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Highly potent and selective cannabinoid receptor 2 agonists: Initial hit optimization of an adamantyl hit series identified from high-through-put screening

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ABSTRACT

A series of highly potent & selective adamantane derived CB2 agonists was identified in a high-throughput screen. A SAR was established and physicochemical properties were significantly improved. This was accompanied by potency of the compounds on the Q63R variant and varying β-arrestin data which will support the insight into their relevance for the in vivo situation.

Throughout evolution the mammalian body has developed numerous protective mechanisms to prevent and limit tissue injury caused by various types of neuronal as well as non-neuronal insults. Lipid signaling through activation of cannabinoid 2 (CB2) receptors is thought to be an important part of this protective machinery.[1] Inflammation/tissue injury causes a rapid increase in local endocannabinoid levels which leads to a fast modulation of signaling pathways in immune and other cells. It has been reported that endocannabinoids, endocannbinoid-like and/or synthetic CB2 receptor agonists positively affect a large number of pathological conditions, spanning from cardiovascular,[2] over gastrointestinal,[3] liver,[4] kidney,[5] lung,[6] neurodegenerative[7] and psychiatric[8] disorders to pain,[9] cancer,[10] bone,[11] reproductive system[12] and skin pathologies.[13] Prototypical CB2 receptor agonists range from endogeneous ligands such as anandamide (AEA)[14] and 2-arachidonoyl glycerol (2-AG)[15] over the plant-derived Δ9-tetrahydrocannabinol ((−)-Δ^9-THC)[14] to exogenous cannabinoid type agonists such as HU-308,[14] JWH-133[16] and HU-910[4] as well as even newer non-cannabinoid type agonists which are described in several recent overviews.[17] These agonists have various degrees of activities and possess different selectivity against the cannabinoid receptor 1 (CB1).[18]

With the goal to identify new CB2 receptor agonist hit structures, a high-throughput screen was performed. Various hit clusters were found. One cluster entailed a considerable number of adamantyl-derivatives with more than 30 members suggesting a specific interaction of this moiety with the CB2 receptor. A very preliminary SAR could be deduced from that data set. In general, all compounds showed high selectivity towards the CB1 receptor with considerably potency range at the CB2 receptor. Representative examples are shown in Table 1.

The majority of compounds in this cluster were amide based derivatives, however also carbamoylthioyl-amides were found, like example **1** with an EC_{50} of 1.4 μM at the CB2 receptor and being inactive at the CB1 receptor. Heteroaryl derivatives were active as well, exemplified with thiazolyl-derivative **2** which was already active in the high nano-molar range. Substituted aryl-amide derivatives yielded a very preliminary SAR. The substitution on the aryl-moiety seemed to be determining the activity at the CB2 receptor. Substituents in the 4-position (like in example **3**) yielded compounds active in the μM range. The nature of the substituent in the 2-position influenced the activity considerably. Derivative **4** was active with 100 nM at the CB2 receptor, compound **5** was active in the low nano-molar range (EC_{50} = 15 nM) and both

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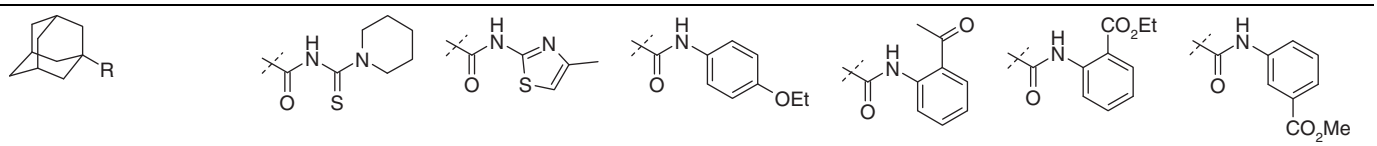
Table 1
Initial SAR from representative members of the adamantyl hit cluster[19]



