CB1 Cannabinoid Receptor Ligands

Ganesh A. Thakur[a,b], Spyros P. Nikas[a,b] and Alexandros Makriyannis*[,a,b,c,d]

[a]*Center for Drug Discovery, Departments of* [b]*Pharmaceutical Sciences,* [c]*Molecular and Cell Biology,* [d]*Institute of Materials Science, University of Connecticut, Storrs, CT 06269, USA*

Abstract: The CB1 receptor is expressed in the central nervous system and numerous other tissues including heart, lung and uterus and has been recognized as an important therapeutic target for pain, appetite modulation, glaucoma, multiple sclerosis and other indications. An interesting feature of this GPCR is its ability to be activated by a number of structurally different classes of compounds, thus, raising the possibility of multiple activated forms of the receptor. Understanding of the structure-activity relationships of cannabinergic ligands has paved the road for the development of novel ligands exhibiting receptor subtype selectivity and efficacy. This review highlights the important CB1 cannabinergic ligands developed to date.

Keywords: Cannabinoid receptors, CB1 agonists, CB1 antagonists, CB1 selectivity.

INTRODUCTION

The medical benefits of cannabis (marijuana), the mixture of natural cannabinoids found in *cannabis sativa* have been recognized for centuries. However, the isolation and structure elucidation [1] of its active ingredient (-)-Δ^9-tetrahydrocannabinol afforded the initial opportunity to investigate the pharmacological properties of cannabinoids and develop detailed correlations between structure and function within this class of compounds [2, 3]. The next milestone in cannabinoid research was the discovery that cannabinoids produce most of their biochemical and pharmacological effects by interacting with CB1 and CB2, the two known $G_{i/o}$-protein-coupled receptors (GPCRs) [4-7]. The presence of saturable, specific, high-affinity cannabinoid CB1 binding sites was demonstrated both in the central nervous system (CNS) as well as in certain peripheral tissues (for reviews see: [8, 9]). In CNS the CB1 receptor is expressed with high density in the cerebellum, hippocampus and striatum [10-14]. It is also found in a variety of other organs including heart, vascular endothelium, vas deferens [15, 16], testis [17], small intestine [15, 16], sperm [18, 19] and uterus [20]. Conversely, the CB2 receptor appears to be associated primarily with the immune system. It is found in the periphery of the spleen and other cells associated with immunochemical functions, but not in the brain [7] and is believed to have an immunomodulatory role. CB1 and CB2 share an overall homology of 44% and 68% in transmembrane domains. The rat [6], mouse [21, 22] and human CB1 receptors [5] have been cloned and show 97-99% sequence identity across species while the mouse CB2 [23, 24] exhibits 82% sequence identity with the human clone [7]. CB1 and CB2 share common signal transduction pathways, such as inhibition of adenylyl cyclase and stimulation of mitogen-activated protein kinase. However, unlike CB1, CB2 has not been shown to affect ion channels (for recent review see: [25, 26]).

*Address correspondence to this author at the Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, 06269, USA; Tel: +001-860-486-2133; Fax: +001-860-486-3089;
E-mail: makriyan@uconnvm.uconn.edu

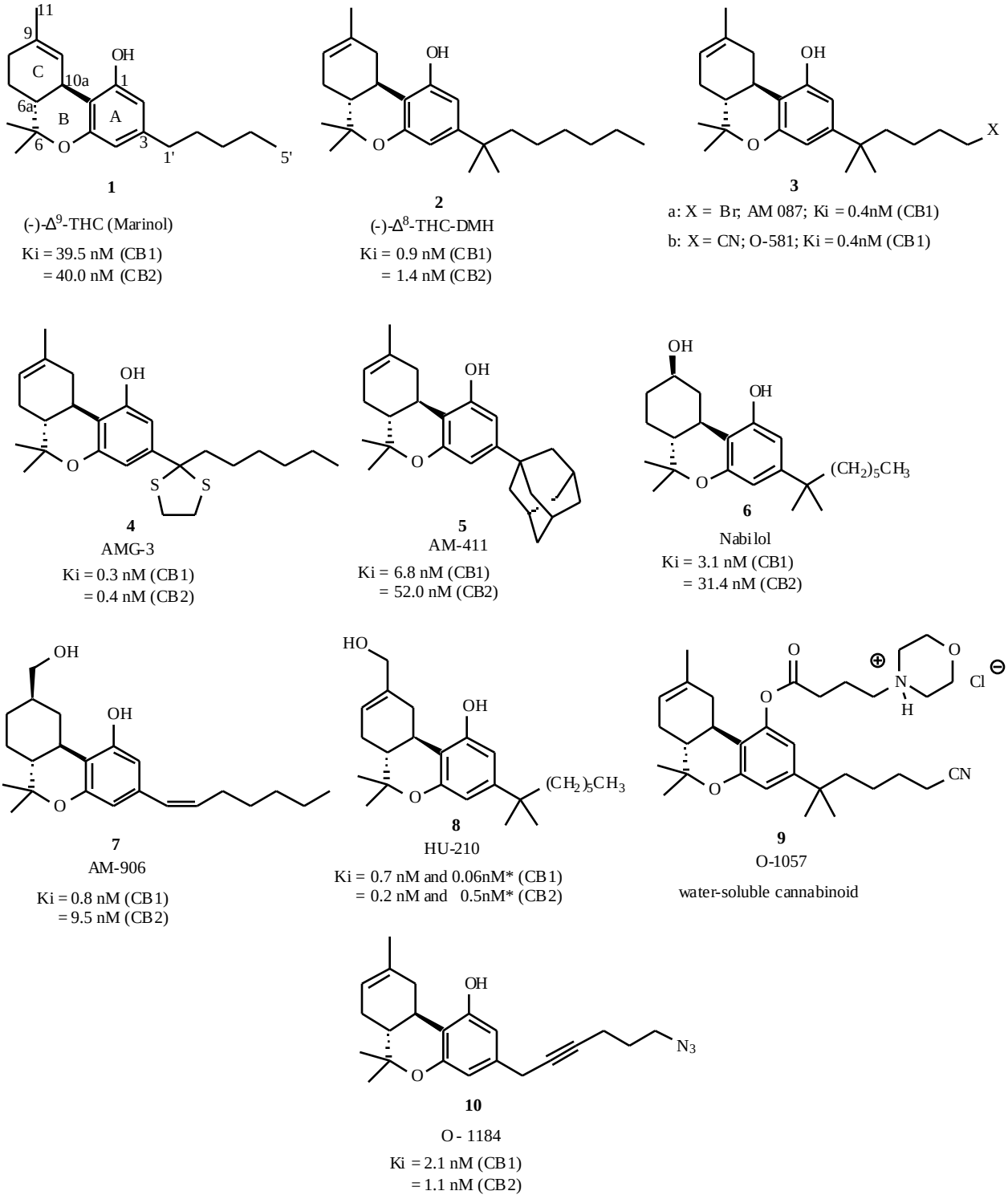
The discovery of the CB1 receptor was followed by the isolation and identification of two key endocannabinoid ligands: *N*-arachidonoylethanolamine (anandamide) [27] and 2-arachidonoyl glycerol (2-AG) [28-30] and has led to a better understanding of the physiological and biochemical roles of the endocannabinoid system. More recently, 2-arachidonyl glyceryl ether (noladin ether) has been proposed as a representative of a third endocannabinoid class [31], although its biochemical relevance remains in question.

Like other polytopic membrane proteins, the CB1 receptor has remained elusive to large-scale purification and, consequently, is not yet a candidate for structural characterization through the use of crystallographic or other biophysical methods. However, a great deal of information regarding molecular recognition of cannabinergic ligands has been obtained from classical structure-activity relationship (SAR) studies summarized in a number of recent reviews [32-36]. This information coupled with the development of three-dimensional models of CB1 [37, 38] based, in part, on the bovine rhodopsin (Rho) crystal structure [39], provided a basis for postulating a number of ligand-receptor binding motifs which have received partial validation from single-site mutation studies along with chimeric constructs [37, 40-43]. More direct information about the binding motifs is now being obtained with the help of suitably designed and highly specific covalent binding probes [44].

The CB1 receptor has been recognized as an important therapeutic target for pain, appetite modulation, glaucoma, multiple sclerosis and several other indications, and is currently receiving increasing attention by the pharmaceutical industry and other drug discovery laboratories. An interesting feature of CB1 is its ability to be activated by a number of structurally different classes of compounds, thus, raising the possibility of multiple activated forms of the receptor. The currently known classes of cannabinergic ligands include (1) classical cannabinoids (CCs) (2) non-classical cannabinoids (NCCs) (3) hybrid cannabinoids (4) arachidonic acid based endocannabinoids and their analogs (5) diarylpyrazoles and (6) other cannabinergic classes.

