis (e.g., *N*-acyltransferase, phosphodiesterase D, diacylglycerol lipase) and deactivation of endocannabinoids (e.g., fatty acid amide hydrolase, monoacylglycerol lipase) belong to the endocannabinoid system.[5,6]

For a long time the CB_2 receptor was regarded as the 'peripheral' CB receptor, since the CB_2 receptor is mainly expressed by hematopoietic cells, where its expression level is almost 100 times higher than the expression level of the CB_1 receptor.[7,8] An important function of the CB_2 receptor in the immune system is the regulation and release of cytokines which play a key role in inflammatory processes and immune response.[9]

However, during the last decades it was shown that the CB_2 receptor is also expressed in the CNS, microglia, neurons and neuronal stem cells.[10–14] It has a regulatory function on the proliferation and survival of neurons.[15–18] This discovery led to an increasing interest in the development of selective CB_2 ligands, which are devoid of psychotropic side effects mediated by the activation of CB_1 receptors.[19–21] Whereas the CB_2 receptor expression in the CNS of healthy men is very low, an increased amount of CB_2 receptors is expressed as reaction on inflammatory stimuli.[22–25]

Many neurodegenerative disorders like Alzheimer's disease,[15,26,27] multiple sclerosis,[7] Chorea Hungtington as well as depression[25] and schizophrenia[25] are linked to neuroinflammation, which is associated with an elevated CB_2 receptor expression.[9,28–31] Moreover, apoptosis of some tumor cells was stimulated by CB_2 receptor agonists.[32,33] Regarding the role of CB_2 receptors in the regulation of neuronal cell proliferation, in neurodegenerative and neuroinflammatory processes, CB_2 receptor stimulation by agonists could lead to reduction of neuroinflammation and stimulation of neurogenesis.

Imaging of CB_2 receptors by positron emission tomography (PET) could be used to determine the current state of CB_2 receptor expression in the CNS, which will serve as biomarker for the judgement of the therapeutic success in the fight against neurodegenerative and neuroinflammatory processes.

During the PET tracer development many aspects have to be considered in parallel. The ligand should bind with high affinity and selectivity at CB_2 receptors. An intermediate lipophilicity is required as very lipophilic ligands show very poor solubility and stick in membranes. On the other hand very polar compounds are not able to pass the blood-brain barrier and cannot reach the CNS.[34] Generally 18-fluorine labeled tracers are preferred over 11-carbon labeled ligands due to the relatively long half-life of 110 min of 18-fluorine compared with 20 min of 11-carbon.

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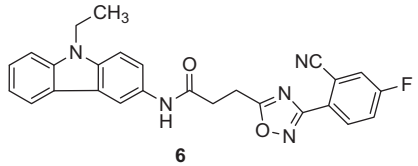
In the literature only few PET tracer candidates for imaging of CB_2 receptors are reported, which are summarized in Figure 1. The quinolin-2-one **1** shows high CB_2 affinity (K_i = 2.8 nM) and excellent selectivity over the CB_1 subtype. However, the radiochemical yields obtained after introduction of 18-fluorine into the phenyl moiety of **1** did not exceed 12%. Moreover, the very poor solubility of **1** inhibits the in vivo application.[35,36] Introduction of the [^{18}F]2-fluoroethyl moiety led to rather low CB_2 affinity of the inverse CB_2 agonist **2a** (K_i = 36 nM). The corresponding [^{11}C]methoxy derivative **2b** reveals a reasonable affinity towards the CB_2 receptor (K_i = 9.6 nM). Both tracers were rapidly metabolized in plasma leaving 41% of [^{18}F]tracer **2a** and 24% of [^{11}C]tracer **2b** unchanged after 10 min.[37] The 11-carbon labeled tracer **2b** showed in a first study with healthy humans the expected uptake in lymphoid tissues and appropriate brain kinetics.[38] The bissulfone **3** represents a promising candidate with affinities towards the human CB_1 and CB_2 receptor of 79 and 4.5 nM, respectively (Fig. 1). Although the log*P* value of **3** is in a favorable range (log*P* = 2.15), the brain uptake was very low. The high activity of efflux transporters at the blood–brain barrier might explain the low penetration of **3** into the central nervous system.[38] In 2011 the 18-fluorine-labeled indole derivative **4a** was reported showing moderate affinity towards the human CB_2 receptor, moderate brain uptake in mice and a considerable fraction of radiometabolites in the brain.[40] Compared to the fluoroethyl derivative **4a**, the corresponding 11-carbon labeled compound **4b** has very similar CB_2 receptor affinity and selectivity over the CB_1 subtype. Both indole derivatives have a low stability in vivo and radiometabolites were trapped in the brain.[41,42] Very high CB_2 affinity and selectivity of the thiazole derivative **5** was reported. The 11-carbon labeled derivative showed specific cerebral uptake in a mouse model of neuroinflammation. However, the high lipophilicity of **5** led to relatively high non-specific binding.[43,44] Although the [^{11}C]methyl ethers **2b**, **4b** and **5** show promising properties, we aim at the development of 18-fluorine labeled PET tracers with a longer half-life of the radioisotope, which is easier to handle and does not require a cyclotron on-site.



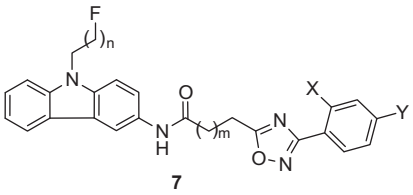
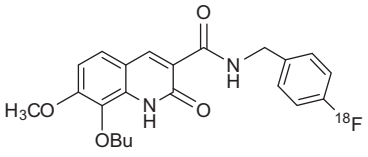
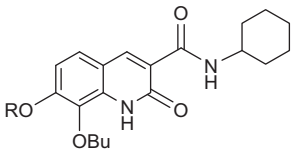


Figure 2. CB_2 receptor agonist **6** reported by Cheng et al.[45] and designed fluorinated CB_2 ligands **7**.

In this work we aim at the synthesis of fluorinated CB_2 receptor ligands, which can be developed into a [^{18}F]fluorinated PET-tracer for imaging of CB_2 receptors in the brain. The starting point of the project is the CB_2 receptor agonist **6** reported by Cheng et al.[45] (Fig. 2). Whereas Whereas only functional data are given in the original manuscript showing the CB_2 agonistic activity of **6**, the affinity towards the human CB receptors was reported by Rühl et al. (K_i (CB_2) = 6.98 nM, K_i (CB_1) >10 μM).[53] The ethyl side chain at the carbazole moiety will be used for the introduction of a fluorine atom. In order to identify the best fluorinated CB_2 ligand for labeling with 18-fluorine, a large set of diverse fluoroalkyl substituted carbazole derivatives **7** will be synthesized and relationships between the structure and the CB_2 affinity will be elaborated. In particular the fluoroalkyl side chain at the carbazole ring will be varied from fluoroethyl (n = 1) to fluorobutyl (n = 3), the length of the alkanamide will be varied from propionamide (m = 1) to butyramide (m = 2) and the substitution pattern of the phenyl residue will be modified by introduction of various substituents in different positions X and Y.

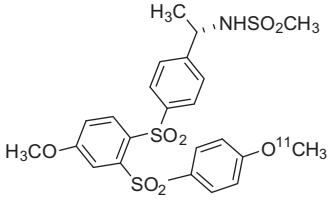


1
K_i (hCB_1) >10 μM
K_i (hCB_2) = 2.8 nM

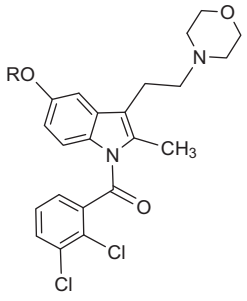


2a: R = $^{18}FCH_2CH_2$
K_i (hCB_1) > 1 μM
K_i (hCB_2) = 36 nM

2b: R = $^{11}CH_3$
K_i (hCB_1) > 1 μM
K_i (hCB_2) = 9.6 nM

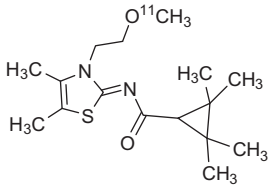


3
K_i (hCB_1) = 79 nM
K_i (hCB_2) = 4.5 nM



4a: R = $^{18}FCH_2CH_2$
K_i (hCB_1) > 10 μM
K_i (hCB_2) = 27 nM

4b: R = $^{11}CH_3$
K_i (hCB_1) = 6 μM
K_i (hCB_2) = 35 nM



5
K_i (hCB_1) = 270 nM
K_i (hCB_2) = 0.64 nM

Figure 1. PET tracer candidates for imaging of CB_2 receptors.

2. Synthesis

The synthesis of the fluorinated carbazole derivatives **7** was performed according to a convergent strategy, that is, various hydroxyalkyl-substituted carbazolamines **12**–**14** were reacted with different oxadiazolylalkanoic acids **9** and **11** to yield a diverse set of coupling products **15**–**19** (Scheme 2).

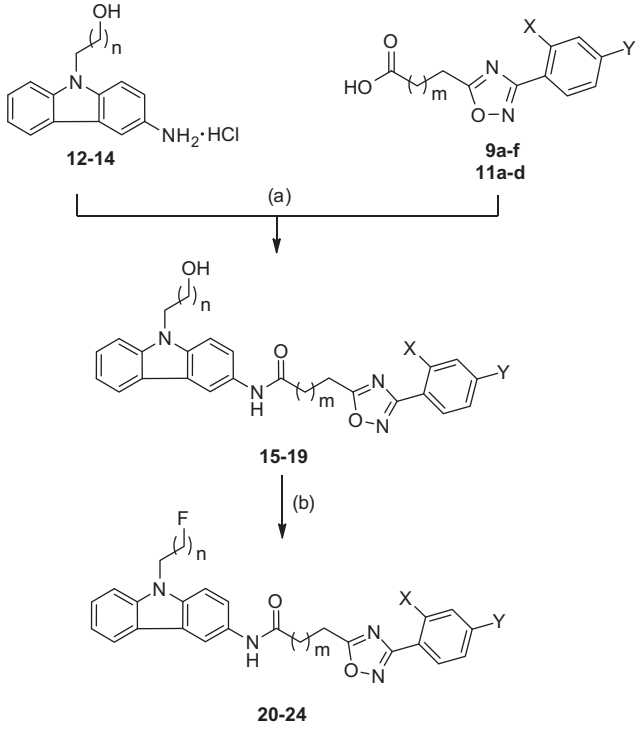
The hydroxalkyl substituent of the carbazole derivatives **12**–**14** was introduced upon hydroxyalkylation of carbazole with cyclic sulfates[46] (ethylene sulfate, trimethylene sulfate) or 1,4-dibromobutane and subsequent substitution with NaOH as key step. Nitration, reduction and precipitation as HCl salt led to the homologous series of hydroxyalkyl substituted carbazolamines **12**–**14**.[47]

The 1,2,4-oxadiazolylpropionic acids **9a**–**e** were prepared according to a literature procedure.[45] Addition of hydroxylamine to various benzonitriles **8a**–**e** afforded the corresponding amidoximes, which were transformed with succinic anhydride into the propionic acids **9a**–**e**. (Scheme 1) For the synthesis of the nitrile **9f** the bromobenzene **9a** was heated with methanol and H_2SO_4 to obtain the ester **10a**. A Rosenmund-von Braun reaction[45] with CuCN in boiling dimethylacetamide converted the bromobenzene **10a** into the cyanobenzene **10f**, which was subsequently hydrolyzed with LiOH to yield the propionic acid **9f**.

The homologous butyric acids **11a**–**d** were prepared according to the same strategy. Reaction of the benzonitriles **8a**–**d** with hydroxylamine led to the intermediate amide oximes, which upon treatment with glutaric anhydride in boiling dimethylformamide provided the butyric acids **11a**–**d** in 42–56% yield (Scheme 1).

Different coupling reagents (EDC, HATU) were investigated for the reaction of the carbazolamines **12**–**14** with the alkanoic acids **9** and **11** (Scheme 2). It was found that the uronium salt COMU® (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-$_{carb}$enium hexafluorophosphate)[48,49] gave the highest yields of amides and therefore COMU® was used as standard reagent for the preparation of all coupling products **15**–**19**. The alcohols **15**–**19** were transformed into the fluoroalkyl substituted carbazoles **20**–**24** using the fluorinating agent diethylaminodifluorosulfinium tetrafluoroborate ($Et_2N{=}SF_2{-}BF_4$, XtalFluor-E®).[50] After addition of $NEt_3{\cdot}3HF$ to the reaction mixture, the fluorinated compounds **20**–**24** were isolated in 4–91% yields.

This synthesis led to a diverse set of fluorinated CB_2 ligands **20**–**24**, which differ in the chain length (*n*) of the fluoroalkyl residue, the length (*m*) of the alkanamide and the substitution pattern (X, Y) of the phenyl moiety. Moreover, the corresponding alcohols **15**–**19** displaying a higher polarity than the fluoro derivatives **20**–**24** were also included into the cannabinoid receptor binding assays.

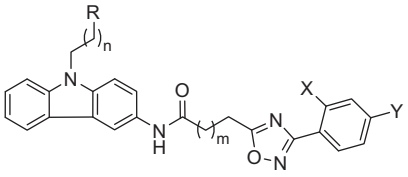


Scheme 2. Reagents and reaction conditions: (a) **9a–f** or **11a–d**, NEt_3, COMU®, then addition of **12**, **13** or **14**, DMF, <10 °C, 35–85%. (b) **15**–**19**, XtalFluor-E® ($Et_2N{=}SF_2{-}BF_4$), $NEt_3{\cdot}3HF$, CH_2Cl_2, −78 °C, rt, 3 h, 4–91%.

3. Receptor affinity

The CB_2 receptor affinity of the carbazole derivatives **15**–**24** was determined in competition experiments with the radioligand [^{3}H]CP-55,940.[51,52] The receptor material was obtained from

Table 1
CB_2 receptor affinity of carbazole derivatives **15**–**24**



15-24

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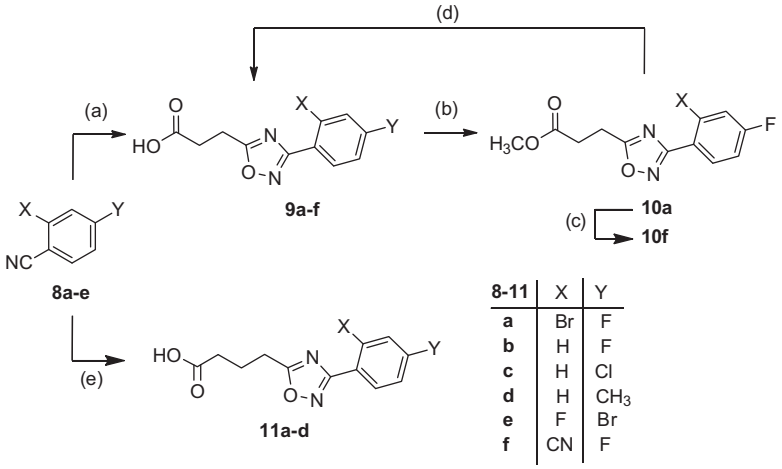
Compd.	R	n	m	X	Y	K_i ± SEM (nM)
15a	OH	1	1	Br	F	367
15b				H	F	1100
15c				H	Cl	990
15d				H	CH_3	10%[a]
15e				F	Br	35%[a]
15f				CN	F	486
16a	OH	2	1	Br	F	33 ± 1.1
16b				H	F	195 ± 45
16c				H	Cl	–
16d				H	CH_3	28%[a]
17a	OH	3	1	Br	F	96 ± 29
18a	OH	1	2	Br	F	0%[a]
18b				H	F	12%[a]
18c				H	Cl	584
18d				H	CH_3	4%[a]
19a	OH	2	2	Br	F	9%[a]
19b				H	F	19%[a]
19c				H	Cl	10%[a]
19d				H	CH_3	13%[a]
20a	F	1	1	Br	F	5.8 ± 2.4
20b				H	F	41 ± 15
20c				H	Cl	291 ± 57
20d				H	CH_3	377
20e				F	Br	476
20f				CN	F	858
21a	F	2	1	Br	F	1800
21b				H	F	10%[a]
21c				H	Cl	43%[a]
21d				H	CH_3	13%[a]
22a	F	3	1	Br	F	35%[a]
23a	F	1	2	Br	F	559
23b				H	F	25%[a]
23c				H	Cl	23%[a]
23d				H	CH_3	0%[a]
24a	F	2	2	Br	F	25%
24b				H	F	0%
24c				H	Cl	–
24d				H	CH_3	0%
CP 55,940						27 ± 6.0
WIN 55,212						70 ± 27
HU 210						18 ± 5.0

[a] Inhibition (%) of the radioligand binding at a concentration of the test compound of 1 μM.



Scheme 1. Reagents and reaction conditions: (a) (1) NH_2OH–HCl, Na_2CO_3, H_2O, rt, 25 min, then addition of **8a–e**, CH_3OH, 65 °C; (2) succinic anhydride, DMF, 148 °C, 30 min, 30–80%. (b) **9a**, CH_3OH, concd H_2SO_4, 45 min, reflux. (c) CuCN, DMA, 18.5 h, 155 °C. (d) **10f**, LiOH, THF/H_2O (3:1), 1 h, rt, 65%. (e) (1) NH_2OH–HCl, Na_2CO_3, H_2O, rt, 25 min, then addition of **8a–d**, CH_3OH, 86 °C; (2) glutaric anhydride, DMF, 148 °C, 30 min, 42–56%.

recombinant CHO cells expressing the human CB_2 receptor in large amounts. The non-specific binding of the radioligand was recorded in the presence of a large amount (10 μM) of non-labeled CP-55,940. The CB_2 affinity of compounds showing higher affinity than 200 nM in the first experiment were repeated twice and the mean value of three experiments are given in Table 1. The CB_1 affinity of the most potent CB_2 ligands was determined in order to prove the selectivity over this subtype.

