CB_2 Receptor Ligands

J.W. Huffman*

Howard L. Hunter Chemistry Laboratory, Clemson University, Box 340973, Clemson, South Carolina 29634-0973, USA

Abstract: The CB_1 receptor is found principally in the central nervous system and is responsible for the overt physiological effects of cannabinoids. In contrast, the CB_2 receptor is expressed primarily in the immune system and is responsible for few, if any, obvious behavioral effects. Although many cannabinoid receptor ligands show little, or at best modest, selectivity for either receptor, a number of synthetic compounds are known which have significant selectivity for the CB_2 receptor. These include cannabimimetic indoles, such as 1-propyl-2-methyl-3-(1-naphthoyl)indole (JWH-015) and 1-(2,3-dichlorobenzoyl)-2-methyl-3-(2-[1-morpholino]ethyl)-5-methoxyindole (L768242), both of which have good affinity for the CB_2 receptor, but weak affinity for the CB_1 receptor. Efforts have been made to develop structure-activity relationships (SAR) at CB_2 for cannabimimetic indoles, but with limited success. Several derivatives of traditional dibenzopyran based cannabinoids have also been found to have significant selectivity for the CB_2 receptor. These include 1-methoxy-Δ^8-THC derivatives, 1-methoxy-Δ^8-THC-DMH (L759633), 1-methoxy-$\Delta^{9(11)}$-THC-DMH (L759656), and 1-methoxy-3-(1',1'-dimethylhexyl)-Δ^8-THC (JWH-229), plus a number of 1-deoxy-Δ^8-THC analogues. In particular, 1-deoxy-3-(1',1'-dimethylbutyl)-Δ^8-THC (JWH-133) shows two hundred-fold selectivity for the CB_2 receptor. Very recently several compounds belonging to other structural groups have also shown selectivity for the CB_2 receptor. This review will describe the current status of the results of these studies and discuss the SAR for these classes of ligands.

Keywords: Cannabinoids, deoxy cannabinoids, structure-activity relationships, CB_2 receptor, aminoalkylindoles.

INTRODUCTION

Marijuana (*Cannabis sativa L.*) has been used for many centuries as both a medicinal and recreational drug [1]. In 1964 the structure of the major psychoactive principal of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**, Fig. **1**), was established [2]. Rather detailed structure-activity relationships (SAR) were established based on the dibenzopyran structure of Δ^9-THC [3], however the mechanism by which these compounds elicited their effects was not known. The presence of a cannabinoid receptor in rat brain was confirmed in1988 using tritium labeled CP-55,940 (**2**, Fig. **1**) a very potent synthetic cannabinoid, and a three point receptor model was presented [4]. This receptor was subsequently cloned [5] and a nearly identical (97% homology) human receptor has also been cloned [6]. In 1993 a second human cannabinoid receptor was identified and cloned [7]. This receptor shows only 44% homology (68% in the helical regions) with the initially described receptor. The receptor which was originally identified in rat brain is known as the CB_1 receptor and is found primarily in the central nervous system, while the second receptor to be identified is known as the CB_2 receptor and was found initially in the spleen. Both the CB_1 and CB_2 receptors belong to the family of G-protein coupled receptors and both inhibit adenylyl cyclase. There are a number of excellent recent reviews which discuss these cannabinoid receptors in considerable detail [8-10]

In an early report of selectivity for the CB_2 receptor, Felder *et al.* Found that WIN-55,212-2 (**3**, Fig. **1**) has considerably greater affinity for this receptor than for the CB_1 receptor [11] and in 1996 reports appeared which described several additional selective ligands for the CB_2 receptor [12-15]. Two of these additional compounds were cannabimimetic indoles, 1-propyl-2-methyl-3-(1-naphthoyl)indole (JWH-015, **4**, Fig. **2**) [12] and 1-(2, 3-dichlorobenzoyl)-2-methyl-3-(2-[1-morpholino]ethyl)-5-methoxyindole (L768242, **5**, Fig. **2**) [13]. Two CB_2 selective compounds based on the dibenzopyran skeleton of THC, 1-methoxy-Δ^8-THC-DMH (L759633, **6**, Fig. **2**) and 1-methoxy-$\Delta^{9(11)}$-THC-DMH (L759656, **7**, Fig. **3**) were described by workers at Merck Frosst [14]. In addition, Huffman *et al.* reported two 1-deoxy-3-(1',1'-dimethylheptyl)-Δ^8-THC derivatives, 1-deoxy-11-hydroxy-Δ^8-DMH (JWH-051, **8**, Fig. **3**) and 1-deoxy-Δ^8-THC-DMH (JWH-057, **9**, Fig. **3**) [15]. 1-Deoxy-Δ^8-THC-DMH was also described by Gareau *et al.* [14]. Subsequently, a series of 1-deoxy-3-(1',1'-dimethylalkyl)-Δ^8-THC analogues was reported, two of which, 1-deoxy-3-(1',1'-dimethylpropyl)-Δ^8-THC (JWH-139, **10** Fig. **4**) and 1-deoxy-3-(1',1'-dimethylbutyl)-Δ^8-THC (JWH-133, **11** Fig. **4**), have very high affinity for the CB_2 receptor, but little affinity for the CB_1 receptor [16]. In 1998, the Sanofi group reported the first CB_2 selective antagonist, a novel pyrazole derivative, SR144258 (**12**, Fig. **4**) which has very low affinity for the CB_1 receptor and high affinity for the CB_2 receptor [17]. It was subsequently shown that cannabimimetic indole AM630 (**13**, Fig. **5**) and SR144258 are inverse agonists at the CB_2 receptor, [18, 19].

