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Monthly Focus: Central & Peripheral Nervous Systems

Recent advances in cannabinoid receptor agonists and antagonists

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This review is an overview of the recent advances in cannabinoid chemistry with a special emphasis on the patent literature. The term cannabinoid includes analogues of the natural components of cannabis, endocannabinoids and a wide array of chemical structures such as 1,5-diarylpyrazoles, indoles, quinolines and arylsulphonamide derivatives capable of acting as cannabinoid receptor agonists and antagonists. These receptors, discovered in the early nineties, seem to be involved in different biochemical processes and thus represent interesting therapeutic targets for drug research.

Keywords: *anandamide, cannabinoid receptor agonists, cannabinoid receptor antagonists, cannabinoids, CB₁, CB₂*

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1. Introduction

Cannabis has been used for medical and recreational purposes with a long history dating from 5000 BC. However, we have learnt more about cannabis in the last three decades than in all the previous centuries.

The main components of *Cannabis sativa*, or marijuana, are the cannabinoids which are tricyclic structures derived from the benzopyran system. However, the original term cannabinoids has now been extended to include other chemical substances: the so-called endogenous cannabinoids or endocannabinoids; and a wide variety of chemical entities which interact with the cannabinoid receptors CB₁ and CB₂.

The discovery and identification of two distinct cannabinoid receptors took place in 1988 and 1993 and stimulated a resurgence of interest in the medicinal chemistry of the cannabinoids. These are CB₁ [1], present in the CNS and to a lesser extent in other tissues, and CB₂ [2]. Although the CB₂ receptor is not present on central neurones it is present elsewhere mostly in peripheral tissue associated with immune functions. The cannabinoid receptors belong to the G protein-coupled superfamily of receptors which are presumed to be involved in the modulation of different functions such as memory, cognition, appetite, immune response and pain. Thus, they are interesting therapeutic targets and synthetic compounds, belonging to different chemical families, which can act as agonists and antagonists are being investigated.

The identification of a specific cannabinoid receptor in the brain suggested the existence of endogenous cannabinoids prompting different groups to

start working in this field, culminating in the identification of arachidonylethanolamide (anandamide) [3] and 2-arachidonoylglycerol (2-Ara-Gl) [4] in animal tissues.

An intensive research effort involving the academic community and the pharmaceutical industry is being devoted to both the synthetic and the endocannabinoids especially with regard to their potential therapeutic applications. These include:

- Treatment of nausea in cancer chemotherapy and anorexia of AIDS. These are probably the most established therapeutical applications of cannabinoids with two compounds, nabilone (Cesamet[®], Eli Lilly) and dronabinol (Marinol[®], United Pharmaceuticals), being commercially available in some countries.
- Neurological disorders and spinal injury symptoms such as muscle spasms and tremor. Many victims of spinal cord injuries such as paraplegia have reported for years, that their painful spasms are greatly alleviated after smoking marijuana. Very recently, a report has appeared in which cannabinoids appear to control spasticity and tremor in an autoimmune model of multiple sclerosis, the so-called CREAE (chronic relapsing experimental encephalomyelitis) [5]. It should be mentioned that, although there have been previous studies on cannabinoids and mouse models, the novelty in this report is that the authors demonstrate that the effects on CREAE are mediated by CB₁ and CB₂ receptors.
- Analgesia. This is probably the therapeutic field that has received the most attention [6]. Extensive studies at Pfizer research laboratories led to the development of a cannabinoid analgesic, nantadol (see later) which, unlike morphine, did not induce tolerance but produced a psychotropic 'high' which made it unsuitable as a prescription drug. There is also interest in anandamide as a potential peripheral analgesic and the possible role of anandamide-like compounds in inflammation since arachidonic acid is the precursor to both anandamide and prostaglandins.
- Glaucoma. It is well known that marijuana and several cannabinoids can reduce intraocular pressure [7], the problem being the extreme water insolubility of some of the compounds which renders them unsuitable for topical application.

