



Invited review

Prospective therapeutic agents for obesity: Molecular modification approaches of centrally and peripherally acting selective cannabinoid 1 receptor antagonists



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ARTICLE INFO

Article history:

Received 10 January 2014

Received in revised form

3 April 2014

Accepted 4 April 2014

Available online 5 April 2014

Keywords:

Endocannabinoid

Cannabinoid 1 (CB1) receptor antagonists

Obesity

Rimonabant

ABSTRACT

Presently, obesity is one of the major health problems in the developed as well as developing countries due to lack of physical work and increasing sedentary life style. Endocannabinoid system (ECS) and especially cannabinoid 1 (CB1) receptor play a key role in energy homeostasis. Food intake and energy storage is enhanced due to the stimulation of ECS hence, inhibition of ECS by blocking CB1 receptors could be a promising approach in the treatment of obesity. Rimonabant, a diaryl pyrazole was the first potent and selective CB1 receptor antagonist that was introduced into the market in 2006 but was withdrawn in 2008 due to its psychiatric side effects. Researchers all over the world are interested to develop peripherally acting potent and selective CB1 receptor antagonists having a better pharmacokinetic profile and therapeutic index. In this development process, pyrazole ring of rimonabant has been replaced by different bioisosteric scaffolds like pyrrole, imidazole, triazole, pyrazoline, pyridine etc. Variations in substituents around the pyrazole ring have also been done. New strategies were also employed for minimizing the psychiatric side effects by making more polar and less lipophilic antagonists/inverse agonists along with neutral antagonists acting peripherally. It has been observed that some of the peripherally acting compounds do not show adverse effects and could be used as potential leads for the further design of selective CB1 receptor antagonists. Chemical modification strategies used for the development of selective CB1 receptor antagonists are discussed here in this review.

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1. Introduction

1.1. Obesity

According to World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation in body that may impair health. More than 1.4 billion adults in the age of 20 and older were overweight in 2008, among which more than 200 million were men and nearly 300 million women were found to be obese. A very staggering fact is that more than 40 million children under the age of five were obese in 2011. At present, obesity has become the fifth leading risk factor for global deaths [1]. Obesity creates a major risk factor for a number of diseases like cardiovascular diseases, type 2 diabetes, osteoarthritis, hypertension, stroke, sleep apnea, and certain types of cancers [2,3]

indicating that obesity is one of the major challenging health problems these days [4].

1.2. Therapeutic targets for the treatment of obesity

Worldwide, researchers are searching for newer targets for the treatment of obesity. Till date various targets have been identified and unfortunately none have provided a potential therapy for obesity. Hence, there is a worldwide demand to develop a "magic bullet" to lose body weight [5]. For the treatment of obesity, peptide targets like cholecystokinin (CCK-1) agonists, glucagon-like peptide 1 (GLP-1) analogs, amylin analogs, neuropeptide Y agonists, peptide YY agonists, ghrelin antagonists, MCH1 receptor antagonists, MC4 receptor agonists and monoamine targets such as 5-HT_{2B} receptor agonists, 5-HT₆ receptor antagonists, 5-HT_{2C} agonists, β3 AR agonists, dopamine agonists as well as lipase inhibitors, anticonvulsants, cannabinoid 1 (CB1) receptor antagonists, μ-opioid receptor antagonists, sympathomimetic agents, AgRP (agouti-related

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Table 1

Current status of developed anti-obesity drugs with their targets [5–8].

Sr. no	Targets	Drug	Year of approval	Year of withdraw	Current status
A. Agonists					
1.	Sympathomimetic agents	Phentermine	1959		Approved for short-term use
2.	Cholecystokinin (CCK-1) agonists	GI181771X			Phase III
3.	Glucagon-like peptide 1 (GLP-1) analogs	Liraglutide			Phase III
4.	Neuropeptide Y agonists	Obineptide			Phase II
		Valneperil			Phase II
		TM30339			Phase I
5.	MC4 receptor agonists	MK-0493			Phase I
6.	5-HT _{2B} receptor agonists	Fenfluramine	1973	1997	Phase II
7.	5-HT _{2C} receptor agonists	Dexfenfluramine	1996	1997	
		Lorcaserin			Approved in 2012 on re-filing
8.	β3 AR agonists	ATH-X105			Phase II
		LY377604			Phase II
		KRP-204			Phase II
B. Antagonists/inhibitors					
9.	MCH1 receptor antagonists	NGD-4715			Phase II
10.	5-HT ₆ receptor antagonists	BVT.74316			Phase I
		PRX-07034			Phase I
11.	Dopamine (D3) antagonists	GSK598809			Phase I
12.	Cannabinoid 1 (CB1) receptor antagonists	Rimonabant	2006	2008	Abandoned in 2011 (Phase II)
13.	Neuropeptide Y5 receptor antagonists	S-2367			Phase I
14.	μ-Opioid receptor antagonists	GSK 1521498			Abandoned in 2010 (Phase I)
15.	Sodium glucose transporter-2 (SGLT-2) antagonists	Remogoflozin etabonate (GSK189075)			Available in market
16.	Lipase inhibitor	Orlistat	1999		Phase III
		Cetilistat			Abandoned in 2010 (Phase II)
17.	Mitochondrial transfer protein inhibitor	SLx-4090			Phase I
18.	Agouti-related protein (AgRP) inhibitor	TPN435			Phase I
19.	Methionine aminopeptidase (MetAP ₂) inhibitors	ZGN-433			Phase I
20.	Diacylglyceride acyltransferase (DGAT ₁) inhibitors	AZD7687			Phase I
		PF-04620110			Phase I
21.	Sodium glucose co-transporter-2 (SGLT ₂) inhibitors	PF-04971729			Phase I
C. Combination therapy					
22.	Norepinephrine/dopamine releasing stimulators	Diethylpropion	1959		Approved for short-term use
		Benzphetamine	1960		Approved for short-term use
		Phendimetrazine	1982		Approved for short-term use
23.	NA/5-HT reuptake inhibitors	Sibutramine	1997	2010	Phase III
24.	Antiepileptic, dopamine/noradrenaline reuptake inhibitor	Empatic (Zonisamide + Bupropion)			
25.	5-HT/DA/NA reuptake blocker	Tesofensine			Phase III
		DOV21947			Phase II
26.	Sympathomimetic agent, weak carbonic anhydrase inhibitors (exact mechanism for obesity is still unknown)	Quexa (Phentermine + topiramate)	Approved in 2012 on re-filing		
27.	Dopamine and noradrenaline reuptake inhibitors	Contrave (Bupropion + naltrexone)			FDA declined in 2011 and asked for data on long term cardiovascular risk
28.	Amylinomimetic/leptin analog	Pramlintide/metreleptin			Phase II programme terminated in 2011

protein) inhibitors, MetAP₂ (methionine aminopeptidase) inhibitors mixed noradrenaline/serotonin reuptake inhibitors, mixed dopamine and noradrenaline reuptake inhibitors and mixed noradrenaline dopamine and serotonin reuptake inhibitors have been identified [6]. Phentermine, a sympathomimetic amine was approved for short-term use by FDA in 1959 as an anti-obesity agent [7]. But phentermine was withdrawn from Europe market due to its risk of cardiovascular effects and abuse potential [6]. Lorcaserin is a selective 5-HT_{2C} receptor agonist. It was initially rejected in 2010 due to carcinogenicity observed in preclinical studies, but on re-filing FDA approved lorcaserin in July 2012. A CB1 receptor antagonist, rimonabant was withdrawn from the market in 2008 due to its psychiatric side effects [8]. Orlistat, a gastrointestinal and pancreatic lipase inhibitor acting peripherally was the first long-term use drug approved by FDA for the treatment of obesity in 1999 and is available in the market. It does not show any clinically significant effects on triglycerides or HDL cholesterol. It exhibited gastrointestinal adverse effects like flatulence,

steatorrhoea, malabsorption, faecal urgency, faecal incontinence, abdominal pain, upset stomach, dyspepsia and reduced absorption of fat soluble vitamins [9–11]. Researchers have begun to develop combination therapy for the treatment of obesity. This strategy was adopted due to the fact that various mechanisms are involved in food intake modulation. It has also been proposed that more favourable weight loss and a better safety profile can be achieved by using multiple targeting agents [7]. Qnexa is a combination of topiramate (anticonvulsant) and phentermine (amphetamine derivative) which has completed phase III clinical trial although FDA did not approve Qnexa in its current form in 2010. The FDA had asked for its data regarding teratogenicity in 2011, Qnexa was approved in 2012 [7] after ensuring its safety. Contrave, another drug, is a combination of naltrexone (opioid antagonist) and bupropion (antidepressant). FDA's Endocrinologic and Metabolic Drug Advisory Committee voted to support Contrave for approval in 2010. But in 2011, the FDA asked for its data regarding long-term cardiovascular risk assessment [7]. Sibutramine a NA/5-HT

reuptake inhibitor was withdrawn from market due to its increased risk of cardiovascular side effects in 2010 [8]. Current status of all these anti-obesity agents is shown in Table 1. Thus, it is clear that the choice of available drugs for the treatment of obesity is highly limited. Hence, there is an urgent need to develop effective anti-obesity drugs [12].

Although rimonabant has been withdrawn from the market and several other CB1 receptor antagonists have been also terminated from development programmes, it can be said that researchers have not yet reached the altar of development of CB1 receptor antagonists for the treatment of obesity [8]. Brain non-penetrant CB1 receptor antagonists that act only at peripheral site might prove as promising therapeutics for obesity [13]. Along with this, two new intriguing suggestions are also in consideration. The first suggestion is based on low-dose combination of rimonabant with other anorectic agents such as opioid receptor antagonists, 5-HT_{2C} receptor agonists or gut peptide CCK-8s. The second one is related to recent genomic studies which state that development of anxiety or depression in response to agents like rimonabant may be contributed by variants (polymorphisms) of the CB1 receptor gene alone or in combination with the gene for serotonin transporter (SLC6A4) [8]. Thus, a lot of work still remains to be done for the design and optimization of existing lead molecules of CB1 receptor antagonists. Discussion on centrally acting selective CB1 receptor antagonists is equally important for the development of peripherally acting selective CB1 receptor antagonists. Hence, in this review we have discussed all the developments that have taken place in the field by considering both centrally and peripherally acting selective CB1 receptor antagonists which have been reported till date.

1.3. Endocannabinoids

The endocannabinoids belong to the biologically active lipid family which bind and activate cannabinoid receptors [14]. Anandamide and 2-arachidonoyl-sn-glycerol (2-AG) are the two main endocannabinoids or endogenous agonists acting as neurotransmitters or neuromodulators [10,14,15]. Both these endocannabinoids are derived from arachidonic acid and released from a variety of different types of cells. They are metabolised or inactivated immediately after performing their function by the enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGLipase), as shown in Fig. 1 [6,10,16]. The functions of these endocannabinoids are related to food intake and control of energy balance including peripheral and central orexigenics. They are present

in the hypothalamus region which is responsible for controlling food intake. When these endocannabinoids are released in the hypothalamic nucleus, they stimulate food intake [10]. Peripheral lipid and glucose metabolism may also be regulated by endocannabinoids after binding to CB1 receptors that are present in the peripheral tissues such as white adipose tissue, liver, skeletal muscles and pancreas [17]. Thus, over-activation of endocannabinoid system or increased endocannabinoid levels cause obesity [9,18]. Blocking the overactivity of endocannabinoids in the peripheral tissues by antagonising the CB1 receptor can control obesity. Thus, there is a focus on CB1 receptor antagonists as a new class of drugs for the treatment of obesity [19,20].

1.4. Cannabinoid receptors

For more than 4000 years, cannabis from *Cannabis sativa* has been utilized for psycho stimulant purposes due to its mind-altering effect, as well as for therapeutic purposes [21]. The cannabis plant contains more than 60 cannabinoids but Δ⁹-tetrahydrocannabinol (THC) is the most active and clinically relevant psychoactive component identified in 1974. Synthetic THC like dronabinol is used in the treatment of post-chemotherapy nausea and emesis, and also in anorexia associated with HIV infection [22]. After the discovery of THC, extensive researches have been investigated to find its specific receptors known as CB1 and CB2 receptor [4]. Data suggest that there may be a third CB3 receptor also but it has yet to be cloned [23,24]. The CB1 receptor was cloned in 1990 [25] and later in 1993 CB2 receptor was also cloned. The CB1 receptor is located mainly in brain areas including basal ganglia, cerebellum, hippocampus and cortex, and in peripheral tissues such as testis, eye, urinary bladder, ileum, adipose tissue, liver, skeletal muscles and pancreas. On the other hand, the CB2 receptor is almost exclusively expressed in cells of the immune system in peripheral tissues, the thymus, tonsils, bone marrow, spleen, pancreas, peripheral nerve terminals, microglial cells, glioma and skin tumour cells as shown in Fig. 2 [26–30].

Both CB1 and CB2 receptors contain seven transmembrane (TM) domains which are connected by three intracellular and three extracellular loops as I1, I2, I3 and E1, E2, E3 respectively. The intracellular C-terminus region starts with a small helical domain and contains a site of palmitoylation. The extracellular N-terminus contains potential N-glycosylation site as shown in Fig. 3. The ligand binding pocket is present in the crevice that is formed by the helix bundle. It has been suggested through site directed mutation

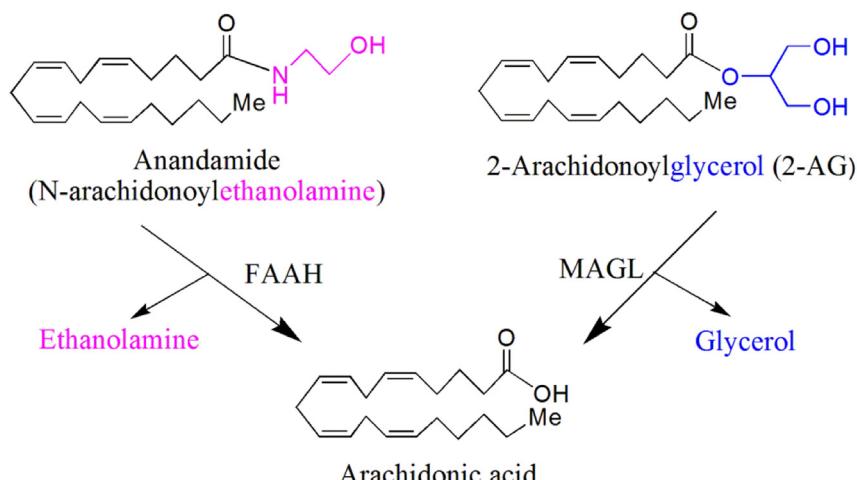


Fig. 1. Metabolism of anandamide and 2-arachidonoylglycerol.

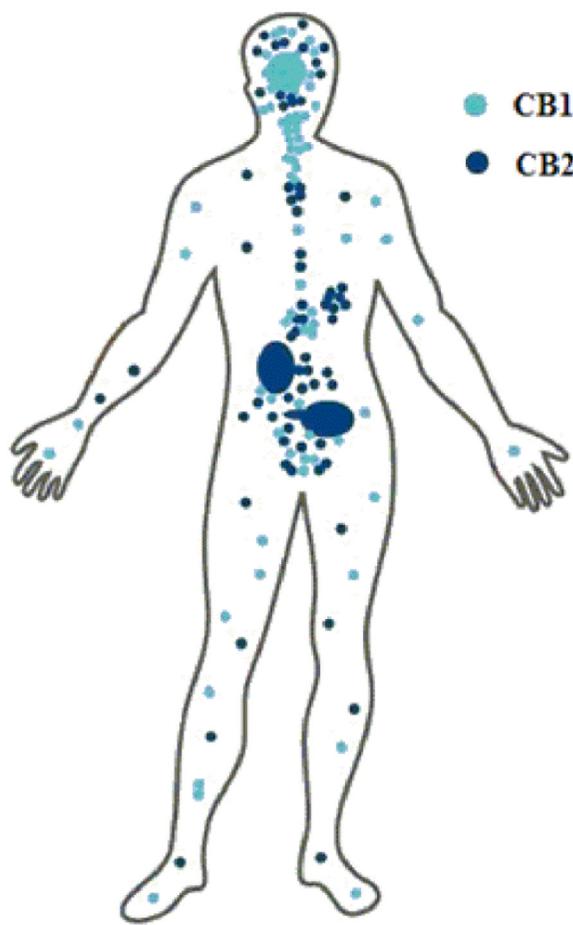


Fig. 2. Location of CB1 and CB2 receptors in human body.

and crystal structures of rhodopsin and the $\beta_{1/2}$ -adrenergic receptors that ligand binding occurs with the residues present in the TM3-5-6-7. But, the mutation of lysine 192 present in TM3 of the CB1 receptor proved critical for the binding of some agonists such as CP55940, HU-210 and anandamide while no effect was observed with WIN55212 which indicated that the binding site was not exactly the same for binding to various ligands. CB receptors do not form a disulfide bond between TM2 and E2 unlike other class A GPCRs, although CB receptors contain two cysteine residues in E2 which can form a disulfide bridge. A 44% amino acid sequence

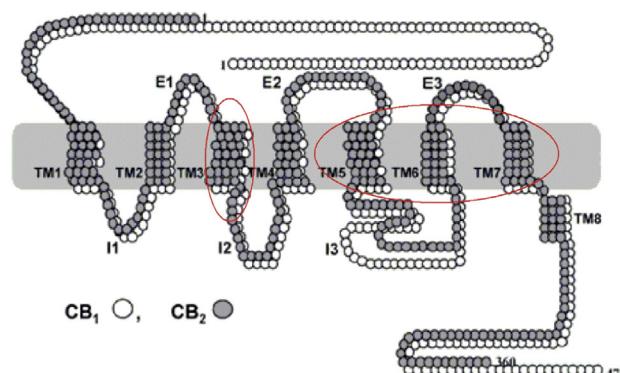
identity exists between CB1 and CB2 receptors encoded by different genes [4].

1.5. Signal transduction mechanisms in CB1 receptors

Both CB1 and CB2 receptors are G-protein-coupled receptors (GPCR) belong to the rhodopsin GPCR family (Class A). Both excitatory and inhibitory neurotransmissions present in most of the brain region are inhibited by the activation of CB1 receptors present on the nerve terminals [31]. In peripheral tissues and neurons, activation of CB1 receptors inhibits adenylate cyclase which decreases the production of cAMP, causing attenuation of the protein kinase A (PKA) signalling cascade [31–33]. PKA phosphorylates the potassium channel protein in the absence of cannabinoids resulting in decreased outward potassium current. But in the presence of cannabinoids, reduction in the phosphorylation of the potassium channel occurs resulting increased outward potassium current [34]. Phosphorylation is regulated by CB1 receptors and activation of CB1 receptors result in stimulation of different members of mitogen activated protein kinase family (MAPKs) including extracellular signal-regulated kinase-1 and -2 (ERK 1/2), p38 MAPK and c-jun N-terminal kinase (JNK) [32,35]. Stimulation of CB1 receptors in neurons inhibit voltage-activated Ca^{2+} channels directly and mediate retrograde signal transduction and activate G-protein coupled ‘inwardly-rectifying K^+ channels’ which decrease neuronal excitability [31,36,37]. CB1 receptor mediated downstream signalling and intracellular protein machinery is shown in Fig. 4 [37]. CB2 receptors have an almost similar mechanism of action as CB1 receptors in inhibiting adenyl cyclase and decreasing the production of cAMP in different types of cells. Stimulation of CB2 receptors also activate MAPK cascades. But CB2 receptors do not act on ion channels [34,38,39].

1.6. Role of CB1 receptors in obesity

It has been well recognised that endocannabinoid system (ECS) and especially CB1 receptor have a vital role in energy homeostasis and modulate both food intake and fat metabolism [40]. The endogenous signalling system in ECS acts on both central as well as peripheral sites. Recent investigations have indicated that the ECS activity is increased in human obesity [41–44]. In the central site, food intake is controlled by the ECS, mainly at two functional levels i.e. the hypothalamus and the limbic systems. The role of hypothalamic ECS is to modulate feeding by decreasing satiety signals and increasing orexigenic signals [45]. After fasting for a short time, the ECS in the hypothalamus becomes activated, stimulating the



Parameters	CB1	CB2
Gene localisation	6q14-q15	1p36
Gene length (kb)	25	39
Exons	4	2
Amino acid sequence length	472	360

Fig. 3. Schematic representation of two-dimensional structures of CB1 and CB2 receptors. Red circles represent the ligand binding site [4]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

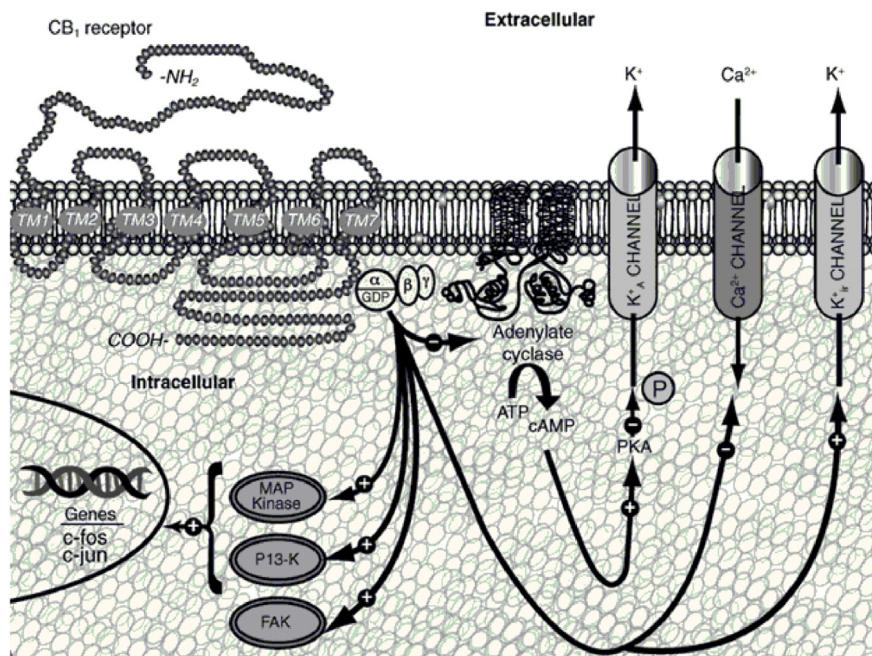


Fig. 4. Mechanism of action of CB1 receptor [37].

appetite subsequently [46]. Endocannabinoids are shown to increase eating incitement, possibly reinforcing the incentive and hedonic value of food. The limbic system also plays a part in controlling over intake of food [45,47]. Stimulation of CB1 receptors on the GABAergic terminals in the Ventral Tegmental Area (VTA) increases dopaminergic neuronal activity resulting in increased release of dopamine in the nucleus accumbens [48]. Release of dopamine in the mesolimbic pathway increases the consumption of food. Thus, it has become clear by the growing evidence that the interaction between mesolimbic endocannabinoid and dopamine systems regulate food intake. In peripheral sites, ECS regulates energy balance by peripheral lipogenic mechanism and modulation of lipid and carbohydrate metabolism. It is proposed on the basis of available evidence that activation of CB1 receptors in the peripheral tissue boosts the lipogenesis, lipid storage, insulin secretion, glucagon secretion and adiponectin modulation [45,47]. Stimulation of CB1 receptors in adipocytes, increases synthesis and storage of triglycerides, decreases adiponectin and facilitates glucose uptake which leads to obesity [49]. Leptin level is decreased due to blocking of CB1 receptors resulting in increase in food intake [50]. Conversely, leptin administration decreases the levels of endocannabinoids in the hypothalamus [51]. Along with this, stimulation of CB1 receptors leads to activation of lipoprotein lipase and enhances the sequestering of free fatty acids by adipocytes. Hence, blocking of CB1 receptors in adipose tissue decreases free fatty acid concentration into the circulation which results in lowering of fat storage and improved insulin sensitivity [41,46,49,52–55]. In the GI tract, the endocannabinoids acting on CB1 receptors reduce the satiety signals generated by cholecystokinin [56]. This CB1 agonist also enhances the ability of ghrelin to stimulate food intake [57]. It has also been reported that inhibition or mutations in the endocannabinoid metabolizing enzyme FAAH, increases the endocannabinoid levels thus accentuating the orexigenic and lipogenic actions of these agents [43]. Activation of CB1 receptors in intestine produces slow peristalsis and prolonged intestinal transit times which may promote weight gain. Therefore, blocking of CB1 receptors produces a pro-kinetic effect [46]. Hepatic CB1 receptors have a vital role in lipogenesis. Activation of CB1 receptors in liver

stimulates several lipogenic factors such as sterol response element-binding protein-1C (SREBP-1C), which increases fatty acid synthesis resulting in the development of fatty liver [58–60]. Glucose metabolism and insulin sensitivity is also controlled by ECS [61]. Hence, blocking of CB1 receptors in skeletal muscles enhances basal oxygen consumption and glucose uptake, resulting in increase in energy expenditure and improvement in insulin sensitivity. Peripheral CB1 receptors therefore have a prominent role in the modulation of metabolism [45–47]. The role of ECS in central and peripheral systems is shown in Fig. 5 [46]. Reducing ECS activity by CB1 receptor antagonists results in decrease in food intake and increased energy expenditure [62]. Thus, development of CB1 receptor antagonists could be a promising strategy in the treatment of obesity.

