REVIEW

Medicinal Chemistry Endeavors around the Phytocannabinoids

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Over the past 50 years, a considerable research in medicinal chemistry has been carried out around the natural constituents of *Cannabis sativa* L. Following the identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) in 1964, critical chemical modifications, *e.g.*, variation of the side chain at C(3) and the opening of the tricyclic scaffold, have led to the characterization of potent and cannabinoid receptor subtype-selective ligands. Those ligands that demonstrate high affinity for the cannabinoid receptors and good biological efficacy are still used as powerful pharmacological tools. This review summarizes past as well as recent developments in the structure–activity relationships of phytocannabinoids.

1. Introduction. – Despite the wide uses of preparations of the hemp *Cannabis sativa* L. during the History, the modern pharmacology of natural cannabinoids has been hampered by the slow progress in the elucidations of the chemical structures of its major components. Indeed, it is nowadays known that more than 70 compounds derived from a diterpene structure are present in the plant [1], and this fact may explain the difficulty to obtain pure chemical entities in the past. In addition, the medicinal research for more than a half century has been driven by the search for the components responsible for the psychoactive effects of cannabis, this era in the history of the chemical research on cannabinoids have been recently reviewed [2][3]. Natural compounds such as cannabidiol (**1**; CBD; *Fig. 1*) and cannabinol (**2**; *Fig. 1*) have been isolated and investigated chemically in the early 1940s [4][5]; however, the correct structure of cannabidiol was only reported in 1963 [6]. None of these two compounds was responsible for the psychoactive effects of the plant. The largely awaited isolation and elucidation of the structure of the main psychoactive constituent from the leaves of *Cannabis sativa* L. came in 1964 when *Gaoni* and *Mechoulam* [7] identified the Δ^9-tetrahydrocannabinol structure (**3**; Δ^9-THC; *Fig. 1*) and later its absolute configuration [8]. Two different numbering systems are used in the benzopyran ring of Δ^9-THC (*Fig. 2*). Thus, according to the authors, the main psychoactive agent can be termed either Δ^9-tetrahydrocannabinol or Δ^1-tetrahydrocannabinol, two names for a single molecule depending of the system used for the numbering for dibenzopyran and monoterpenoid systems, respectively. Its *IUPAC* name is *(6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol.*

Until the eighties, the term '*cannabinoids*' represented by definition the group of typical diterpenic C_{21} compounds present in *Cannabis sativa* L., their carboxylic acids,

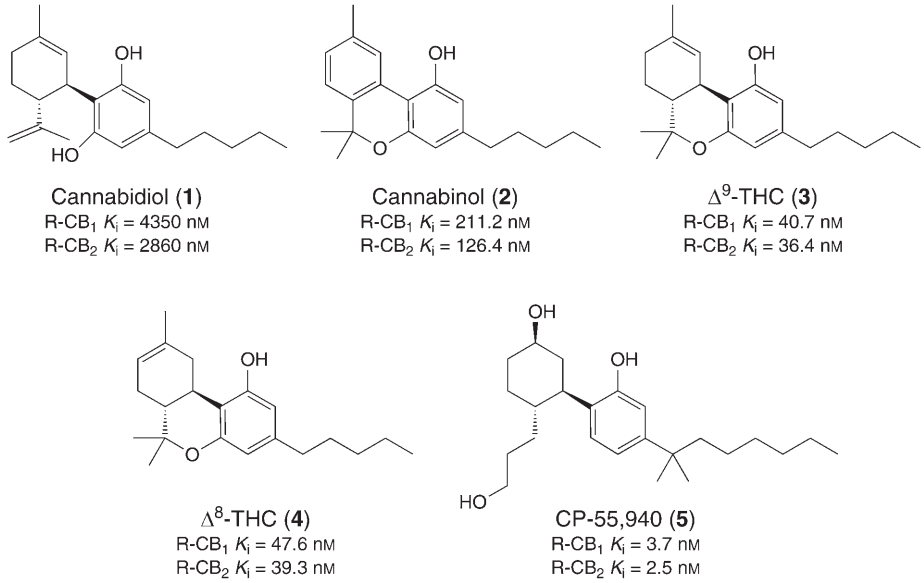


Fig. 1. *Structures of cannabidiol* (**1**), *cannabinol* (**2**), *Δ⁹-THC* (**3**), *Δ⁸-THC* (**4**), *and CP-55,940* (**5**)

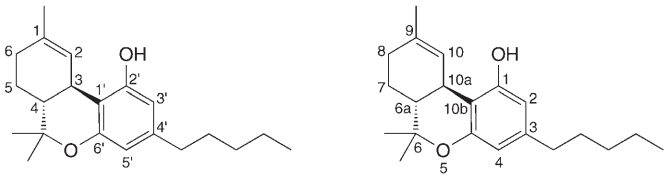


Fig. 2. *Numbering system for* **3** *using monoterpenoid* (left) *or dibenzopyran* (right) *systems yielding to Δ¹-THC and Δ⁹-THC, respectively.* The latter is the most commonly used.

analogs, and transformation products. They are now sometimes termed phytocannabinoids, as 'cannabinoids' represent now the whole set of endogenous, natural, and synthetic ligands of the cannabinoid receptors, belonging to a wide variety of chemical families.

Between the elucidation of the major psychoactive ingredient and the first clues of its molecular target [9–11] – the CB_1 cannabinoid receptor – almost 20 years elapsed. The cloning of the CB_1 cannabinoid receptor by *Matsuda et al.* [12] finally provided a consensual target for the psychoactive effect of Δ^9-THC. During this long period, the cannabinoid character of a compound was assessed through a panel of *in vivo* assays. Even if some *in vitro* assays have been developed, the absence of cannabinoid antagonists also hampered significant progress in the molecular pharmacology of the phytocannabinoids [13]. Behavioral *in vivo* assays for cannabinoid activity were used, initially with the dog ataxia test [14] and with the characterization of overt changes in

behaviors in rhesus monkeys [15]. But the most widely used set of assays was the '*cannabinoid tetrad*' test [16]. This assay comprised four different behavioral tests performed mostly in mice: diminution of temperature (hypothermia), immobility in a multiple photoelectric cell chamber (diminution of locomotion), a ring test or bar test (catalepsy), and hot-plate or tail-flick tests (analgesia). Albeit each test *per se* is rather unspecific, a positive response in all four tests was the criteria to consider any compound as cannabinoid [16]. Nowadays, the observed effects in the 'cannabinoid tetrad' are attributed to the CB_1 cannabinoid receptor activation. In a large compilation back in 1986, thus before the availability of a radioligand and the ultimate demonstration *via* the cloning of the existence of cannabinoid receptors, *R. K. Razdan* analyzed the structure–activity relationships (SAR) of *ca.* 300 cannabinoid analogues and/or metabolites based in the activity in typical animal models [17]. One of the key contributions regarding the receptor-mediated effects is due to *Allyn Howlett* who demonstrated during the eighties the regulation by cannabinoids of cAMP levels through adenylate cyclase inhibition. In a set of three papers, biochemical evidences have been reported that cannabinoids (Δ^9-tetrahydrocannabinol and levonantradol) inhibited the adenylate cyclase activity through the recruitment of Gi-type proteins. In the first paper [9], Δ^9-tetrahydrocannabinol and levonantradol were found to decrease initial levels of cAMP on prostanoid-stimulated neuroblastoma cells, hypothesizing that cannabinoid drugs may act through a receptor associated to adenylate cyclase inhibition. Then, using the membranes of cultured neuroblastoma cells, the cannabinoid inhibition of adenylate cyclase was found to be concentration-dependent, rapid, reversible, and sensitive to GppNHP – a nonhydrolyzable analogue of GTP – and to forskolin, an allosteric stimulator of adenylate cyclase [10][18]. Finally, the requirement for a functional receptor coupled to Gi protein has been assessed with the use of pertussis toxin, which induces the ADP ribosylation of Gi [11].