- Vascular effects. Cannabinoids exert significant vascular effects in humans and laboratory animals, producing vasodilatation and hypotension [8].
- Malignant gliomas. A recent report [9] provides evidence for the role of cannabinoids in treating malignant gliomas, the most common class of primary brain tumour. This report is the first evidence of the *in vivo* antiproliferative effects of cannabinoids since the report of its *in vitro* effects.

Therefore, this review will focus on the cannabinoids in general, with a special emphasis on the patent literature which has appeared in the last three years and not dealt with in the previous review of this series [10]. It should be mentioned here, that general reviews [11-13] on the subject have appeared recently but do not, in general, cover the patent literature.

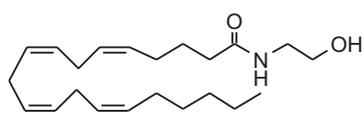
2. CB receptor agonists and antagonists

2.1 Anandamide and related fatty acid derivatives

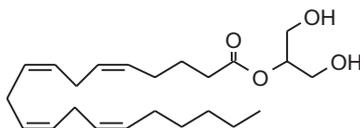
Since the discovery of anandamide (N-arachidonyl ethanolamide) (AN) (**1**) and 2Ara-Gl (2-arachidonylglycerol) (**2**) as endogenous ligands for the CB₁ and CB₂ receptors, numerous studies and derivatives of this system have been published [14,15]. In general, anandamide and its analogues exhibit modest to very low affinity for the CB₂ receptor and certain selectivity for the CB₁ receptor. Anandamide itself has only marginal CB₁ selectivity but some analogues, such as ACEA (arachidonyl-2'-chloroethylamide) and ACPA (arachidonyl cyclopropylamide), recently described [16], are potent high affinity agonists. Very recently, there has been some discussion on whether anandamide is an endogenous agonist at the vanilloid receptor (VR1) [17].

Although many derivatives and analogues have been prepared and the SARs are well established [18], some new analogues have been reported in these last years. Such is the case of arachidonylglycerols in which the carbonyl group was reduced to methylene yielding novel arachidonyl ether derivatives, such as HU-310 (**3**) patented by the University of Jerusalem and claimed to have similar *in vivo* effects to anandamide and 2Ara-Gl [101].

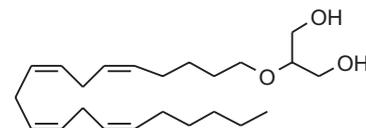
However, the search for novel analogues of anandamide has recently dealt more with metabolically stable derivatives. It is now a well-established fact that the short duration of action of anandamide,



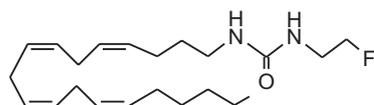
1 AN



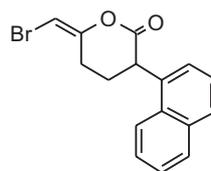
2 2-Ara-Gl



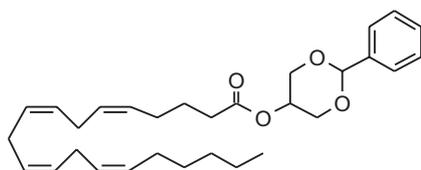
3 HU-310 [101]



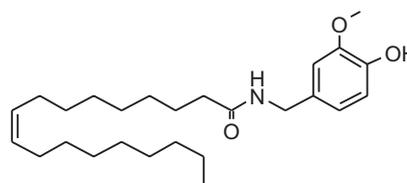
4



5 [102]



6 [103]



7 [104]

which has a more rapid onset of action but a shorter duration than Δ^9 -THC, is mainly due to the effect of two proteins: an amidohydrolase named both anandamide amidohydrolase (AAH) and fatty acid amidohydrolase (FAAH), which catalyses the hydrolysis of anandamide to arachidonic acid and ethanolamine [19]; and anandamide transporter (ANT), a carrier protein involved in the transport of anandamide across the cell membrane [20].