The alcohols **15**–**19** show a considerably lower CB_2 affinity than the corresponding fluoro substituted compounds **20**–**24**. As a general trend the hydroxypropyl substituted derivatives **16** have higher CB_2 affinity than the corresponding hydroxyethyl substituted derivatives **15** (e.g., **15a**/**16a**, **15b**/**16b**). A further extension of the carbazole substituent to a hydroxybutyl side chain (**17a**, K_i = 96 nM) led to slight reduction of the CB_2 affinity. Extension of the propionamides **15**, **16** to butyramides **18**, **19** led to an almost complete loss of the CB_2 receptor affinity. Within this series of alcohols **15**–**19** the propionamide **16a** (m = 1) with a 3-hydroxypropyl side chain (n = 2) at the carbazole system and the 2-bromo-4-fluoro substitution pattern at the phenyl ring revealed the strongest interactions with the CB_2 receptor.

Transformation of the alcohols into the corresponding fluoroalkyl derivatives led to increased CB_2 receptor affinity. Generally the 2-fluoroethyl derivatives **20** display higher CB_2 affinity than the corresponding 3-fluoropropyl (**21**) and 4-fluorobutyl (**22**) homologs. Elongation of the spacer between the carbazole system and the 1,2,4-oxadiazole ring afforded the butyramides **23** and **24** (m = 2) with considerably reduced CB_2 receptor affinity.

The substitution pattern of the phenyl moiety at the 1,2,4-oxadiazole ring has a strong influence on the CB_2 affinity. The 4-fluorophenyl substituted compound **20b** possesses a CB_2 affinity of 41 nM. Replacement of the fluorine atom with a chlorine atom (**20c**) or a methyl moiety (**18d**) led to reduced CB_2 affinity. An additional large substituent in 2-position as in the 2-bromophenyl derivative **20a** increased the CB_2 affinity to 5.8 nM. Obviously two substituents attached to the phenyl moiety (i.e., a fluorine atom in 4-position and a large substituent in 2-position) appear to be favorable for high CB_2 affinity. However, an unexpected reduction of the CB_2 affinity was observed for **20e** and **20f**. Compound **20e** has the same but inverted substitution pattern (4-bromo-2-fluorophenyl residue) as the very potent CB_2 ligand **20a** and

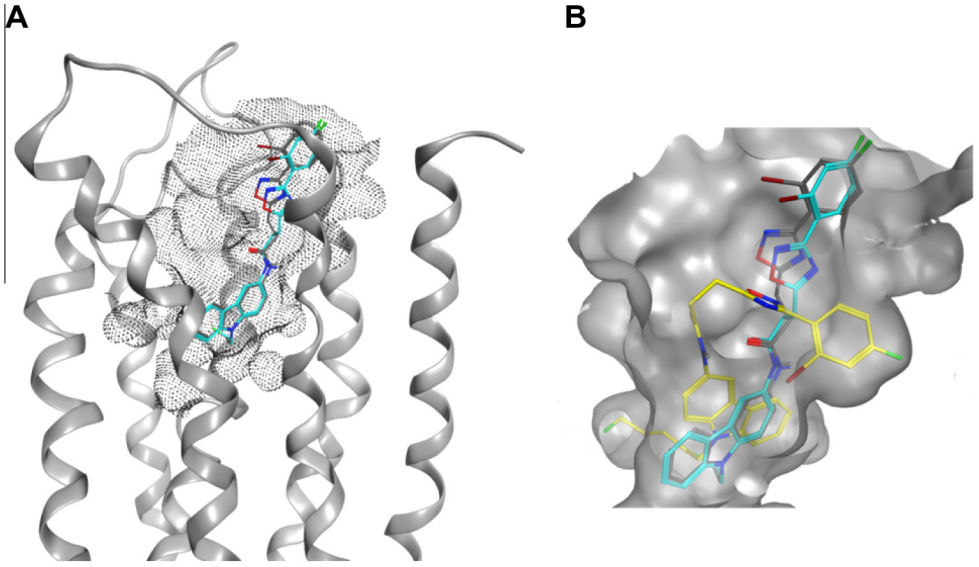


Figure 3. Predicted binding modes of selected compounds to human CB_2 receptors. (A) Binding mode of compounds **6** (grey) and **20a** (cyan) after docking into the human CB_2 receptor binding pocket (indicated by dots). (B) Comparison of the binding modes of **6**, **20a** and **22a** (yellow). The CB_2 receptor is shown with the extracellular site up. This figure was prepared with MOE (Chemical Computing Group Inc. Montreal, Canada).

the benzonitrile **20f** represents the cyano analog of **20a** as well as the 2-fluoroethyl analog of the lead compound **6**.

In order to prove the selectivity the CB_1 affinity of the most promising CB_2 ligands **16a**, **17a**, **20a**, **20b**, and **20f** was recorded in receptor binding studies. It was shown that the CB_1 affinity of these compounds was negligible (IC_{50} >1 μM)[53] indicating a very high selectivity for the CB_2 receptor over the CB_1 receptor.

4. Molecular modeling

In order to gain more insight into the interaction of the compounds with the CB_2 receptor molecular docking studies were performed. For this purpose, our recently published model of the human CB_2 receptor was used.[53] The fluoroethyl and fluorobutyl substituted compounds **20a** and **22a** were docked into the binding site of the CB_2 receptor to compare their interactions with the proposed binding mode of the lead compound **6**. Figure 3 shows that the attachment of a fluorine atom to the ethyl moiety has virtually no impact on the binding geometry of the compound. This is in excellent agreement with the measured affinity data for the ethyl derivative **6** (K_i = 4.3 nM)[45] and the fluoroethyl derivative **20a** (K_i = 5.8 nM).

Elongation of the alkyl chain leads to a drastic reduction of affinity, as shown in Table 1. The docking studies with the fluorobutyl derivative **22a** suggest, that the longer chain results in a different binding mode, which is illustrated in Figure 3B. The different binding mode might explain the reduced CB_2 receptor affinity.

5. Conclusion

A series of more than 30 carbazole based CB_2 ligands was synthesized and the affinity towards the human CB_2 receptor was recorded in receptor binding studies. The substitution pattern of the phenyl ring is crucial for high CB_2 affinity. Elongation of the 2-fluoroethyl side chain at the carbazole N-atom to a 3-fluoropropyl and 4-fluorobutyl side chain (variation of *n* in **7**) as well as elongation of the propionamide to a butyramide (variation of *m* in **7**) lead to a remarkable decrease of the CB_2 affinity. The high CB_2 affinity (K_i = 5.8 nM) and CB_2 over CB_1 selectivity (>200) renders the fluoroethyl derivative **20a** a promising candidate for radiolabeling with [^{18}F]fluorine for PET studies.

6. Experimental chemistry

6.1. Chemistry, general

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, eluent, fraction size, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electro spray ionization: HRMS: MicroTof (Bruker Daltronics, Bremen), calibration with sodium formate clusters before measurement. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity Mercury Plus 400 spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 μm), 250–4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: 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%, 31–31.5 min: gradient from 0% to 90%, 31.5–40 min: 90%.

6.2. General procedures

6.2.1. General procedure A for the synthesis of 3-[(3-phenyl)-1,2,4-oxadiazol-5-yl]propanoic acids 9[45] (modified (solvent, time, purification) according to Ref. 45)

Hydroxylamine hydrochloride (1.0 equiv) was dissolved in H_2O (0.4 mL per mmol) and sodium carbonate (0.5 equiv) was added. The mixture was stirred for 25 min at rt. A solution of the respective benzonitrile **8** (1.0 equiv) in CH_3OH (1.8 mL per 1 mmol) was added to the solution under vigorous stirring. The reaction mixture was stirred at 65 °C until the starting material was converted. Then, CH_3OH was removed under reduced pressure, and the residue was diluted with brine and extracted with CH_2Cl_2 until the product was extracted completely. The organic layer was dried (Na_2SO_4) and removed under reduced pressure. Afterwards, succinic anhydride (0.9 equiv) and DMF (0.5 mL) were added to the residue and the reaction mixture was stirred for 30 min at 148 °C. The solvent was removed in vacuo and the residue was purified by fc (cyclohexane/ethyl acetate/formic acid 50:50:0.01). The product was purified by recrystallization (CH_2Cl_2/H_2O).

6.2.2. General procedure B for the synthesis of 3-[(3-phenyl)-1,2,4-oxadiazol-5-yl]butanoic acids 11

Hydroxylamine hydrochloride (1.0 equiv) was dissolved in H_2O (0.4 mL per mmol) and sodium carbonate (0.5 equiv) was added. The mixture was stirred for 25 min at rt. A solution of the respective benzonitrile **8** (1.0 equiv) in CH_3OH (1.8 mL per 1 mmol) was added to the solution under vigorous stirring. The reaction mixture was stirred at 86 °C until the starting material was converted. Then, CH_3OH was removed under reduced pressure and the residue was diluted with brine and extracted with CH_2Cl_2 until the product was extracted completely. The organic layer was dried (Na_2SO_4) and removed under reduced pressure. Afterwards, glutaric anhydride (1.0 equiv) and DMF (0.5 mL) were added to the residue and the reaction mixture was stirred for 30 min at 148 °C. The solvent was removed in vacuo and the residue was purified by fc (cyclohexane/ethyl acetate/formic acid 50:50:0.01). The product was purified by recrystallization (CH_2Cl_2/H_2O).

6.2.3. General procedure C for the COMU®-coupling of alkanoic acids 9 and 11 with carbazole-3-amines 12–14

(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy))dimethylamino-morpholinecarbenioum hexafluorophosphate (COMU®, 1.2–1.5 equiv) was added to a mixture of the respective 1,2,4-oxadiazole carboxylic acid **9** or **11** (1.0 equiv) and triethylamine (2.0–3.0 equiv) in DMF, and the mixture was stirred for 30 min at rt. The reaction mixture was cooled down to 0 °C and a solution of the respective 3-aminocarbazole hydrochloride **12–14** (1.0 equiv) in DMF was added dropwise. This mixture was stirred for 24 h at <10 °C. Then H_2O and brine were added and the mixture was extracted with $CHCl_3$ until the product was extracted completely. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by fc and finally by recrystallization with CH_2Cl_2.

6.2.4. General procedure D for the fluorination of the alcohols 15–19 with XtalFluor-E®

Under N_2, diethylaminodifluorosulfinium tetrafluoroborate ($Et_2N{=}SF_2{-}BF_3$, XtalFluor-E®, 1.5–3.0 equiv) was suspended in

CH_2Cl_2. Triethylamine trihydrofluoride (1.5–3.0 equiv) and a solution of the respective alcohol 15–19 (1.0 equiv) in CH_2Cl_2 were added to the suspension via cannula at −78 °C. The resulting mixture was warmed up to rt during 1 or 3 h. An aqueous solution of Na_2CO_3 (5% m/m) was added and the reaction mixture was stirred for 15 min at rt. After addition of brine the mixture was extracted with CH_2Cl_2 until the product was extracted completely. The organic layer was dried (Na_2SO_4), the organic concentrated in vacuo, the product was recrystallized from ethyl acetate.

6.3. Synthetic procedures

3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (**9a**)[45]3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (**9b**)[45]3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (**9c**)[45]3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (**9d**)[45]3-[3-(4-bromo-2-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (**9e**)[45]

The propanoic acids **9a**–**e** were prepared according to General Procedure A, which has been modified according to reported procedure.[45]

6.3.1. 3-[3-(2-Cyano-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoic acid (9f)[45]

The ester **10f** (440 mg, 1.6 mmol) and LiOH (336 mg, 8.0 mmol) were dissolved in THF (30 mL) and H_2O (10 mL) and the mixture was stirred for 1 h at rt. Afterwards, the mixture was neutralized with 1 M HCl, diluted with ethyl acetate and washed twice with brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from CH_2Cl_2 (cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.66). Colorless solid, mp 75–78 °C, yield 334 mg (80%). $C_{12}H_8FN_3O_3$ (261.2 g/mol). Exact mass (APCI): m/z = calcd for $C_{12}H_8FN_3O_3H$ 262.0622 found 262.0619. Purity (HPLC): 98.8% (t_R = 14.79 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.82 (t, J = 7.0 Hz, 2H, $CH_2CH_2CO_2H$), 3.17 (t, J = 7.0 Hz, 2H, $CH_2CH_2CO_2H$), 7.83 (td, J = 8.6/2.7 Hz, 1H, 5-H), 7.86 (dd, J = 8.7/2.6 Hz, 1H, 3-H), 8.20 (dd, J = 8.9/5.4 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.7 (1C, $CH_2CH_2CO_2H$), 29.9 (1C, $CH_2CH_2CO_2H$), 111.8 (d, J = 10.4 Hz, 1C, C-2), 116.1 (d, J = 2.6 Hz, 1C, CN), 121.6 (d, J = 21.9 Hz, 1C, C-5), 122.5 (d, J = 26.1 Hz, 1C, C-3), 125.0 (d, J = 3.6 Hz, 1C, C-1), 132.6 (d, J = 9.4 Hz, 1C, C-6), 162.8 (d, J = 252.1 Hz, 1C, C-4), 165.0 (1C, C-$5_{oxadiazole}$), 172.7 (1C, $CH_2CH_2CO_2H$), 180.2 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3170–2310 (m, COOH), 2220 (w, CN), 1705 (s, C=O).

6.3.2. Methyl 3-[3-(2-bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoate (10a)[45]

The carboxylic acid **9a** (1.0 g, 3.2 mmol) was dissolved in CH_3OH (50 mL) and H_2SO_4 concd (0.03 mL, 0.7 mmol) was added. The mixture was heated to reflux for 45 min. Then the reaction mixture was neutralized with saturated $NaHCO_3$. The mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed twice with brine. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was recrystallized from ethyl acetate (cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.70). Colorless solid, mp 114–116 °C, yield 1.0 g (98%). $C_{12}H_{10}BrFN_2O_3$ (329.0 g/mol). Exact mass (APCI): m/z = calcd for $C_{12}H_{10}{}^{79}BrFN_2O_3H$ 328.9932 found 328.9915. ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.95 (t, J = 7.1 Hz, 2H, $CH_2CH_2CO_2CH_3$), 3.29 (t, J = 7.1 Hz, 2H, $CH_2CH_2CO_2CH_3$), 3.73 (s, 3H, $CH_2CH_2CO_2CH_3$), 7.15 (ddd, J = 8.7/7.7/2.6 Hz, 1H, 5-H), 7.48 (dd, J = 8.2/2.6 Hz, 1H, 3-H), 7.85 (dd, J = 8.7/6.0 Hz, 1H, 6-H). IR (neat): ν (cm^{-1}) = 2966–2322 (m, COOH), 1735 (s, C=O).

6.3.3. Methyl 3-[3-(2-cyano-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanoate (10f)[45]

According to literature[45] **10a** (500 mg, 1.3 mmol) and CuCN (716 mg, 8.0 mmol) were suspended in *N*,*N*-dimethylacetamide (5 mL) under N_2. The mixture was heated to 155 °C for 18.5 h. Saturated NH_4Cl (4 mL) and ethyl acetate (16 mL) were added. The precipitated CuCN was filtered off and the filtrate was washed once with brine. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and purified by fc (d = 8 cm, l = 14 cm, cyclohexane/ethyl acetate 70:30, R_f 0.50). Colorless solid, mp 80–82 °C, yield 240 mg (65%). $C_{13}H_{10}FN_3O_3$ (275.2 g/mol). Exact mass (APCI): m/z = calcd for $C_{13}H_{10}FN_3O_3H$ 276.0779 found 276.0769. Purity (HPLC): 91.9% (t_R = 17.57 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.96 (t, J = 7.1 Hz, 2H, $CH_2CH_2CO_2CH_3$), 3.31 (t, J = 7.1 Hz, 2H, $CH_2CH_2CO_2CH_3$), 3.73 (s, 3H, $CH_2CH_2CO_2CH_3$), 7.43 (ddd, J = 8.7/7.7/2.6 Hz, 1H, 5-H), 7.54 (dd, J = 8.2/2.6 Hz, 1H, 3-H), 8.15 (dd, J = 8.7/6.0 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.6 (1C, $CH_2CH_2CO_2CH_3$), 30.7 (1C, $CH_2CH_2CO_2CH_3$), 51.8 (1C, $CH_2CH_2CO_2CH_3$), 111.9 (d, J = 10.4 Hz, 1C, C-2), 116.1 (d, J = 2.6 Hz, 1C, CN), 121.6 (d, J = 21.9 Hz, 1C, C-5), 122.5 (d, J = 26.1 Hz, 1C, C-3), 125.0 (d, J = 3.6 Hz, 1C, C-1), 132.6 (d, J = 9.4 Hz, 1C, C-6), 162.9 (d, J = 252.1 Hz, 1C, C-4), 165.0 (1C, C-$5_{oxadiazole}$), 171.7 (1C, CO_2CH_3), 180.0 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 2210 (w, CN), 1712 (s, C=O).

6.3.4. 4-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butanoic acid (11a)

According to General Procedure B, benzonitrile **8a** (2.5 g, 12.5 mmol) was treated with NH_2OH–HCl (869 mg, 12.5 mmol) and sodium carbonate (670 mg, 6.25 mmol) in H_2O (5 mL) and CH_3OH (15 mL). The reaction mixture was stirred at 86 °C for 17.5 h. Afterwards, glutaric anhydride (1.4 g, 12.5 mmol) was added to the intermediate and the reaction mixture was stirred for 30 min at 148 °C. The residue was purified by fc (d = 6 cm, l = 15 cm, cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.29). Colorless solid, mp 94–95 °C, yield 1.3 g (32%). $C_{12}H_{10}BrFN_2O_3$ (329.1 g/mol). Exact mass (APCI): m/z = calcd for $C_{12}H_{10}{}^{79}BrFN_2O_3H$ 330.0030 found 330.0048. Purity (HPLC): 97.3% (t_R = 17.29 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.20–2.22 (m, 2H, $CH_2CH_2CH_2CO_2H$), 2.58 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 3.08 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 7.15 (ddd, J = 8.7/7.7/2.6 Hz, 1H, 5-H), 7.48 (dd, J = 8.2/2.6 Hz, 1H, 3-H), 7.85 (dd, J = 8.7/6.0 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.4 (1C, $CH_2CH_2CH_2CO_2H$), 25.0 (1C, $CH_2CH_2CH_2CO_2H$), 30.2 (1C, $CH_2CH_2CH_2CO_2H$), 115.5 (d, J = 21.6 Hz, 1C, C-5), 121.3 (d, J = 25.1 Hz, 1C, C-3), 122.2 (d, J = 10.2 Hz, 1C, C-2), 124.5 (d, J = 3.5 Hz, 1C, C-1), 133.7 (d, J = 9.5 Hz, 1C, C-6), 162.9 (d, J = 254.0 Hz, 1C, C-4), 166.6 (1C, C-$5_{oxadiazole}$), 173.8 (1C, $CH_2CH_2CO_2H$), 179.5 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3297–2965 (m, COOH), 1712 (s, C=O).

