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Pharmacology of Cannabinoid Receptors

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Introduction

Until 20 years ago, only vague explanations existed over the mechanism of action of products from *Cannabis sativa*. It was thought, for example, that the main psychotropic compound in the plant, Δ^9-tetrahydrocannabinol, acts by changing cell membrane properties due to its high lipophilicity[1]. This scarcity of knowledge started to change in 1990 with the identification of a G protein-coupled receptor for Δ^9-tetrahydrocannabinol, the CB_1 cannabinoid receptor. Since then, a tremendous amount of information accumulated: additional receptors were discovered and endogenous agonists (endocannabinoids) of the receptors were identified. Many new synthetic agonists and antagonists of the receptors have been developed. Intensive research is carried out to clarify the physiological and pathophysiological roles of endocannabinoids. And, it is probed how diseases can be treated by exogenous cannabinoid receptor agonists or antagonists or by modulators of the biosynthesis or degradation of endocannabinoids.

Cannabinoid receptors

Two G protein-coupled receptors are firmly established as targets of cannabinoids, CB_1 and CB_2 receptors[2,3] (for review see refs.[4,5]). Both belong to the family A of G protein-coupled receptors, and lipid (sphingolipid) and prostaglandin receptors are rather near on the phylogenetic tree of receptors[6]. The amino acid identity between the two cannabinoid receptors is 44% (68 % within the transmembrane domains). The CB_1 and CB_2 receptors are typical $G\alpha_{i/o}$ protein-coupled receptors: they are sensitive to pertussis toxin and their activation leads to inhibition of adenylate cyclase (for review see refs.[4,7]). The CB_1 receptor mediates inhibition of N-, P/Q- and L-type voltage-gated calcium channels and activation of G protein coupled inwardly rectifying potassium (GIRK) channels[8,9]. In addition, several other types of potassium channels (mediating I_M, I_A) are also modulated. Interestingly, activation of CB_2 receptors did not lead to ion channel modulation, at least in one study[10]. Both receptors can activate the mitogen-activated protein kinase (MAPK) signaling cascade[11,12].

The CB_1 receptor is widely distributed in the central and peripheral nervous system (for review see ref.[13]). Two properties deserve to be particularly mentioned. First, compared with other G protein-coupled receptors, the density of CB_1 receptors is especially high in the brain. Second, the CB_1 receptors are preferentially located on axon terminals - their concentration in the cell membrane of somatodendritic neuronal regions is unexpectedly low. In addition to neurons, the CB_1 receptor has been found in the adrenal gland, bone marrow, heart, lung, prostate and testicles.

The CB_2 receptor is less widely expressed than the CB_1 receptor[3,14] (for review see ref.[15]): it was detected in immune-related organs / tissues like the tonsils, spleen, thymus and bone marrow and in B lymphocytes, monocytes / macrophages, mast cells and microglial cells. It was recently discovered that the CB_2 receptor also occurs in neurons, but only in a few regions in the periphery and the brain, and at much lower concentrations than the CB_1 receptor[16,17].

Repeatedly, effects of cannabinoids were observed which could not be explained by the involvement of CB_1 or CB_2 receptors (for review see refs.[18,19]), and a search was started for identifying additional cannabinoid receptors. It was discovered quite recently that the G protein-coupled orphan receptor GPR55 is activated by a series of phytocannabinoids, synthetic cannabinoids and endocannabinoids with remarkable potency[20,21] (for review see ref.[6]). Therefore, GPR55 is a serious candidate to become an additional cannabinoid receptor. According to one study, the post-receptor transmission pathway for GPR55 involves the $G\alpha_{13}$ protein and activation of the small GTP binding proteins rhoA, cdc42 and rac1. Remarkably, the amino acid sequence homology between GPR55 and CB_1 and between GPR55 and CB_2 is low (< 15 %), and on the phylogenetical tree of receptors GPR55 is far away from the CB_1 and CB_2 receptors. In one study, GPR55 responded to lysophosphatidylinositol, but not to cannabinoids; therefore, it was suggested that it is not a cannabinoid receptor[22].

For promotion of studies of the roles of cannabinoid receptors in physiological and pharmacological phenomena, the cannabinoid receptors were genetically deleted in mice. At present, mice exist in which the CB_1 receptor[23,24], CB_2 receptor[25], CB_1 and CB_2 receptors (double knockout)[26] or GPR55 were knocked out[20].

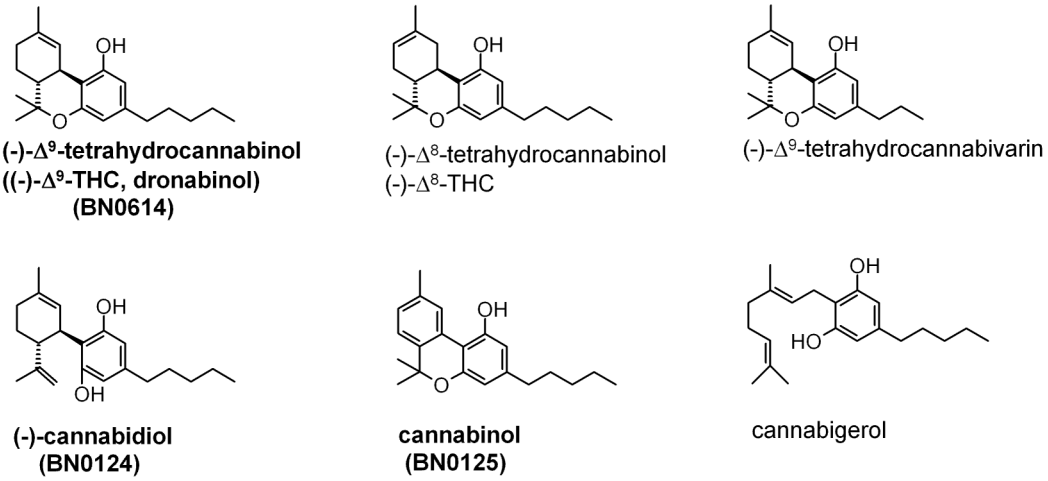


Fig. 1. Cannabinoids in Cannabis sativa.
Dronabinol is the International Nonproprietary Name (INN) of (-)-Δ^9-tetrahydrocannabinol. Bold text indicates compounds available from ***BIOTREND*** *(with catalogue numbers).*