No.	1	2	3	4	5	6
hCB2: cAMP EC_{50} (μM)	1.4	0.6	1.2	0.1	0.015	>10
hCB2: β-arrestin EC_{50} (μM)	0.5	0.9	—	—	0.076	—
hCB1: cAMP EC_{50} (μM)	>10	>10	>10	>10	>10	>10
*c*log*P*, MW	4.0, 306	3.5/327	4.4/299	4.1/297	4.7/313	4.2/313

compounds had EC_{50}s well above 10 μM at the CB1 receptor. Shifting the ester moiety to position **3** yielded inactive derivative **6**. The ability of CB2 agonists to recruit β-arrestin, which ultimately leads to the steric inhibition of G protein coupling and termination of signaling independent of G protein classes, was determined. The fact that various partial agonists might constitutively stimulate receptor activation without causing β-arrestin recruitment might be considered as a crucial parameter for the translation of in vitro potency into in vivo efficacy.[20] Compounds **1** and **2** showed an EC_{50} in the β-arrestin assay in the high nano-molar range and derivative **5** was active with an EC_{50} of 76 nM. Calculated molecular properties of these derivatives revealed in general a low molecular weight of ~300 Da and *c*log*P* values ~4. This adamantyl-cluster offered a preliminary SAR on the human CB2 and CB1 cAMP read-out and on the activation potential of the human CB2 β-arrestin. Several derivatives in this adamantyl-cluster displayed high ligand efficiencies[21] with *c*log*P* values generally ~4 or above. JWH-133 and HU-910 are both highly lipophilic compounds (*c*log*P*: 7.99 and 8.79, respectively) and active in the cAMP assay in the low nano-molar range (4.3 nM and 5.3 nM, respectively) which corroborated our confidence into the HTS derived adamantyl-cluster being a valuable starting point for optimization. Adamantane groups are well known moieties in approved drugs (i.e., Amantadine or Vildagliptin) useful in the treatment of diseases related to the CNS as well as diseases to be treated peripherally.[22] The adamantane moiety, optimally substituted, can entail favorable properties like high bioavailability, good metabolic stability and half-life. Literature analysis[23] yielded a competitor compound **7**, an analog of a clinically evaluated derivative, which was reported with sub-nano molar activity at the CB2 receptor to have some selectivity for the CB1 receptor. Superimposition and fitting into the homology model of the hit structure **5** and adamantane derivative **7** yielded similar specific interactions thus even further supporting our confidence in this hit-cluster in combination with CB2 agonism (Fig. 1).

There is a nice match of pharmacophoric features of the hydrophobic adamantane, the aromatic moiety as well as donor/acceptor features of the amide and inverse amide, respectively. The vector at the aromatic moiety has the same directionality. Thus, the conformation of the HTS hit is determined through intra-molecular H-bond interaction and therefore suggested the replacement of the anthranilic acid moiety through bicyclic systems offering opportunities for optimization of these CB2 receptor agonists. To prove this initial hypothesis, adamantane concept compounds with varying bi-cyclic amide substitutions were designed. The synthesis entails a one-step transformation of an activated adamantane acid derivative with the respective amine moiety to access novel derivatives (**8–11**) which were profiled under various aspects; that is, CB2 function and binding, additionally CB2 β-arrestin function and preliminary molecular properties (i.e., lipohilicity (log*D*), solubility (LYSA), permeability (Pe) and stability in human microsomes (MAB-maximal achievable bioavailability)[24] (Table 2).[25] Furthermore, functional activity on the Q63R variation of the CB2 receptor was assessed. This relevant polymorphism is suggested to be associated, for example, with liver damage in obese children,[26] increases of risk of celiac disease,[27] and with the risk for schizophrenia[28] and therefore might have significant impact on the efficacy of CB2 receptor agonist derived drugs for the human situation.

As expected from our 'modeling hypothesis' the tetrahydroquinoline is a good replacement for the anthranilic acid moiety. Already the un-substituted compound **8** was active in the nano-molar range on functional CB2 with high selectivity for CB1.[29] Micromolar activity in the binding assay was observed, the compound was though inactive on human CB2 β-arrestin. In the CB2 human Q63R variant the compound was as well active in the nano-molar range. Preliminary molecular properties assessment confirmed the compound to be insoluble with a MAB value of 23% in human microsomes. Further substitution of the tetrahydroquinoline with a methoxy functionality yielded derivative **9** which was even more