1.7. Selectivity issues

Selectivity is a very critical part in the designing of CB1 receptor antagonists. Two types of selectivity must be seen in CB1 receptor antagonists. First selectivity is related to CB1 over CB2 receptors. Agonists of the CB2 receptors have been shown to possess cardioprotective effects which are mediated through attenuation of TNF- α and endothelial inflammatory mediators. Thus, it may be speculated that blockade of these receptors may worsen cardiometabolic conditions like myocardial infarction and/or atherosclerosis [63,64]. Blockade of CB2 receptors reduced apoptosis of peritoneal macrophages induced by oxLDL thus accentuating foam cell formation [65]. Additionally, CB2 receptor activation has been shown to exhibit immunosuppressive actions. Blockade of these receptors can lead to worsening of autoimmune disorders like colitis [66]. CB2^{-/-} mice showed enhanced cisplatin-induced kidney inflammation, oxidation/nitrosative stress, cell death and dysfunction in the renal capsule; effects which might have been shown upon treatment with CB2 receptor antagonists [67]. In rodents, CB2 receptor antagonists increased dermal thickness and leucocyte infiltration in the skin leading to a fibrosis like condition [68,69]. CB2^{-/-} mice have been reported to have a condition similar to post-menopausal osteoporosis which could be attributed to the

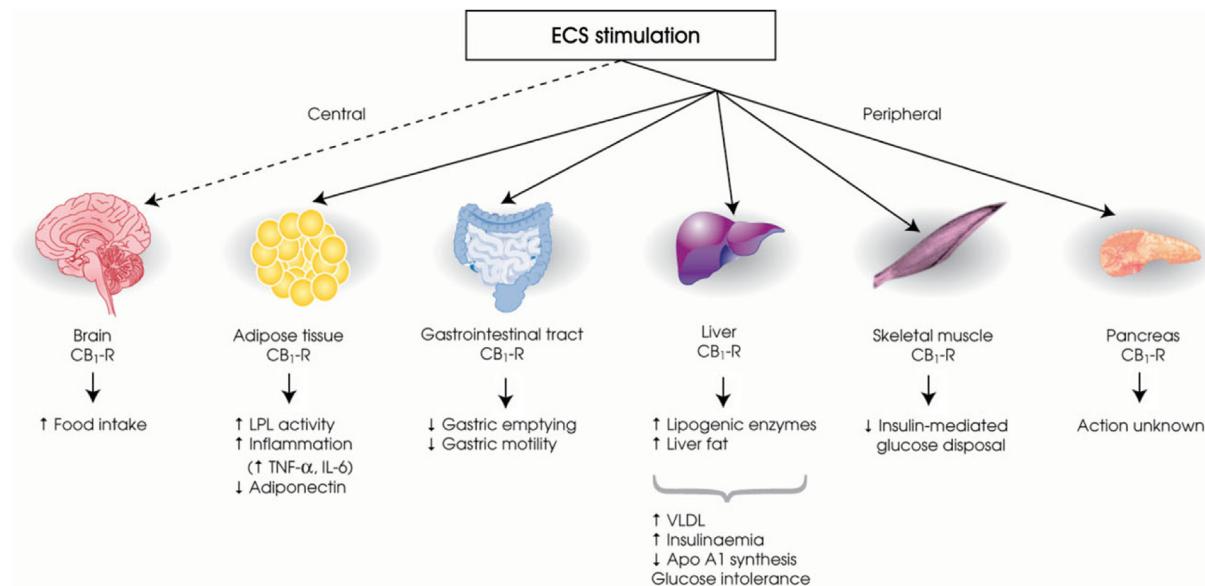


Fig. 5. Effect of overactivity of the ECS at both central and peripheral levels and the effect of the CB1 receptor blockade [46].

decreased inhibition of osteoclast activity [70]. In light of these findings, it would be prudent to design agents which avoided CB2 receptor antagonism.

Second selectivity aspect is concerned with peripherally acting over centrally acting CB1 receptor antagonists. Centrally acting CB1 receptor antagonists exhibited psychiatric side effects like depression, anxiety, irritability or even suicidal tendency as well as gastrointestinal disorders like nausea and neurological alterations like headaches and vertigo [10]. Hence, compounds should be designed keeping the fact in mind that the designed compounds should not cross the blood brain barrier (BBB) and should act only peripherally.

Using of molecular modelling techniques, McAllister et al. [71] reported the binding region for CB1 receptor. The transmembrane helix (TMH) 3-4-5-6 of cannabinoid receptor formed aromatic domain which contained F3.25, F3.36, W4.64, Y5.39, W5.43 and W6.48 residues. Selective CB1 receptor antagonist, rimonabant and CB1/CB2 receptor agonist WIN55212-2 both were bound within this microdomain as shown in Fig. 6. Rimonabant exhibited direct aromatic stacking interactions with F3.36, Y5.39 and W5.43 residues as well as hydrogen bonding with K3.28. In a similar micro-domain, WIN55212-2 also showed direct aromatic stacking

interactions with F3.36, W5.43 and W6.48 residues. Mutation in F3.36 produced 3-fold loss in affinity for rimonabant and 9-fold loss in affinity for WIN55212-2 indicating that F3.36 had direct interactions with rimonabant and WIN55212-2. The W5.43 mutation showed 8-fold loss in affinity for WIN55212-2 and deleterious effect upon rimonabant binding. The obtained results supported the modelling studies that W5.43 oriented centrally in the aromatic cluster interaction with rimonabant. The model suggested that W5.43 had direct stacking interactions with both monochlorophenyl and dichlorophenyl rings of rimonabant. W5.43 also helps rimonabant to orient in the binding pocket. Mutation in W6.48 showed 4-fold and 7-fold loss in affinity for WIN55212-2 and rimonabant respectively. W6.48 does not interact directly with rimonabant but interact through F3.36. It has become clear by the mutation studies that F3.36, W5.43, and W6.48 are part of the binding pocket for both rimonabant and WIN55212-2. Along with this, it was also observed that mutation in K3.28 resulted in 17-fold loss in binding affinity for rimonabant but the binding affinity and receptor activity for WIN55212-2 was retained. This indicates that K3.28 is one of the key residues which directly interacts with rimonabant by forming hydrogen bond but it does not interact with WIN55212-2 [72,73].

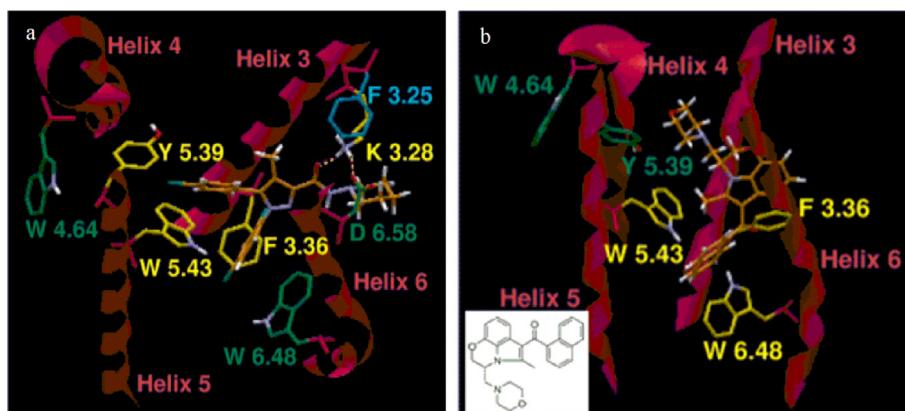


Fig. 6. (a) CB1 receptor antagonist rimonabant and (b) CB agonist WIN55212-2 docked in CB1 receptor [71].

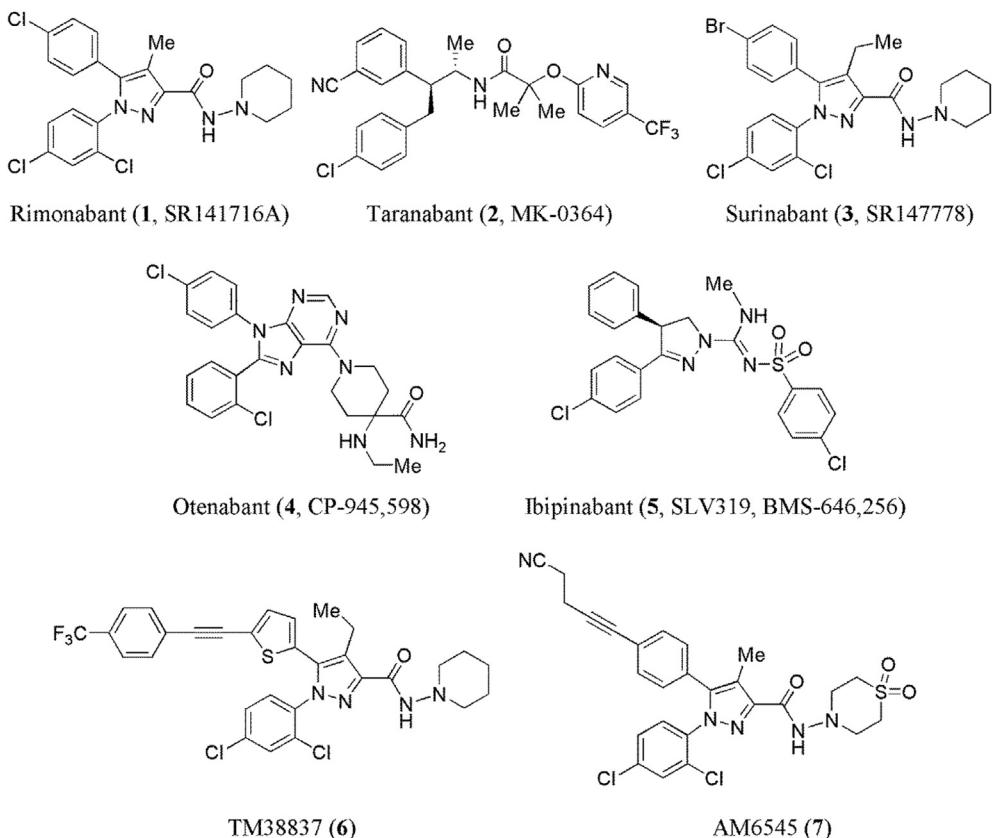


Fig. 7. Chemical structures of some centrally and peripherally acting CB1 receptor antagonists (1–7).

As far as binding region of CB2 receptor is concerned, Leu108, Ser112, Pro168, Leu169, Trp194 and Trp258 residues present in TMH 3-4-5 formed the active site for CB2 receptor. Selectivity for CB2 receptor is mainly produced by the interaction of S3.31 and F5.46 residues present in CB2. It has been observed that the selectivity for CB2 receptor was increased when a lipophilic group of the ligand interacted with F5.46 and another group was capable of forming a hydrogen bond with S3.31 [74–76]. Thus, molecular modelling studies can help in the designing of newer selective CB1 receptor antagonists.

Designing of CB1 receptor antagonists showing selectivity towards CB1 receptors over CB2 receptors as well as selectivity for peripheral sites over central action is of prime importance. Hence, peripherally acting selective CB1 receptor antagonists could act as a safe strategy for the treatment of obesity.

1.8. Centrally and peripherally acting CB1 receptor antagonists

In the late 1980's, the structure of THC was modified for the first time to develop a selective CB1 receptor antagonist, but the results obtained were disappointing [77]. After long research efforts, Rinaldi-Carmona and co-workers from Sanofi Recherche finally discovered rimonabant (1, Fig. 7) in 1994. Rimonabant was the first potent CB1 receptor antagonist having 1000 fold CB1 selectivity over CB2 [78]. In 2006, Rimonabant was approved by European Commission as an anti-obesity agent. Unfortunately, European Medicine Agency had to withdraw the drug from the market due to the risk posed by the drug like serious psychiatric disorders including drug induced suicidal tendency. Still rimonabant was considered as the most promising lead compound in the treatment of obesity [77]. Taranabant (2, Fig. 7) was developed by Merck

Research Laboratory as a CB1-inverse agonist for the treatment of obesity due to its anorectic effect [79]. But the compound was suspended in phase III clinical development programme for the same reasons of psychiatric problems. Other compounds like surinabant [80] (3, Fig. 7) and otenabant [81] (4, Fig. 7) were also terminated in phase III development programme [77]. Solvay Pharmaceuticals Research Laboratories discovered ibipinabant (5, Fig. 7) as a CB1 receptor antagonist [82].

Recently, TM38837 (6, Fig. 7) was discovered by 7TM Pharma as a peripherally acting CB1 receptor antagonist devoid of CNS penetration and showing brain plasma ratio of 1:33 [83]. At 100 mg dose, TM38837 does not cross BBB thus causing no effect on CNS [84]. AM6545 (7, Fig. 7) was developed as a peripheral neutral antagonist [85,86]. Neutral antagonists were designed with the assumption that such compounds would be devoid of or have decreased psychiatric and other side effects while retaining their metabolic action [9]. Compound 7 was a rimonabant derivative exhibiting very promising properties with more convincing evidence for peripherally effective selective CB1 receptor antagonism. Compound 7 had a marked ability to improve glucose tolerance, caused increased adiponectin levels, lowered leptin and insulin levels and caused reduction in triglycerides [61]. Thus, designing of neutral CB1 receptor antagonists was considered to be a safer and effective strategy for the treatment of obesity [87].

Researchers at present are focussing on the development of peripherally acting CB1 receptor antagonists for minimization or prevention of CNS adverse effects [9]. Generally, polar compounds are poor brain entrants while increasing lipophilicity enhances brain penetration [88]. Thus, peripheral acting CB1 receptor antagonists can be designed by increasing polar surface area (PSA) and lowering the lipophilicity. Neutral compounds have also been

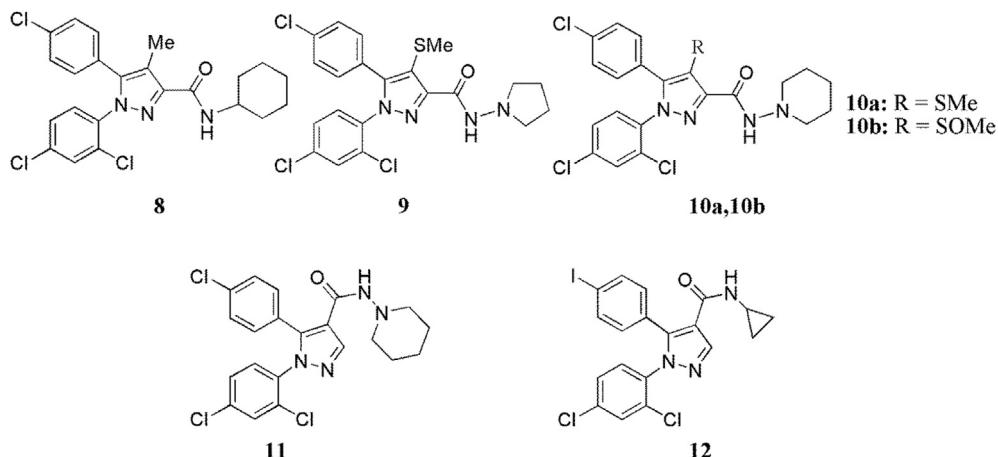


Fig. 8. Chemical structures of diaryl pyrazole derivatives (8–12).

developed as peripherally acting CB1 receptor antagonists devoid of adverse effects showing little or no brain penetration [87,89,90]. Some charged compounds have also been developed because charged moieties do not cross BBB. Thus, at present designing of peripherally acting CB1 receptor antagonists is the prime task which could be proved as a potential target for the treatment of obesity. Till date various reviews [91–98] covering the development of compounds acting on CB1 and/or CB2 receptors are reported along with some patented compounds [99–102]. In this article, various chemical modification strategies and computational studies used in the direction of development of selective CB1 receptor antagonists are focussed upon.

2. Development of CB1 receptor antagonists

As rimonabant was the first compound to be recognized as a CB1 receptor antagonist for the treatment of obesity, most of the structural modifications have been done on the basic scaffold of 1,5-diaryl pyrazole of rimonabant with substituents at different positions on the basic scaffold. The pyrazole ring has been replaced with different five and six membered rings and also by bicyclic or tricyclic ring systems. Diaryl rings of rimonabant have been eliminated in some cases to design selective CB1 receptor antagonists. In other cases different positions especially 3, 4 and 5 of pyrazole ring of rimonabant have been substituted with a variety of groups.

2.1. Diaryl pyrazole derivatives

Francisco et al. [103] synthesized various analogs of rimonabant (**1**) by substituting the aminopiperidinyl moiety with alkyl hydrazines, amines, and hydroxyalkylamines of varying lengths. The *N*-cyclohexyl amide derivative **8** (Fig. 8) exhibited the highest affinity toward CB1 receptor ($K_i = 2.46 \text{ nM}$).

Substitution with methylsulfanyl at 4th position of pyrazole ring such as compounds **9** and **10a** (Fig. 8) showed more potent activity ($K_i = 3$ and 13 nM respectively) than rimonabant ($K_i = 25 \text{ nM}$). The *in vitro* studies for compound **9** and **10a** was carried out using displacement of the specific binding of [^3H] CP-55,940 in Chinese Hamster Ovary (CHO) cells. Compound **9** showed higher selectivity (221) towards CB1/CB2 receptor subtype than rimonabant (63). Unfortunately compounds **9** and **10a** showed $A \log P$ value of 6.2 and 6.7 respectively similar to the rimonabant ($A \log P = 6.6$). It was also observed that substitution with more polar group like methysulfanyl, compound **10b** (Fig. 8), exhibited K_i value of 20 nM as

well as had a limited brain exposure ($A \log P = 5.6$) of P-glycoprotein substrates as compared to rimonabant [104].

Menozzi et al. [105] replaced the hydrazide/amide group from position 3 to position 4 of the pyrazole ring. The designed compound **11** (Fig. 8) was structurally similar to rimonabant. It showed a competitive binding of 79% and 37% for *hCB1* and *hCB2* receptors (Radioligand displacement [%] at $10 \mu\text{M}$). Binding interactions of rimonabant and the analog **11** are shown in Fig. 9. Interaction with Lys192 is essential for CB1 receptor antagonistic activity [71]. Similar hydrogen bonds were formed by rimonabant and **11** with Lys192 and Ser383 which favoured the displacement of hydrazide/amide group from position 3 to position 4. From this series, compound **12** (Fig. 8) was obtained as the most active compound ($K_i = 0.21 \mu\text{M}$) but found to be 10-fold less active than rimonabant.

Srivastava et al. [106] synthesized diaryl pyrazolesulfonamide derivatives by replacing CO group of rimonabant with SO_2 . Rimonabant and its sulfonamide derivative **13** were oriented similarly as shown in Fig. 10. Both the oxygens of carboxamide and sulfonamide groups formed hydrogen bonds with the Lys192 fragment. But, the CB1 receptor antagonistic activity of compound **13** was found to be less in the *in vitro* cAMP *hCB1* functional assay and in preliminary *ex-vivo* experiments. This study suggested that the bulky $-\text{SO}_2$ group was a misfit in place of $-\text{CO}$ group although it gave favourable PLP value and docking score.

Lan et al. [107] designed and synthesized a series of pyrazole derivatives in which iodine was substituted to serve as an effective probe for single photon emission computed tomography (SPECT) for radioimaging of CB1 receptors *in vivo* for the development of highly selective CB1 ligands. The *p*-iodophenyl analog AM251 (**14a**, Fig. 11) was the most potent compound in the series with high degree of selectivity ($K_i = 7.5 \text{ nM}$, $\text{CB2}/\text{CB1} = 306$) and an excellent candidate for SPECT probe. Further, Lan et al. [108] synthesized AM281 (**14b**, Fig. 11) by replacing the piperidine ring with a morpholine ring which resulted in an increase in selectivity for CB1 receptors (K_i value of 12 nM with $\text{CB2}/\text{CB1}$ ratio of 350).

Later, Katoch-Rouse et al. [109] focused on the development of a series of rimonabant (**1**) analogs as potential tracers for positron emission tomography (PET) with higher affinity and low lipophilicity compared to the existing CB1 radiotracers. The methyl group at C4 of pyrazole ring was replaced by bromo substituent in compound **15** (Fig. 11) with enhanced binding affinity ($K_i = 1.4 \text{ nM}$, $c\log D = 4.94$) but unfortunately it possessed higher lipophilicity than rimonabant ($K_i = 1.8 \text{ nM}$, $c\log D = 4.81$). Substitution of methoxy group at 4 position of phenyl ring in compound **16** (Fig. 11) showing significant receptor affinity and lowered lipophilicity

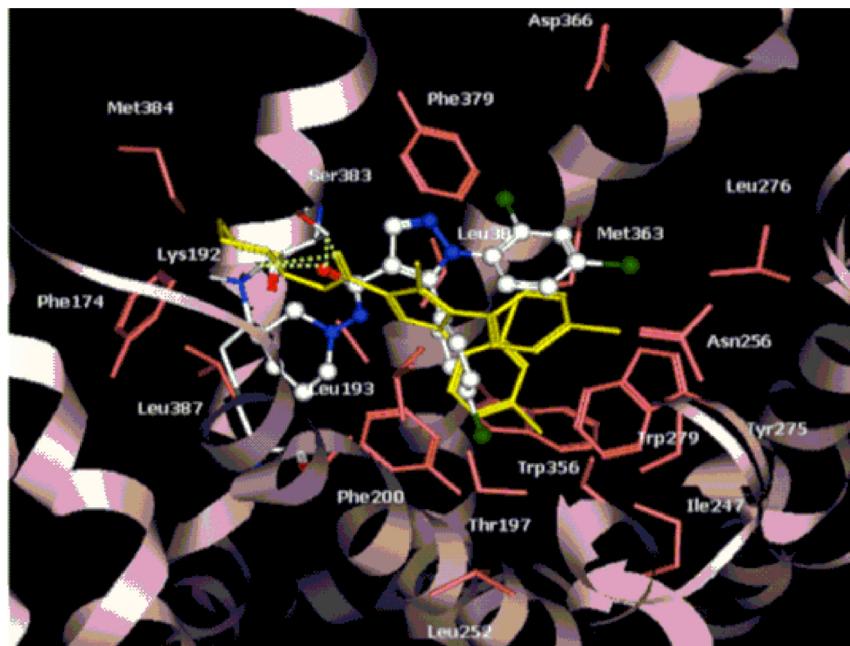


Fig. 9. Binding mode of rimonabant (1) shown in yellow colour and its structurally related analog 11 coloured by atom type, inside hCB1 receptor; H-bonds are displayed as dashes [105]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

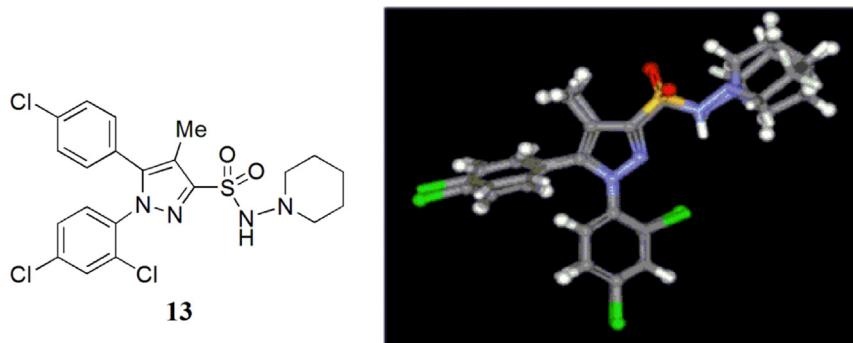


Fig. 10. Overlay of energy-minimized structures of molecule 13 with 1 [106].

($K_i = 4.1$ nM, clogD = 4.06) than rimonabant and was considered as a potential lead for the development of CB1 receptor antagonists. Donohue et al. [110] were also interested in the development of PET or SPECT radioligands that could be utilized for molecular imaging of brain CB1 receptors. Compound 17 (Fig. 11) was the most potent and selective radioligand in the series with 11 nM antagonist binding affinity (K_B) and CB1 selectivity > 773 for *in vivo* imaging of brain CB1 receptors with PET.

Fan et al. [111] synthesized a novel series of analogs of JHU75528 (18, Fig. 11) which were the first PET radioligands for CB1 receptors showing reasonable imaging properties in animals with high affinity and reduced lipophilicity than rimonabant ($K_i = 11$ nM; log D_{7,4} = 3.3–3.6). Compounds 19a, 19b and 20 (Fig. 11) were obtained and evaluated as potential radioligands for PET imaging of CB1 receptors in human subjects ($K_i = 13, 2$ and 10.3 nM respectively).

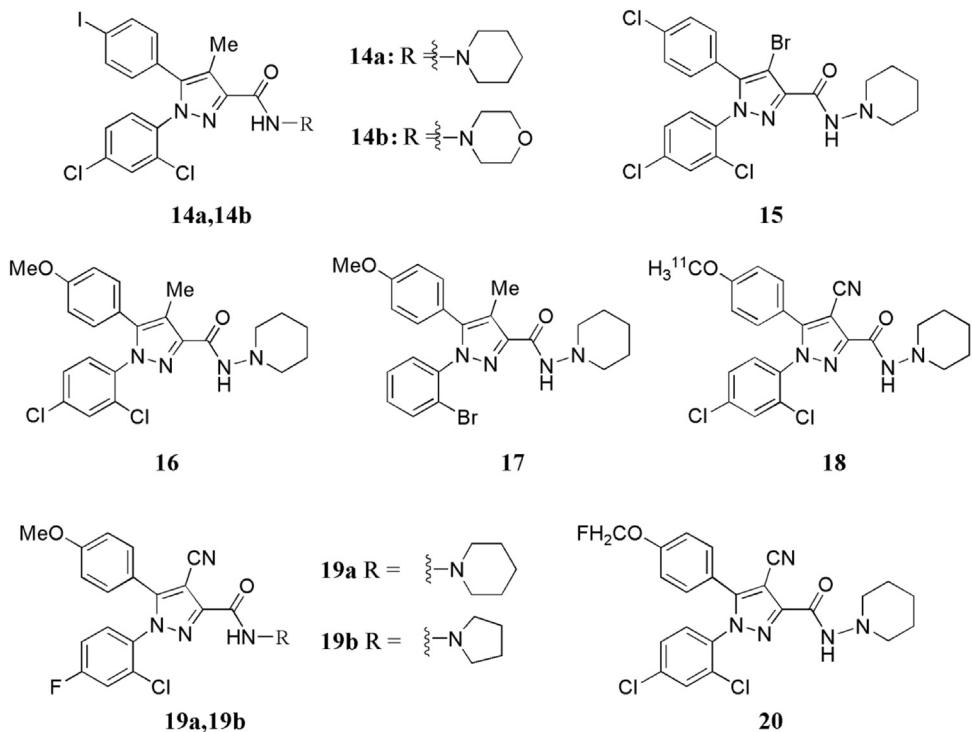
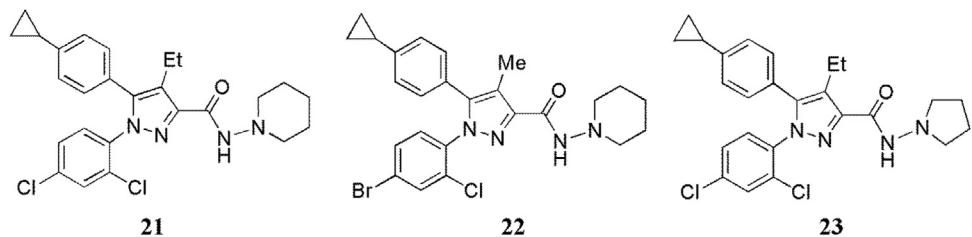
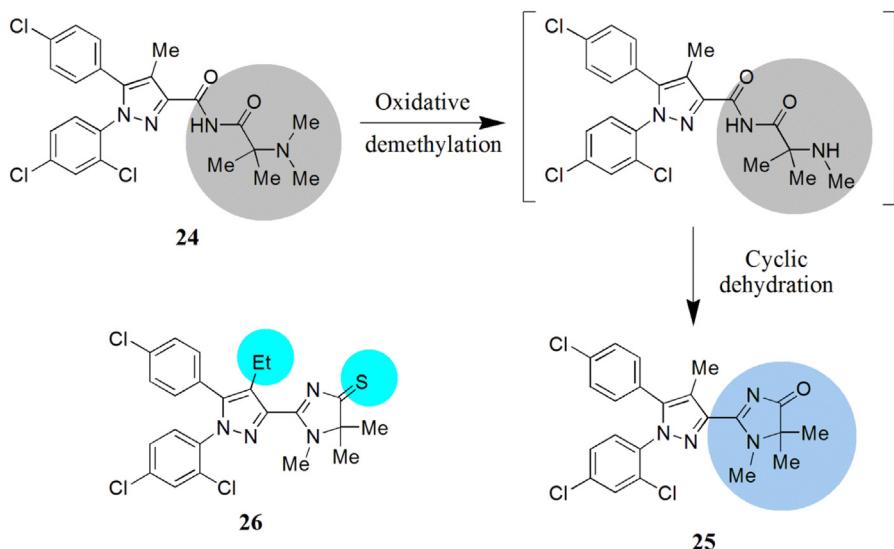
Szabo et al. [112] identified a series of cycloalkyl containing diaryl pyrazole derivatives as CB1 receptor antagonists. In the animal model used for the study, the cyclopropyl substituted compounds 21–23 were found to be potent CB1 receptor antagonists with significant anti-obesity effect ($K_i = 4, 3$ and 4 nM respectively) as shown in Fig. 12. Additionally, compound 23 showed excellent

efficacy in reducing serum lipid parameters of metabolic syndrome compared to rimonabant.