Constituents of *cannabis sativa*

The plant *Cannabis sativa* synthesizes about 70 compounds which are chemically related to Δ^9-tetrahydrocannabinol (many of them are terpeno-phenols)[27]. These compounds are called cannabinoids. The psychotropic effects of the *cannabis* products marijuana and hashish are mostly attributed to Δ^9-tetrahydrocannabinol which is an agonist at CB_1 and CB_2 receptors. Δ^8-Tetrahydrocannabinol behaves pharmacologically similarly as Δ^9-tetrahydrocannabinol. Cannabinol is a low potency partial agonist at CB_1 and CB_2 receptors[28]. Cannabidiol was long considered to be inactive at CB_1 and CB_2 receptors, because it has low affinity in radioligand binding studies[29,30]. However, it was shown quite recently that it is an antagonist at CB_1 receptors and antagonist / inverse agonist at CB_2 receptors[31,32] (for review see ref. [33]). It is remarkable that Δ^9-tetrahydrocannabivarin is an antagonist at both CB_1 - and CB_2 receptors[34,35]: the deletion of only 2 C atoms at the C3 side chain (see Fig. 1) transforms the agonist Δ^9-tetrahydrocannabinol into the antagonist Δ^9-tetrahydrocannabivarin.

Endocannabinoids

Soon after the identification of the CB_1 receptor, it was discovered that the brain produces endogenous cannabinoids (endocannabinoids) which are capable of activating the CB_1 receptor. At first, arachidonoyl ethanolamide was identified as an endocannabinoid; it received the name anandamide[36]. Three years later 2-arachidonoylglycerol was identified as a second endogenous cannabinoid receptor agonist[37,38] (for review see ref.[39]). The concentration of 2-arachidonoylglycerol in the brain is 50-500fold higher than the concentration of anandamide[39-41]. Anandamide is a partial agonist at CB_1 and CB_2 receptors, whereas 2-arachidonoylglycerol is a full agonist at both receptors in the majority of the studies. In addition to being a cannabinoid receptor agonist, anandamide also activates TRPV1 (vanilloid) receptors[42-44].

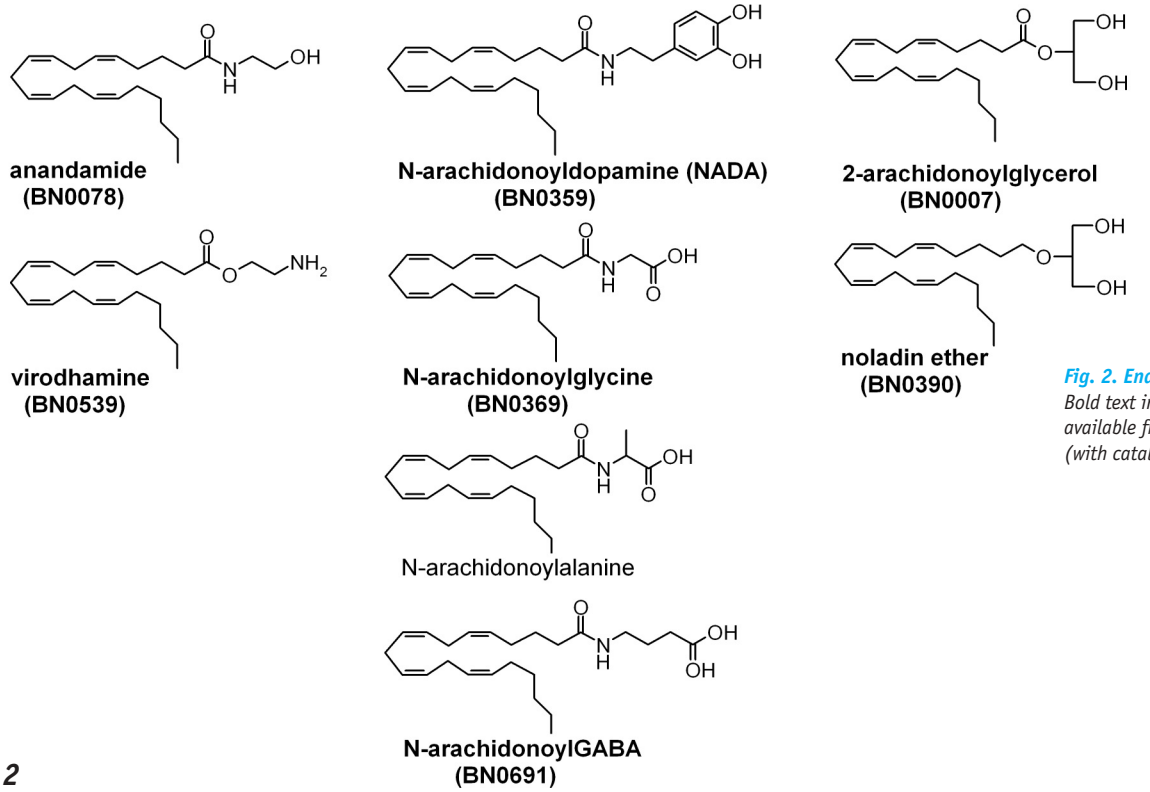


Fig. 2. Endocannabinoids.
Bold text indicates compounds available from ***BIOTREND*** *(with catalogue numbers).*

Several derivatives of anandamide and 2-arachidonoylglycerol have been identified in biological tissues. Virodhamine - a derivative of anandamide - has similar concentrations in the brain as anandamide; it is a weak partial agonist at the CB_1 receptor and a weak agonist at the CB_2 receptor[45]. The ether derivative of 2-arachidonoylglycerol, noladin ether, was also suggested to be an endocannabinoid; it is a potent agonist of CB_1 receptors, but has low affinity for CB_2 receptors[46]. Whereas in the original study noladin ether was identified in the brain[46], no appreciable amounts of noladin ether were found in the brain in a later study[47]. N-arachidonoyldopamine (NADA) is found at appreciable concentrations in the corpus striatum; it activates TRPV1 receptors and at higher concentrations also CB_1 receptors[44,48,49]. The arachidonoyl amino acids N-arachidonoylglycine, N-arachidonoyl γ-aminobutyric acid and N-arachidonoylalanine were also isolated from the brain[50].