In a very recent review it was stated that "…the biological role of the CB_2 receptor remains unclear…" [20] and in an even more recent review it was noted that "Less is known about the physiological roles of CB_2 receptors, (than

*Address correspondence to this author at the Howard L. Hunter Chemistry Laboratory, Clemson University, Box 340973, Clemson, South Carolina 29634-0973, USA; E-mail: huffman@clemson.edu

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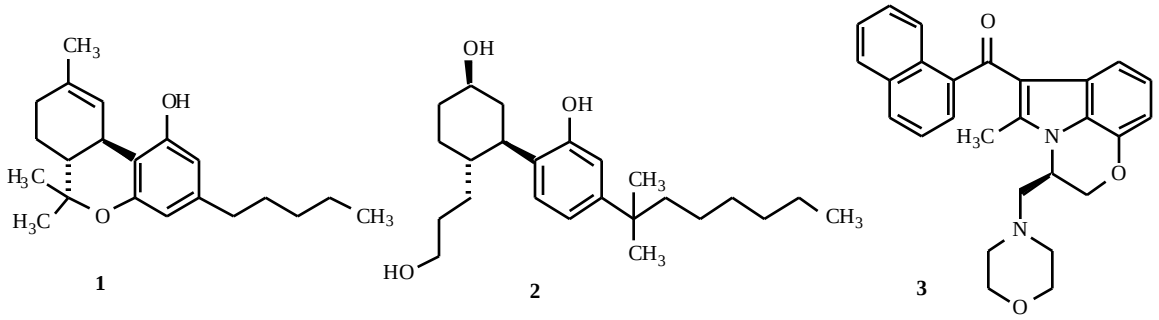


Fig. (1). Structures of Δ^9-THC, CP-55,940 and WIN-55,212-2.

CB_1 receptors)…" [10]. However, recent work is beginning to provide evidence for the role of the CB_2 receptor in a number of biological functions. These include peripheral antinociception [21, 22] and the inhibition of tumor growth [23-26]. As a result of the recognition of the importance of the CB_2 receptor, there is current interest in the further development of additional highly selective ligands for this receptor, and in particular for ligands which have high affinity for the CB_2 receptor and little affinity for the CB_1 receptor. Since the CB_1 receptor is responsible for the psychoactive effects of cannabinoids, most CB_2 selective ligands with low affinity for the CB_1 receptor do not show psychoactivity. After a brief description of the bioassay methods employed to determine cannabinoid receptor affinities, the bulk of this review will be concerned with the recent efforts to develop highly selective agonists for the CB_2 receptor and to define the SAR for CB_2 receptor ligands. The detailed discussion will be restricted to those compounds which have from moderate to high affinity for the CB_2 receptor, combined with modest to negligible affinity for the CB_1 receptor.

Fig. **1**), [^{3}H] CP-55,940 (**2**, Fig. **1**) which has high, and approximately equal, affinity for both the CB_1 and CB_2 receptor is the most commonly used radioligand [8, 10]. These assays may employ brain membranes which contain principally CB_1 receptors or spleen tissue which contains CB_2 receptors, with few CB_1 receptors. Alternatively membranes obtained from CB_1 or CB_2 transfected cells are used which ensures that only one type of receptor is present. The affinities reported by different groups or employing different types of membranes may vary considerably, although the various membrane preparations may contain the same or very similar receptors. A frequent source of the discrepancies in affinities reported by various groups is the difference in receptor homogeneity between brain or spleen membrane preparations and membranes obtained from transfected cell lines. In addition to binding assays two functional *in vitro* bioassays for the efficacy of ligands at CB_1 and CB_2 receptors have been employed. One of these measures agonist stimulated [^{35}S]GTPγS binding to G protein which occurs as a result of binding of the ligand to the receptor. The other measures agonist induced inhibition

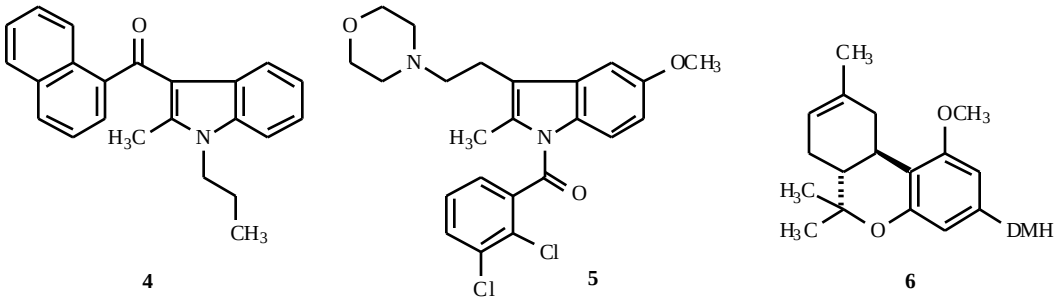


Fig. (2). Structures of JWH-015, L768242 and 1-methoxy-Δ^8-THC-DMH. DMH = 1,1-dimethylheptyl.

BIOASSAY METHODS

The affinities of cannabinoid receptor ligands are determined by displacement assays which employ tritium labeled cannabinoids [8, 10]. Although several tritiated ligands have been used, including [^{3}H] WIN-55,212-2 (**3**, of basal or drug induced cyclic AMP production, which is a result of the negative coupling of the cannabinoid receptors to adenylyl cyclase [8, 10].

Cannabinoid receptor ligands have also been evaluated *in vivo*, frequently in the mouse using a protocol which

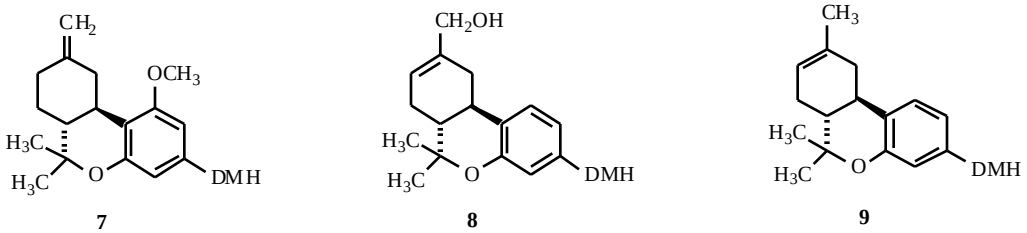
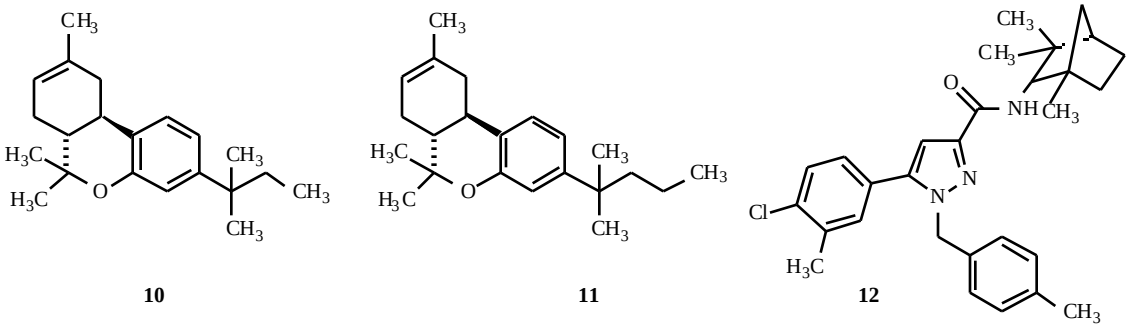


Fig. (3). Structures of 1-methoxy-$\Delta^{9(11)}$-THC-DMH, JWH-051 and 1-deoxy-Δ^8-THC-DMH. DMH = 1, 1-dimethylheptyl.