Currently, our laboratory is involved in a broadly based cannabinoid receptor program, which encompasses all major classes of cannabinergic ligands. This mini-review will focus

1389-5575/05 $50.00+.00



*ref: Felder *et al.* 1995 [72]

Fig. (1). Representative classical cannabinoid CB1 ligands.

on the important CB1 receptor ligands that exhibit high affinity, selectivity and /or efficacy.

CLASSICAL CANNABINOIDS

Classical cannabinoids are ABC-tricyclic terpenoid compounds bearing a benzopyran moiety (Fig. **1**). This class includes the natural product (-)-Δ^9-tetrahydrocannabinol((-)-Δ^9-THC, **1**), the more stable and almost equipotent isomer (-)-Δ^8-THC, other pharmacologically active constituents of the plant *cannabis sativa* and their synthetic analogs. A review of structure-activity relationship studies [2, 3, 32, 34-36, 45, 46] recognizes three pharmacophores (Fig. **2**) within this class of compounds: a phenolic hydroxyl (PH), a lipophilic side chain (SC), and a northern aliphatic hydroxyl (NAH). An additional fourth pharmacophore, the southern

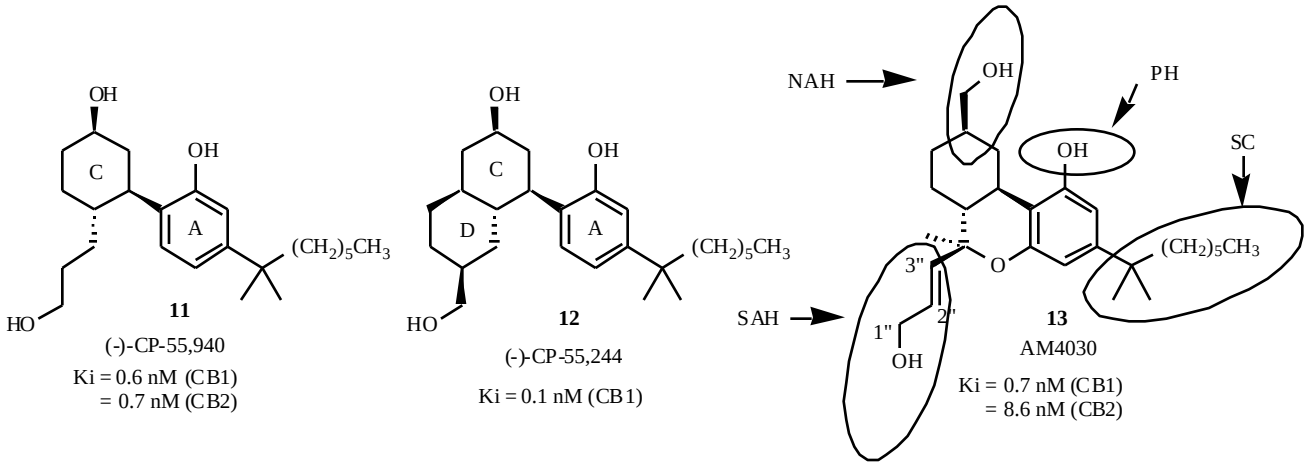


Fig. (2). Representative non-classical and hybrid CB1 agonists.

aliphatic hydroxyl (SAH, **13**, Fig. **2**), is encompassed in the synthetic non-classical cannabinoids developed by Pfizer (e.g. **11**). (-)-Δ^9-THC binds equally well to both CB1 and CB2 receptors and is a partial agonist with regard to both receptor subtypes. In this class of compounds the phenolic hydroxyl group at C-1 is essential for CB1 affinity as its replacement by a methoxy group, hydrogen or fluorine atom diminishes CB1 affinity [47-51] with lesser effects on CB2. Variation of the *n*-pentyl side chain of natural cannabinoids leads to wide variations in potency and selectivity. Optimal activity is obtained with a seven or eight carbon length substituted with 1′,1′- or 1′,2′-dimethyl groups as was first demonstrated by Adams (e.g. **2**) [52-54], while incorporation of halogen, cyano or azido group at the end of the side chain enhances CB1 affinity [55-60]. Thus, AM087 (**3a**) and O-581 (**3b**) bearing bromo and cyano substituents respectively at the end of the dimethylpentyl side chain exhibit subnanomolar affinities for the CB1 receptor. More recent studies have focused on novel side chains bearing 1′,1′-cyclic moieties [61-64]. Some of the synthesized analogs exhibited remarkably high affinities for both CB1 and CB2 receptors while *in vitro* pharmacological testing found the dithiolane analog **4** to be a potent CB1 selective agonist. The results of these studies suggest the presence of subsite within CB1 and CB2 binding domain at the level of the benzylic side chain carbon in the THC series [64].

Replacement of the *n*-pentyl side chain of Δ^8-THC with a 1-adamantyl group led to AM411 (**5**), the high potency and efficacy CB1 agonist developed by Makriyannis. This ligand exhibits about 7-fold CB1 selectivity with relatively slow receptor desensitization [65]. AM411 acts as a potent full agonist and was shown to suppress locomotion, induce catalepsy, reduce temperature, and induce analgesia as measured by the tail-flick response (Salamone and Makriyannis unpublished results).

Incorporation of a hydroxyl group at the C-9 or C-11 position (northern aliphatic hydroxyl, NAH) in hexahydro- or tetrahydrocannabinols leads to significant enhancement in affinity and potency for both CB1 and CB2. Hexahydrocannabinols, in which the C-ring is fully saturated, include 9α and 9β isomers based on the relative configuration at the C-9 position. Of these, the β-epimer in which the C-9 hydroxyl or hydroxylmethyl group is equatorial (e.g. **6** and **7** respectively) have been shown to be more potent than their α-axial counterparts [66-68]. Thus, nabilol (**6**) and AM906 (**7**) [69] behave as potent CB1 agonists.

A tetrahydrocannabinol derivative, HU-210 (**8**), developed by Mechoulam [70, 71] is one of the most potent classical cannabinoids reported. This ligand binds with subnanomolar affinity to both CB1 and CB2 and in one report it has been shown to exhibit preference for CB1 [72]. It acts as a potent CB1/CB2 receptor agonist and inhibits forskolin-stimulated *c*AMP production. Both the affinity and potency of HU-210 are much higher than those of its synthetic (+)-6a*S*, 10a*S* enantiomer (HU-211, dexanabilol), thus, mirroring the steroselectivity in CB receptor-ligand interactions.

Another classical cannabinoid that behaves as a agonist at both receptor subtypes and has received considerable attention because of its water solubility is O-1057 (**9**). This ligand exhibits high affinity for both receptors (Ki = 4.4 nM (CB1) and 11.2 nM (CB2)) with a preference for CB1 and its potency at CB1 matching that of (-)-CP-55,940 and exceeding that of Δ^9-THC [33, 73, 74].

A classical cannabinoid ligand, 6′-azidohex-2′-yne-Δ^8-THC (O-1184, **10**) was reported to behave as a potent selective cannabinoid receptor antagonist in the myenteric plexus-longitudinal muscle preparation of guinea-pig small intestine [75]. Later binding experiments with rat cerebellar membranes using [^{35}S]-GTPγS found this compound to behave as a low-efficacy agonist at CB1 receptors [76, 77].

NON-CLASSICAL CANNABINOIDS (NCCs)

This class of cannabinoid receptor agonists designated as non-classical cannabinoids and possessing close similarity with CCs was developed by Pfizer in an effort to simplify the CC structure, while maintaining or improving biological activity [78, 79]. These ligands are characterized by AC bicyclic (e.g. **11**) and ACD tricyclic (e.g. **12**) structures lacking the pyran B-ring of CCs. The best known example of this class is (-)-CP-55,940 (**11**) a crystalline ligand displaying high and roughly equal affinities for both cannabinoid receptors (Ki = 0.6-5.0 nM (CB1); 0.7-2.6 nM (CB2)). As a radioligand, [^{3}H] CP-55,940 was the key

compound that led to the discovery of CB1 [4]. A representative of the ACD tricyclic NCCs is the CB1 agonist (-)-CP-55,244 (**12**) which displays higher CB1 affinity and relative intrinsic activity than that of (-)-CP-55,940 [10, 79-81]. NCCs share some of the key pharmacophores of CCs namely, the phenolic hydroxyl, the side chain and the northern aliphatic hydroxyl groups. Additionally, they incorporate a hydroxylalkyl chain on the cyclohexyl ring contiguous and *trans* to the aromatic phenolic group generally designated as southern aliphatic hydroxyl (SAH) [82].