Wu et al. [113] utilized the active metabolite 25 ($IC_{50} = 54.7$ nM; CB2/CB1 = 9) of the imide 24 ($IC_{50} = 82.9$ nM; CB2/CB1 = 35) as a lead molecule as shown in Fig. 13. Introduction of sulphur atom in place of oxygen in the imidazol-4-one moiety at C3-position of pyrazole resulted into the thiolactone 26 (Fig. 13) which was highly potent and a selective CB1 inverse agonist ($IC_{50} = 12.0$ nM, CB2/CB1 = 396).

Thomas et al. [114] extended the diaryl pyrazole series and synthesized alkyl side-chain analogs of even greater lengths. A slight increase in binding affinity was observed with increase in the size of carbon chain from C4 to C5. Further, modest decrease in the binding affinity for C6 and slightly greater decrease for C7 chain length were observed. Beyond this length, the receptor affinity decreased further but it was not analogous with the branched alkyl amides. The pentyl and hexyl amides showed the highest affinity whereas heptyl and decyl the lowest.

Mussinu et al. [115] applied rigid analog approach to minimize the flexibility of the lead molecule by making conformationally restricted analogs. Thus, they designed a new series of rigid 1,4-

**Fig. 11.** Chemical structures of PET and SPECT diaryl pyrazole analogs (**14a–20**).**Fig. 12.** Chemical structures of cycloalkyl containing diaryl pyrazole derivatives (**21–23**).**Fig. 13.** Proposed mechanism of formation of the active metabolite **25** from the imide **24** [113].

dihydroindeno[1,2-c]pyrazol derivatives **27** by using rimonabant (**1**) as a benchmark as shown in Fig. 14, for binding to CB1 and CB2 receptors. But unfortunately, several of these compounds showed high degree of activity and selectivity for CB2 over CB1. Compound **27a** (Fig. 15) was found to be the most potent and selective CB2 antagonist ($K_i = 0.037$ nM and CB1/CB2 = 9810). To further extend the studies, Murineddu et al. [116] designed homologous 4,5-dihydro-1H-benzo[g]indazoles **28** (Fig. 14). Compound **28a** (Fig. 15) was found to be the most potent compound ($K_i = 4.11$ nM) in the series with selectivity over CB2 up to 262-fold. Murineddu et al. [117] further modified the 4,5-dihydro-1H-benzo[g]indazoles **28** to benzocycloheptapyrazole carboxamides **29** (Fig. 14). It became to be known by the receptor binding assay that azacyclic derivatives of the C3 carboxamide group of the compounds (e.g. **29a**, Fig. 15, NESS 0327, $K_i = 0.00035$ nM) have excellent affinity for CB1 receptors and selectivity over CB2 receptors (CB2/CB1 = 60,000) in comparison to the cyclohexyl or an aryl moiety. Zhang et al. [118] further expanded the ring in benzocycloheptapyrazole carboxamides **29** to benzocyclooctapyrazole carboxamide **30** (Fig. 15). Compound **30** showed CB1 affinity at approximately 15 nM and for CB2 at 492 nM. It indicated that ring strain in the molecule decreased its CB1 receptor affinity more dramatically than its CB2 receptor affinity.

Tai et al. [119] focused on the strategy of bioisosterism to develop CB1 receptor antagonists. For generating the novel rimonabant-mimicking molecules, vinylene unit ($-\text{CH}=\text{CH}-$) or imine group ($-\text{CH}=\text{N}-$) in the aromatic ring at 5-position could be replaced with a “ring equivalent” like sulphur (S), oxygen (O), selenium (Se), or NH group resulting in the corresponding heterocyclic rings with equivalent steric and electronic characteristics. Thus, phenyl ring at 5th position of pyrazole was replaced by its bioisostere thiophene ring to offer a novel series of 5-[5-(1-pentenyl)thiophen-2-yl]pyrazoles as CB1 receptor antagonists. Amongst all the compounds, the most promising candidates obtained in terms of potency and selectivity were derivatives **31a–31c** ($\text{IC}_{50} = 8.7, 7.1$ and 4.0 nM and CB2/CB1 = 637, 197 and 275 respectively) as shown in Fig. 16.

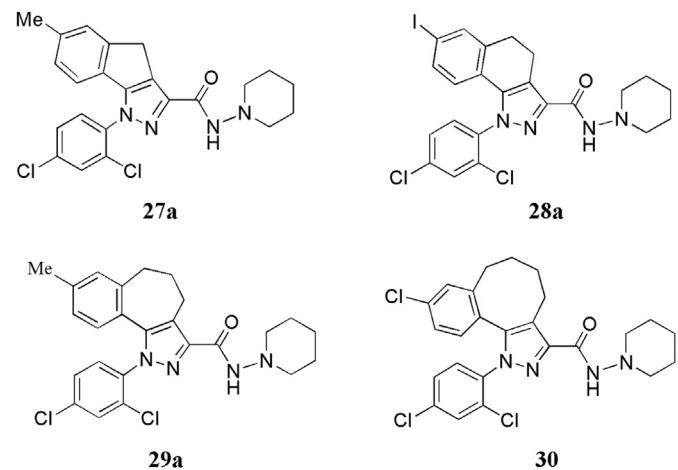


Fig. 15. Extended diaryl pyrazole derivatives (27a–30).

Tseng et al. [120] from the same team expanded this series and obtained compound **32** (Fig. 16) having IC_{50} value of 6.1 nM and selectivity CB2/CB1 of 151 which showed significant weight reduction in diet-induced obese mouse model to prove that the concept of bioisosteric replacement offered favourable results. Compound **33** (Fig. 16) was obtained as the most potent and selective CB1 receptor antagonist in the series ($\text{IC}_{50} = 2.3$ nM; CB2/CB1 = 168).

Srivastava et al. [121] replaced C-5 aryl group of rimonabant by thienyl group to develop a selective CB1 receptor antagonist for the control of obesity. A bromothienyl derivative **34a** (Fig. 16) ($\text{EC}_{50} = 0.40 \mu\text{M}$) structurally mimiced rimonabant (**1**, $\text{EC}_{50} = 0.24 \mu\text{M}$). It was 1.6-fold less active on CB1 receptors in diet-induced obese C57BL/6J mice model. The most active compound in the series was found to be iodothienyl derivative **34b** (Fig. 16) which was 1.3-fold less active ($\text{EC}_{50} = 0.32 \mu\text{M}$) than rimonabant on the CB1 receptors as anti-obesity agent.

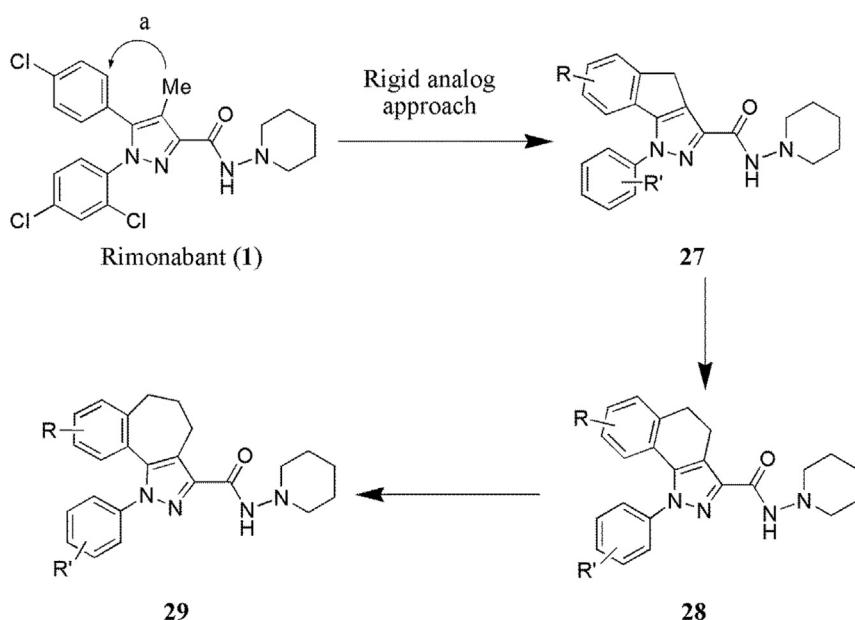
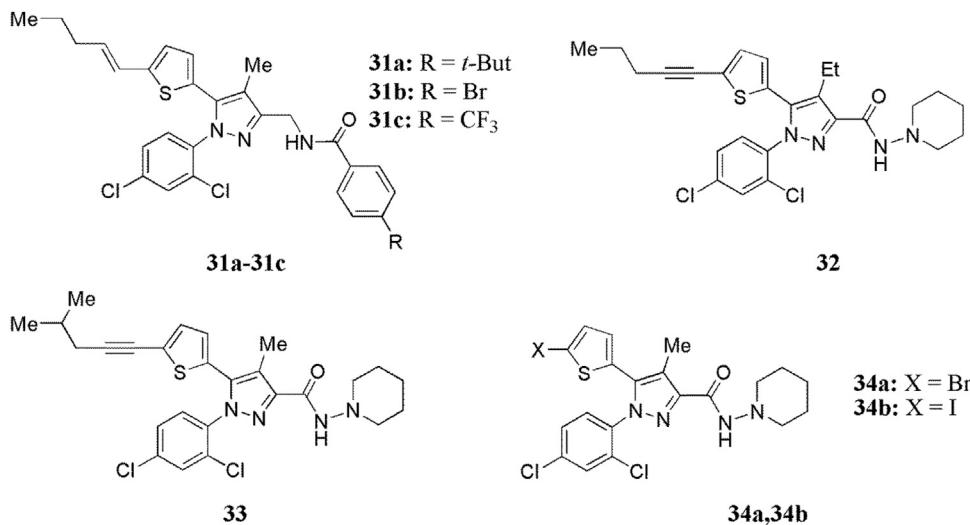


Fig. 14. Rigid analog approach via arrow a to obtain 1,4-dihydroindeno[1,2-c]pyrazole derivative **27** [115], extended further to its homologs 4,5-dihydro-1H-benzo[g]indazoles **28** and benzocycloheptapyrazoles **29**.

**Fig. 16.** Chemical structures of thiophene containing diaryl pyrazole derivatives (31a–34b).

Silvestri et al. [122] decided to replace the 4-chlorophenyl group by pyrrole ring at position 5 of rimonabant using bioisosteric approach. Compound **35** (Fig. 17) was found to be the most selective (*S.I.* = 140.7) one whereas compound **36** (Fig. 17) was found to be the most potent compound (K_i = 5.6 nM) in the series in the cAMP assay for CB1 receptor.

Silvestri et al. [123] continued their research work with compounds **35** and **36** as the lead molecules. Compound **35** was modified by replacing 2,4-dichlorobenzyl at the 3-carboxamide nitrogen with differently substituted phenyl rings and by varying the length of the alkyl spacer. In compound **36**, the cyclohexyl group was modified using other cyclohomologs. It was observed that the chloro derivatives showed higher potency than their fluorinated

counterparts and both the groups 5-(2,5-dimethylpyrrole) and 1-(2,4-dihalophenyl) offered compounds with greater affinity towards the *hCB1* receptors. Regarding selectivity it was found that 1-(2,4-dichlorophenyl)pyrazoles were more CB1 selective than the corresponding 3,4-dichlorophenyl analogs. Interestingly, the methylene spacer also increased *hCB1* selectivity offering the most potent compounds **37** and **38** (Fig. 17) in the series (K_i = 3.4 and 5.6 nM respectively). Docking studies and molecular dynamics (MD) simulations showed that H-bonds were formed between carboxamide oxygens of **37** and **38** and K3.28 (192), similar to rimonabant. It was found by *in vivo* pharmacological set up that compounds **35** and **39** (K_i = 50 nM) suppressed appetite and also showed anorectic effect on acute administration in rats. Silvestri

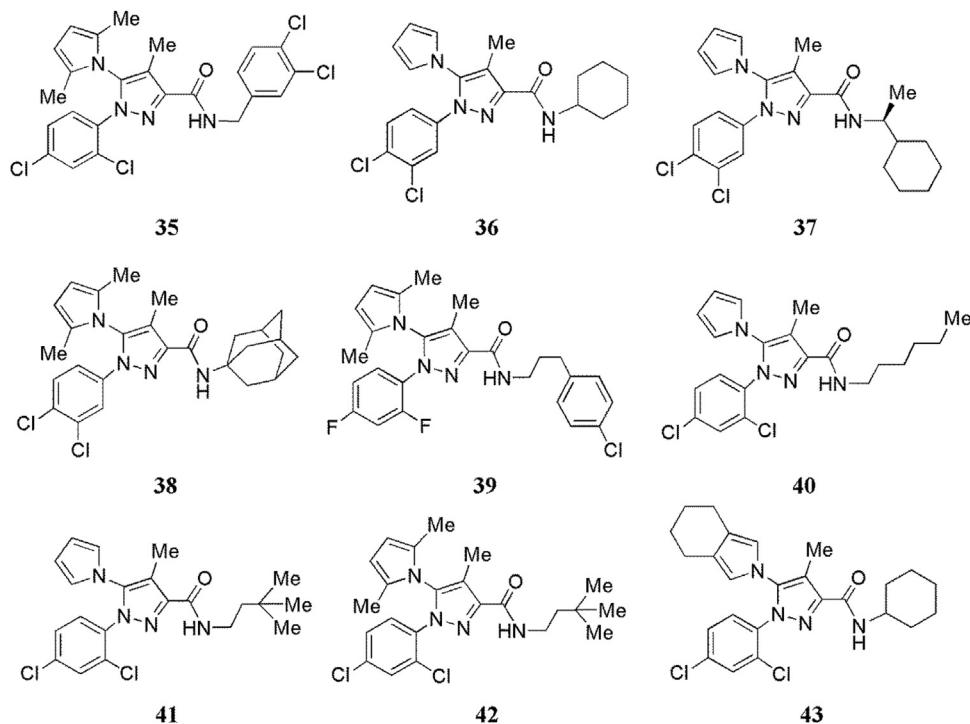
**Fig. 17.** Chemical structures of pyrrole containing diaryl pyrazole derivatives (35–43).

Table 2
Pharmacokinetic parameters of compound **40** [124].

Parameters	Plasma	Brain
C_{\max} (ng/mL or ng/g)	170 ± 61	110 ± 13
T_{\max} (min)	30	30
$T_{1/2}$ (min)	836	862
MRT (min)	889	860
AUC (min ng/mL)	20414	19801
Brain penetration (%)	—	97

et al. [124] further extended the aliphatic side chain at the nitrogen atom to give birth to compound **40**. Significant plasma and brain concentrations were achieved by compound **40** (Fig. 17) with K_i value of 124.1 nM showed anorectic effect in the rat. At 10 mg/kg i.p. administration, compound **40** showed quite similar pharmacokinetics in plasma and brain with 97% brain penetration as shown in Table 2. It was observed that greater *h*CB1 receptor affinity was obtained in unsubstituted pyrrole derivatives containing a *tert*-alkyl chain at the amide nitrogen. *h*CB1 receptor affinity was effectively improved when *tert*-butyl moiety was placed as the terminal group in compounds **41** and **42** (Fig. 17) with K_i value of 45.6 and 37.5 nM respectively. H-bond was also formed by carboxamide oxygen of compound **42** with K3.28(192) as seen in MD simulations, similar to rimonabant (Fig. 18). Additionally, *N*-*tert*-butyl group of compound **42** fitted into the lipophilic pocket containing I1.34(119), F2.57(170), F2.61(174), F2.64(177) and A7.36(380) residues. The 2,5-dimethylpyrrole ring showed interactions with hydrophobic residues V3.32(196) and C7.42(386), and the two methyl groups projected towards the lipophilic residues L6.51(359) and W5.43(196). The 2,4-dichlorophenyl ring was enclosed in hydrophobic pocket containing L3.29(193), Y5.39(275), W5.43(279), L6.51(359), M6.55(363) and V6.59(367), and established favourable $\pi-\pi$ stacking interactions with the indole ring of W5.43(279). Aromatic residue-rich TM3-4-5-6 region of *h*CB1 covered all these interactions. Piscitelli et al. [125] continued with this series by modifying the substituents on both pyrazole and pyrrole nuclei with the new unexplored ones. Compound **43**

(Fig. 17) was found to be the most potent and selective CB1 receptor antagonists in the series, superior than rimonabant and AM251 ($K_i = 2.3$ nM, CB2/CB1 = 163.6).

Seo et al. [126] introduced 1,2,4-triazolylmethyl moiety onto the pyrazole-3-carboxamide as shown in Fig. 19 to identify more potent CB1 receptor antagonists. It was observed that introduction of 1,2,4-triazolylmethyl moiety via a methylene linker resulted significant improvement in CB1 receptor binding affinity with excellent selectivity. Compound **44** (Fig. 19) was found to be the most potent and selective CB1 receptor antagonist ($IC_{50} = 1.1$ nM, CB2/CB1 = 1627).

Lee et al. [127] identified a new series of diaryl pyrazolylthiadiazoles with excellent activity and selectivity by the incorporation of 1,2,4-triazolylmethyl moiety onto diaryl pyrazolylthiadiazole as shown in Fig. 20. Pyrazolyl-*t*-butylthiazole derivative **45** (Fig. 20) was observed to have the highest affinity against rat CB1 receptor ($IC_{50} = 0.681$ nM) with high *h*CB2/rCB1 receptor selectivity of 807. Compound **45** (GCC2680) was selected as a preclinical candidate for the treatment of obesity on the basis of its excellent *in vivo* efficacy in animal models and favourable pharmacokinetic and toxicological profile. It was evaluated at a dose of 10 mg/kg in high fat diet induced obese (DIO) mice. It was found to be more efficacious ($32.55 \pm 2.58\%$ body weight reduction) in comparison to rimonabant (**1**) and taranabant (**2**) which caused $18.02 \pm 2.05\%$ and $29.55 \pm 2.54\%$ body weight reduction respectively. To examine the dose dependency, a chronic evaluation study was performed with oral administration of the compound for 13 days in a DIO mouse model. The results indicated that the compound had a dose-dependent response. At 10 and 20 mg/kg doses it showed 34.90 ± 1.89 and $38.06 \pm 3.01\%$ reductions in body weight respectively. At 3 mg/kg dose of the compound proved to be as effective as the reference compound **2**. It exhibited slightly higher exposure ($F = 67.6\%$) than the reference compounds (**1** and **2**; $F = 53.1\%$ and 61.7% respectively) with $T_{1/2} 14.80 \pm 0.31$ h after 5 mg/kg oral administration. The clearance ($CL = 40.83 \pm 5.26$ mL/min/kg) of compound **45** was obtained from pharmacokinetic (PK) studies, on i.v. administration.

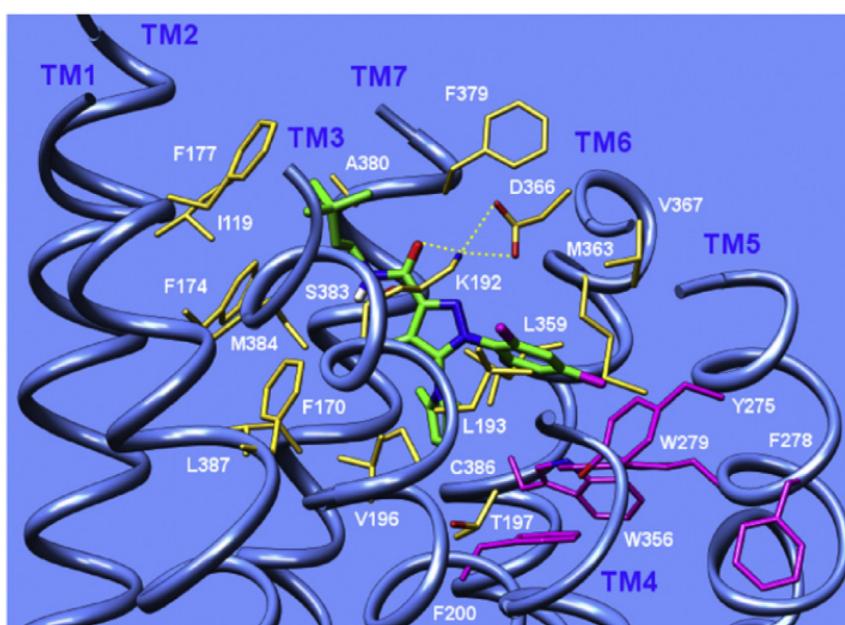
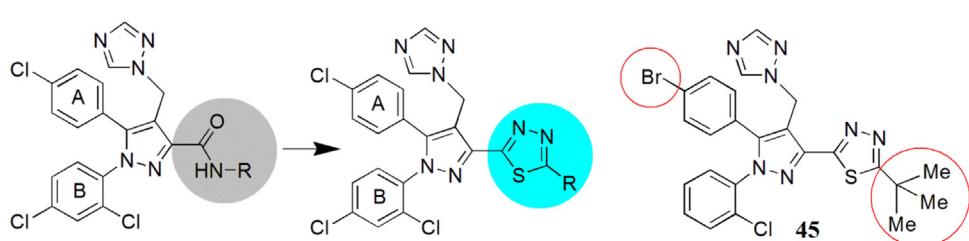
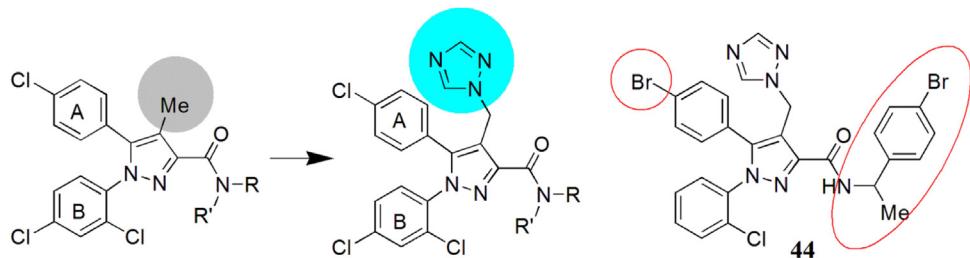


Fig. 18. Orientation of compound **42** in *h*CB1 receptor. Amino acids presented within 4 Å distance from the ligand (green) are shown in yellow and labelled. Residues that form part of the aromatic cluster complex with the ligand are coloured in magenta. H-bonds are indicated by dashed yellow lines [124]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Dow et al. [128] further prepared a new series of compounds in which the hydrazide moiety of rimonabant was replaced by the isosteric imidazole-based moiety. This modification was logically done to preserve the hydrogen bond acceptor feature that could mimic the carbonyl oxygen of rimonabant because it was observed that a hydrogen bond was formed between the oxygen of the amide and Lys192 of the CB1 receptor. Proper disposition of the substituent was also taken into account so as to attain good overlap with the piperidinyl group of rimaonabant. The minimized conformations of **46** (Fig. 21) and **1** were overlayed and it was observed that *N*-3 nitrogen atom of imidazole of **46** was suitably overlapping on carbonyl oxygen of rimonabant to preserve the hydrogen bond acceptor role with CB1 receptor as shown in Fig. 22. Thus, cyclohexylimidazole derivative **46** ($K_i = 8.6$ nM) was used as an initial probe for the development of CB1 receptor antagonists. The isopropyl substituted compound **47** (Fig. 21) showed better activity ($K_i = 5.3$ nM) in the tetrad assay and was found to be orally-active in a food intake model.

Kang et al. [129] identified a novel tetrazole-based diaryl pyrazole series having CB1 receptor antagonistic activity. They replaced amide moiety of rimonabant by a tetrazole as a bioisostere. Tetrazoles substituted by different groups like alkyl, aryl or heteroaryl moieties showed moderate potency for CB1R binding. The best results were obtained when cycloalkyl tetrazoles were utilized in this series. Thus, cyclopentyltetrazole **48** (Fig. 21) exhibited high level of activity as well as good selectivity for CB1R over CB2R ($IC_{50} = 11.6$ nM and $CB2/CB1 = 366$). Further, the same group used 1,3,4-oxadiazole as a bioisostere of the amide moiety of rimonabant. Among the 1,3,4-oxadiazole analogs, compound **49** (Fig. 21) was the most promising precandidate for the development of anti-obesity agents. Compound **50** (Fig. 21) was shown ($IC_{50} = 0.57$ nM) to be the most potent one *in vitro* with the highest $CB2/CB1$ receptor selectivity of 1842. By modelling studies, it was observed that 1,3,4-oxadiazole ring formed bidentate H-bond with Lys192. It was predicted that the bidentate H-bond interaction was stronger than the monodentate H-bond interaction formed by the amide carbonyl oxygen of rimonabant. In addition to this, introduction of a 1,2,4-triazole ring at 4th position of pyrazole scaffold via a methylene linker also showed favourable effects for the development of CB1 receptor antagonists [130].

The C-4 region of the pyrazole scaffold was further modified by introducing polar amide group as it was felt that this region was capable of embracing substituents of varying functionality, size and polarity. Compounds **51a** and **51b** (Fig. 21) showed good binding affinity and decent selectivity for CB1 receptor ($IC_{50} = 1.35$ nM, $CB2/CB1 = 286$ for **51a**; $IC_{50} = 1.46$ nM, $CB2/CB1 = 256$ for **51b**) [131]. Lee et al. [132] designed a series of pentacyclic derivatives using bioisosteres of polar amide group in the C-4 region of pyrazole. Compound **52** (Fig. 21) showed the highest binding affinity and good selectivity for CB1R over CB2R ($IC_{50} = 1.72$ nM, $CB2/CB1 = 142$) and was also found to be potent in the CHO-hCB1R-Luciferase assay, with an IC_{50} value of 38.5 nM, thus demonstrating inverse agonistic activity in this series. Song et al. [133] from the same laboratory replaced the *N*-piperidinylcarboxamide group of rimonabant with the corresponding sulfonamide, imide, *N*-methylimide and methylenediamide moieties. It was observed that imide derivatives linked to diaryl pyrazole moiety showed significant CB1 binding affinities. Among the tested derivatives, compounds **53a** and **53b** (Fig. 21) were the most potent ones ($IC_{50} = 24.8$ nM and 21.2 nM, respectively) in terms of CB1R binding affinity. In the DIO mice test, compound **53c** (Fig. 21) showed moderate *in vivo* efficacy ($IC_{50} = 32.7$ nM).