The existence of cannabinoid receptors was confirmed in 1988 when an open analogue of Δ^9-THC, the *Pfizer* compound CP-55,940 (**5**; *Fig. 1*), was made available [19]. This compound is less lipophilic than Δ^9-THC and, upon tritiation, was used as the first probe of cannabinoid receptors by competitive binding assays [20][21]. It still remains a widely used radioligand, among others developed and/or commercially available (*Table 1*). Two years after the discovery of the CB_1 cannabinoid receptor, *Sean Munro et al.* deorphanized one of their GPCR clones as the CB_2 cannabinoid receptor [30]. This receptor was first described as a peripheral GPCR receptor, mainly expressed in the immune system; however, it appears nowadays that the situation is more complex, as CB_2 receptor expression was reported in the brain, not only in cells derived from the immune system, but also in neurons [31]. Pharmacological evidences and double knock-out CB_1/CB_2 mice suggest that additional cannabinoid receptors might exist. Among them, some orphan receptors (GPR35, GPR55, GPR119) have been reported to bind the endocannabinoids or close endogenous analogues [32–35]. At the time of writing this review, it is still too early to clearly claim that Δ^9-THC or other phytocannabinoids are able to bind these targets, as only partial informations mostly in an abstract or patent form are available.

2. Medicinal-Chemistry Variations around Phytocannabinoids. – To date, among the phytocannabinoids discovered, Δ^9-THC remains the main compound in terms of

Table 1. *Structures,* K_d *Values, and Functionality of Some of the Most Used Cannabinoid Radioligands*

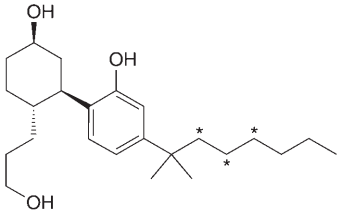
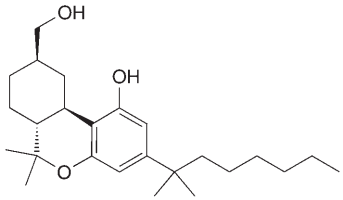
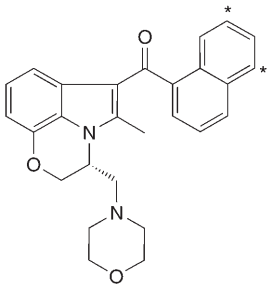
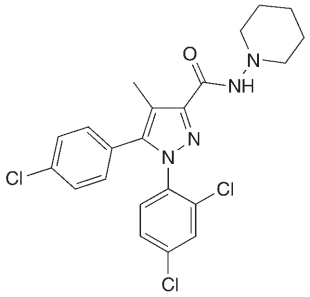
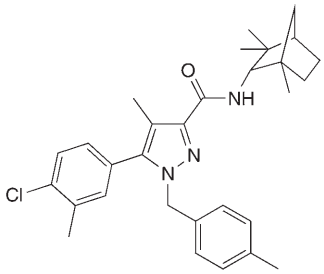
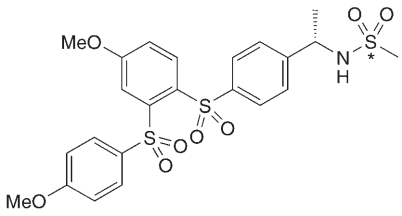
Compound		Ref.	K_d (CB_1) [nM]	K_d (CB_2) [nM]	Functionality
CB_1/CB_2 Radioligands:					
	[^{3}H]-CP-55,940	[19]	0.4–3.3[a])	0.2–7.4[a])	Agonist
	[^{3}H]-HU-243	[23]	0.045[b])	0.061 [b])	Agonist
	[^{3}H]-WIN-55,212-2	[25]	16.2[a])	3.80[a])	Agonist
CB_1 Selective Radioligands:					
	[^{3}H]-SR-141716A	[26]	1.13[c])	–	Inverse agonist/ antagonist

Table 1 (cont.)

Compound	Ref.	K_d (CB_1) [nM]	K_d (CB_2) [nM]	Functionality
CB_2 Selective Radioligands:				
 [^{3}H]-SR-144528	[28]	–		Inverse agonist/ antagonist
 [^{35}S]-Sch225336	[29]	–	0.065–0.13[d])	Inverse agonist

[a]) Data from [22]. [b]) Data from [24]. [c]) Data from [27]. [d]) Data from [29].

affinity for the cannabinoid receptors. The affinity and functionality data obtained with this compound are summarized below (*Table 2*).

2.1. *Side-Chain Structure–Activity Relationships of Δ^9- and Δ^8-THC*. Based on the monoterpenoid numbering system, Δ^9-tetrahydrocannabinol (Δ^9-THC) was first described by *Gaoni* and *Mechoulam* [7] as Δ^1-THC. The other physiologically active isomer, Δ^8-THC (**4**; alternative name Δ^6-THC) is only found in a few varieties of the plant. This compound was found in a burial tomb dating few centuries B.C. providing the first scientific evidence of cannabis use [48]. As further discussed below, Δ^8-THC (**4**) presents a higher chemical stability compared to Δ^9-THC, explaining its presence in the tomb. Other two isomers with a 6a,10a-*cis* ring junction are *cis*-Δ^9-THC and *cis*-Δ^8-THC; both have been synthesized and are relatively inactive [49], but, so far, only the former has been found in the plant. As expected, the *trans*-isomers are thermodynamically more stable than the *cis*-compounds. In the *trans*-series, the Δ^8-THC is more stable than Δ^9-THC, since the latter is easily isomerized to its Δ^8-isomer upon acid treatment. These two compounds are almost equipotent in terms of cannabinoid-receptor recognition as shown by their respective affinities for CB_1 and CB_2 receptors (Δ^9-THC, R-CB_1 K_i = 40.7 nM, R-CB_2 K_i = 36.4 nM; Δ^8-THC, R-CB_1 K_i = 47.6 nM, R-CB_2 K_i = 39.3 nM) [13].

Changes of the pentyl group of natural cannabinoids led to wide variations in affinity, selectivity, and potencies for the cannabinoid receptors. It is now well

Table 2. *Functionality of Δ⁹-THC in Different Cell and Tissue Preparations from Mouse, Rat, and Human Origins*

Cell or tissue type[a])	Assay	Function	Ref.
mCB_1 (brain)	[^{35}S]-GTPγS Binding	Partial agonist	[36][37]
rCB_1 (COS cells)	cAMP Accumulation	Fairly active agonist[b])	[38]
rCB_1 (CHO cells)	cAMP Accumulation	Agonist	[12]
rCB_1 (cerebellum)	[^{35}S]-GTPγS Binding	Partial agonist	[39]
rCB_1 (cerebellum)	[^{35}S]-GTPγS Binding	Partial agonist	[40]
rCB_1 (cerebellum)	[^{35}S]-GTPγS Binding cAMP levels	Partial agonist	[41]
rCB_1 (cerebellum)	[^{35}S]-GTPγS Binding	Partial agonist	[42]
rCB_1 (cerebellum)	[^{35}S]-GTPγS Binding	Partial agonist	[43]
hCB_1 (CHO cells)	cAMP Accumulation	Partial agonist[c])	[44]
hCB_1 (SF9)	[^{35}S]-GTPγS Binding	Partial agonist	[45]
mCB_2 (CHO cells)	cAMP Accumulation	Agonist	[46]
hCB_2 (CHO cells)	cAMP Accumulation	Antagonist	[38]
hCB_2 (COS cells)	cAMP Accumulation	Antagonist	[38]
hCB_2 (CHO cells)	cAMP Accumulation	Partial agonist	[47]
hCB_2 (CHO cells)	[^{35}S]-GTPγS	Inverse agonist	[42]

[a]) Abbreviations: m, mouse; r, rat; h, human. [b]) In the study of *Bayewitch et al.* [38], the effect of Δ⁹-THC was not compared to other cannabinoids, so the maximal inhibition is not known. [c]) Not stated as such in [44] but evidenced when compared to maximal inhibition values obtained with CP-55,940.

established that this alkyl side chain at C(3) represents the most critical pharmacophoric group [13][50]. That is why most of the medicinal-chemistry work is focused on this chemical moiety.