HYBRID CANNABINOIDS

Combining the structural features of classical and non-classical cannabinoids led to a hybrid class of cannabinoids represented by **13** (Fig. **2**). This new class (CC/NCC hybrids) had the added advantage of serving as conformationally more defined three-dimensional probes for the CB1 and CB2 active sites than their non-classical counterparts. Receptor binding data showed that at C-6 the equatorial β-hydroxypropyl analog had higher affinity than the α-axial epimer [83]. Further refinement of the CC/NCC hybrids was obtained by imposing restricted rotation around this SAH pharmacophore which was accomplished through the introduction of double and triple bonds at the C2" position of the 6β-hydroxypropyl chain (**13**). This promising class of compounds encompassing four asymmetric centers is amongst the most structurally complex and potent cannabinergics synthesized to date [83-89].

ENDOGENOUS CB1 LIGANDS

The discovery of cannabinoid receptors was followed in 1992 by the demonstration that *N*-arachidonoylethanolamine (anandamide, AEA, **14**) is an endogenous ligand for these receptors [27]. AEA is a highly lipophilic compound isolated from porcine brain and shown to encompass four non-conjugated cis double bonds. This ligand is sensitive to both oxidative metabolism mainly by COX-2 [90] and cytochrome P450 [91] and enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) [92-95]. It was shown to bind to the CB1 receptor with moderate affinity (Ki = 61nM) and has low affinity for the CB2 receptor (Ki = 1930nM). Pharmacologically, anandamide resembles (-)-Δ^9-THC by behaving as a partial CB1 and CB2 agonist with higher CB1 efficacy.

2-Arachidonoyl glycerol (2-AG, **15**) a monoglyceride is another endogenous ligand representing a new class of endocannabinoids. 2-AG was isolated from intestinal and brain tissues, is capable of binding to both CB1 and CB2 and behaves as a full CB1 agonist [28, 29]. 2-AG is at the crossroads of multiple pathways of lipid metabolism where it can serve interchangeably as end-product for one pathway and precursor for another. These diverse roles can explain its high concentrations in brain tissues (approximately 170-fold higher than anandamide) [28-30, 96].

An ether type endocannabinoid agonist, 2-arachidonyl glyceryl ether (noladin ether, **16**) was reported to be isolated from porcine brain [31]. It was found to bind selectively to the CB1 receptor (Ki = 21.2nM) and cause sedation, hypothermia, intestinal immobility and mild antinociception in mice, effects typically produced by cannabinoid agonists. However, its agonist activity was found to be significantly lower than that of 2-AG. Noladin ether's biosynthetic pathway has not been characterized and its occurrence in the normal brain has been questioned [97].

Two other endogenous ligands *N*-docosatetraenoyl ethanolamine (DEA, **17**) and *N*-arachidonoyldopamine (NADA, **18**) were reported to behave as CB1 receptor agonists. The former was found to activate CB1 receptors in microglia and binds to rat synaptosomal membranes (Ki = 34.4 nM) [98, 99] whereas the latter (NADA), an amide of dopamine and arachidonic acid, was isolated from rat and bovine nervous tissues [100, 101]. It is metabolically stable, binds to the CB1 receptor with similar affinity as anandamide and exhibits equal efficacy but does not bind to the dopamine receptors. NADA is a potent VR1 agonist ($EC_{50} \approx 50$nM) and competitively inhibits FAAH and the anandamide transport. Recent studies showed that like anandamide, NADA is a potent vasorelaxant [102]. These effects are mediated by activation of CB1, VR1 and possibly a novel endothelial cannabinoid-like receptor.

Oleamide (*cis*-9,10-octadecenoamide, ODA, **19**) was first isolated from the cerebrospinal fluid of sleep-deprived cats and was found to induce physiological sleep in animals [103]. It exhibits cannabinoid-like behavioral responses without binding significantly to CB receptors (Ki = 1.14μM for CB1) [104-106]. ODA behaves as a full agonist at rat and human CB1 receptors [106] and has been found to modulate serotonin receptors [104, 107-110], benzodiazepine-sensitive $GABA_A$ receptors [111, 112], and antagonize glial gap junction cell communication [113, 114]. Its physiological role remains to be fully elucidated.

Another endogenous cannabinoid *O*-arachidonoylethanolamine (virodhamine, **20**) the ester of arachidonic acid and ethanolamine was identified by researchers at Lilly [115]. Concentrations of virodhamine in rat brain and human hippocampus were similar to anandamide while at peripheral tissues they were 2- to 9-fold higher. It has been shown that virodhamine behaves as a partial agonist and *in vivo* antagonist at the CB1 receptor, whereas at CB2 it behaves as a full agonist. Recently it was shown that virodhamine relaxes the rat small mesenteric artery by endothelium-dependent activation of Ca^{2+} activated K^+ channels, perhaps through a putative 'abnormal-cannabidiol receptor'. These effects are inhibited by O-1938, a pharmacological antagonist for this receptor but not by the CB1 selective antagonist AM251 or by CB2 selective antagonists SR144528 and AM630 [116].

SYNTHETIC ENDOCANNABINOID-LIKE CB1 AGONISTS

Anandamide has served as a template for the development of CB1 agonists in this class of compounds [117, 118]. Its chemical structure can be divided into two major molecular fragments: a polar ethanolamido head group and a hydrophobic arachidonyl chain. In the head group modifications, the CB1 versus CB2 selectivity of anandamide has been significantly enhanced by substituting 2-hydroxyl group with a chloro [119, 120] (AM881, also

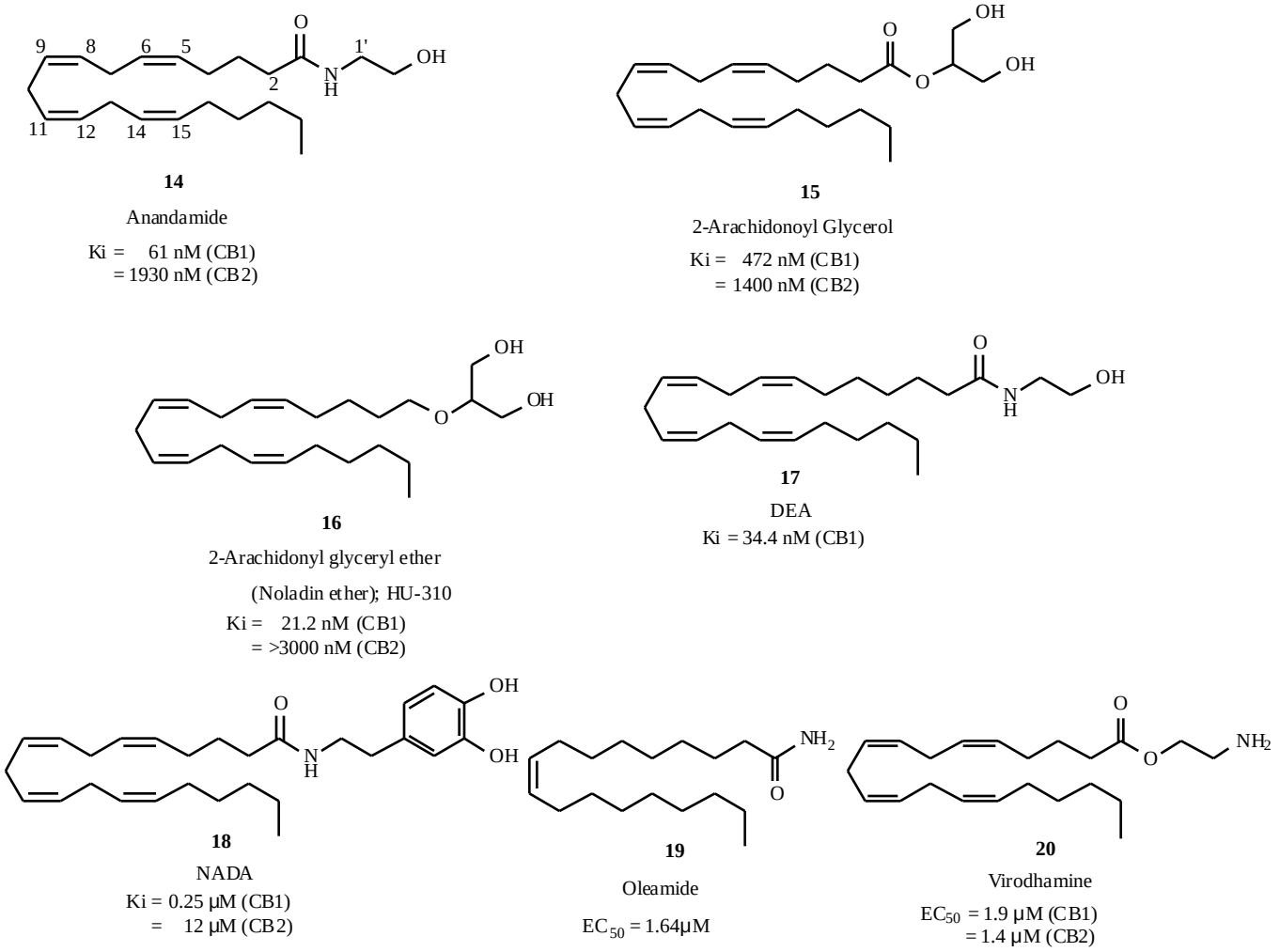


Fig. (3). Endogenous CB1 agonists.

known as ACEA, **21**) or by a fluoro group (O-585) [121]. Both ligands behave as excellent CB1 selective agonists. Substitution of ethanolamine with a *N*-cyclopropylamine group leads to a ligand exhibiting high affinity and selectivity for CB1 receptors (ACPA, **22**). This compound exhibits 325-fold selectivity over CB2 and is active *in vivo* [120]. Both ACPA and AM881 behave as potent CB1 receptor agonists with reasonably high efficacy but show susceptibility to enzymatic hydrolysis.