10 **11** **12**

Fig. (4). Structures of JWH-139, JWH-133 and SR144258.

employs a battery of three or four procedures which measure spontaneous activity (SA), antinociception (as tail flick, TF), hypothermia (as decrease in rectal temperature, RT) and in some cases, catalepsy (as ring immobility, RI) [27]. These overt effects of cannabinoids are caused by the interaction of the ligand with the CB_1 receptor since they are blocked by SR14176A, a highly selective CB_1 receptor antagonist/inverse agonist [28], and are absent in CB_1 receptor knockout mice [29]. Although most CB_2 selective ligands with low affinity for the CB_1 receptor do not elicit these effects, the dimethylpropyl, pentyl and hexyl analogues of JWH-133 (**11**, Fig. **4**) which have CB_1 affinities from 295 nM to 2,290 nM show typical cannabinoid behavior in the mouse which is blocked by SR141716A [30]. At the present time an explanation for these anomalous results is lacking.

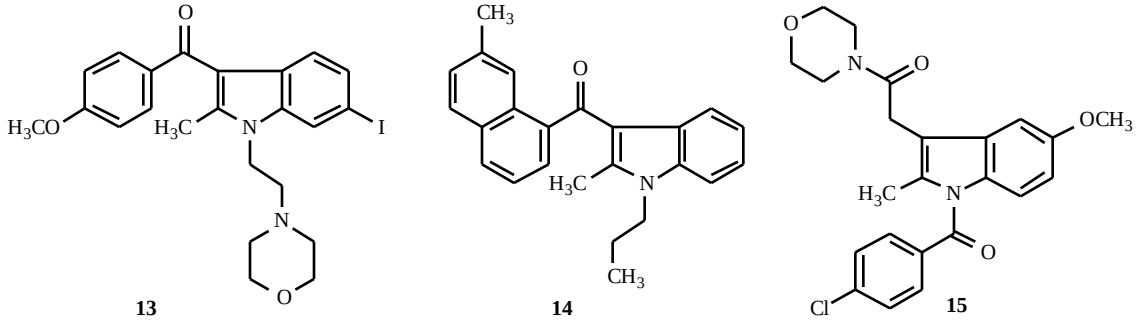
CB_2 SELECTIVE LIGANDS

Indoles

Following the observation that WIN-55,212-2 (**3**, Fig. **1**) shows significant CB_2 selectivity (K_i = 62.3 nM at CB_1 and 3.3 nM at CB_2) [11], Showalter *et al.* investigated the structure-activity relationships (SAR) of ligands for the CB_2 receptor and found that JWH-015 (**4**, Fig. **2**) has high affinity for the CB_2 receptor (K_i = 13.8 nM), but very little affinity for the CB_1 receptor (K_i = 383 nM) [12] and has low potency *in vivo* [31]. Almost simultaneously the Merck Frosst group reported that several indoles structurally related to L768242 (**5**, Fig. **2**) are selective for the CB_2 receptor [13]. Indole **5** has high affinity (K_i = 14 nM) for the CB_2 receptor and little affinity for the CB_1 receptor (K_i = 2043 nM) [13].

Using JWH-015 (**4**, Fig. **2**) as a lead compound the Clemson group undertook a program directed toward the development of CB_2 selective ligands with greater affinity for the CB_2 receptor and attenuated affinity for the CB_1 receptor. An additional goal of this program was the development of SAR at both receptors for cannabimimetic indoles. Although considerable progress has been made toward understanding the SAR for these compounds, particularly at CB_1 [20, 31, 32], only one additional highly selective CB_2 ligand JWH-046, 1-propyl-2-methyl-3-(7-methyl-1-naphthoyl)indole (**14**, Fig. **5**, K_i = 16 ± 5 nM at CB_2 and K_i = 343 ± 38 nM at CB_1) has been identified [20, 32]. In general, cannabimimetic indoles with a 1-pentyl substituent have greater affinity for both receptors than compounds with other *N*-alkyl substituents, and 2-alkyl substituents larger than methyl reduce affinity considerably [30, 32]. Reducing the length of the *N*-alkyl group to three carbons has a more profound effect upon CB_1 affinity than upon CB_2 affinity while a 4-methoxynaphthoyl substituent increases the affinity for both receptors [20, 32]. More detailed SAR at both the CB_1 and CB_2 receptors will require the synthesis and pharmacological evaluation of additional cannabimimetic indoles.

Recent work has provided evidence that BML-190, indomethacin morpholinoamide (**15**, Fig. **5**) is an inverse agonist at the CB_2 receptor [33], however this compound has at best modest affinity for the CB_2 receptor (K_i = 435 ± 43 nM) [13]. BML-190 dose dependently increased the forskolin stimulated levels of cyclic AMP in HEK-293 cells, transfected with human CB_2 receptor. This is in contrast to CB_2 agonists, WIN-55,212-2 (**3**, Fig. **1**) and JWH-015 (**4**, Fig. **2**) which decrease the levels of cyclic AMP [33]. This cannabimimetic indole and AM630, (**13**, Fig. **5**) are both indole derived, CB_2 selective inverse agonists, however, AM630 has considerably greater affinity for the CB_2 receptor (K_i = 37.5 ± 15.4 nM) than BML-190 [19].



13 **14** **15**

Fig. (5). Structures of AM-630, JWH-046 and BML-190.

Traditional Cannabinoids

In early work describing the CB_2 receptor affinities of cannabinoid ligands, it was found that traditional cannabinoids, such as Δ^9-THC (**1**, Fig. **1**) have similar affinities for both the CB_1 and CB_2 receptors [11, 12]. Bicyclic cannabinoids such as CP-55,940 (**2**, Fig. **1**) also show little selectivity for either receptor [8, 10, 11]. These data have been summarized in recent reviews [8, 34], and the affinities of Δ^9-THC for both the CB_1 and CB_2 receptors are included in Table **1**. Several years ago it was found that 1-methoxy-Δ^8-THC-DMH (L759633, JWH-143, **6**, Fig. **2**), and 1-methoxy-$\Delta^{9(11)}$-THC-DMH (L759656, JWH-142, **7**, Fig. **3**) both have high affinity for the CB_2 receptor, but negligible affinity for the CB_1 receptor and that 1-deoxy-Δ^8-THC-DMH (JWH-057, **9**, Fig. **3**) has considerably greater affinity for the CB_2 receptor than for the CB_1 receptor [14-16, 19].