Cooper et al. [134] were interested in increasing the polar surface area (PSA) and lowering the log *D* value of the inhibitors to limit their blood brain penetration. Hence, they planned to replace 4-methyl group of pyrazole moiety by a more polar nitrile group because it could be further functionalized into a wide range of polar groups like neutral (amides, amidoximes), positively charged (amidines) and negatively charged (carboxylic acids, tetrazoles) ones as shown in Fig. 23. Compound **54** (Fig. 23) obtained on introduction of nitrile moiety was comparable in activity with rimonabant ($IC_{50} = 7.5$ and 4.5 nM respectively) with decreased lipophilicity ($clog P = 4.9$ and 6.4 respectively) and higher PSA (73.9 and 50.2 Å^2 respectively). Compound **55** (Fig. 24) obtained by further modifications in the amide component showed IC_{50} of 3.4 nM and $clog P$ of 4.8 whereas the most potent compound **56** (Fig. 24) in the series depicted an IC_{50} value of 0.41 nM but unfortunately it had higher lipophilicity ($clog P = 6.0$). Receveur et al. [135] from the same team further extended this series by replacing the nitrile group with a more polar neutral amide, amidoxime or

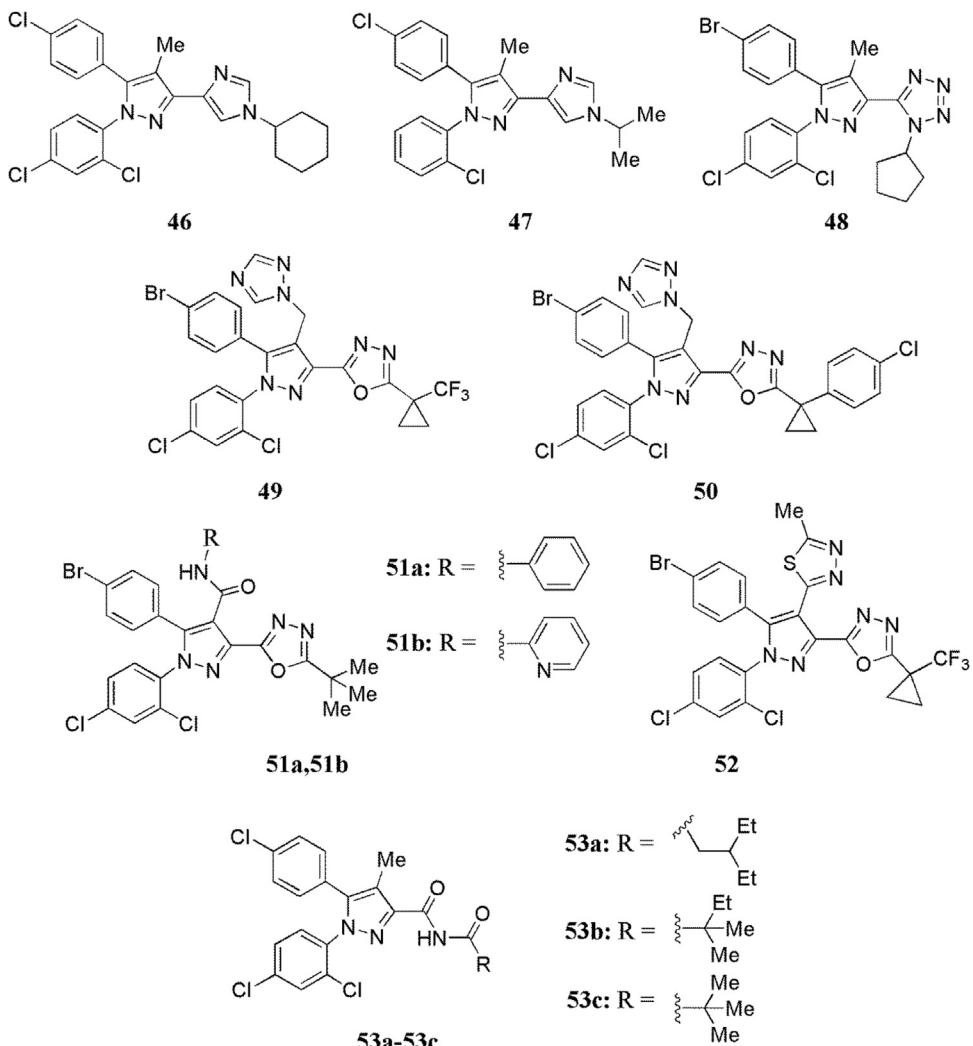


Fig. 21. Chemical structures of diaryl pyrazole derivatives (**46–53c**).

positively charged (amidine) functional groups. Amide derivative **57** (Fig. 24) was the most potent compound with lower lipophilicity ($IC_{50} = 0.19$ nM, $\log D = 2.8$) and improved plasma/brain ratio of 10.2. This study concluded that the introduction of more polar

groups in place of methyl increased the PSA and lowered the clog P value. A wide range of amide substituents at 3 position of pyrazole was tolerated but the CB1 receptor antagonistic activity decreased when polar and charged groups were placed in this part [134].

Sasmal et al. [136] from Dr. Reddy's Laboratory synthesized and biologically evaluated novel pyrazole-3-carboxamide derivatives with the objective of identifying novel peripherally restricted CB1 receptor antagonists with limited BBB penetration. It was a crucial step in the development of such kind of compounds that do not cross the BBB so as to prevent serious psychiatric disorders. It was possible to design compounds having considerably higher PSA and lower lipophilicity. In this direction, they replaced the hydrazide functionality with an amide and introduced polar moieties to reduce CNS exposure. By using chemically diverse motifs, various modifications were done on the amide function of rimonabant. Compound **58a** (Fig. 24) was obtained as a lead molecule with significant CB1 receptor binding affinity ($IC_{50} = 8$ nM) in a DIO mice model with high tPSA value of 105.3 \AA^2 . It exhibited significant weight loss of 12% in 15 days at 10 mg/kg, q.d. on oral administration. The most polar peripherally active compound **58b** (Fig. 24, tPSA = 148.6 \AA^2) had high CB1 potency ($IC_{50} = 0.5$ nM) with very high selectivity (>1000 fold). In this study, polar groups were introduced in 3, 4 and 5 positions of pyrazole ring. Thus, several peripherally active compounds were obtained with high polar surface area depicting excellent potency and selectivity. Further,

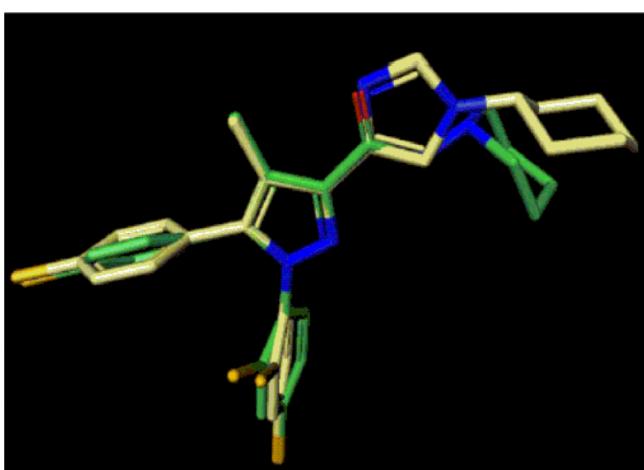


Fig. 22. Superimposition of minimized conformations of **1** (green) and **46** (yellow) [128]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

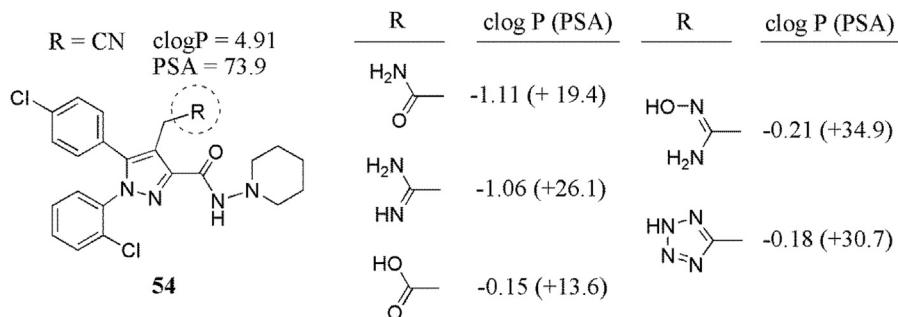


Fig. 23. Variations in clog P and PSA (parentheses) by modifying the nitrile group in **54** into amide, amidoxime, amidine, carboxylic acid and tetrazole [134].

Sasmal et al. [137] pursued their efforts with the exploration of amide chain and replaced it with conformationally constrained motifs and imidazole moieties. The oxadiazole containing compound **59** (Fig. 24) showed excellent potency ($IC_{50} = 0.1\text{ nM}$) with high selectivity and good oral PK profile in the series. Dose dependent weight reduction was observed in compound **59** in acute food intake when tested at 10 and 30 mg/kg po in Swiss Albino Mice (SAM) model. At 10 mg/kg po dose, rimonabant showed better effect than the highest tested dose of 30 mg/kg po of compound **59** which indicated that rimonabant was having more pronounced central effect than the more polar compound **59**. After 1 h of rimonabant (**1**) and compound **59** showed brain to plasma ratio 3.64 and 0.21 respectively at 30 mg/kg po in SAM. Compound **59** showed significant 11% weight loss in 15 days at 10 mg/kg, q.d. on oral administration.

Fulp et al. [138] focused their efforts to develop peripherally acting CB1 receptor antagonists by using two strategies. The first one was to design charged compounds so that such compounds would not cross the BBB, but unfortunately these compounds exhibited poor activity in the calcium flux assay, and the second strategy was to increase the total PSA for lower penetration into the CNS. So, sulfonamides and sulfamides with increased PSA were designed and synthesized. The *cis*-isomers **60a** and **60b** (Fig. 24) were the most potent compounds ($K_e = 0.030$ and $0.093\text{ }\mu\text{M}$ respectively; tPSA = 101 and $127\text{ }\text{\AA}^2$ respectively) showing less than 1% transport from apical to basal side of membrane whereas rimonabant and otenabant exhibited 15% and 90% transport respectively, which indicated little brain penetration of compounds **60a** and **60b**. Further, Fulp et al. [139] converted the sulfonamide into carboxamide at C-3 position of the pyrazole ring. Compound **61a** (Fig. 24) was obtained as a potent and highly selective CB1 receptor antagonist ($K_e = 0.44\text{ nM}$, CB2/CB1 = 1600) with higher tPSA value than rimonabant. Phenyl group of compound **61a** was replaced by secondary amine resulting in decrease in selectivity in compound **62** (Fig. 24). Amide group of compound **61a** was also modified as reverse amide in compound **61b** (Fig. 24) but this time its potency was decreased. Further, compound **61c** (Fig. 24) with higher tPSA was obtained by substituting sulfonamide group offering potent but moderate selectivity for CB1 over CB2. Finally, urea **61d** (Fig. 24) and carbamate **63** (Fig. 24) derivatives were found to be potent and selective CB1 receptor antagonists with little or no CNS penetration ($K_e = 2.4$ and 4.7 nM respectively; CB2/CB1 = 426 and 877 respectively).

Manca et al. [140] focused on to identify peripherally acting neutral CB1 receptor selective antagonists with reduced side effects. Neutral CB1 receptor antagonists were obtained by avoiding hydrogen bond with K3.28(192) in compounds **64a** and **64b** (Fig. 24) [141]. An enantiomeric mixture of alcohol derivatives (\pm)-**65** (Fig. 24) and fluorovinyl derivative (*Z*)-**66** (Fig. 24) showed significant efficacy ($K_i = 175.0\text{ nM}$ and 25.8 nM respectively) in the

control of food intake. Interestingly, no adverse effects were observed in case of treatment with compounds **65** and **66** at doses up to 20 mg/kg whereas rimonabant at 20 mg/kg showed psychiatric side effects like anxiety and depression. Thus, such substituents on the pyrazole ring at 3 position supported development of neutral CB1 receptor antagonists [140].

Alvarado et al. [142] researched to identify novel anti-obesity agents and synthesized fatty acid amide analogs of LH21 and rimonabant (**1**). The results obtained showed that the pyrazole derivative **67** (Fig. 24) had higher affinity and selectivity towards CB2 receptors. Although the hexadecyl pyrazole carboxamides without chloro substitution showed significant reduction in food intake in animal models, these compounds did not show any sort of cannabinoid activity.

Carpino et al. [143] from Pfizer Global Research and Development designed a new series of conformationally constrained bicyclic derivatives of rimonabant (**1**) and evaluated them as *h*CB1-R antagonists and inverse agonists. 2,6-Dihydropyrazolo[4,3-*d*]pyrimidin-7-one (PP) derivatives **68a** and **68b** ($K_i = 20$ and 12 nM respectively) as shown in Fig. 25 were found to be slightly less active in *h*CB1-R binding assay than rimoanabant ($K_i = 2.1\text{ nM}$) and had poor structural overlap with rimonabant as shown in Fig. 26. The most active compounds obtained in the series were **69a** and **69b** (Fig. 25, $K_i = 0.3$ and 0.6 nM respectively). The PK profile of these compounds is also reported as given in Table 3.

Although, compounds of pyrazolopyrimidinone series had good *in vitro* and *in vivo* affinity for CB1 receptors, these were not developed further due to impaired absorption (solubility-limited) and narrow therapeutic index (TI) in preclinical safety models. Dow et al. [144] from the same team designed novel bicyclic six-/seven membered lactam-based CB1 receptor antagonists on the basis of the structure of the promising compound **69b**. Compounds **70** and **71** (Fig. 25) were found to be the most potent compounds ($K_i = 0.7$ and 1.0 nM respectively) in the series in the *in vitro* profile and were selected for further evaluation. Overlaid crystal structures of **70** (green), **71** (yellow) and rimonabant have been given in Fig. 27. The amide functionality of rimonabant was presumed to be closer to the amide substituents of lactams of **70** and **71** that were interacting with Lys192 of the CB1 receptor. Compound **71** was selected for further evaluation on the basis of its good *in vitro* biochemical and pharmacokinetic profiles in rat (1 mg/kg iv, 5 mg/kg po, $F = 42\%$, $T_{1/2} = 3.5\text{ h}$, $V_{ss} = 2.6\text{ L/kg}$). Compound **71** exhibited 23% reduction in food intake at 1 mg/kg dose whereas 21% reduction was obtained for rimonabant at 3 mg/kg of oral dosing in diet-induced obese mice in 7 days. Over a period of 7 days, a significant reduction in weight gain of $5.9 \pm 0.8\%$ and $5.2 \pm 0.8\%$ was obtained for compound **71** and **1** respectively, at a dose of 1 mg/kg and 3 mg/kg respectively.

Further, Dow et al. [145] planned to develop peripherally restricted CB1 receptor antagonists for obtaining desired efficacy

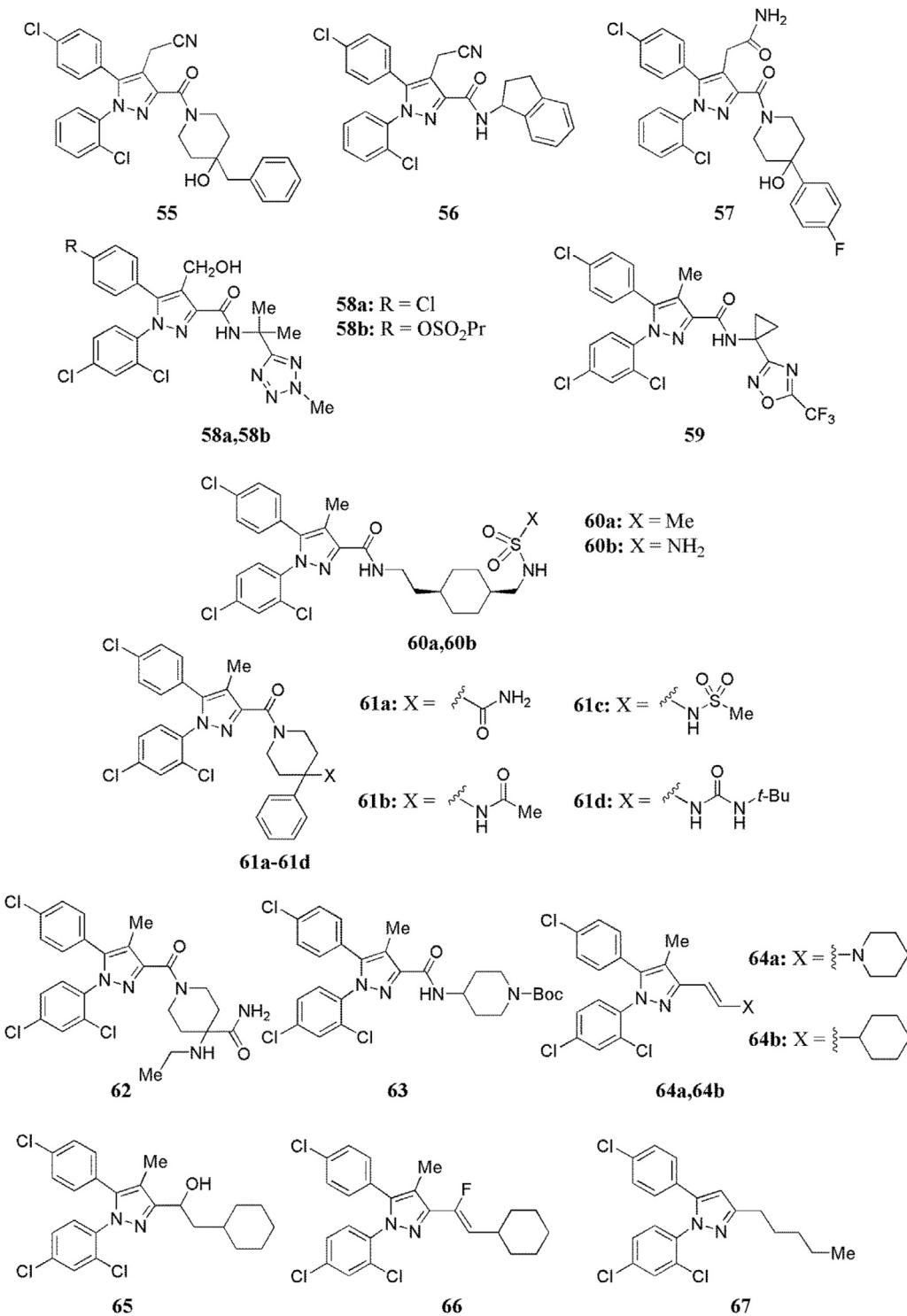


Fig. 24. Chemical structures of peripherally acting pyrazole containing compounds (55–67).

and reduced CNS side effects. It was tried to improve the physicochemical profile of the core structure of **71** which led to the development of compound **72a** (Fig. 25). Compound **72a** showed slightly increased PSA as compared to **1** and **71** (PSA = 56.1, 50.4 and 47.4 Å² respectively). Compound **72b** (Fig. 25) showed *in vivo* functional antagonistic activity (*K_i* = 0.14 nM) for CB1 receptors and oral activity in a rodent model of feeding. Overlaid minimized conformations of **1** and **72b** are shown in Fig. 28. The acylamino substituent was observed to be closely coplanar with the pyrazole

ring similar to the hydrazide group of **1**. Structure–activity relationship studies showed that introduction of polar functionality into the acylamino substituent was tolerated. At three different doses(0.3, 1, 3 mg/kg), compound **72b** exhibited statistically significant reduction in cumulative food intake with respect to the vehicle as control at 0.5 and 2 h. Compound **72b** at a dose of 0.3 mg/kg showed comparable effect to that observed for rimonabant at 3 mg/kg. Introduction of more polar substituents resulted in compounds **72c** and **72d** (Fig. 25) as potential peripherally targeted

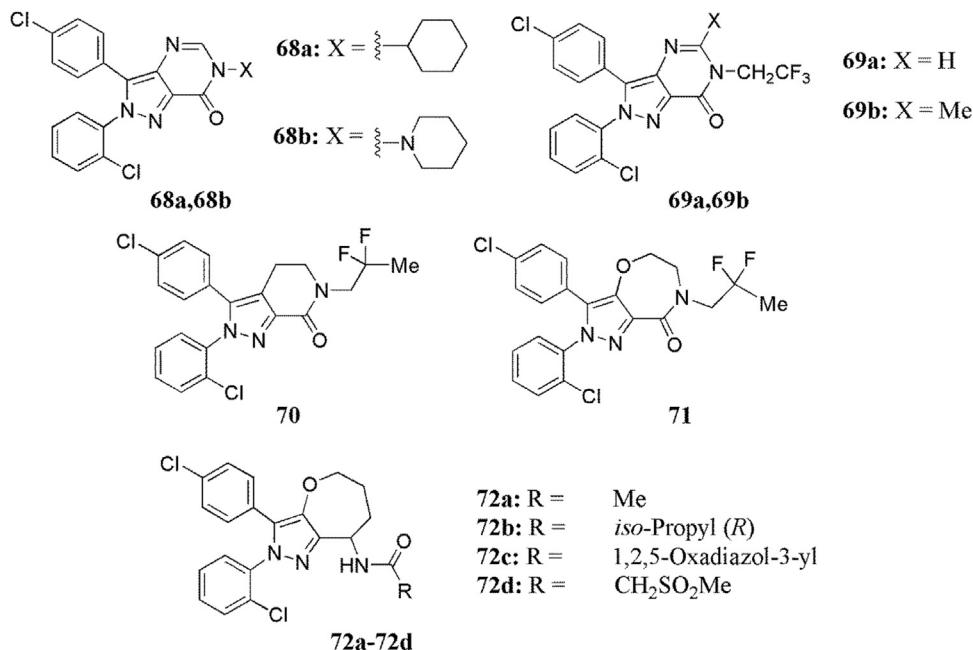


Fig. 25. Chemical structures of fused pyrazole containing compounds (68a–72d).

agents exhibiting K_i values of 1.7 and 0.54 nM and PSA of 95.1 and 98.7 Å² respectively. These compounds could be used as lead molecules for further optimization of peripheral CB1 receptor antagonists.

2.2. Diaryl pyrrole derivatives

Hortala et al. [146] from Sanofi-aventis designed a new series of 2,3-diaryl pyrroles as CB1 receptor antagonists with the aim of developing peripherally-restricted drugs to avoid the psychiatric side effects. With the aim of increasing topological PSA compound **73** (Fig. 29) was used for further modifications. Compound **73** inhibited 86% of CP55940 binding in homogenized brain (without the cerebellum) in the *in vitro* assay indicating a good brain penetration. The calculated TPSA of compound **73** was 68 Å² which was in accordance with its good brain penetration. Various substituents were tried to increase the TPSA of compound **73**. Introduction of

ethylcyano substituent in place of methyl group in compound **73** resulted in an increase in TPSA to 83 Å² with moderate brain penetration. A more polar compound (TPSA above 100 Å²) was obtained by introduction of carboxylic acid group into the molecule but unfortunately it resulted in decreased affinity for the CB1 receptors. Finally introduction of sulfonamide group increased the TPSA to 126 Å² with increased microsomal stability, higher affinity and low brain penetration for compounds **74a** and **74b** (Fig. 29) having IC₅₀ value of 4.3 and 1.0 nM respectively. Compound **74b** showed 100-fold higher concentration in plasma than in brain.

LoVerme et al. [147] identified the first peripherally restricted mixedCB1 antagonist/CB2 agonist which did not enter the brain for antagonizing centralCB1 receptors. They identified URB447 (**75**, IC₅₀ = 313 nM) (Fig. 29) that reduced food intake and body weight gain in mice by blocking CB1 receptor in peripheral organs. Unfortunately, it was not a selective CB1 receptor antagonist. After systemic administration of URB447 (20 mg·kg⁻¹ i.p.) drug levels were measured in various tissues such as after 30 min, plasma URB447 level peaked at C_{max} = 596 ± 117 nM and maximal tissue levels were obtained 15 min post injection in liver (C_{max} = 4.3 ± 0.7 nmol/g) and white adipose fat (C_{max} = 42 ± 12.2 nmol/g). So, it was observed that URB447 was not present in brain tissue at any time after the administration which indicated that URB447 did not penetrate the brain. By these finding, URB447 might be serve as a starting point for the development of CB1 receptor antagonists which are devoid of central side effects.

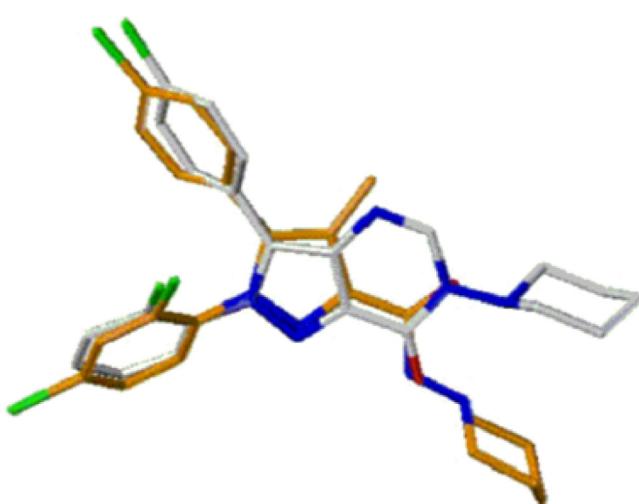


Fig. 26. Overlay of minimized structures of **1** and **68b** [143].

Table 3
Pharmacokinetic properties of compounds **69a** and **69b** [143].

	Pharmacokinetic properties	Compound 69a	Compound 69b
Rat PK	Cl (mL/min/kg)	45	32
	V _d (1/kg)	9.2	7.7
	Half life, t _{1/2} (h)	2.6	4.7
	F (%)	62	7
Dog PK	Cl (mL/min/kg)	0.54	10
	V _d (1/kg)	10	17
	Half life, t _{1/2} (h)	223	39

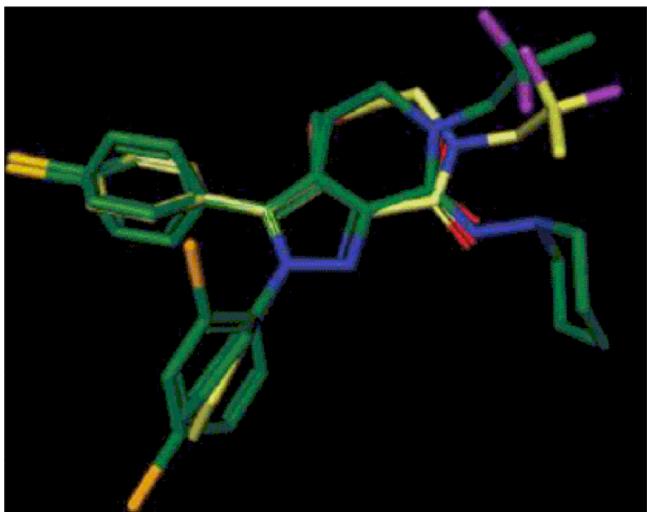


Fig. 27. Superimposition of crystal structures of **70** (green), **71** (yellow) and the minimized structure of **1** [144]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Diaryl imidazole derivatives

Dyck et al. [148] designed and synthesized diaryl imidazole-carboxamide and diaryl triazolecarboxamide derivatives related to rimonabant (**1**) and found that the imidazole derivatives were more potent. The bicyclic hydrazide substituent offered the most potent compounds **76a–76c** (Fig. 30) in the series ($K_i = 11, 9$ and 14 nM respectively). From this study, Dyck et al. drew the conclusion that high affinity of the compounds for the CB1 receptor depended more on the nature of the side chain than on the type of the heterocyclic ring itself. It was also observed that small substituents like methyl or cyano on the azole core proved to be important for high affinity binding.

