# Cannabinoid System in Neurodegeneration: New Perspectives in Alzheimer's Disease

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**Abstract:** Alzheimer's disease is a chronic and progressive neurodegenerative disorder. The presence of functional cannabinoid CB2 receptors in central nervous system (CNS) has provoked that this receptor and its agonist ligands are now considered as promising pharmacological targets for neurological diseases. Herein, we review the evidences supporting the potential role of the ECS as a therapeutic target, focused on CB2 receptor and its ligands, for the treatment of Alzheimer´s disease.

**Key Words**: Cannabinoid, endocannabinoid, cannabinoid receptors, alzheimer's disease, dementia, CB2 agonist.

## INTRODUCTION

Alzheimer´s disease is the most common form of dementia in the elderly people associated with cognitive decline and characterized by the deposition of β–amyloid protein and hyperphosphorylation of tau [1]. In 2005, epidemiological data from WHO estimated that, globally, 24.3 million people had dementia, with 4.6 million new cases annually. According to this data, numbers of people affected will double every 20 years to 81.1 million by 2040. Most people with dementia live in developing countries: 60% in 2001 rising to an estimated 71% by 2040 [2].

It is, therefore, to be expected that the cost of taking care of these patients can be enormous, considering the actual level of incidence and future generations of patients affected by Alzheimer's disease. Besides the monetary cost, it is impossible to quantify the suffering the families that take care of people with Alzheimer's disease during years.

Unfortunately, no cure for Alzheimer's disease has been found yet. However, these last few years have seen the appearance of cholinesterase inhibitor drugs which alleviate the clinical features and promote daily activities, at least to some extent.

The endocannabinoid system has been implicated in a vast variety of biological processes, both in the central and peripheral nervous systems and in peripheral organs. As a consequence, an array of potential therapeutic targets is currently being studied including specific cannabinoid agonists, antagonists and inverse agonists as well as compounds that interrupt the synthesis, uptake or metabolism of the endocannabinoids [3-5]. This system appears to be related with the pathology of several neurological diseases and thus it is involved in the control of movement and formation of memories. In relation to motor disorders, the cannabinoid related compounds are a promising field of therapeutic application for Parkinson's disease since the control of movement is one of the more relevant physiological roles of the endocannabinoid transmission in the brain. The mechanisms involved in the neuroprotection provided by cannabinoids include cannabinoid receptor independent effects aimed at reducing the oxidative injury, and also effects mediated by CB2 receptors [6, 7]. Alzheimer's disease, although not considered a motor disorder, is a neurological pathology characterized by strong alteration in the control of movement and has also been a subject of interesting research. In this context, abundant data associated with cannabinoid drugs suggest their efficacy in inflammatory diseases such as Alzheimer's disease [4, 8].

The neuroprotective effect of cannabinoids based on the antioxidant, anti-inflammatory and anti-excitotoxic properties offer a promising new approach for therapeutic treatment in different neurodegenerative pathologies by providing neuroprotection and reducing neuroinflammation.

This article reviews the current knowledge on the role of cannabinoid system and the recent progress in understanding the potential application of this system to the therapy of Alzheimer´s disease.

## 1. ENDOCANNABINOID SYSTEM

The endogenous cannabinoid system is a complex signalling organization (structure) that comprises transmembrane endocannabinoid receptors, their endogenous ligands (the endocannabinoids), the specific uptake mechanisms and the enzymatic systems related with their biosynthesis and degradation.

### 1.1. Cannabinoid Receptors

The existence of CBRs was confirmed when Howlett showed that cannabinoids decreased cAMP in neuroblastoma cell cultures [9], suggesting mediation by a $G_{i/o}$-coupled receptor [10-12]. There are two types of CBRs that have so far been identified, CB1 cloned in 1990 [13], and CB2 cloned in 1993 [14]. Both cannabinoid receptors belong to the family of G-protein coupled receptors (GPCRs), one of the largest and most studied superfamily of transmembrane proteins

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[15]. The CB1 receptor exhibits 97 to 99% amino acid sequence identity across species and CB2 receptor shows a 93% amino acid identity between rat and mouse and 81% amino acid identity between rat and human. Human CBRs exhibit 68% amino acid sequence identity within the transmembrane region and 44% amino acid sequence identity throughout the total protein.

Both receptors are coupled with $G_i$ or $G_o$ protein, negatively to adenylyl cyclase and positively to mitogen-activate protein (MAP) kinase (Fig. (**1**)). CB1 coupling to the G protein signal transduction pathways in presynaptic nerve terminals transduces the cannabinoid stimulation of MAP kinase and inhibition of adenylyl cyclase, attenuating the production of cAMP. CB1 and CB2 are also coupled to ion channels through Gi/o proteins. Cannabinoids, acting at CB1 receptors, are recognized to reduce pre-synaptic neurotransmitters released *via* an inhibition of voltage-operated calcium channels [16-19]. On the other hand, Fisyunov *et. al.* [20] have shown that synthetic and endogenous cannabinoids inhibit post-synaptic P-type currents in *Purkinje* neurones independently of CB1 receptors.

The CBRs have been described in many species, including human, monkey, pig, dog, rat and mouse, but not insects [21]. Initially, it was believed that the distribution of CB1 was predominantly in the brain, whereas the CB2 was localised in peripheral cells and tissues derived from the immune system. However, the CB1 has been found also in a number of peripheral tissues, such as the cardiovascular and reproductive systems as well as the gastrointestinal tract [22-26] and the CB2 has been detected also in the CNS, such as microglia cells [27] and neurons [28, 29]. Regarding to the distribution of the CBRs in CNS [30], the CB1 receptor has been found in the hippocampus, some olfactory regions, caudate, putamen, accumbens nucleus, the substantia nigra pars reticulata (SNr), globus palidus, and the horizontal limb of the diagonal band. .A high density of CB1 receptor has been found in the hippocampus pointing out the relationships with disruptive effects of cannabinoids on memory and cognition [31,32]. The existence of CB1 in the basal ganglia and the effects of cannabinoids in these structures imply that endogenous cannabinoids may play an essential role in the fine-tuning of motor control. In this sense, several studies have shown disturbances in CB1 receptor expression and binding in neurological disorders of the extrapyramidal system. Thus, CB1 binding is decreasing in neurodegenerative diseases, such as Parkinson´s [33].

As mentioned above, the first studies showed that CB2 was exclusively present in tissues and cells of the immune system. Recent studies have suggested that CB2 might be induced in glial cells (reactive microglia) in response to different damaging conditions associated with local inflammatory [34] or even Onavi *et. al.* [35] have proposed that CB2 receptor may be present in the brain even in healthy conditions. These studies identified CB2 receptors in glial cells (microglia and astrocytes) [36-38], neural [39] and oligodendrogial [40] and certain neuronal subpopulations [41-45] in different brain structures of various species, including human samples [36]. The CB2 receptor has been implicated in control of the proliferation, differentiation and survival of both neuronal and non-neuronal cells [30].

The CB1 and CB2 receptors have been shown to have a high level of ligand-independent activation (i.e., constitutive