One of the shortcomings of anandamide and their analogs as effective pharmacological tools is their facile *in vivo* and *in vitro* enzymatic degradation. It was, thus, important to develop analogs that are resistant to the hydrolytic action of anandamide amidohydrolase. To address this shortcoming four chiral C-1′ or C-2′ methyl analogs were synthesized [119, 122, 123]. Of these the 1′-R-methyl isomer *R*-(+)-methanandamide (AM356, **23**) exhibited four-fold higher CB1 affinity than anandamide while exhibiting excellent metabolic stability. This analog is now being used as an important pharmacological tool in cannabinoid research.

As discussed earlier, the side chain SAR of cannabinoids has been studied extensively and it is known that 1′,1′-dimethylheptyl (DMH) substitution generally leads to optimal potency. There is also evidence that classical cannabinoids and anandamide interact with similar residues at the CB1 binding site. It was, thus, postulated that similar substitution in anandamide should result in an increase in receptor affinity and potency. This postulate proved to be true when it was shown that the dimethylalkyl analogs (**24** and **25**) [124-126] exhibit increased receptor affinities (CB1 = 2.2nM and CB2 = >10,000nM) and *in vivo* potencies.

DIARYLPYRAZOLE CB1 ANTAGONISTS

The most widely studied compound of this class, SR141716A (Rimonabant, **26**) was developed by Rinaldi-Carmona and co-workers at Sanofi [127] and is currently undergoing clinical trials as an antiobesity medication. This highly potent and selective CB1 receptor ligand has served as a unique pharmacological and biochemical tool for the characterization of the CB1 receptor [128, 129]. *In vitro*, SR141716A antagonizes the inhibitory effects of cannabinoid agonists on both mouse vas deferens contractions and adenylyl cyclase activity in rat brain membranes. SR141716A also antagonizes the pharmacological and behavioral effects produced by CB1 agonists after intraperitoneal (ip) or oral administrations [127].

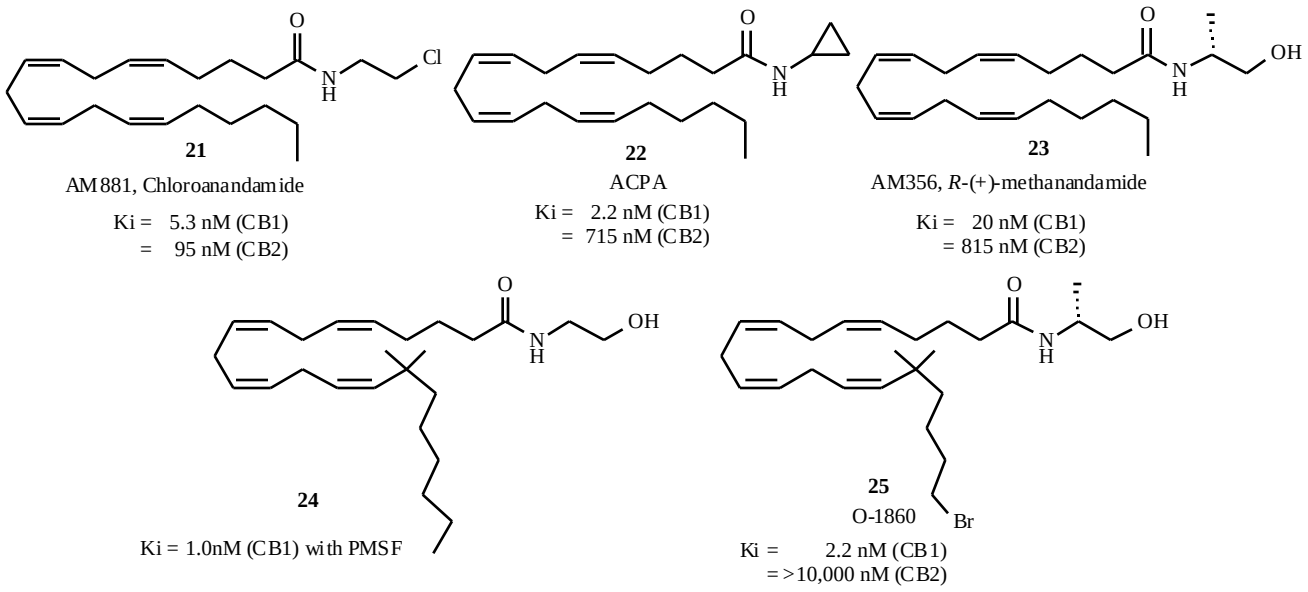


Fig. (4). Synthetic endocannabinoid-like CB1 agonists.

Other diarylpyrazole ligands that have contributed to our understanding of CB1 pharmacology are AM251 (**27**) and AM281 (**28**) both of which are CB1 antagonist/inverse agonists capable of displacing [^{3}H] SR141716A and [^{3}H] CP-55,940 in CB1 receptor membrane preparations [128]. Both AM251 and AM281 share the ability of SR141716A to attenuate the responses to established cannabinoid receptor agonists like WIN-55,212-2 or CP-55,940. However, recent evidence indicates that AM251 may have a more "CB1 selective" role than SR141716A [130].

Very recently, Sanofi reported [131] a new potent, orally active and selective CB1 antagonist SR147778 (**29**). This compound displays nanomolar affinities, Ki = 0.56nM and 3.5nM, for the rat brain and human CB1 recombinant

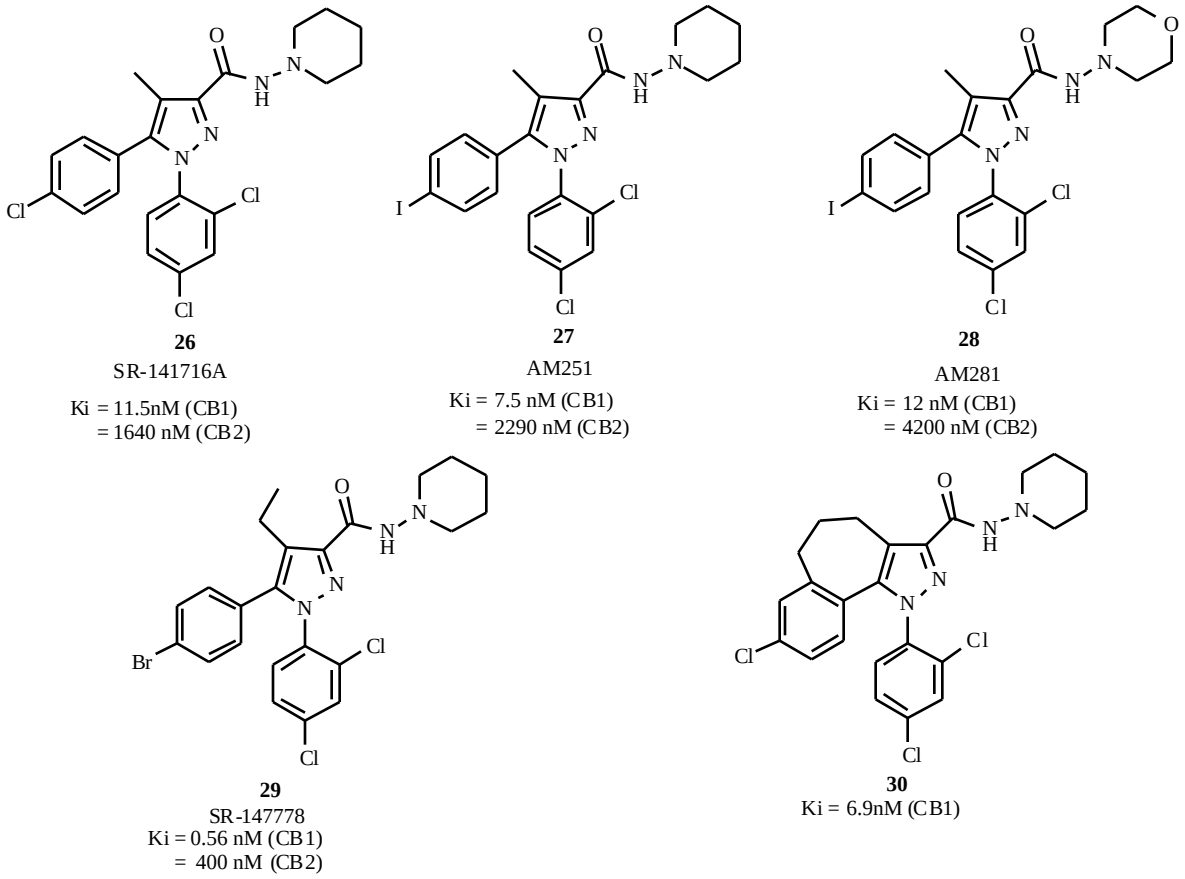


Fig. (5). Diarylpyrazole CB1 selective ligands.

receptors, respectively, and has low affinity (Ki = 400nM) for both the rat spleen and human CB2 receptors. *In vivo* SR147778 was shown to reduce both ethanol and sucrose consumption in mice and rats and food intake in fasted and non-deprived rats.