Lange et al. [149] from Solvay Pharmaceuticals replaced the pyrazole motif of rimonabant by bioisosteres like thiazole, triazole and imidazole. Interestingly, it was observed that all of the bioisosteres showed *in vitro* selective CB1 receptor antagonistic activity. Some of the imidazole compounds depicted potent *in vivo* activity after oral administration. Further, Lange et al. [104] focused on position-5 substituents of the 1,2-diaryl imidazole-4-

carboxamides. Introducing methylsulfonyl group at 5-position in compound **77b** (Fig. 30) resulted into greater than 840-fold CB1/CB2 subtype selectivity. The imidazole containing compound **77a** (Fig. 30) substituted with methylsulfanyl showed more potent ($ID_{50} = 1.9$ mg/kg) oral activity *in vivo* than rimonabant ($ID_{50} = 3.2$ mg/kg). It was observed that more polar compounds **77b** and **77c** (Fig. 30) had limited brain exposure of P-glycoprotein substrates ($A \log P = 5.3$ and 5.2 respectively) whereas rimonabant had $A \log P = 6.6$.

Smith et al. [150] were interested to increase the oral availability of the developed compounds hence, they incorporated hydroxyl group into the cyclohexyl ring. Further optimization led to the development of compound **78** (Fig. 30) showing *h*CB-1 $K_i = 3.7$ nM with a significant anorexigenic effect in the fasted-refed Wistar rat model, as well as dose-dependent reduction in body weight gain in the chronic Zucker rat model. Kim et al. [151] reported diaryl imidazoloxyadiazole and thiadiazole scaffolds as CB1 receptor antagonists designed on the principle of bioisosteric replacement. There was a high similarity in the three-dimensional structures of imidazole and pyrazole rings. Compound **79** (Fig. 30) had the highest potency for CB1 receptor antagonism ($IC_{50} = 1.91$ nM).

Plummer et al. [152] from Merck Research Laboratories performed high-throughput screening (HTS) of the Merck samples collection to find out promising leads as CB1 receptor antagonists. Moderate affinity for CB1 receptor ($IC_{50} = 7$ μ M) was exhibited by 4,5-diaryl imidazole **80** (Fig. 30). Compound **80** was modified to the corresponding amide **81** (Fig. 30) as the lead molecule. 4-(2,4-Dichlorophenyl)-5-(4-chlorophenyl) analogs **82a** and **82b** (Fig. 30) were found to be the most potent compounds in the series ($IC_{50} = 6.1$ and 4.0 nM respectively).

2.4. Diaryl triazole derivatives

Jagerovic et al. [153] identified a novel series of 1,2,4-triazoles as silent cannabinoid antagonists. Triazole derivative **83** (LH-21, Fig. 31) behaved as a CB1 receptor antagonist. CB1 receptor affinity of this compound was evaluated by radioligand displacement assay in rat cerebellar membranes using [3 H]-SR141716A and [3 H]-WIN 55,212-2 as labelled ligands offering moderate affinity ($K_i = 855.6$ nM and 748.0 nM respectively) for CB1 receptors. Hence, for designing cannabinoid receptor antagonists, compound **83** could be considered as a silent lead molecule.

Shu et al. [154] thought to replace the basic pyrazole moiety of rimonabant (**1**) to other bioisosteres and finally replaced pyrazole ring by 1,2,3-triazole ring skeleton **84a** (Fig. 31). Compound **84a** showed lesser lipophilicity as compared to rimonabant ($clog P = 5.33$ and 6.26 respectively) with enhanced bioavailability. Hence, compound **84a** was considered as an attractive target for the development of CB1 receptor antagonists. Although compound **84b** (Fig. 31) and the phenyl ester **84c** (Fig. 31) from the series exhibited a slightly increase in affinity ($K_i = 4.6$ nM and 11 nM respectively) as compared to rimonabant (**1**, $K_i = 11.5$ nM). But they had no advantage over the latter because the lipophilicity of the compounds was similar to rimonabant (**1**).

Hou et al. [155] designed *N*1 or *N*2 substituted 1,2,3-triazole derivatives. It was observed that *N*2 substituted symmetrical 1,2,3-triazoles were more potent ligands than the unsymmetrical analogs. Introduction of a methylene group between the central core and carbonyl side chain of triazole ring improved the *in vitro* activity. Compounds **85a** and **85b** (Fig. 31) containing benzyl amides were the most potent derivatives from the series ($IC_{50} = 11.6$ nM and 19.3 nM respectively) showing excellent selectivity for CB1 over CB2 receptors ($IC_{50} > 10$ μ M for CB2; $CB2/CB1 > 1000$).

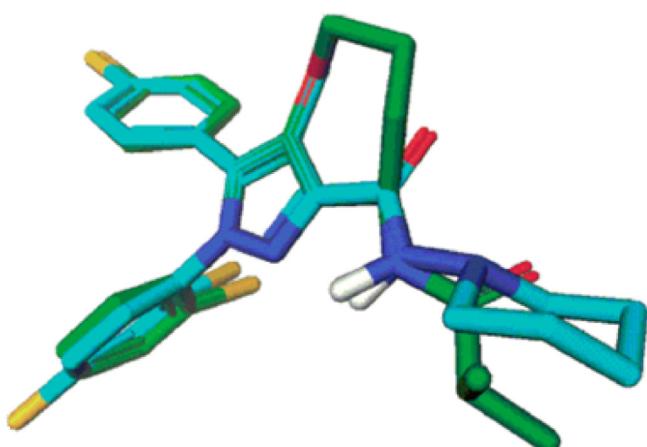
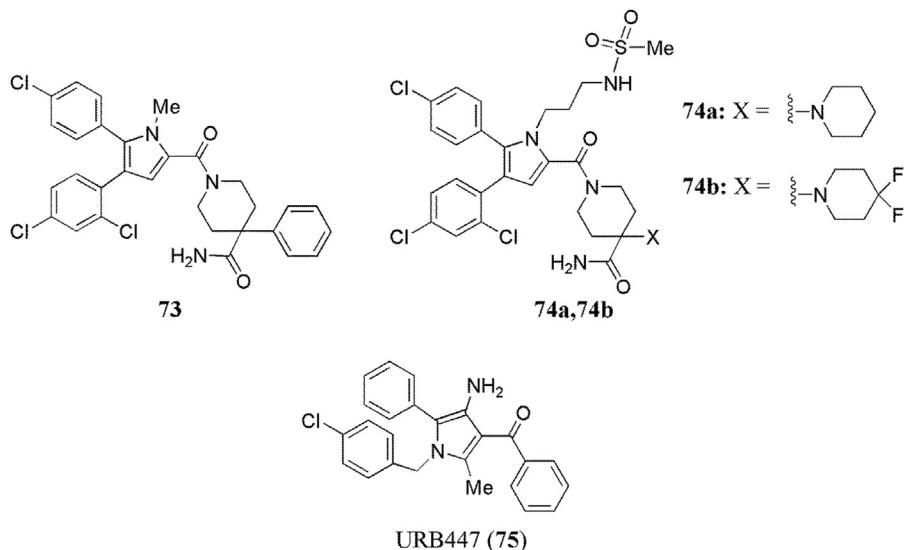


Fig. 28. Superimposition of minimized conformations of **1** (cyan) and **72b** (green) [145]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

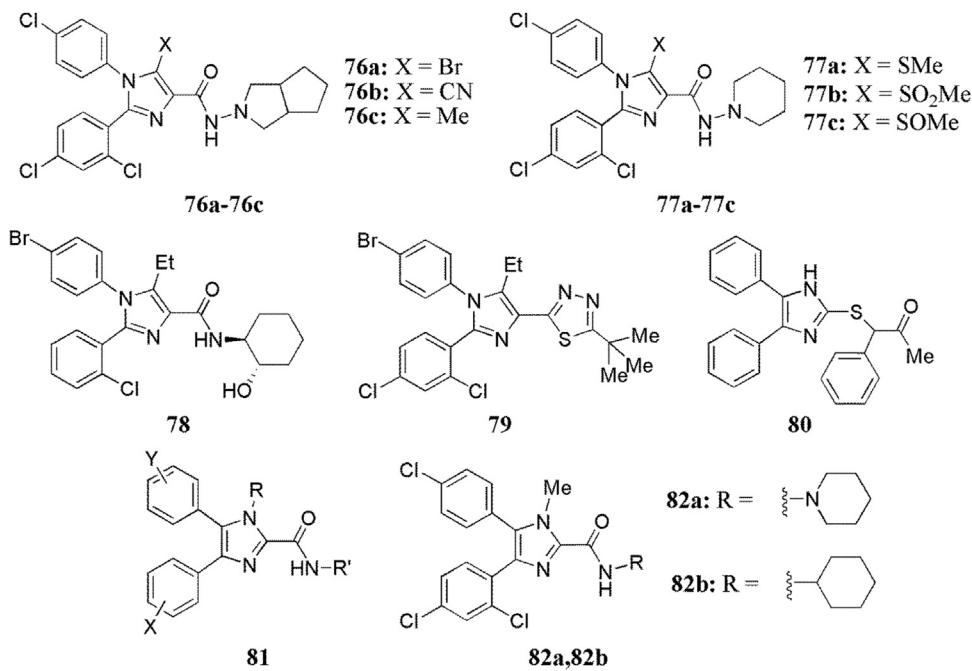
**Fig. 29.** Chemical structures of diaryl pyrrole derivatives (73–75).

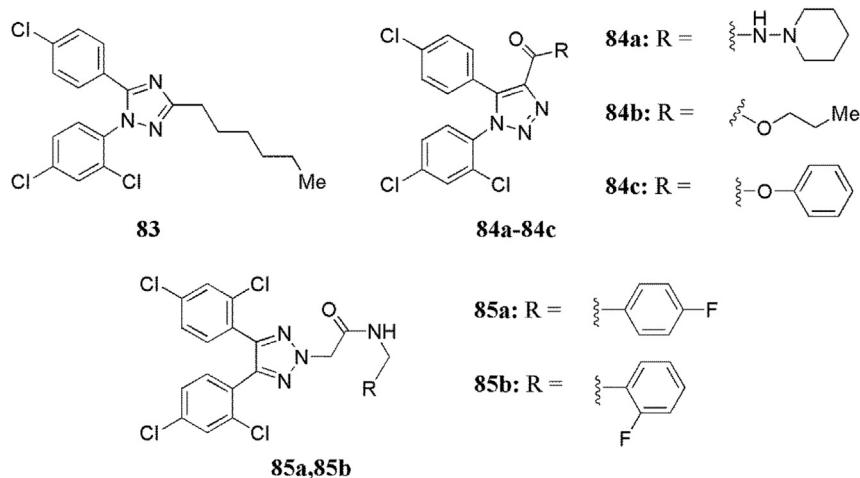
2.5. Diaryl pyrazoline derivatives

Lange et al. [82] from Solvay Pharmaceuticals synthesized a novel series of 3,4-diaryl pyrazolines for CB1 antagonism. Compound **86** (Fig. 32) was utilized as a lead molecule having K_i value of 197 nM for the development of two most potent compounds **87a** (Fig. 32) and **5**, $K_i = 35.9$ and 7.8 nM respectively, in the series. Orientations of rimonabant and compound **5** are presented in Fig. 33. A hydrogen bond was formed by one of the oxygens of SO_2 of **5** with Asp366-Lys192. Interestingly, additional hydrogen bond was also formed by the other oxygen of SO_2 of **5** with Ser383 which enhanced the binding affinity of **5** as compared to **1**. The *p*-chlorophenyl ring attached with SO_2 of **5** was possibly interacting with Phe170. Two aromatic rings attached to the pyrazoline core were

wrapped up by an arrangement of stacked aromatic residues. The *p*-chlorophenyl ring bound in Trp279/Phe200/Trp356 pocket and the other phenyl ring fitted in Tyr275/Trp255/Phe278 cavity. Lange et al. [156] replaced the aryl sulfonyl group by a dialkyl amino-sulfonyl moiety for designing compounds with lower lipophilicity as compare to SLV319 (**5**). Lower log P value was obtained for compound **87b** ($\log P = 4.8$) than rimonabant and SLV319 ($\log P = 5.5$ and 5.1 respectively). Compound **87b** (Fig. 32) showed a close molecular fit with rimonabant and SLV319 (**5**) in a CB1 receptor-based model as shown in Fig. 34. In this series, compound **87c** (Fig. 32) obtained, was the most potent lead ($K_i = 24$ nM) with high CB1/CB2 subtype selectivity (147-fold).

Wittgen et al. [157] designed 3,4-diaryl pyrazolines as peripherally acting CB1 receptor antagonists. Rimonabant and the

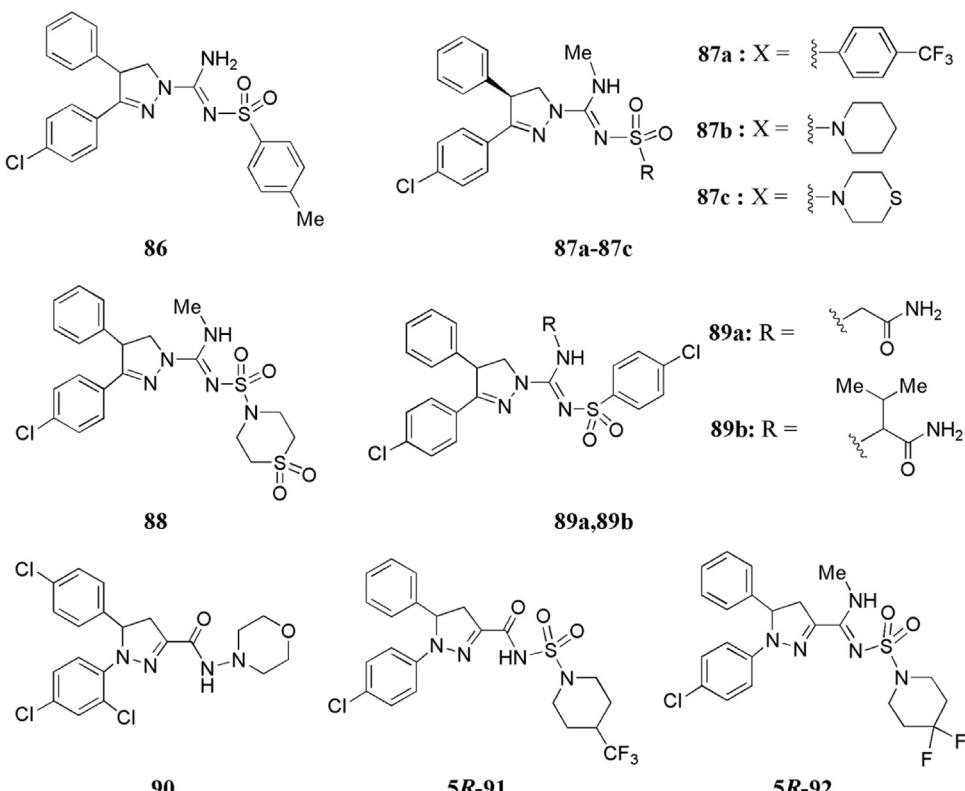
**Fig. 30.** Chemical structures of diaryl imidazole derivatives (76a–82b).

Fig. 31. Chemical structures of diaryl triazole derivatives (**83–85b**).

3,4-diaryl pyrazoline derivatives inhibited P-gp transport activity in membrane vesicles isolated from HEK293 cells. But the 1,1-dioxothiomorpholino analog **88** (Fig. 32) with K_i value of 830 ± 170 nM showed reduced accumulation ($-38 \pm 2\%$) in these cells. The ratio of brain/plasma concentration of compound **88** was significantly lower than rimonabant in the *in vivo* study on rats (0.4 ± 0.1 vs 6.2 ± 1.6 , $p < 0.001$). Compound **88** showed lower lipophilicity and higher cPSA value than rimonabant ($cLog P = 3.00$ and 6.47 respectively, $cPSA = 112$ and 48 \AA^2 respectively). Thus, compound **88** offered a good starting point for further development of peripherally acting CB1 receptor antagonists.

Chorvat et al. [158] synthesized analogs of SLV-319 (ibipinabant, **5**) with the aim of reducing the unwanted CNS side effect associated with penetration or passive diffusion of compounds into the brain. Tissue distribution and receptor occupancy studies exhibited that two lead compounds **89a** (JD-5006) and **89b** (JD-5037) (Fig. 32) showed little brain presence ($IC_{50} = 18$ and 2 nM respectively). Hence, for the treatment of obesity, peripherally restricted (PR) CB1 inverse agonists were developed with safer alternatives as compared to rimonabant.

Srivastava et al. [159] synthesized diaryl dihydropyrazole-3-carboxamide analogs. Compound **90** (Fig. 32) exhibited the highest affinity towards CB1 receptors and showed significant body

Fig. 32. Chemical structures of diaryl pyrazoline derivatives (**86–92**).

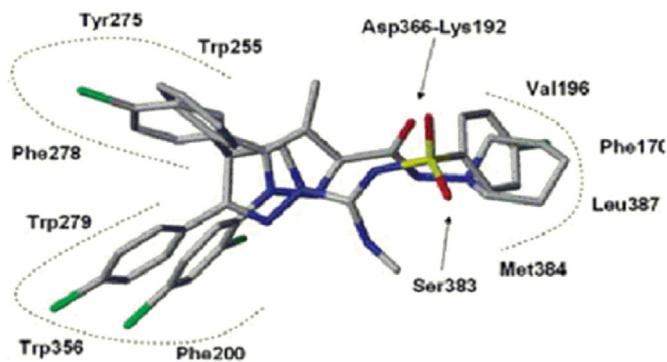


Fig. 33. Receptor-based alignments of SLV319 (5) and rimonabant (1) [82].

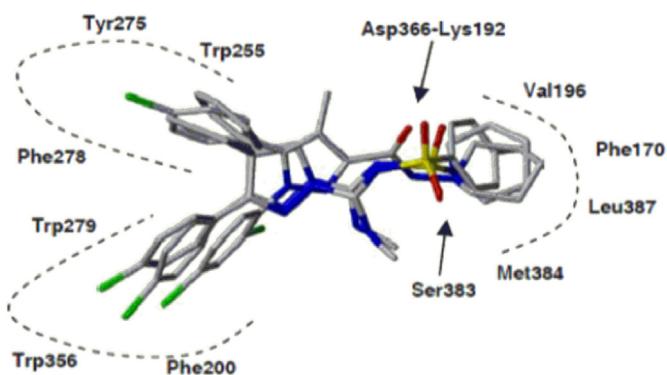


Fig. 34. Alignment of rimonabant (1), SLV319 (5) and 87b in the CB1 receptor binding site [156].

weight reduction in the *in vivo* ($K_i = 0.150 \mu\text{M}$) studies. Diaryl dihydropyrazole-3-carboxamide analogs also depicted similar interactions in homology modelling as shown by rimonabant and ibipinabant. Further, Srivastava et al. [160] replaced the 4,5-dihydro-1*H*-pyrazole moiety of ibipinabant by imidazole and oxazole rings on the basis of bioisosterism, but none of the compounds showed promising CB1 receptor antagonistic activity.

Lange et al. [161] synthesized 1,3,5-trisubstituted 4,5-dihydropyrazoles. The dextrorotatory enantiomers **91** and **92** (Fig. 32) showed high CB1 receptor affinities ($K_i = 2.0$ and 9.2 nM respectively).

2.6. Diaryl 1,2,4-triazolone derivatives

On the basis of scaffold hopping approach and privileged structure-oriented approaches, Han et al. [162] designed and synthesized 1,2,4-triazolone derivatives. The designed compounds showed interesting antagonistic activity towards either CB1 or CB2 receptors. The most active compound **93** (Fig. 35) with a *p*-tolyl group exhibited IC_{50} value of 222 nM and selectivity for the CB1 receptor. The binding mode of compound **93** in the active site of CB1 receptor was quite similar as compared to rimonabant (1). Oxygen atom of amide group of compound **93** formed a hydrogen bond with K192 as shown in Fig. 35.

2.7. Diaryl pyridine derivatives

Meurer et al. [163] from Merck Research Laboratories performed HTS of the Merck samples collection and found 5,6-diaryl pyridine derivative **94** (Fig. 36) having a moderate affinity for CB1 receptors ($\text{IC}_{50} = 530 \text{ nM}$) and utilised it as a lead molecule for the development of CB1 receptor antagonists. Compound **94** was modified to afford the 6-(4-chlorophenyl) substituted pyridine derivative **95** (Fig. 36) showing poor *hCB1* binding affinity ($\text{IC}_{50} = 2800 \text{ nM}$). Like rimonabant, additional chlorination on the phenyl moiety afforded compound **96** (Fig. 36) having greater than 200-fold *hCB1* binding ($\text{IC}_{50} = 11 \text{ nM}$) and more than 200-fold higher selectivity for *hCB1* over *hCB2* in the binding assay. The 3-cyano-2-(3,4-difluorobenzoyloxy)pyridine derivative **97** (Fig. 36) and the 3-(*N*-propylcarboxamido) derivative **98** (Fig. 36) showed equal affinity for the *hCB1* receptor ($\text{IC}_{50} = 1.3$ and 1.7 nM respectively) and 400-fold higher selectivity for *hCB1* over *hCB2* in the binding assays.

2.8. Diaryl pyrazine derivatives

Ellsworth et al. [164] from Bristol Myers Squibb Co., performed HTS and discovered many lead compounds including compound **99** (Fig. 37) having K_i value of 650 nM . As H-bond was formed between Lys192 and rimonabant (1) for the CB1 receptor antagonistic activity it was thought that incorporation of a carboxamide group into the molecule should be important, and hence synthesized pyrazine carboxamide derivatives **100** (Fig. 37) with K_i value of 52 nM . Compound **101** (Fig. 37) exhibited K_i value of 14 nM was developed by incorporating the polar hydroxyl moiety to improve the physicochemical and PK properties including lowering of clog *P* that resulted in enhanced oral exposures and *in vivo* efficacy in a food intake model in rats.

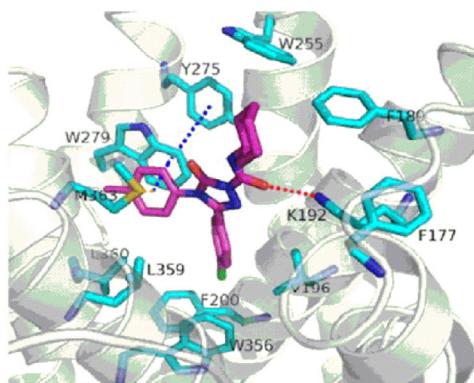
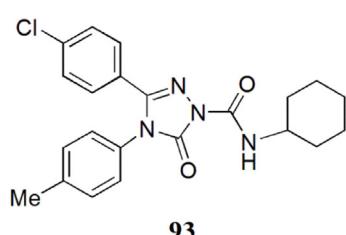


Fig. 35. Chemical structure of diaryl 1,2,4-triazolone derivatives and interactions with CB1 receptor.

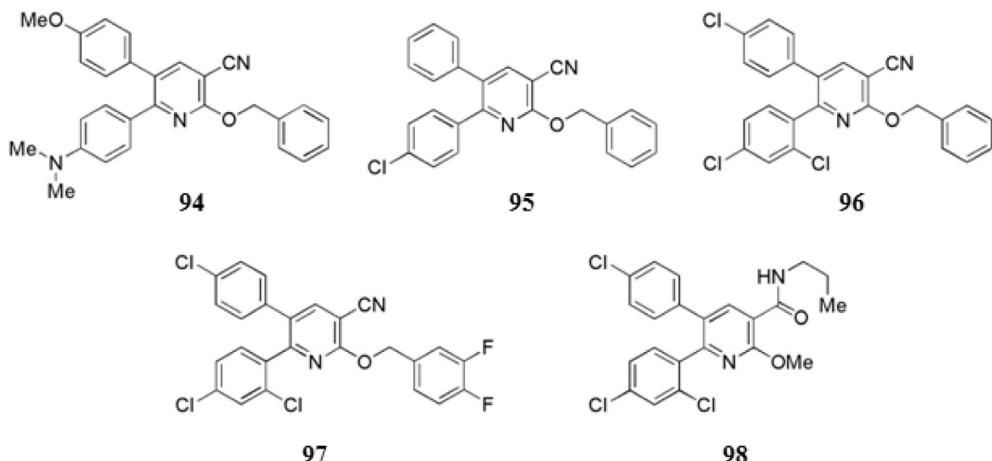


Fig. 36. Chemical structures of diaryl pyridine derivatives (94–98).

Wustrow et al. [165] from Neurogen Corporation prepared a novel class of pyrazine CB1 receptor inverse agonists. Simultaneous optimization was performed for CB1 receptor potency, solubility and CYP3A4 inhibition in the development of CB1 inverse agonists. Compound **102** (Fig. 37) was the optimized compound obtained from the series having similar or better *in vivo* properties compared to rimonabant in feeding model and CB1 receptor occupancy studies. It was found that in terms of inhibition of food intake and weight loss that occurred at 1 mg/kg, **102** had effects similar to 5 mg/kg of rimonabant. Compound **102** at 5 mg/kg dose induced approximately double weight loss compared to the animals treated with 5 mg/kg of rimonabant after 18 days dosing.