Endocannabinoid biosynthesis, membrane transport and degradation (Fig. 3 and Table 1 show modulators of these processes)

Endocannabinoids are not stored in synaptic vesicles as classical transmitters are. They are produced "on demand" and leave the cells by diffusion or via a carrier. Their action on receptors is terminated by uptake into neurons and glial cells followed by enzymatic cleavage.

Anandamide. Depolarization followed by calcium influx into the cells triggers anandamide production which can proceed via several pathways (for review see ref.[51]). The first step of anandamide production is synthesis of N-arachidonoyl-phosphatidylethanolamine (an N-acyl-phosphatidylethanolamine; NAPE) by transfer of an arachidonoyl group from phosphatidylcholine to the ethanolamine moiety of phophatidylethanolamine[52-54]. During the second step, N-arachidonoyl-phosphatidylethanolamine is cleaved by one or several types of NAPE-specific phospholipases (of the D class) to yield anandamide[55,56]. Recently, alternative mechanisms of anandamide production have also been described. Thus, N-arachidonoyl-phosphatidylethanolamine can be sequentially cleaved by phospholipase C and the protein tyrosine phosphatase PTPN22[57]. Anandamide can also be produced from N-arachidonoyl-phosphatidylethanolamine by lipases (generating glycerophospho-anandamide) and a phosphodiesterase[58].

After release from cells, anandamide diffuses into surrounding cells. It is thought that the diffusion is facilitated by a special transporter, the endocannabinoid membrane transporter (EMT) (for review see ref.[59]).

Table 1. Modulators of endocannabinoid production, membrane transport and degradation

Target protein	Inhibitor	IC_{50} (nM)	References
anandamide			
endocannabinoid membrane transporter (EMT)	AM404[a]	1000-5000	60
	VDM11[a]	10200-11200	61
	UCM707	800	140
	LY2183240[a]	0.270	62
fatty acid amide hydrolase (FAAH)	MAFP	6	72
	ATFMK	~1000 <7500	72 71
	arachidonoyl-5-HT	5600-12000	73
	OL-92	0.28	74
	OL-135	2.1	141
	URB597	4.6	75
2-arachidonoylglycerol			
diacylglycerol lipase (DAGL)	orlistat (also called tetrahydrolipstatin)	60	87
	RHC-80267	~5000	86
monoglyceride lipase (MGL)	MAFP	2-3 2	72 93
	ATFMK	20000-30000 66000	72 93
	N-arachidonoyl -maleimide (NAM)	140	94
	URB602	28000	95

[a] These compounds are also inhibitors or competitive substrates of FAAH[64,142,143].

EMT is inhibited by the compounds AM404, VDM11 and LY2183240[60-62]. However, it should be mentioned that the existence of the EMT is not unanimously accepted. Because many inhibitors of EMT also inhibit the intracellular cleavage of anandamide by fatty acid amide hydrolase (FAAH), it was suggested that anandamide is simply diffusing through the plasma membrane, and the diffusion is driven by the low intracellular concentration of anandamide due to hydrolysis by FAAH[63,64]. Once in the cell, anandamide is cleaved by the membrane-bound enzyme FAAH[65] (for review see ref.[66]). The molecular identity of this hydrolase is identified, and its genetic deletion leads to a marked decrease in anandamide degradation in the tissues[67-69]. It has been recently described that in some species, also in humans, a second FAAH enzyme can also hydrolyze anandamide, although at a much lower rate than the original enzyme[70].

MAFP and ATFMK are non-selective inhibitors of FAAH[71-72]. More selective inhibitors of FAAH have been recently discovered, for example, arachidonoyl-5-HT, OL-92 and URB597[73-75]. In addition, anandamide can be metabolized by cyclooxygenase-2 (COX-2) which generates prostaglandin ethanolamides from anandamide (for example, PGE_2 ethanolamide)[76].

2-Arachidonoylglycerol. Many cell types, including neurons[41,77-80], glial cells[81], platelets[82] and macrophages[83], can produce and release 2-arachidonoylglycerol. Typical triggers of production are an increase in the intracellular calcium concentration and activation of $G\alpha_{q/11}$ protein-coupled receptors (for review see refs.[39,84]). The most established pathway for 2-arachidonoylglycerol production includes hydrolysis of phosphatidylinositol-diphosphate (PIP_2) by phospholipase C (PLC) and cleavage of the resulting diacylglycerol by diacylglycerol lipase (DAGL). DAGL was cloned by Bisogno et al.[85]. RHC-80267 and orlistat (also called tetrahydrolipstatin) are two identified inhibitors of DAGL, and orlistat is more potent and selective than RHC-80267[86,87]. In addition to the above pathway, alternative ways for 2-arachidonoylglycerol production were suggested[88,89] (for review see ref.[39]). One alternative pathway would include generation of diacylglycerol from phosphatidic acid by a phosphatase and the subsequent action of DAGL. Another alternative way would be production of 2-arachidonoylglycerol from 2-arachidonoylglycerol-*sn*-glycero-3-phosphate (a species of lysophosphatidic acid) by a phosphatase.