6.3.5. 4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]butanoic acid (11b)

According to General Procedure B, benzonitrile **8b** (5.0 g, 41.2 mmol) was treated with NH_2OH–HCl (2.9 g, 41.2 mmol) and sodium carbonate (2.18 g, 20.6 mmol) in H_2O (16.5 mL) and CH_3OH (65 mL). The reaction mixture was stirred at 86 °C for 3.5 h. Afterwards, glutaric anhydride (4.7 g, 41.2 mmol) was added to the intermediate and the reaction mixture was stirred for 30 min at 148 °C. The residue was purified by fc (d = 6 cm, l = 15 cm, cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.38). Colorless solid, mp 89–91 °C, yield 5.8 g (56%). $C_{12}H_{11}FN_2O_3$ (250.2 g/mol). Exact mass (APCI): m/z = calcd for $C_{12}H_{11}FN_2O_3H$ 251.0826 found 251.0824. Purity (HPLC): 87.0% (t_R = 16.48 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.22 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 2.56 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 3.05 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 7.12–7.20 (m, 2H, 3-H, 5-H), 8.03–8.10 (m, 2H, 2-H, 6-H).

^{13}C NMR (DMSO-d_6): δ (ppm) = 21.4 (1C, $CH_2CH_2CH_2CO_2H$), 25.1 (1C, $CH_2CH_2CH_2CO_2H$), 32.5 (1C, $CH_2CH_2CH_2CO_2H$), 116.4 (d, J = 22.2 Hz, 2C, C-3, C-5), 122.9 (d, J = 3.1 Hz, C-1), 129.5 (d, J = 9.0 Hz, 2C, C-2, C-6), 163.9 (d, J = 249.2, C-4), 166.7 (1C, C-$5_{oxadiazole}$), 173.8 (1C, $CH_2CH_2CH_2CO_2H$), 180.3 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3107–2357 (m, COOH), 1693 (s, C=O).

6.3.6. 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]butanoic acid (11c)

According to General Procedure B, benzonitrile **8c** (6.0 g, 43.6 mmol) was treated with NH_2OH–HCl (3.0 g, 43.6 mmol) and sodium carbonate (2.3 g, 21.8 mmol) in H_2O (17 mL) and CH_3OH (70 mL). The reaction mixture was stirred at 86 °C for 3.5 h. Afterwards, glutaric anhydride (5.0 g, 43.6 mmol) was added to the intermediate and the reaction mixture was stirred for 30 min at 148 °C. The residue was purified by fc (d = 6 cm, l = 15 cm, cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.31). Colorless solid, mp 108–110 °C, yield 5.6 g (48%). $C_{12}H_{11}ClN_2O_3$ (266.7 g/mol). Exact mass (APCI): m/z = calcd for $C_{12}H_{11}{}^{35}ClN_2O_3H$ 267.0531 found 267.0518. Purity (HPLC): 90.7% (t_R = 17.87 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.21 (quint, J = 7.2 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 2.55 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 3.04 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 7.42–7.47 (m, 2H, 3-H, 5-H), 7.97–8.01 (m, 2H, 2-H, 6-H). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.4 (1C, $CH_2CH_2CH_2CO_2H$), 25.8 (1C, $CH_2CH_2CH_2CO_2H$), 32.8 (1C, $CH_2CH_2CH_2CO_2H$), 125.3 (1C, C-1), 128.9 (2C, C-2, C-6), 129.3 (2C, C-3, C-5), 137.5 (1C, C-4), 167.6 (1C, C-$5_{oxadiazole}$), 178.6 (1C, $CH_2CH_2CH_2CO_2H$), 179.3 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3110–2347 (m, COOH), 1691 (s, C=O).

6.3.7. 4-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]butanoic acid (11d)

According to General Procedure B, benzonitrile **8d** (6.0 g, 51.2 mmol) was treated with NH_2OH–HCl (3.6 g, 51.2 mmol) and sodium carbonate (2.7 g, 25.6 mmol) in H_2O (20.5 mL) and CH_3OH (102 mL). The reaction mixture was stirred at 86 °C for 3.5 h. Afterwards, glutaric anhydride (5.9 g, 51.2 mmol) was added to the intermediate and the reaction mixture was stirred for 30 min at 148 °C. The residue was purified by fc (d = 6 cm, l = 15 cm, cyclohexane/ethyl acetate/formic acid 50:50:0.01, R_f 0.33). Colorless solid, mp 80–82 °C, yield 5.5 g (44%). $C_{13}H_{14}N_2O_3$ (246.3 g/mol). Exact mass (APCI): m/z = calcd for $C_{13}H_{14}N_2O_3H$ 247.1077 found 247.1075. Purity (HPLC): 95.3% (t_R = 17.26 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.21 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 2.40 (s, 3H, CH_3), 2.55 (t, J = 7.2 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 3.03 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_2CO_2H$), 7.27 (d, J = 7.3 Hz, 2H, 3-H, 5-H), 7.94 (d, J = 8.2 Hz, 2 H, 2-H, 6-H). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.6 (1C, CH_3), 21.9 (1C, $CH_2CH_2CH_2CO_2H$), 25.8 (1C, $CH_2CH_2CH_2CO_2H$), 32.9 (1C, $CH_2CH_2CH_2CO_2H$), 124.0 (1C, C-1), 127.5 (2C, C-2, C-6), 129.7 (2C, C-3, C-5), 141.6 (1C, C-4), 168.4 (1C, C-$5_{oxadiazole}$), 178.6 (1C, $CH_2CH_2CH_2CO_2H$), 179.3 (1C, C-$3_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3210–2461 (m, COOH), 1708 (s, C=O).

6.3.8. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-carbazol-3-yl]propanamide (15a)

According to the General Procedure C, 9a (400 mg, 1.3 mmol) was treated with **12** (222 mg, 0.9 mmol), COMU® (652 mg, 1.5 mmol) and triethylamine (0.54 mL, 3.9 mmol) in DMF (15 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 15:85, R_f 0.51 (ethyl acetate)). Colorless solid, mp 163–165 °C, yield 368 mg (80%). $C_{25}H_{20}BrFN_4O_3$ (523.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{25}H_{20}{}^{79}BrFN_4O_3H$ 523.0776 found 523.0783. Purity (HPLC): 97.7% (t_R = 20.24 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.99 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.35 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.76 (q, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.40 (t, J = 5.5 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2H$), 7.15 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.41 (t, J = 6.5 Hz, 1H, 7-H_{carb}), 7.46 (td, J = 8.5/2.6 Hz, 1H, 5-H_{phenyl}), 7.51 (dd, J = 8.8/1.7 Hz, 1H, 2-H_{carb}), 7.54 (d, J = 8.8 Hz, 1H, 1-H_{carb}), 7.57 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.83 (dd, J = 8.6/2.6 Hz, 1H, 3-H_{phenyl}), 7.89 (dd, J = 8.7/6.1 Hz, 1H, 6-H_{phenyl}), 8.02 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.39 (s, 1H, 4-H_{carb}), 10.13 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, CH_2CH_2CONH), 32.0 (1C, CH_2CH_2CONH), 45.3 (1C, NCH_2CH_2OH), 59.6 (1C, NCH_2CH_2OH), 109.5 (1C, C-8_{carb}), 109.7 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 115.5 (d, J = 21.6 Hz,1C, C-5_{phenyl}), 118.5 (1C, C-2_{carb}), 118.7 (1C, C-6_{carb}), 120.0 (1C, C-5_{carb}), 121.4 (d, J = 24.9 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 122.2 (d, J = 10.1 Hz, 1C, C-2_{phenyl}), 124.5 (d, J = 3.4 Hz, 1C, C-1_{phenyl}), 125.6 (1C, C-7_{carb}), 131.0 (1C, C-3_{carb}), 133.6 (d, J = 9.3 Hz, 1C, C-6_{phenyl}), 137.0 (1C, C-$9a_{carb}$), 140.9 (1C, C-$8a_{carb}$), 162.9 (d, J = 253.4 Hz, 1C, C-4_{phenyl}), 166.4 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 179.6 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3421 (m, O–H), 3329 (m, N–H), 3078 (m, C–H, arom), 2935 (m, C–H, aliph), 1678 (s, NH–C=O).

6.3.9. 3-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-carbazol-3-yl]propanamide (15b)

According to the General Procedure C, **9b** (1.0 g, 4.2 mmol) was treated with **12** (0.86 g, 3.8 mmol), COMU® (2.2 g, 5.1 mmol) and triethylamine (1.7 mL, 12.6 mmol) in DMF (23 mL). This mixture was stirred for 25 h at <10 °C. The residue was purified by fc (d = 8 cm, l = 12 cm, cyclohexane/ethyl acetate 10:90, R_f 0.55 (ethyl acetate)). Colorless solid, mp 193–194 °C, yield 1.7 g (89%). $C_{25}H_{21}FN_4O_3$ (444.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{25}H_{21}FN_4O_3H$ 445.1670 found 445.1666. Purity (HPLC): 96.3% (t_R = 19.84 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.00 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.76 (q, J = 5.5 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2H$), 7.15 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.37–7.44 (m, 3H, 7-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.48–7.55 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 8.02 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.03–8.08 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 10.14 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 45.3 (1C, $NCH_2CH_2OHCH_2CH_2H$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2H$), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 116.5 (d, J = 22.2 Hz, 2C, C-3_{phenyl}, C-5_{phenyl}), 118.4 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 119.9 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 122.9 (d, J = 3.1 Hz, 1C, C-1_{phenyl}), 125.6 (1C, C-7_{carb}), 129.5 (d, J = 9.3 Hz, 2C, C-2_{phenyl}, C-6_{phenyl}), 131.0 (1C, C-3_{carb}), 137.0 (1C, C-$9a_{carb}$), 140.8 (1C, C-$8a_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4_{phenyl}), 166.7 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 180.2 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3429 (m, O–H), 3329 (m, N–H), 2935 (m, C–H, aliph), 1678 (s, NH–C=O).

6.3.10. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-carbazol-3-yl]propanamide (15c)

According to the General Procedure C, **9c** (200 mg, 0.8 mmol) was treated with **12** (210 mg, 0.8 mmol), COMU® (340 mg, 0.9 mmol) and triethylamine (0.2 mL, 1.4 mmol) in DMF (12 mL). This mixture was stirred for 20 h at <10 °C. The residue was purified by fc (d = 8 cm, l = 12 cm, cyclohexane/ethyl acetate 15:85, R_f 0.51 (ethyl acetate)). Colorless solid, mp 206–208 °C, yield 230 mg (65%). $C_{25}H_{21}FN_4O_3$ (461.0 g/mol). Exact mass (ESI): m/z = calcd for $C_{25}H_{21}{}^{35}ClN_4O_3H$ 461.1375 found 461.1374. Purity (HPLC): 98.4% (t_R = 20.53 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.00 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.30 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.76 (q, J = 5.5 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2H$), 7.15 (t, J = 7.4 Hz, 1H, 6-

H_{carb}), 7.41 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.48–7.55 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.60–7.66 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 8.03–8.08 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 10.14 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 45.3 (1C, $NCH_2CH_2OHCH_2CH_2H$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2H$), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 118.4 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 119.9 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 125.2 (1C, C-7_{carb}), 125.6 (1C, C-3_{carb}), 128.8 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.5 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.0 (1C, C-1_{phenyl}), 136.2 (1C, C-4_{phenyl}), 137.0 (1C, C-$9a_{carb}$), 140.8 (1C, C-$8a_{carb}$), 166.7 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 180.4 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3278 (m, N–H), 2931 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.11. *N*-[9-(2-Hydroxyethyl)-9*H*-carbazol-3-yl]-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanamide (15d)

According to the General Procedure C, **9d** (500 mg, 2.2 mmol) was treated with **12** (242 mg, 0.92 mmol), COMU® (1.1 g, 2.6 mmol) and triethylamine (0.6 mL, 4.4 mmol) in DMF (17 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 5:95, R_f 0.51 (ethyl acetate)). Colorless solid, mp 172–174 °C, yield 600 mg (63%). $C_{26}H_{24}N_4O_3$ (440.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{24}N_4O_3H$ 441.1915 found 441.1917. Purity (HPLC): 95.3% (t_R = 20.07 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.37 (s, 3H, CH_3), 2.99 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.30 (t, J = 7.2 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.72–3.79 (m, 2H, $NCH_2CH_2OHCH_2CH_2H$), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$-H), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2H$), 7.15 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.36 (d, J = 8.2 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.41 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.49–7.54 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.89 (d, J = 8.1 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 8.02 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.39 (s, 1H, 4-H_{carb}), 10.13 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.5 (1C, CH_3), 22.6 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.7 (1C, $CH_2CH_2CONHCH_2$-CH_2), 45.9 (1C, $NCH_2CH_2OHCH_2CH_2$), 60.2 (1C, $NCH_2CH_2OHCH_2$-CH_2), 110.3 (1C, C-8_{carb}), 111.6 (1C, C-1_{carb}), 119.1 (1C, C-4_{carb}), 119.4 (1C, C-2_{carb}), 120.6 (1C, C-6_{carb}), 122.4 (1C, C-5_{carb}), 122.6 (1C, C-$4a_{carb}$), 124.2 (1C, C-$4b_{carb}$), 126.2 (1C, C-1_{phenyl}), 127.6 (1C, C-7_{carb}), 130.5 (2C, C-3_{phenyl}, C-5_{phenyl}), 131.7 (2C, C-2_{phenyl}, C-6_{phenyl}), 137.6 (1C, C-3_{carb}), 137.7 (1C, C-$9a_{carb}$), 141.5 (1C, C-4_{phenyl}), 142.1 (1C, C-$8a_{carb}$), 168.1 (1C, C-$3_{oxadiazole}$), 169.3 (1C, CONH), 180.6 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3356 (m, O–H), 3278 (m, N–H), 2931 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.12. 3-[3-(4-Bromo-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]propanamide (15e)

According to the General Procedure C, **9e** (200 mg, 0.64 mmol) was treated with **12** (144 mg, 0.635 mmol), COMU® (326 mg, 0.76 mmol) and triethylamine (0.27 mL, 1.9 mmol) in DMF (15 mL). This mixture was stirred for 26 h at <10 °C. The residue was purified by fc (d = 5.5 cm, l = 17 cm, cyclohexane/ethyl acetate 15:85, R_f 0.60 (ethyl acetate)). Colorless solid, mp 208 °C, yield 140 mg (42%). $C_{25}H_{20}BrFN_4O_3$ (523.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{25}H_{20}{}^{79}BrFN_4O_3H$ 523.0776 found 523.0717. Purity (HPLC): 92.3% (t_R = 19.10 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.02 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.29 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.76 (q, J = 5.5 Hz, 2H, $NCH_2CH_2OHCH_2$-CH_2), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.15 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.41 (t, J = 7.2 Hz, 1H, 7-H_{carb}), 7.48–7.55 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.80 (td, J = 8.6/ 2.7 Hz, 1H, 5-H_{phenyl}), 8.02 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.13 (dd, J = 8.7/2.7 Hz, 1H, 3-H_{phenyl}), 8.18 (dd, J = 8.8/5.5 Hz, 1H, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 45.3 (1C, $NCH_2CH_2OHCH_2CH_2$), 59.6 (1C, $NCH_2CH_2OHCH_2CH_2$), 109.5 (1C, C-8_{carb}), 109.7 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 115.5 (d, J = 21.7 Hz, 1C, C-1_{phenyl}), 118.5 (1C, C-2_{carb}), 118.7 (1C, C-6_{carb}), 120.0 (1C, C-5_{carb}), 121.4 (d, J = 24.9 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 122.2 (d, J = 10.1 Hz, 1C, C-4_{phenyl}), 124.5 (d, J = 3.4 Hz, 1C, C-5_{phenyl}), 125.6 (1C, C-7_{carb}), 131.0 (1C, C-3_{carb}), 133.6 (d, J = 9.3 Hz, 1C, C-6_{phenyl}), 137.0 (1C, C-$9a_{carb}$), 140.9 (1C, C-$8a_{carb}$), 162.9 (d, J = 252.9 Hz, 1C, C-2_{phenyl}), 166.6 (d, J = 9.4 Hz, 1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 179.7 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3429 (m, O–H), 3332 (m, N–H), 2935 (m, C–H, aliph), 1681 (s, NH–C=O).

6.3.13. 3-[3-(2-Cyano-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]propanamide (15f)

According to the General Procedure C, **9f** (240 mg, 0.92 mmol) was treated with **12** (242 mg, 0.92 mmol), COMU® (590 mg, 1.4 mmol) and triethylamine (0.5 mL, 3.5 mmol) in DMF (13 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 20 cm, cyclohexane/ethyl acetate 15:85, R_f 0.43 (ethyl acetate)). Colorless solid, mp 210 °C, yield 60 mg (14%). $C_{26}H_{20}FN_5O_3$ (470.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{20}FN_5O_3H$ 470.1623 found 470.1611. Purity (HPLC): 98.1% (t_R = 18.95 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.02 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.28 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.73–3.78 (m, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.40 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.4 Hz, 1H, NCH_2-$CH_2OHCH_2CH_2$), 7.15 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.41 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.49–7.53 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.80 (td, J = 8.5/2.7 Hz, 1H, 5-H_{phenyl}), 8.03 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.13 (dd, J = 8.7/2.7 Hz, 1H, 3-H_{phenyl}), 8.19 (dd, J = 8.7/5.4 Hz, 1H, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, CH_2CH_2-$CONHCH_2CH_2$), 31.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 45.3 (1C, NCH_2-$CH_2OHCH_2CH_2$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2$), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 116.2 (d, J = 2.7 Hz, 1C, CN), 118.5 (1C, C-2_{carb}), 118.7 (1C, C-6_{carb}), 120.0 (1C, C-5_{carb}), 121.6 (d, J = 21.9 Hz, 1C, C-5_{phenyl}), 121.7 (d, J = 5.5 Hz, 1-C, C-2_{phenyl}), 122.0 (1C, C-$4a_{carb}$), 122.5 (d, J = 26.0 Hz, 1C, C-3_{phenyl}), 122.6 (1C, C-$4b_{carb}$), 125.1 (d, J = 3.5 Hz, 1C, C-1_{phenyl}), 125.6 (1C, C-7_{carb}), 132.0 (1C, C-3_{carb}), 132.6 (d, J = 9.7 Hz, 1C, C-6_{phenyl}), 137.0 (1C, C-$9a_{carb}$), 140.8 (1C, C-$8a_{carb}$), 162.7 (d, J = 259.2 Hz, 1C, C-4_{phenyl}), 165.0 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 180.6 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3506 (m, O–H), 3329 (m, N–H), 2935 (m, C–H, aliph), 2233 (w, CN), 1685 (s, NH–C=O).

