2. Review of literature

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 made 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 3rd, 4th and 5th of pyrazole of rimonabant have been substituted with a variety of groups. A systematic chemical classification of different CB1 receptor antagonists is given below:

2.1 Vicinal diaryl substituted heterocyclic compounds

2.1.1 Five membered heterocycles

2.1.1.1 Thiophene derivatives

2.1.1.2 Pyrrole derivatives

2.1.1.3 Pyrazole derivatives

2.1.1.4 Imidazole derivatives

2.1.1.5 Triazole derivatives

2.1.1.6 Pyrrolidine derivatives

2.1.1.7 Pyrazoline derivatives

2.1.1.8 Imidazoline derivatives

2.1.2 Six membered heterocycles

2.1.2.1 Pyridine derivatives

2.1.2.2 Pyrazine derivatives

2.1.2.3 1,4,5,6-Tetrahydropyridazine derivatives

2.1.2.4 Piperidine derivatives

2.1.2.5 Morpholine derivatives

2.1.3 Fused diaryl heterocycles

2.1.3.1 Purine derivatives

2.1.3.2 Fused pyridine ring derivatives

2.1.3.3 Fused pyrimidine derivatives

2.2 Non-vicinal diaryl containing compounds

2.2.1 Acyclic derivatives

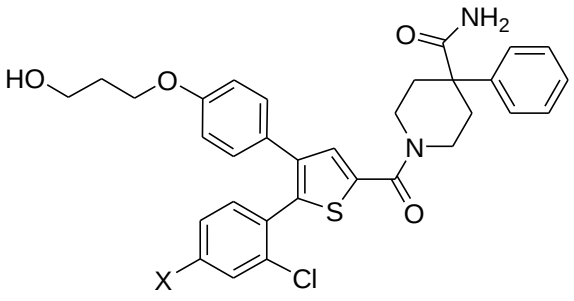
2.3 Miscellaneous compounds

2.4 Molecular modeling studies

2.1.1 Five membered heterocycles

2.1.1.1 Thiophene derivatives

Barth et al.[105] reported a series of novel 4,5-diarylthiophene-2-carboxamide derivatives as potent and selective CB1 receptor antagonists acting on both central and peripheral sites. Compounds (**8** and **9**) showed IC_{50} value of 0.5 μM. At 3 mg/kg i.v. dose, rimonabant and compound (**8**) showed brain to plasma ratios of 1.8 and 0.04 respectively. At 10 mg/kg i.v. doses, rimonabant and compounds (**8** and **9**) showed 100 %, 13 % and 32 % inhibition respectively of the binding of [^{3}H]-CP55940 to the CB1 receptors present in the brain suggesting that the thiophene derivatives (**8** and **9**) poorly penetrated into the CNS and acted peripherally.



(**8**) X = Cl

(**9**) X = H

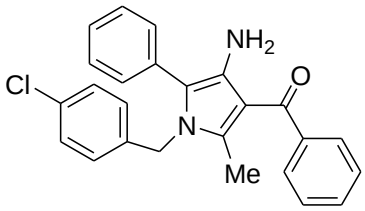
(**8**, **9**)

2.1.1.2 Pyrrole derivatives

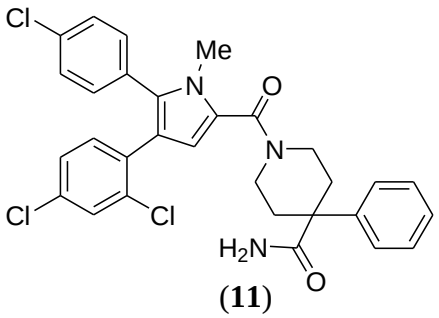
LoVerme et al.[106] reported first diaryl pyrrole derivatives as peripherally restricted mixed CB1 antagonist/CB2 agonist devoid of brain penetration. By blocking

CB1 receptor in peripheral organs in mice, compound URB447 (**10**) was identified having IC_{50} value of 313 nM with reduced food intake and body weight gain. But, unfortunately it did not show selectivity towards CB1 receptors. At 20 mg/kg i.p. dose, URB447 showed peak plasma level (C_{max} = 596 ± 117 nmol/g) after 30 min indicating its peripheral activity. URB447 can be considered as a starting lead for the development of peripherally acting CB1 receptor antagonists devoid of CNS side effects.