After production, 2-arachidonoylglycerol leaves the cells and acts on receptors. The action of 2-arachidonoylglycerol is terminated by diffusion into cells - a membrane transporter may facilitate this diffusion, as in the case of anandamide. Within the cells, 2-arachidonoylglycerol is hydrolyzed by monoglyceride lipase (MGL), which was cloned and characterized[72,90,91] (for review see ref.[92]). The products of hydrolysis, arachidonic acid and glycerol, are devoid of effects on cannabinoid receptors. Additonal enzymes play only minor roles in 2-arachidonoylglycerol elimination, degrading less than 15% of the produced 2-arachidonoylglycerol. MGL can be inhibited by the nonspecific inhibitors MAFP and ATFMK (they also inhibit FAAH)[71,72,93]. N-arachidonoylmaleimide (NAM) also inhibits MGL[94]. URB602 is a recently discovered moderately potent and selective (vs. FAAH) inhibitor of MGL[95]. COX-2 can also contribute to 2-arachidonoylglycerol degradation, producing glyceryl prostaglandins[96].

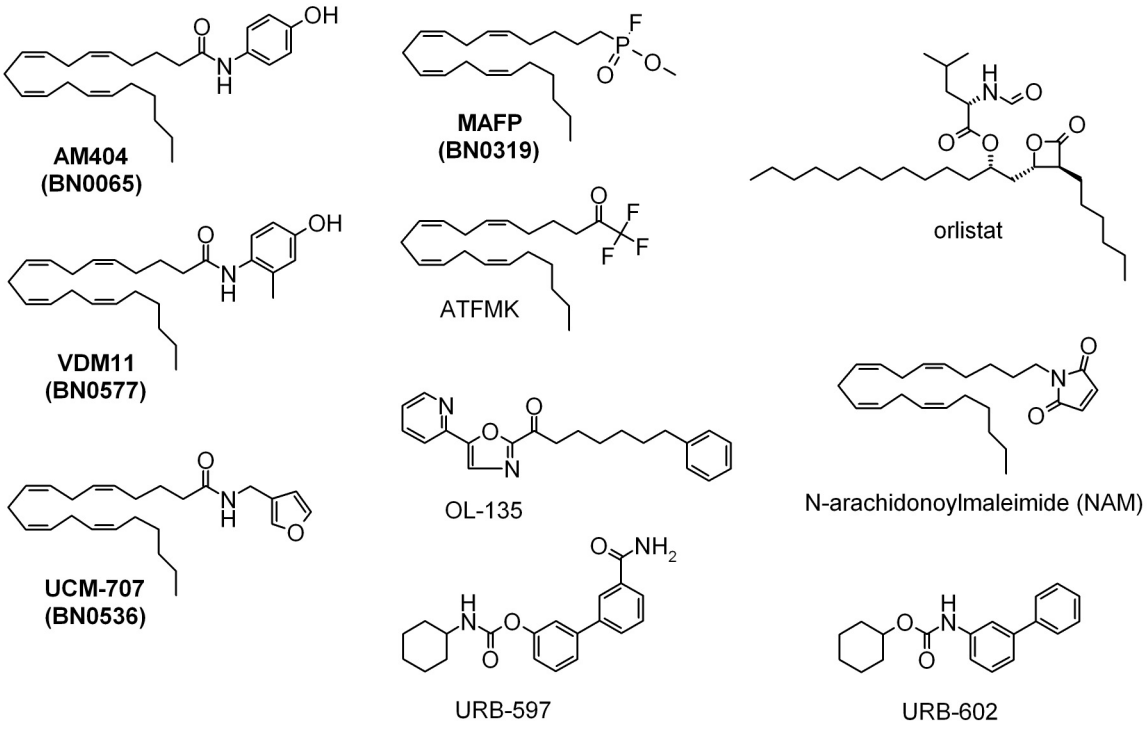
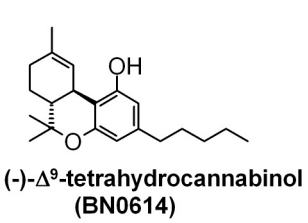
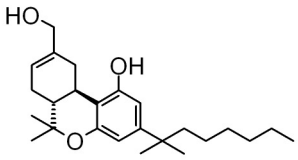


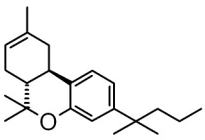
Fig. 3. Modulators of endocannabinoid production, membrane transport and degradation.
Bold text indicates compounds available from ***BIOTREND*** *(with catalogue numbers).*



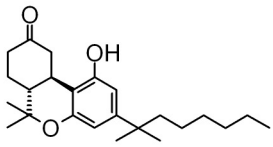
(-)-Δ^9-tetrahydrocannabinol
(BN0614)



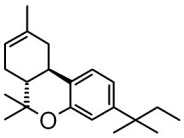
HU-210
(BN0622)



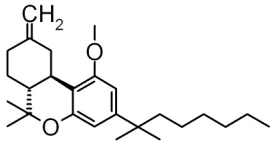
JWH-133
(BN0633)



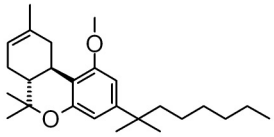
nabilone



JWH-139



L759656

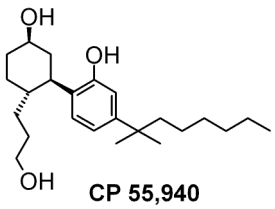


L759633
(BN0692)

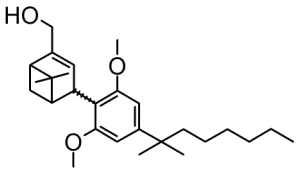
Fig. 4. Agonists of CB_1 and CB_2 receptors: classical cannabinoids.
*Bold text indicates compounds available from **BIOTREND** (with catalogue numbers).*

Cannabinoid receptor agonists

Cannabinoid receptor agonists can be divided into different chemical classes: classical cannabinoids (Fig. 4), synthetic nonclassical cannabinoids (Fig. 5), aminoalkylindoles (Fig. 6) and eicosanoids (Fig. 7). Table 2 shows affinities of the agonists for CB_1 and CB_2 receptors; the compounds are grouped according to their receptor selectivity. The classical cannabinoids are synthesized by *Cannabis sativa* or are chemically closely related relatives of such substances. The structure of synthetic nonclassical cannabinoids resemble that of classical cannabinoids. Another line of cannabinoid agonists, that of the "eicosanoids" derives from the endocannabinoids. The first aminoalkylindole-type cannabinoid ligand (R-(+)-WIN55212) was discovered by serendipity; therefore, it is not not surprizing, that the structures within this group do not resemble the structure of phytocannabinoids or endocannabinoids.