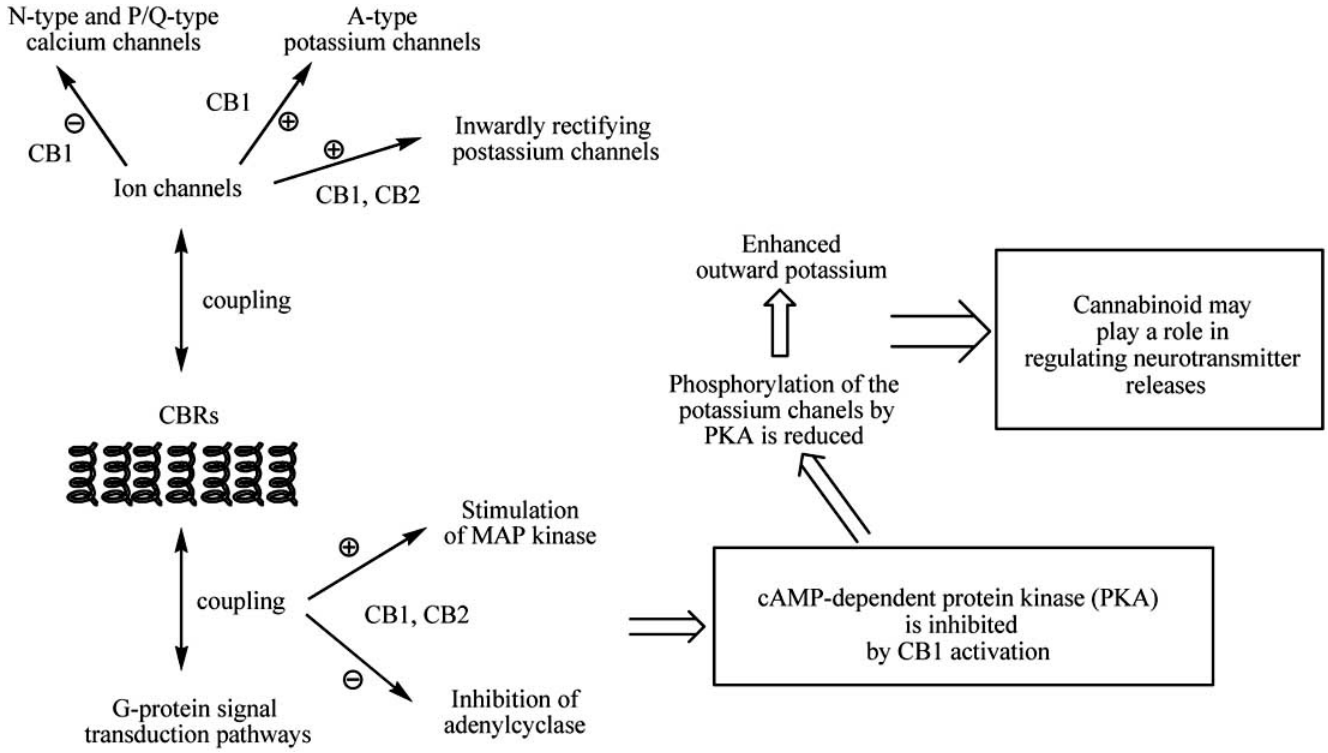



**Fig. (1).** Signaling pathways coupled to the CB1 and CB2 receptor.

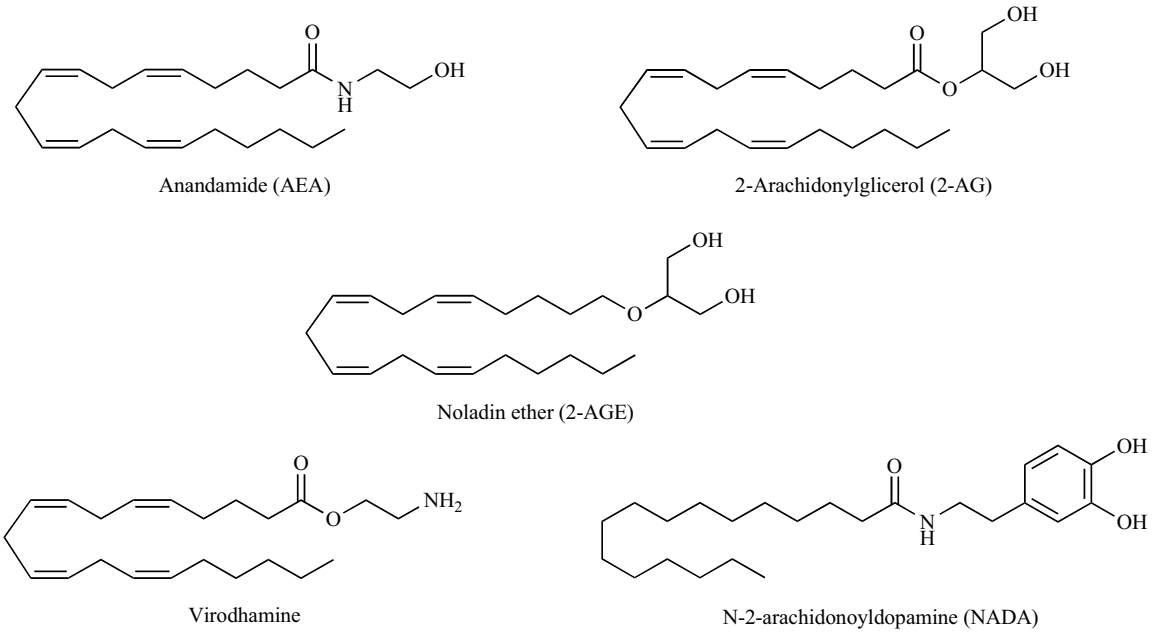



**Fig. (2).** Chemical structures of endocannabinoid like molecules.

activity) in transfected cell lines and in cells that naturally express the CB1 receptor [46-49]. It has been estimated that in a population of wild-type CB1, 70% exist in the inactive state (R) and 30% exist in the activated state (R*) [50].

As revealed by the crystal structure of *bovine rhodopsin* at different resolutions [51-54], the general architecture of a GPCR is defined as a counter clockwise arrangement of seven transmembrane α-helices (TMHs) of ~25 to 35 residues long (TMHs 1 to 7), which span the cellular membrane connected by three extracellular (EC 1 to 3) and three cytoplasmatic loops (IC 1 to 3). The N-terminal region, which varies in length and function, is located on the extracellular side of the membrane, while the C-terminal region is on the intracellular side.

Cannabinoid receptors as GPCRs change their conformations, in response to agonist binding, to activate the associated G-proteins. There are two main hypotheses, conformational selection [55] and ligand induction [56] models. According to the conformational selection model, the receptor exists in two conformations, the inactive (R) and the active (R*), the agonist preferentially binds the receptor in the R* conformation, thus increasing the duration of the period in which the receptor remains in the active state. The ligand induction model explains the transition between the R and R* as induction of the agonist when binds to R. Regarding this hypothesis the transition between both states is very rare in the absence of the agonist. Bovine rhodopsin provided the first direct visualization of the receptor in the inactive state [51]. Regarding the activated state, spectroscopic techniques on purified receptor preparation permitted the first insight of this conformational change [56].

### 1.2. Endocannabinoids

The discovery of the cannabinoid receptors and the availability of highly selective and potent cannabimimetics could be justified only by the existence of endogenous ligands capable of binding to them. The characterization, cloning of the first cannabinoid receptor (CB1) led two years later to the isolation and characterization of the first endocannabinoid, the arachidonoylethanolamide (AEA), named anandamide from the Sanskrit 'internal bliss' [57] and subsequent identification of a family of lipid transmitters that serve as natural ligands for the CB1 receptor. Endocannabinoids are endogenous compounds that activate the CB1 and/or CB2 receptors. The brain produces at least five endogenous ligands that possess affinity for cannabinoid receptors (Fig. (**2**)). These endocannabinoids are amides, esters and ethers of long chain polyunsaturated fatty acids, which act as new lipidic mediators. The first endogenous ligands for CB receptors were discovered and characterized as arachidonoylethanolamide (AEA) [57] and the fatty acid ester 2-arachidonoylglycerol (2-AG) [58,59]. Other possible endocannabinoids have been proposed, such as a fatty acid ether, 2-arachidonylglyceryl ether (Noladin ether) [60], O-arachidonoylethanolamine (Virodhamine) [61] and N-arachidonoyldopamine (NADA) [62] but their natural occurrence and their roles are still unclear.

Although the primary endogenous ligand of cannabinoid receptors remains uncertain, the ethanolamine of arachidonic acid anandamide (AEA) and 2-arachidonylglycerol (2-AG) are the main endogenous agonists of cannabinoid receptors.

*Anandamide* (arachidonylethanolamide or AEA) was the first ligand to be identified as an endogenous ligand of the G-protein coupled CB1 receptor [57]. Two other polyunsaturated fatty acid ethanolamides were isolated from porcine brain and identified as N-homo-γ-linolenylethanolamide and 7,10,13,16- docosatetraenylethanolamide binding to the CB1 receptor with high affinity [63]. AEA binds to both CB1 and CB2 receptors [64] but its affinity for the CB2 receptor is approximately four-fold less than for CB1 receptor [65] (Table **1**). The highest levels of anandamide were found in areas of the brain with high densities of CBRs, such as the hippocampus, striatum, cerebellum and cortex. Anandamide is

**Table 1. Selected $K_i$ Values of Cannabinoids Ligands for the *In Vitro* Displacement [$^3$H]CP55940 from CB1 and CB2 Specific Binding Sites**

| | CB1 $K_i$ (nM) | CB2 $K_i$ (nM) | CB1/CB2 | References |
|---|---|---|---|---|
| **Endocannabinoids (Fig. (2))** | | | | |
| Anandamide | 89 ± 10 | 371 ± 102 | | [162] |
| AG | 472 ± 55 [a] | 1400 ± 172 [a] | | [58] |
| Noladinether | 21.2 ± 0.5 [a] | >3 [a] | | [69] |
| **Phytocannabinoid** | | | | |
| $\Delta^9$-THC | 5.05 ± 0.65 | 3.13 ± 0.34 | 1.6 | [140] |
| $\Delta^9$-THC | 21 | 36.4 | | [162] |
| $\Delta^9$-THC | 53.3 | 75.3 | | [65] |
| $\Delta^8$-THC | 44 ± 12 | 44 ± 17 | 1.0 | [152] |
| Cannabinol | 326 | 96.3 | 3.4 | [162] |
| Cannabinol | 1130 | 301 | 3.8 | [65] |
| $\Delta^9$-THCV | 75.4 | 62.8 | | [141] |
| Cannabidiol | 4350 | 2860 | 1.5 | [162] |
| **THC analogs (Fig. (6))** | | | | |
| CP 55940 | 2.11 | 1.08 | 2.0 | [169] |
| CP 55940 | 3.72 | 2.55 | 1.5 | [65] |
| Nabilone | 1.84 | 2.19 | | [147] |
| HU-210 | 0.06 | 0.52 | | [65] |
| HU-308 | >10000 [a] | 22.7 ± 3.9 [a] | >440 | [246] |
| JWH-133 | 677 ± 132 | 3.4 ± 1.0 | 199 | [152] |
| JWH-352 | >10,000 | 47 ± 2 | 212 | [155] |
| JWH-359 | 2918 ± 450 | 13 ± 0.2 | 224 | [155] |
| **1** | 370 | 0.81 | 500 | [158] |
| AM1714 | 400 | 0.82 | 490 | [157] |
| O-1966A | 5055 ± 984 | 23 ± 2.1 | 220 | [247] |
| **AAIndoles (Fig. (7))** | | | | |
| WIN55212-2 | 1.9 ± 0.1 | 0.3 ± 0.2 | 6.8 | [162] |
| WIN55212-2 | 13.3 | 1.30 | 10 | [169] |
| WIN55212-2 | 9.87 ± 1.52 | 0.29 ± 0.12 | 34 | [140] |
| JWH-015 | 164 ± 22 | 13.8 ± 4.6 | 11.9 | [248] |
| JWH-015 | 383 | 13.8 | 27.8 | [162] |
| JWH-120 | 1054 ± 31 | 6.1 ± 0.7 | 172.8 | [153] |
| JWH-151 | >10000 | 30 ± 1.1 | >333 | [153] |
| L768242 (GW405833) | 1917 ± 381 | 12 ± 0.2 | 159.8 | [163] |
| L768242 (GW405833) | 282 | 7.62 | 37 | [169] |
| AM1241 (racemic) | 1270 | 11.5 | 110 | [169] |

**(Table 1. Contd….)**

| | CB1 $K_i$ (nM) | CB2 $K_i$ (nM) | CB1/CB2 | References |
|---|---|---|---|---|
| AM1241 (racemic) | >10000 | 28.7 ± 2.01 | >348 | [165] |
| AM1241(R) | 5000 ± 300 | 15.1 ± 4.18 | >330 | [165] |
| AM1241(S) | >10000 | 658 ± 44.2 | >15 | [165] |
| **2** | 4000 | 8 | 500 | [168] |
| A-796260 | 845 | 4.37 | 193 | [169] |
| **Other classes (Fig. (8))** | | | | |
| **3** | >1000 | 3.3 ± 0.4 | > 330 | [176] |
| **4** | 1925 ± 179 | 13.4 ± 1.2 | 143.7 | [177] |
| Sch35966 | 2633 ± 829 | 6.8 ± 2.3 | 387 | [178] |
| **5** | >5000 | 9 | >550 | [179] |

[a] Experiments were performed with [$^3$H]HU243.

synthesised by postsynaptic neurons and acts as a retrograde messenger molecule to modulate neurotransmitter release from CB1-expressing presynaptic terminals [66].