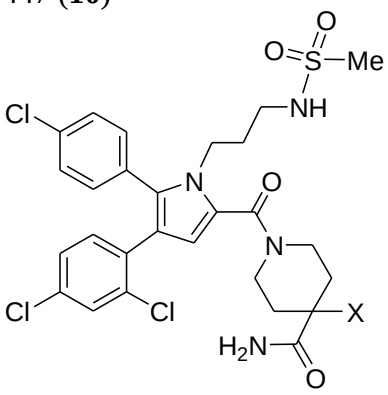
Hortala et al.[107] from Sanofi-Aventis reported a novel series of 2,3-diaryl pyrroles as peripherally-restricted CB1 receptor antagonists devoid of psychiatric side effects. In the *in vitro* assay, compound (**11**) showed 86 % inhibition of CP55940 binding in homogenized brain suggesting a good brain penetration. Compound (**11**) showed PSA value of 68 $Å^2$ having good brain penetration. Different polar groups such as ethylcyano, carboxylic acid and sulfonamide were introduced to increase the PSA. The highest PSA value of 126 $Å^2$ was obtained by introduction of sulfonamide group showing higher affinity and low brain penetration. Sulfonamide derivatives (**12** and **13**) showed good IC_{50} values of 1.4 and 1.0 nM respectively. 100-Fold higher concentration was found in plasma than in brain for compound (**13**) indicating its peripherally restricted activity.

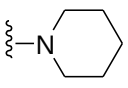
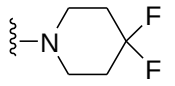


URB447 (**10**)



(**11**)

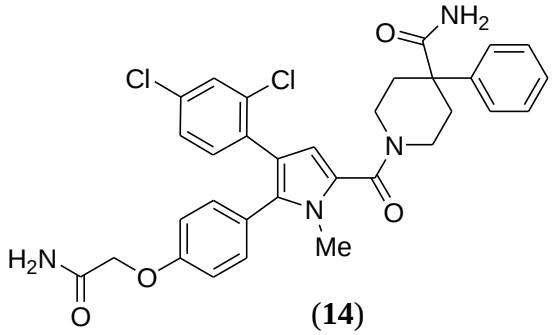


Comp	X
12	
13	

(**12**, **13**)

Barth et al.[108] patented a novel series of 4,5-diarylpyrrole-2-carboxamides as peripheral CB1 receptor antagonists. At 3 mg/kg i.v. dose, rimonabant and compound (**14**) showed the brain to plasma concentration ratios of 1.8 and 0.05 respectively.

Rimonabant and compound (**15**) showed 100 % and 1 % inhibition of [^{3}H]-CP55940 binding respectively in the brain at 10 mg/kg dose. Compound (**15**) showed 100 % reversion effect of CP55940 on GIT indicating its peripheral activity. Barth et al.[109] further patented novel 1,5-diphenylpyrrole-3-carboxamide derivatives (**16** and **17**) as CB1 receptor antagonists having IC_{50} values of ≤ 0.5 μM. Rimonabant and compound (**16**) showed brain to plasma ratios of 1.8 and 0.06 respectively at 3 mg/kg i.v. dose. Rimonabant and compound (**17**) showed 100 % and 5 % inhibition of the binding of [^{3}H]-CP55940 in the brain respectively. Thus, the diaryl pyrrole derivatives were found to exhibit better peripheral distribution and less penetration in the brain.