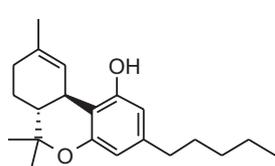
Since AAH seems to be located intracellularly, both proteins contribute to the termination of the activity of anandamide. Therefore, the focus has been centred on anandamide analogues capable of inhibiting these pathways.

Structural modifications of the ethanolamido headgroup of anandamide have been investigated [21,22] for hydrolytic stability toward anandamide amidase. These studies led to quite strict stereoelectronic requirements discussed by Razdan [22]. Some structural modifications, such as branching of the chain, enhance the enzymatic stability and in some cases, the introduction of electronic groups decreases this metabolic stability while increasing CB_1 binding affinity. A series of arachidonyl ethers and carbamates, and norarachidonyl carbamates and

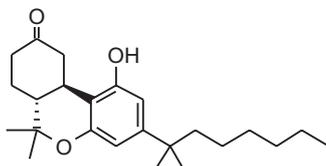
ureas have been prepared. The norarachidonyl ureas showed an interesting pharmacological profile, especially the urea analogue (**4**), twice as potent as anandamide and more stable to amidase hydrolysis than anandamide. In this context, inhibitors of rat brain AAH have been patented [102] for preventing inflammation, pain and mental diseases. (E)-6-bromoethylene-tetrahydro-3-(naphthalen-1-yl)-2H-pyran-2-one (**5**), the only compound specifically claimed, showed IC_{50} values of 0.7 and 97 μ M for rat brain and liver AAH, respectively.

Inhibitors of ANT as analgesic agents have been patented by Makriyannis [103]. Besides their use in pain relief, they are claimed to produce fewer side effects than direct activation of CB_1 agonists. Five compounds are exemplified by synthesis and the 2-phenyl-1,3-dioxan-5-yl ester of 2-Ara-Gl (**6**) is one of the three ANT inhibitors tested.

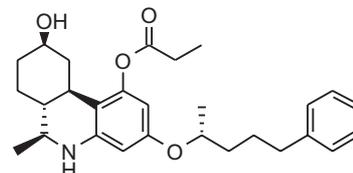
In relation to metabolically stable derivatives, the biologically relevant conformations of ANT and 2-Ara-Gl have been explored using the so-called conformational memories [23]. According to the authors, the rigid analogues may be useful in deducing the bioactive conformation of the endogenous cannabinoids, not only at the CB receptors, but



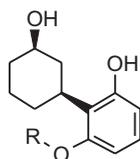
8
(-) Δ^9 -tetrahydrocannabinol
(THC, Dronabinol)



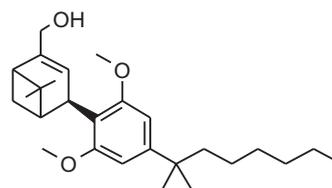
9
Nabilone



10
Levonantradol



11



12
HU-308

also at the AAH enzyme active site and at the binding site(s) of ANT.

Besides, a derivation of a pharmacophore model for anandamide using constrained conformational searching and comparative molecular field analysis has been reported [24].

Finally, a patent from InnoVet Italia has recently appeared dealing with N-acylvanillinamide derivatives of general formula **7** capable of activating peripheral CB₁ receptors. Their use in combination with a CB₂ receptor agonist is claimed to have synergistic antiproliferative activity against human breast carcinoma EFM-19 cells [104].

2.2 Classical and non-classical cannabinoids

The term classical cannabinoids refers usually to tricyclic structures which, from a chemical point of view, can be described as a terpene joined to an alkyl substituted resorcinol. However, in terms of CAS nomenclature they are benzopyran ring systems and so, Δ^9 -THC (**8**), the principal psychoactive component of cannabis, is (6a,10aR)-(-)- Δ^9 -6a,10a-*trans*-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol. Despite the variety of analogues prepared, many of which were synthesised even before the discovery of the CB₁ and CB₂ receptors, there are only two commercially available derivatives: nabilone (**9**) a synthetic cannabinoid, with a greater water solubility than Δ^9 -THC and dronabinol, the synthetic Δ^9 -THC, these compounds are used in the UK and USA as anti-emetics and appetite stimulants. On the other hand, levonantradol (**10**), a considerably modified cannabinoid structure, developed by Pfizer

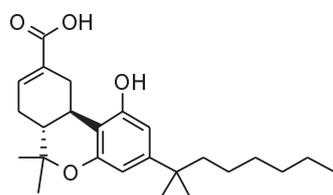
with potent analgesic activity, had to be withdrawn due to considerable psychotropic side effects.