*2-Arachidonoylglycerol (2-AG)* was the second endocannabinoid originally isolated from canine intestine [58] and rat brain [59]. 2-AG is a full agonist at both CB1 and CB2 receptors [67,68]. Although it exhibits a lower affinity for CB1 than anandamide, it is present in the brain at higher levels. Whereas AEA is a partial CB1 receptor agonist, 2-AG is considered the primary endogenous agonist for CB1 and CB2 receptors with similar affinity for both.

*2-Arachidonoylglyceryl ether* (Noladin ether) a third ether type endocannabinoid isolated from porcine brain [69] has much higher affinity for CB1 than for CB2 receptors. Thus, it has been shown to bind to CB1 receptor with nanomolar affinity and to CB2 receptor with low affinity (Table **1**). The highest amount of this compound was detected in the thalamus and hippocampus and much lower amounts in the spinal cord [70].

*O-arachidonoylethanolamine (Virodhamine)* was reported in 2002 as a novel endocannabinoid with antagonist properties at CB1 receptor [61]. Concentrations of virodhamine in rat brain and human hippocampus were similar to anandamide whereas in peripheral tissues that express CB2 receptor, virodhamine concentrations were 2- to 9-fold higher than anandamide.

N-arachidonoyldopamine (NADA) is another molecule with the arachidonic acid backbone that was found in rat and bovine brain [62]. It activates CB1 receptors and shows cannabimimetic effects as analgesia and it interacts with FAAH and the anandamide transporter [71]. The distribution pattern of endogenous NADA in various brain areas differs from that of anandamide, with the highest levels found in the striatum and hippocampus [62].

### *Biosynthesis, Transport and Degradation*

Endocannabinoids are lipophilic metabolites of arachidonic acid, synthesized, released, reuptaken and/or metabolized in the nervous cells (For reviews see: [72-75]). The endocannabinoids are not present in vesicular stores but they are biosynthesized on demand and undergo rapid metabolic deactivation. These characteristics of on demand synthesis and rapid degradation indicate that endocannabinoids act close to where they are synthesized. In neurons, membrane depolarization of postsynaptic cells induces *de novo* formation of 2-AG and AEA through phospholipid dependent pathways. The synthesis or release of these lipids messengers endocannabinoids requires both neuronal depolarization and increased intracellular calcium.

The biosynthesis of anandamide is accepted to occur through the enzymatic hydrolysis by phospholipase D of the membrane precursor N-arachidonoylphosphatidylethanolamine (NArPE) [76]. It is worth mentioning that a novel N-acylphosphatidylethanolamine phospholipase D (NAPE-PLD) has been described as responsible for the generation of anandamide [77] and the recent characterization of the molecular composition of the major endogenous NArPE species generating anandamide [78].The 2-AG is biosynthesized from diacylglycerol (DAG) by a sequential action of Phospholipase C and diacylglycerol lipase (DAGL) [79]. A biosynthesis of 2-AG from Phospholipase C independent process has also been described [80,81].Regarding the generation of the N-Arachidonoyldopamine (NADA, Fig. (**2**)), it has been suggested two alternative routes [62]. A simple *via* is the direct condensation of an arachidonoyl precursor (possibly arachidonoyl-CoA) with dopamine. A more complex synthetic route for NADA involved production of an N-acylamino acid, N-arachinodoyltyrosine, and then sequential hydroxylation (*via* tyrosine hydroxylase) and decarboxylation presumably *via* aromatic amino acid decarboxylase [62]. The biosynthetical routes of the noladin ether and virodhamine are much less clear and remain to be described.

Endocannabinoids can diffuse passively through lipid membranes according to their lipophilic nature. However, it appears that the diffusion is accelerated by a rapid and selective carrier system that would use a facilitated diffusion mechanism [82-84]. This carrier might work bi-directionally and could also facilitate the release of endocannabinoids [82]. Therefore, AEA and 2-AG are taken up by a putative

facilitated transport mechanism known as the AEA membrane transporter(s) (AMT). Although biochemical data support the existence of an AMT protein, it remains to be isolated and cloned.

The action of endocannabinoids at their receptors is terminated by an endogenous mechanism of deactivation that involves transport inside of the cell and a metabolic degradation by at least two specific enzymes, a fatty acid amide hydrolase (FAAH) and a monoacylglycerol lipase (MAGL). FAAH is the main AEA hydrolase, whereas MAGL is critical in degrading 2-AG (For reviews see: [75,85-87]). The distribution of anandamide and 2-AG in CNS, together with the fact that FAAH and MAGL only partially overlap with CB1 receptors, suggests that both enzymes play different roles in the modulation of neurotransmission [88,89]. Therefore, it have been suggested that specific inhibitors of AMT, FAAH or MAGL may serve as attractive therapeutic targets for the treatment of human diseases [73,87,90,91], nevertheless these topics are not discussed in the present review.

### Functions of Endocannabinoid System

The endocannabinoid system is postulated to exert multiple functions in the brain and in peripheral tissues and thus, it is related with a wide variety of physiologic processes, including the immune regulation [92,93], the cardiovascular system [94-96], the reproductive endocrine processes [97-99] and the control of energetic metabolism [100].

In the brain, endocannabinoids participate in processes such as the control of movement [6,101-104], memory and learning [8,105,106], nociception [107-110], reward processes [111], cognition, emotionality, fear and anxiety [112]. There are studies that have shown several evidences regarding the influence of ECS on adult neurogenesis, however due to the variability among the different studies (strain and models) it is complicated to make a comparison of the results. Consequently, it is still not clear how endocannabinoid regulate neurogenesis [3]. Besides, recent studies have revealed the possible neuroprotective role of endocannabinoids and their modulating action on neurotransmitter system which is affected in several neurodegenerative diseases such as Alzheimer's disease (AD), Huntington's disease (HD) and multiple sclerosis (MS) [4,6,8,105,106,113-115].

The endocannabinoid system is a highly complex organization where the endocannabinoids like molecules can interact with 7-transmembrane receptors (CB1, CB2, GPR18, GPR55 and GPR119), nuclear receptor (PPARα, PPARβ/δ and PPARγ) and transmitter-gated channels (TPRV1) [72]. The ECS appears to interact with other receptor systems that include the serotonin (5-HT3) receptor, the N-methyl-D-aspartate (NMDA) receptor and nicotinic acetylcholine receptors (nAChRs). Futhermore, the endocannabinoid system has also an important role in signalling of rewarding events through to the dopaminergic mesolimbic system which is the brain neurotransmisser system most clearly involved in this type of process [111].

## 2. CANNABINOID RECEPTOR LIGANDS

The term cannabinoid was first used to describe the tricyclic naturals compounds isolated from *Cannabis sativa* of which (-)-$\Delta^9$-*trans*-THC is the principal psychoactive component. The hemp plant *Cannabis sativa L.* is very complex in its chemical composition due to the vast number of its constituents. It contains at least 70 compounds derived from a diterpene structure that can be classified in at least 11 groups [116] (Fig. (**3**)): Cannabigerol (CBG) type (7 known), Cannabichromene (CBC) type (5 known), Cannabidiol (CBD) type (7 known), (−)-$\Delta^9$-*trans*-Tetrahydrocannabinol ($\Delta^9$-THC) type (9 known), (−)-$\Delta^8$-*trans*-Tetrahydrocannabinol ($\Delta^8$-THC) type (2 known), Cannabicyclol (CBL) type (3 known), Cannabielsoin (CBE) type (5 known), Cannabinol (CBN) type (7 known), Cannabinodiol (CBND) type (2 known), Cannabitriol (CBT) type (9 known), miscellaneous types (14 known).

### 2.1. Agonists CB2

Taking into account the major interest of the cannabinoids agonists for the Alzheimer's disease, this section will be focus mainly on these ligands with special emphasis in the properties of compounds at CB2 receptor.

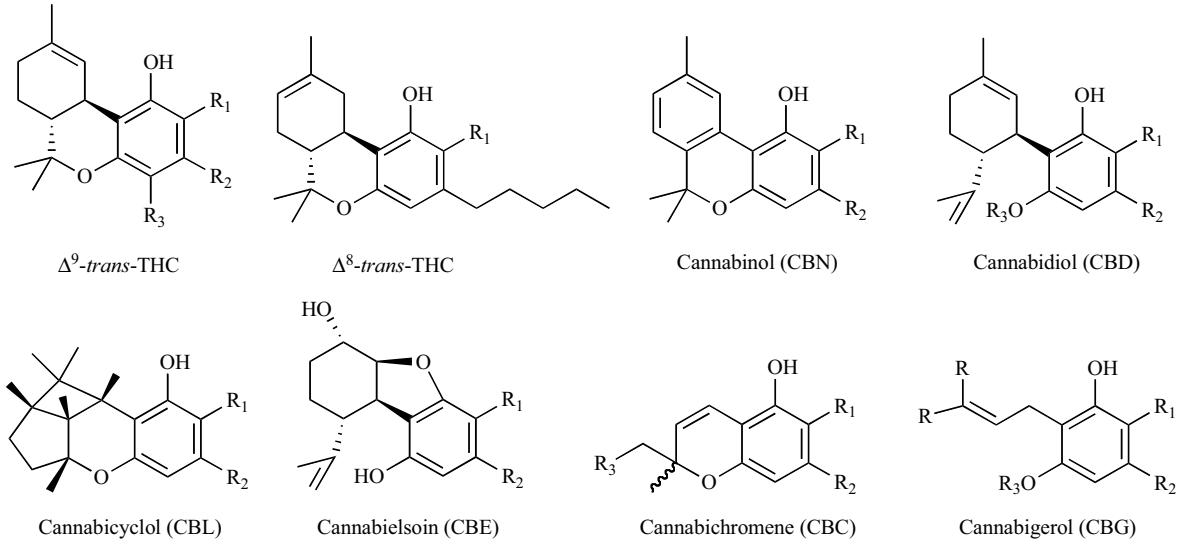



**Fig. (3).** Selected constituents type of *Cannabis sativa L.*

Therefore, we will drive the attention to cannabinoid agonists by emphasizing those features that define their interaction with the cannabinoid receptors and analyzing the most important aspects of their activity and selectivity (For reviews see: [117-123]).