As a variation in the diarylpyrazole structure, Solvay reported [132] some CB1 selective tricyclic rigid analogs of SR141716A in which the 4- and 5-substituents are conformationally restricted through the formation of a relatively rigid tricyclic system. In these compounds the 4-methyl group is connected with the ortho position of the aromatic 5-aryl substituent to form benzocycloheptapyrazole analogs as represented by **30**, a ligand exhibiting higher CB1 affinity than the parent SR141716A. However, the compound had poor oral bioavailability.

OTHER CANNABINERGIC CLASSES

Very recently, Solvay Pharmaceuticals reported a novel class of 3,4-disubstituted pyrazoline analogs exhibiting high CB1 selectivity [133]. The (-)-enantiomer SLV-326 (**31**), exhibited high CB1 affinity and selectivity (Ki = 35.9 nM (CB1), Ki = 3,515 nM (CB2)) and was shown to *in vivo* antagonize CP-55,940 induced hypotension in a rat model, whereas the (+)-isomer was inactive.

A notable CB1 receptor selective antagonist, structurally distinct from aminoalkyl indoles (AAIs) and diarylpyrazoles was developed by Eli Lilly is LY320135 (**32**) [134] which was shown to bind to CB1 receptor preferentially although with a lower affinity than that of SR141716A. LY320135 also shares the ability of SR141716A to exhibit inverse agonist activity at some signal transduction pathways of the CB1 receptors and binds to muscarinic and 5-HT2 receptors at low micromolar concentrations.

Aventis reported [135] a new class of CB1 receptor antagonists, which are represented by the diarylmethyleneazetidine analog (**33**). Recently a novel class of diarylsulfonylester cannabinoid agonist was reported by Bayer Health Care (Wuppertal, Germany) [136-138]. The representative analog (-)-(*R*)-3-(2-hydroxyl-methylindanyl-4-oxy) phenyl-4,4,4-difluoro-1-sulfonate (**34**, BAY 38-7271) is a high affinity CB1 ligand (Ki = 0.46-1.85nM) as assessed in rat brain or human cortex membranes and recombinant human CB1 receptor. BAY 38-7271 behaves as a potent CB1 agonist *in vivo* and possesses neuroprotective properties [139].

CONCLUSIONS

Prior to its discovery, the CB1 receptor had been targeted for the development of novel analgesic agents. However, our improved understanding of the extensive physiological roles of this very interesting GPCR has opened the door for additional therapeutic indications such as neurodegeneration, appetite modulation as well as pathologies of the cardiovascular and reproductive systems. Furthermore, the recognition that CB1 can be activated by structurally dissimilar ligands through diverse binding motifs offers the opportunity to develop tissue specific CB1-based medications. Such compounds can also find utility as pharmacological probes for the further elucidation of the biological role of the endocannabinoid system. For these reasons the development of novel CB1 ligands remains an important priority in cannabinoid research.

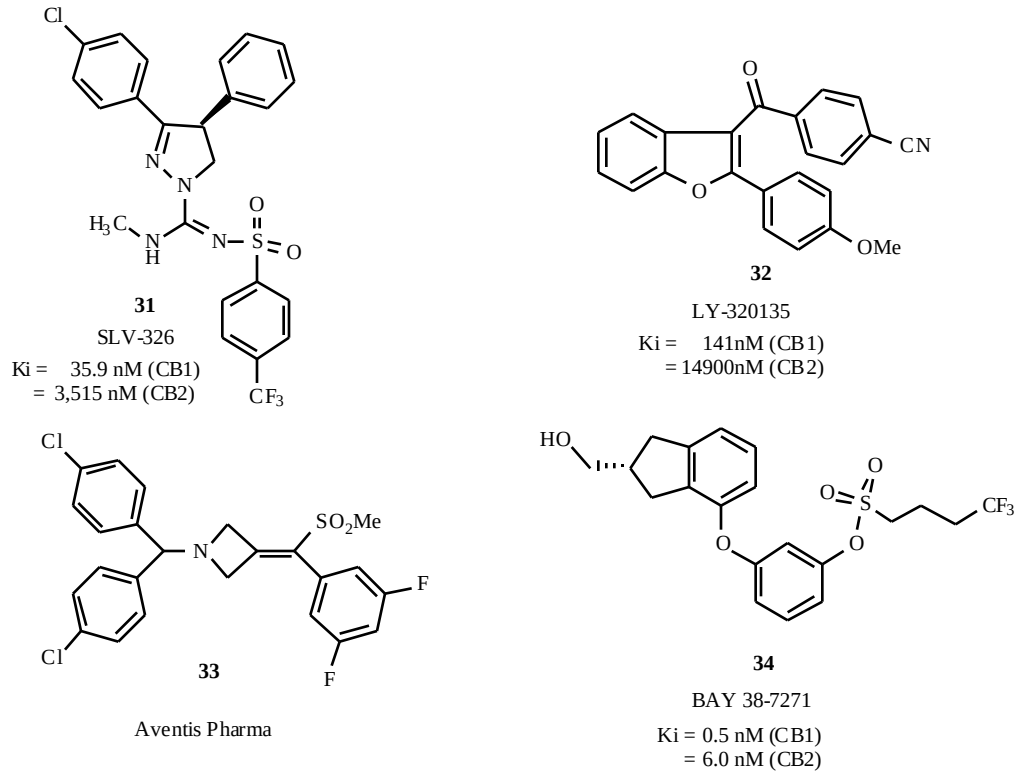


Fig. (6). Other classes of CB1 ligands.

ACKNOWLEDGEMENTS

Supported by grants from National Institutes of Drug Abuse (DA9158, DA03801 and DA07215).