In a general manner, decreasing the length of the pentyl side chain of both Δ⁹- and Δ⁸-THC results in a reduction of potency (*i.e.*, propyl at C(3) reduces potency by 75%) [17], while increasing the side-chain length to hexyl, heptyl, or octyl provides a systematic increase in affinity (with K_i values ranging from 41 to 8.5 nM) and potency [51]. Interestingly, varying the chain length led to the characterization of agonists, partial agonists or antagonists. For example, the propyl analog, also named tetrahydrocannabivarin (**6**; *Fig. 3*), is an antagonist of both CB_1 and CB_2 cannabinoid receptors with respective K_i values of 75.4 and 62.8 nM) [52].

The effect of side-chain branching was also explored for different side chains in THCs. First modulations led to the introduction of a steric bulk with two methyl groups at C(1) and C(2) of the alkyl side chain. In 1948, *Adams Jr. et al.* already found that 1′,2′-dimethylhexyl side chain of the Δ^{6a,10a}-THC analog greatly increased the potency. The eight stereoisomers arising from these three stereogenic centers were tested as a mixture. The branching provides an increased potency in the Δ⁸-THC series [53]. Each of these eight stereoisomers was later individually synthesized, and pharmacological studies showed that only two of them were very potent [54]. This branching was next realized on Δ⁹-THC and Δ⁸-THC [55][56]. This substitution pattern of the side chain introduces two additional stereogenic centers. Although all four stereoisomers are very potent cannabinoids ligands, the (1′*S*,2′*R*)-isomer **7** possesses the highest affinity for the CB_1 cannabinoid receptor [57].

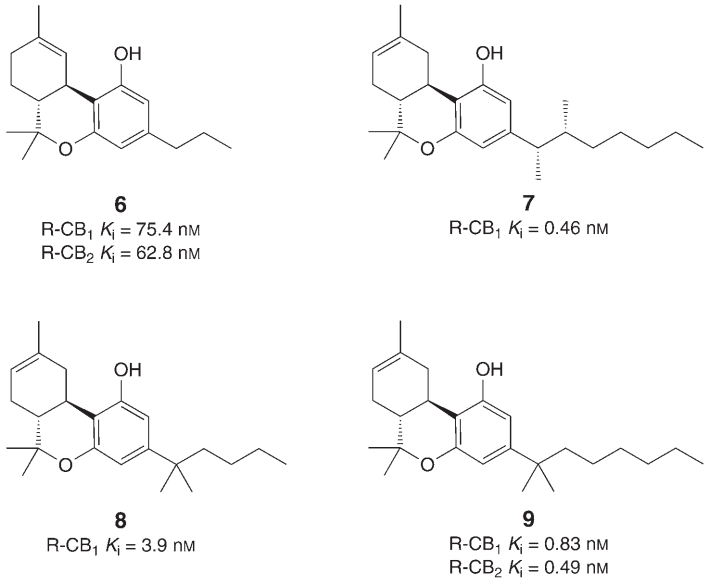


Fig. 3. *Structures of tetrahydrocannabivarin* (**6**), *1′,2′-dimethylheptyl-Δ⁸-THC* (**7**), *1′,1′-dimethylpentyl-Δ⁸-THC* (**8**), *and 1′,1′-dimethylheptyl-Δ⁸-THC* (**9**)

1′,1′-Dimethyl-branched derivatives (*i.e.*, 1′,1′-dimethylpentyl and 1′,1′-dimethylheptyl derivatives, **8** and **9**, resp.) were next investigated by *Huffman et al.* [57]. This structural modification also induced an increase in affinity, for example **9** (K_i (CB_1) = 0.83 nM) was approximately equipotent to **7** (K_i (CB_1) = 0.46 nM) [50]. The stereochemical features of an alkyl substituent on the alkyl side chain were further explored in a series of compounds bearing only one methyl group at either the C(1′), C(2′), C(3′), or C(4′) of the side chain [58]. Only C(1′) and C(2′) analogs exhibited greater affinities than Δ^8-THC. Of the two C(1′)-methyl isomers, the (*R*)-isomer exhibited higher CB_1 affinity (K_i (CB_1) = 7.6 nM) compared with the (*S*)-isomer (K_i (CB_1) = 20 nM) [58]. From all these results, both factors, branching site and configuration within the chain, clearly influence the affinity and potency of cannabinoids. As the 1′,1′-dimethylheptyl branching in the side chain leads to a significant improvement in affinity and potency of cannabinoids, this modification has been extensively found during the exploration of other pharmacophores in classical, non-classical, and hybrid cannabinoids [59].

To further examine the ligand-binding pocket of the cannabinoid receptors, analogs constrained on the side chain were also synthesized and tested (*Fig. 4*). A significant degree of conformational restriction can be imposed by introducing unsaturations such as double or triple bonds. Rigidification induced variable effects on CB_1 affinities and efficacies. Introduction of a C=C or a C≡C bond at C(1′) (**10**) and C(2′) position of the side chain results in a greater affinity for both cannabinoid receptors [60–62]. Interestingly, analogs bearing a triple bond at C(2′) and a polar moiety at the terminal C-atom of the side chain exhibited high affinities for cannabinoid receptors (*i.e.*, O-823

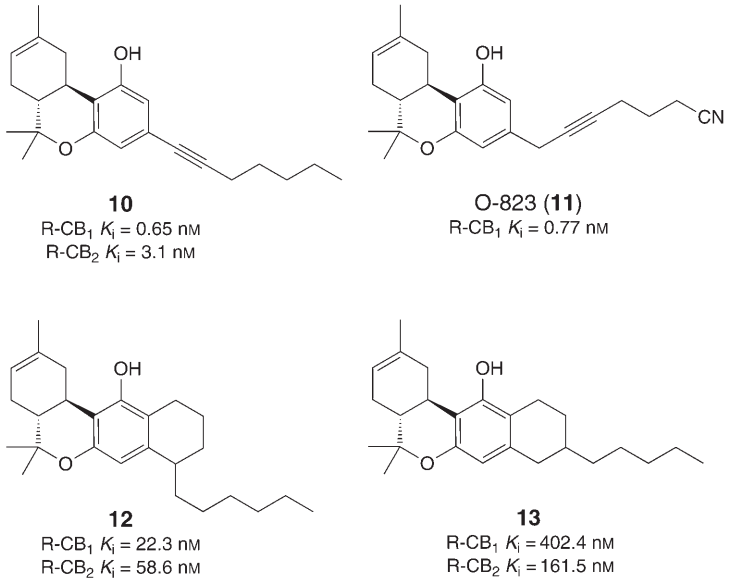


Fig. 4. *Examples of side-chain modification in the structures of analogues of Δ⁸-THC*

(**11**)); however, they behave either as partial agonists or antagonists compared to Δ^8-THC [51][63][64]. Some tetracyclic analogues of Δ^8-THC were also prepared [65]. On the basis of the affinity of analogues **12** and **13**, in which the alkyl side chain is fused as a fourth cyclohexyl ring to the phenolic ring, it has been suggested that the cannabinoid receptor affinities decreased significantly when the side chain is forced into a lateral orientation and further away from the phenolic ring.