Cannabinoid receptor antagonists have also been reviewed elsewhere, specially those compounds of the 1,2-diarylpyrazole class, where the most representative compound is SR141716A (Rimonabant; Acomplia®) reported in 1994 by the Sanofi group as a selective CB1 antagonist [124-127]. In addition, novel antagonists and inverse agonists at the CB2 receptor have been described; these are however, outside the scope of the current review (for reviews on antagonist and inverse agonists, see [128-136]). In addition to 1,2-diarylpyrazoles, aminoalkylindole (AAIs) and analog ligands appeared to be quite interesting not only due to their selectivity of some derivatives but also to their agonist or antagonist properties. Thus, the aminoalkylindole AM630 (Fig. (**4**)) was the first described as CB2-selective antagonist derived from this class of compounds [137].

From a chemical point of view, cannabinoid receptor agonists can be classified in different groups: phytocannabinoids which include the natural products isolated from *Cannabis sativa*, synthetic analogs of natural cannabinoids, usually bicyclic systems lacking the pyran ring as CP-55,940 [138], the aminoalkylindoles being WIN55212-2 the most representative member [65]. By the last, the endocannabinoids (endogenous ligands) which are fatty acid derivatives, such as anandamide and 2-arachydonylglycerol (Fig. (**2**)). In addition to these major groups, other chemical structures have proven cannabinoid properties and are being the subject of intensive research.

### *Phytocannabinoids*

These cannabinoids are tricyclic terpenoid derivatives bearing a benzopyran moiety that include the natural product (-)$\Delta^9$-tetrahydrocannabinol [139] and other pharmacologically active constituents of the plant *Cannabis Sativa* as well as analog tricyclic lacking the pyran ring of THC (Fig. (**5**), Table **1**). $\Delta^9$-THC, the main psychotropic constituent of cannabis, is a CB1 and CB2 receptor partial agonist. Cannabinol bound with higher affinity in the nM range at both receptors, showing a modest selectivity [140] whereas the $\Delta^9$-THCV behaves as a potent CB2 receptor partial agonist *in vitro* [141]. For recent reviews about the pharmacological properties of $\Delta^9$-THC see [142,143]. Currently, the most therapeutically attractive compound of this class is the cannabidiol as a consequence of its pharmacological effect as antagonist CB1R and agonist CB2R [143-145].

### *Synthetic Analogs of Natural Cannabinoids*

In the early 1980s a second class of cannabimimetics was developed by Pfizer based upon the dibenzopyran structure of THC, which includes the well-known ligand CP-55,940. This compound which was found to be more potent than $\Delta^9$-THC *in vivo* is considered as the prototypical example of this class and extensively used for evaluation of potential cannabinoid ligands in binding assays [31,146]. A high number of analog tricyclic THC and non traditional cannabinoids analogs of CP-55,940, where the oxygen containing pyran ring of THC have been removed, were synthesized and studied by different groups (Fig. (**6**)). Thus, there are a lot of tricyclic or bicyclic compounds described with cannabinoid properties with low selectivity for either CB1 and the CB2 receptor, being Nabilone [147], CP55,940 [148] and HU-210

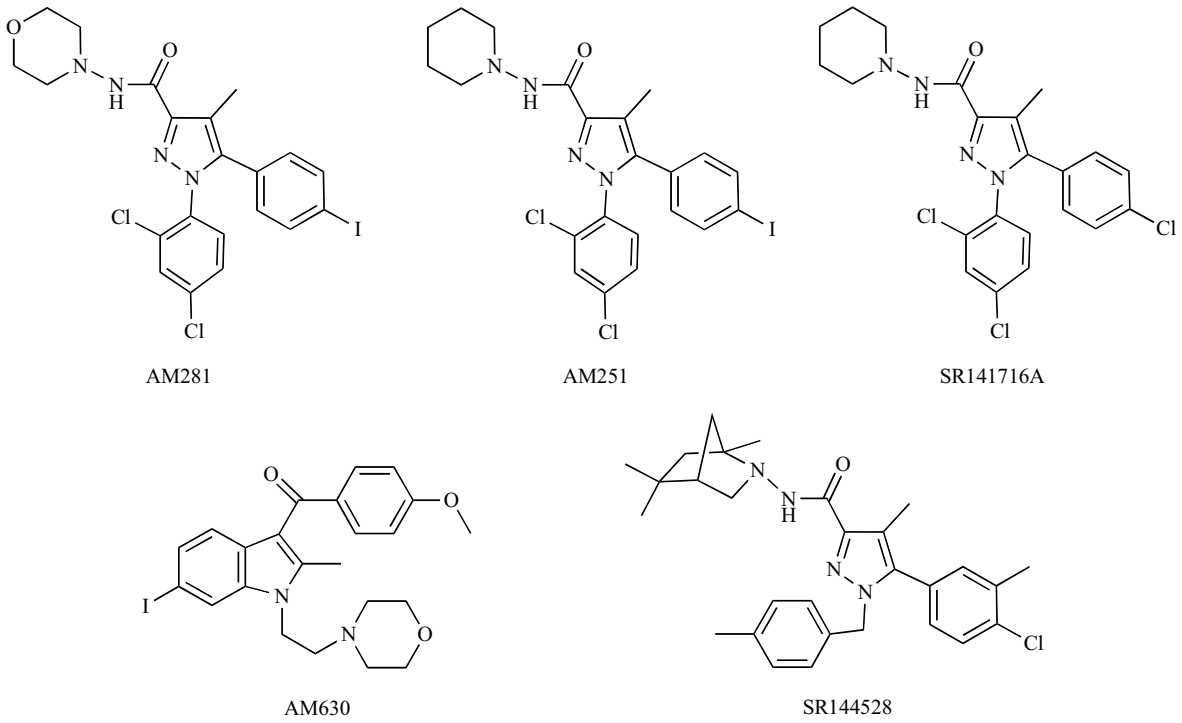



**Fig. (4).** Structures of the selective CB1 receptor antagonists (AM251, AM281, SR141716A) and selective CB2 receptor antagonists (AM630, SR144528).

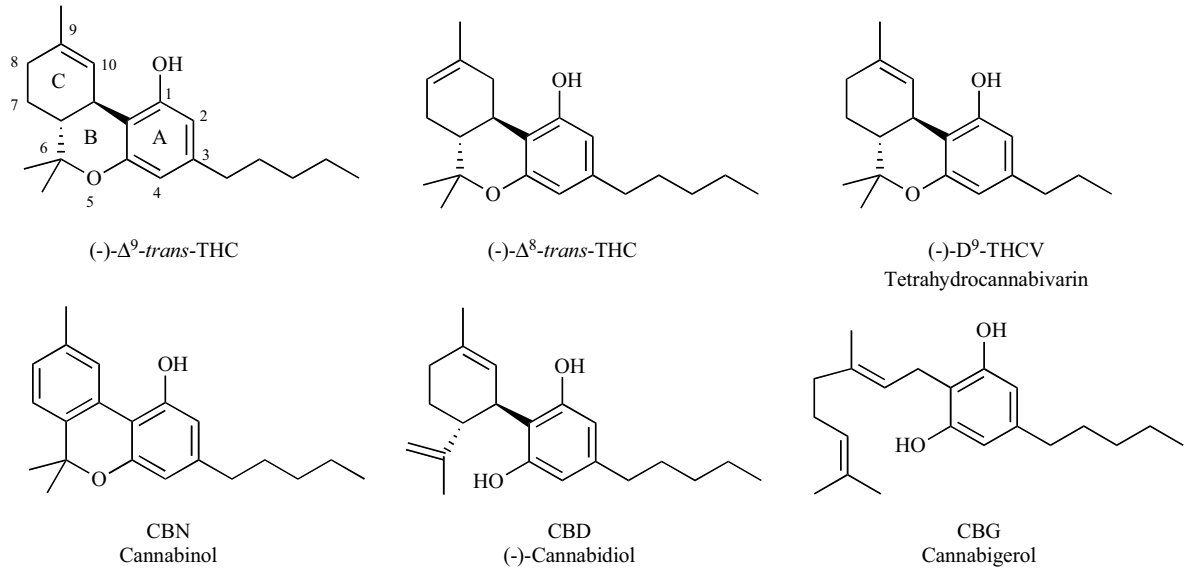



**Fig. (5).** Representative structures of the constituents of Cannabis sativa.

[149,150] the most representative. The last compound bearing a hydroxymethyl group at C-9 was synthesized by Mechoulam *et. al.* and it is one of the most potent used agonists of the cannabinoid receptors [151].

Subsequently there have been reported some tricyclic compounds structurally analog of $\Delta^9$ and $\Delta^8$-THC and bicyclic non traditional cannabinoids which have shown selectivity at the CB2 receptor. Based on the similar effect (*in vitro* and *in vivo*) that $\Delta^8$-THC derivatives show in relation to $\Delta^9$-THC and taking into account that they are synthetically easier to prepare due to the increased stability of the $\Delta^8$-double bond, several analogs of the tricyclic $\Delta^8$-THC have been synthesized and studied, allowing to get a broad spectrum of compounds with cannabinoid properties that show selectivity for CB2 receptor. It is worth mentioning that compounds JWH-133 [152,153] and HU-308 [154] are the most representative members of this family showing very high affinity for the CB2 receptor, but little affinity for the CB1 receptor. The tricyclic JWH-133 has been characterized as a full agonist in a GTPγS-binding assay at the human CB2 receptor, and HU-308 has been also described as a selective full agonist in human CB2 cyclic GMP assays.