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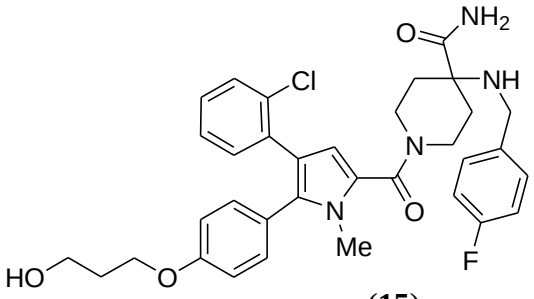

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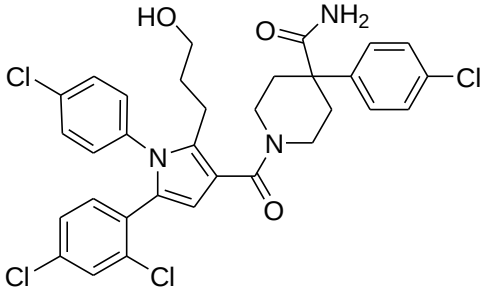
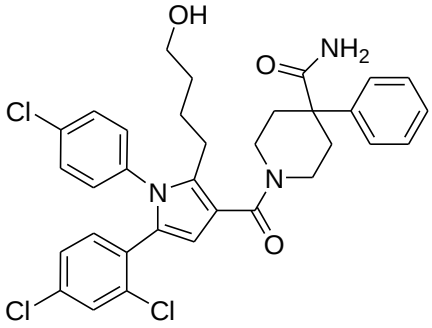


(**16**)



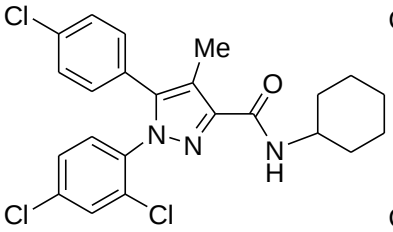
(**17**)

2.1.1.3 Pyrazole derivatives

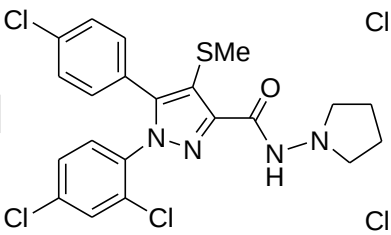
Francisco et al.[110] reported various rimonabant (**1**) analogs by substituting the aminopiperidinyl moiety with amines, alkyl hydrazines, and hydroxyalkylamines of varying lengths. The *N*-cyclohexyl amide substituted compound (**18**) showed the highest affinity toward CB1 receptor having K_i value of 2.46 nM. Replacement of methyl group by methylsulfanyl at 4th position of pyrazole ring in compounds (**19**) showed K_i value of 3 nM with good selectivity (CB2/CB1 = 221). But, compounds (**19**) showed *AlogP* value of 6.2 similar to rimonabant (*AlogP* = 6.6). Substitution with more polar group like methylsulfinyl in compound (**20**) showed K_i value of 20 nM with lowered *AlogP* (5.6) as compared to rimonabant.[111]

The amide/hydrazide group was replaced from 3rd position to 4th position of the pyrazole ring.[112] The designed compound (**21**) was structurally quite similar to rimonabant. Compound (**21**) showed a competitive binding assay for *h*CB1 and *h*CB2 receptors having 79 % and 37 % inhibition at 10 μM concentration. In the current series, the most potent compound (**22**) was found having K_i value of 0.21 μM which was 10 times lower than rimonabant.

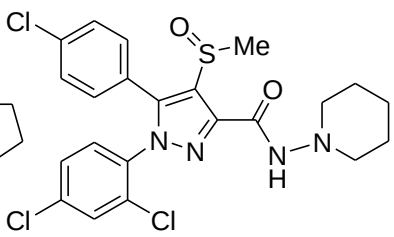
Srivastava et al.[113] reported diaryl pyrazolesulfonamide derivatives in which CO group of rimonabant was replaced with SO_2. The oxygens of sulfonamide groups formed hydrogen bonds with Lys192 residue. It was observed in the *in vitro* cAMP *h*CB1 functional assay and in preliminary *ex vivo* experiments that compound (**23**) showed less CB1 receptor antagonistic activity although it gave favourable piece-wise linear potential (PLP) value and docking score. This study suggested that the replacement of CO group by bulkier SO_2 was not favourable for CB1 receptor antagonistic activity.