CP 55,940
(BN0156)



HU-308

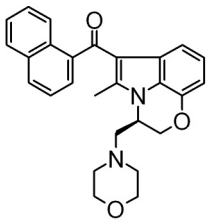
Fig. 5. Agonists of CB_1 and CB_2 receptors: synthetic nonclassical cannabinoids.
*The bold text indicates a compound available from **BIOTREND** (with catalogue number).*

Table 2. CB_1 and CB_2 receptor agonists

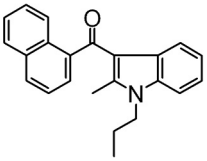
	*Affinity for **CB_1***[a] (nM)	*Affinity for **CB_2***[a] (nM)	***References***
CB_1-selective			
ACEA	1.4	>2000	144
ACPA	2.2	715	144
O-1812	3.4	3870	145
noladin ether	21	>3000	46
O-585	8.6	324	29
CB_2-selective			
L759656	4888	12	146
L759633	1043	6	146
JWH-139	2290	14	147
JWH-133	677	3	147
HU-308	> 10000	23	148
JWH-015	336	14	149
AM1241	580	7	150
Sch35966	2633	7	151
non-selective			
(-)-Δ^9-tetrahydro-cannabinol	41[b]	36[b]	29
Δ^8-tetrahydro-cannabinol	44	44	147
HU-210	0.7	0.2	29
nabilone	2.2	1.8	152
CP 55,940	0.6	0.7	29
R-(+)-WIN55212 (WIN 55,212-2)	1.9	0.3	29
anandamide	89[b]	371[b]	29
R-(+)-methanan-damide	28[b]	868	153
virodhamine	1906[b]	1401	45
2-arachidonoyl-glycerol	58	145	154

[a] The values are K_i or K_d values determined in radioligand binding studies carried out on membranes prepared from native tissues or transfected cells expressing CB_1 or CB_2 receptors. In some cases, EC_{50}/IC_{50} values determined in functional studies (membrane binding of [^{35}S]GTPγS or inhibition of forskolin-stimulated adenylate cyclase) are given.
Note that the affinity values of the eicosanoids can greatly vary depending whether metabolizing enzymes are inhibited or not.

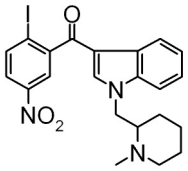
[b] These compounds behave in several test systems as partial agonists.



WIN 55,212-2
(BN0544)



JWH-015
(BN0280)



AM1241

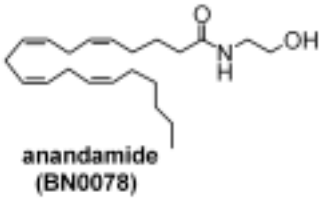
Fig. 6. Agonists of CB_1 and CB_2 receptors: aminoalkylindoles.
Bold text indicates compounds available from ***BIOTREND*** *(with catalogue numbers).*

It is remarkable that many CB_1-selective agonists are eicosanoids (all the compounds shown in Table 2). The CB_2-selective agonists are chemically more heterogenous: classical cannabinoids (L759656, L759633, JWH-133, JWH-139), synthetic nonclassical cannabinoids (HU-308) and aminoalkylindoles (JWH-015, AM1241) are all represented in the group. The group of agonists which do not distinquish between CB_1- and CB_2 receptors is also chemically heterogenous. It is remarkable that the phytocannabinoids Δ^9-tetrahydrocannabinol and Δ^8-tetrahydrocannabinol and the endocannabinoids anandamide and 2-arachidonoylglycerol are not selective for the one or the other cannabinoid receptor. The synthetic nonclassical cannabinoid CP 55,940 and the aminoalkylindole R-(+)-WIN55212 are the most frequently used synthetic cannabinoid agonists. R-(+)-methanandamide is an anandamide analogue which is rather resistant against enyzymatic hydrolysis; this is an obvious advantage in studies on organs *in vitro* or *in vivo*.

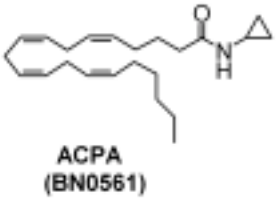
Some of the compounds shown in Table 2 (e.g., (-)-Δ^9-tetrahydrocannabinol, R-(+)-WIN55212, CP 55,940, HU-210 and R-(+)-methanandamide) possess stereoisomers which have markedly lower affinity for the cannabinoid receptors.

It must be noted that not all agonists shown in Table 2 are capable of fully activating the cannabinoid receptors. The two important cannabinoids Δ^9-tetrahydrocannabinol and anandamide are notorious partial agonists at stimulating [^{35}S]GTPγS binding, at inhibiting adenylate cyclase and at inhibiting synaptic transmission[97-104].

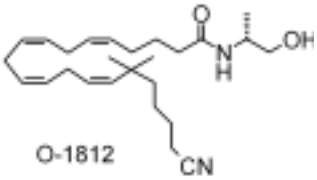
Fig. 7. Agonists of CB_1 and CB_2 receptors: eicosanoids.
Bold text indicates compounds available from ***BIOTREND*** *(with catalogue numbers).*



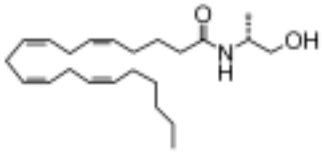
anandamide
(BN0078)



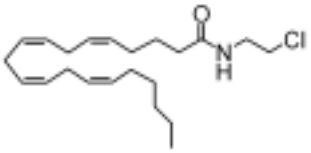
ACPA
(BN0561)



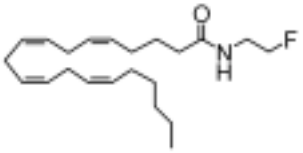
O-1812



(*R*)-(+)-methanandamide
(BN0331)



ACEA
(BN0049)