Although the SAR of classical cannabinoids are well established [25], work in this field has continued and new derivatives have appeared. SAR studies have established that the alkyl side chain of THC plays a crucial role in the activation of the cannabinoid receptors. A QSAR analysis of Δ^8 -THC analogues has been published relating the side chain conformation to receptor affinity and pharmacological potency, the conclusion being that for optimum affinity and potency the side chain must have conformational freedom [26]. The cyclisation of the side chain to give an additional ring significantly reduces pharmacological activity [27]. Manipulation of the side chain by incorporation of double or triple bonds delineates agonists, partial agonists and antagonists revealing that it is a crucial structural feature for receptor activation [28,29].

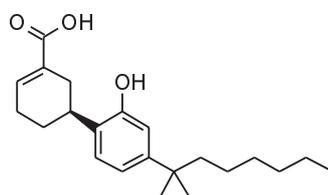
Non-classical bicyclic analogues with analgesic properties such as the phenylcyclohexanols (**11**) have been reported [30]. Mechoulam and his group have continued working in this field and have reported HU-308 (**12**), a specific agonist for the CB₂ receptor [31].

As far as the patent literature is concerned, Atlantic Pharma, who have continued work on CT-3 (**13**) [32], have patented bicyclic structures such as **14**, as anti-inflammatory agents and analgesics [105], which are claimed to be non-psychoactive compounds.

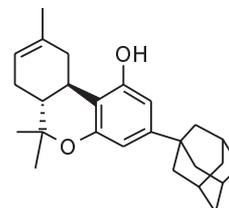
The University of Connecticut (A Makryannis) have continued to be very active in the field; two patents



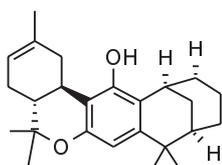
13
CT3



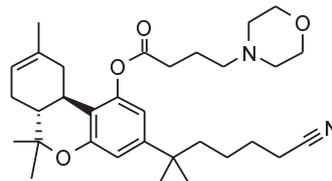
14
[105]



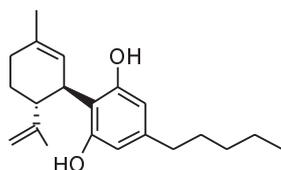
15
AM-411 [106]



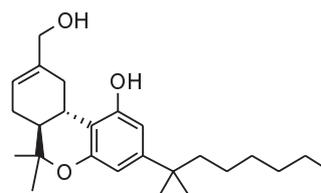
16
AM-724 [107]



17
[108]



18
Cannabidiol [111,112]



19
HU-211 (Dexanabinol) [113]

appeared in 1999. One presents novel analgesic and immunomodulatory cannabinoids, which are CB₁ or CB₂ agonists exemplified in the case of AM-411 (**15**), a Δ⁸-THC with a side chain adamantyl group [106] (with a K_i value for the CB₁ receptor of 6.9 nM and of 52 nM for the CB₂ receptor) which may be useful for glaucoma and autoimmune diseases. The other patent [107] deals with selective agonists for the CB₂ receptor claimed to have utility for autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, psoriasis or multiple sclerosis. Twelve compounds are specifically claimed, among them AM-724 (**16**).