New CB2 selective compounds structurally similar to 1-deoxy analogs of $\Delta^8$-THC, such as the 1-deoxy JWH-352 and 1-methoxy JWH-359 have been described by Huffman [155] with a high selectivity at CB2 receptor (224 and 212 fold, respectively). Albeit, no functional data has been published to demonstrate their agonist properties.

Some derivatives of resorcinol dimethyl ether have been reported, showing compounds that have high selectivity, like compounds O-1966 (Fig. (**6**)) that has a selectivity of 220 fold for the CB2 receptor and very low affinity for the CB1 receptor [156].

Recently, new tricyclic cannabinolactone derivatives of benzo[*c*]chromen-6-one have been published [157] where the great importance of lactone functionality in the observed CB2 selectivity is highlighted. Optimal receptor subtype selectivity of 490-fold and subnanomolar affinity for the CB2 receptor is exhibited by the 9-hydroxyl analog, AM1714 (Fig. (**6**)). In functional assays, all compounds were found to act as agonists, with activities comparable to WIN55212-2 and with analgesic activity.

Worm *et. al.* have described new biaryl cannabinoids mimetic where the phenol group has been replaced by a methylmorpholino acetate group leading to compound **1** (Fig. (**6**)), a 500-fold selective CB2 receptor agonist [158].

### *Aminoalkylindoles (AAIs) and analogs*

A third chemical class of cannabinergics is the aminoalkyldindoles, developed by Sterling Winthrop as potential non-steroidal anti-inflammatory agents. In 1991 the unexpected inhibition of the electrically simulated mouse vas deferens by the Pravadoline ((4-methoxyphenyl)-[2-methyl-1-(2-morpholin-4-ylethyl)indol-3-yl]methanone) was published [159]. Other indol derivatives were developed with increased cannabinoid potency like WIN55212-2 which it is a potent CB1 and CB2 agonist with high stereoselectivity and a slight preference for CB2 [65,160]. This compound is not very useful from a pharmacological point of view, however is extensively used for receptor evaluation of potential cannabinoid ligands. A great number of indole derivatives have been synthesized by structural modifications of all position of the ring (see reviews [120,121,161]).

The aminoalkylindole derivatives are structurally dissimilar to other classes of cannabimimetics. Some of these compounds have shown good affinity at CB1 and CB2 receptors but most of them possess a high degree of selectivity for CB2R. In addition to this, there are a lot of cannabinoid ligands with a high affinity at CB1R, however the selectivity is extremely low. The most interesting compounds from affinity and selectivity point of view are mentioned in Table **1**.

Several groups have worked in the development of selective ligands for CB2 receptor. These efforts have allowed the description of two different series of cannabimimetic indoles, where the most representative compounds are 2-

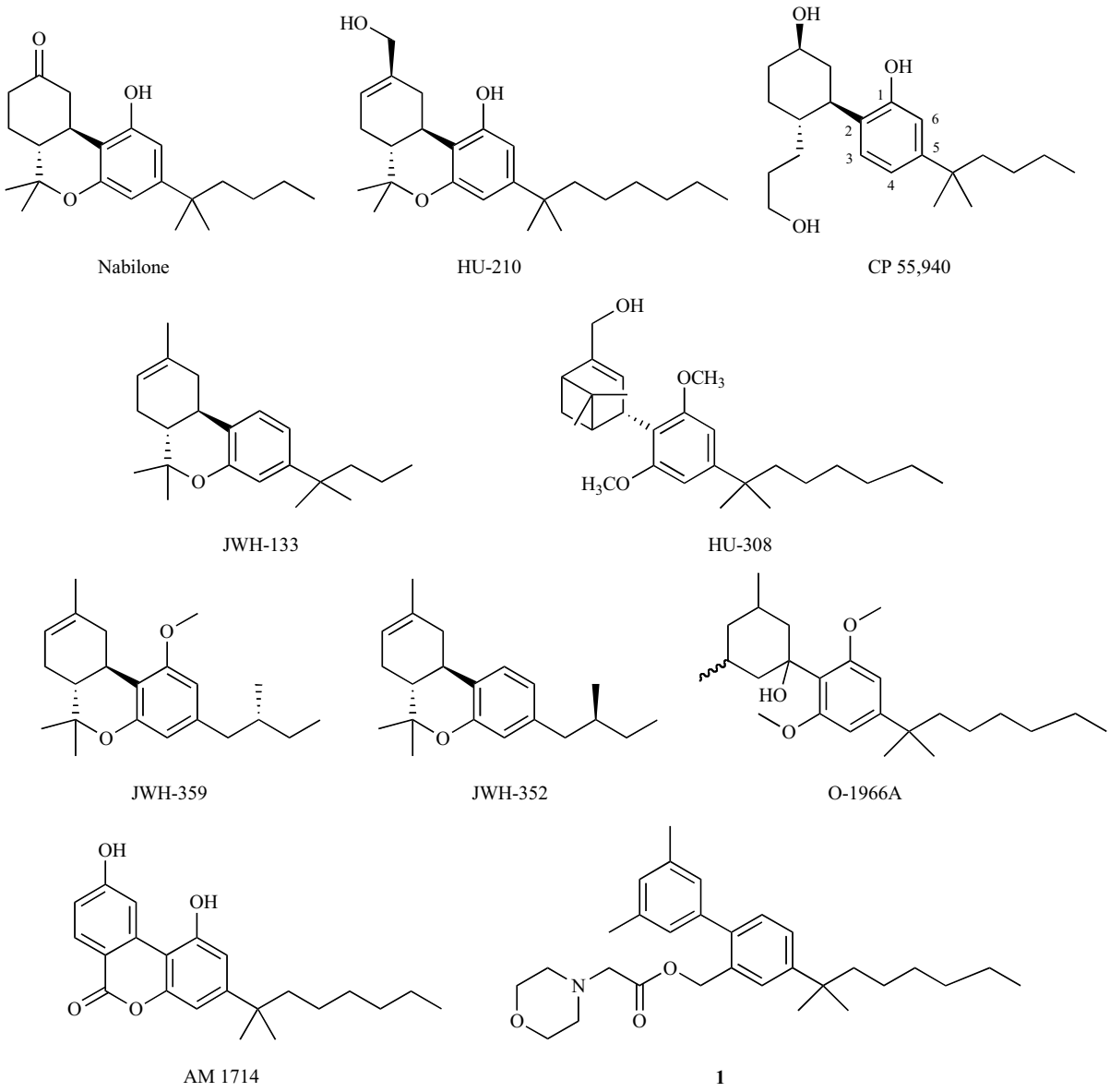



**Fig. (6).** Structures of synthetic natural cannabinoids analogs.

methyl-1-propyl-3-(1-naphthoyl)indole (JWH-015) [162] and 1-(2,3-dichlorobenzoyl)-2-methyl-3-(2-[1-morpholino]ethyl)-5-methoxyindole (L768242) [163]. These derivatives have high affinity for the CB2 receptor and low affinity for the CB1 receptor (Fig. (**7**), Table **1**). Functionally speaking, L768242 displays partial agonist activity in human CB2 receptor-mediated inhibition of forskolin-stimulated cAMP release assays [164].

Huffman *et. al.* have published a great number of aminoalkylindoles and alkyindoles cannabimimietic using JWH-015 as leading compound. Some of them have shown high affinity for CB2 receptor (Table **1**, Fig. (**6**)). Among them, JWH-120 and JWH-151 should be highlighted for their good affinity at CB2R and selectivity of 173 and >333 fold, respectively [153].

Another interesting cannabimimetic aminoalkylindole is the AM1241 that it has been found to exhibit high affinity at human, rat and mouse CB2 receptors [165]. The behavioural profile of AM1241 across multiple pain models is consistent with CB2 agonist activity. The efficacy of AM1241 in models of inflammatory [166] and neuropathic pain [167] has been shown to be mediated by the CB2 receptor, as the effects are blocked by CB2-but not CB1-selective antagonists. However, the agonist efficacy profile of AM1241 (as the racemate) is complex and condition-dependent. This compound has also been described as inverse agonist or partial agonist at the human CB2 receptor and as apparent inverse agonist at the rat CB2 receptor [165].

Different series of indole derivatives have been published by Bristol-Myers Squibb, being the most interesting the compound **2** (Fig. (**7**)). This structure is an amido-indole derivative that has been described as a very selective CB2 agonist and inhibits pro-inflammatory responses in a murine model of acute inflammation [168].