6.3.14. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-$_{carb}$azol-3-yl]propanamide (16a)

According to the General Procedure C, **9a** (453 mg, 1.4 mmol) was treated with **13** (400 mg, 1.4 mmol), COMU® (740 mg, 1.7 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (15 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 5:95, R_f 0.20 (ethyl acetate)). Colorless solid, mp 155–157 °C, yield 229 mg (30%). $C_{26}H_{22}BrFN_4O_3$ (537.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{22}{}^{79}BrFN_4O_3H$ 537.0935 found 537.0932. Purity (HPLC): 96.6% (t_R = 20.53 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.82–1.91 (m, 2H, $NCH_2CH_2CH_2OH$), 2.97 (t, J = 7.1 Hz, 2H, CH_2CH_2-$CONHCH_2CH_2$), 3.12 (t, J = 7.2 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.33–3.36 (m, 2H, $NCH_2CH_2CH_2OH$), 4.40 (t, J = 6.7 Hz, 2H, NCH_2CH_2-CH_2OH), 4.86 (t, J = 4.9 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.13 (t, J = 7.5 Hz, 1H, 6-H_{carb}), 7.38–7.47 (m, 2H, 7-H_{carb}, 5-H_{phenyl}), 7.52–7.54 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.78–7.90 (m, 2H, 3-H_{phenyl}, 6-H_{phenyl}), 8.01 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.38 (s, 1H, 4-H_{carb}), 10.12 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.8 (1C, $NCH_2CH_2CH_2$

OH), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 58.0 (1C, $NCH_2CH_2CH_2OH$), 109.1 (1C, C-8_{carb}), 109.3 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 115.5 (d, J = 21.8 Hz, 1C, C-5_{phenyl}), 118.5 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.4 (d, J = 24.6 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 122.3 (d, J = 8.7 Hz, 1C, C-2_{phenyl}), 125.8 (d, J = 10.6 Hz, 1C, C-6_{phenyl}), 126.9 (1C, C-7_{carb}), 129.8 (1C, C-3_{carb}), 131.1 (d, J = 3.8 Hz, 1C, C-1_{phenyl}), 136.7 (1C, C-$9a_{carb}$), 141.4 (1C, C-$8a_{carb}$), 163.7 (d, J = 258.9 Hz, 1C, C-4_{phenyl}), 167.4 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 179.9 (1C, C-$5_{oxadiazole}$). The signal for $NCH_2CH_2CH_2OH$ is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3667 (m, O–H), 3290 (m, N–H), 1654 (s, NH–C=O).

6.3.15. 3-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-$_{carb}$azol-3-yl]propanamide (16b)

According to the General Procedure C, **9b** (350 mg, 1.5 mmol) was treated with **13** (370 mg, 1.3 mmol), COMU® (762 mg, 1.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (24 mL). This mixture was stirred for 22.5 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 12 cm, cyclohexane/ethyl acetate 10:90, R_f 0.48 (ethyl acetate)). Colorless solid, mp 167–168 °C, yield 480 mg (71%). $C_{26}H_{23}FN_4O_3$ (458.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{23}FN_4O_3H$ 459.1827 found 459.1809. Purity (HPLC): 97.4% (t_R = 20.15 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.85–1.94 (m, 2H, $NCH_2CH_2CH_2OH$), 3.00 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.39 (m, 2H, $NCH_2CH_2CH_2OH$), 4.40 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_2OH$), 4.64 (t, J = 5.4 Hz, 1H, $NCH_2CH_2CH_2OH$), 7.16 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.36–7.46 (m, 3H, 7-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.53 (s, 2H, 1-H_{carb}, 2-H_{carb}), 7.57 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 8.00–8.08 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.40 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.8 (1C, $NCH_2CH_2CH_2OH$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 58.0 (1C, $NCH_2CH_2CH_2OH$), 109.2 (1C, C-8_{carb}), 109.3 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 116.5 (d, J = 22.2 Hz, 2C, C-3_{phenyl}, C-5_{phenyl}), 118.5 (1C, C-2_{carb}), 118.8 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 122.9 (d, J = 3.1 Hz, 1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 129.5 (d, J = 9.0 Hz, 2C, C-2_{phenyl}, C-6_{phenyl}), 131.1 (1C, C-3_{carb}), 136.7 (1C, C-$9a_{carb}$), 140.5 (1C, C-$8a_{carb}$), 163.9 (d, J = 249.0 Hz, 1C, C-4_{phenyl}), 166.7 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 180.3 (1C, C-$5_{oxadiazole}$). The signal for $NCH_2CH_2CH_2OH$ is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3286 (m, N–H), 3059 (w. C–H, arom), 2935 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.16. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-$_{carb}$azol-3-yl]propanamide (16c)

According to the General Procedure C, **9c** (550 mg, 2.2 mmol) was treated with **13** (598 mg, 2.1 mmol), COMU® (1.1 g, 2.6 mmol) and triethylamine (0.6 mL, 4.4 mmol) in DMF (14 mL). This mixture was stirred for 20 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 12 cm, cyclohexane/ethyl acetate 5:95, R_f 0.50 (ethyl acetate)). Colorless solid, mp 190 °C, yield 822 mg (80%). $C_{26}H_{23}FN_4O_3$ (474.9 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{23}{}^{35}ClN_4O_3H$ 475.1531 found 475.1534. Purity (HPLC): 96.1% (t_R = 21.05 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.89 (quint, J = 6.5 Hz, 2H, $NCH_2CH_2CH_2OH$), 3.00 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.32 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.36–3.42 (m, J = 5.5 Hz, 2H, $NCH_2CH_2CH_2OH$), 4.40 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_2OH$), 4.65 (t, J = 4.9 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.15 (t, J = 7.5 Hz, 1H, 6-H_{carb}), 7.43 (t, J = 8.2 Hz, 1H, 7-H_{carb}), 7.48–7.55 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.56 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.61–7.65 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.99–8.04 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.40 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.8 (1C, $NCH_2CH_2CH_2OH$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 58.0 (1C, $NCH_2CH_2CH_2OH$), 109.1 (1C, C-8_{carb}), 109.2 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 118.5 (1C, C-2_{carb}), 118.8 (1C, C-6_{carb}), 120.9 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 125.2 (1C, C-7_{carb}), 125.7 (1C, C-3_{carb}), 128.7 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.5 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.0 (1C, C-1_{phenyl}), 136.2 (1C, C-4_{phenyl}), 136.6 (1C, C-$9a_{carb}$), 140.5 (1C, C-$8a_{carb}$), 166.7 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 180.4 (1C, C-$5_{oxadiazole}$). The signal for $NCH_2CH_2CH_2OH$ is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3420 (m, O–H), 3290 (m, N–H), 2931 (m, C–H, aliph), 1643 (s, NH–C=O).

6.3.17. *N*-[9-(3-Hydroxypropyl)-9*H*-$_{carb}$azol-3-yl]-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanamide (16d)

According to the General Procedure C, **9d** (350 mg, 1.5 mmol) was treated with **13** (375 mg, 1.4 mmol), COMU® (775 mg, 1.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (15 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 12 cm, cyclohexane/ethyl acetate 10:90, R_f 0.43 (ethyl acetate)). Colorless solid, mp 192 °C, yield 456 mg (67%). $C_{27}H_{26}N_4O_3$ (454.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{26}N_4O_3H$ 455.2078 found 455.2087. Purity (HPLC): 97.5% (t_R = 20.65 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.9 (quint, J = 6.5 Hz, 2H, $NCH_2CH_2CH_2OH$), 2.37 (s, 3H, CH_3), 3.00 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 7.2 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.37–3.43 (m, 2H, $NCH_2CH_2CH_2OH$), 4.40 (t, J = 5.6 Hz, 2H, $NCH_2CH_2CH_2OH$), 4.65 (t, J = 4.9 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.16 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.36 (d, J = 8.3 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.43 (t, J = 7.3 Hz, 1H, 7-H_{carb}), 7.49–7.52 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.56 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.89 (d, J = 8.1 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 8.03 (d, J = 7.7 Hz, 1H, 5-H_{carb}), 8.41 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.1 (1C, CH_3), 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.7 (1C, $NCH_2CH_2CH_2OH$), 32.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 58.0 (1C, $NCH_2CH_2CH_2OH$), 109.2 (1C, C-8_{carb}), 109.3 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 118.5 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 123.6 (1C, C-7_{carb}), 125.8 (1C, C-1_{phenyl}), 126.9 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.8 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.1 (1C, C-3_{carb}), 136.7 (1C, C-$9a_{carb}$), 140.5 (1C, C-$8a_{carb}$), 141.4 (1C, C-4_{phenyl}), 167.5 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 179.9 (1C, C-$5_{oxadiazole}$). The signal for $NCH_2CH_2CH_2OH$ is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3383 (m, O–H), 3290 (m, N–H), 2935 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.18. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(4-hydroxybutyl)-9*H*-$_{carb}$azol-3-yl]propanamide (17a)

According to the General Procedure C, **9a** (275 mg, 0.87 mmol) was treated with **14** (270 mg, 1.2 mmol), COMU® (560 mg, 1.3 mmol) and triethylamine (0.36 mL, 3.6 mmol) in DMF (15 mL). This mixture was stirred for 22.5 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 15:85, R_f 0.43 (ethyl acetate)). Colorless solid, mp 158–161 °C, yield 158 mg (33%). $C_{27}H_{24}BrFN_4O_3$ (551.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{24}{}^{79}BrFN_4O_3H$ 551.1089 found 551.1052. Purity > 99%. ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.37–1.45 (m, 2H, $NCH_2CH_2CH_2CH_2OH$), 1.73–1.82 (m. 2H, $NCH_2CH_2CH_2CH_2OH$), 2.98 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (m, 2H, $NCH_2CH_2CH_2CH_2OH$), 3.36 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.36 (q, J = 6.7 Hz, 2H, $NCH_2CH_2CH_2CH_2OH$), 4.46 (t, J = 6.7 Hz, 1H, $NCH_2CH_2CH_2CH_2OH$), 7.16 (t, J = 7.7 Hz, 1H, 6-H_{carb}), 7.40–7.47 (m, 2H, 7-H_{carb}, 5-H_{phenyl}), 7.52–7.54 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.56 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.81 (dd, J = 8.4/2.4 Hz, 1H, 3-H_{phenyl}), 7.87 (dd, J = 8.7/6.0 Hz, 1H, 6-H_{phenyl}), 8.02 (d, J = 7.6 Hz, 1H, 5-H_{carb}), 8.38 (s, 1H, 4-H_{carb}), 10.16 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.81 (1C, $CH_2CH_2CONHCH_2CH_2$), 25.36 (1C, $NCH_2CH_2CH_2CH_2OH$), 29.98 (1C, $NCH_2CH_2CH_2CH_2OH$), 31.97 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.19 (1C, $NCH_2CH_2CH_2CH_2OH$), 60.43 (1C, $NCH_2CH_2CH_2CH_2OH$), 109.2 (1C, C-8_{carb}), 109.4 (1C, C-1_{carb}), 111.0 (1C, C-4_{carb}), 115.5 (d, J = 21.6 Hz, 1C, C-5_{phenyl}), 118.5 (1C, C-2_{carb}), 118.8 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.4 (d,

J = 25.1 Hz, 1C, C-3_{phenyl}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 122.2 (d, J = 10.1 Hz, 1C, C-2_{phenyl}), 124.5 (d, J = 3.5 Hz, 1C, C-1_{phenyl}), 125.7 (1C, C-7_{carb}), 131.0 (1C, C-3_{carb}), 133.6 (d, J = 9.5 Hz, 1C, C-6_{phenyl}), 136.1 (1C, C-$9a_{carb}$), 140.4 (1C, C-$8a_{carb}$), 162.9 (d, J = 253.3 Hz, 1C, C-4_{phenyl}), 166.6 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 179.6 (1C, C-$5_{oxadiazole}$).

6.3.19. 4-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]butanamide (18a)

According to the General Procedure C, **11a** (586 mg, 1.8 mmol) was treated with **12** (400 mg, 1.8 mmol), COMU® (920 mg, 2.1 mmol) and triethylamine (0.5 mL, 3.5 mmol) in DMF (21 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 5:95, R_f 0.55 (ethyl acetate)). Colorless solid, mp 173–174 °C, yield 702 mg (73%). $C_{26}H_{22}BrFN_4O_3$ (537.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{22}{}^{79}BrFN_4O_3H$ 537.0935 found 537.0933. Purity (HPLC): 98.4% (t_R = 20.53 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.10–2.20 (m, 2H, $CH_2CH_2CH_2CONH$), 3.14 (t, J = 7.3 Hz, 2H, CH_2-CH_2CH_2CONH), 3.76 (q, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.40 (t, J = 5.7 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.2 Hz, 1H, NCH_2-$CH_2OHCH_2CH_2$), 7.16 (t, J = 7.5 Hz, 1H, 6-H$_{carb}$), 7.38–7.47 (m, 2H, 7-H$_{carb}$, 5-H$_{phenyl}$), 7.52 (s, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.3 Hz, 1H, 8-H$_{carb}$), 7.84 (dd, J = 8.6/2.5 Hz, 1H, 3-H$_{phenyl}$), 7.89 (dd, J = 8.7/6.2 Hz, 1H, 6-H$_{phenyl}$), 8.02 (d, J = 7.8 Hz, 1H, 5-H$_{carb}$), 8.39 (s, 1H, 4-H$_{carb}$), 9.95 (s, 1H, CONH). The signal for CH_2CONH is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.3 (1C, CH_2-CH_2CH_2CONH), 34.9 (1C, $CH_2CH_2CH_2CONH$), 45.3 (1C, NCH_2CH_2-$OHCH_2CH_2$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2$), 109.4 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 111.0 (1C, C-4_{carb}), 115.5 (d, J = 21.6 Hz, 1C, C-5_{phenyl}), 118.5 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 119.9 (1C, C-5_{carb}), 121.3 (d, J = 25.2 Hz, 1C, C-3_{phenyl}), 121.6 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 122.2 (d, J = 10.1 Hz, 1C, C-2_{phenyl}), 123.5 (d, J = 3.9 Hz, 1C, C-1_{phenyl}), 125.6 (1C, C-7_{carb}), 131.1 (1C, C-3_{carb}), 133.7 (d, J = 9.3 Hz, 1C, C-6_{phenyl}), 137.0 (1C, C-$9a_{carb}$), 140.8 (1C, C-$8a_{carb}$), 163.2 (d, J = 261.0 Hz, 1C, C-4_{phenyl}), 166.6 (1C, C-$3_{oxadiazole}$), 169.8 (1C, CONH), 179.6 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3367 (m, N–H), 1662 (s, NH–C=O).

6.3.20. 4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]butanamide (18b)

According to the General Procedure C, **11b** (450 mg, 1.8 mmol) was treated with **12** (400 mg, 1.8 mmol), COMU® (920 mg, 2.1 mmol) and triethylamine (0.5 mL, 3.5 mmol) in DMF (21 mL). This mixture was stirred for 25 h at <10 °C. The residue was purified by fc (d = 8 cm, l = 12 cm, cyclohexane/ethyl acetate 10:90, R_f 0.41 (ethyl acetate)). Colorless solid, mp 170–171 °C, yield 566 mg (69%). $C_{26}H_{23}FN_4O_3$ (458.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{23}FN_4O_3H$ 459.1847 found 459.1827. Purity (HPLC): 95.7% (t_R = 20.04 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.11–2.15 (m, 2H, $CH_2CH_2CH_2CONH$), 3.11 (t, J = 6.9 Hz, 2H, CH_2-CH_2CH_2CONH), 3.75 (q, J = 5.2 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.4 Hz, 1H, NCH_2-$CH_2OHCH_2CH_2$), 7.15 (t, J = 7.9 Hz, 1H, 6-H$_{carb}$), 7.37–7.44 (m, 3H, 7-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.48–7.55 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.3 Hz, 1H, 8-H$_{carb}$), 8.01 (d, J = 7.8 Hz, 1H, 5-H$_{carb}$), 8.03–8.07 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.38 (s, 1H, 4-H$_{carb}$), 9.94 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, $CH_2CH_2CH_2CONH$), 35.0 (1C, $CH_2CH_2CH_2CONH$), 45.3 (1C, $NCH_2CH_2OHCH_2CH_2$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2$), 109.4 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 116.4 (d, J = 22.2 Hz, 2C, C-3_{phenyl}, C-5_{phenyl}), 118.4 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 119.9 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 121.9 (1C, C-$4b_{carb}$), 122.9 (d, J = 3.1 Hz, 1C, C-1_{phenyl}), 125.6 (1C, C-7_{carb}), 129.5 (d, J = 9.3 Hz, 2C, C-2_{phenyl}, C-6_{phenyl}), 131.0 (1C, C-3_{carb}), 137.0 (1C, C-$9a_{carb}$), 140.8 (1C, C-$8a_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4_{phenyl}), 166.7 (1C, C-$3_{oxadiazole}$), 169.8 (1C, CONH), 180.2 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3444 (m, O–H), 3286 (m, N–H), 2966 (m, C–H, aliph), 1651 (s, NH–C=O).