REFERENCES

[1] Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.*, **1964,** *86*, 1646-1647.
[2] Razdan, R. K. *Pharmacol. Rev.*, **1986,** *38*, 75-149.
[3] Makriyannis, A.; Rapaka, R. S. *Life Sci.*, **1990,** *47*, 2173-2184.
[4] Devane, W. A.; Dysarz, F. A.; Johnson, R. M.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.*, **1988,** *34*, 605-613.
[5] Gerard, C.; Mollereau, C.; Vassart, G.; Parmentier, M. *Nucleic. Acids Res.*, **1990,** *18*, 7142.
[6] Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature*, **1990,** *346*, 561-564.
[7] Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature*, **1993,** *365*, 61-65.
[8] Pertwee, R. *Gen. Pharmacol.*, **1993,** *24*, 811-824.
[9] Pertwee, R. G. *Pharmacol. Ther.*, **1997,** *74*, 129-180.
[10] Herkenham, M.; Lynn, A. B.; Little, M. D.; Johnson, M. R.; Melvin, L. S.; de Costa, B. R.; Rice, K. C. *Proc. Natl. Acad. Sci. USA*, **1990,** *87*, 1932-1936.
[11] Herkenham, M. *NIDA Research Monograph*, **1991,** *112*, 129-145.
[12] Mailleux, P.; Parmentier, M.; Vanderhaeghen, J. J. *Neurosci. Lett.*, **1992,** *143*, 200-204.
[13] Matsuda, L. A.; Bonner, T. I.; Lolait, S. J. *J. Comp. Neurol.*, **1993,** *327*, 535-550.
[14] Gatley, S. J.; Lan, R.; Volkow, N. D.; Pappas, N.; King, P.; Wong, C. T.; Gifford, A. N.; Pyatt, B.; Dewey, S. L.; Makriyannis, A. *J. Neurochem.*, **1998,** *70*, 417-423.
[15] Pertwee, R. G.; Stevenson, L. A.; Elrick, D. B.; Mechoulam, R.; Corbett, A. D. *Br. J. Pharmacol.*, **1992,** *105*, 980-4.
[16] Pertwee, R. G.; Joe-Adigwe, G.; Hawksworth, G. M. *Eur. J. Pharmacol.*, **1996,** *296*, 169-72.
[17] Gerard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. *Biochem. J.*, **1991,** *279*, 129-134.
[18] Chang, M. C.; Berkery, D.; Schuel, R.; Laychock, S. G.; Zimmerman, A. M.; Zimmerman, S.; Schuel, H. *Mol. Reprod. Dev.*, **1993,** *36*, 507-16.
[19] Schuel, H.; Chang, M. C.; Burkman, L. J.; Picone, R. P.; Makriyannis, A.; Zimmerman, A. M.; Zimmerman, S., Cananbinoid receptors in sperm. In *Marihuana and Medicine.*, ed.; Nahas, G. G.; Sutin, K. M.; Agurell, S., Eds. Humana Press.: Totowa, **1999**; pp 335-345.
[20] Paria, B. C.; Ma, W.; Andrenyak, D. M.; Schmid, P. C.; Schmid, H. H. O.; Moody, D. E.; Deng, H.; Makriyannis, A.; Dey, S. K. *Biol. Reprod.*, **1998,** *58*, 1490-1495.
[21] Abood, M. E.; Ditto, K. E.; Noel, M. A.; Showalter, V. M.; Tao, Q. *Biochem. Pharmacol.*, **1997,** *53*, 207-214.
[22] Chakrabarti, A.; Onaivi, E. S.; Chaudhuri, G. *DNA Seq.*, **1995,** *5*, 385-388.
[23] Shire, D.; Calandra, B.; Delpech, M.; Dumont, X.; Kaghad, M.; LeFur, G.; Caput, D.; Ferrar, P. *J. Biol. Chem.*, **1996,** *271*, 6941-6946.
[24] Shire, D.; Calandra, B.; Rinaldi Carmona, M.; Oustric, D.; Pessegue, B.; Bonnin Cabanne, O.; Le Fur, G.; Caput, D.; Ferrara, P. *Biochimica et Biophysica Acta*, **1996,** *1307*, 132-136.
[25] Mukhopadhyay, S.; Shim, J. Y.; Assi, A. A.; Norford, D.; Howlett, A. C. *Chem. Phys. Lipids*, **2002,** *121*, 91-109.
[26] Piomelli, D. *Nat. Rev. Neurosci.*, **2003,** *4*, 873-84.
[27] Devane, W. A.; Hanus, L.; Brewer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. *Science*, **1992,** *258*, 1946-1949.
[28] Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, M.; Kaminski, N. E.; Schatz, A. R.; Gopher, A.; Almog, S.; Martain, B. R.; Comton, D. R. *Biochem. Pharmacol.*, **1995,** *50*, 83-90.
[29] Stella, N.; Schweitzer, P.; Piomelli, D. *Nature*, **1997,** *388*, 773-778.
[30] Di Marzo, V.; Bisogno, T.; Sugiura, T.; Melck, D.; De Petrocellis, L. *Biochemical J.*, **1998,** *331*, 15-9.
[31] Hanus, L.; Abu-Lafi, S.; Fride, E.; Breuer, A.; Vogel, Z.; Shalev, D. E.; Kustanovich, I.; Mechoulam, R. *Proc. Natl. Acad. Sci. USA*, **2001,** *98*, 3662-3665.
[32] Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.*, **2002,** *54*, 161-202.
[33] Pertwee, R. G. *Expert Opin. Investig. Drugs*, **2000,** *9*, 1553-71.
[34] Palmer, S. L.; Thakur, G. A.; Makriyannis, A. *Chem. Phys. Lipids*, **2002,** *121*, 3-19.
[35] Thakur, G.A.; Nikas, S.P.; Li, C.; Makriyannis, A. in *Handbook of Experimental Pharmacology*, Ed.; Pertwee, R.G., Springer-Verlag: **2005**, *168*, pp. 209-246.
[36] Makriyannis, A.; Goutopoulos, A. In *Drug discovery strategies and methods*, Makriyannis, A. and Biegel. D., Eds.; Marcel Dekker: New York, **2004**, 89-128.
[37] Bramblett, R. D.; Panu, A. M.; Ballesteros, J. A.; Reggio, P. H. *Life Sci.*, **1995,** *56*, 1971-82.
[38] Shim, J. Y.; Welsh, W. J.; Howlett, A. C. *Biopolymers*, **2003,** *71*, 169-89.
[39] Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H.; Fox, B. A.; Le Trong, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E.; Yamamoto, M.; Miyano, M. *Science*, **2000,** *289*, 739-45.
[40] Tao, Q.; McAllister, S. D.; Andreassi, J.; Nowell, K. W.; Cabral, G. A.; Hurst, D. P.; Bachtel, K.; Ekman, M. C.; Reggio, P. H.; Abood, M. E. *Mol. Pharmacol.*, **1999,** *55*, 605-13.
[41] Song, Z. H.; Slowey, C. A.; Hurst, D. P.; Reggio, P. H. *Mol. Pharmacol.*, **1999,** *56*, 834-40.
[42] McAllister, S. D.; Tao, Q.; Barnett-Norris, J.; Buehner, K.; Hurst, D. P.; Guarnieri, F.; Reggio, P. H.; Nowell Harmon, K. W.; Cabral, G. A.; Abood, M. E. *Biochem. Pharmacol.*, **2002,** *63*, 2121-36.
[43] Barnett-Norris, J.; Hurst, D. P.; Lynch, D. L.; Guarnieri, F.; Makriyannis, A.; Reggio, P. H. *J. Med. Chem.*, **2002,** *45*, 3649-59.
[44] Picone, R. P.; Fournier, D. J.; Makriyannis, A. *J. Pept. Res.*, **2002,** *60*, 348-56.
[45] Mechoulam, R.; Devane, W. A.; Glaser, R. In *Marijuana and Medicine*; Nahas, G.G.; Sutin, K.M.; Agurell, S., Eds.; Humana Press: Totowa, **1999**, pp. 65-90.
[46] Khanolkar, A. D.; Palmer, S. L.; Makriyannis, A. *Chem. Phys. Lipids*, **2000,** *108*, 37-52.
[47] Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; Compton, D. R.; Martin, B. R.; Bramblett, R. D.; Reggio, P. H. *J. Med. Chem.*, **1996,** *39*, 3875-3877.
[48] Gareau, Y.; Dufresne, C.; Gallant, M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Tremblay, N.; Weech, P. K.; Metters, K. M.; Labelle, M. *Bioorg. Med. Chem. Lett.*, **1996,** *6*, 189-194.
[49] Huffman, J. W.; Liddle, J.; Yu, S.; Aung, M. M.; Abood, M. E.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.*, **1999,** *7*, 2905-2914.
[50] Huffman, J. W.; Bushell, S. M.; Miller, J. R. A.; Wiley, J. L.; Martin, B. R. *Bio. Med. Chem.*, **2002,** *10*, 4119-4129.
[51] Martin, B. R.; Jefferson, R. G.; Winckler, R.; Wiley, J. L.; Thomas, B. F.; Crocker, P. J.; Williams, W.; Razdan, R. K. *Eur. J. Pharmacol.*, **2002,** *435*, 35-42.
[52] Adams, R.; Harfenist, M.; Loewe, S. *J. Am. Chem. Soc.*, **1949,** *71*, 1624-1628.
[53] Huffman, J. W.; Miller, J. R. A.; Liddle, J.; Yu, S.; Thomas, B. F.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.*, **2003,** *11*, 1397-1410.
[54] Liddle, J.; Huffman, J. W. *Tetrahedron*, **2001,** *57*, 7607-7612.
[55] Martin, B. R.; Compton, D. R.; Semus, S. F.; Lin, S.; Marciniak, G.; Grzybowska, J.; Charalambous, A.; Makriyannis, A. *Pharmacol. Biochem. Behav.*, **1993,** *46*, 295-301.
[56] Charalambous, A.; Lin, S.; Marciniak, G.; Banijamali, A.; Friend, F. L.; Compton, D. R.; Martin, B. R.; Makriyannis, A. *Pharmacol. Biochem. Behav.*, **1991,** *40*, 509-512.
[57] Charalambous, A.; Yan, G.; Houston, D. B.; Howlett, A. C.; Compton, D. R.; Martin, B. R.; Makriyannis, A. *J. Med. Chem.*, **1992,** *35*, 3076-3079.
[58] Crocker, P. J.; Saha, B.; Ryan, W. J.; Wiley, J. L.; Martin, B. R.; Ross, R. A.; Pertwee, R. G.; Razdan, R. K. *Tetrahedron*, **1999,** *55*, 13907-13926.
[59] Nikas, S. P.; Grzybovska, J.; Papahatjis, D. P.; Charalambous, A.; Banijamali, A. R.; Chari, R.; Fan, P.; Kourouli, T.; Lin, S.; Nitowski, A. J.; Marciniak, G.; Guo, Y.; Li, X.; Wang, C.-L. J.; Makriyannis, A. *AAPS Journal*, **2004**, *6*(4), Article 40 (http://www.aapsj.org).