These observations led Huffman *et al.* to prepare a number of 1-deoxy-Δ^8-THC analogues, several of which have high affinity for the CB_2 receptor, with poor affinity for the CB_1 receptor [16]. In particular, 1-deoxy-Δ^8-THC (JWH-056, **16**, Fig. **6**), 1-deoxy-3-(1', 1'-dimethylpropyl)-Δ^8-THC (JWH-139, **10**, Fig. **4**), 1-deoxy-3-(1', 1'-dimethylbutyl)-Δ^8-THC (JWH-133, **11**, Fig. **4**) and 1-deoxy-3-(1', 1'-dimethylpentyl)-Δ^8-THC (JWH-065, **17**, Fig. **6**) have high affinity for the CB_2 receptor, but very low affinity for the CB_1 receptor. The CB_1 and CB_2 receptor affinities for these compounds are included in Table **1**. In order to develop additional CB_2 selective ligands and gain further insight into the SAR for the CB_2 receptor three additional series of analogues were prepared and their receptor affinities were determined [35]. It had been noted previously that an 11-hydroxyl substituent enhanced CB_2 receptor affinity [15, 16] and it was expected that one or more 1-deoxy-11-hydroxy-1',1'-dimethylalkyl-Δ^8-THC analogues (**18**, R = CH_3 to C_6H_{13}, Fig. **6**) and 1-methoxy-11-hydroxy-1',1'-dimethylalkyl-Δ^8-THC (**19**, R = CH_3 to C_6H_{13}, Fig. **6**) analogues would show enhanced affinity for the CB_2 receptor without a corresponding increase in CB_1 receptor affinity. Since previous work had indicated that 1-methoxy-Δ^8-THC-DMH (**6**, Fig. **2**) was a selective ligand for the CB_2 receptor [14, 16] a series of 1-methoxy-3-(1',1'-dimethylalkyl)-Δ^8-THC analogues (**20**, R = CH_3 to C_6H_{13}, Fig. **6**) was also prepared [35]. The CB_1 and CB_2 receptor affinities for these three series of compounds are also included in Table **1**.

Although the 1-deoxy-11-hydroxy-1', 1'-dimethylalkyl-Δ^8-THC analogues (**18**, R = CH_3 to C_6H_{13}, Fig. **6**) show from quite high affinity for the CB_2 receptor for the lowest member of the homologous series (**18**, JWH-188, R = CH_3) with K_i = 18 ± 2 nM to exceptionally high affinity for the dimethylheptyl analogue (**8**, JWH-051, Fig. **3**) with K_i = 0.03 ± 0.02 nM. This compound which was described several years ago has the highest affinity for the CB_2 receptor reported to date, but JWH-051 also has very high affinity for the CB_1 receptor (K_i = 1.2 ± 0.1 nM) and is a potent cannabinoid *in vivo* [15]. The two lowest members of this series, JWH-188 (**18**, R = CH_3) and JWH-186 (**18**, R = C_2H_5) each have modest affinity for the CB_1 receptor (K_i = 270 ± 58 and 187 ± 23 nM respectively) and show 15- and 33-fold selectivity for the CB_2 receptor. For the other members of this series (**18**, R = C_3H_7 to R = C_5H_{11}) the CB_2 receptor affinities are very high, however the CB_1 affinities are sufficiently high that the compounds would be expected to exhibit the overt physiological effects characteristic of CB_1 receptor agonists (Table **1**).

In the 11-hydroxy-1-methoxy series (**19**, R = CH_3 to C_6H_{13}, Fig. **6**) both the CB_1 and CB_2 receptor affinities are lower than those of the corresponding 1-deoxy analogues (**18**, Fig. **6**). Two of the compounds in this series, JWH-215 and JWH-224 (**19**, R = C_2H_5 and R = C_3H_7) show modest 12-fold selectivity for the CB_2 receptor, but their CB_2 affinities (K_i = 85 ± 21 nM and K_i = 28 ± 1 nM, respectively) are considerably weaker than those of a number of other CB_2 selective ligands [35]. It is apparent that in both these series that the 11-hydroxy substituent does enhance CB_2 receptor affinity, but it also leads to an increase in CB_1 affinity, the net result of which is decreased CB_2 selectivity relative to compounds of the unsubstituted 1-deoxy-Δ^8-THC analogues related to JWH-133 (**11**, Fig. **4**).

The compounds in the 1-methoxy-3-(1', 1'-dimethylalkyl)-Δ^8-THC series (**20**, Fig. **6**) have uniformly poor affinity for the CB_1 receptor, with K_i > 10,000 for the

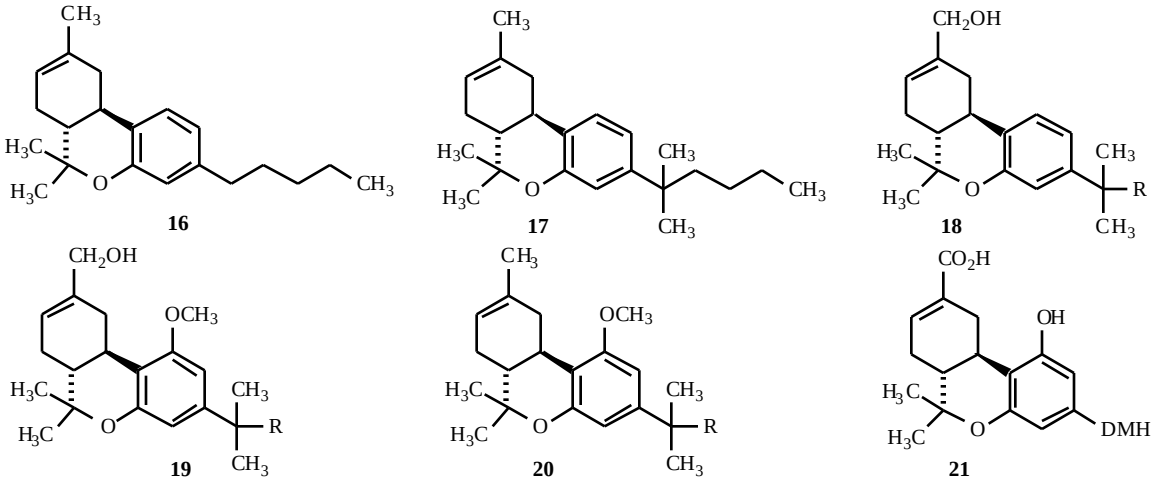


Fig. (6). Structures of JWH-056, JWH-065, 1-deoxy-11-hydroxy-, 1-methoxy-11-hydroxy-, 1-methoxy-Δ^8-THC analogues and ajulemic acid.