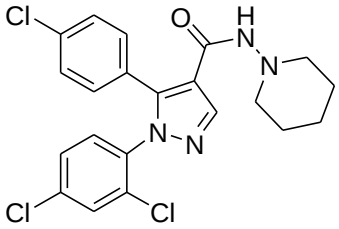
(**18**)



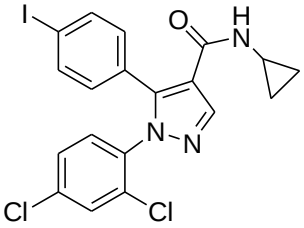
(**19**)



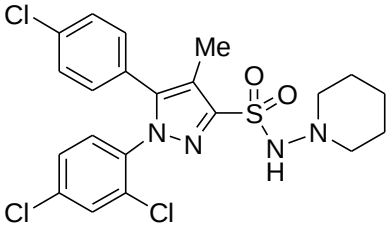
(**20**)



(**21**)



(**22**)



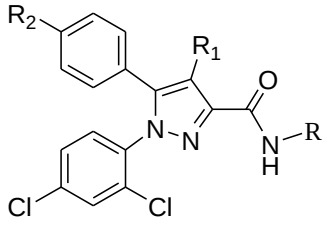
(**23**)

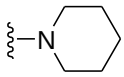
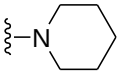
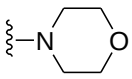
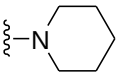
Lan et al.[114] reported diaryl pyrazole derivatives in which iodo was substituted in place of chloro at *para* position of phenyl ring. The most potent compound in the series was *p*-iodophenyl analog AM251 (**24**) having K_i value of 7.5 nM with good selectivity (CB2/CB1 = 306). Further, Lan et al.[115] replaced the piperidine ring with morpholine ring in compound AM281 (**25)** which resulted in an enhanced selectivity for CB1 receptors (K_i = 12 nM, CB2/CB1 = 350).

Later, Katoch-Rouse et al.[116] reported various rimonabant (**1**) analogs having high affinity and low lipophilicity. Replacement of the methyl group at 4th position of pyrazole

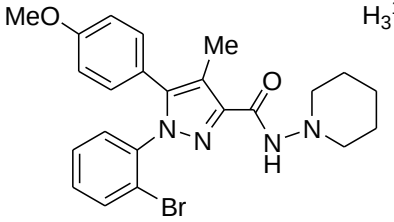
ring with bromo substituent formed compound (**26**) having increased binding affinity (K_i = 1.4 nM, *c*logD = 4.94) but its lipophilicity was higher than rimonabant (K_i = 1.8 nM, *c*logD = 4.81). Replacement of chloro group with methoxy group at 4th position of phenyl ring formed compound (**27**) having significant binding affinity and lowered lipophilicity (K_i = 4.1 nM, *c*logD = 4.06). Donohue et al.[117] reported some PET or SPECT radioligands in which compound (**28**) was the most potent (K_B = 11 nM) and more than 773 times more selective CB1 receptor radioligand antagonist.

Fan et al.[118] reported JHU75528 (**29**) analogs showing higher affinity and lower lipophilicity than rimonabant (K_i = 11 nM; log$D_{7.4}$ = 3.3 - 3.6). The most potent compound (**30**) was showing K_i value of 2 nM.

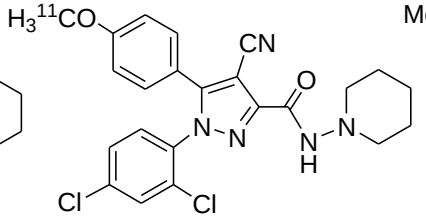


Comp	R	R1	R2	Comp	R	R1	R2
24		Me	I	**26**		Br	Cl
25		Me	I	**27**		Me	OMe

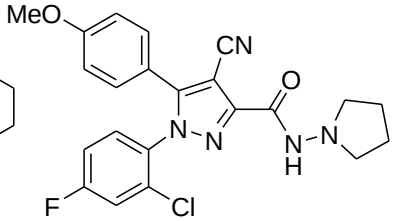
(**24**-**27**)



(**28**)