The next step in the SAR establishment with respect to the alkyl side chain was the study of effects generated by introduction of various substituents (*Fig. 5*). Introduction of a bulky halogen substitution (Br, I) at the terminal C-atom produced a marked effect as illustrated by the 5′-bromo-1′,1′-dimethylpentyl Δ^8-THC (AM087, **14**), which exhibited an affinity of 0.43 nM for the CB_1 cannabinoid receptor [66–68]. These compounds, and especially the 5-fluorinated Δ^8-THC, constituted important tools for the localization of cannabinoid receptors in primate brain by positron imaging (PET) [69]. One of the most interesting features of the side-chain substitution was the synthesis of water-soluble analogues of Δ^8-THC. Addition of an 1*H*-imidazol-1-yl moiety (O-2545, **15**) or a morpholino moiety (O-3226, **16**) on the 1′,1′-dimethylpentyl side chain did not affect the affinity, as these compounds exhibited 1.3 and 2.8 nM affinities for the CB_1 cannabinoid receptor, and 0.12 and 1.0 nM for the CB_2 cannabinoid receptor, respectively [70].

It is now well-established that introduction of a dimethylalkyl side chain resulted in increased affinity. These results suggested that introduction of bulky substituents enhanced the affinity of the CB receptor ligands (*Fig. 6*). To evaluate this hypothesis, *Papahatjis et al.* have synthesized different 1′,1′-dimethylheptyl-Δ^8-THC analogs, in which the methyl substituents were included in three- and six-membered heterocyclic

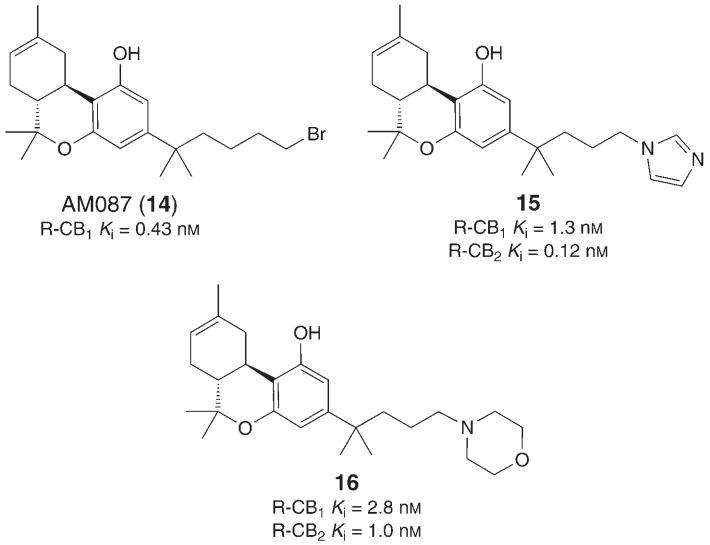


Fig. 5. *Examples of Δ^8-THC side-chain substitution*

or carbocyclic rings [61][71–73]. One of the most potent compounds was the *C(1′)*-spiro-dithiolane analog (AMG3, **17**) exhibiting 0.32 and 0.52 nM affinities for CB_1 and CB_2 cannabinoid receptors, respectively. These data showed that the CB receptor binding sites seem to be able to accommodate bulky substituents at C(1′) of Δ^8-THC, thus novel analogs carrying various aromatic/aliphatic substituents have been developed (*Fig. 6*). Interestingly, modification of the size of the cycloalkyl substituents at C(1′) of the side chain resulted in potent but non-selective ligands (*i.e.*, **18**) [74]. *Krishnamurthy et al.* later reported that replacement of the cyclohexyl moiety of **18** by a phenyl moiety, leading to the compound **19**, results in an enhanced selectivity for the CB_2 receptor [75]. Recently, *Papahatjis et al.* have described novel Δ^8-THC analogs characterized by the presence of an aromatic moiety directly linked to the tricyclic template of classical cannabinoids [76]. These compounds, represented here by **20**, are potent but non-selective cannabinoid receptor ligands. These data highlighted the possibility of introducing bulky substituents directly on the tricyclic moiety. This observation was supported by the adamantyl-cannabinoid analogues recently described by *Lu et al.* [77]. These compounds are characterized by the presence of a bulky adamantyl substituent at C(3) of the Δ^8-THC (*i.e.*, AM411, **21**; AM729, **22**). More recently, oxaza-adamantyl cannabinoids have been published by *Le Goanvic* and *Tius*, but affinities for both CB_1 and CB_2 cannabinoid receptors have not been reported yet [78]. More original analogues have also been described as AM724 (**23**), which is characterized by a very bulky bicyclo[3.3.1]nonane moiety [79]. This compound exhibits a very strong selectivity for the CB_2 cannabinoid receptor subtype. In 2000, *Huffman et al.* have described the pharmacology of a novel pentacyclic analog of Δ^8-THC (**24**) [80]. This compound combines structural elements of a classical cannabinoid and cannabimimetic indoles.