6.3.21. 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]butanamide (18c)

According to the General Procedure C, **11c** (475 mg, 1.8 mmol) was treated with **12** (400 mg, 1.8 mmol), COMU® (920 mg, 2.1 mmol) and triethylamine (0.5 mL, 3.5 mmol) in DMF (16 mL). This mixture was stirred for 22 h at <10 °C. The residue was purified by fc (d = 8 cm, l = 12 cm, cyclohexane/ethyl acetate 20:80, R_f 0.38 (ethyl acetate)). Colorless solid, mp 221–222 °C, yield 648 mg (77%). $C_{26}H_{23}ClN_4O_3$ (475.0 g/mol). Exact mass (ESI): m/z = calcd for $C_{26}H_{23}{}^{35}ClN_4O_3Na$ 497.1272 found 497.1279. Purity (HPLC): 97.7% (t_R = 20.31 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.16 (quint, J = 7.2 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.12 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.76 (q, J = 5.5 Hz, 2H, $NCH_2CH_2OHCH_2$-CH_2), 4.39 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.15 (t, J = 7.1 Hz, 1H, 6-H$_{carb}$), 7.41 (t, J = 7.7 Hz, 1H, 7-H$_{carb}$), 7.49–7.53 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.60–7.64 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.98–8.04 (m, 3H, 5-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 8.38 (s, 1H, 4-H$_{carb}$), 9.95 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.7 (1C, $CH_2CH_2CH_2CONH$), 26.1 (1C, $CH_2CH_2CH_2CONH$), 35.6 (1C, $CH_2CH_2CH_2CONH$), 45.9 (1C, NCH_2-$CH_2OHCH_2CH_2$), 60.2 (1C, $NCH_2CH_2OHCH_2CH_2$), 110.0 (1C, C-8_{carb}), 110.3 (1C, C-1_{carb}), 111.7 (1C, C-4_{carb}), 119.1 (1C, C-2_{carb}), 119.5 (1C, C-6_{carb}), 120.5 (1C, C-5_{carb}), 122.3 (1C, C-$4a_{carb}$), 122.6 (1C, C-$4b_{carb}$), 125.9 (1C, C-7_{carb}), 126.2 (1C, C-1_{phenyl}), 129.5 (2C, C-3_{phenyl}, C-5_{phenyl}), 130.1 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.8 (1C, C-3_{carb}), 136.9 (1C, C-$9a_{carb}$), 137.7 (1C, C-4_{phenyl}), 142.5 (1C, C-$8a_{carb}$), 167.4 (1C, C-$3_{oxadiazole}$), 170.5 (1C, CONH), 181.0 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1})=3376 (m, O–H), 3278 (m, N–H), 2970 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.22. 4-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-hydroxyethyl)-9*H*-$_{carb}$azol-3-yl]butanamide (18d)

According to the General Procedure C, **11d** (440 mg, 1.8 mmol) was treated with **12** (400 mg, 1.8 mmol), COMU® (915 mg, 2.1 mmol) and triethylamine (0.5 mL, 3.5 mmol) in DMF (18 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 20:80, R_f 0.39 (ethyl acetate)). Colorless solid, mp 206–207 °C, yield 439 mg (54%). $C_{27}H_{26}N_4O_3$ (454.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{26}N_4O_3Na$ 476.1818 found 476.1819. Purity (HPLC): 96.7% (t_R = 20.41 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.16 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2CONH$), 2.38 (s, 3H, CH_3), 3.10 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.76 (q, J = 5.7 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.40 (t, J = 5.6 Hz, 2H, $NCH_2CH_2OHCH_2CH_2$), 4.86 (t, J = 5.4 Hz, 1H, $NCH_2CH_2OHCH_2CH_2$), 7.15 (t, J = 7.1 Hz, 1H, 6-H$_{carb}$), 7.36 (d, J = 8.0 Hz, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.42 (t, J = 8.2 Hz, 1H, 7-H$_{carb}$), 7.49–7.53 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.91 ((d, J = 8.2 Hz, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.01 (d, J = 7.7 Hz, 1H, 5-H$_{carb}$), 8.38 (s, 1H, 4-H$_{carb}$), 9.95 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.1(1C, CH_3), 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, CH_2-CH_2CH_2CONH), 35.0 (1C, $CH_2CH_2CH_2CONH$), 45.3 (1C, NCH_2CH_2-$OHCH_2CH_2$), 59.5 (1C, $NCH_2CH_2OHCH_2CH_2$), 109.4 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 111.1 (1C, C-4_{carb}), 118.5 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 119.9 (1C, C-5_{carb}), 121.7 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 123.6 (1C, C-1_{phenyl}) 125.6 (1C, C-7_{carb}), 127.0 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.8 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.1 (1C, C-3_{carb}), 137.0

(1C, C-9a$_{carb}$), 140.8 (1C, C-8a$_{carb}$), 141.4 (1C, C-4$_{phenyl}$), 167.5 (1C, C-3$_{oxadiazole}$), 168.8 (1C, CONH), 179.9 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3363 (m, O–H), 3275 (m, N–H), 2970 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.23. 4-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-carbazol-3-yl]butanamide (19a)

According to the General Procedure C, **11a** (250 mg, 0.8 mmol) was treated with **13** (183 mg, 0.8 mmol), COMU® (390 mg, 0.9 mmol) and triethylamine (0.2 mL, 1.4 mmol) in DMF (14 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 20:80, R_f 0.28 (ethyl acetate)). Colorless solid, mp 128–129 °C, yield 400 mg (90%). $C_{27}H_{24}BrFN_4O_3$ (551.4 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{24}{}^{79}BrFN_4O_3H$ 551.1089 found 551.1077. Purity (HPLC): 96.4% (t_R = 20.84 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.82–1.92 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 2.07–2.18 (m, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.11 (t, J = 7.2 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.33–3.41 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.40 (t, J = 6.7 Hz, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.61 (t, J = 4.9 Hz, 1H, NCH$_2$CH$_2$CH$_2$OH), 7.13 (t, J = 7.4 Hz, 1H, 6-H$_{carb}$), 7.36–7.40 (m, 2H, 7-H$_{carb}$, 5-H$_{phenyl}$), 7.52–7.54 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.54 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.81 (dd, J = 8.6/2.5 Hz, 1H, 3-H$_{phenyl}$), 7.86 (dd, J = 8.7/6.0 Hz, 1H, 6-H$_{phenyl}$), 8.01 (d, J = 7.7 Hz, 1H, 5-H$_{carb}$), 8.37 (s, 1H, 4-H$_{carb}$), 9.94 (s, 1H, CONH). The signal for CH$_2$CH$_2$CH$_2$CONH is overlaid by the solvent peak, but can be seen in CDCl$_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 25.3 (1C, CH$_2$CH$_2$CH$_2$CONH), 31.8 (1C, NCH$_2$CH$_2$CH$_2$OH), 35.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 58.0 (1C, NCH$_2$CH$_2$CH$_2$OH), 109.1 (1C, C-8$_{carb}$), 109.3 (1C, C-1$_{carb}$), 111.2 (1C, C-4$_{carb}$), 115.4 (d, J = 21.6 Hz, 1C, C-5$_{phenyl}$), 118.5 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.3 (d, J = 25.0 Hz, 1C, C-3$_{phenyl}$), 121.7 (1C, C-4a$_{carb}$), 121.9 (1C, C-4b$_{carb}$), 122.2 (d, J = 10.1 Hz, 1C, C-2$_{phenyl}$), 124.5 (d, J = 3.5 Hz, 1C, C-1$_{phenyl}$), 125.7 (1C, C-7$_{carb}$), 131.2 (1C, C-3$_{carb}$), 133.7 (d, J = 9.6 Hz, 1C, C-6$_{phenyl}$), 136.6 (1C, C-9a$_{carb}$), 140.5 (1C, C-8a$_{carb}$), 163.7 (d, J = 253.3 Hz, 1C, C-4$_{phenyl}$), 166.6 (1C, C-3$_{oxadiazole}$), 169.8 (1C, CONH), 179.6 (1C, C-5$_{oxadiazole}$). The signal for NCH$_2$CH$_2$CH$_2$OH is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3670 (w, O–H), 3278 (m, N–H), 1647 (s, NH–C=O).

6.3.24. 4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-carbazol-3-yl]butanamide (19b)

According to the General Procedure C, **11b** (380 mg, 1.5 mmol) was treated with **13** (365 mg, 1.5 mmol), COMU® (380 mg, 1.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (14 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 12 cm, cyclohexane/ethyl acetate 15:85, R_f 0.37 (ethyl acetate)). Colorless solid, mp 161–162 °C, yield 335 mg (41%). $C_{27}H_{25}FN_4O_3$ (472.5 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{25}FN_4O_3H$ 473.1983 found 473.1988. Purity (HPLC): 98.2% (t_R = 20.22 min). ^{1}H NMR (CDCl$_3$): δ (ppm) = 2.06–2.13 (m, 2H, CH$_2$CH$_2$CH$_2$CONH), 2.34–2.43 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 2.60 (t, J = 7.1 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.14 (t, J = 7.1 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.60 (t, J = 5.8 Hz, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.46 (t, J = 6.6 Hz, 2H, NCH$_2$CH$_2$OHCH$_2$CH$_2$), 7.17 (m, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.19–7.24 (m, 1H, 6-H$_{carb}$), 7.38–7.52 (m, 5H, 1-H$_{carb}$, 2-H$_{carb}$, 4-H$_{carb}$, 7-H$_{carb}$, 8-H$_{carb}$), 748–7.55 (m, 3H, 5-H$_{carb}$, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.32 (s, 1H, CONH). A signal for the OH-moiety is not been seen. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 25.4 (1C, CH$_2$CH$_2$CH$_2$CONH), 31.8 (1C, NCH$_2$CH$_2$CH$_2$OH), 35.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 59.5 (1C, NCH$_2$CH$_2$CH$_2$OH), 109.0 (1C, C-8$_{carb}$), 109.3 (1C, C-1$_{carb}$), 111.2 (1C, C-4$_{carb}$), 116.4 (d, J = 22.2 Hz, 2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 118.5 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.7 (1C, C-4a$_{carb}$), 121.9 (1C, C-4b$_{carb}$), 122.9 (d, J = 3.1 Hz, 1C, C-1$_{phenyl}$), 125.7 (1C, C-7$_{carb}$), 129.5 (d, J = 9.1 Hz, 2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.2 (1C, C-3$_{carb}$), 136.6 (1C, C-9a$_{carb}$), 140.5 (1C, C-8a$_{carb}$), 163.9 (d, J = 247.2 Hz, 1C, C-4$_{phenyl}$), 166.7 (1C, C-3$_{oxadiazole}$), 169.8 (1C, CONH), 180.2 (1C, C-5$_{oxadiazole}$). The signal for NCH$_2$CH$_2$CH$_2$OH is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3414 (m, O–H), 3298 (m, N–H), 2935 (m, C–H, aliph), 1640 (s, NH–C=O).

6.3.25. 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-carbazol-3-yl]butanamide (19c)

According to the General Procedure C, **11c** (405 mg, 1.5 mmol) was treated with **13** (365 mg, 1.5 mmol), COMU® (782 mg, 1.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (14 mL). This mixture was stirred for 22 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 12 cm, cyclohexane/ethyl acetate 20:80, R_f 0.36 (ethyl acetate)). Colorless solid, mp 163–165 °C, yield 412 mg (56%). $C_{27}H_{25}ClN_4O_3$ (489.0 g/mol). Exact mass (ESI): m/z = calcd for $C_{27}H_{25}{}^{35}ClN_4O_3H$ 489.1688 found 489.1724. Purity (HPLC): 98.9% (t_R = 21.15 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.85–1.92 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 2.11–2.21 (quint, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.10 (t, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.36–3.44 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.40 (t, J = 6.5 Hz, 2H, NCH$_2$CH$_2$OHCH$_2$CH$_2$), 4.64 (t, J = 4.8 Hz, 1H, NCH$_2$CH$_2$CH$_2$OH), 7.15 (t, J = 7.3 Hz, 1H, 6-H$_{carb}$), 7.43 (t, J = 8.2 Hz, 1H, 7-H$_{carb}$), 7.49–7.53 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.61 (d, J = 8.5 Hz, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.99–8.01 (m, 3H, 5-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 8.39 (s, 1H, 4-H$_{carb}$), 9.96 (s, 1H, CONH). The signal for CH$_2$CH$_2$CH$_2$CONH is overlaid by the solvent peak, but can be seen in CDCl$_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, CH$_2$CH$_2$CH$_2$CONH), 25.2 (1C, CH$_2$CH$_2$CH$_2$CONH), 31.5 (1C, NCH$_2$CH$_2$CH$_2$OH), 34.7 (1C, CH$_2$CH$_2$CH$_2$CONH), 57.8 (1C, NCH$_2$CH$_2$CH$_2$OH), 108.8 (1C, C-8$_{carb}$), 109.0 (1C, C-1$_{carb}$), 111.0 (1C, C-4$_{carb}$), 118.2 (1C, C-2$_{carb}$), 118.7 (1C, C-6$_{carb}$), 119.8 (1C, C-5$_{carb}$), 121.4 (1C, C-4a$_{carb}$), 121.7 (1C, C-4b$_{carb}$), 125.0 (1C, C-1$_{phenyl}$) 125.5 (1C, C-7$_{carb}$), 128.5 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.1 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 130.9 (1C, C-3$_{carb}$), 135.9 (1C, C-4$_{phenyl}$), 136.4 (1C, C-9a$_{carb}$), 140.8 (1C, C-8a$_{carb}$), 166.5 (1C, C-3$_{oxadiazole}$), 169.6 (1C, CONH), 180.1 (1C, C-5$_{oxadiazole}$). The signal for NCH$_2$CH$_2$CH$_2$OH is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3376 (m, O–H), 3282 (m, N–H), 2970 (m, C–H, aliph), 1651 (s, NH–C=O).

6.3.26. 4-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-hydroxypropyl)-9*H*-carbazol-3-yl]butanamide (19d)

According to the General Procedure C, **11d** (375 mg, 1.5 mmol) was treated with **13** (365 mg, 1.5 mmol), COMU® (780 mg, 1.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in DMF (15 mL). This mixture was stirred for 24 h at <10 °C. The residue was purified by fc (d = 5 cm, l = 12 cm, cyclohexane/ethyl acetate 20:80, R_f 0.43 (ethyl acetate)). Colorless solid, mp 162–163 °C, yield 411 mg (58%). $C_{28}H_{28}N_4O_3$ (468.6 g/mol). Exact mass (ESI): m/z = calcd for $C_{28}H_{28}N_4O_3H$ 469.2234 found 469.2237. Purity (HPLC): 98.1% (t_R = 21.15 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.84–1.94 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 2.16 (quint, J = 7.3 Hz, 2H, NCH$_2$CH$_2$CH$_2$OH), 2.37 (s, 3H, CH$_3$), 3.12 (t, J = 7.4 Hz, 2H, CH$_2$CH$_2$CH$_2$CONH), 3.36–3.44 (m, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.40 (t, J = 6.8 Hz, 2H, NCH$_2$CH$_2$CH$_2$OH), 4.64 (t, J = 4.9 Hz, 1H, NCH$_2$CH$_2$OHCH$_2$CH$_2$), 7.16 (t, J = 7.4 Hz, 1H, 6-H$_{carb}$), 7.43 (t, J = 7.1 Hz, 1H, 7-H$_{carb}$), 7.50–7.53 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.57 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.59–7.64 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 7.99–8.04 (d, J = 7.7 Hz, 3H, 5-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 8.39 (s, 1H, 4-H$_{carb}$), 9.96 (s, 1H, CONH). The signal for CH$_2$CH$_2$CH$_2$CONH is overlaid by the solvent peak, but can be seen in CDCl$_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, CH$_3$), 22.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 25.4 (1C, CH$_2$CH$_2$CH$_2$CONH), 31.8 (1C, NCH$_2$CH$_2$CH$_2$OH), 35.0 (1C, CH$_2$CH$_2$CH$_2$CONH), 58.0 (1C, NCH$_2$CH$_2$CH$_2$OH), 109.0 (1C, C-8$_{carb}$), 109.3 (1C, C-1$_{carb}$), 111.2 (1C, C-4$_{carb}$), 118.5 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.7 (1C, C-4a$_{carb}$), 121.9 (1C, C-4b$_{carb}$), 125.2 (1C, C-7$_{carb}$), 125.7 (1C, C-1$_{phenyl}$), 128.8 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.4

(2C, C-2_{phenyl}, C-6_{phenyl}), 131.2 (1C, C-3_{carb}), 136.2 (1C, C-$9a_{carb}$), 136.6 (1C, C-4_{phenyl}), 140.5 (1C, C-$8a_{carb}$), 166.7 (1C, C-$3_{oxadiazole}$), 169.8 (1C, CONH), 180.3 (1C, C-$5_{oxadiazole}$). The signal for NCH_2CH_2-CH_2OH is overlaid by the solvent peak. IR (neat): ν (cm^{-1}) = 3468 (m, O–H), 3290 (m, N–H), 2947 (m, C–H, aliph), 1639 (s, NH–C=O).