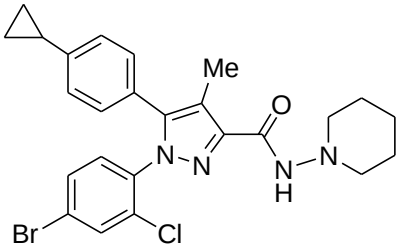


(**29**)

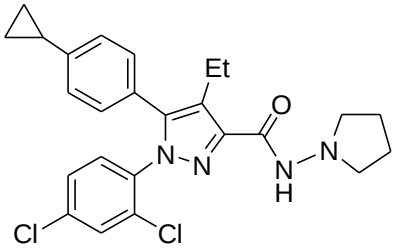


(**30**)

Szabo et al.[119] reported cycloalkyl containing diaryl pyrazole derivatives as CB1 receptor antagonists. The cyclopropyl containing compounds (**31** and **32**) showed K_i values of 3 and 4 nM respectively. Compound (**32**) was found to possess excellent efficacy in lowering serum lipid parameters of the metabolic syndrome when compared to rimonabant.

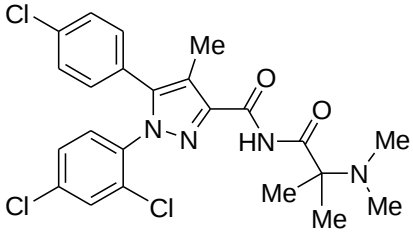


(**31**)

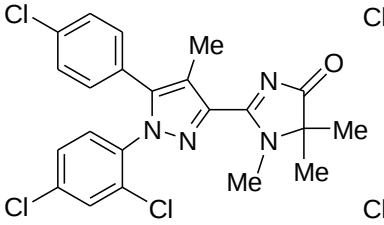


(**32**)

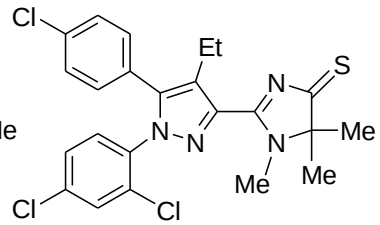
Wu et al.[120] converted the imide (**33**) (IC_{50} = 82.9 nM; CB2/CB1 = 35) to its active metabolite (**34**) (IC_{50} = 54.7 nM; CB2/CB1 = 9) which was utilized as a lead molecule. Replacement of oxygen in the imidazol-4-one moiety of compound (**34**) with sulphur atom resulted into the thioketone (**35**) showing an IC_{50} value of 12.0 nM and good selectivity (CB2/CB1 = 396).



(**33**)

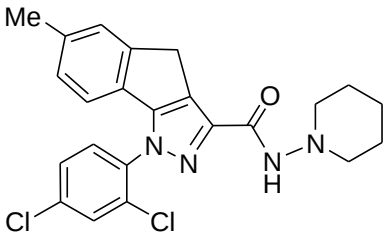


(**34**)

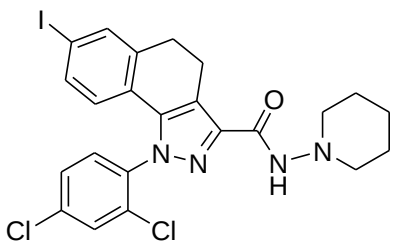


(**35**)

Mussinu et al.[121] designed a new series of rigid 1,4-dihydroindeno[1,2-*c*]pyrazole derivatives as CB1 receptor antagonists but unfortunately, several of these compounds showed higher activity for CB2 receptors. The most potent compound in the series was compound (**36**) showing selectivity towards CB2 receptor (K_i = 0.037 nM; CB1/CB2 = 9810). Further, Murineddu et al.[122] designed 4,5-dihydro-1*H*-benzo[*g*]indazole derivatives having selectivity towards CB1 receptors. Compound (**37**) was obtained as the most potent compound (K_i = 4.11 nM) with CB1 selectivity (CB2/CB1 = 262). Further, benzocycloheptapyrazole carboxamides (**38**) showed good affinity for CB1 receptor (K_i = 0.00035 nM) with excellent selectivity (CB2/CB1 = 60,000).[123] Compound (**38**) was further expanded to benzocyclooctapyarazole carboxamide (**39**) showing K_i value of 15 nM for CB1 receptors and 492 nM for CB2 receptors.[124]