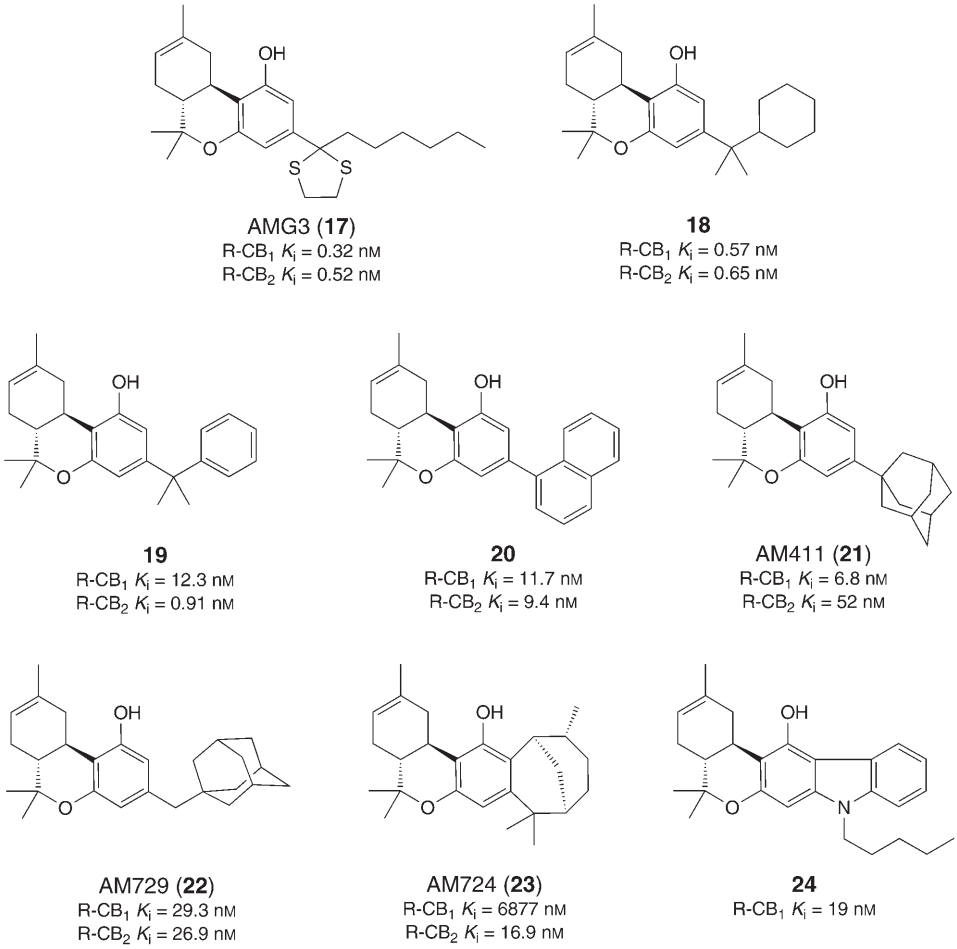


Fig. 6. *Examples of bulky substituted analogues of Δ^8-THC*

2.2. *Ring Opening.* Ring opening is found in Nature, as cannabidiol is one of the phytocannabinoids. It received these last years considerable interest, as it does not exhibit psychomimetic properties (see in this issue the contribution by *Mechoulam et al.* entitled '*Cannabidiol – Recent Advances*' [81]). In addition, a synthetic derivative named 'abnormal cannabidiol' [82], (−)-4-(3,4-*trans*-*p*-mentha-1,8-dien-3-yl)olivetol (**25**; *Fig. 7*) has been recently highlighted, as it acts on a GPCR receptor, which has been, some years ago, presented as a new endothelial target for cannabinoids [83] and often cited as the 'CB_3' receptor [84].

Apart cannabidiol derivatives, pure synthetic compounds often called non-classical cannabinoids are characterized by an opened ring. The historical prototype of this family is CP 55,940.

2.2.1. *Cannabidiol Derivatives.* Although the alkyl side chain of Δ^8-THC represents the most accessible site for pharmacomodulations, various studies have been carried

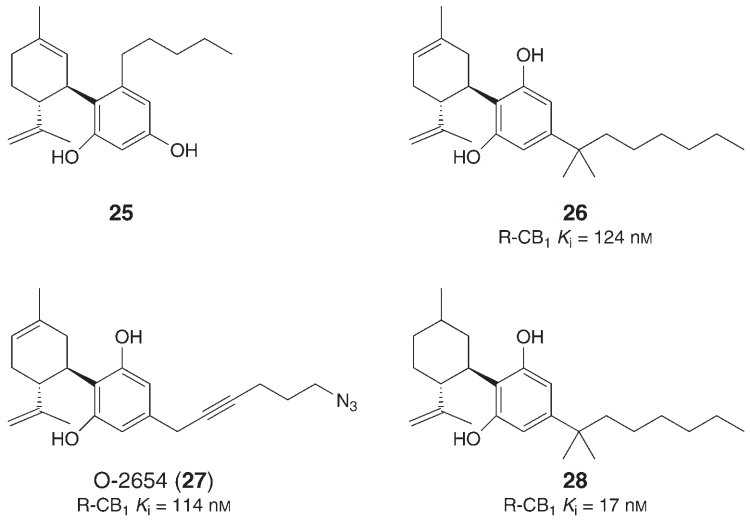


Fig. 7. *Examples of abnormal cannabidiol and cannabidiol analogues*

out on the tricyclic nuclei leading to the non-classical cannabinoids. These compounds generally resulted from the opening of the pyran ring of Δ^8-THC. This modification led to the cannabidiol derivatives. Although cannabidiol is the most abundant non-psychotropic phytocannabinoid, it has received considerably less attention than Δ^9-THC, even if, recently, a renewal of interest appears in the literature for this compound. Unlike Δ^9-THC and its analogs, cannabidiol does not bind with a high affinity to the known cannabinoid receptors, and hence has no psychotropic activity [85]. However, some structural modulations led to the characterization of various derivatives, as dimethylheptylcannabidiol (**26**) or O-2654 (**27**) that bind to the cannabinoid receptors [86]. Very recently, various hydrogenated analogues of cannabidiol, *e.g.*, **28**, have been published and evaluated as anti-inflammatory agents [87].

2.2.2. *Non-Classical Cannabinoids.* During a decade starting in 1984, scientists at *Pfizer* developed a program aiming at discovering new antinociceptive agents derived from classical cannabinoids. New analogs lacking the dihydropyran ring of Δ^9-THC were developed based on 9-nor-9β-hydroxyhexahydrocannabinol (**29**; *Fig. 8*), a synthetic tricyclic benzopyran derivative known from the seventies to retain the analgesic properties of **3** [88].

CP-47,497 (**30**; *Fig. 8*), an *AC*-bicyclic compound, was disclosed in 1984 [89], its synthesis and *in vivo* pharmacological profile in different rodent analgesic models were described. Two close analogs, the corresponding ketone and the axial alcohol, were found less active in the battery of pain assays.

Further pharmacomodulations gave the *AC*-bicyclic and *ACD*-tricyclic cannabinoid analogs of which structure–activity relationships have been described [90]. As mentioned above, the bicyclic analog CP-55,940 (**5**), once tritiated (*Table 1*), has allowed the discovery and characterization of the CB_1 cannabinoid receptor [19].