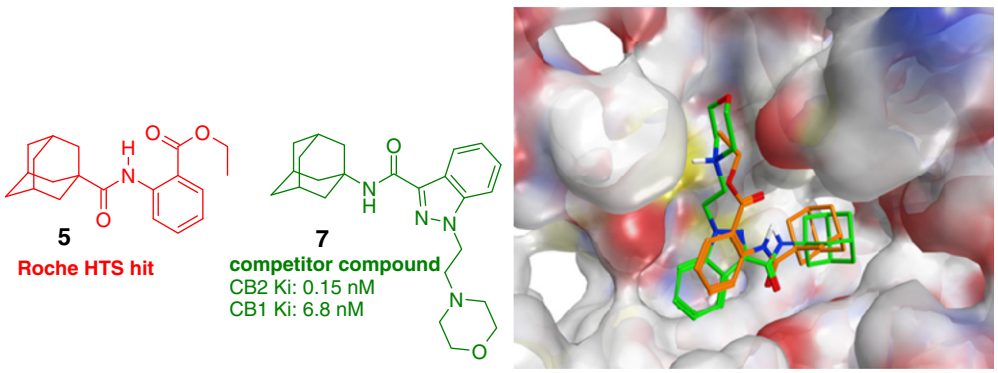


Figure 1. Superimposition of compound **5** (orange) and **7** (green) in the binding site of a CB2 homology model.

Table 2
Properties of adamantane concept compounds **8**–**11**

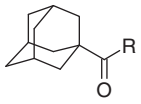
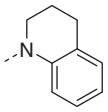
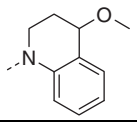
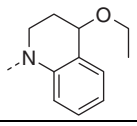
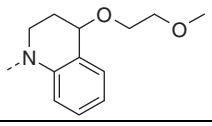
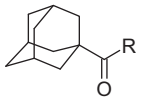
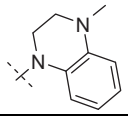
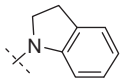
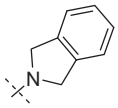
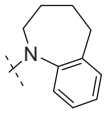
					
No.	**8**	**9**	**10**	**11**
h/m CB2: cAMP EC_{50} (μM)	0.072/0.126	0.027/0.023	0.0018/0.028	0.02/0.02
hCB2 Q63R var. EC_{50} (μM)	0.055	0.078	—	0.024
h/m CB2: K_i (μM)	0.79/4.3	0.77/5.2	0.99/>10	0.35/1.5
hCB2: β-arrestin EC_{50} (μM)	>10	1.3	—	0.9
h/m CB1: cAMP EC_{50} (μM)	>10/>10	>10/>10	>10/5	>10/>10
log*D*, LYSA (μg/mL)	—/<1	3.79, 10	4.09, 17	3.82, 97
Pe (10^{-6} cm/s), % acc	Precip.	3.3, 4.6	0.7/0.9	4.4, 5.7
MAB h %	23	12	6	5

Table 3
Properties of adamantane compounds **12**–**15**

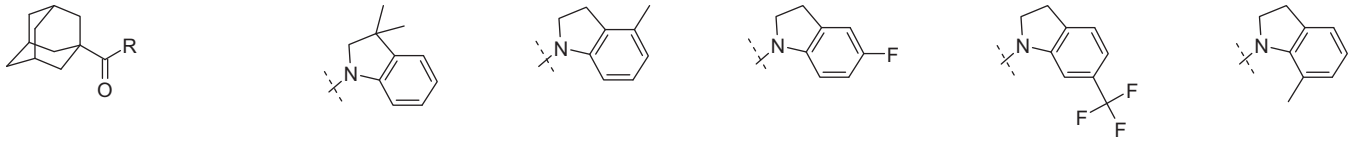
					
No.	**12**	**13**	**14**	**15**
h/m CB2: cAMP EC_{50} (μM)	0.029/0.022	0.023/0.026	0.02/0.007	>10/>10
hCB2 Q63R var. EC_{50} (μM)	0.071	—	—	
h/m CB2: K_i (μM)	0.5/2.8	0.46/>10	0.5/0.9	
hCB2: β-arrestin EC_{50} (μM)	>10	0.22	0.6	
h/m CB1: cAMP EC_{50} (μM)	>10/>10	>10/>10	>10/>10	
log*D*, LYSA (μg/mL)	4.09, <1	—/<1	—, <1	
Pe (10^{-6} cm/s), % acc	0, 0	0.4, 2	0.5, 14	
MAB h %	10	45	51	