Table 1. Receptor Affinities (CB_1 and CB_2) for Δ^9-THC (1), 1-Deoxycannabinoids 10, 11, 16, 17 and 11-Hydroxycannabinoids 18, 19; 1-Methoxycannabinoids 20

	K_i (nM)	
Compound	**CB_1**	**CB_2**
$\Delta^{9\text{-THC}}$	41 ± 2[a]	36 ± 10[b]
3-(1',1'-Dimethylpropyl)-1-deoxy-Δ^8-THC (**10**, JWH-139)	2290 ± 505[c]	14 ± 10[c]
3-(1',1'-Dimethylbutyl)-1-deoxy-Δ8-THC (**11**, JWH-133)	677 ± 132[c]	3.4 ± 1.0[c]
3-(1',1'-Dimethylpentyl)-1-deoxy-Δ^8-THC (**17**, JWH-065)	399 ± 76[c]	10 ± 2[c]
1-Deoxy-Δ8-THC (**16**, JWH-056)	>10,000[c]	32 ± 9[c]
11-Hydroxy-3-(1',1'-dimethylethyl)-Δ^8-THC (**18**, JWH-188, R = CN_3)	270 ± 58[d]	18 ± 2[d]
11-Hydroxy-3-(1',1'-dimethylpropyl)-Δ^8-THC (**18**, JWH-186, R = C_2H_5)	187 ± 23[d]	5.6 ± 1.7[d]
11-Hydroxy-3-(1',1'-dimethylbutyl)-Δ^8-THC (**18**, JWH-187, R = C_3H_7)	84 ± 16[d]	3.4 ± 0.5[d]
11-Hydroxy-3-(1',1'-dimethylpentyl)-Δ^8-THC (**18**, JWH-190, R = C_4H_9)	8.8 ± 1.4[d]	1.6 ± 0.03[d]
11-Hydroxy-3-(1',1'-dimethylhexyl)-Δ^8-THC (**18**, JWH-191, R = C_5H_{11})	1.8 ± 0.3[d]	0.52 ± 0.03[d]
11-Hydroxy-3-(1',1'-dimethylethyl)-1-methoxy-Δ^8-THC (**19**, JWH-216, R = CH_3)	1856 ± 148[d]	333 ± 104[d]
11-Hydroxy-3-(1',1'-dimethylpropyl)-1-methoxy-Δ^8-THC (**19**, JWH-215, R = C_2H_5)	1008 ± 117[d]	85 ± 21[d]
11-Hydroxy-3-(1',1'-dimethylbutyl)-1-methoxy-Δ^8-THC (**19**, JWH-224, R = C_3H_7)	347 ± 34[d]	28 ± 1[d]
11-Hydroxy-3-(1',1'-dimethylpentyl)-1-methoxy-Δ^8-THC (**19**, JWH-227, R = C_4H_9)	40 ± 6[d]	4.4 ± 0.3[d]
11-Hydroxy-3-(1',1'-dimethylhexyl)-1-methoxy-Δ^8-THC (**19**, JWH-230, R = C_5H_{11})	15 ± 3[d]	1.4 ± 0.12[d]
11-Hydroxy-3-(1',1'-dimethylheptyl)-1-methoxy-Δ^8-THC (**19**, JWH-233, R = C_6H_{13})	14 ± 3[d]	1.0 ± 0.3[d]
3-(1',1'-Dimethylethyl)-1-methoxy-Δ^8-THC (**20**, R = CH_3)	>10,000[d]	1867 ± 867[d]
3-(1',1'-Dimethylpropyl)-1-methoxy-Δ^8-THC (**20**, JWH-217, R = C_2H_5)	>10,000[d]	1404 ± 66[d]
3-(1',1'-Dimethylbutyl)-1-methoxy-Δ^8-THC (**20**, JWH-225, R = C_3H_7)	>10,000[d]	325 ± 70[d]
3-(1',1'-Dimethylpentyl)-1-methoxy-Δ^8-THC (**20**, JWH-226, R = C_4H_9)	4001 ± 282[d]	43 ± 3[d]
3-(1',1'-Dimethylhexyl)-1-methoxy-Δ^8-THC (**20**, JWH-229, R = C_5H_{11})	3134 ± 110[d]	18 ± 2[d]

[a]Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol Exp. Ther*. **1993**, *265*, 218[b] ref. 12[c] ref. 16[d] ref. 35.

three lowest members of this series (**20**, R = CH_3 through C_3H_7). The other three members of this series (**20**, R = C_4H_9 through C_6H_{13}) have only slightly greater CB_1 receptor affinity (K_i = 4001 ± 282 nM, 3134 ± 110 nM and 924 ± 104 nM, respectively). Two of these 1-methoxy-Δ^8-THC analogues, JWH-226 (**20**, R = C_4H_9) and JWH-229 (**20**, R = C_5H_{11}) are highly selective for the CB_2 receptor. JWH-226 has moderate affinity for the CB_2 receptor (K_i = 43 ± 3 nM) which is 93-fold greater than its affinity for the CB_1 receptor (K_i = 4001 ± 282 nM). JWH-229, 3-(1', 1'-dimethylhexyl-1-methoxy-Δ^8-THC (**20**, R = C_5H_{11}) has high affinity (K_i = 18 ± 2 nM) for the CB_2 receptor and is one of the most selective ligands reported to date with 174-fold selectivity for the CB_2 receptor with K_i = 3134 ± 110 nM at the CB_1 receptor [35]. The data for all the compounds of structures **18**, **19** and **20** are included in Table **1**.