O-585

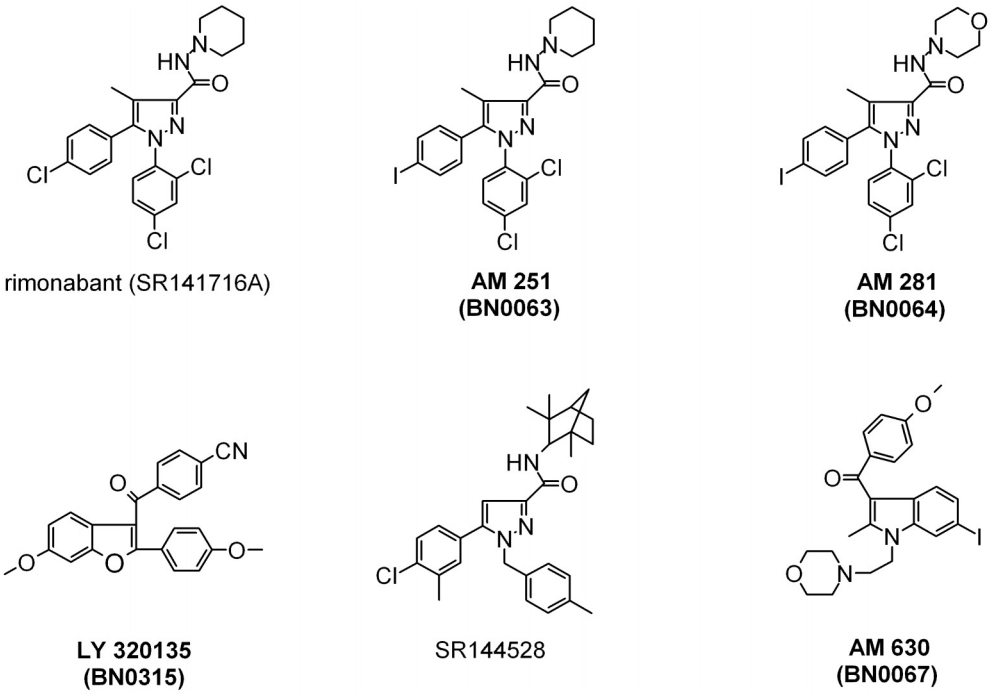


*Fig. 8. CB_1 and CB_2 receptor antagonists. Bold text indicates compounds available from **BIOTREND** (with catalogue numbers).*

Table 3. CB_1 and CB_2 receptor antagonists

	*Affinity for **CB_1***[a] (nM)	*Affinity for **CB_2***[a] (nM)	***References***
CB_1-selective			
rimonabant (SR141716)	2 (IA)	> 1000	155
AM 251	8 (IA)	2290	156
AM 281	12 (IA)	4200	157
LY320135	141 (IA)	14900	158
MK0364	0.3 (IA)	290	159
SLV319	8	7943	160
"Neutral" antagonists			
NESS0327	0.00035	21	161
VCHSR	31		162
O-2654	114		31
CB_2-selective			
SR144528	437	0.6 (IA)	163
AM 630	5152	31 (IA)	146
JTE907	2370	36 (IA)	164
Sch336	905	0.4 (IA)	165

[a] The values are K_i or K_d values determined in radioligand binding studies or antagonist K_b values determined in functional agonist / antagonist interaction assays. Most of the studies were carried out on membranes prepared from native tissues or transfected cells expressing CB_1 or CB_2 receptors. IA indicates inverse agonistic proterty.

Cannabinoid receptor antagonists (Fig. 8 and Table 3)

For a review of cannabinoid receptor antagonists see ref.[105]. The first selective CB_1 receptor antagonist, SR141716 (now called rimonabant) was discovered in 1994 at Sanofi pharmaceutical company. Rimonabant is a diaryl pyrazole derivative, and the chemical structures of several other CB_1 antagonists (AM 251, AM 281, SR147778) resemble the structure of rimonabant. However, several antagonists belonging to different chemical classes have been developed (e.g., LY320135).

Most of the CB_1 antagonists are not neutral: they do not only block the effects of exogenous or endogenous agonists, but due to their inverse agonistic action, they inhibit constitutively active CB_1 receptors[106,107] (for review see ref.[108]). Often, it cannot be determined whether an in vivo effect is due to blockade of the effects of endocannabinoids or to an inverse agonistic action. However, the solution for the problem is in progress: recently, CB_1 antagonists without inverse agonistic properties were synthesized (e.g., NESS0327, VCHSR, O-2654).

CB_1 antagonists were invaluable for verifying the involvement of CB_1 receptors in the pharmacological effects of exogenous cannabinoids and in the physiological effects of endocannabinoids. The prototype compound, rimonabant, has been recently introduced for the treatment of obesity. Thus, remarkably, a CB_1 antagonist is the first licensed cannabinoid drug which is available for a broad patient population.

The first CB_2 receptor antagonist, SR144528, was also synthesized by Sanofi researchers. Other CB2-selective antagonists are: AM 630, JTE-907 and Sch336. Notably, most of the CB_2 antagonists are also inverse agonists. Compared with the CB_1 antagonists, the development of the clinical application of CB_2 antagonists is less advanced. But, based on the presence of CB_2 receptors in many types of immune cells, it is thought that CB_2 antagonists might function as antiinflammatory and antiallergic drugs.