6.3.27. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]propanamide (20a)

According to the General Procedure D, **15a** (400 mg, 0.8 mmol) was treated with XtalFluor-E® (263 mg, 1.2 mmol) and triethylamine trihydrofluoride (0.2 mL, 1.2 mmol) in CH_2Cl_2 (35 mL) at –78 °C. The product was purified by fc (d = 6 cm, l = 15 cm, cyclohexane/ethyl acetate 20:80, R_f = 0.53 (ethyl acetate)). Colorless solid, mp 201 °C, yield 82 mg (20%). $C_{25}H_{19}BrF_2N_4O_2$ (525.3 g/mol). Exact mass (APCI): m/z = calcd for $C_{25}H_{19}{}^{79}BrF_2N_4O_2H$ 525.0732 found 525.0757. Purity (HPLC): 96.7% (t_R = 21.46 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.97 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.39 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.51 (dt, J = 24.2/5.1 Hz, 2H, NCH_2CH_2F), 4.72 (dt, J = 46.8/5.1 Hz, 2H, NCH_2CH_2F), 7.03–7.09 (m, 1H, 5-H_{phenyl}), 7.16 (t, J = 7.0 Hz, 1H, 6-H_{carb}), 7.27 (d, J = 8.6 Hz, 1H, 1-H_{carb}), 7.32 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.36–7.43 (m, 3H, 2-H_{carb}, 7-H_{carb}, 3-H_{phenyl}), 7.56 (s, 1H, CONH), 7.76 (dd, J = 8.7/6.0 Hz, 1H, 6-H_{phenyl}), 7.97 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.41 (d, J = 1.8 Hz, 1H, 4-H_{carb}). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 19.7 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.9 Hz, 1C, NCH_2CH_2F), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 110.9 (1 C, C-4_{carb}), 115.5 (d, J = 21.7 Hz,1C, C-5_{phenyl}), 118.8 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 120.0 (1C, C-5_{carb}), 121.4 (d, J = 25.1 Hz, 1C, C-3_{phenyl}), 121.9 (1C, C-$4a_{carb}$), 122.1 (1C, C-$4b_{carb}$), 122.2 (d, J = 9.9 Hz, 1C, C-2_{phenyl}), 124.5 (d, J = 3.4 Hz,1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 131.4 (1C, C-3_{carb}), 133.6 (d, J = 9.3 Hz, 1C, C-6_{phenyl}), 136.7 (1C, C-$9a_{carb}$), 140.6 (1C, C-$8a_{carb}$), 162.9 (d, J = 253.2 Hz, 1C, C-4_{phenyl}), 166.4 (1C, C-$3_{oxadiazole}$), 168.5 (1C, CONH), 179.6 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3267 (m, N–H), 2954 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.28. *N*-[9-(2-Fluoroethyl)-9*H*-carbazol-3-yl]-3-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]propanamide (20b)

According to the General Procedure D, **15b** (200 mg, 0.5 mmol) was treated with XtalFluor-E® (70 mg, 0.3 mmol) and triethylamine trihydrofluoride (0.1 mL, 0.6 mmol) in CH_2Cl_2 (40 mL) at –78 °C. The product was purified by fc (d = 3 cm, l = 12 cm, cyclohexane/ethyl acetate 20:80, R_f 0.69 (ethyl acetate)). Colorless solid, mp 206–208 °C, yield 26 mg (13%). $C_{25}H_{20}F_2N_4O_2$ (446.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{25}H_{20}F_2N_4O_2H$ 447.1627 found 447.1597. Purity (HPLC): 98.3% (t_R = 21.14 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.00 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 6.8 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.69 (dt, J = 13.9/4.1 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 37.5/4.8 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.3 Hz, 1H, 6-H_{carb}), 7.36–7.45 (m, 3H, 7-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.56 (d, J = 8.7 Hz, 1H, 1-H_{carb}), 7.52 (dd, J = 8.8/1.8 Hz, 1H, 2-H_{carb}), 7.56 (d, J = 8.7 Hz, 1H, 8-H_{carb}), 8.01–8.09 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.41 (s, 1H, 4-H_{carb}), 10.16 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 20.1 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 168.0 Hz, 1C, NCH_2CH_2F), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 110.9 (1C, C-4_{carb}), 116.5 (d, J = 22.1 Hz, 2C, C-3_{phenyl}, C-5_{phenyl}), 118.8 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.9 (1C, C-$4a_{carb}$), 122.1 (1C, C-$4b_{carb}$), 122.9 (d, J = 3.1 Hz, 1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 129.5 (d, J = 9.0 Hz, 2C, C-2_{phenyl}, C-6_{phenyl}), 131.3 (1C, C-3_{carb}), 136.8 (1C, C-$9a_{carb}$), 140.6 (1C, C-$8a_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4_{phenyl}), 166.9 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 180.2 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3267 (m, N–H), 2939 (m, C–H, aliph), 1643 (s, NH–C=O).

6.3.29. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]propanamide (20c)

According to the General Procedure D, **15c** (400 mg, 0.9 mmol) was treated with XtalFluor-E® (300 mg, 1.3 mmol) and triethylamine trihydrofluoride (0.2 mL, 1.2 mmol) in CH_2Cl_2 (50 mL) at –78 °C. The product was purified by fc (d = 5.5 cm, l = 15 cm, cyclohexane/ethyl acetate 25:75, R_f 0.25 (cyclohexane/ethyl acetate 50:50)). Colorless solid, mp 220–221 °C, yield 120 mg (30%). $C_{25}H_{20}ClFN_4O_2$ (462.9 g/mol). Exact mass (APCI): m/z = calcd for $C_{25}H_{20}{}^{35}ClFN_4O_2H$ 463.1332 found 463.1304. Purity (HPLC): 98.6% (t_R = 22.00 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.04 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.43 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.58 (dt, J = 24.5/4.9 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 46.8/5.1 Hz, 2H, NCH_2CH_2F), 7.23 (t, J = 7.3 Hz, 1H, 6-H_{carb}), 7.30–7.40 (m, 2H, 1-H_{carb}, 7-H_{carb},), 7.41–7.50 (m, 4H, 2-H_{carb}, 8-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.65 (s, 1H, CONH), 8.00–8.07 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.31 (s, 1H, 4-H_{carb}). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 20.1 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.8 Hz, 1C, NCH_2CH_2F), 109.5 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 111.0 (1C, C-4_{carb}), 118.8 (1C, C-2_{carb}), 118.9 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.9 (1C, C-$4a_{carb}$), 122.1 (1C, C-$4b_{carb}$), 125.2 (1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 129.5 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.5 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.3 (1C, C-3_{carb}), 136.2 (1C, C-4_{phenyl}), 136.8 (1C, C-$9a_{carb}$), 140.6 (1C, C-$8a_{carb}$), 166.7 (1C, C-$3_{oxadiazole}$), 168.6 (1C, CONH), 180.4 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3302 (m, N–H), 2954 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.30. *N*-[9-(2-Fluoroethyl)-9*H*-carbazol-3-yl]-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanamide (20d)

According to the General Procedure D, **15d** (300 mg, 0.7 mmol) was treated with XtalFluor-E® (233 mg, 1.0 mmol) and triethylamine trihydrofluoride (0.2 mL, 1.2 mmol) in CH_2Cl_2 (40 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.48 (cyclohexane/ethyl acetate 40:60)). Colorless solid, mp 187–188 °C, yield 60 mg (20%). $C_{26}H_{23}FN_4O_2$ (442.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{23}FN_4O_2H$ 443.1878 found 443.1860. Purity (HPLC): 98.8% (t_R = 21.67 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.37 (s, 3H, CH_3), 3.00 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 6.3 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.69 (dt, J = 13.9/4.1 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 37.5/4.8 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.5 Hz, 1H, 6-H_{carb}), 7.36 (d, J = 7.9 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.56 (d, J = 8.7 Hz, 1H, 1-H_{carb}), 7.43 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.52 (dd, J = 8.8/1.9 Hz, 1H, 2-H_{carb}), 7.56 (d, J = 8.7 Hz, 1H, 8-H_{carb}), 7.89 (d, J = 8.2 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 8.04 (d, J = 7.6 Hz, 1H, 5-H_{carb}), 8.41 (s, 1H, 4-H_{carb}), 10.16 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.1 (1C, CH_3), 22.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 35.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 19.8 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.8 Hz, 1C, NCH_2CH_2F), 109.4 (1C, C-8_{carb}), 109.6 (1C, C-1_{carb}), 111.2 (1C, C-4_{carb}), 118.9 (1C, C-2_{carb}), 119.0 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.9 (1C, C-$4a_{carb}$), 122.1 (1C, C-$4b_{carb}$), 123.6 (1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 127.0 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.8 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.5 (1C, C-3_{carb}), 136.8 (1C, C-$9a_{carb}$), 140.7 (1C, C-$8a_{carb}$), 141.4 (1C, C-4_{phenyl}), 167.5 (1C, C-$3_{oxadiazole}$), 169.1 (1C, CONH), 179.9 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3275 (m, N–H), 2927 (m, C–H, aliph), 1639 (s, NH–C=O).

6.3.31. 3-[3-(4-Bromo-2-fluorophenyl)-1,2,4-oxadiazol-5-yl)]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]propanamide (20e)

According to the General Procedure D, **15e** (100 mg, 0.2 mmol) was treated with XtalFluor-E® (66 mg, 0.3 mmol) and triethylamine trihydrofluoride (0.14 mL, 0.9 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The product was purified by fc (d = 2 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f = 0.41 (cyclohexane/ethyl acetate 40:60)). Colorless solid, mp 207–210 °C, yield

90 mg (89%). $C_{25}H_{19}BrF_2N_4O_2$ (525.3 g/mol). Exact mass (APCI): m/z = calcd for $C_{25}H_{19}{}^{79}BrF_2N_4O_2H$ 525.0732 found 525.0724. Purity (HPLC): 98.3% (t_R = 20.46 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.02 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.37 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.69 (dt, J = 18.3/4.3 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 38.5/4.5 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.43 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.50–7.58 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.60 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.80 (td, J = 8.6/2.7 Hz, 1H, 5-H_{phenyl}), 8.05 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.13 (dd, J = 8.7/2.6 Hz, 1H, 3-H_{phenyl}), 8.18 (dd, J = 8.9/5.5 Hz, 1H, 6-H_{phenyl}), 8.41 (s, 1H, 4-H_{carb}), 10.17 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 19.7 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.9 Hz, 1C, NCH_2CH_2F), 109.5 (1C, C-8$_{carb}$), 109.6 (1C, C-1$_{carb}$), 111.0 (1 C, C-4$_{carb}$), 111.8 (d, J = 10.3 Hz,1C, C-4$_{phenyl}$), 116.2 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.5 (d, J = 21.8 Hz, 1C, C-1$_{phenyl}$), 121.9 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 122.5 (d, J = 26.1 Hz, 1C, C-3$_{phenyl}$), 125.1 (d, J = 3.4 Hz,1C, C-5$_{phenyl}$), 125.8 (1C, C-7$_{carb}$), 131.3 (1C, C-3$_{carb}$), 132.6 (d, J = 9.3 Hz, 1C, C-6$_{phenyl}$), 136.8 (1C, C-9a$_{carb}$), 140.7 (1C, C-8a$_{carb}$), 162.8 (d, J = 252.2 Hz, 1C, C-2$_{phenyl}$), 165.0 (1C, C-3$_{oxadiazole}$), 168.5 (1C, CONH), 180.6 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3332 (m, N–H), 2935 (m, C–H, aliph), 1689 (s, NH–C=O).

6.3.32. 3-[3-(2-Cyano-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]propanamide (20f)

According to the General Procedure D, **15f** (250 mg, 0.5 mmol) was treated with XtalFluor-E® (170 mg, 0.8 mmol) and triethylamine trihydrofluoride (0.25 mL, 1.6 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The product was purified by fc (d = 3.5 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.50 (cyclohexane/ethyl acetate 40:60)). Colorless solid, mp 203–205 °C, yield 97 mg (41%). $C_{26}H_{19}F_2N_5O_2$ (471.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{19}F_2N_5O_2H$ 472.1580 found 472.1521. Purity (HPLC): 98.0% (t_R = 21.49 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 3.01 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.34 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.69 (dt, J = 14.6/4.2 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 38.5/4.1 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.43 (t, J = 7.7 Hz, 1H, 7-H_{carb}), 7.51–7.65 (m, 4H, 1-H_{carb}, 2-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.63 (d, J = 8.6 Hz, 1H, 8-H_{carb}), 7.95 (t, J = 8.0 Hz, 1H, 6-H_{phenyl}), 8.04 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.40 (s, 1H, 4-H_{carb}), 10.16 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, $CH_2CH_2CONHCH_2CH_2$), 31.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 42.9 (d, J = 19.7 Hz, 1C, NCH_2CH_2F), 82.0 (d, J = 167.9 Hz, 1C, NCH_2CH_2F), 109.4 (1C, C-8$_{carb}$), 109.5 (2C, C-1$_{carb}$, C-2$_{phenyl}$), 110.9 (1C, C-4$_{carb}$), 118.8 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 119.2 (d, J = 3.2 Hz, 1C, CN), 120.1 (1C, C-5$_{carb}$), 120.2 (d, J = 22.0 Hz, 1C, C-5$_{phenyl}$), 122.5 (d, J = 24.3 Hz, 1C, C-3$_{phenyl}$), 121.9 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 125.8 (1C, C-7$_{carb}$), 128.5 (d, J = 3.6 Hz, 1C, C-1 phenyl), 131.3 (1C, C-3$_{carb}$), 132.6 (d, J = 9.7 Hz, 1C, C-6$_{phenyl}$), 136.8 (1C, C-9a$_{carb}$), 140.8 (1C, C-8a$_{carb}$), 157.1 (d, J = 250.3 Hz, 1C, C-4$_{phenyl}$), 166.4 (1C, C-3$_{oxadiazole}$), 168.6 (1C, CONH), 179.9 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3329 (m, N–H), 2943 (m, C–H, aliph), 2233 (w, -CN), 1685 (s, NH–C=O).

6.3.33. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl]propanamide (21a)

According to the General Procedure D, **16a** (300 mg, 0.6 mmol) was treated with XtalFluor-E® (192 mg, 0.8 mmol) and triethylamine trihydrofluoride (0.14 mL, 0.8 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The product was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 25:75, R_f 0.68 (ethyl acetate)). Colorless solid, mp 161–162 °C, yield 107 mg (33%). $C_{26}H_{21}BrF_2N_4O_2$ (539.4 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{21}{}^{79}BrF_2N_4O_2H$ 539.0889 found 539.0881. Purity (HPLC): 97.4% (t_R = 22.41 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.00–2.09 (m, 2H, $NCH_2CH_2CH_2F$), 2.99 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.98 (dt, J = 38.5/4.3 Hz, 2H, $NCH_2CH_2CH_2F$), 4.38 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_2F$), 7.14 (t, J = 7.1 Hz, 1H, 6-H_{carb}), 7.32–7.46 (m, 2H, 7-H_{carb}, 5-H_{phenyl}), 7.47–7.57 (m, 3H, 1-H_{carb}, 2-H_{carb}, 8-H_{carb}), 7.81 (dd, J = 8.6/2.6 Hz, 1H, 3-H_{phenyl}), 7.88 (dd, J = 8.7/6.0 Hz, 1H, 6-H_{phenyl}), 8.02 (d, J = 7.7 Hz, 1H, 5-H_{carb}), 8.41 (d, J = 1.7 Hz, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.8 (1C, $CH_2CH_2CONHCH_2CH_2$), 29.4 (d, J = 19.6 Hz, 1C, $NCH_2CH_2CH_2F$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 38.4 (d, J = 5.1 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 167.9 Hz, 1C, $NCH_2CH_2CH_2F$), 109.0 (1C, C-8$_{carb}$), 109.2 (1C, C-1$_{carb}$), 111.1 (1 C, C-4$_{carb}$), 115.5 (d, J = 21.6 Hz,1C, C-5$_{phenyl}$), 118.7 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 120.2 (1C, C-5$_{carb}$), 121.4 (d, J = 25.1 Hz, 1C, C-3$_{phenyl}$), 121.8 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 122.2 (d, J = 9.9 Hz, 1C, C-2$_{phenyl}$), 124.5 (d, J = 3.5 Hz,1C, C-1$_{phenyl}$), 125.9 (1C, C-7$_{carb}$), 131.3 (1C, C-3$_{carb}$), 133.6 (d, J = 9.4 Hz, 1C, C-6$_{phenyl}$), 136.5 (1C, C-9a$_{carb}$), 140.4 (1C, C-8a$_{carb}$), 162.9 (d, J = 253.4 Hz, 1C, C-4$_{phenyl}$), 166.6 (1C, C-3$_{oxadiazole}$), 168.6 (1C, CONH), 179.6 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3286 (m, N–H), 2970 (m, C–H, aliph), 1643 (s, NH–C=O).

6.3.34. 3-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl]propanamide (21b)

According to the General Procedure D, **16b** (240 mg, 0.5 mmol) was treated with XtalFluor-E® (180 mg, 0.8 mmol) and triethylamine trihydrofluoride (0.12 mL, 0.8 mmol) in CH_2Cl_2 (30 mL) at –78 °C. The product was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.71 (cyclohexane/ethyl acetate 50:50)). Colorless solid, mp 175–176 °C, yield 218 mg (91%). $C_{26}H_{22}F_2N_4O_2$ (460.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{22}F_2N_4O_2H$ 461.1783 found 461.1781. Purity (HPLC): 99.2% (t_R = 22.49 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.06–2.20 (m, 2H, $NCH_2CH_2CH_2F$), 3.00 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.28 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.40 (dt, J = 41.7/5.7 Hz, 2H, $NCH_2CH_2CH_2F$), 4.47–4.50 (m, 2H, $NCH_2CH_2CH_2F$), 7.17 (t, J = 7.1 Hz, 1H, 6-H_{carb}), 7.36–7.47 (m, 3H, 7-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.51–7.54 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.56 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 8.02–8.08 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.41 (s, 1H, 4-H_{carb}), 10.16 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 29.4 (d, J = 19.7 Hz, $NCH_2CH_2CH_2F$), 35.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 38.5 (d, J = 5.3 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 161.9 Hz, 1C, $NCH_2CH_2CH_2F$), 108.9 (1C, C-8$_{carb}$), 109.1 (1C, C-1$_{carb}$), 111.3 (1C, C-4$_{carb}$), 116.4 (d, J = 22.2 Hz, 2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 118.7 (1C, C-2$_{carb}$), 119.1 (1C, C-6$_{carb}$), 120.2 (1C, C-5$_{carb}$), 121.8 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 122.9 (d, J = 2.9 Hz, 1C, C-1$_{phenyl}$), 125.8 (1C, C-7$_{carb}$), 129.5 (d, J = 9.0 Hz, 2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.4 (1C, C-3$_{carb}$), 136.5 (1C, C-9a$_{carb}$), 140.4 (1C, C-8a$_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4$_{phenyl}$), 166.8 (1C, C-3$_{oxadiazole}$), 169.9(1C, CONH), 180.2 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3302 (m, N–H), 2954 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.35. 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl]propanamide (21c)

According to the General Procedure D, **16c** (300 mg, 0.6 mmol) was treated with XtalFluor-E® (220 mg, 1.0 mmol) and triethylamine trihydrofluoride (0.3 mL, 1.8 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 8 cm, cyclohexane/ethyl acetate 25:75, R_f 0.40 (cyclohexane/ethyl acetate 50:50)). Colorless solid, mp 174–175 °C, yield 139 mg (48%). $C_{26}H_{22}ClFN_4O_2$ (477.0 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{22}{}^{35}ClFN_4O_2H$ 477.1488 found 477.1508. Purity (HPLC): 96.9%