(**36**)



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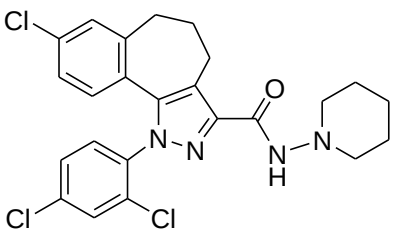
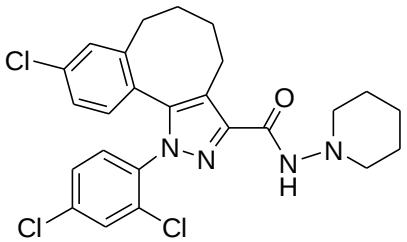
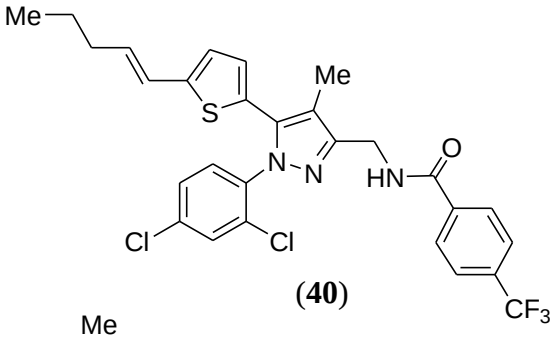


(**38**)

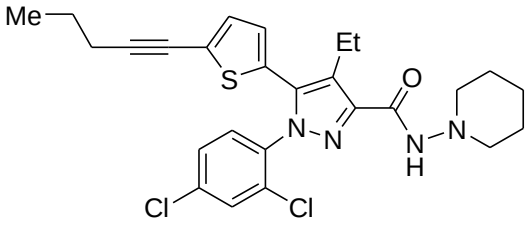


(**39**)

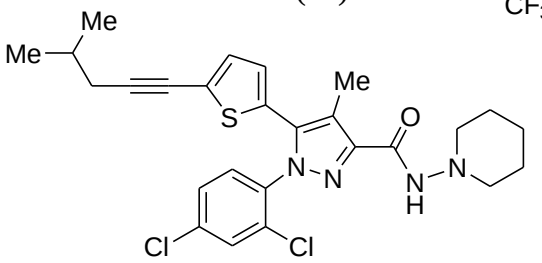
For designing purpose, Tai et al.[125] focused on bioisosterism strategy. The phenyl ring at 5th position of pyrazole was replaced by its bioisostere thiophene ring offering a novel series of 5-[5-(1-pentenyl)thiophen-2-yl]pyrazoles as potent and selective CB1 receptor antagonists. Compounds (**40**) was found to be the most potent and selective CB1 receptor antagonist (IC_{50} = 4 nM; CB2/CB1 = 275). Further, Tseng et al.[126] reported compound (**41**) (IC_{50} = 6.1 nM, CB2/CB1 = 151) having significant weight reduction in diet-induced obese mouse model which proved that the bioisosteric replacement was favourable for the activity. Compound (**42**) was found to be the most potent and selective CB1 receptor antagonist (IC_{50} = 2.3 nM; CB2/CB1 = 168). Srivastava et al.[127] also replaced phenyl group by thienyl group. The iodothienyl derivative (**43**) showed EC_{50} value of 0.32 μM which was 1.3-fold lesser active than rimonabant (EC_{50} = 0.24 μM).