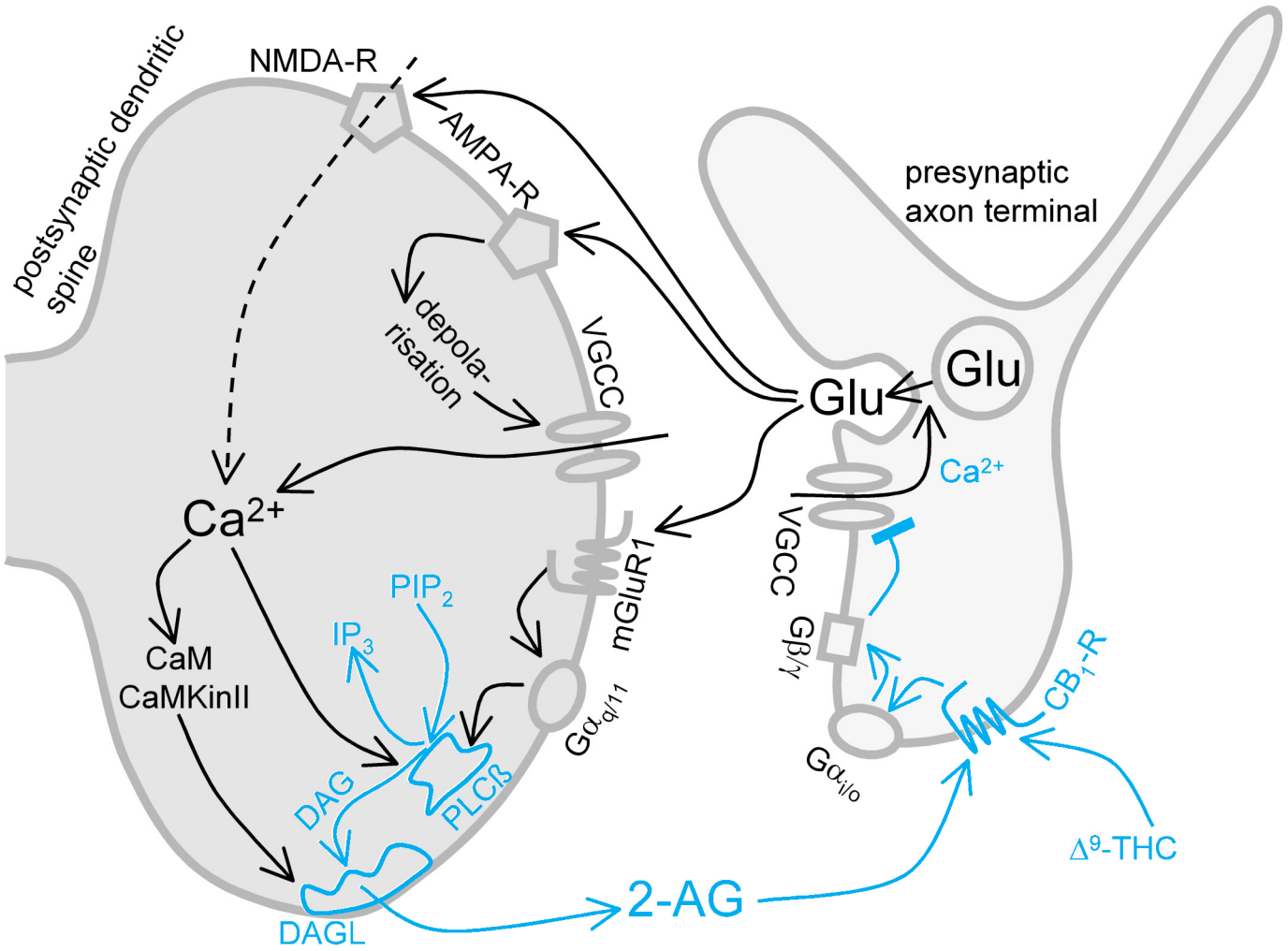


Figure 9. Inhibition of synaptic transmission by exogenous and endogenous cannabinoids.
CB_1 receptors are localized on the presynaptic axon terminal. Their activation leads to activation of $G\alpha_{i/o}$ proteins, liberation of β/γ proteins, inhibition of voltage-gated calcium channels (VGCCs) and, finally, to inhibition of glutamate (Glu) release from synaptic vesicles. The CB_1 receptors can be activated by exogenous cannabinoids, for example Δ^9-THC, or by the endocannabinoid 2-arachidonoylglycerol (2-AG) which is released from the dendritic spine of the postsynaptic neuron. For the production of 2-AG, at first phosphatidylinositol-diphosphate (PIP_2) is cleaved by phospholipase Cß (PLCß), then the resulting diacylglycerol (DAG) is hydrolyzed by diacylglycerol lipase (DAGL). 2-AG production is triggered by two mechanisms: 1) Calcium entering the spine via VGCCs can stimulate DAGL or PLCβ; 2) Activated metabotropic glutamate receptors can stimulate PLCβ via $G\alpha_{q/11}$ proteins. This 2-AG-mediated retrograde synaptic signaling is the basis of several types of short- and long-term synaptic plasticity.

Effects mediated by cannabinoid receptors

In agreement with the widespread distribution of the cannabinoid receptors, many pharmacological effects of exogenous cannabinoids and physiological effects of endocannabinoids have been observed. There are more observations on the involvement of CB_1 receptors than on the involvement of CB_2 receptors. Intensive research is going on to utilize the cannabinoid receptors as therapeutic targets (for review see ref.[109]). Some examples of cannabinoid receptor-mediated effects are mentioned below.

Administration of CB_1 receptor-activating cannabinoids elicits a characteristic "tetrad" of effects in mice: depression of locomotion, antinociception, hypothermia and catalepsy[110]. Cannabinoids are self-administered and induce conditioned place preference. Moreover, continued administration leads to tolerance and dependence. All these observations indicate that cannabinoids are rewarding and addictive also in animals (for review see refs.[111-115]). Anticonvulsive effects of exogenous agonists and endocannabinoids and CB_1 receptor-mediated neuroprotection during ischemia and after traumatic brain injury can be potentially used in therapy[116,117] (for review see ref.[118]). Exogenous cannabinoids and endocannabinoids released during different circulatory shock conditions cause cardiovascular depression including lowered sympathetic transmitter release and vasodilation[119-121].

CB_1 receptor-mediated analgesia has attracted much interest, because of its obvious therapeutic implications (for review see refs.[122,123]). Activation of CB_1 receptors at several levels of the ascending pain transmission / processing pathway can lead to analgesia. Recent results point to a prominent role of CB_1 receptors on axon terminals of primary nociceptive neurons in the analgesia produced by systemically administered cannabinoids[124]: this observation opens up the way for generation of peripherally acting cannabinoid analgesics without centrally elicited side effects. Interestingly, endocannabinoids released during inflammation, neuropathic conditions and stress also modulate nociception[95,125].