Based on the number of analogues of 1-methoxy- and 1-deoxy-Δ^8-THC prepared and evaluated to date, it is possible to formulate some preliminary SAR for these compounds [15, 16, 35]. Affinity for both the CB_1 and CB_2 receptors is enhanced by the presence of a 1', 1'-dimethylalkyl side chain, but the length of the chain is far more critical for CB_1 receptor affinity than for CB_2 affinity. This is particularly the case in the 1-deoxy-Δ^8-THC series in which compounds with very short side chains have significant affinity for the CB_2 receptor, but very little affinity for the CB_1 receptor. An 11-hydroxy group enhances affinity for both receptors to the extent that none of the compounds of this type which have been prepared to date show useful CB_2 selectivity. In general, the 1-methoxy-Δ^8-THC compounds have lower affinity for both cannabinoid receptors than the corresponding 1-deoxy-Δ^8-THC analogues. One member of the 1-deoxy-Δ^8-THC series, JWH-133 (1-deoxy-3-(1', 1'-dimethylbutyl-Δ^8-THC, **11**, Fig. **4**) has found some use as a selective ligand for the CB_2 receptor on the basis of its nearly 200-fold selectivity for this receptor [16] and its inactivity *in vivo* [30]. JWH-229, 3-(1',1'-dimethylhexyl-1-methoxy-Δ^8-THC (**20**, R = C_5H_{11}, Fig. **6**) is nearly as selective for the CB_2 receptor, and has lower affinity for the CB_1 receptor, however the pharmacology of this compound has not been evaluated *in vivo* [35].

There is recent evidence that ajulemic acid (11-nor-9-carboxy-3-(1', 1'-dimethylheptyl)-Δ^8-THC, **21**, Fig. **6**), a non-psychoactive cannabinoid, is a potential anti-tumor drug [36]. Both acid **21** and THC (**1**, Fig. **1**) inhibit the growth of C6 glioma tumor cells in mice, and both inhibit the

growth of a number of human cancer cell lines. The enantiomer of acid **21** is markedly less effective in the inhibition of the growth of tumor cells, indicating that this effect is stereospecific and receptor mediated. Also, the anti-tumor effects of acid **21** are reversed by the CB_2 receptor antagonist/inverse agonist SR144528 (**12**, Fig. **4**) suggesting that ajulemic acid is acting via CB_2 receptors [36]. Acid **21** has significant affinity for the CB_1 receptor (K_i = 32.3 ± 3.7 nM) and very modest affinity for the CB_2 receptor (K_i = 170.5 ± 7.8 nM), but is not psychoactive [37, 38]. Acid **21** inhibits CB_1 mediated adenlyl cyclase relatively weakly (EC_{50} = 927.0 ± 39.6 nM), but inhibits CB_2 mediated adenlyl cyclase with EC_{50} = 170.5 ± 7.8 nM. Thus, acid **21** signals more effectively via the CB_2 receptor than via the CB_1 receptor although it has considerably greater affinity for the CB_1 receptor [37].

Razdan's group investigated the SAR of a number of cannabinol derivatives as possible selective ligands for either the CB_1 or CB_2 receptor [39]. Three series of cannabinol analogues were prepared (**22**, R = CH_3, CH_2OH or CO_2CH_3, Fig. **7**), in which R' = OH, OCH_3 or H and R" = C_3H_7 or C_6H_{13}. In addition to methyl esters (**22**, R = CO_2CH_3) several other esters, such as **22**, R = $CO_2CH_2C_6H_5$ were examined. The only compounds in these series which had significant affinity for either receptor were those with hydroxyl groups at C-11, and/or C-9. However, in general those compounds which have significant CB_2 receptor affinity also have good affinity for the CB_1 receptor. The greatest selectivity for the CB_2 receptor is shown by the 3-(1',1'-dimethylbutyl) analogue of cannabinol (**22**, R = CH_3, R' = OH and R" = C_6H_{13}) which has seven-fold selectivity for the CB_2 receptor (K_i = 6 ± 2 nM at CB_2; K_i = 42 ± 2 nM at CB_1) [39].

OTHER STRUCTURAL CLASSES

Very recently, Italian workers designed a group of tricyclic pyrazoles (**23**, Fig. **7**, in which R, R' and R" are various substituents), several of which are highly selective for the CB_2 receptor [40]. These compounds were based on the Sanofi CB_1 and CB_2 inverse agonists, SR141716A (**24**, Fig. **7**) and SR144528 (**12**, Fig. **4**), but with the addition of a one carbon bridge from C-4 of the pyrazole to the *ortho*-position of the C-5 aromatic ring. These authors described the synthesis and CB_1 and CB_2 receptor affinities of 18 compounds, seven of which have greater than 1,900 fold selectivity for the CB_2 receptor. The CB_1 and CB_2 receptor affinities of several of these compounds (**25**, Fig. **8**) are summarized in Table **2**. Unfortunately, these authors do not present data to establish whether these compounds are agonists or antagonists/inverse agonists.

Table 2. Receptor Affinities (CB_1 and CB_2) of Pyrazoles 25[a]

K_i (nM)		
Compound	**CB_1**	**CB_2**
25, R = Cl	2050 ± 90	0.34 ± 0.06
25, R = F	1268 ± 0.02	0.225 ± 0.02
25, R= Br	1570 ± 15	0.27 ± 0.02
25, R= I	333 ± 0.5	5.5 ± 0.5
25, R= H	1152 ± 65	0.385 ± 0.04
25, R= CH_3	363 ± 30	0.037 ± 0.003
25, R= OCH_3	399 ± 24	12.3 ± 1

[a]Ref. 40.

The highly selective members of this series maintain the 1-aminopiperidine ring characteristic of SR141716A (**24**, Fig. **7**) and four of the five compounds in this series with the greatest CB_2 receptor affinity contain a relatively small substituent at C-6 of the aryl group (numbered as an indeno[1, 2, *c*]pyrazole derivative) at C-5 of the pyrazole ring (**25**, Fig. **8**, R = Cl, Br, F, CH_3). The aryl group of the fifth highly selective compound has a 5-chloro substituent. A slightly less selective ligand lacks a substituent on this aryl group (**25**, Fig. **8**, R = H), and a 6-iodo or 6-methoxy group (**25**, Fig. **8**, R = I, OCH_3) decreases selectivity considerably. Most other structural modifications in this series resulted in a decrease in CB_2 and/or CB_1 receptor affinity. These pyrazole derivatives are among the most highly CB_2 selective ligands described to date, and **25**, R = CH_3 has nearly 10,000 fold selectivity for this receptor [40].