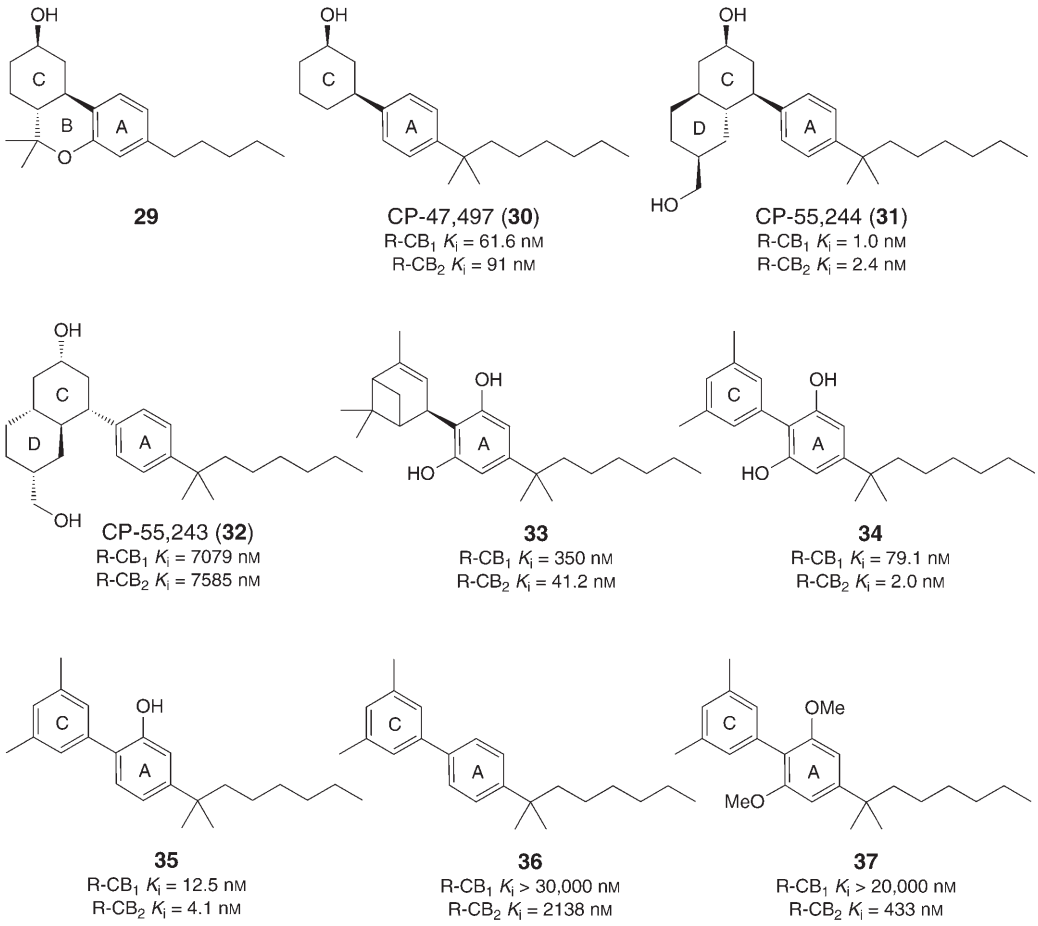


Fig. 8. *Examples of non-classical cannabinoids*

Albeit not selective, it is still one of the most widely used cannabinoid derivatives, acting as a full agonist at both receptor subtypes.

The typical *ACD*-tricyclic non-classical cannabinoid CP-55,244 (**31**; *Fig. 8*) is also a compound of interest, with high affinity and high relative intrinsic activity, for CB_1 [20][42][44][91] and CB_2 cannabinoid receptors [42]. Its enantiomer CP-55,243 (**32**) was found to be a far less potent cannabinoid ligand, but, interestingly enough, it acts as an inverse agonist at the human CB_1 cannabinoid receptor keeping a moderate agonist activity at the human CB_2 cannabinoid receptor [42].

Other biphenyl compounds such as **33**–**37** have been synthesized at *Merck Frost*, Canada, and their affinities (and relative selectivities) have been determined on recombinant human cannabinoid receptors. Interestingly enough, the bicyclic analogs **33** and **34** possess a selectivity ratio of 10 and >50 for the CB_2 cannabinoid receptor, respectively [92].

2.3. *Substituting the Ring* C. Together with Δ^9-THC sold as *dronabinol* (synthetic Δ^9-THC dispersed in sesame oil), nabilone (*Cesamet*®; **38**; *Fig. 9*) was the only cannabinoid agonist to reach the market with the indication of treating chemotherapy-induced nausea and vomiting. Initially discovered by *Eli Lilly*, nabilone was approved in Canada, the United States, and the United Kingdom in the eighties but was rapidly eclipsed by the arrival of 5-HT_3 antagonists. However, it was not marketed in the USA, and *Eli Lilly* discontinued the drug in 1989. In 2004, *Valeant Pharmaceuticals International* acquired nabilone from *Eli Lilly*, and, two years later, obtained from the U.S. Food and Drug Administration the marketing approval for nabilone oral capsules in the following indications: *Cesamet*® is used to treat nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments [93][94]. The affinity of **38** for the cannabinoid receptors was thus not known when it reached the Canadian and Britain market, as the cannabinoid receptors were not characterized in the mid-eighties. Thus, few information is available on the affinity of nabilone for cannabinoid receptors. On the one hand, *Hirst et al.*, using cerebellum homogenates as source of CB_1 cannabinoid receptors and [^{3}H]-SR-141716A, found an affinity of 5.1 nM, while, under the same experimental conditions, Δ^9-THC and Δ^8-THC exhibit affinities of 51 and 295 nM respectively [95]. On the other hand, *Lagu et al.* reported in a molecular-modeling study paper the following affinities: nabilone with a K_i of 120 nM is similar to (−)-9-nor-9-β-hydroxyhexahydrocannabinol ($K_i = 124$ nM), and tenfold superior to Δ^9-THC [96]. A single study [92] compares the relative affinity of nabilone for human recombinant cannabinoid receptors subtypes: the affinity of nabilone was found similar for both receptors with K_i values of 1.8 and 2.2 nM for the CB_1 and CB_2 cannabinoid receptors,

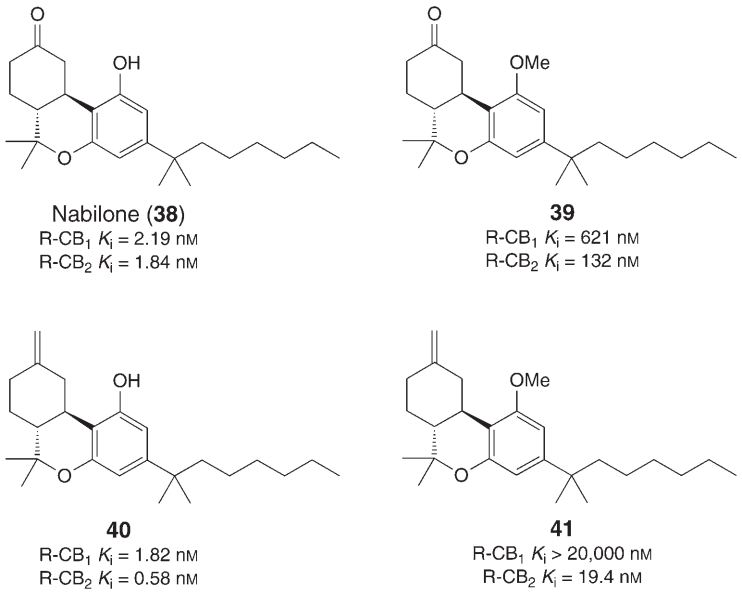


Fig. 9. *Nabilone and derivatives*

respectively. In the same study, the phenol of **38** has been methylated to give the corresponding **39** for which relative affinities were found reduced, but some selectivity (a ratio of *ca.* 5) for the CB_2 was noticed. The 9-methylidene analogue **40** gave only a modest gain in affinity and CB_2 selectivity, but combining the two modifications, *i.e.*, methylidene and MeO substituents, led to a potent and selective CB_2 ligand **41**.

Combining the advantages in terms of analgesic potencies of the hydroxylation of the methyl group at C(9) and the ramification of the alkyl chain (*i.e.*, dimethylheptyl like in **9**), *Mechoulam* and co-workers discovered HU-210 (**42**; *Fig. 10*), one of the most potent and still used agonists of the cannabinoid receptors [97–99]. Relative affinities and potencies have been compared in different species [42][100].