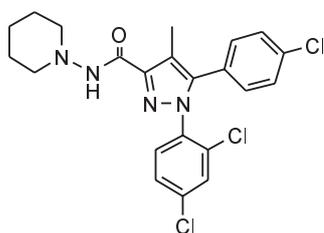
Water soluble derivatives of cannabinoids are the subject of a patent from Virginia Commonwealth University which are suitable for aqueous formulations. No characterisation data for the novel tetrahydrocannabinoids are provided and only compound **17** is specifically claimed. Its hydrochloride salt produced analgesia with an ED₅₀ of 0.02 mg/kg in mice [108].

Dronabinol has been the subject of two different patents. In one by Unimed Pharm, which involved a 12 week double-blind placebo study, the compound

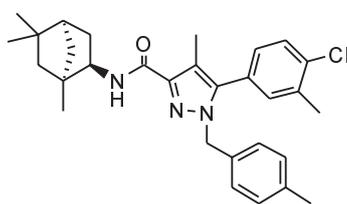
is claimed to be useful for the treatment of dementia of the Alzheimer type [109]. The other by Danbiosyst deals with compositions comprising cannabinoids in a biphasic delivery system (oil-in water or microsphere system); a novel nasal formulation of the compound is described [110].

Formulations comprising cannabinoids have also appeared and thus, the use of cannabinoids isolated from natural sources, or synthesised by previously disclosed methods, optionally in combination with a second anti-inflammatory agent, have been patented by the Kennedy Institute of Rheumatology for the treatment of anti-inflammatory diseases. Cannabidiol (**18**) is one of the two compounds specifically claimed in this patent [111]. Cannabidiol is also claimed as an anti-oxidant and neuroprotectant by the US Department of Health and Human Services [112].

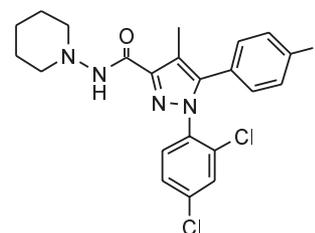
In a patent dealing with solid co-precipitates for enhanced bioavailability of lipophilic substances, dexanabinol (HU-211) (**19**) appears in one of the formulations. These solid compositions, comprising the active lipophilic compound tocopherol polyethylene glycol succinate (TPGS) and a dispersion



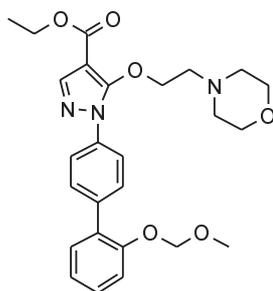
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SR141716



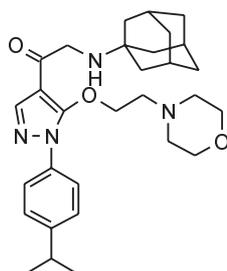
21
SR144528



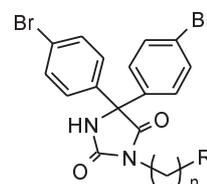
22



23
[114]



24
[115]



25 R = N(CH₂CH₂)₂O, n = 2
26 R = OH, n = 3
27 R = CH₃, n = 6

adjuvant, are claimed to have improved drug release characteristics [113].

2.3 Pyrazole derivatives

Since the discovery by researchers at Sanofi in 1994 of the first potent, selective and orally-active antagonist of CB₁, SR141716 (**20**), several 1,5-diarylpyrazoles with cannabinoid properties have been reported.

Structural modifications of SR141716 led to the first selective CB₂ antagonist. In the same way as SR141716 played a crucial role in the characterisation of the CB₁ receptor, SR144528 (**21**) represents a very useful tool to evaluate the functions of CB₂. It has been demonstrated [33] that CB₂, expressed in Chinese hamster ovary-expressing cells, is auto-activated and that SR144528 acts as an inverse agonist in this system, as does SR141716 in the corresponding CB₁ system.