Bostrom et al. [166] from AstraZeneca performed drastic structural modifications in the diaryl heterocyclic ring system with the aim of retaining the global shape of rimonabant in the designed derivatives. It was observed that the pyrazine containing compound **103** (Fig. 37) was slightly lower in shape overlay as compared to the other selected five-membered counterparts such as pyrrole and thiazole derivatives. The shape of **103** (0.90), pyrrole (0.94) and thiazole (0.92) derivatives was almost equal to rimonabant in terms of Tanimoto index, which indicated that **103** was virtually identical to rimonabant in terms of shape (Fig. 38). A piperidino derivative **104** (Fig. 37) was found to be the most potent CB1 receptor antagonists ($IC_{50} = 1$ nM) in which bromine atoms

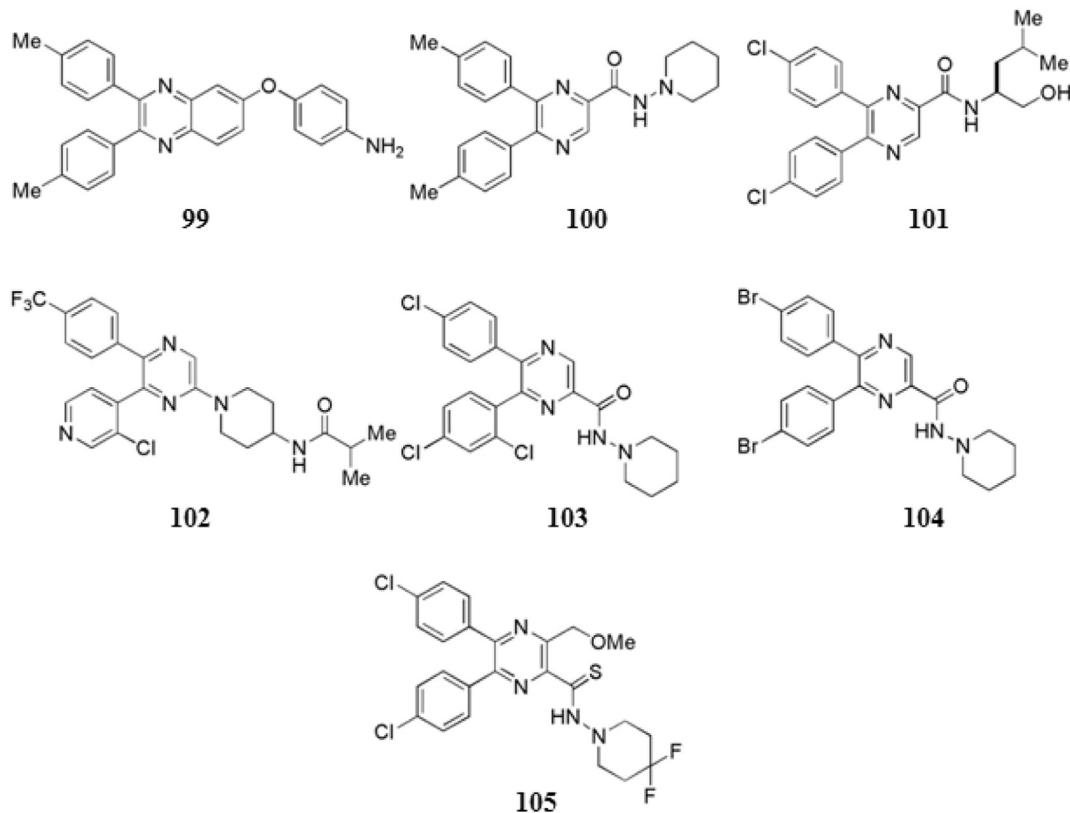


Fig. 37. Chemical structures of diaryl pyrazine derivatives (99–105).

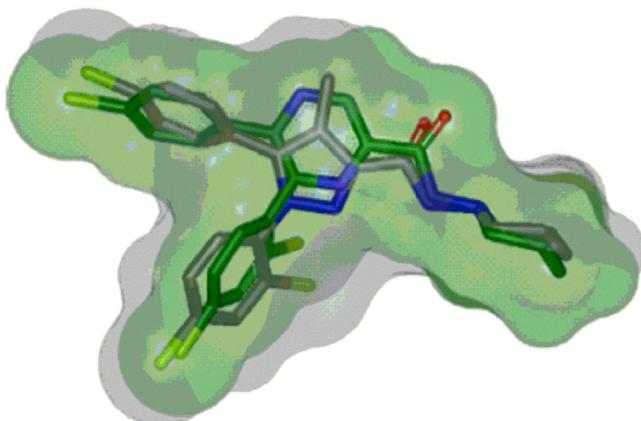


Fig. 38. Overlay of compounds **1** and **103**. The methylpyrazole moiety in rimonabant (**1**) is exchanged for a pyrazine in compound **103** [166]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

were incorporated at both of the para positions of phenyl rings. Further, Bostrom et al. [167] have applied a linker hopping approach in which carboxamide linker was replaced by a thioamide linker hypothesizing that if the hydrogen bond strength in the linker region was modified potent and neutral CB1 receptor antagonists could be designed which suppressed appetite as well as avoided undesirable side effects. The thioamide derivatives retained CB1 potency below 10 nM with improved solubility in comparison to the corresponding carboxamides. A neutral antagonist **105** (Fig. 37) ($IC_{50} = 2.4$ nM) reduced body weight significantly in cafeteria diet obese mice.

2.9. Diaryl piperidine derivatives

On the basis of literature survey 1,6-diaryl piperidin-2-ones were developed [168]. Scott et al. [169] from Merck Research Laboratory thought to elaborate the requirements of position-3 of the piperidin-2-one scaffold. The piperidinone group in compound **106** (Fig. 39) was reduced to piperidine derivative **107a** (Fig. 39) with a K_i value of 72 nM. The (*R,R*)-enantiomer of **107a** was overlaid on rimonabant as shown in Fig. 40. The diphenyl ring of compound **107a** was perfectly aligned on the diphenyl ring of rimonabant (**1**).

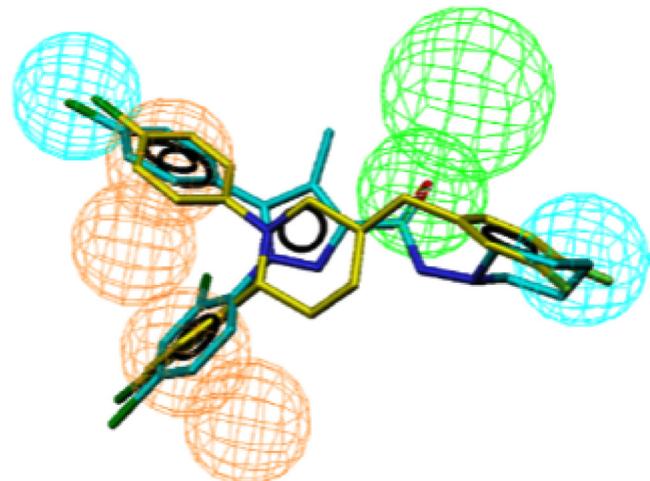


Fig. 40. Molecular superimposition of the (*R,R*)-enantiomer of **107a** and rimonabant on the CB1 receptor pharmacophore model. The pharmacophore features are represented by meshed spheres. Aromatic ring features are represented by pairs of solid brown spheres. Nitrogen atoms are coloured as dark blue, oxygen atoms are red and the halogen atoms are green. Carbon atoms of the rimonabant are coloured light blue, and those of **107a** are coloured yellow [169]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

It has been reported in literature [107,168] that 2,4-dichloro substitution on one of the phenyl rings in a compound exhibited 10-fold improved affinity compared to the corresponding 4-chlorophenyl analogs. Compound **107b** (Fig. 39) with 2,4-dichlorophenyl substituent showed six-fold improved binding affinity ($K_i = 15$ nM) compared to the analog **107a** which is in accordance with the literature report [107,168]. Thus, 5-substituted 1,2-diaryl piperidine derivatives were designed as a new class of CB1 receptor antagonists. The most potent compound in the series was the sulfonamide derivative **108** (Fig. 39) having K_i value of 3.4 nM that produced a robust reduction of food intake in DIO mouse assay over 24-h period.

2.10. Diaryl 1,4,5,6-tetrahydropyridazine derivatives

Lange et al. [170] applied bioisosteric approaches and replaced the 4,5-dihydropyrazole moiety of ibipinabant with a non-aromatic six membered 1,4,5,6-tetrahydropyridazine scaffold. Compounds

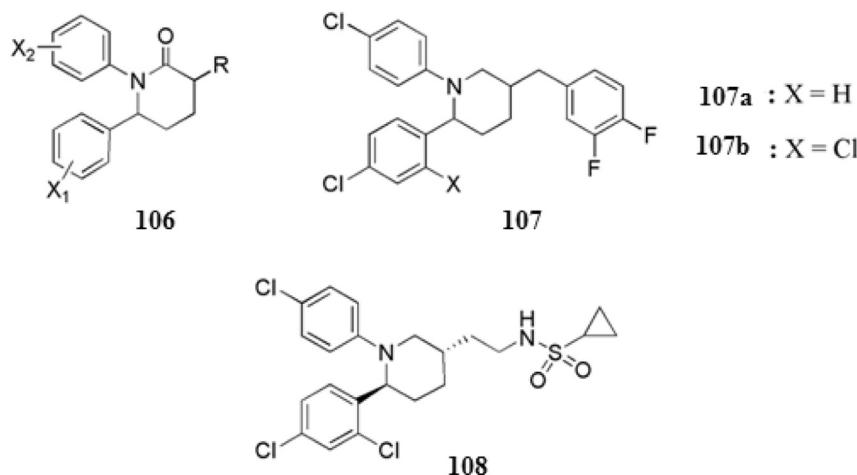


Fig. 39. Chemical structures of diaryl piperidine derivatives (**106–108**).

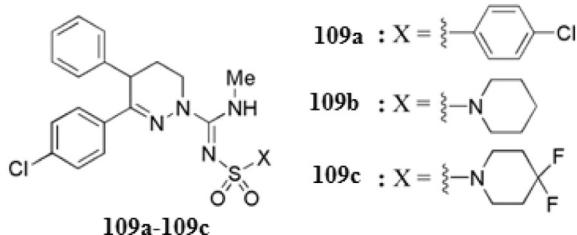


Fig. 41. Chemical structures of diaryl 1,4,5,6-tetrahydropyridazine derivatives (**109a–109c**).

109a–109c (Fig. 41) were obtained as potential CB1 receptor antagonists having K_i values of 43, 74 and 47 nM respectively with significant selectivity for the CB1 receptor.

2.11. Diaryl pyrrolopyridinone derivatives

Smith et al. [171] designed and synthesized a new series of pyrrolopyridinones as constrained analogs of rimonabant. Computational studies were performed on rimonabant and it was found that the preferred conformer having a *trans*-amide with the carboxamide oxygen closely matched with the pyrazole ring and was oriented in the same direction as the pyrazole C-4 methyl group as shown in Fig. 42(a). Modelling studies also indicated that a constrained analog of this conformation could be easily obtained by having an ethylene bridge in between pyrrole C-2 position and the carboxamide nitrogen. Compound **110** (Fig. 43) was thus obtained having a 1,5,6,7-tetrahydro-4-H-pyrrolo[3,2-c]pyridin-4-one scaffold with K_i value of 2.2 nM. An overlay of the low-energy conformation of **1** and compound **110** is shown in Fig. 42(b). A leading analog **111** (Fig. 43) in the series was established to cause a significant anorectic effect ($K_i = 20$ nM) in the fasted-refed Wistar rat model with $C_{max} = 0.62 \mu\text{M}$ and $AUC_{(0-2\text{h})} = 0.58 \mu\text{M}\cdot\text{h}$ at 10 mg/kg p.o., and a significant reduction in body weight gain in the chronic Zucker rat model.

2.12. Diaryl purine derivatives

Griffith et al. [81] discovered a new series of purine derivatives as CB1 receptor antagonists. Compound **4** (Fig. 7) showed good human CB1 binding ($K_i = 0.7$ nM) and functional activities ($K_i = 0.12$ nM) as well as good *in vivo* activity in rodent model of feeding. Further, Fulp et al. [172] designed novel analogs of compound **4** with the aim of developing peripherally acting selective CB1 receptor antagonists. A number of functional groups like carbamates, amines, sulfonamides, ureas and amides were substituted on the aminopiperidine terminus and all were found to be well tolerated. The sulfonamide derivative **112** (Fig. 44) showed high

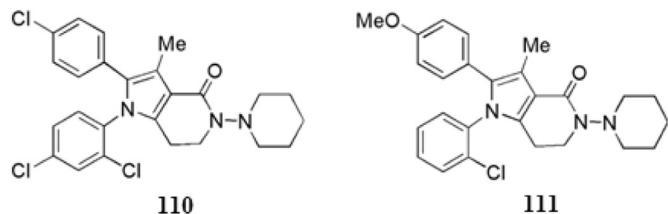


Fig. 43. Chemical structures of diaryl pyrrolopyridinone derivatives (**110,111**).

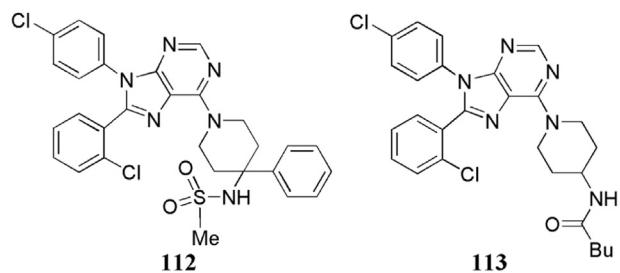


Fig. 44. Chemical structures of diaryl purine derivatives (**112,113**).

TPSA value of 101 Å² with excellent potency, selectivity and oral absorption in rat as well as lowered brain penetration ($K_e = 2.9$ nM; CB2/CB1 = 153). An oral dose of 10 mg/kg of compound **112** in SD rats showed very poor brain penetration with the brain to plasma ratio ranging from 0.05 to 0.11 after 8 h postdose (Table 4). Thus, compound **112** was used as the starting lead for compounds with still lowered brain penetration. Fulp et al. [173] continued their work with compound **112** and designed compound **113** (Fig. 44), a potent (K_e value 4.9 nM), orally absorbable derivative with more than 50 fold higher selectivity for CB1 over CB2 receptors. Plasma levels of compound **113** were found to be higher over compound **112** [C_{max} (1965 vs 1653 ng/mL) and after 8 h time point (1965 vs 914 ng/mL)]. Brain-to-plasma ratios of compound **113** ranged from 0.01 to 0.07 indicating minimal or no penetration into the CNS as shown in Table 5.

2.13. α, β-Diaryl fused pyridine ring derivatives

Debenham et al. [174] from Merck Research Laboratories developed furo[2,3-*b*]pyridine scaffold in which compounds **114a** and **114b** (Fig. 45) having IC₅₀ value of 5.4 and 4.3 nM respectively showed high affinity toward CB1 receptors and effectively modulated feeding behaviour to suppress both food intake and body weight gain. Further, this group [175] thought of fusing two pyridine rings and designed 1,8-naphthyridinone core system. In this series compound **115** (Fig. 45) was obtained as an orally active,

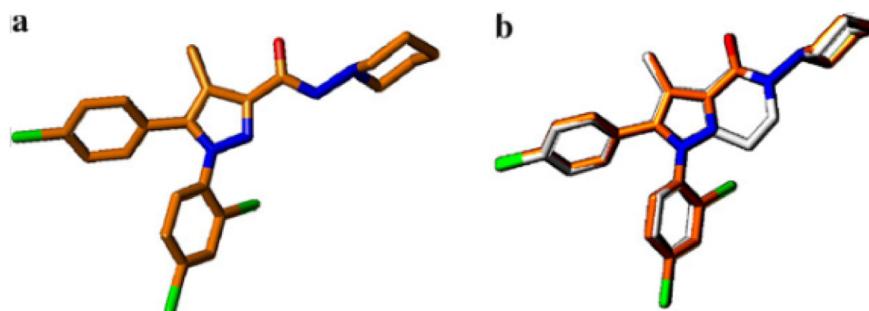


Fig. 42. (a) Low-energy conformation of **1**. (b) Superimposition of low energy conformation of **1** with compound **110** [171].

Table 4
Pharmacokinetic analysis of 112 [172].

Dose mg/kg oral	Sacrifice time (min)	Plasma conc. (ng/mL)	Brain conc. (ng/mL)	Brain/plasma ratio
10	30	752	38	0.05
	60	767	58	0.08
	120	1188	122	0.10
	240	1653	184	0.11
	480	914	89	0.10

Table 5
Pharmacokinetic evaluation of compound 113 (*in vivo*) [173].

Time (h)	Plasma conc. (ng/mL)	Brain conc. (ng/mL)	Brain/plasma ratio
1	730	24.3	0.03
2	1750	71.5	0.04
4	1565	103	0.07
8	1965	62.5	0.03
24	438	5.35	0.01

highly potent and selective CB1 inverse agonist ($IC_{50} = 7.5$ nM; CB2/CB1 = 546). They [176] pursued further modification of the core ring system and designed pyridopyrimidine derivatives. Compounds 116 and 117 (Fig. 45) showed high potency and selectivity with oral activity in the series ($IC_{50} = 9.5$ and 1.6 nM respectively).

Yan et al. [177] from Merck Research Laboratories used pyranopyridine derivative 118 (Fig. 45) with an IC_{50} value of 4.8 nM as a lead molecule in the discovery of a potent and effective CB1R inverse agonist 119 (Fig. 45). Compound 119 ($IC_{50} = 1.0$ nM; CB2/CB1 > 1000) reported to have a pharmacological efficacy similar to that of taranabant with a good PK profile in preclinical studies and an acceptable safety margin.

Madsen-Duggan et al. [178] from the same laboratory synthesized a series of dihydro-pyrano[2,3-*b*]pyridine and tetrahydro-1,8-naphthyridine bicyclic core scaffolds. Compounds 120a–120c, 121 (Fig. 45) were found to be orally active CB1 receptor antagonists which effectively modulated food intake and body weight in a rodent model ($IC_{50} = 1.7, 4.8, 3.0$ and 3.7 nM respectively). Compound 121 showed 25% bioavailability while compounds 120a and 120c had more than 80% oral bioavailability.

2.14. Acyclic diaryl derivatives

Lin et al. [79] from Merck Research Laboratories discovered a series of novel acyclic amide CB1 inverse agonists that were potent, selective and orally bioavailable. After the optimization process, the most potent compound (2, $IC_{50} = 0.3$ nM) was identified with over 900 fold selectivity for CB1 receptors with a good pharmacokinetic profile in three animal species as a clinical candidate for the treatment of obesity. Armstrong et al. [179] from the same group designed a sulfonamide analog of taranabant (2) as a CB1 receptor inverse agonist. Compound 122 (Fig. 46) was found to be the most potent compound ($IC_{50} = 2.8$ nM) with good pharmacokinetic characteristics but with non-acceptable levels of brain penetration. An oral dose of 2 mg/kg of 122 exhibited low clearance ($Cl = 10.6$ mL/min/kg), good distribution ($V_d = 6.9$ L/kg) with plasma C_{max} of 343 nM as shown in Table 6 and brain/plasma ratio as shown in Table 7.

Liu et al. [180] from Merck Research Laboratories utilized compound 122 as a lead molecule for further structural optimization for reducing the lipophilicity and increasing affinity towards CB1 receptors. Compound 123 (Fig. 46) was obtained as the most potent compound ($IC_{50} = 0.7$ nM) with low lipophilicity ($\log D = 4.0$) in the series.

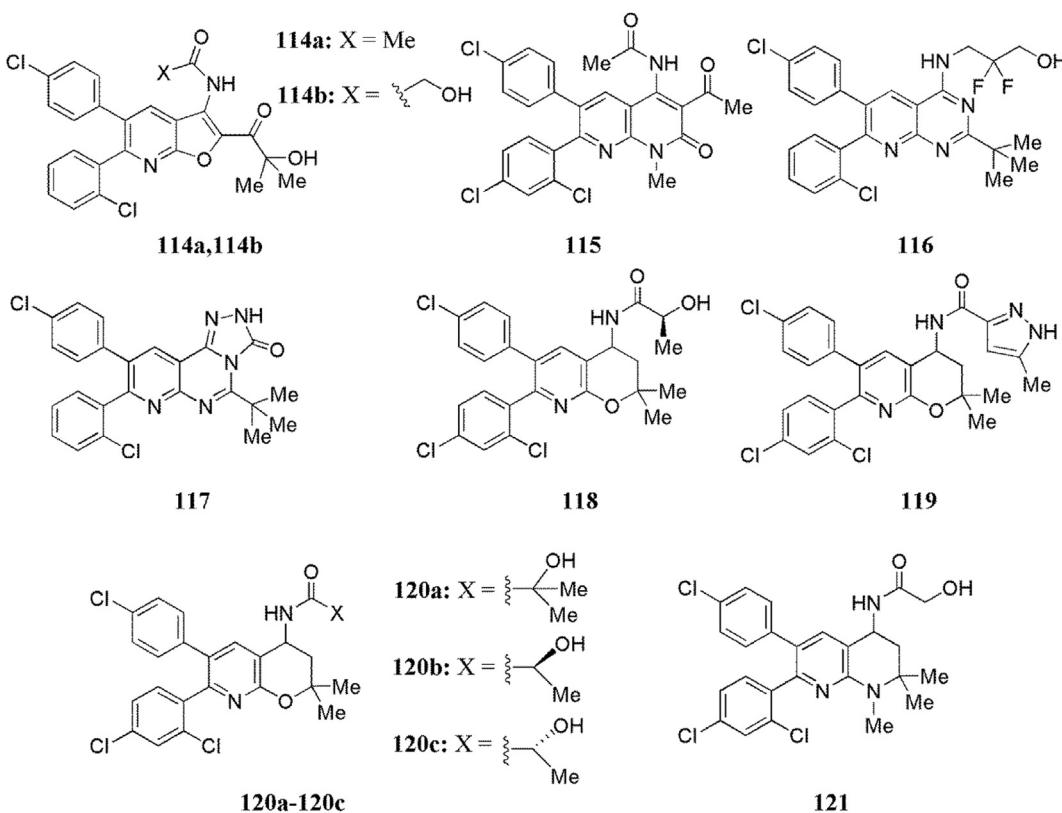


Fig. 45. Chemical structures of α, β -diaryl fused pyridine ring derivatives (114a–121).

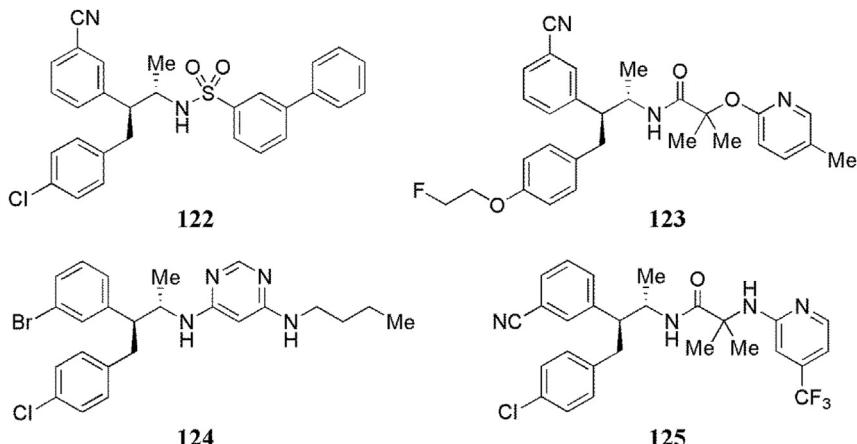


Fig. 46. Chemical structures of acyclic diaryl derivatives (122–125).

Table 6
Pharmacokinetics of biphenylsulfonamide 122 (*in vivo*) [179].

F (%)	$t_{1/2}$ (h)	Cl (mL/min/kg)	V_d (L/kg)	C_{max} (nM)
48%	8.4	10.6	6.9	343

Table 7
Rat brain/plasma penetration (1 mg/kg iv) [179].

Time (h)	Plasma conc (nM)	Brain conc (nM)	Ratio (b/pl)
0.25	220	146	0.66
1	113	92	0.82
2	54	54	1.00

On the basis of chemical structure of Merck's taranabant (2), Kim et al. [181] designed a substituted pyrimidine series for CB1 receptor antagonism. But, the resulting compounds showed less binding affinity for the CB1 receptors compared to taranabant. Compound 124 (Fig. 46) was the most potent compound obtained from the series having IC₅₀ value of 16.3 nM and selectivity index (CB2/CB1) of 181. Du et al. [182] from Merck Research Laboratories designed second generation CB1R inverse agonists from the acyclic amide scaffold in which the oxygen linker was replaced by

nitrogen. Compound 125 (Fig. 46) was obtained as the most potent compound in the series but compounds with nitrogen linkage in general, offered less affinity for the CB1 receptor than the compounds with oxygen linkage.

2.15. Diaryl (thio)hydantoin derivatives

3-Substituted 5,5-diphenylimidazolidinedione derivatives also known as 3-substituted 5,5-diphenylhydantoins were identified as cannabinoid receptor antagonists having moderate affinity for CB1 receptors [183]. Ooms et al. [184] identified compounds 126a–126c (Fig. 47) as neutral antagonists of CB1 receptors ($K_i = 70.3, 103.2$ and 97.9 nM and $\log P = 3.86, 3.76$ and 7.45 respectively). Muccioli et al. [185] introduced sulphur atom in place of oxygen in the second position of the hydantoin ring resulting in 3-substituted 5,5-diphenyl-2-thioxoimidazolidin-4-one derivatives. Compounds 127a and 127b (Fig. 47) showed the highest affinity for the CB1 receptor ($K_i = 724$ and 589 nM respectively) in the series. Further, modification by Muccioli et al. [186] resulted in 1,5-diphenylimidazolidine-2,4-dione and 1,3,5-triphenylimidazolidine-2,4-dione series. Unfortunately, 1,5-diphenylimidazolidine-2,4-dione derivatives showed no affinity for CB1 receptors. The most active compounds were obtained by

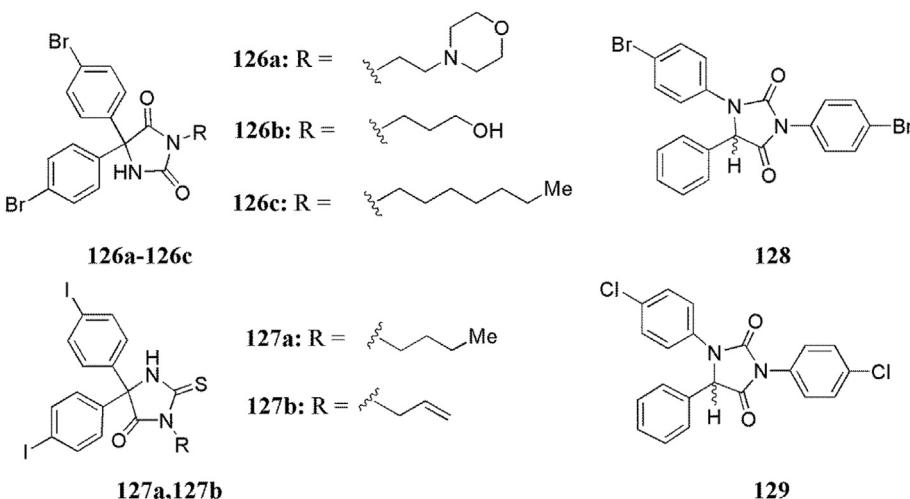


Fig. 47. Chemical structures of diaryl (thio)hydantoin derivatives (126a–129).

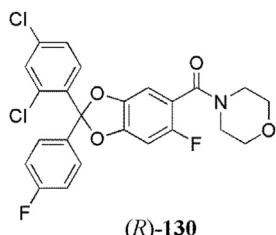


Fig. 48. Chemical structure of diaryl benzodioxole derivative (R)-130.

the substitution of chloro and bromo groups in the para positions of the *N*1 and *N*3 phenyl rings whereas additional substitution of halogens on the C5 phenyl ring decreased CB1 receptor affinity. Compounds **128** and **129** (Fig. 47) were obtained with the highest affinity for the CB1 receptor in the series ($K_i = 311$ and 247 nM respectively).