Often used, similarly to CP-55,940 (**5**), as a classical cannabinoid agonist of reference, HU-210 (**42**) is a very potent GTPγS-binding enhancer with a Emax yielding to $200 \pm 15\%$ compared to basal level. Even though CP-55,940 and HU-210 seem to be

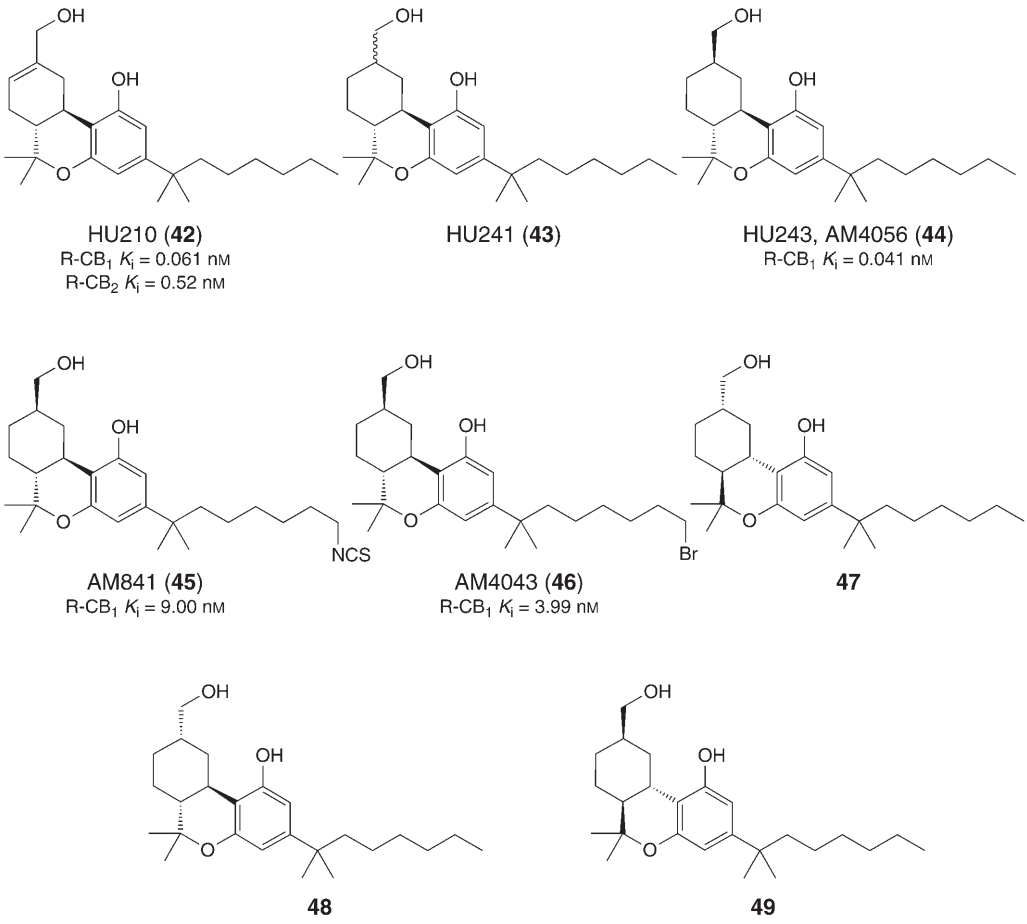


Fig. 10. *Structural variations of HU210*

used worldwide as cannabinoid interchangeable reference agonists, we just reported subtle but major differences of these two compounds on tyrosine hydroxylase expression trough different regulating events of functional cannabinoid CB_1 receptors present in N1E-115 neuroblastoma [101]. Exposure of the cells to the high-affinity agonist HU-210 (5 h) resulted in a significant decrease in TH content ($pEC_{50} = 6.40$), while, in contrast, no change was observed after a similar treatment with the structurally unrelated agonist CP-55,940. These opposite influences on TH gene promoter suggest an agonist-selective trafficking of cannabinoid CB_1 receptor signaling [101][102].

Hydrogenation of **42** over PtO affords a mixture of the C(9)-epimers of 3-(1,1′-dimethylheptyl)hexahydro-11-hydroxycannabinol (**43**) [103]. This mixture, called HU-241, has been tested and found to be a high-affinity ligand. Tritiated HU-241 has been prepared and not surprisingly behaves as a high-affinity radioligand, with an impressive K_d value of 142 pM. Stereospecific reductions with *Wilkinson*'s reagent or *Kagan*'s reagent gave a single epimer **44**, named HU-243. This ligand, which is the equatorial C(9)-epimer, binds to the cannabinoid CB_1 receptor with a K_i value of 41 pM.

Starting from racemic nabilone, **44** was obtained by *Yan et al.* by a *Wittig–Horner–Emmons* olefination, followed by a semipreparative chiral HPLC [104]. Other compounds were **47**, the (+)-enantiomer of **44**, and racemic diastereoisomers **48** and **49**. Recent developments around **44** afforded two electrophilic cannabinoid ligands, **45** and **46**. The affinity of **44** found at the human cannabinoid CB_1 receptor was much lower than that reported on rat preparations, with a K_i value of 3 nM [105]. The isocyanate compound **45**, with a somewhat similar affinity ($K_i = 9$ nM), interacts covalently with a cysteine residue in TM helix six of the CB_1 cannabinoid receptor. Using different mutants, the authors suggest that this compound maintains the cannabinoid receptor in its active state.

2.4. *Stereoinversion of the Ring.* The absolute configuration of (−)-**3** was shown to be *trans* (6*aR*,10*aR*) [8]. The preparation of the *cis*-enantiomer, *i.e.*, (+)-**3**, and assessing the pharmacological comparison of the two enantiomers could give a decisive argument demonstrating the stereospecificity of the binding and consequently reinforcing the cannabinoid-receptor interaction hypothesis. However, these goals albeit aimed were hampered by the laborious and inefficient separation of the (+)-enantiomers from the corresponding (−)-enantiomers. Using a pair of synthetic analogs (−)-4′-(1′,1′-dimethylheptyl)-7-hydroxy-Δ^6-tetrahydrocannabinol (HU-210; **42**) and (+)-4′-(1′,1′-dimethylheptyl)-7-hydroxy-Δ^6-tetrahydrocannabinol (HU-211; **50**) stereospecific effects were evidenced in the immune system of mice [106] (*Fig. 11*). Indeed, several authors reported that, on cannabinoid receptors and/or cannabinoid activities, HU-211 (**50**) is less active by more than three orders of magnitude [107][108]. HU-211 (**50**; other names: dexanabinol, sinnabidol, PA 50211, PRS 211007) exhibits, at least in animal models, a strong neuroprotective effect on motor and memory functions, after closed head injury in the rat [109], in a global ischemia model in the Mongolian gerbil [110], in 20 min common carotid artery occlusion in adult *Sprague–Dawley* rats [111], and on rat brain damages resulting from soman-induced seizures [112]. Dexanabinol's mode of action remains complex, as it interacts with different targets, including NMDA receptor [113–116] where HU-211 exhibits a competitive antagonism behavior. Thus, dexanabinol (**50**) affects various pathophysiological mechanisms such as glutamate