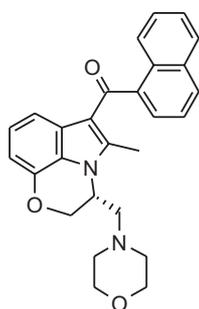
Makryannis has published an SAR study of 1,5-diarylpyrazoles [34] and the requirements for potent antagonistic activity are: a *p*-substituted phenyl ring at the 5-position, a carboxamido group at the 3-position and a 2,4-dichloro-phenyl substituent at the 1-position of the pyrazole ring. From this study, the most potent pyrazole corresponds to the 4'-iodine derivative (**22**) of SR141716. This result is in agreement with a comparative receptor binding analysis of a series of alternatively halogenated analogues of SR141716 [35]. According to the authors,

substitution of a 4'-chlorine by a 4'-iodine seems to increase affinity and alter selectivity of binding.

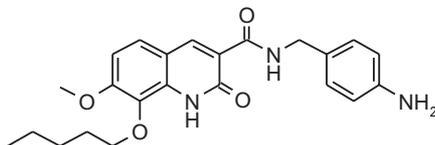
Two new patents have appeared from SmithKline Beecham [114,115]. In the first one, novel 1-phenyl-5-(morpholinylethoxy)pyrazole-4-carboxylic acid derivatives (**23**) are described as antagonists of the CB₂ receptor and their use for treating immunological inflammatory diseases and arthritic disorders is claimed. The second one deals with novel substituted pyrazoles **24** as cannabinoid agonists (for the first time, usually antagonists) and their use for the treatment of immunologically mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and osteoporosis (amongst others).

Some new derivatives have also appeared in the literature. Interestingly, 3-alkyl-(5,5'-diphenyl)imidazolidinediones [36] have been reported, which were designed taking into account the structural features of diarypyrazoles and aminoalkylindoles. Compounds **25** - **27** had K_i values of ~ 100 nM against [³H]-SR141716 binding obtained from human CB₁ transfected Chinese hamster ovary cells membranes.

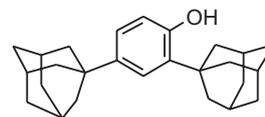
The lead compound SR141716 has continued to be the subject of different studies including patents from Elf-Sanofi [116]. The use of compositions comprising a CB₁ antagonist (SR141716) and a β₃ adrenergic receptor agonist for eating disorders is claimed. Two other patents [117,118] disclose two different



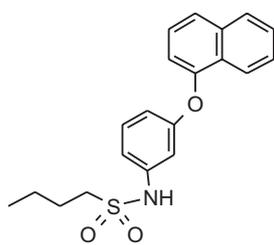
28
WIN 55212-2



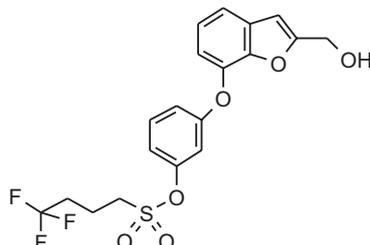
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[121]



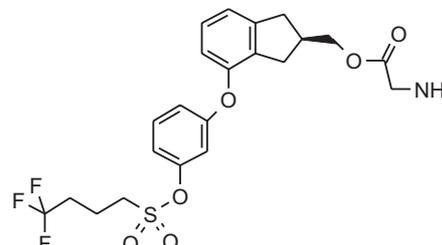
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[122]



31
[123]



32
[124]



33
[125]

pharmaceutical compositions for oral administration of the compound useful for the treatment of psychosis. In another patent from Virginia Commonwealth University [119] the use of SR141716 for cardiovascular purposes is claimed.

2.4 Miscellaneous structures

While working on analogues of the analgesic pravadoline, researchers at Sterling discovered that 1-aminoalkylindoles (AAI) had affinity for the brain CB₁ receptor. The most interesting compound of the AAI series is WIN-55212-2 (**28**), which shows high affinity for both CB receptors with a slight selectivity for CB₂ over CB₁.

In these two last years no patents dealing with this class of cannabimimetics have been found, although the AAIs encouraged the synthesis of related structures such as pyrroles and indenes (recently reviewed [37]).

There is however, a patent from Bayer [120] dealing with CB₁ agonists for treating and preventing neurodegenerative diseases. No synthetic details or chemical data are presented but WIN52212-2 is one of 38 compounds specifically claimed.