2.16. Diaryl benzodioxole derivatives

Alig et al. [187] identified a novel benzodioxole series as CB1 receptor antagonists. Compound (R)-**130** (Fig. 48) showed high affinity towards the CB1 receptor ($K_i = 4$ nM) and a robust reduction in the body weight gain in a 16 days DIO rat model.

2.17. Benzhydrylpiperazine derivatives

A novel series of piperazine derivatives were designed by Song et al. [188] as CB1 receptor antagonists. Modest CB1 and extremely weak CB2 binding affinities were observed in urea derivatives linked with 1-[(2-chlorophenyl)(4-chlorophenyl)methyl]piperazine; as **131a** and **131b** (Fig. 49) were the most potent compounds having IC₅₀ values of 72.8 nM and 66.5 nM respectively in terms of rat CB1R binding affinity. Better functional activity has been observed in compounds **132a** and **132b** (Fig. 49) with an IC₅₀ value of 62.8 nM and 49.4 nM respectively in comparison to rimonabant (IC₅₀ = 120 nM) in cell line studies using cell line expressing hCB1R.

By utilizing the privileged structure-based approach Meng et al. [189] identified benzhydrylpiperazine moiety as a lead scaffold for the development of CB1 receptor antagonists. Compound **133** (Fig. 49), a cyclohexylurea derivative with a *p*-methyl substituent, has been observed with the highest potency ($K_i = 0.15$ nM) and selectivity (>2000) for CB1 receptors. Compound **133** at 10 mg/kg

Table 8

Pharmacokinetic studies of the racemic compound **133** and its enantiomers **133(S)** and **133(R)** in Sprague Dawley rats after 10 mg/kg p.o. administration [190].

Pharmacokinetic parameters	Compounds		
	133(RS)	133(S)	133(R)
t _{max} (h)	2.4 ± 0.2	1.3 ± 0.3	1.2 ± 0.3
C _{max} (ng/mL)	179.5 ± 31.5	128.5 ± 10.5	115.7 ± 19.3
t _{1/2} (h)	2.3 ± 0.1	3.4 ± 1.0	3.8 ± 0.6
AUC _{0-∞} (ng h/mL)	883 ± 112	695 ± 34	655 ± 68
F (%)	8%	6%	15%
B/P @9 h postdose	0.91 ± 0.07	1.47 ± 0.17	0.88 ± 0.06

Table 9

Assay results of enantiomers of **133** [190].

Compound	Absolute configuration (optical rotation)	K _i hCB1 (nM)	K _i hCB2 (nM)	IC ₅₀ hCB1 Ca ²⁺ (nM)
133(RS)		0.15 ± 0.04	329 ± 71	2.7 ± 0.5
133(S)	S (+4.3°)	1.1 ± 0.1	242 ± 119.0	21.5 ± 8.3
133(R)	R (-4.3°)	0.2 ± 0.03	226.8 ± 45.9	0.9 ± 0.4

dose showed plasma half-life of approximately 2.4 h and the plasma-to-brain concentration ratios were observed to be 0.5 and about 1.0 at 3 and 12 h postdose respectively, whereas rimonabant showed plasma-to-brain concentration ratios of 1.6 and nearly 4.4 at the same dose and time respectively. Compound **133** was a slow and low brain-entrant as compared to rimonabant. A single dose of compound **133** at 10 mg/kg (p.o.) suppressed 3 h and overnight (18 h) food intake by 39 and 22% respectively in diet-induced obesity (DIO) rats. Further, Gao et al. [190] from the same group performed asymmetric synthesis of compound **133**. *R*-form was found to be more potent than the *S*-form on the basis of pharmacokinetic profiles and the *in vitro* and *in vivo* evaluations are shown in Tables 8 and 9. Although over 95% enantiomeric excess (ee) was observed in the desired products, **133S**/**133R** indicated no *in situ* epimerization.

2.18. Benzhydryl derivatives

Muccioli et al. [191] have reported a new series of 1-benzhydryl-3-phenylurea and 1-benzhydryl-3-phenylthiourea derivatives as selective CB1 receptor inverse agonists. Compound **134** (Fig. 50)

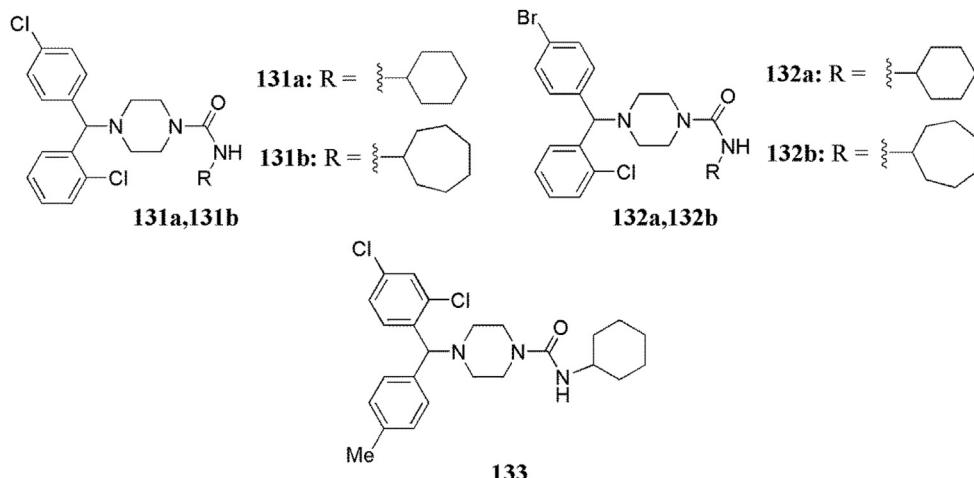


Fig. 49. Chemical structures of benzhydrylpiperazine derivatives (131a–133).

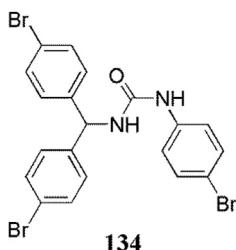


Fig. 50. Chemical structure of benzhydryl derivative **134**.

was found to be having the highest affinity for CB1 receptors in the series ($K_i = 500$ nM).

2.19. Indole derivatives

Letourneau et al. [192] from Webba Ligand Pharmaceuticals discovered a novel class of CB1 receptor antagonists using HTS. By HTS campaign, different active structural hits were identified. Out of these, benzimidazole-based compound **135** (Fig. 51) was selected on the basis of target independent (e.g., physicochemical properties) and target dependent (e.g., potency) properties. In the process of the development of CB1 receptor antagonists, isosteric replacement of benzimidazole scaffold with indole and ‘inverted’ indole and incorporation of hydroxyl moiety into the amide side-chain was carried out. This kind of modification produced structures with improved properties like low log P , enhanced aqueous solubility and better stability to both human and mouse liver microsomes. Compound **136** (Fig. 51) was found to be the most potent compound ($IC_{50} = 0.005$ μ M) in the luciferase assay and exhibited decent HLM stability (i.e., >50% remaining at 0.5 h) with considerably less lipophilicity than rimonabant. Compound **136** and rimonabant gave A log P values of 3.60 and 7.02 respectively.

Further, Cowley et al. [193] from the same team identified a novel series of indole-2-carboxamides as CB1 receptor antagonists. They performed medium throughput screening campaign in which

compound **137** (Fig. 51) was identified as a lead molecule for an optimisation program. The primary task was to increase the potency and improve the physico-chemical properties of the lead molecule **137** as it showed relatively weak potency and higher lipophilicity ($CB1 IC_{50} = 0.42$ μ M, clog $P = 6.32$). Compound **138** (Fig. 51) was obtained having moderate potency with reduced lipophilicity ($IC_{50} = 0.26$ μ M, clog $P = 4.78$) by *N*-(3-hydroxy-2,2-dimethylpropyl)carboxamide substitution in compound **137**. C-5 position of the indole ring in the compound **138** was substituted with a polar electron withdrawing nitrile group resulting in compound **139** (Fig. 51) in which a dramatic increase in CB1 potency ($IC_{50} = 1.8$ nM) was observed. Final optimisation cycle was performed around the benzyl substituent of compound **139** resulting in compound **140** (Fig. 51) as a selective CB1 receptor antagonist with higher potency and lower lipophilicity ($IC_{50} = 1.1$ nM, clog $P = 4.76$). Subsequently, Cowley et al. [194] performed pharmacokinetic-based optimisation of the same series and obtained compound **141** (Fig. 51) as a highly potent and selective CB1 receptor antagonist with a high predicted human oral bioavailability as compared to compound **140**.

2.20. Benzofuran derivatives

Foloppe et al. [195] performed ligand-based virtual screening in which a new class of benzofurans as potent and selective CB1 receptor antagonists was identified. A pharmacophore model developed by using rimonabant (**1**) and ibipinabant (**5**) included (i) two aromatic rings (green spheres; 1.5 radius) and the projection points of the vectors normal to these rings (white spheres; 2.0 radius) and (ii) a hydrogen-bond acceptor (magenta sphere; 1.8 radius) as shown in Fig. 52.

Commercially available Vernalis electronic catalogue was used for virtual screening wherein compound **142** (Fig. 53) fitted well in the developed pharmacophore model. Furan and the benzyl moieties of compound **142** were matching the aryl pharmacophore points and the sulfonamide group matched with the hydrogen-bond acceptor region. Thus, compound **142** was identified as a

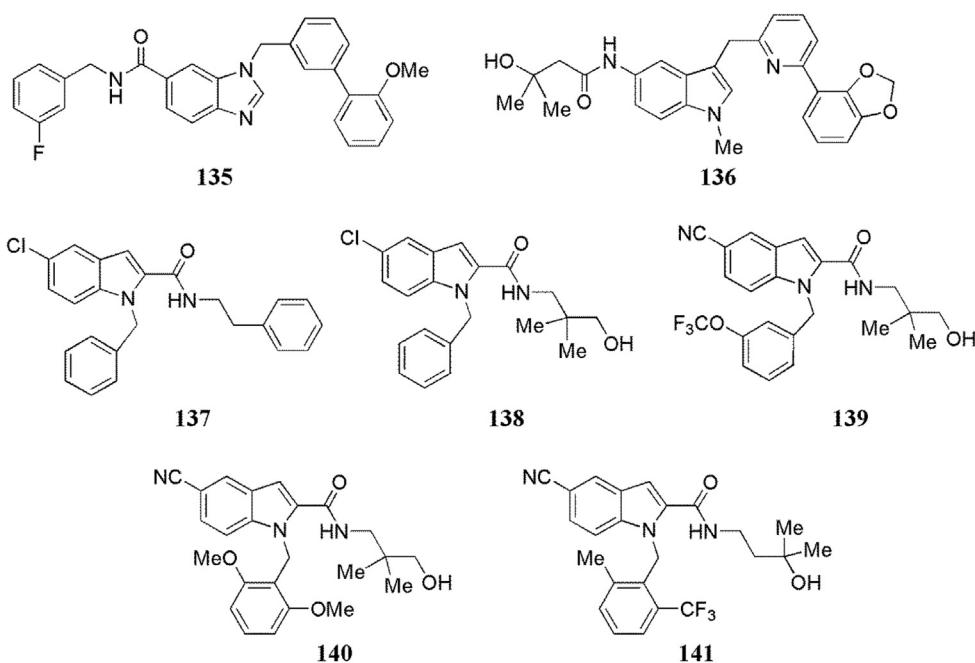


Fig. 51. Chemical structures of indole derivatives (135–141).

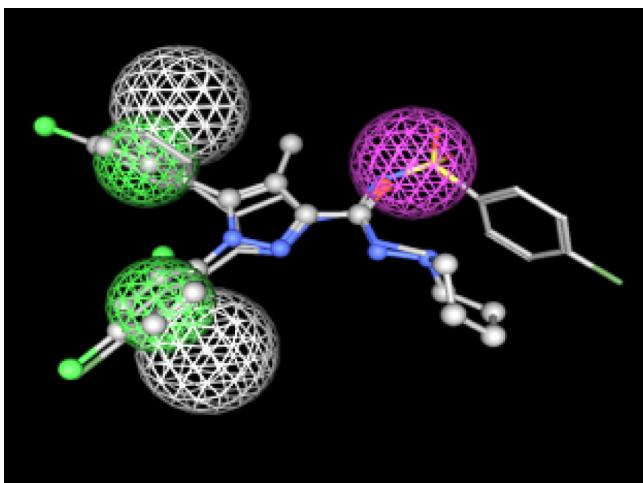


Fig. 52. CB1 receptor antagonist pharmacophore developed from an alignment of **1** (ball and stick) and **5** (stick) [195].

lead molecule ($K_i = 91.6$ nM; $hCB2/hCB1 = 34$). The most potent and highly selective compound in the series was **143** (Fig. 53) having K_i value of 5 nM and $hCB2/hCB1 = 4560$.

2.21. Coumarin derivatives

Behrenswerth et al. [196] synthesized a new series of coumarin and related 2*H*-coumarin derivatives. Thus, a new lead structure was identified in the form of 5-substituted 3-benzylcoumarin derivatives in the developmental process showing CB1 and CB2 antagonistic activity. Compound **144a** (Fig. 54) was the most potent compound having K_i value of 0.738 μ M for CB1 and K_i value of 0.944 μ M for CB2 receptors in the series. Rempel et al. [197] designed and synthesized a series of 7-alkyl/aryl-3-benzylcoumarins. Compound **144b** (Fig. 54) was the most potent and selective CB1 receptor antagonist in the series ($K_i = 0.022$ μ M; CB2/CB1 = 18).

Pasquini et al. [198] synthesized a series of 7-substituted 4-quinolone-3-carboxamides as cannabinoid ligands selective for either CB1 or CB2 receptors. They observed that replacement of 1-adamantyl group by a fenchyl moiety intensely enhanced CB1 affinity with minimal effects on receptor selectivity. Interestingly, substitution of adamantyl group by 3,4-dichlorobenzyl group

showed marked increase in CB1 selectivity. Compounds **145a** and **145b** (Fig. 54) were the first selective CB1 receptor antagonists in the 4-quinolone-3-carboxamide family ($K_i = 390$ and 420 nM respectively).

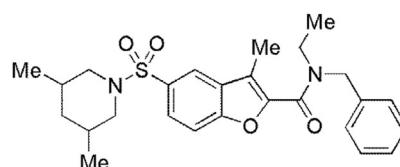
2.22. Dibenzothiazepine derivatives

Pettersson et al. [199] from ACADIA Pharmaceuticals AB performed a HTS of a library of 270,000 compounds. For screening of CB1 inverse agonists, they employed a proprietary mammalian cell-based functional assay and receptor selection and amplification technology (R-SAT), and identified compound **146** (Fig. 55) showing affinity for the CB1 receptors ($pIC_{50} = 6.5$ in R-SAT). Introduction of the acid hydrazide side chain and a cyclohexyl group in place of *n*-propyl group offered compound **147** (Fig. 55) with pIC_{50} value of 7.6 in R-SAT which was equipotent to rimonabant and SLV319. When *n*-butyl group was attached to the amide chain and 4-chlorophenyl group was introduced in place of cyclohexyl group in compound **147**, compound **148** (Fig. 55) resulted which was used further as a lead molecule in designing more selective CB1 receptor antagonists ($pIC_{50} = 8.1$ in R-SAT). Overlay of compound **148** with rimonabant and taranabant is presented in Fig. 56. Poor solubility of the lead compound **148** was improved in compound **149** (Fig. 55) by introducing a 3,4-dihalogenated phenyl group ($pIC_{50} = 8.4$ M in R-SAT).

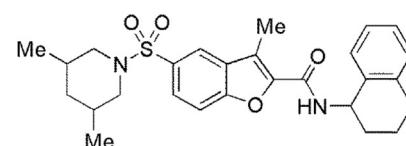
2.23. Pyrrolo[1,2-*a*]quinoxaline derivatives

Szabo et al. [200] performed HTS campaign using a functional Ca^{2+} assay and obtained several hits having a pyrrolo[1,2-*a*]quinoxaline scaffold as shown in compound **150a** (Fig. 57) as a lead molecule with K_i value of 831 nM. Three regions were focused to improve the potency of compound **150a** (Fig. 57): i) the alkyl side chain (R), ii) the acyl group (R_1) and iii) the aryl group (R_2) on the pyrrolo-quinoxaline ring. Compound **150b** was found to be the most potent compound ($K_i = 45$ nM) in the pyrrolo-quinoxaline series and the binding mode was analyzed by docking studies which revealed that compound **150b** had a similar mode of interaction as that of rimonabant as shown in Fig. 58.

Vachal et al. [201] performed HTS and identified a novel series of 1-sulfonyl-4-acylpiperazines as selective CB1R inverse agonists. From the Merck sample collection, compound **151** (Fig. 57) was identified as a potent inverse agonist of CB1R. Cyclic-AMP (cAMP) levels of compound **151** were measured ($EC_{50} = 1$ nM) in a CB1R functional assay but it had only modest activity in a CB1R

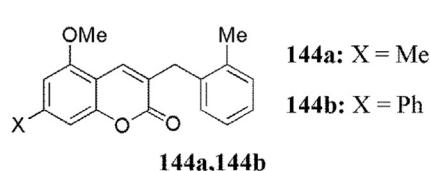


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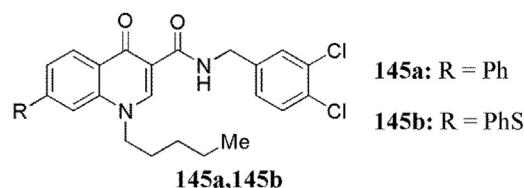
143

Fig. 53. Chemical structures of benzofuran derivatives (**142,143**).



144a: X = Me
144b: X = Ph

144a,144b



145a: R = Ph
145b: R = PhS

145a,145b

Fig. 54. Chemical structures of coumarin derivatives (**144a–145b**).

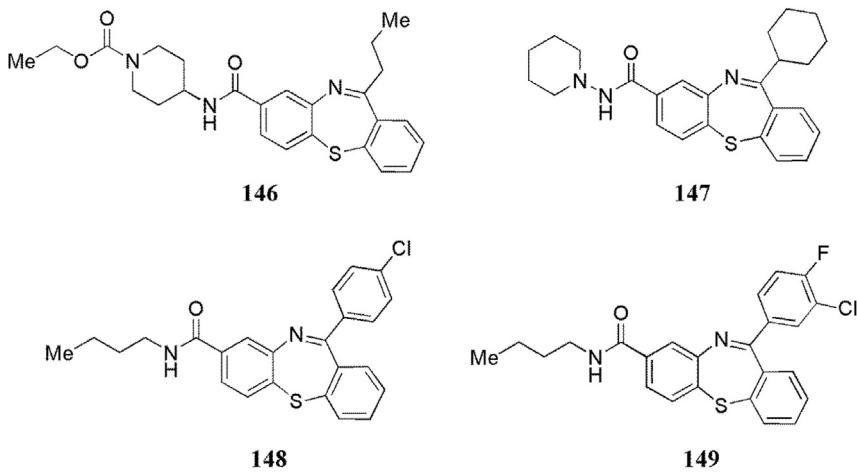


Fig. 55. Chemical structures of dibenzothiazepine derivatives (146–149).

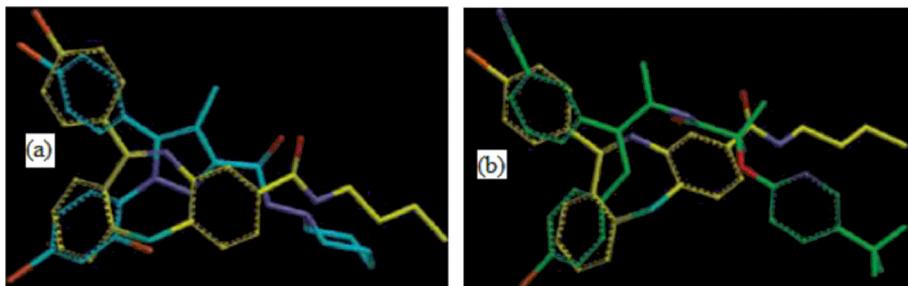


Fig. 56. Superimposition of 148 (yellow) with (a) rimonabant (cyan) and (b) taranabant (green) [199]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

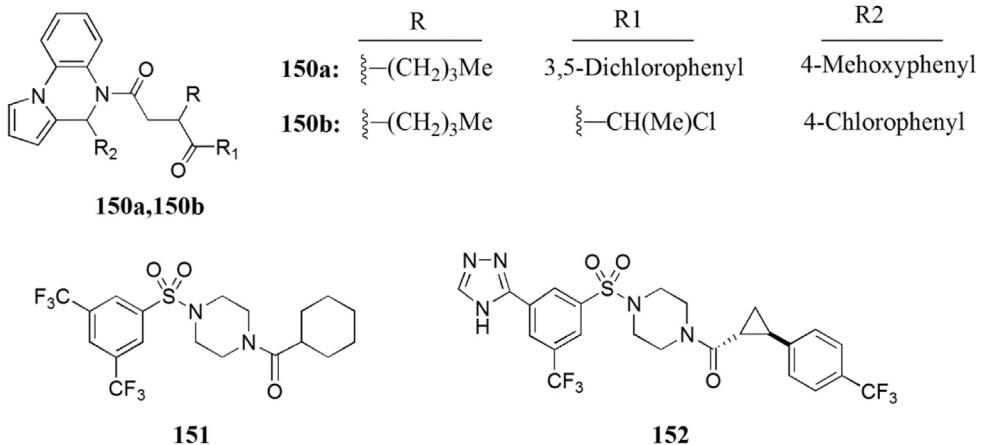


Fig. 57. Chemical structures of pyrrolo[1,2-a]quinoxaline derivatives and piperazine derivatives (150a–152).

competition binding assay ($\text{IC}_{50} = 260 \text{ nM}$). After the optimisation process it was found that compound 152 (Fig. 57), a 1,3,4-triazole derivative, possessed a superior CB1R potency profile in DIO rats, and reduced hERG activity ($\text{IC}_{50} > 1 \mu\text{M}$).

3. Molecular modelling studies in the designing of CB1 receptor antagonists

Now days, molecular modelling has become an integral part of drug design and development process. Here, the molecular

modelling studies of cannabinoid receptor antagonists is incorporated for better understanding of ligand receptor interactions as well as for further development or designing of selective CB1 receptor antagonists. Molecular modelling studies have been carried out by various groups for the designing and optimization of CB1 receptor antagonists. Ligand based designing tools like 3D-QSAR, pharmacophore and virtual screening have been utilized and various structure based designing tools like homology modelling and docking reported in the literature have been discussed below in detail.

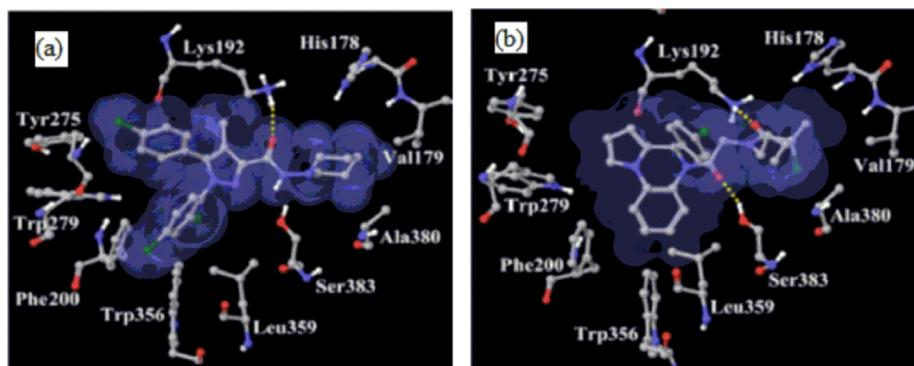


Fig. 58. Binding mode of (a) rimonabant and (b) compound **150b**, vander Waals surfaces of the ligands are shown in light blue. H-bonds are shown as yellow dotted lines [200]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

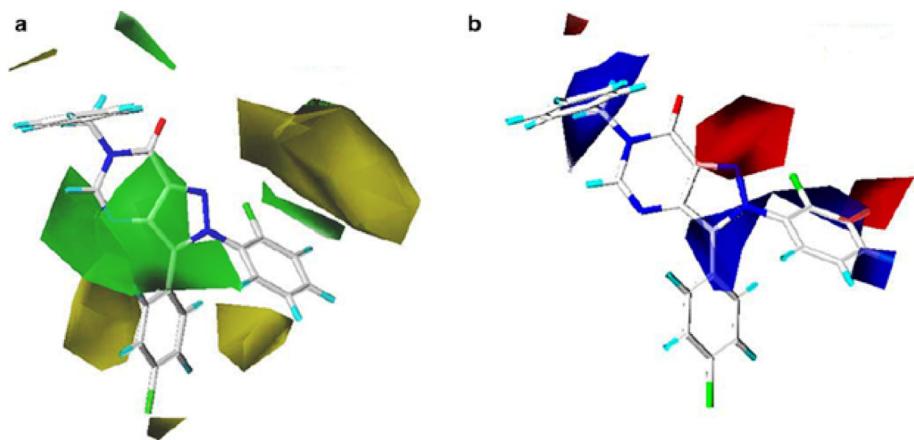


Fig. 59. Steric (a) and electrostatic (b) CoMFA contour maps [202].

3.1. Ligand based designing

Ligand based drug designing plays a key role in the identification of new ligands which can be used as lead molecules. Various methods such as 3D-QSAR, pharmacophore and virtual screening have been utilized for designing purposes to obtain drug like molecules.

Cichero et al. [202] developed a CoMFA model by using a dataset of seventy eight compounds having different scaffolds which include pyrazoles, tetrahydropyrrolopyridines, 1,4-dihydroindeno[1,2-c]pyrazoles, pyrazolopyrimidines and acyclic sulphonamide derivatives. The electrostatic component showed higher value of relevance in the developed CoMFA model. The steric and electrostatic contour maps are shown in Fig. 59. It was observed from the CoMFA model that the *m*-substituent on the 1-phenyl ring of rimonabant having cyano group or hydrogen acceptor group was favourable for higher biological activity. A pharmacophore model was also developed by the same group for identification of important key features responsible for the activity. Three pharmacophoric features including two hydrophobic-aromatic features (HY1 and HY2) and one hydrogen bond acceptor function (HA) form a triangle. HA feature implies the area covered by H-bond between the ligand and Lys192. Furthermore, the hydrophobic or $\pi-\pi$ stacking interactions also play a crucial role as other two pharmacophores HY1 and HY2 feature in the ligand and receptor interactions as shown in Fig. 60.

Foloppe et al. [203] identified thirty novel, diverse and drug-like ligands as CB1 receptor antagonists by performing ligand-based

virtual screening using a 3D pharmacophore model. These compounds could be used as lead molecules for designing CB1 receptor antagonists. Out of these lead compounds, compound **153** (Fig. 61) with highest affinity exhibited K_i value 92 nM and good selectivity over CB2 receptor ($hCB2/hCB1 = 33.7$).