(t_R = 22.79 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.07–2.20 (m, 2H, $NCH_2CH_2CH_2F$), 3.01 (t, J = 7.4 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.31 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.41 (dt, J = 45.2/5.0 Hz, 2H, $NCH_2CH_2CH_2F$), 4.78 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_2F$), 7.17 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.44 (t, J = 7.4 Hz, 1H, 7-H_{carb}), 7.51–7.56 (m, 3H,1-H_{carb}, 2-H_{carb}, 8-H_{carb}), 7.63 (d, J = 8.2 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 8.01 (d, J = 8.1 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 8.04 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.42 (s, 1H, 4-H_{carb}), 10.17 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 29.4 (d, J = 19.5 Hz, $NCH_2CH_2CH_2F$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 38.4 (d, J = 5.0 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 162.1 Hz, 1C, $NCH_2CH_2CH_2F$), 109.0 (1C, C-8$_{carb}$), 109.2 (1C, C-1$_{carb}$), 111.1 (1C, C-4$_{carb}$), 118.7 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 120.2 (1C, C-5$_{carb}$), 121.9 (1C, C-4a$_{carb}$), 122.0 (1C, C-4b$_{carb}$), 125.2 (1C, C-1$_{phenyl}$), 125.9 (1C, C-7$_{carb}$), 128.8 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.2 (1C, C-3$_{carb}$), 136.2 (1C, C-4$_{phenyl}$), 136.5 (1C, C-9a$_{carb}$), 140.4 (1C, C-8a$_{carb}$), 166.7 (1C, C-3$_{oxadiazole}$), 168.6 (1C, CONH), 180.4 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3298 (m, N–H), 2958 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.36. *N*-[9-(3-Fluoropropyl)-9*H*-carbazol-3-yl]-3-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanamide (21d)

According to the General Procedure D, **16d** (456 mg, 1.0 mmol) was treated with XtalFluor-E® (344 mg, 1.5 mmol) and triethylamine trihydrofluoride (0.25 mL, 1.6 mmol) in CH_2Cl_2 (55 mL) at −78 °C. The product was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.55 (cyclohexane/ethyl acetate 40:60)). Colorless solid, mp 173–174 °C, yield 177 mg (38%). $C_{27}H_{25}FN_4O_2$ (456.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{25}FN_4OH$ 457.2034 found 457.2055. Purity (HPLC): 98.3% (t_R = 22.22 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.06–2.20 (m, 2H, $NCH_2CH_2CH_2F$), 2.37 (s, 3H, CH_3), 2.99 (t, J = 6.9 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.30 (t, J = 7.1 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.41 (dt, J = 45.0/5.7 Hz, 2H, $NCH_2CH_2CH_2F$), 4.48 (t, J = 6.8 Hz, 2H, $NCH_2CH_2CH_2F$), 7.17 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.36 (d, J = 8.1 Hz, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.44 (t, J = 7.8 Hz, 1H, 7-H_{carb}), 7.49–7.54 (m, 2H,1-H_{carb}, 2-H_{carb}), 7.56 (d, J = 8.2 Hz, 1H, 8-H_{carb}), 7.89 (d, J = 8.1 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 8.05 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.401 (s, 1H, 4-H_{carb}), 10.15 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.1 (1C, CH_3), 21.9 (1C, $CH_2CH_2CONHCH_2CH_2$), 29.4 (d, J = 19.6 Hz, $NCH_2CH_2CH_2F$), 32.0 (1C, $CH_2CH_2CONHCH_2CH_2$), 38.4 (d, J = 5.1 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 162.1 Hz, 1C, $NCH_2CH_2CH_2F$), 109.0 (1C, C-8$_{carb}$), 109.1 (1C, C-1$_{carb}$), 111.1 (1C, C-4$_{carb}$), 118.8 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 120.2 (1C, C-5$_{carb}$), 121.9 (1C, C-4a$_{carb}$), 122.0 (1C, C-4b$_{carb}$), 123.6 (1C, C-1$_{phenyl}$), 125.9 (1C, C-7$_{carb}$), 126.9 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.8 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.3 (1C, C-3$_{carb}$), 136.5 (1C, C-9a$_{carb}$), 140.7 (1C, C-8a$_{carb}$), 141.4 (1C, C-4$_{phenyl}$), 167.4 (1C, C-3$_{oxadiazole}$), 168.6 (1C, CONH), 179.9 (1C, C-5$_{oxadiazole}$C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3305 (m, N–H), 2970 (m, C–H, aliph), 1651 (s, NH–C=O).

6.3.37. 3-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(4-fluorobutyl)-9*H*-carbazol-3-yl] propanamide (22a)

According to the General Procedure D, **17a** (180 mg, 0.3 mmol) was treated with XtalFluor-E® (110 mg, 0.5 mmol) and triethylamine trihydrofluoride (0.16 mL, 1.0 mmol) in CH_2Cl_2 (30 mL) at –78 °C. The product was purified by fc (d = 5 cm, l = 15 cm, cyclohexane/ethyl acetate 25:75, R_f 0.86 (ethyl acetate)). Colorless solid, mp 169–162 °C, yield 28 mg (14%). $C_{27}H_{23}BrF_2N_4O_2$ (553.4 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{23}{}^{79}BrF_2N_4O_2H$ 553.1045 found 553.1004. Purity (HPLC): 98.7% (t_R = 22.61 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.70–1.80 (m, 2H, $NCH_2CH_2CH_2CH_2F$), 1.82–1.92 (m, 2H, $NCH_2CH_2CH_2CH_2F$), 2.99 (t, J = 6.7 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 3.35 (t, J = 7.0 Hz, 2H, $CH_2CH_2CONHCH_2CH_2$), 4.18 (dt, J = 41.5/5.6 Hz, 2H, $NCH_2CH_2CH_2CH_2F$), 4.48 (t, J = 6.0 Hz, 2H, $NCH_2CH_2CH_2CH_2F$), 7.16 (t, J = 7.2 Hz, 1H, 6-H_{carb}), 7.40–7.49 (m, 2H, 7-H_{carb}, 5-H_{phenyl}), 7.50–7.57 (m, 2H, 2-H_{carb}, 8-H_{carb}), 7.60 (d, J = 8.5 Hz, 1H, 1-H_{carb}), 7.83 (dd, J = 8.6/1.8 Hz, 1H, 3-H_{phenyl}), 7.88 (dd, J = 8.1/6.6 Hz, 1H, 6-H_{phenyl}), 8.04 (d, J = 7.4 Hz, 1H, 5-H_{carb}), 8.40 (s, 1H, 4-H_{carb}), 10.14 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 25.5 (d, J = 10.6 Hz, 1C, $NCH_2CH_2CH_2CH_2F$), 29.5 (d, J = 27.6 Hz, 1C, $NCH_2CH_2CH_2CH_2F$), 35.1 (1C, $CH_2CH_2CONHCH_2CH_2$), 43.1 (d, J = 5.1 Hz, 1C, $NCH_2CH_2CH_2CH_2F$), 81.4 (d, J = 167.9 Hz, 1C, $NCH_2CH_2CH_2CH_2F$), 109.6 (1C, C-8$_{carb}$), 109.8 (1C, C-1$_{carb}$), 111.9 (1 C, C-4$_{carb}$), 116.1 (d, J = 21.6 Hz,1C, C-5$_{phenyl}$), 119.4 (1C, C-2$_{carb}$), 119.7 (1C, C-6$_{carb}$), 120.9 (1C, C-5$_{carb}$), 122.0 (d, J = 25.0 Hz, 1C, C-3$_{phenyl}$), 122.5 (1C, C-4a$_{carb}$), 122.7 (1C, C-4b$_{carb}$), 122.8 (d, J = 10.0 Hz, 1C, C-2$_{phenyl}$), 125.2 (d, J = 3.5 Hz,1C, C-1$_{phenyl}$), 126.5 (1C, C-7$_{carb}$), 132.0 (1C, C-3$_{carb}$), 134.3 (d, J = 9.4 Hz, 1C, C-6$_{phenyl}$), 137.1 (1C, C-9a$_{carb}$), 140.0 (1C, C-8a$_{carb}$), 163.5 (d, J = 253.3 Hz, 1C, C-4$_{phenyl}$), 167.3 (1C, C-3$_{oxadiazole}$), 170.5 (1C, CONH), 180.3 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3267 (m, N–H), 3074 (m, C–H, arom), 1651 (s, NH–C=O).

6.3.38. 4-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]butanamide (23a)

According to the General Procedure D, **18a** (500 mg, 0.9 mmol) was treated with XtalFluor-E® (320 mg, 1.4 mmol) and triethylamine trihydrofluoride (0.3 mL, 1.8 mmol) in CH_2Cl_2 (32 mL) at –78 °C. The product was purified by fc (d = 6 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.44 (ethyl acetate)). Colorless solid, mp 158–159 °C, yield 118 mg (24%). $C_{26}H_{21}BrF_2N_4O_2$ (539.4 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{21}{}^{79}BrF_2N_4O_2H$ 539.0889 found 539.0924. Purity (HPLC): 98.7% (t_R = 21.95 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.36 (quint, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CONH$), 2.60 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.16 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.57 (dt, J = 24.2/5.1 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 46.8/5.1 Hz, 2H, NCH_2CH_2F), 7.10–7.17 (m, 1H, 6-H_{carb}), 7.20–7.25 (m, 1H, 7-H_{carb}), 7.33 (d, J = 8.6 Hz, 1H, 1-H_{carb}), 7.38 (d, J = 8.1 Hz, 1H, 8-H_{carb}), 7.44–7.50 (m, 3H, 2-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 7.65 (s, 1H, CONH), 7.84 (dd, J = 8.7/6.0 Hz, 1H, 6-H_{phenyl}), 8.05 (d, J = 7.8 Hz, 1H, 5-H_{carb}), 8.34 (d, J = 2.0 Hz, 1H, 4-H_{carb}). ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.3 (1C, $CH_2CH_2CH_2CONH$), 34.9 (1C, $CH_2CH_2CH_2CONH$), 42.9 (d, J = 20.2 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.8 Hz, 1C, NCH_2CH_2F), 109.4 (1C, C-8$_{carb}$), 109.6 (1C, C-1$_{carb}$), 111.1 (1 C, C-4$_{carb}$), 115.4 (d, J = 21.6 Hz,1C, C-5$_{phenyl}$), 118.8 (1C, C-2$_{carb}$), 118.9 (1C, C-6$_{carb}$), 120.0 (1C, C-5$_{carb}$), 121.2 (1C, C-4a$_{carb}$), 121.5 (1C, C-4b$_{carb}$), 122.0 (d, J = 21.9 Hz, 1C, C-3$_{phenyl}$)122.2 (d, J = 10.2 Hz, 1C, C-2$_{phenyl}$), 124.5 (d, J = 3.4 Hz,1C, C-1$_{phenyl}$), 125.8 (1C, C-7$_{carb}$), 131.5 (1C, C-3$_{carb}$), 133.7 (d, J = 9.4 Hz, 1C, C-6$_{phenyl}$), 136.7 (1C, C-9a$_{carb}$), 140.6 (1C, C-8a$_{carb}$), 162.8 (d, J = 253.2 Hz, 1C, C-4$_{phenyl}$), 166.6 (1C, C-3$_{oxadiazole}$), 169.9 (1C, CONH), 179.6 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3290 (m, N–H), 2935 (m, C–H. aliph), 1639 (s, NH–C=O).

6.3.39. *N*-[9-(2-Fluoroethyl)-9*H*-carbazol-3-yl]-4-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]butanamide (23b)

According to the General Procedure D, **18b** (428 mg, 1.0 mmol) was treated with XtalFluor-E® (320 mg, 1.4 mmol) and triethylamine trihydrofluoride (0.25 mL, 1.6 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 8 cm, cyclohexane/ethyl acetate 25:75, R_f 0.62 (ethyl acetate)). Colorless solid, mp 119–180 °C, yield 113 mg (27%). $C_{26}H_{22}F_2N_4O_2$ (460.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{22}F_2N_4O_2H$ 461.1783 found 461.1750. Purity (HPLC): 95.1% (t_R = 21.57 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.32–2.42 (m, 2H, $CH_2CH_2CH_2CONH$), 2.59 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.14 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.59 (dt, J = 24.2/5.2 Hz, 2H, NCH_2CH_2F), 4.79 (dt, J = 46.9/5.2 Hz, 2H, NCH_2CH_2F), 7.16 (t, J = 8.7 Hz, 1H, 6-H_{carb}), 7.20–7.25 (m, 1H, 7-H_{carb}), 7.35 (d, J = 8.8 Hz, 1H, 1-H_{carb}), 7.40 (d, J = 8.1 Hz, 1H, 8-

H_{carb}), 7.45–7.50 (m, 3H, 2-H_{carb}, 3-H_{phenyl}, 5-H_{phenyl}), 8.06 (d, J = 7.1 Hz, 1H, 5-H_{carb}), 8.07–8.10 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 8.35 (d, J = 2.0 Hz, 1H, 4-H_{carb}). A signal for NH is not seen in the spectrum. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, $CH_2CH_2CH_2$-CONH), 25.4 (1C, $CH_2CH_2CH_2CONH$), 35.0 (1C, $CH_2CH_2CH_2CONH$), 42.9 (d, J = 20.3 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.9 Hz, 1C, NCH_2-CH_2F), 109.4 (1C, C-8$_{carb}$), 109.6 (1C, C-1$_{carb}$), 111.1 (1C, C-4$_{carb}$), 116.4 (d, J = 22.2 Hz, 2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 118.9 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.9 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 122.9 (d, J = 2.9 Hz, 1C, C-1$_{phenyl}$), 125.8 (1C, C-7$_{carb}$), 129.5 (d, J = 9.0 Hz, 2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.5 (1C, C-3$_{carb}$), 136.8 (1C, C-9a$_{carb}$), 140.6 (1C, C-8a$_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4$_{phenyl}$), 166.7 (1C, C-3$_{oxadiazole}$), 169.9(1C, CONH), 180.2 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3286 (m, N–H), 2951 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.40. 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(2-fluoroethyl)-9*H*-carbazol-3-yl]butanamide (23c)

According to the General Procedure D, **18c** (150 mg, 0.3 mmol) was treated with XtalFluor-E® (110 mg, 0.5 mmol) and triethylamine trihydrofluoride (0.1 mL, 0.6 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 9 cm, cyclohexane/ethyl acetate 25:75, R_f 0.51 (cyclohexane/ethyl acetate 30:70)). Colorless solid, mp 201–202 °C, yield 69 mg (46%). $C_{26}H_{22}$-$ClFN_4O_2$ (477.0 g/mol). Exact mass (APCI): m/z = calcd for $C_{26}H_{22}{}^{35}$-$ClFN_4O_2H$ 477.1488 found 477.1434. Purity (HPLC): 99.9% (t_R = 22.00 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.10–2.20 (m, 2H, $CH_2CH_2CH_2CONH$), 3.10 (t, J = 7.4 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.27 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.68 (dt, J = 20.1/4.2 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 39.6/4.8 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.4 Hz, 1H, 6-H$_{carb}$), 7.36 (d, J = 7.9 Hz, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.43 (t, J = 7.7 Hz, 1H, 7-H$_{carb}$), 7.51–7.56 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.60 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.90 (d, J = 8.1 Hz, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.03 (d, J = 7.7 Hz, 1H, 5-H$_{carb}$), 8.40 (s, 1H, 4-H$_{carb}$), 9.97 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, CH_2-CH_2CH_2CONH), 25.4 (1C, $CH_2CH_2CH_2CONH$), 35.0 (1C, $CH_2CH_2CH_2$-CONH), 42.9 (d, J = 20.0 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.3 Hz, 1C, NCH_2CH_2F), 109.4 (1C, C-8$_{carb}$), 109.6 (1C, C-1$_{carb}$), 111.1 (1C, C-4$_{carb}$), 118.9 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.0 (1C, C-5$_{carb}$), 121.9 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 125.2 (1C, C-1$_{phenyl}$), 125.7 (1C, C-7$_{carb}$), 129.4 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.5 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.5 (1C, C-3$_{carb}$), 136.2 (1C, C-4$_{phenyl}$), 136.8 (1C, C-9a$_{carb}$), 140.7 (1C, C-8a$_{carb}$), 166.8 (1C, C-3$_{oxadiazole}$), 169.9 (1C, CONH), 180.4 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3294 (m, N–H), 2954 (m, C–H, aliph), 1654 (s, NH–C=O).

6.3.41. *N*-[9-(2-Fluoroethyl)-9*H*-carbazol-3-l]-4-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]butanamide (23d)

According to the General Procedure D, **18d** (200 mg, 0.4 mmol) was treated with XtalFluor-E® (152 mg, 0.7 mmol) and triethylamine trihydrofluoride (0.15 mL, 0.8 mmol) in CH_2Cl_2 (25 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 8 cm, cyclohexane/ethyl acetate 25:75, R_f 0.60 (cyclohexane/ethyl acetate 40:60)). Colorless solid, mp 197–198 °C, yield 80 mg (38%). $C_{27}H_{25}$-FN_4O_2 (456.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{25}FN_4$-O_2Na 479.1775 found 479.1785. Purity (HPLC): 99.5% (t_R = 22.25 min). ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.16 (quint, J = 7.4 Hz, 2H, $CH_2CH_2CH_2CONH$), 2.37 (s, 3H, CH_3), 3.27 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.68 (dt, J = 20.1/4.2 Hz, 2H, NCH_2CH_2F), 4.78 (dt, J = 39.6/4.8 Hz, 2H, NCH_2CH_2F), 7.18 (t, J = 7.4 Hz, 1H, 6-H$_{carb}$), 7.36 (d, J = 7.9 Hz, 2H, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.43 (t, J = 7.7 Hz, 1H, 7-H$_{carb}$), 7.51–7.56 (m, 2H, 1-H$_{carb}$, 2-H$_{carb}$), 7.60 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.90 (d, J = 8.1 Hz, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.03 (d, J = 7.7 Hz, 1H, 5-H$_{carb}$), 8.40 (s, 1H, 4-H$_{carb}$), 9.97 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, CH_3), 22.05 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, $CH_2CH_2CH_2CONH$), 35.0 (1C, $CH_2CH_2CH_2CONH$), 42.9 (d, J = 20.0 Hz, 1C, NCH_2CH_2F), 82.6 (d, J = 167.5 Hz, 1C, NCH_2CH_2F), 109.4 (1C, C-8$_{carb}$), 109.6 (1C, C-1$_{carb}$), 111.2 (1C, C-4$_{carb}$), 118.9 (1C, C-2$_{carb}$), 119.0 (1C, C-6$_{carb}$), 120.1 (1C, C-5$_{carb}$), 121.9 (1C, C-4a$_{carb}$), 122.1 (1C, C-4b$_{carb}$), 123.6 (1C, C-1$_{phenyl}$), 125.8 (1C, C-7$_{carb}$), 127.0 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.8 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 131.5 (1C, C-3$_{carb}$), 136.8 (1C, C-9a$_{carb}$), 140.7 (1C, C-8a$_{carb}$), 141.4 (1C, C-4$_{phenyl}$), 167.5 (1C, C-3$_{oxadiazole}$), 169.1 (1C, CONH), 179.9 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3282 (m, N–H), 2959 (m, C–H, aliph), 1647 (s, NH–C=O).