A high resolution 2D NMR and computer modelling study providing detailed information on the conformation of WIN52212-2 has been published [38]. A molecular modelling study has been reported which strongly supports the higher affinity of WIN-52212 for CB₂ over the CB₁ receptor [39].

Concerning other heterocyclic structures, Japan Tobacco has continued work in the cannabinoid field and has patented quinoline derivatives having both agonist and antagonist activity at the CB receptors and so claimed for the treatment of autoimmune diseases and, additionally, as the active component of immunomodulators [121]. Quinoline (**29**) is an example of the four compounds claimed.

A method of modulating a cannabinoid receptor using 2,4-*bis*(adamant-1-yl)phenol (**30**) is claimed in a patent by SmithKline Beecham [122] and the affinity of the compound for CB₁ and CB₂ receptors was studied (K_i values ranging from 1 - 10 nM).

A new class of synthetic cannabinoids, arylsulphonamide derivatives, have been disclosed in three patents by Bayer. In an extensive patent [123], 309 compounds are disclosed, 33 specifically claimed, one example being the naphthyloxyphenyl

butanesulphonamide **31**. These are claimed to be CB₁ agonists and useful for treating and preventing neurodegenerative diseases. The other two patents [124,125] describe novel arylsulphonamide derivatives claimed to act as highly potent agonists at the CB₁ receptor and some are additionally active at the CB₂. The structures disclosed are exemplified by **32** and **33** and both have in common a trifluorobutylsulphonyloxyphenoxy chain linked to different heterocyclic rings benzofurane and indene.

3. Expert opinion

Since the renewed interest in the cannabinoid field, which occurred with the discovery of the two receptors CB₁ and CB₂ and the endogenous system, cannabinoid research has continued to develop. However, the important advances in the biochemical aspects have not, in general, been paralleled by development in the synthetic and therapeutic area.

Apart from some new compounds such as arylsulphonamides and quinolines patented by Bayer and Japan Tobacco, not so many completely novel chemical entities have appeared these last years.

Several of the recent patents deal with newer formulations or applications of existing cannabinoids or with the synthesis of new derivatives of well established cannabinoids such as the 1,5-diaryl-pyrazoles structures.

In the endocannabinoid field, patents dealing with inhibitors of AAH and ANT, as already mentioned, are worth noting.

The potential therapeutic applications, of which some examples have been given, are sometimes observations from marijuana consumers and remain to be confirmed by multicentre studies. Some ongoing research in this field is already in progress.

There are only two commercially available cannabinoids on the market: dronabinol and nabilone, the use of the latter as anti-emetic has declined with the introduction of compounds such as Glaxo Wellcome's ondansetron.

The introduction of new cannabinoid drugs will be conditioned and limited by several issues:

- Clinical trials: the placebo-controlled trials are more complicated in these cases due to the psychoactive nature of some of the compounds.

- The modes of administration and dosage forms, especially in the case of the natural cannabinoids: for example, taken orally, Δ^9 -THC seems to undergo variable absorption and it is difficult to establish an oral dose that will be effective without producing significant unwanted effects [40]. Therefore, there is a need to investigate better cannabinoid formulations and modes of administration.
- Legal wrangles: there has always been great debate concerning the legalisation of marijuana for medical use, and research in cannabinoids has sometimes been hampered by the stigma attached to this kind of drug.
- Cannabinoid receptor subtype selectivity: despite all other issues mentioned above, the most important limiting factor in cannabinoids research is the receptor subtype selectivity. CB₁ receptors are the main target associated with undesirable psychotropic effects and so selective CB₂ ligands may represent the key to future research in this field. However, many cannabinoids bind to both receptors showing only slight selectivity over one or other subtype and there are few examples of real selective ligands.

Nevertheless, the future of cannabinoids is promising. Research in this area will continue to open many new possibilities and, very likely, the study of the receptors and pharmacophores, aided by molecular modelling techniques, will provide useful tools for the design of new selective ligands.

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