[60] Singer, M.; Ryan, W. J.; Saha, B.; Martin, B. R.; Razdan, R. K. *J. Med. Chem.*, **1998,** *41*, 4400-7.

[61] Papahatjis, D. P.; Kourouli, T.; Abadji, V.; Goutopoulos, A.; Makriyannis, A. *J. Med. Chem.*, **1998,** *41*, 1195-1200.

[62] Papahatjis, D. P.; Nikas, S.; Tsotinis, A.; Vlachou, M.; Makriyannis, A. *Chem. Lett.*, **2001,** *3*, 192-193.

[63] Papahatjis, D. P.; Nikas, S. P.; Andreou, T.; Makriyannis, A. *Bioorg. Med. Chem. Lett.*, **2002,** *12*, 3583-3586.

[64] Papahatjis, D. P.; Nikas, S. P.; Kourouli, T.; Chari, R.; Xu, W.; Pertwee, R. G.; Makriyannis, A. *J. Med. Chem.*, **2003,** *46*, 3221-3229.

[65] Luk, T.; Jin, W.; Zvonok, A.; Lu, D.; Lin, X. Z.; Chavkin, C.; Makriyannis, A.; Mackie, K. *Br. J. Pharmacol.*, **2004,** *142*, 495-500.

[66] Devane, W. A.; Breuer, A.; Sheskin, T.; Jarbe, T. U.; Eisen, M. S.; Mechoulam, R. *J. Med. Chem.*, **1992,** *35*, 2065-2069.

[67] Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. L. *J. Med. Chem.*, **1976,** *19*, 1165-1167.

[68] Yan, G.; Yin, D.; Khanolkar, A. D.; Compton, D. R.; Martin, B. R.; Makriyannis, A. *J. Med. Chem.*, **1994,** *37*, 2619-2622.

[69] Busch-Petersen, J.; Hill, W. A.; Fan, P.; Khanolkar, A.; Xie, X. Q.; Tius, M. A.; Makriyannis, A. *J. Med. Chem.*, **1996,** *39*, 3790-3796.

[70] Mechoulam, R.; Lander, N.; Srebnik, M.; Breuer, A.; Segal, M.; Feigenbaum, J. J.; Jarbe, T. U.; Consroe, P. *NIDA Research Monograph*, **1987,** *79*, 15-30.

[71] Mechoulam, R.; Feigenbaum, J. J.; Lander, N.; Segal, M.; Jarbe, T. U.; Hiltunen, A. J.; Consroe, P. *Experientia*, **1988,** *44*, 762-764.

[72] Felder, C. C.; Joyce, K. E.; Briley, E. M.; Mansouri, J.; Mackie, K.; Blond, O.; Lai, Y.; Ma, A. L.; Mitchell, R. L. *Mol. Pharmacol.*, **1995,** *48*, 443-50.

[73] Lichtman, A. H.; Peart, J.; Poklis, J. L.; Bridgen, D. T.; Razdan, R. K.; Wilson, D. M.; Poklis, A.; Meng, Y.; Byron, P. R.; Martin, B. R. *Eur. J. Pharmacol.*, **2000,** *399*, 141-9.

[74] Pertwee, R. G.; Gibson, T. M.; Stevenson, L. A.; Ross, R. A.; Banner, W. K.; Saha, B.; Razdan, R. K.; Martin, B. R. *Br. J. Pharmacol.*, **2000,** *129*, 1577-84.

[75] Ross, R. A.; Brockie, H. C.; Fernando, S. R.; Saha, B.; Razdan, R. K.; Pertwee, R. G. *Br. J. Pharmacol.*, **1998,** *125*, 1345-51.

[76] Griffin, G.; Wray, E. J.; Rorrer, W. K.; Crocker, P. J.; Ryan, W. J.; Saha, B.; Razdan, R. K.; Martin, B. R.; Abood, M. E. *Br. J. Pharmacol.*, **1999,** *126*, 1575-84.

[77] Ross, R. A.; Gibson, T. M.; Stevenson, L. A.; Saha, B.; Crocker, P.; Razdan, R. K.; Pertwee, R. G. *Br. J. Pharmacol.*, **1999,** *128*, 735-743.

[78] Johnson, M. R.; Melvin, L. S. In *Cannabinoids as therapeutic agents*; Mechoulam, R. Ed.; CRC Press: Boca Raton, FL., **1986**, pp. 121-145.

[79] Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.*, **1988,** *247*, 1046-51.

[80] Howlett, A. C.; Johnson, M. R.; Melvin, L. S.; Milne, G. M. *Mol. Pharmacol.*, **1988,** *33*, 297-302.

[81] Griffin, G.; Atkinson, P. J.; Showalter, V. M.; Martin, B. R.; Abood, M. E. *J. Pharmacol. Exp. Ther.*, **1998,** *285*, 553-60.

[82] Makriyannis, A.; Rapaka, R. S. *Life Sciences*, **1990,** *47*, 2173-2184.

[83] Drake, D. J.; Jensen, R. S.; Busch-Petersen, J.; Kawakami, J. K.; Fernandez-Garcia, M. C.; Fan, P.; Makriyannis, A.; Tius, M. A. *J. Med. Chem.*, **1998,** *41*, 3596-3608.

[84] Tius, M. A.; Makriyannis, A.; Long Zou, X.; Abadji, V. *Tetrahedron*, **1994,** *50*, 2671-2680.

[85] Tius, M. A.; Hill, W. A.; Zou, X. L.; Busch-Petersen, J.; Kawakami, J. K.; Fernandez Garcia, M. C.; Drake, D. J.; Abadji, V.; Makriyannis, A. *Life Sci.*, **1995,** *56*, 2007-2012.

[86] Tius, M. A.; Busch-Petersen, J.; Marris, A. R. *J. Chem. Soc. Chem. Commun.*, **1997,** *19*, 1867-1868.

[87] Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.*, **2000,** *65*, 6576-6582.

[88] Chu, C.; Ramamurthy, A.; Makriyannis, A.; Tius, M. A. *J. Org. Chem.*, **2003,** *68*, 55-61.

[89] Thakur, G. A.; Palmer, S. L.; Harrington, P. E.; Stergiades, I. A.; Tius, M. A.; Makriyannis, A. *J. Biochem. Biophys. Methods.*, **2002,** *54*, 415-422.

[90] Kozak, K. R.; Prusakiewicz, J. J.; Marnett, L. J. *Curr. Pharm. Des.*, **2004,** *10*, 659-67.

[91] Bornheim, L. M.; Kim, K. Y.; Chen, B.; Correia, M. A. *Biochem. Pharmacol.*, **1995,** *50*, 677-86.

[92] Schmid, P. C.; Zuzarte-Augustin, M. L.; Schmid, H. H. *J. Biol. Chem.*, **1985,** *260*, 14145-9.

[93] Ueda, N.; Kurahashi, Y.; Yamamoto, S.; Tokunaga, T. *J. Biol. Chem.*, **1995,** *270*, 23823-7.

[94] Cravatt, B. F.; Giang, D. K.; Mayfield, S. P.; Boger, D. L.; Lerner, R. A.; Gilula, N. B. *Nature*, **1996,** *384*, 83-7.

[95] Bracey, M. H.; Hanson, M. A.; Masuda, K. R.; Stevens, R. C.; Cravatt, B. F. *Science*, **2002,** *298*, 1793-6.

[96] Mechoulam, R.; Ben Shabat, S.; Hanus, L.; Fride, E.; Vogel, Z.; Bayewitch, M.; Sulcova, A. E. *J. Lipid Mediat. Cell Signal*, **1996,** *14*, 45-9.

[97] Oka, S.; Tsuchie, A.; Tokumura, A.; Muramatsu, M.; Suhara, Y.; Takayama, H.; Waku, K.; Sugiura, T. *J. Neurochem.*, **2003,** *85*, 1374-1381.

[98] Hanus, L.; Gopher, A.; Almog, S.; Mechoulam, R. *J. Med. Chem.*, **1993,** *36*, 3032-4.

[99] Barg, J.; Fride, E.; Hanus, L.; Levy, R.; Matus-Leibovitch, N.; Heldman, E.; Bayewitch, M.; Mechoulam, R.; Vogel, Z. *Eur. J. Pharmacol.*, **1995,** *287*, 145-52.

[100] Bisogno, T.; Melck, D.; Bobrov, M.; Gretskaya, N. M.; Bezuglov, V. V.; De Petrocellis, L.; Di Marzo, V. *Biochem. J.*, **2000,** *351 Pt 3*, 817-24.