Wiley *et al.* have described a number of resorcinol derivatives which were designed as selective ligands for the CB_2 receptor [41]. Two series of compounds were prepared (**26**, Fig. **8**, R = various cycloalkyl and heterocyclic groups) in which the phenolic hydroxyls were not derivatized and which had at best modest selectivity for the CB_2 receptor. All but two of the compounds in these two series have a 1, 1-dimethylheptyl group at the 5-position of the resorcinol. Several of these compounds are from 14 to 50-fold selective for the CB_2 receptor, but some of the most highly selective

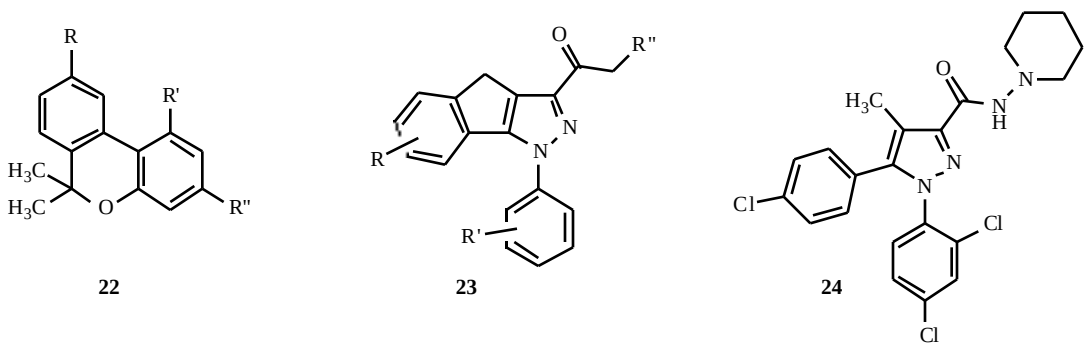


Fig. (7). Structures of cannabinol analogues, bridged tricyclic pyrazoles and SR141716A.

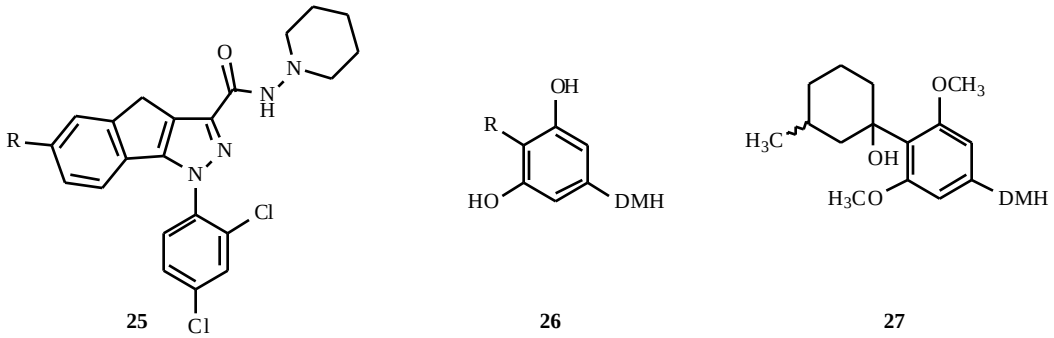


Fig. (8). Structures of bridged tricyclic pyrazoles, cannabimimetic resorcinols and O-1966A.

have significant affinity for the CB_1 receptor combined with very high affinity for the CB_2 receptor. Those compounds with significant affinity for the CB_1 receptor are also potent cannabinoids in the mouse model of cannabinoid activity. Two compounds of this structural type have a combination of modest affinity for the CB_1 receptor and weak activity *in vivo*. One of these compounds was the cyclopentyl analogue (**26**, R = cyclopentyl) for which the affinity for the CB_2 receptor was 14 fold greater than for the CB_1 receptor (K_i = 95 ± 6 nM at CB_1 and K_i = 7 ± 0.4 nM at CB_2). This compound shows modest activity *in vivo* in the mouse model of cannabinoid activity. The other compound is the isomeric mixture of *cis*- and *trans*-4-phenylcyclohexyl derivatives (**26**, R = 4-phenylcyclohexyl) which shows 16-fold selectivity for the CB_2 receptor (K_i = 144 ± 22 nM at CB_1 and K_i = 9 ± 2 nM at CB_2). This compound shows very slight *in vivo* activity.

Table 3. Receptor Affinities (CB_1 and CB_2) of JTE-907 (28, Fig. 9)[a]

	K_i (nM)	
Receptor	**CB_1**	**CB_2**
Human	2370 ± 297	35.9 ± 7.32
Mouse	1060 ± 90	1.55 ± 0.09
Rat	1050 ± 35.4	0.38 ± 0.1

[a]Ref. 42.

Wiley *et al.* also described two closely related series of resorcinol dimethyl ethers none of which have significant affinity for the CB_1 receptor [41]. Of the 19 compounds of this type, one O-1966A (**27**, Fig. **8**) has 220-fold selectivity for the CB_2 receptor with K_i = 5,055 ± 984 nM at CB_1 and K_i = 23 ± 2.1 nM at CB_2. No *in vivo* pharmacology data were presented for this compound, but the affinity for the CB_1 receptor is sufficiently weak that it is most unlikely that this compound would show any of the overt effects characteristic of CB_1 receptor agonists. In these two series of resorcinol derivatives those compounds with moderate to high affinity for the CB_2 receptor have a 1, 1-dimethylheptyl group at C-5 of the aromatic ring.

A novel CB_2 selective inverse agonist, JTE-907 (**28**, Fig. **9**) was described recently by Iwamura *et al*. at Japan Tobacco [42]. This compound is a derivative of 7,8-dihydroxy-2-quinolone-3-carboxylic acid which shows somewhat different levels of selectivity in human, mouse and rat cannabinoid receptors. These data are reported in Table **3**. These authors also reported CB_1 and CB_2 receptor affinities for SR144528 (**12**, Fig. **4**), WIN-55,212-2 (**3**, Fig. **1**) and Δ^9-THC (**1**, Fig. **1**) which differed considerably from the data reported by other workers, however, it is not uncommon for different workers to report somewhat diverse affinities for the same compound due to differences in technique, radioligand, receptor cell line or other variables [8, 10]. For the human receptors Iwamura *et al.* used CHO cells which expressed the CB_1 and CB_2 receptors, for the mouse a cerebellum preparation was used for CB_1 and for CB_2, CHO cells which expressed the receptor were used. For the rat receptors, a cerebellum membrane preparation was used to determine CB_1 receptor affinity and for CB_2, rat splenocytes were employed [42]. [^{3}H] CP55,940 was used as the radioligand. JTE-907 also showed a concentration dependent increase in cAMP production in forskolin stimulated CHO cells expressing human or mouse CB_2 receptors. It is known that cannabinoid receptor agonists inhibit cAMP production in forskolin stimulated receptors [11], and that ligands which increase cAMP production are inverse agonists.