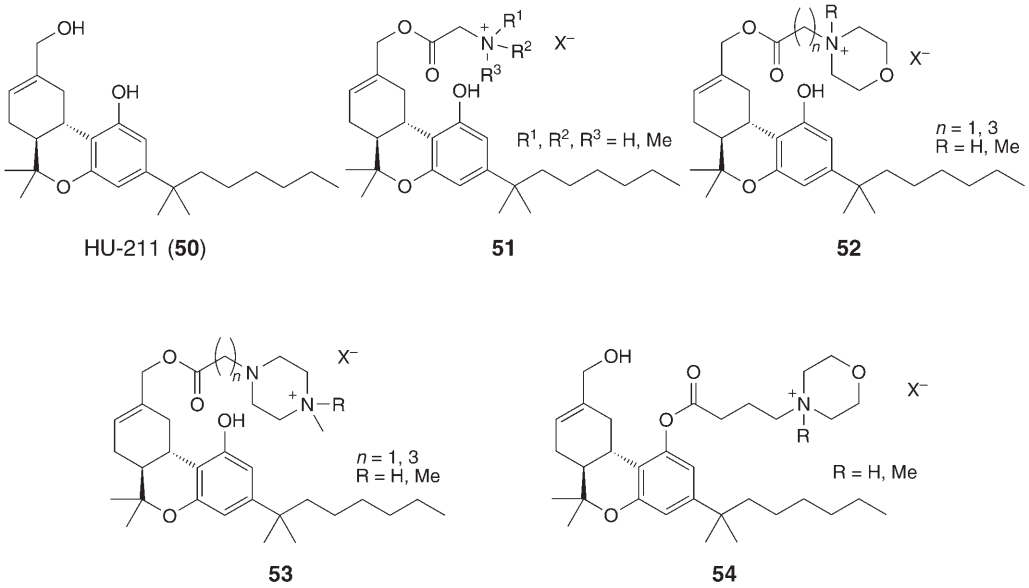


Fig. 11. *Dexanabinol* (HU-211) *and related prodrugs*

excitotoxicity [113–116], free-radical damages trough antioxidant effects [117] and inflammation [118] by inhibition of tumor necrosis factor [118–120], and nitric oxide production [120]. Considering the absence of psychotropic activity, due to the lack of significant interaction with the cannabinoid receptors, it entered the human clinical trials [121–123] for different indications including traumatic brain injury (head injuries), glaucoma and mild cognitive impairment, multiple sclerosis, and neuropathic pain. Phases I, II, and III have been completed, and the results have been published. In healthy volunteers, dexanabinol (**50**) at doses from 48 up to 200 mg did not elicit safety problems in healthy volunteers. The pharmacokinetics of dexanabinol was evaluated in a phase-I clinical trial, following short *i.v.* infusions in a cremophor-ethanol vehicle diluted with saline [124]. This last point illustrates the difficulties in handling the high lipophilicity of cannabinoids. Some medicinal-chemistry approaches have been tested to improve the solubility of **46** [125][126]. Glycinates **51** have been synthesized as dexanabinol prodrugs with an increased solubility in water and an efficient release [125]. Salts of amino acid esters **52**–**54** containing tertiary and quaternary heterocyclic N-atoms with increased solubility in water have been also prepared [126]. From the pharmaceutical-technology point of view, submicron emulsions of dexanabinol (**50**) have been evaluated to lower the intraocular pressure [127][128]. The phase-II study enrolled 67 patients with severe closed head injuries (*Glasgow Coma Scale* score of 4–8, injured within 6 h of treatment). Intracranial pressure, cerebral perfusion pressure, blood pressure, and heart rate were recorded continuously in the intensive care unit. In the drug-treated group, a significant improvement of the control of intracranial pressure has been observed, with a highly significant reduction in the percentage of time with intracranial pressure >25, cerebral perfusion pressure <50, and systolic

blood pressure <90 mmHg. Dexanabinol (**50**) was found safe and well-tolerated in severe head injuries [129]. Unfortunately, the results of randomized, placebo-controlled phase-III clinical trial performed on three continents (15 countries) and enrolling 861 patients with severe traumatic injuries failed to detect a significant improvement in the dexanabinol group (150 mg/kg given within 6 h after the injury as a 15-min infusion in a co-solvent mixture containing ethanol and cremophor) compared to placebo. Dexanabinol (**50**) was, however, found safe, as no hepatic, renal, or cardiac toxic effects have been detected [130]. The effect of configuration has been also investigated in the pharmacological activity of cannabidiol derivatives [131]. (+)-CBD, (+)-4′-(1′,1′-dimethylheptyl)-CBD and (+)-7-OH-4′-(1′,1′-dimethylheptyl)-CBD each exhibit greater affinity for CB_1 and CB_2 receptors than their corresponding (−)-enantiomers **1** and **26**, respectively, illustrating that stereochemical prerequisites are not the same in the cannabidiol series compared to the tetrahydrocannabinol series for the cannabinoid receptors. Interestingly, the configuration of cannabidiol derivatives has no influence on the vanilloid receptor-agonism properties [131].

2.5. *Miscellaneous Variations of Rings* A *and* B. In the seventies, the pharmacological properties of levonantradol (**55**; *Fig. 12*), a synthetic derivative featuring an octahydrophenantridine moiety, have been intensively investigated. They include analgesic [132–138] and anti-emetic [139–141] effects, but also anticonvulsant [142][143] and reducing narcotic withdrawal symptoms [144][145]. This compound entered the clinical trials for preventing nausea associated with chemotherapy [144–148]. The affinity and the efficacy of levonantradol (**55**) were determined on rat brain membranes, and a K_i value of 2.3 nM and a full agonism in [^{35}S]-GTPγS binding assay [41].

Desacetyllevonantradol (**56**, DALN) was used to study the implication of adenylate cyclase in the cannabinoid cellular responses [9–11]. The absence of the acetyl moiety

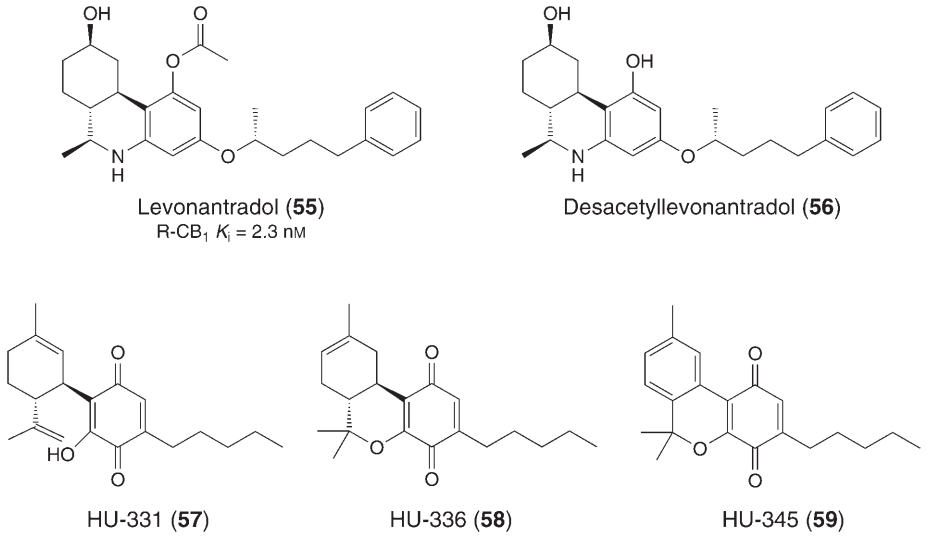


Fig. 12. *Modifications in rings* A *and* B

compared to **55** does not significantly influence the affinity. Therefore, this compound has been widely used as a cannabinoid agonist reference [149]. Finally, in the last three years, cannabinoid quinines received considerable interest for their properties in cancer cell proliferation. In 2004, *Kogan et al*. re-visited the oxidation of cannabis constituents. Cannabidiol, Δ^8-tetrahydrocannabinol, and cannabinol were oxidized to the corresponding *para*-quinones **57**–**59**. These compounds displayed antiproliferative activity in several human cancer cell lines *in vitro* [150].

Cannabidiol hydroxyquinone (**57**, HU-331) was found effective against tumor xenografts in nude mice *via* an inhibition of angiogenesis [151]. It was then demonstrated that it acts as a topoisomerase type-II inhibitor [152], and a recent *in vivo* comparative study evidences that HU-331 was more effective and less cardiotoxic than doxorubicin [153].

3. Conclusions. – The phytocannabinoids present in the plant were a constant source of inspiration for medicinal chemists. Modifying the structure of the phytocannabinoids sometimes leads to a better understanding of the endocannabinoid targets, but also to either unsuspected pharmacological targets or unidentified mechanisms of action. Along this line, and albeit not exhaustive, the purpose of this review was to give the reader a flavor of the chemical diversity explored in the last fifty years.

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