potent at the CB2 receptor maintaining the selectivity versus CB1 and similarly active in the binding assay as derivative **8**. The β-arrestin value was improved to 1.3 μM while the activity at the Q63R variant was maintained. The methoxy group rendered the compound **9** less lipophilic and more soluble with good permeation properties. Metabolic stability though was decreased. Further elongation of this vector towards an ethoxy- (compound **10**) and also methoxyethoxy-substituent (compound **11**) contributed further to the preliminary SAR. Compounds **10** and **11** were active in the nano-molar range at CB2 with excellent selectivity versus CB1. Binding data in the micro-molar range and a β-arrestin/Q63R variant value for **11** of 0.9/0.024 μM, respectively were found. Lipophilicity values of around 4 paired with some solubility and low metabolic stability required improvement of this sub-series. Our initial hypothesis was substantiated with values from the shown concept compounds which led to further establishing an SAR around this series. Ring sizes and nature of the bi-cyclic amide-substituent was investigated. The results are shown in Table 3.

Tetrahydro-quinoxaline derivatives, exemplified with compound **12**, were potent, selective and showed binding activities versus CB2 in the micro-molar range. Compound **12** was inactive in the β-arrestin assay though maintained its nano-molar activity in the Q63R CB2 variant in the nano-molar range. Molecular properties of these derivatives in general revealed high lipophilicity, low solubility and almost no permeability. In human microsomes compound **12** was only weakly stable. Investigating the ring-size potential of these bi-cycles showed that dihydro-indole derivative **13** and iso-indoline derivative **14** had very similar profiles. Already when unsubstituted they were active at the CB2 receptor in the low nano-molar range with high selectivity for the CB1 receptor. Binding affinities were in the low micro-molar range as were the β-arrestin values. Derivatives **13** and **14** were rather lipophilic, poorly soluble though highly permeable. Microsomal stability was greatly improved to human MAB values around 50%. This initiated a more in depth profiling of these two bi-cyclic systems as adamantyl derivatives with either dihydo-indole or iso-indoline moieties were not systematically unstable in human microsomes. This investigation was complemented by the result that seven-membered bi-cyclic systemes like tetrahydro-1*H*-benzo[*b*]azepine derivatives were inactive **15**. A broader array of dihydro-indole derivatives was synthesized to establish a more in depth SAR also thereby establishing the general molecular property profile. Representative examples (**16–20**) are listed in Table 4.

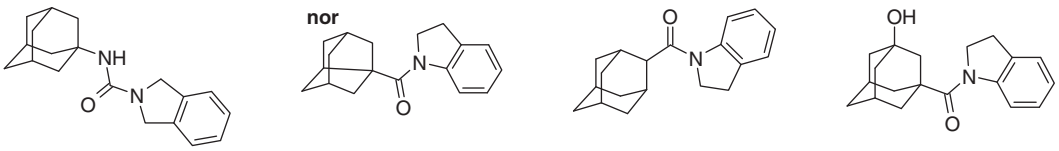
Compounds which are substituted in the 2-position of the dihydro-indole moiety are generally inactive on the CB2 receptor. Substituting the 3-position (like in example **16**) yielded compounds which were active and selective with binding values in the micro-molar range. Activity on the Q63R variant was found in the nano-molar range. Substituting the 4-position had the most pronounced effect on CB2 agonism (while keeping the selectivity). Highly potent and selective compounds, like derivative **17** were identified. Substituting position 5, 6 or 7 led as well to potent and selective compounds (**18–20**). Depending on the nature of the substituent EC_{50} on the CB2 receptor were found to be below 100 nM, keeping high selectivity towards the CB1 receptor. Binding values as well as β-arrestin values varied in the low μM range. Q63R variant values were always in the low nM range. Compounds with such profiles that is, highly potent on CB2 and the Q63R variant with high selectivity versus CB1 and varying values in the β-arrestin recruitment assay will be used to assess the relevance of CB2 receptor desensitization for the respective pharmacodynamics effects in in vivo models. Physicochemical properties for all derivatives were generally very similar, that is, highly lipophilic, poorly soluble with varying permeation ability. The MAB in human microsomes though was pleasingly in the 40–50% range.