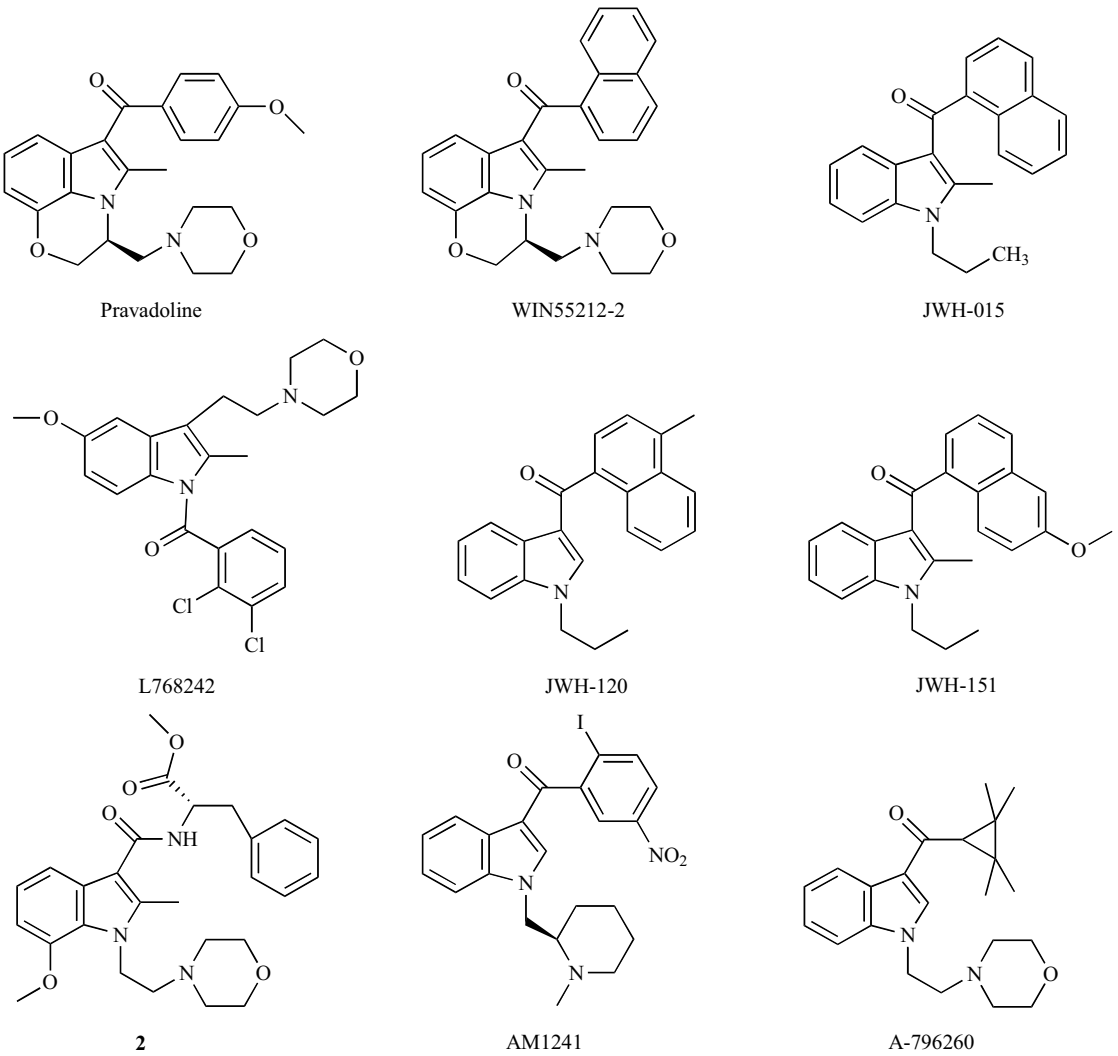



**Fig. (7).** Structures of analogs of AAI.

Finally, new series of indolyltetramethylcyclopropil ketones have been described by Abbot [169,170]. An interesting new ligand derivative of indole, A-796260 ([1-(2-morpholin-4-yl-ethyl)-1H-indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)-methanone) has been described as a potent and selective CB2 agonist with antihyperalgesic and antiallodynic properties in models of chronic inflammatory and neuropathic pain [169].

### *Other Synthetic Canabinoid Structures*

There are other different structures reported with high affinity for cannabinoid receptors with modest selectivity to CB2 receptor as resorcinol derivatives [171], naphtoylpyrroles [172], new conformationally constrained derivatives of the indolopyridone with anti-inflammatory properties [173], and 1,8-naphthyridinone-3-carboxamide derivatives [174].

Other different structures reported as cannabimimetics with high selectivity to CB2 receptor are the 1,4-dihydroindeno[1,2-c]pyrazol derivatives [175]. However, no data are presented about the agonist or antagonist/inverse agonist properties of these compounds.

Some interesting structures as quinolin-4(1H)-one-3-carboxamide have been reported to exhibit selectivity for CB2R. Thus, the compound **3** shows a high affinity at CB2 receptor with a selectivity >300 fold (Fig. (**8**), Table **1**). This compound behaved as an agonist according to [$^{35}$S]GTPγ binding assays and functional studies [176] . Besides, other set of 4-oxo-1,4-dihydroquinoline-4-one-3-carboxamides have been reported. The most interesting derivative **4** is reported as CB2 agonist with high selectivity for CB2 receptor [177] (Fig. (**8**), Table **1**).

Recently, new cannabinoid ligands derivatives of quinolizin-6-one have been described. Sch35966 (8,10-bis[(2,2-dimethyl-1-oxopropyl)oxy]-11-methyl-1,2,3,4-tetrahydro-6*H*-benzo[*b*]quinolizin-6-one) displays high affinity for the CB2 receptor and possesses >380-fold selectivity for CB2 binding *vs* the central cannabinoid receptor (CB1) (Fig. (**8**), Table **1**). Sch35966 is an agonist and it effectively inhibited forskolin-stimulated cAMP synthesis in CHO-hCB2 cells, stimulated [$^{35}$S]GTPγS exchange and directed chemotaxis in cell membranes expressing CB2. In all species examined, Sch35966 was more potent, more efficacious and more selective than JWH-015 used as reference CB2 selective agonist [178].

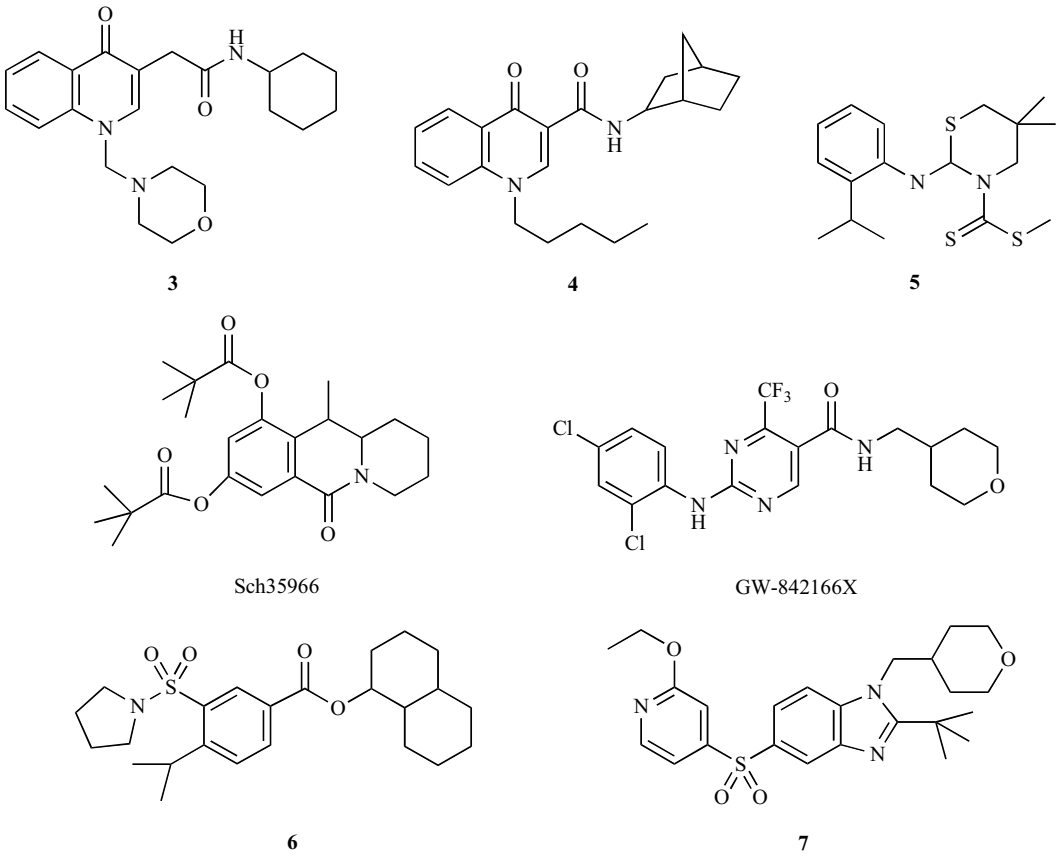



**Fig. (8).** Structures of other selective CB2 receptor agonists.

A series of 1,3-thiazines has been synthesized to find the optimal structure exhibiting the strongest binding affinity. The most potent compound 2-phenylimino-5,6-dihydro-4*H*-1,3-thiazine **5** (Fig. (**8**)) displays $k_i$ values of >5000 and 9 nM at CB1 and CB2 receptors, respectively. Functional assays indicate that this thiazine behaves as cannabinoid receptor agonist with analgesic activity due to the activation of CB2 receptor [179,180].

Another interesting ligand derivative of 5-pyrimidinecarboxamide GW-842166X has been described by GlaxoSmithKline as a selective CB2 receptor agonist for the treatment of inflammatory pain [181,182].

Finally, new arylsulfonamide [183] (compound **6** as example, Fig. (**8**)) and new series of benzimidazole [184] CB2-receptor agonists have been described (compound **7** as example, Fig. (**8**)). In the case of benzimidazole, the group at 2-position determines the level of agonism, ranging from inverse agonism to partial agonism or full agonism. The most promising derivative is the compound **7** (Fig. (**8**)) that showed agonistic activities with an $EC_{50}$ up to 0.3 nM and excellent selectivity (>4000-fold) over the CB1 receptor [184] .