Unexpectedly, CB_2 receptors can also elicit analgesia, even in the case of neuropathic pain[126-128]. CB_2 receptors expressed on immune and glial cells are likely targets of cannabinoids eliciting antinociception[129]. However, evidence was recently obtained that the CB_2 receptor is expressed in pain processing neurons after sensory neuron injury[130]. The obvious advantage of CB_2 agonists for analgesia would be the lack of unwanted psychotropic effects which are connected with the use of agonists activating CB_1 receptors.

It seems that behind many complex cannabinoid effects on the nervous system in vivo, there is one single basic neurophysiological action: inhibition of neurotransmitter release from axon terminals (Fig. 9). Presynaptic CB_1 receptors are present on terminals of many GABAergic, glutamatergic, cholinergic and noradrenergic axons in the central and peripheral nervous system and their activation leads to presynaptic inhibition of neurotransmission[131-134] (for review see refs.[135,136]). The most likely primary mechanism behind the inhibition of neurotransmitter release is inhibition of voltage-gated calcium channels in the axon terminals - mediated by the G protein $\beta\gamma$ subunits.

The presynaptic CB_1 receptors can be activated by exogenous cannabinoids and endocannabinoids. The somatodendritic regions of many neurons produce endocannabinoids in response to two stimuli: depolarization followed by opening of voltage-gated calcium channels and activation of $G\alpha_{q/11}$ protein-coupled receptors. After synthesis, the endocannabinoids are released from the postsynaptic neurons and diffuse to presynaptic axon terminals, where they activate presynaptic CB_1 receptors and thereby inhibit transmitter release (Fig. 9). This kind of retrograde synaptic signaling has been observed at many GABAergic and glutamatergic synapses of the central nervous system (for an example see ref.[137]; for review see refs.[138,139]). In many cases, it is the basis of short- and long-term synaptic plasticity. Thus, endocannabinoid-mediated retrograde signaling is thought to be important for memory and learning.

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Cannabinoid Receptor Compounds

CB_1 Receptor Selective

Cat. No.	Product	Category
BN0049	ACEA	Selective, potent CB_1 agonist
BN0561	ACPA	Selective, potent CB_1 agonist
BN0176	DEA	Endogenous CB_1 agonist
BN0331	(R)-(+)-Methanandamide	Selective, potent CB_1 agonist
BN0359	NADA†	Endogenous CB_1 agonist, FAAH/AMT inhibitor, VR1 agonist
BN0390	Noladin ether	Endogenous CB_1 agonist
BN0397	Oleamide	CB_1 agonist, potentiator at 5-$HT_{2A/2C}$ receptors
BN0063	AM 251	Selective, potent CB_1 antagonist
BN0064	AM 281	Selective, potent CB_1 antagonist/inverse agonist
BN0315	LY 320135	CB_1 antagonist/inverse agonist
BN0318	Lylamine hydrochloride	CB_1 agonist and antifungal agent
BN0319	MAFP	CB_1 irreversible ligand, potent FAAH inhibitor

† NADA = N-Arachidonoyldopamine

CB_2 Receptor Selective

Cat. No.	Product	Category
BN0125	Cannabinol	CB_2 agonist
BN0558	GW 405833	Cannabinoid CB_2 partial agonist
BN0280	JWH 015	Selective CB_2 agonist
BN0633	JWH 133	Selective, potent CB_2 agonist
BN0692	L-759,633	Selective, potent CB_2 agonist
BN0405	Palmitoylethanolamide	Endogenous CB_2 agonist
BN0067	AM 630	CB_2 antagonist/inverse agonist
BN0113	BML-190	Selective, potent CB_2 inverse agonist
Non-selective		
BN0078	Anandamide	Endogenous CB agonist, VR1 agonist
BN0007	2-Arachidonoylglycerol	Endogenous CB agonist
BN0156	CP 55,940	Potent CB agonist
BN0622	HU-210	Potent CB agonist
BN0614	(-)-Δ^9-Tetrahydrocannabinol	CB agonist
BN0539	Virodhamine	Endogenous CB_2 agonist and CB_1 partial agonist/antagonist
BN0544	WIN 55,212-2 mesylate	CB agonist
BN0545	WIN 55,212-3 mesylate	Less active CB agonist, enantiomer of Cat. No. BN0544

Cannabinoid Receptors / Metabolism

Cat. No.	Product	Category
BS0016	AACOCF3	Anandamide hydrolysis inhibitor
BN0045	Abn-CBD	Cannabinoid (abn-CBD)
BN0065	AM 404	Anandamide transport (AMT) inhibitor, VR1 agonist
BN0691	N-ArachidonoylGABA	Arachidonoyl amino acid that inhibits pain
BN0369	N-Arachidonoylglycine	Carboxylic analogue of anandamide, FAAH inhibitor
BN0562	Arvanil	AMT inhibitor, CB_1 and VR1 agonist
BN0124	(-)-Cannabidiol	Weak CB_1 antagonist, AMT inhibitor
BN0193	(-)-5'-DMH-CBD	Anandamide transport inhibitor
BN0399	OMDM-2	Potent AMT inhibitor
BN0015	2-Palmitoylglycerol	Cannabinoid endocannabinoid enhancer
BN0406	Palmitoylisopropylamide	FAAH inhibitor
BN0508	STEARDA	Cannabinoid 'entourage effect', also 5-lipoxygenase inhibitor
BN0536	UCM 707	Endocannabinoid transport inhibitor
BN0577	VDM 11	Potent AMT inhibitor
Related Radioligands		
ART-0626	[^{3}H]-Anandamide	Endogenous CB agonist, VR1 agonist
ART-1448	[^{3}H]-Δ^9-Tetrahydrocannabidiol	CB agonist
ART-0741	[^{3}H]-Palmitoyl ethanolamide	Endogenous lipid

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