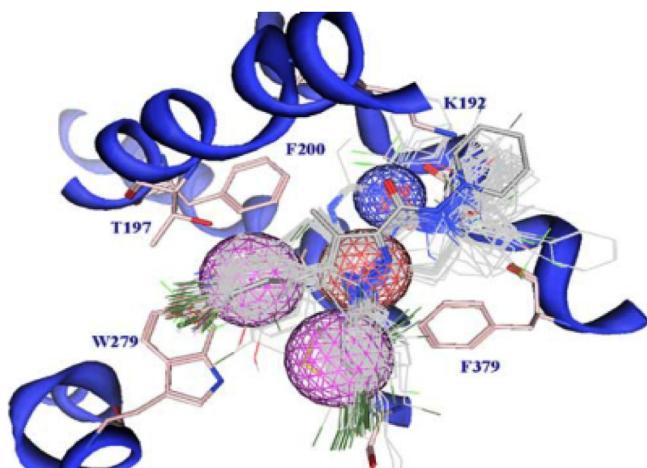


Fig. 60. The three key pharmacophoric features shared by all of the compounds utilized to develop pharmacophore model are shown in coloured spheres. The hydrophobic/aromatic features are shown in purple while the acceptor features are coloured in blue [202]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

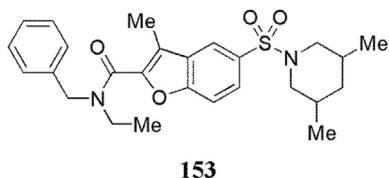


Fig. 61. Chemical structure of most active compound **153** obtained through ligand-based virtual screening.

Ye et al. [204] performed Hologram QSAR (HQSAR) studies on a series of seventy five compounds of biaryl pyrazolyloxadiazole based CB1 receptor antagonists. It was found by the contribution maps that 1,2,4-trizole and cyclopropane fragments participated in a big way for the biological activities (Fig. 62). Red and green colour in the spectrum indicated negative and positive contributions respectively while white colour reflected intermediate contributions. Compounds containing 1,2,4-trizole and cyclopropane rings showed high biological activity whereas nitrogen at position 1 of the pyrazole ring and the oxygen of the 1,3,4-oxadiazole gave intermediate-high contributions for the activity.

Weber et al. [205] performed HQSAR and CoMFA studies on fifty five compounds of diaryl pyridines. The additional information obtained from this study was that the CB1 receptor antagonistic activity could be increased by balancing electrostatic and hydrophobic features in the substituents neighbouring the pyridine nitrogen, and modifications of steric and electrostatic fields could be strongly favourable to increase CB1 receptor antagonistic activity. On that basis, new CB1 receptor ligands with improved anti-obesity profile could be designed.

Kang et al. [206] generated the common pharmacophore features by using the Hip-Hop Refine algorithm. Two types of alignments were performed for this study. One was based on a receptor-aligned model from the docking pose and the second was based on pharmacophore-aligned model from the HipHop Refine generation. This study also showed that the carbonyl oxygen of rimonabant formed H-bond with K192 and three hydrophobic sites containing aromatic features were present on 5, 6 and 7 Helix. 2,4-Dichlorophenyl ring interacted with the first site in F200/W279/W356 residues, 4-chlorophenyl ring interacted with second site in W255/Y275/F278 residues and piperidine group of rimonabant comfortably fitted in the third hydrophobic cavity formed by V196/F170/M385/L387/residues. All this information was used for high throughput virtual screening and for illustrating the binding interactions of CB1 receptor with the antagonists.

Lee et al. [207] performed virtual screening to find out new scaffolds as CB1 receptor antagonists. Different filter criteria like physicochemical properties, pharmacophoric features, CoMFA maps and docking interactions were applied to obtain the new scaffolds. For better understanding, pharmacophore mapping poses of compounds **154** and **155** as shown in Fig. 63 reflect the fitting of compounds **154** and **155** forming H-bond with K192 and D366 is shown in Fig. 64.

Wang et al. [208] developed a pharmacophore model based on known representative CB1 receptor antagonists and employed the developed model to screen a database of about half a million Schering-Plough compounds. The most potent compound **156** (Fig. 65) so obtained showed affinity for CB1 receptor (K_i value of 53 nM) and more than 5-fold selectivity for CB1 over the CB2 receptors.

3.2. Structure based designing

Structure based drug designing is a very useful strategy for understanding the interactions of ligands with the receptors. This technique can provide important information about ligand receptor interactions which could be fruitful for designing of selective molecules.

Various groups have developed homology models so that they could be utilized for designing of CB1 receptor antagonists. Three-dimensional crystal structure of cannabinoid receptor is still unknown. Mahmoudian et al. [209] developed a three dimensional model of human cannabinoid receptor by using bacteriorhodopsin as a structural template. But, the bacterial rhodopsin is not a GPCR and it also differs by helix packing arrangement from other GPCRs. So, a high-resolution crystal structure of a real GPCR was the initial necessity [210]. In 2000, Palczewski et al. [211] determined X-ray crystal structure of bovine rhodopsin. Shim et al. [212] developed a homology model of CB1 cannabinoid receptor using this bovine rhodopsin as a template for cannabinoid receptor–agonist interaction. With this study, binding site residues were predicted for CB1 receptor as K3.28(192), L3.29(193), T3.33(197), F3.36(200), F5.42(278), W5.43(279), V5.46(282), T5.47(283), L6.44(352), W6.48(356), L6.51(359), L6.52(360), M6.55(363), S7.39(383) and L7.43(387) by using CB1 agonist CP55244. Consecutively, Salo et al. [210] developed a novel comparison homology model for the human cannabinoid CB1 receptor using similar bovine rhodopsin as a template. Results of the ligand docking studies proved the significant role of lysine K3.28 (192) in the binding interactions for

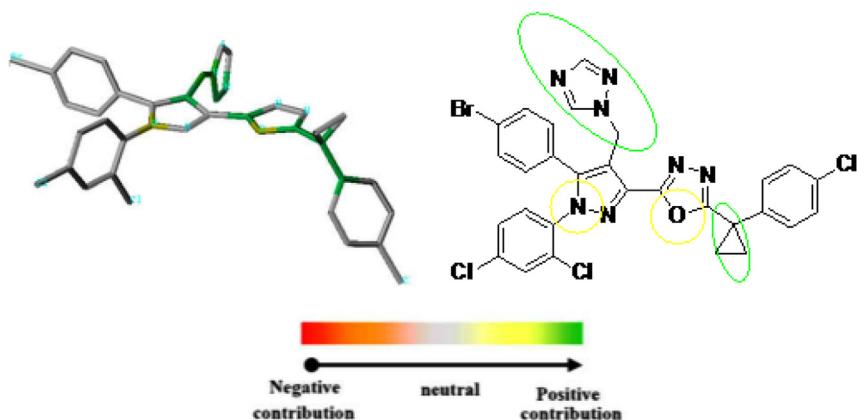


Fig. 62. The HQSAR contribution map for the most active compound [204].

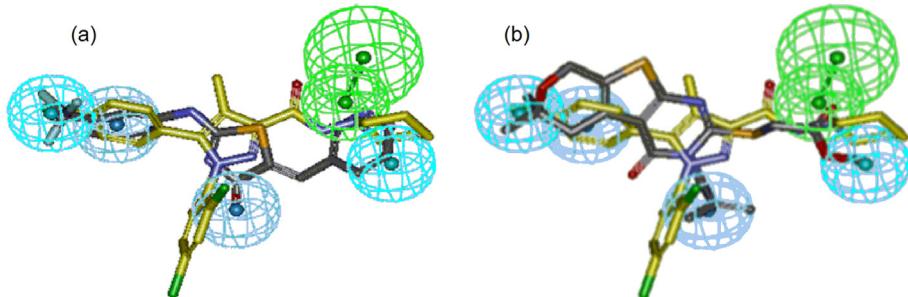
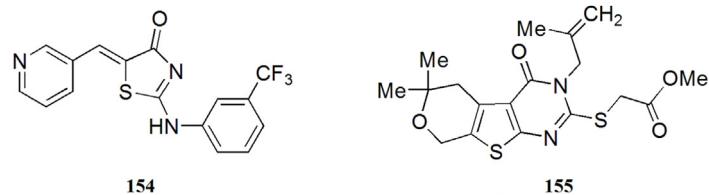


Fig. 63. The pharmacophore mapping of compounds (a) 154 and (b) 155. H-bond acceptor, hydrophobic and hydrophobic aromatics are shown in green, cyan, and blue spheres. Yellow stick compound is rimonabant. The compounds 154 and 155 showed 'fit value' between 3 and 3.5 [207]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

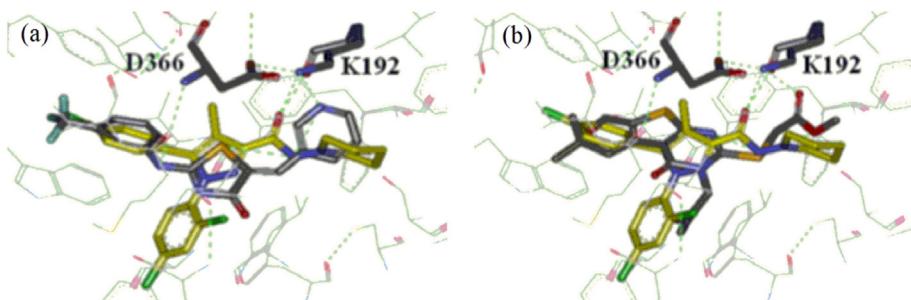


Fig. 64. Docked poses of compounds (a) 154 and (b) 155 in receptor homology model. The H-bond interactions are displayed in dotted lines and yellow sticks compound is rimonabant. The compounds 154 and 155 showed total docking scores between 5 and 7.5 values [207]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

WIN55212-2 and SR141716A. Comparison of CB1 receptor model with the rhodopsin crystal structure is depicted in Fig. 66. The E2 loop of rhodopsin bends over the ligand binding site which indicated that the loop was almost at the similar level as the critical K3.28(192) residue present. Montero et al. [213] developed 3D models of both CB1 and CB2 human receptors by using bovine Rhodopsin (Fig. 67). Hydrogen bond interactions, aromatic and hydrophobic interactions, energy of binding and the Difference Accessible Surface Area (DASA) were used for the analysis of the receptor–ligand complex models. According to this study,

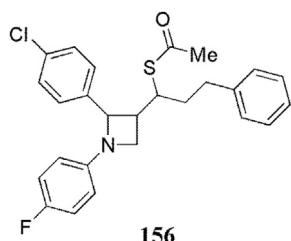


Fig. 65. Chemical structure of compound 156 obtained through pharmacophore based virtual screening.

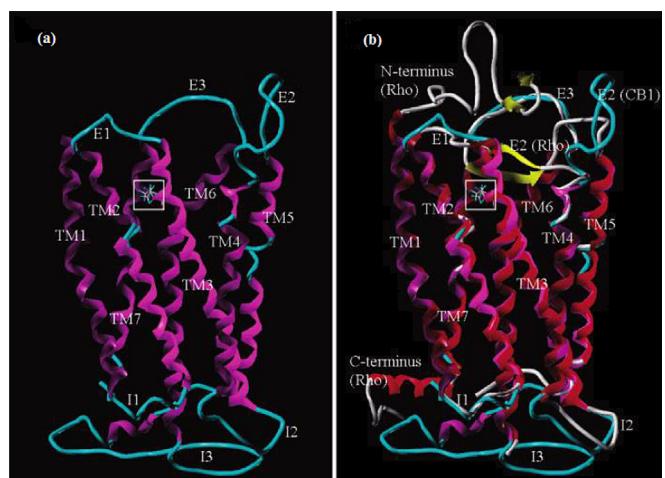


Fig. 66. CB1 receptor model is compared with the rhodopsin crystal structure (Rho). The critical lysine K3.28(192) is boxed. Secondary structure coding: α -helix, purple (CB1)/red (Rho); β -sheet, yellow; other, cyan (CB1)/white (Rho). (a) CB1 receptor model, (b) CB1 receptor model superimposed with rhodopsin [210]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

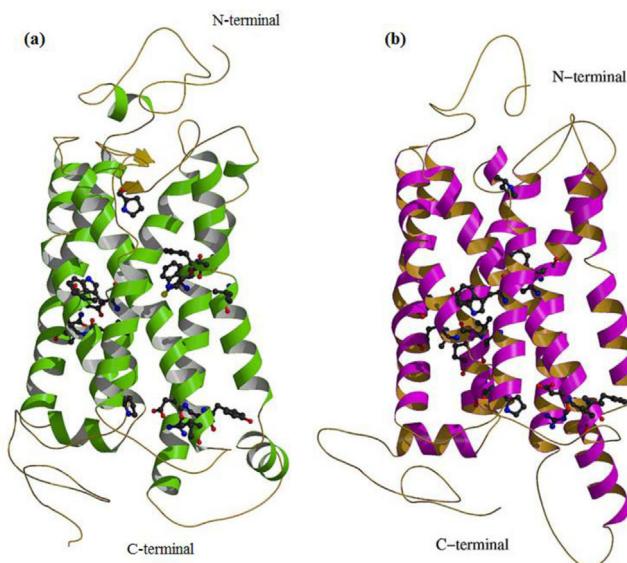


Fig. 67. The models of (a) CB1 and (b) CB2 receptors. The conserved patterns are shown as ball-and-sticks models [213].

rimonabant was bound in the TM4-E2-TM5 region of the CB1 receptor. Durdagi et al. [214] and Gonzalez et al. [215] also developed and studied comparative models and molecular dynamics simulations for cannabinoid receptors. It was suggested that the CB1 receptor was made up of structural microdomains which could reorganise its ligand binding site in response to structural changes which might be useful to justify the diversity of ligands with affinity for CB1 receptor.

Durdagi et al. [216] developed homology models of both CB1 and CB2 receptors by using β_2 -adrenergic receptor (PDB: 3D4S) as a structural template. Similar binding sites obtained in both the models, generated by bovine rhodopsin and β_2 -adrenergic receptor, confirmed the ligand-binding pockets. Homology models of CB1 receptor generated by rhodopsin and β_2 -adrenergic receptor were superimposed as shown in Fig. 68. The ligand-binding pockets are also shown in Fig. 69.

Latek et al. [217] developed homology model of cannabinoid receptor by using human A_{2A} adenosine receptor as a structural template. Ai et al. [218] developed homology model of CB1 receptor by using human β_2 -adrenergic receptor and human A_{2A} adenosine receptor as structural templates. In this study, four ligands HU-210, ACEA, WIN55212-2 and rimonabant were used to study the protein conformational changes in ligand bound state. HU-210 is a classical cannabinoid agonist which is a structural analog of THC. ACEA is a selective CB1 agonist which is an endogenous cannabinoid analog. WIN55212-2 is a typical aminoalkylindole that produced similar effects as THC and the fourth ligand rimonabant was used as a CB1 receptor antagonist. First, cannabinoid agonist HU-210 was bound to the TMH3-6-7 region of CB1 receptor. The alkyl chain of HU-210 was oriented inside of the binding cavity near the residues of I6.46(354), C6.47(355), W6.48(356), L6.51(359) and L6.52(360) and the tricyclic scaffold was oriented towards F2.64(177), F3.25(189), K3.28(192), M6.55(363), F7.35(379) and S7.39(383) as shown in Fig. 70(a). K3.28(192) residue plays an important role in CB1 activity by forming a hydrogen bond. The phenolic oxygen of HU-210 also formed a hydrogen bond with K3.28(192) residue. In this study, it was found that K3.28(192) residue acted as a hydrogen bond donor to F3.25(189) present near the tricyclic scaffold of HU-210 and facilitated stabilization of HU-210 binding. The oxygen of pyran ring in HU-210 acted as a hydrogen bond acceptor to S7.39(383). The end of the alkyl chain of HU-210 showed a close contact with C6.47(355) residue. Selective CB1 agonist ACEA was bound to TMH2-3-6-7 region and oriented in a folded j-shape to form hydrophobic intermolecular contacts with CB1 receptor. ACEA was oriented in the lipophilic region containing K3.28(192), S7.39(383), F3.25(189), F7.35(379), F7.37(381), Y5.39(275), F3.36(200) and W6.48(356) residues. In this study, the carbonyl oxygen of ACEA was seen forming a hydrogen bond with K3.28(192) residue. Furthermore, two other hydrogen bonds were formed by K3.28(192) residue in which first was intra-molecular hydrogen bond with its own carbonyl oxygen and second with N3.23(187) as shown in Fig. 70(b). The Y5.39(275) residue was present very near to ACEA which should contribute to the ligand binding. Aminoalkylindole derivative WIN55212-2 was located at TMH3-5-6-7 region. An aromatic microdomain for the WIN55212-2 formed the binding region with F2.61(174), F2.64(177), F3.25(189), F3.36(200), Y5.39(275), W5.43(279), W6.48(356), F7.35(379) and F3.37(381) residues in which the naphthyl ring of WIN55212-2

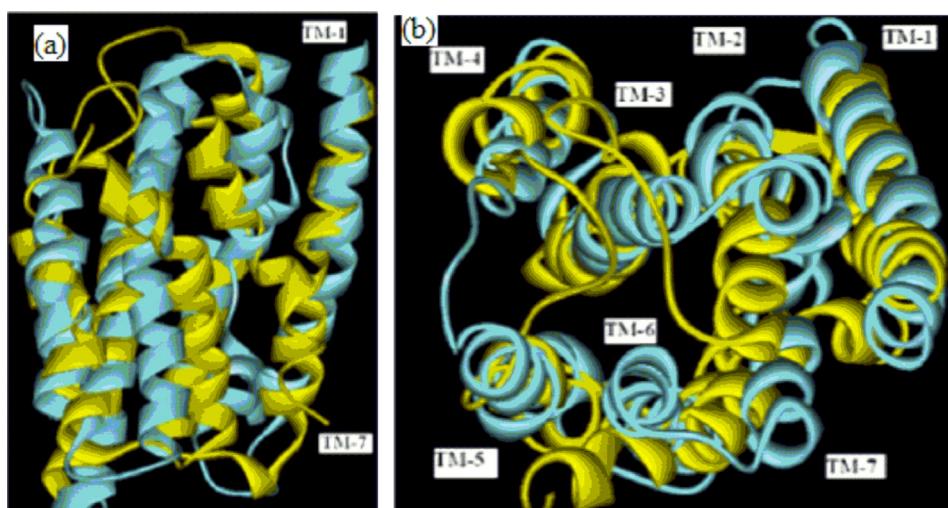


Fig. 68. Superimposition of rhodopsin (yellow coloured)- and β_2 -adrenergic (cyan coloured)-based CB1 receptor models from (a) side and (b) top views [216]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

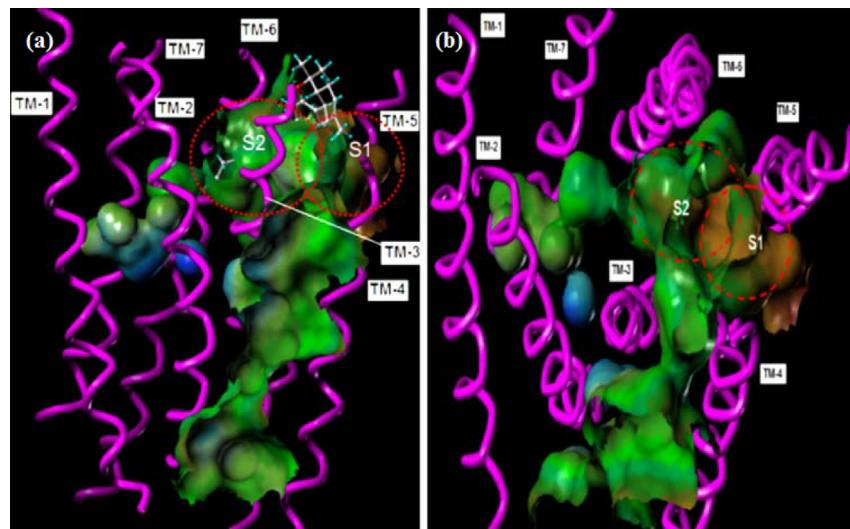


Fig. 69. (a) CB1 receptor model obtained by using template of human β_2 -adrenergic receptor and (b) the two ligand-binding pockets between the TM3–TM6 as it was observed in the CB1 receptor model based on rhodopsin [216].

made close contacts to F2.61(174), F2.64(177), F3.25(189), F7.35(379) and F3.37(381) residues, the indole ring with F3.25(189), Y5.39(275) and W5.43(279) residues, and the morpholinyl moiety with F3.36(200), W5.43(279) and W6.48(356)

residues. In this study, WIN55212-2 did not show hydrogen bonding to K3.28(192) residue as shown in Fig. 70(c). In case of CB1 receptor antagonist, rimonabant was located at the TMH 3–4–5–6–7–region and bound to the similar aromatic microdomain as

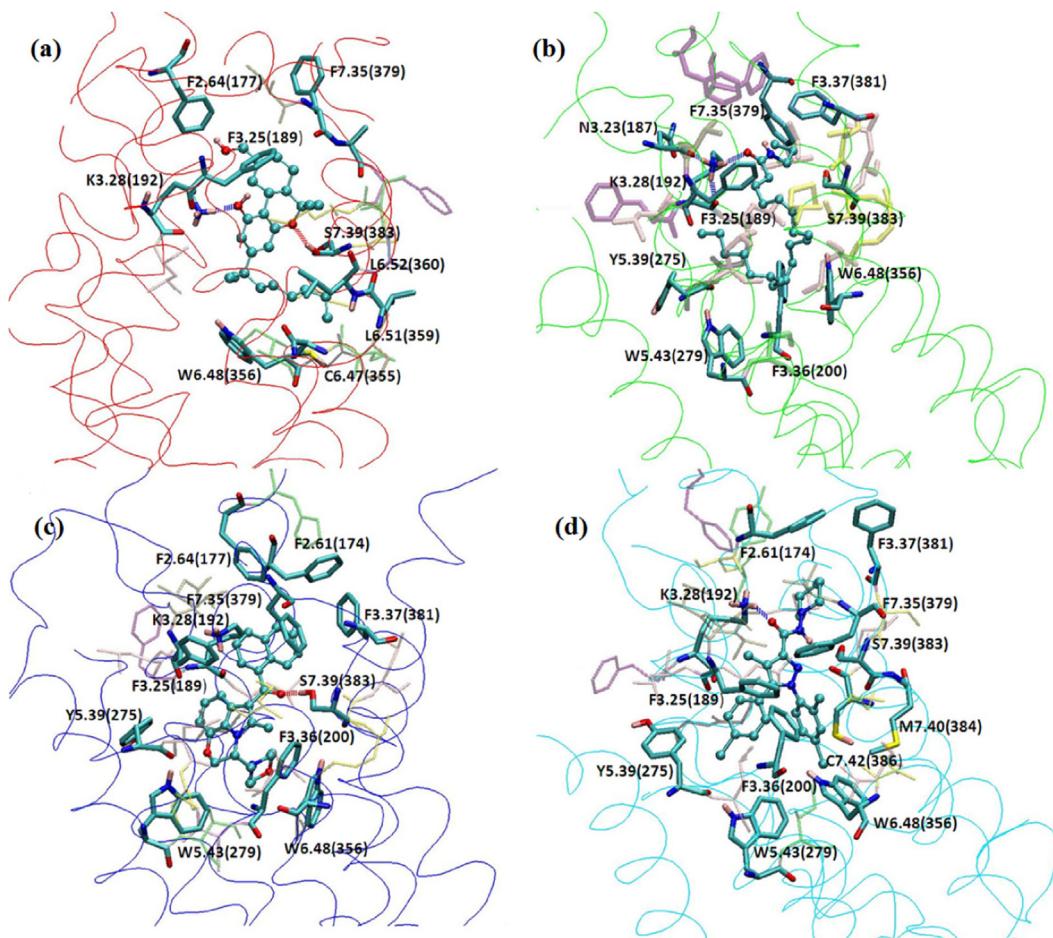


Fig. 70. Binding sites of CB1 receptor models trained by (a) HU-210, (b) ACEA, (c) WIN55212-2 and (d) SR141716A. Ligands are in ball-and-stick depiction. Residues that are directly in contact with ligands are in opaque stick depiction. Residues that are within 6 Å of the ligands are in transparent stick depiction [218].

WIN55212-2. The binding site of this CB1 receptor model was composed by F2.61(174), F3.25(189), K3.28(192), F3.36(200), Y5.39(275), W5.43(279), W6.48(356), F7.35(379), F7.37(381), S7.39(383) and M7.40(384) residues. Carbonyl oxygen of rimonabant formed hydrogen bond with K3.28(192) residue and two more hydrogen bonds were formed with nearby N3.23(187) and S2.60(173) as shown in Fig. 70(d). The monochlorophenyl ring of rimonabant directly made single aromatic stacking interactions with F3.25(189) and Y5.39(275). It was also observed that the W5.43(279) residue interacted with the monochlorophenyl and dichlorophenyl rings of rimonabant. In this model, F3.36(200) and W6.48(356) residues formed a parallel-displaced stacking and constituted the aromatic microdomain for rimonabant binding. Furthermore, C7.42(386) residue was located right at the dichlorophenyl ring of rimonabant. Rimonabant binding might be inhibited if bulky group was introduced on C7.42(386) residue. Hence, conformational changes in the CB1 receptor binding site have been observed by structurally diverse cannabinoid ligands.

4. Conclusions

Being a multifactorial health problem there is no effective therapy available currently for the treatment of obesity. CB1 receptor antagonists may prove to be promising therapeutics and one such antagonist rimonabant (**1**) acting centrally was introduced in the market as an anti-obesity drug in 2006 but unfortunately due to some psychiatric side effects it was withdrawn in 2008. Other centrally acting molecules such as taranabant (**2**), surinabant (**3**) and otenabant (**4**) have also been withdrawn from the phase III clinical trials. Since then efforts are continuing to develop potent and selective CB1 receptor antagonists with fewer side effects for the control of obesity. Several CB1 receptor antagonists containing different heterocyclic moieties have been reported in literature. Currently, researchers are focussing on designing peripherally acting selective CB1 receptor antagonists by lowering the log P and increasing the PSA for the designed compounds so that the compounds would not be able to cross the BBB. Recently developed peripherally acting compounds like purine derivatives **112** and **113**, piperazine derivative **133** have shown excellent potency and selectivity with lowered brain penetration. Along with these, pyrazole derivatives **72b–72d** having higher PSA have also exhibited excellent potency. Similarly, the pyrazoline derivative **88** possesses low lipophilicity and high PSA but with a moderate potency. Interestingly, peripherally acting neutral compounds **65** and **66** do not show adverse effects at doses upto 20 mg/kg. These compounds can be used as lead molecules for designing peripherally acting CB1 receptor antagonists devoid of central effects. Thus, an era of peripherally acting CB1 receptor antagonists has begun which may prove to be a new line of treatment for obesity.

Acknowledgement

MKS is thankful to University Grants Commission, New Delhi for the award of Junior Research Fellowships under the RFSMS-BSR programme [No. F. 7-129/2007 (BSR)].

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