Table 4
Properties of adamantane compounds **16**–**20**



No.	**16**	**17**	**18**	**19**	**20**
h/m CB2: cAMP EC_{50} (μM)	0.016/0.04	0.004/0.007	0.0046/0.009	0.015/0.0029	0.055/0.05
hCB2 Q63R var. EC_{50} (μM)	0.036	0.011	—	0.049	0.081
h/m CB2: K_i (μM)	0.5/4.9	0.17/1.3	0.2/2.4	2.5/2.8	0.6/>10
hCB2: β-arrestin EC_{50} (μM)	0.9	0.29	0.2	0.75	1.6
h/m CB1: cAMP EC_{50} (μM)	>10/>10	>10/>10	>10/>6	>10/>10	>10/>10
log*D*, LYSA (μg/mL)	—, <1	—, <1	—, <1	—, <1	—, <1
Pe (10^{-6} cm/s), % acc	0, 0	Precip.	2.3, 4.7	Precip.	Precip.
MAB h %	39	46	52	36	51

Table 5
Properties of adamantane compounds **21**–**24**



No.	**21**	**22**	**23**	**24**
h/m CB2: cAMP EC_{50} (μM)	0.022/0.019	0.022/0.051	0.007/0.02	0.49/1
hCB2 Q63R var. EC_{50} (μM)	0.027	—	0.011	0.531
h/m CB2: K_i (μM)	0.27/0.4	0.5/>10	0.32/2.2	—
hCB2: β-arrestin EC_{50} (μM)	0.7	0.9	0.16	2.6
h/m CB1: cAMP EC_{50} (μM)	>10/>10	>10/>10	>10/>10	>10
log*D*, LYSA (μg/mL)	4.26, <1	3.7, <1	—, <1	2.77, >318
Pe (10^{-6} cm/s), % acc	12, 26	1.9, 0.5	0.1, 5	10.3, 25
MAB h %	37	55	37	90

To further broaden the SAR of the adamantyl-derivatives and influence the physicochemical properties new derivatives were designed in which the nature of the linkage between the adamantane and the substituent as well as the nature of any adamantane substitution was investigated. Representative examples (**21–24**) are shown in Table 5.

In adamantane-derivative **21** the amide linkage was changed to a urea moiety and the compound was still active in the low nano-molar range on CB2/CB2 Q63R variant and selective versus the CB1 receptor. Binding and β-arrestin values were found in the micromolar range. Urea derivatives in general showed an improved ability to permeate through membranes as indicated by the high Pe value of 12 for compound **21**. Microsomal stability was maintained in the 40% range. Introduction of a nor-adamantane moiety was well tolerated and yielded compound **22** with a very similar profile as in the respective adamantane derivative **13**. This offers now a new and unexplored vector for diversification. Shifting the amide moiety to the 2-position of the adamantane scaffold furnished very potent derivatives, exemplified with compound **23**. The profile is again very similar to the one of the isomeric adamantane derivative **13** offering another vector for diversification and differentiation. Substitution of the adamantane scaffold with solubilizing groups like hydroxyl yielded derivatives, as exemplified with compound **24**, with preliminarily promising in vitro values. The physicochemical properties profile was improved considerably that is, in compound **24** the lipophilicity was reduced by a factor 10–100 and the solubility was greatly enhanced. This combined with high permeation and high human microsomal bioavailability potential opened up new, unexplored and promising vectors for further derivatisation in the optimization phase of this adamantane hit cluster.

In summary, a series of highly potent & selective adamantyl derived CB2 agonists was identified in a high-throughput screen. Conformational analysis of the most active derivatives suggested the replacement of the anthranilic acid ester moiety with bi-cyclic systems. This was studied and a SAR around various bi-cycles was established. Dihydro-indole and isoindoline derived adamantane derivatives were discovered and a more in depth SAR was established. Vectors for further optimization were found, physicochemical properties were significantly improved and room for further improvement was discovered. This was accompanied by potency of the compounds on the Q63R variant and varying β-arrestin data which will support the insight into their relevance for the in vivo situation.

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29. *General experimental description for the synthesis of adamantyl derivatives, exemplified with the preparation procedure of* ***8***: A mixture of 24.5 mg (0.18 mmol) 1,2,3,4-tetrahydroquinoline, 37.3 mg (0.188 mmol) 1-adamatanecarbonyl chloride and 44.4 mg (0.34 mmol) DIPEA in 1 mL DCM was shaken at room temperature for 4 h. The mixture was evaporated, dissolved in DMF and subjected to column chromatography on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid to yield after evaporation of the product containing fractions 34.9 mg (64%) of the title compound as white solid. MS (*m*/*e*): 296.3 (MH^+).