## 2.2. Cannabinoid Receptors Modeling

To date, no experimental 3D structure of CB receptors have been obtained. The knowledge of the structural features of cannabinoid receptors is of the utmost importance for the understanding of their function and for their use for drug design. For these purposes, many biochemical, pharmacological, and computational studies have been carried out on cannabinoid receptors. In the following lines we will summarise the computational studies performed with the cannabinoid receptors. The first 3D model of the CB1 receptor was based upon Fourier transform analyses of the α–helical periodicity in the sequences of the CB1 receptor and a set of homologous GPCRs. The low-resolution projection structure of rhodopsin and mutation data from other GPCRs were used to refine the model [185-187]. Mahmoudian *et. al.* [188] developed other CB1 model based on the crystal structure of *bacterial rhodopsin* [189]. The problem is that *bacterial rhodopsin* is not a GPCR and its helix-packing arrangement differs from that of GPCRs. Thanks to the determination of the ground state of rhodopsin at 2.8Å resolution by X-ray crystallography by Palczeski *et. al.* [51], it was possible to develop 3D models more accuracy. By far, the most common way to get the inactive state of the cannabinoid receptors is by homology modeling based on the crystal structure of *bovine rhodopsin*. Since the publication of the rhodopsin structure, several cannabinoids receptors (CB1 and CB2) models as inactive or active forms have been developed by homology modeling and molecular dynamics using the different 3D structures at different resolutions as templates [177,190-201]. Recently Maccarrone *et. al.* [202] have constructed a 3D model of CB1 and CB2 using the crystal structure of β–adrenergic receptor [203-205] as template. Regarding to the activation of CB receptors seems to be determined by a different rearrangement of TM3 and TM6. Experimental and

simulation studies indicate that conformational switches in transmembrane α-helices can be generated by proline-containing motifs that form molecular hinges [206]. Regarding the activation of CB receptors, Singh *et. al.* suggested that W6.48(356)/F3.36(200) interaction may act as the toggle switch for CB1 activation, with W6.48_gauche+/F3.36_trans representing the inactive and W6.48_transs/F3.36_gauche+ the CB1 active form [207]. During these movements, different structural change take place, as the broken the salt bridge in the inactive state between R3.50(214) and D6.30(338) and Cys 6.47 becomes accessible from inside the binding site crevice [208] .

Thanks to the computational efforts (homology modelling and docking studies) together with the mutagenesis studies it has been possible to identify some of the most important residues involved in the binding sites of cannabinoid receptors and to propose the binding mode of agonist [190,197-199] and antagonist ligands [192,196,198-200, 209]. Fig. (**9**) shows an example of interactions of a classical agonist (CP55940) with CB1R.

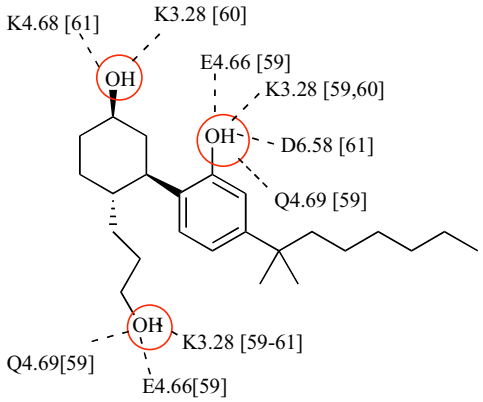



**Fig. (9).** Hydrogen bonding interactions of CP55940 docked in CB1 model.

The Fig. (**10**) and Fig. (**11**) show the most important residues of the binding site of cannabinoid receptors with an agonist (WIN55212,2) and antagonist (SR141716A). Several interesting reviews have been published about the different computational methods and mutagenesis studies of CB1 and CB2 receptors [210,211,123].

## 3. CANNABINOID SYSTEM AND ALZHEIMER´S DISEASE

During the last years different studies (*in vitro* and *in vivo*) have shown that exogenous and endogenous cannabinoids are neuroprotective. Although the mechanism of this effect is not clear yet, it is known that it involves CB1 receptor (decreases in glutamate release, production of pro-inflammatory molecules and stimulation of GABAergic transmission), CB2 receptor (antiinflammation) and non receptor-mediated (antioxidative) mechanism (for reviews see: [4,212]). Among different models of chronic neurodegeneration, the usefulness of cannabinoids has been proposed for Huntington´s disease (HD), Parkinson´s disease (PF), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and Alzheimer´s disease (AD). This review will focus on the performance of cannabinoid system on Alzheimer´s disease.

The strategies or hypothesis to fight the Alzheimer disease could be clustered in two main groups, symptomatic and therapeutic strategies.

### 3.1. Symptomatic Strategies for Alzheimer´s Disease

The main symptomatic strategies could be summarised in the following lines (see reviews: [1,212,213]).

#### *Cholinergic Deficit*

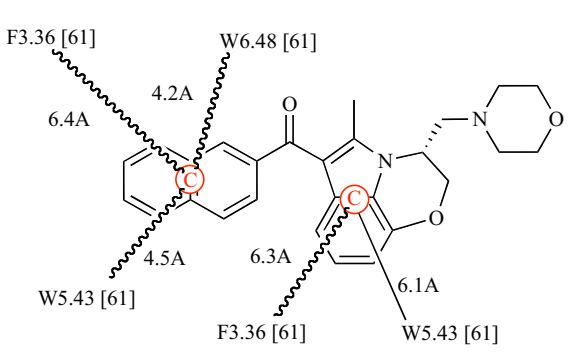
Choline acetyltransferase (ChAT) and acetyl cholinesterase AChE are involved in the synthesis and degradation of acetylcholine, respectively. The activity of the cholinergic system is reduced in AD, suggesting a selective destruction of cholinergic neurons [213-216].

#### *Inhibition of Brain Cholinesterase Activity*

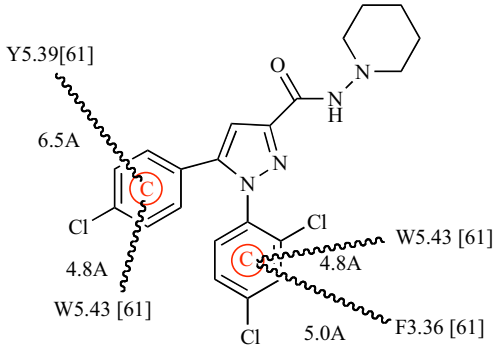
Recent evidence suggest that butirylcholinesterases (BuChE) can also hydrolyse acetylcholine in the brain and may play a role in cholinergic transmission [217-220].

#### *Glutamate Mediated Neurotoxicity*

Glutamate excitotoxicity mediated through excessive activation of NMDA receptors is believed to play a role in the neuronal death observed in Alzheimer´s disease and other neurodegenerative conditions. Glutamate represents the main excitatory neurotransmitter in the central nervous system and a physiological level of glutamate-receptor activity is essential for normal brain function [221,222].




a) WIN55212,2




b) SR1417A

**Fig. (10).** Ligand-aromatic stacking interactions of a) WIN55212,2 and b) SR1417A docked in CB1R* and CB1R respectively.

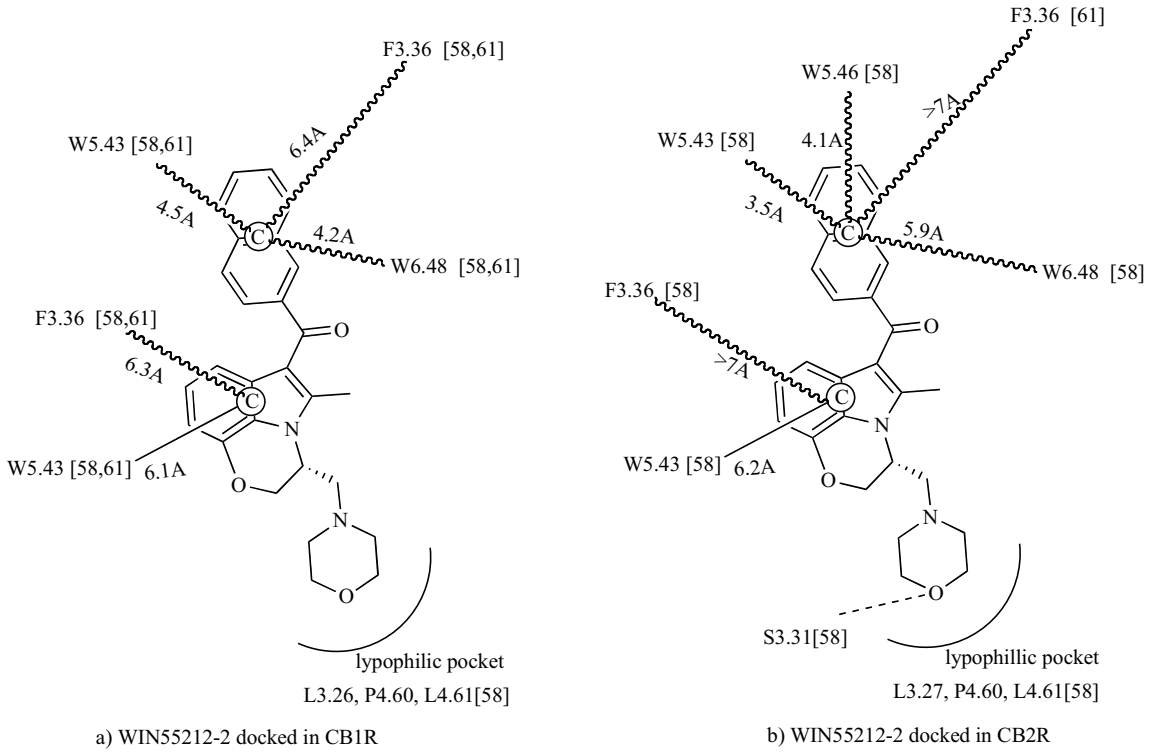



**Fig. (11).** Ligand-aromatic stacking interactions of WIN55212,2 docked in a) CB1R and b) CB2R. © means centroid.

### 2.2. Therapeutic Strategies for Alzheimer´s Disease

The characteristic neuropathological hallmarks of Alzheimer´s disease include neuritic plaques and neurofibrillary tangles (NFTs). Neuritic plaques are extracellular lesions composed of a central core of aggregate amyloid-β peptide and NFTs are intracellular bundles of filaments that are composed of tau protein in an abnormally hyperphosphorylated form. It appears that these *pseudoproteins* lesions are at the root of the pathogenesis of Alzheimer´s disease [1,212, 213].

#### *Amyloid Hypothesis*

It is believed that accumulation in the brain of β–amyloid that is produced proteolytically from the amyloid precursor protein (APP), initiates a cascade of events that originate neuronal dysfunction, neurodegeneration and dementia.

#### *Protein Tau*

Neurofibrillary lesions made up from aggregated hyperphosphorylated forms of the microtubule-associated protein tau represent a second defining neuropathological feature of Alzheimer´s disease.

### 2.3. Cannabinoid System on Alzheimer´s Disease

During the last years, interesting and elegant studies have allowed to open new perspectives in the prevention and/or treatment of AD focus on cannabinoid system (see reviews [4, 223-225].