6.3.42. 4-[3-(2-Bromo-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl]butanamide (24a)

According to the General Procedure D, **19a** (180 mg, 0.3 mmol) was treated with XtalFluor-E® (221 mg, 0.9 mmol) and triethylamine trihydrofluoride (0.13 mL, 0.8 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 10 cm, cyclohexane/ethyl acetate 25:75, R_f 0.78 (ethyl acetate)). Colorless solid, mp 129–131 °C, yield 126 mg (71%). $C_{27}H_{23}BrF_2N_4O_2$ (553.4 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{23}{}^{79}BrF_2N_4O_2H$ 553.1049 found 553.1044. Purity (HPLC): 99.0% (t_R = 22.31 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.15–2.30 (m, 2H, $NCH_2CH_2CH_2F$), 2.37 (quint, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CONH$), 2.60 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 3.17 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.39 (dt, J = 47.8/5.4 Hz, 2H, $NCH_2CH_2CH_2F$), 4.45 (t, J = 6.3 Hz, 2H, $NCH_2CH_2CH_2F$), 7.15 (t, J = 8.3 Hz, 1H, 6-H$_{carb}$), 7.23 (t, J = 7.4 Hz, 1H, 7-H$_{carb}$), 7.36 (d, J = 8.7 Hz, 1H, 1-H$_{carb}$), 7.41 (d, J = 8.2 Hz, 1H, 8-H$_{carb}$), 7.44–7.52 (m, 3H, 2-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 7.66 (s, 1H, CONH), 7.85 (dd, J = 8.6/6.0 Hz, 1H, 6-H$_{phenyl}$), 8.05 (d, J = 7.7 Hz, 1H, 5-H$_{carb}$), 8.35 (d, J = 1.7 Hz, 1H, 4-H$_{carb}$). ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.6 (1C, $CH_2CH_2CH_2CONH$), 26.0 (1C, CH_2-CH_2CH_2CONH), 30.0 (d, J = 19.7 Hz, 1C, $NCH_2CH_2CH_2F$), 35.6 (1C, $CH_2CH_2CH_2CONH$), 39.1 (d, J = 5.3 Hz, 1C, $NCH_2CH_2CH_2F$), 82.1 (d, J = 167.2 Hz, 1C, $NCH_2CH_2CH_2F$), 109.6 (1C, C-8$_{carb}$), 109.8 (1C, C-1$_{carb}$), 111.9 (1 C, C-4$_{carb}$), 116.1 (d, J = 21.6 Hz,1C, C-5$_{phenyl}$), 119.4 (1C, C-2$_{carb}$), 119.7 (1C, C-6$_{carb}$), 120.9 (1C, C-5$_{carb}$), 122.0 (d, J = 25.0 Hz, 1C, C-3$_{phenyl}$), 122.5 (1C, C-4a$_{carb}$), 122.7 (1C, C-4b$_{carb}$), 122.8 (d, J = 10.0 Hz, 1C, C-2$_{phenyl}$), 125.2 (d, J = 3.5 Hz,1C, C-1$_{phenyl}$), 126.5 (1C, C-7$_{carb}$), 132.0 (1C, C-3$_{carb}$), 134.3 (d, J = 9.4 Hz, 1C, C-6$_{phenyl}$), 137.1 (1C, C-9a$_{carb}$), 140.0 (1C, C-8a$_{carb}$), 163.5 (d, J = 253.3 Hz, 1C, C-4$_{phenyl}$), 167.3 (1C, C-3$_{oxadiazole}$), 170.5 (1C, CONH), 180.3 (1C, C-5$_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3286 (m, N–H), 2966 (m, C–H, aliph), 1639 (s, NH–C=O).

6.3.43. 4-[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl]butanamide (24b)

According to the General Procedure D, **19b** (300 mg, 0.6 mmol) was treated with XtalFluor-E® (221 mg, 1.0 mmol) and triethylamine trihydrofluoride (0.2 mL, 1.2 mmol) in CH_2Cl_2 (30 mL) at –78 °C. The product was purified by fc (d = 5 cm, l = 9 cm, cyclohexane/ethyl acetate 25:75, R_f 0.73 (ethyl acetate)). Colorless solid, mp 146–147 °C, yield 116 mg (38%). $C_{27}H_{24}F_2N_4O_2$ (474.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{24}F_2N_4O_2H$ 475.1940 found 475.1926. Purity (HPLC): 97.1% (t_R = 22.05 min). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.16–2.31 (m, 2H, $NCH_2CH_2CH_2F$), 2.37 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2CONH$), 2.59 (t, J = 7.1 Hz, 2H, CH_2CH_2-CH_2CONH), 3.14 (t, J = 7.1 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.39 (dt, J = 47.2/5.4 Hz, $NCH_2CH_2CH_2F$), 4.46–4.48 (m, 2H, $NCH_2CH_2CH_2F$), 7.16 (t, J = 8.7 Hz, 1H, 6-H$_{carb}$), 7.23 (t, J = 7.7 Hz, 1H 7-H$_{carb}$), 7.37 (d, J = 8.7 Hz, 1H, 1-H$_{carb}$), 7.42 (d, J = 8.1 Hz, 1H, 8-H$_{carb}$), 7.45–7.53 (m, 3H, 2-H$_{carb}$, 3-H$_{phenyl}$, 5-H$_{phenyl}$), 8.06 (d, J = 8.3 Hz, 1H, 5-H$_{carb}$), 8.08–8.11 (m, 2H, 2-H$_{phenyl}$, 6-H$_{phenyl}$), 8.35 (s, 1H, 4-H$_{carb}$). A signal for NH is not seen in the spectrum. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.1 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, CH_2-CH_2CH_2CONH), 29.4 (d, J = 19.8 Hz, $NCH_2CH_2CH_2F$), 35.0 (1C, CH_2-

CH_2CH_2CONH), 38.5 (d, J = 5.3 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 162.0 Hz, 1C, $NCH_2CH_2CH_2F$), 108.9 (1C, C-8_{carb}), 109.1 (1C, C-1_{carb}), 111.3 (1C, C-4_{carb}), 116.4 (d, J = 22.2 Hz, 2C, C-3_{phenyl}, C-5_{phenyl}), 118.7 (1C, C-2_{carb}), 119.1 (1C, C-6_{carb}), 120.1 (1C, C-5_{carb}), 121.8 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 122.9 (d, J = 3.2 Hz, 1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 129.5 (d, J = 9.0 Hz, 2C, C-2_{phenyl}, C-6_{phenyl}), 131.4 (1C, C-3_{carb}), 136.5 (1C, C-$9a_{carb}$), 140.4 (1C, C-$8a_{carb}$), 163.9 (d, J = 249.1 Hz, 1C, C-4_{phenyl}), 166.7 (1C, C-$3_{oxadiazole}$), 169.9 (1C, CONH), 180.2 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3294 (m, N–H), 2974 (m, C–H, aliph), 1643 (s, NH–C=O).

6.3.44. 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-*N*-[9-(3-fluoropropyl)-9*H*-carbazol-3-yl] butanamide (24c)

According to the General Procedure D, **19c** (200 mg, 0.4 mmol) was treated with XtalFluor-E® (140 mg, 0.6 mmol) and triethylamine trihydrofluoride (0.2 mL, 1.2 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The product was purified by fc (d = 6 cm, l = 8 cm, cyclohexane/ethyl acetate 25:75, R_f 0.65 (cyclohexane/ethyl acetate 30:70)). Colorless solid, mp 178–180 °C, yield 109 mg (54%). $C_{27}H_{24}ClFN_4O_2$ (491.0 g/mol). Exact mass (APCI): m/z = calcd for $C_{27}H_{24}{}^{35}ClFN_4O_2H$ 491.1645 found 491.1649. Purity (HPLC): 97.8% (t_R = 22.47 min). ^1H NMR (DMSO-d_6): δ (ppm) = 2.10–2.22 (m, 4H, $NCH_2CH_2CH_2F$, $CH_2CH_2CH_2CONH$), 3.28 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CONH$), 4.41 (dt, J = 42.6/5.7 Hz, 2H, $NCH_2CH_2CH_2F$), 4.47–4.49 (m, 2H, NCH_2-CH_2CH_2F), 7.17 (t, J = 7.5 Hz, 1H, 6-H_{carb}), 7.44 (t, J = 7.6 Hz, 1H, 7-H_{carb}), 7.50 (d, J = 8.6 Hz, 1H,1-H_{carb}), 7.53 (dd, J = 8.3 Hz, 1H, 2-H_{carb}), 7.56 (d, J = 8.3 Hz, 1H, 8-H_{carb}), 7.59–7.63 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 8.00–8.04 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 9.97 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, $CH_2CH_2CH_2CONH$), 29.4 (d, J = 19.2 Hz, $NCH_2CH_2CH_2F$), 35.0 (1C, $CH_2CH_2CH_2CONH$), 38.5 (d, J = 5.3 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 162.0 Hz, 1C, $NCH_2CH_2CH_2F$), 108.9 (1C, C-8_{carb}), 109.1 (1C, C-1_{carb}), 111.3 (1C, C-4_{carb}), 118.7 (1C, C-2_{carb}), 119.1 (1C, C-6_{carb}), 120.2 (1C, C-5_{carb}), 121.8 (1C, C-$4a_{carb}$), 122.0 (1C, C-$4b_{carb}$), 125.2 (1C, C-1_{phenyl}), 125.8 (1C, C-7_{carb}), 128.8 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.4 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.3 (1C, C-3_{carb}), 136.5 (1C, C-4_{phenyl}), 136.5 (1C, C-$9a_{carb}$), 140.4 (1C, C-$8a_{carb}$), 166.8 (1C, C-$3_{oxadiazole}$), 168.9 (1C, CONH), 180.3 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3267 (m, N–H), 2970 (m, C–H, aliph), 1643 (s, NH–C=O).

6.3.45. *N*-[9-(3-Fluoropropyl)-9*H*-carbazol-3-yl]-4-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl] butanamide (24d)

According to the General Procedure D, **19d** (300 mg, 0.6 mmol) was treated with XtalFluor-E® (220 mg, 0.8 mmol) and triethylamine trihydrofluoride (0.26 mL, 1.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The product was purified by fc (d = 5 cm, l = 8 cm, cyclohexane/ethyl acetate 25:75, R_f 0.66 (cyclohexane/ethyl acetate 30:70)). Colorless solid, mp 177–178 °C, yield 208 mg (69%). $C_{28}H_{27}FN_4O_2$ (470.5 g/mol). Exact mass (APCI): m/z = calcd for $C_{28}H_{28}FN_4O_2Na$ 494.2088 found 494.2080. Purity (HPLC): 99.7% (t_R = 21.89 min). ^1H NMR (DMSO-d_6): δ (ppm) = 2.11–2.19 (m, 4H, $NCH_2CH_2CH_2F$, $CH_2CH_2CH_2CONH$), 2.37 (s, 3H, CH_3), 3.42 (t, J = 5.6 Hz, 2H, CH_2CH_2-CH_2CONH), 4.38 (dt, J = 42.5/5.7 Hz, 2H, $NCH_2CH_2CH_2F$), 4.68 (t, J = 6.2 Hz, 2H, $NCH_2CH_2CH_2F$), 7.18 (t, J = 7.4 Hz, 1H, 6-H_{carb}), 7.45 (t, J = 7.6 Hz, 1H, 7-H_{carb}), 7.47–7.52 (m, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.56 (d, J = 8.5 Hz, 1H, 8-H_{carb}), 7.60–7.64 (m, 2H, 1-H_{carb}, 2-H_{carb}), 7.97–8.05 (m, 3H, 5-H_{carb}, 2-H_{phenyl}, 6-H_{phenyl}), 8.39 (s, 1H, 4-H_{carb}), 9.97 (s, 1H, CONH). The signal for $CH_2CH_2CH_2CONH$ is overlaid by the solvent peak, but can be seen in $CDCl_3$. ^{13}C NMR (DMSO-d_6): δ (ppm) = 21.9 (1C, CH_3), 22.0 (1C, $CH_2CH_2CH_2CONH$), 25.4 (1C, CH_2-CH_2CH_2CONH), 29.4 (d, J = 19.6 Hz, 1C, $NCH_2CH_2CH_2F$), 35.0 (1C, $CH_2CH_2CH_2CONH$), 42.9 (d, J = 5.0 Hz, 1C, $NCH_2CH_2CH_2F$), 81.4 (d, J = 162.1 Hz, 1C, $NCH_2CH_2CH_2F$), 108.9 (1C, C-8_{carb}), 109.2 (1C, C-1_{carb}), 111.3 (1C, C-4_{carb}), 118.7 (1C, C-2_{carb}), 119.1 (1C, C-6_{carb}), 120.2 (1C, C-5_{carb}), 121.8 (1C, C-$4a_{carb}$), 122.1 (1C, C-$4b_{carb}$), 122.1 (1C, C-1_{phenyl}), 125.9 (1C, C-7_{carb}), 128.8 (2C, C-3_{phenyl}, C-5_{phenyl}), 129.4 (2C, C-2_{phenyl}, C-6_{phenyl}), 131.4 (1C, C-3_{carb}), 136.2 (1C, C-$9a_{carb}$), 136.8 (1C, C-4_{phenyl}), 140.7 (1C, C-$8a_{carb}$), 167.8 (1C, C-$3_{oxadiazole}$), 169.9 (1C, CONH), 180.4 (1C, C-$5_{oxadiazole}$). IR (neat): ν (cm^{-1}) = 3267 (m, N–H), 2970 (m, C–H, aliph), 1643 (s, NH–C=O).

7. Experimental receptor binding studies

7.1. Materials

The recombinant CHO cells expressing the CB_2 receptor were a generous donation of Professor Paul Prather (Little Rock, Arkansas, USA). Cell incubator: Heracell 120 (Thermo Fisher Scientific, Langenselbold, Germany). Homogenizers: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany) and Soniprep 150, MSE, London, UK). Centrifuges: Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Vortexer: Vortex Genie 2 (Thermo Fisher Scientific, Langenselbold, Germany). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany). Chemicals and reagents were purchased from different commercial sources and of analytical grade.

7.2. Cell culture and preparation of membrane homogenates from CB_2 cells

The cell culture was modified according to Ref.[51]

CHO cells stably transfected with the gene for the human CB_2 receptor were grown in Dulbecco Modified Earl's Medium (DMEM) containing 10% of standardized FCS (Biochrom AG, Berlin, Germany) and 250 μg/mL Geneticin. The cells were harvested by scraping off the surface, resuspended in PBS buffer and pelleted (10 min, 5000×g) and the number of cells was determined using an improved Neubauer's counting chamber (VWR, Darmstadt, Germany). Subsequently, the cells were lysed by sonication (4 °C, 6 × 10 s cycles with breaks of 10 s). The resulting cell fragments were centrifuged with a high performance cool centrifuge (20,000×g, 4 °C). The supernatant was discarded and the pellet resuspended in a defined volume of TRIS buffer (50 mM TRIS, 12 mM $MgCl_2$, 4 mM EDTA, pH 7.4) yielding cell fragments of approximately 2,000,000 cells/mL. The suspension of membrane homogenates was sonicated again (4 °C, 2 × 10 s cycles with breaks of 10 s) and stored at −80 °C.

7.3. General protocol for the binding assays

The test compound solutions were prepared by dissolving approximately 10 μmol (usually 2–4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in 96-well multiplates. The concentrations given are the final concentrations in the assay. Generally, the assays were performed by addition of 50 μL of the respective assay buffer, 50 μL test compound solution in various concentrations (10-5, 10-6, 10-7, 10-8, 10-9 and 10-10 mol/L), 50 μL of

corresponding radioligand solution and 50 μL of the respective receptor preparation into each well of the multiplate (total volume 200 μL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500–600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 μL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC_{50}-values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i-values using the equation of Cheng and Prusoff.[54] The K_i-values of most active compounds are given as mean value ± SEM from three independent experiments.

7.4. Protocol of the CB_2 receptor binding assay

The assay was modified according to Ref.[51]

The assay was performed with the radioligand [^{3}H]CP-55,940 (Perkin Elmer). The CB_2 receptor containing cell membrane fragments (fragments of approximately 100,000 cells/well) were incubated with various concentrations of the test compound, 1 nM [^{3}H]CP-55,940 and binding buffer (50 TRIS pH 7.4, 12 mM $MgCl_2$, 4 EDTA and 2% BSA) at 37 °C. The non-specific binding was determined with 10 μM non-labeled CP-55,940. The K_d value of [^{3}H]CP-55,940 is 11.8 nM (determined by a saturation experiment).

8. Molecular modeling

All molecular modeling tasks were performed using the modeling software program Molecular Operation Environment (MOE, version 2012.10, Chemical Computing Group Inc. Montreal, Canada). For the molecular docking studies, our receptor model of human CB_2 receptor[53] based on the 3D structure of the agonist-bound human A2A adenosine receptor [PDB:3QAK][55] was employed.

The compounds were generated in MOE according to the precedure described previously.[53] The binding pocket was defined using the Site-Finder module of MOE with residue $Y190^{5.39}$ (numbering scheme according to Ballesteros and Weinstein[56]) in the centre. Molecular docking were performed with the program GOLD[57] (version 5) with default parameters. The conformation of the small ligands was allowed to change by leaving all single bonds of the small molecules freely rotatable. The computed receptor-ligand complexes were clustered with a cut-off of 1.0 Å (heavy atoms only) within GOLD. Subsequent geometry optimization of the complexes with the protein backbone kept fixed delivered the final poses.

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