CONCLUSIONS

The CB_1 cannabinoid receptor has been studied extensively and its physiological role is reasonably well understood, however, the role and detailed function of the

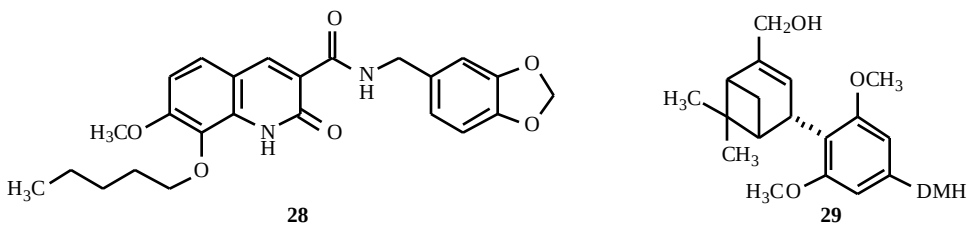


Fig. (9). Structures of JTE-907 and HU-308.

CB_2 receptor remain unclear. The CB_2 receptor is found primarily in the immune system and the immunomodulatory effects of cannabinoids are absent in CB_2 receptor knockout mice [43]. It is generally considered that the CB_2 receptor is absent from normal tissues in the central nervous system [8-10], however it is found in rat C6 glioma cells [23, 24] and CB_2 mRNA is expressed in adult rat retina [44].

Although the function of the CB_2 receptor is not well understood, CB_2 selective ligands have been found to have effects which are of potential therapeutic importance. These include the finding that JWH-133 (**11**, Fig. **4**) and ajulemic acid (**21**, Fig. **6**) inhibit the growth of glioma tumors in mice [25, 36]. However, Jacobson *et al*. concluded that the cannabinoid induced inhibition of C6 glioma cell proliferation involved both cannabinoid and vanilloid receptors [45]. JWH-133 and the mixed CB_1/ CB_2 agonist, WIN-55,212-2 (**3**, Fig. **1**) also inhibit the growth of nonmelanoma skin cancers [23]. This inhibition was prevented by both the CB_1 antagonist/inverse agonist, SR141716A (**24**, Fig. **7**) and the CB_2 antagonist, SR144528 (**12**, Fig. **4**), indicating that both the CB_1 and CB_2 receptors are involved in the inhibition of growth of these skin cancers. The CB_2 selective agonist, JWH-015 (**4**, Fig. **2**) induces apoptosis in several malignancies of the immune system [26]. In the same study it was found that THC (**1**, Fig. **1**), the endogenous cannabinoid, anadamide, and the potent traditional cannabinoid HU-210 but not WIN-55,212-2 (**3**) also induce apoptosis in malignancies of the immune system. These data indicate that CB_2 selective ligands are potentially useful anticancer agents.

Several workers have found that in addition to their tumor inhibitory action, CB_2 receptor agonists are effective antiinflammatory agents, which also alleviate inflammatory pain [21, 22, 46, 47]. The compounds which were investigated include CB_2 selective ligands GW405833 (**5**, Fig. **2**) [46], which was originally reported by Gallant *et al*. as L768242 [13], HU-308 (**29**, Fig. **9**) [47] and AM-1241 [21]. HU-308 (**29**) is a resorcinol dimethyl ether derivative, somewhat similar structurally to O-1966A (**27**, Fig. **8**). The structure of AM-1241 was not included in the publication which describes its antiinflammatory properties [21]. Nabilone, a synthetic traditional cannabinoid which has high affinity for both the CB_1 and CB_2 receptors [14] is active in a rat model of acute inflammation [22]. This action is blocked by the antagonist/inverse agonist SR144258 (**12**, Fig. **4**), implying that these effects are mediated by the CB_2 receptor.

It is apparent that the CB_2 receptor is involved in a complex manner with the immune system, tumor cells and inflammation, at least in the periphery. At the present time there are several highly selective ligands for the CB_2 receptor, which belong to several structural classes of cannabinoids. The selective indoles include JWH-015 (**4**, Fig. **2**), JWH-046 (**14**, Fig. **5**), AM-630 (**13**, Fig. **5**) and BML-190 (**15**, Fig. **5**). There are several highly selective 1-deoxy-Δ^8-THC analogues, including the parent compound, JWH-056 (**16**, Fig. **6**), JWH-133 (**11**, Fig. **4**) and JWH-065 (**17**, Fig. **6**). Other selective classical cannabinoid derivatives are 1-methoxy-Δ^8-THC-DMH (**6**, Fig. **2**), its $\Delta^{9(11)}$-isomer (**7**, Fig. **3**) and its next lower homologue, JWH-229 (**20**, R = C_5H_{11}, Fig. **6**). Other structural types which show selectivity for the CB_2 receptor include resorcinol derivatives such as HU-308 (**29**, Fig. **9**), pyrazoles, SR14258 (**12**, Fig. **4**), bridged pyrazoles (**25**, Fig. **8**) and a 2-quinololone, JTE-907 (**28**, Fig. **9**).

Currently the only class of CB_2 receptor ligands for which preliminary SAR have been developed are the 1-deoxy- and 1-methoxy-Δ^8-THC analogues [16, 35]. In spite of the synthesis of a number of indole derivatives, it has not been possible to develop SAR for this class of cannabinoids at the CB_2 receptor [20, 32]. Similarly, the SAR for cannabimimetic pyrazoles and resorcinols remain unclear and the structurally unique CB_2 selective quinolone, JTE-907 is apparently the only CB_2 receptor ligand with this molecular architecture. As a result of molecular modeling studies and the preparation of mutant receptors there is now considerable knowledge regarding the detailed structure of the CB_1 receptor and the manner in which it interacts with various classes of receptor ligands [48]. There is, however, considerably less known regarding the manner in which receptor ligands interact with the CB_2 receptor. The synthesis of additional CB_2 receptor ligands will not only aid in developing an understanding of ligand-receptor interactions, but may provide new highly selective compounds of potential therapeutic importance.

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