Several *in vitro* studies in models of neuronal damage about the neuroprotective properties of endogenous and exogenous cannabinoids have been reported. Thus, Milton [226] has reported that anandamide (AEA) and noladin ether are potent inhibitors of Aβ-toxicity *in vitro* (human nervous cell line (Ntera 2/cl-D1) being effective at nanomolar concentrations. The authors concluded that these effects are exerted through a CB1-dependent, MAPK-mediated mechanism. Other reports clearly show that CB2 activation leads to an inhibition of Aβ-induced microglial activation. Ramirez *et al.* [227] demonstrated that the agonist HU-210 was capable of preventing Aβ1-40 induced changes in microglial morphology and that the HU-210, WIN55,212-2 and JWH-133 agonists significantly inhibit the microglial production of TNF-α, a known cytokine that participates in Aβ-triggered damage. Ehrhart *et al.* [228] found that the CB2 agonist JWH-015 induced a decrease in CD40 receptor expression by mouse microglial cells in primary culture after exposure to interferon-gamma and prevented the Aβ-triggered production of proinflammatory cytokines. Therefore the role of CB2 receptors on *in vitro* microglial function after exposure to Aβ seems to be confirmed. Other more recent *in vitro* studies have shown that the endocannabinoid system is highly activated during CNS inflammation and the endocannabinoid anandamide (AEA) protects neurons from inflammatory damage by CB(1/2) receptor-mediated rapid induction of mitogen-activated protein kinase phosphatase-1 (MKP-1) in microglial cells [229].

In addition to the above described CB1 and CB2-mediated effects on *in vitro* cell responses against Aβ, other non receptor mediated roles of cannabinoids have been published [230-233].

Regarding to *in vivo* studies, it has explored the role of the ECS in AD using Aβ administration directly into the CNS. Ramírez *et al*. [227] has reported that the cannabinoid agonist WIN55,212-2 prevented the cognitive impairment

induced by Aβ25-35 i.c.v. administration to Wistar rats. In addition to this, microglial activation was also prevented by WIN55,212-2 administration. It is currently well-known that microglia plays a pivotal role in the response to amyloid deposition, modulating the immunological response of the brain. It seems reasonable to think that the reported prevention of microglial activation also collaborates in the neuroprotective effect of WIN55,212-2 in this rat model of AD.

Van der Stelt *et al.* [234] show that, as in other models of brain insult [235,236], endocannabinoid levels were significantly elevated as a consequence of toxic damage to the brain, although only 2-AG levels were sensitive to Aβ1-42 administration. Interestingly, no change in CB1 receptor expression was detected 12 days after damage induction, whereas a significant increase in CB2 expression was found at that time point.

It is important to note that cannabinoids have been also reported to be beneficial in other animal models of neuroinflammation. Recently, Marchalant *et al*. [237] have shown that WIN55,212-2 decreases the microglial activation induced by chronic infusion of bacterial lipopolysaccharide (LPS). However these authors did not find any improvements in locomotor activity. In addition, cannabinoid receptors of the CB1 type were not detected in microglial or astroglial cells, being restricted the presence of these receptors to neurons and thus pointing to an indirect action of the cannabinoid agonist on LPS-treated rats.

The psychoactive properties of cannabinoid compounds have limited human studies. In relation to AD patients, their use as appetite stimulants has attracted considerable attention. One study showed a positive effect of dronabinol on body weight increase accompanied by improvements in disturbed behaviours, partially because of decreased agitation [238]. Other study reported by Walther *et al*. [239] has shown that a low dose of dronabinol was able to significantly improve several clinical parameters (such as nocturnal motor activity, agitation, etc), without undesired side effects.

However, recent data of human post-mortem brain samples from AD patients has provided information on the neuropathology of the ECS. Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively over-expressed in neuritic plaque-associated glia in Alzheimer's disease brains. Also, both CB2 receptors and FAAH enzyme are induced in Aβ plaque-associated microglia and astroglia, respectively, in Down's syndrome, sometimes referred to as a human model of Alzheimer-like β-amyloid (Aβ) deposition [88].

Fernandez-Ruiz *et al*. [225] propose three possible mechanisms of performance of CB2 receptors to neuroprotection level: 1) Up-regulation/induction of CB2 receptors in pathological brains. Although there are some evidences that indicate the presence of CB2 receptor in normal brains [35], it is clear that there is an increase of the CB2 receptors in certain brain regions after pathological neuroinflammatory damage [240]. This increase might entail either their induction in cells as reactive microglial cells [37] or the up-regulation of CB2 receptors in cells that naturally express them as astrocytes [225,240]. 2) Neuroprotective action of CB2 receptors. The neuroprotective action of CB2 receptor has been demonstrated through different *in vivo* and *in vitro* studies using CB2 receptor agonists as such HU-308 or AM1241 in different neurodegenerative disorders [240-244] except in Parkinson´s disease [240,245]. 3) Control of glial-mediated effects by CB2 receptors. The activation of CB2 receptors after brain damage would entail the reduction of generation of neurotoxic factors, such as nitric oxide, proinflammatory cytokines and reactive oxygen species by the reactive glial cell [34,225].

All this data show the CB2 receptors´ role in neuroprotective processes of the ECS by decreasing glial reactivity. The selective presence in microglial cells may be indicative of the importance of ECS in disease-associated neuroinflammatory processes. Therefore, the activation of the CB2 receptor makes it an attractive target for the development of novel anti-inflammatory therapies against different types of chronic injury of the human CNS

## CONCLUSIONS AND PERSPECTIVES

Neurodegenerative diseases are characterised by a net loss of neurons from specific regions of the central nervous system (CNS). Until recently, research has been focused on identifying mechanisms that lead to neurodegeneration, while therapeutic approaches have been primarily targeted to prevent neuronal loss. It is necessary therefore to consider that development of future drugs must consider neurogenesis.

Recent studies have demonstrated that inflammation in the CNS regulates neurogenesis, making possible that altered neurogenesis is at least partially responsible for the effects. Studies on CB2 receptor have been consistent with anti-neurotoxicity, inhibition of pro-inflammatory factor release, suppression of microglial activation, and potentially benign effects in non-reactive microglia. In addition, CB2 stimulation has recently been shown to be pro-neurogenic. Targeting the CB2 receptor to reduce neuroinflammation while stimulating neurogenesis is likely to be of particular interest, given the reduced risk of psychoactive activity and the close association of the CB2 receptor with the senile plaque. The results of these studies have shown the importance of the CB2 in Alzheimer's diseases. In this contest, the recent synthesis of CB2-selective agonist without CB1 psychoactivity effects opens an interesting therapeutic window to develop new drugs.

The importance of cannabinoid system has done that the scientific world has worked very hard trying to understand a bit more this complex system. During the past decade there has been a great growth in the knowledge of the CB2 receptor and their ligands. Several studies about structure activity relationships have been published even though the interest of these studies are more academic than practical having a limited usefulness to the design of new cannabinoids with greater diversity molecular. Studies of protein-ligand complexes are very useful for the search of new compounds with cannabinoid properties. At this moment it is necessary a major knowledge of the binding site of CB2 and the binding mode of agonist ligands CB2. Of course the major challenge would be to get the X-ray structure of CBs receptors.

It will also be important to establish the pharmacological effects of the selective cannabinoid receptor ligands at CB1

and CB2 receptors to study independent actions and their contribution to the effects *in vivo*. There is not an ideal example of selective CB1 agonist for biological and biochemical studies and therefore it would be extremely useful to develop a selective agonists CB1R, in order to understand a bit more the role played by CB2R.

It is necessary to work on the development of different chemical structures more selective at cannabinoid receptor as agonists, as well as on novel drugs of this family with better selectivity in relation to others receptors, distribution patterns, and pharmacokinetics, and in order to be able to separate the desired clinical action and the psychoactivity.

The physiological actions of endocannabinoids are mediated by cannabinoid receptors, and also by others receptors. The interplay between these endocannabinoids and related cannabinoids in the regulation of neurogenesis and inflammation is emerging as a promising future direction of research into basic neurochemical mechanisms of brain physiology and novel pharmacotherapy for treating of Alzheimer's disease.

There are, therefore, many questions yet to be answered concerning to the agonist cannabinoid and their abilities to not only interact with the receptors but to generate biological activity that can be used therapeutically in Alzheimer's disease. The time will say what will be the utility of these promising cannabinoid agonists within the therapeutic arsenal against the Alzheimer's disease.

## ACKNOWLEDGEMENTS

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## ABBREVIATIONS

| | | |
|---|---|---|
| AChE | = | Acetylcholinesterase |
| AEA | = | *N*-arachidonoylethanolamine |
| AE | = | Alzheimer's disease |
| 2-AG | = | 2-arachidonoylglycerol |
| 2-AGE | = | 2-arachidonylglyceryl ether |
| AMT | = | Anandamide membrane transporter |
| APP | = | Amyloid precursor protein |
| BuChE | = | Butrylcholinesterase |
| cAMP | = | Cyclic adenosine monophosphate |
| CB1R | = | Type 1 of cannabinoid receptor |
| CB2R | = | Type 2 of cannabinoid receptor |
| ChAT | = | Choline acetyltransferase |
| DAG | = | Diacylglycerol |
| DAGL | = | Diacylglycerol lipase |
| ELM | = | Endocannabinoids like molecules |
| ECS | = | Endocannabinoid system |
| FAAH | = | Fatty acid amide hydrolase |
| $[^{35}S]GTP\gamma S$ | = | $[^{35}S]$guanosine 5'-[gamma-thio] triphosphate |
| MAGL | = | Monoacylglycerol lipase |
| MAP | = | Mitogen-activate protein |
| NADA | = | N-arachidonoyldopamine |
| NAPE-PLD | = | N-acylphosphatidylethanolamine specific phospholipase D |
| NArPE | = | N-arachidonoylphosphatidylethanolamine |
| NFTs | = | Neurofibrillary tangles |
| SNr | = | Substantia nigra pars reticulata |
| TNF-α | = | Tumor necrosis factor-α |

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