[101] Huang, S. M.; Bisogno, T.; Trevisani, M.; Al-Hayani, A.; De Petrocellis, L.; Fezza, F.; Tognetto, M.; Petros, T. J.; Krey, J. F.; Chu, C. J.; Miller, J. D.; Davies, S. N.; Geppetti, P.; Walker, J. M.; Di Marzo, V. *Proc. Natl. Acad. Sci. USA*, **2002,** *99*, 8400-5.

[102] O'Sullivan, S. E.; Kendall, D. A.; Randall, M. D. *Br. J. Pharmacol.*, **2004,** *141*, 803-12.

[103] Cravatt, B. F.; Prospero-Garcia, O.; Siuzdak, G.; Gilula, N. B.; Henriksen, S. J.; Boger, D. L.; Lerner, R. A. *Science*, **1995,** *268*, 1506-9.

[104] Cheer, J. F.; Cadogan, A. K.; Marsden, C. A.; Fone, K. C.; Kendall, D. A. *Neuropharmacology*, **1999,** *38*, 533-41.

[105] Mechoulam, R.; Fride, E.; Hanus, L.; Sheskin, T.; Bisogno, T.; Di Marzo, V.; Bayewitch, M.; Vogel, Z. *Nature*, **1997,** *389*, 25-6.

[106] Leggett, J. D.; Aspley, S.; Beckett, S. R.; D'Antona, A. M.; Kendall, D. A. *Br. J. Pharmacol.*, **2004,** *141*, 253-62.

[107] Huidobro-Toro, J. P.; Harris, R. A. *Proc. Natl. Acad. Sci. USA*, **1996,** *93*, 8078-82.

[108] Thomas, E. A.; Carson, M. J.; Neal, M. J.; Sutcliffe, J. G. *Proc. Natl. Acad. Sci. USA*, **1997,** *94*, 14115-9.

[109] Boger, D. L.; Patterson, J. E.; Jin, Q. *Proc. Natl. Acad. Sci. USA*, **1998,** *95*, 4102-7.

[110] Thomas, E. A.; Cravatt, B. F.; Sutcliffe, J. G. *J. Neurochem.*, **1999,** *72*, 2370-8.

[111] Yost, C. S.; Hampson, A. J.; Leonoudakis, D.; Koblin, D. D.; Bornheim, L. M.; Gray, A. T. *Anesth. Analg.*, **1998,** *86*, 1294-300.

[112] Verdon, B.; Zheng, J.; Nicholson, R. A.; Ganelli, C. R.; Lees, G. *Br. J. Pharmacol.*, **2000,** *129*, 283-90.

[113] Guan, X.; Cravatt, B. F.; Ehring, G. R.; Hall, J. E.; Boger, D. L.; Lerner, R. A.; Gilula, N. B. *J. Cell. Biol.*, **1997,** *139*, 1785-92.

[114] Boger, D. L.; Patterson, J. E.; Guan, X.; Cravatt, B. F.; Lerner, R. A.; Gilula, N. B. *Proc. Natl. Acad. Sci. USA*, **1998,** *95*, 4810-5.

[115] Porter, A. C.; Sauer, J. M.; Knierman, M. D.; Becker, G. W.; Berna, M. J.; Bao, J.; Nomikos, G. G.; Carter, P.; Bymaster, F. P.; Leese, A. B.; Felder, C. C. *J. Pharmacol. Exp. Ther.*, **2002,** *301*, 1020-4.

[116] Ho, W. S.; Hiley, C. R. *J. Pharm. Pharmacol.*, **2004,** *56*, 869-75.

[117] Khanolkar, A. D.; Makriyannis, A. *Life Sci.*, **1999,** *65*, 607-616.

[118] Khanolkar, A. D.; Abadji, V.; Lin, S.; Hill, W. A.; Taha, G.; Abouzid, K.; Meng, Z.; Fan, P.; Makriyannis, A. *J. Med. Chem.*, **1996,** *39*, 4515-9.

[119] Lin, S.; Khanolkar, A. D.; Fan, P.; Goutopoulos, A.; Qin, C.; Papahadjis, D.; Makriyannis, A. *J. Med. Chem.*, **1998,** *41*, 5353-5361.

[120] Hillard, C. J.; Manna, S.; Greenberg, M. J.; Dicamelli, R.; Ross, R. A.; Stevenson, L. A.; Murphy, V.; Pertwee, R. G. *J. Pharmacol. Exp. Ther.*, **1999,** *289*, 1427-1433.

[121] Adams, I. B.; Ryan, W.; Singer, M.; Thomas, B. F.; Compton, D. R.; Razdan, R. K.; Martin, B. R. *J. Pharmacol. Exp. Ther.*, **1995,** *273*, 1172-1181.

[122] Abadji, V.; Lin, S.; Taha, G.; Griffin, G.; Stevenson, L. A.; Pertwee, R. G.; Makriyannis, A. *J. Med. Chem.*, **1994,** *37*, 1889-1893.

[123] Goutopoulos, A.; Fan, P.; Khanolkar, A. D.; Xie, X. Q.; Lin, S.; Makriyannis, A. *Bioorg. Med. Chem.*, **2001,** *9*, 1673-84.

[124] Di Marzo, V.; Bisogno, T.; De Petrocellis, L.; Brandi, I.; Jefferson, R. G.; Winckler, R. L.; Davis, J. B.; Dasse, O.; Mahadevan, A.; Razdan, R. K.; Martin, B. R. *Biochem. Biophys. Res. Commun.*, **2001,** *281*, 444-451.

[125] Ryan, W. J.; Banner, W. K.; Wiley, J. L.; Martin, B. R.; Razdan, R. K. *J. Med. Chem.*, **1997,** *40*, 3617-3625.

[126] Seltzman, H. H.; Fleming, D. N.; Thomas, B. F.; Gilliam, A. F.; McCallion, D. S.; Pertwee, R. G.; Compton, D. R.; Martin, B. R. *J. Med. Chem.*, **1997,** *40*, 3626-3634.

[127] Rinaldi Carmona, M.; Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat, G.; Caput, D. *FEBS Lett.*, **1994,** *350*, 240-224.

[128] Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R. G.; Makriyannis, A. *J. Med. Chem.*, **1999,** *42*, 776-779.

[129] Nakamura-Palacios, E. M.; Moerschbaecher, J. M.; Barker, L. A. *CNS Drug Rev.*, **1999,** *5*, 43-58.

[130] Hajos, N.; Freund, T. F. *Neuropharmacology*, **2002,** *43*, 503-10.

[131] Rinaldi-Carmona, M.; Barth, F.; Congy, C.; Martinez, S.; Oustric, D.; Perio, A.; Poncelet, M.; Maruani, J.; Arnone, M.; Finance, O.; Soubrie, P.; Le Fur, G. *J. Pharmacol. Exp. Ther.*, **2004**, *310*, 905-914.

[132] Stoit, A. R.; Lange, J. H. M.; den Hartog, A. P.; Ronken, E.; Tipker, K.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.*, **2002,** *50*, 1109-1113.

[133] Lange, J. H. M.; Coolen, H. K. A. C.; Van Stuivenberg, H. H.; Dijksman, J. A. R.; Herremans, A. H. J.; Ronken, E.; Keizer, H. G.; Tipker, K.; McCreary, A. C.; Veerman, W.; Wals, H. C.; Stork, B.; Verveer, P. C.; den Hartog, A. P.; de Jong, N. M. J.; Adolfs, T. J. P.; Hoogendoorn, J.; Kruse, C. G. *J. Med. Chem.*, **2004,** *47*, 627-643.

[134] Felder, C. C.; Joyce, K. E.; Briley, E. M.; Glass, M.; Mackie, K. P.; Fahey, K. J.; Cullinan, G. J.; Hunden, D. C.; Johnson, D. W.; Chaney, M. O.; Koppel, G. A.; Brownstein, M. *J. Pharmacol. Exp. Ther.*, **1998,** *284*, 291-297.

[135] Mignani, S.; Hittinger, A.; Achard, D.; Bouchard, H.; Bouquerel, J.; Capet, M.; Grisoni, S.; Malleron, J. l. USA Patent No. WO 0015609, **2000**, pp. 1-239.

[136] Mauler, F.; Mittendorf, J.; Horvath, E.; De Vry, J. *J. Pharmacol. Exp. Ther.*, **2002,** *302*, 359-368.

[137] Mauler, F.; Horvath, E.; de Vry, J.; Jaeger, R.; Schwarz, T.; Sandmann, S.; Weinz, C.; Heinig, R.; Boettcher, M. *CNS Drug Rev.*, **2003,** *9*, 343-358.

[138] De Vry, J.; Denzer, D.; Reissmueller, E.; Eijckenboom, M.; Heil, M.; Meier, H.; Mauler, F. *J. Pharmacol. Exp. Ther.*, **2004,** *310*, 620-32.

[139] De Vry, J.; Rudiger Jentzsch, K. *Eur. J. Pharmacol.*, **2002,** *457*, 147-52.