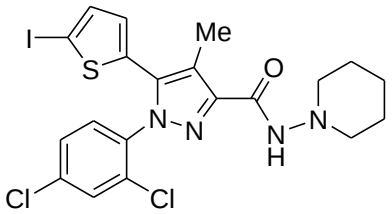
(**40**)



(**41**)

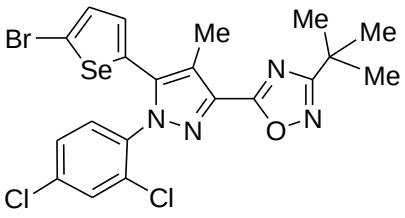


(**42**)

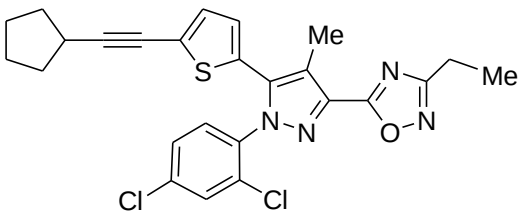


(**43**)

Shia et al.[128] replaced phenyl ring at 5th position of the rimonabant by substituted or unsubstituted thiophene ring. Shia et al.[129] patented a series in which 1,2,4-oxadiazole ring was attached to the 3rd position of the pyrazole ring, and selenophene and thiophene rings at 5th position of pyrazole which resulted in compounds (**44** and **45**) respectively showing IC_{50} values between 0.001 μM to 10 μM in the competitive binding assay.

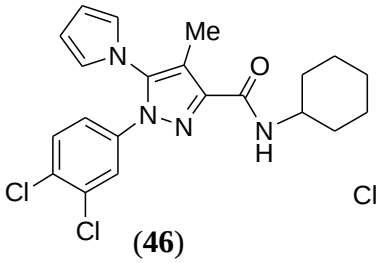


(**44**)

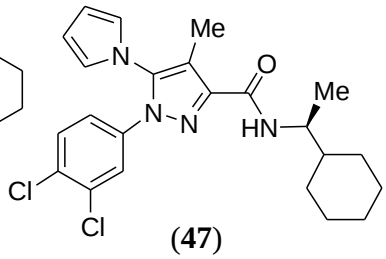


(**45**)

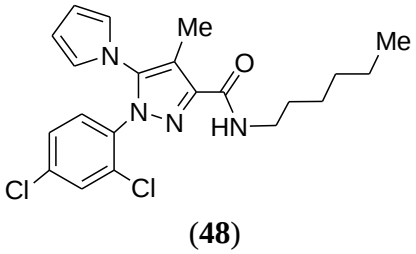
In a similar way, Silvestri et al.[130] replaced the 4-chlorophenyl group by pyrrole ring on the basis of bioisosteric approach resulting in compound (**46**) having K_i value of 5.6 nM. Silvestri et al.[131] introduced the methylene spacer in compound (**47**) having a better K_i value of 3.4 nM. Silvestri et al.[132] attached aliphatic side chain at the nitrogen atom resulting in compound (**48**) having K_i value of 124.1 nM which showed anorectic effect in the rat. Introduction of a *tert*-butyl moiety as the terminal group resulted in compound (**49**) showing significantly improved *h*CB1 receptor affinity (K_i = 45.6 nM). Further, Piscitelli et al.[133] indroduced 4,5,6,7-tetrahydroisoindol-2-yl group at 5th position of the pyrazole ring yielding compound (**50**) having K_i value of 2.3 nM and good selectivity towards CB1 receptor (CB2/CB1 = 163.6).



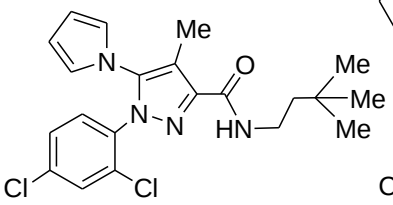
(**46**)



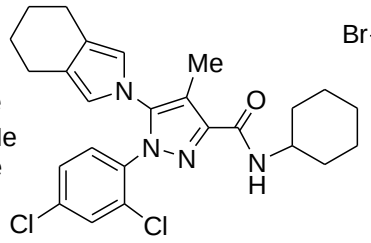
(**47**)



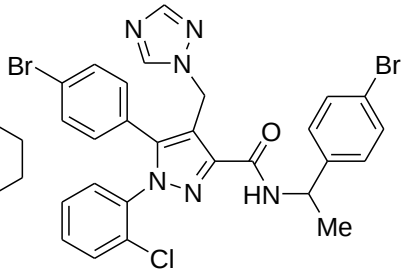
(**48**)



(**49**)



(**50**)



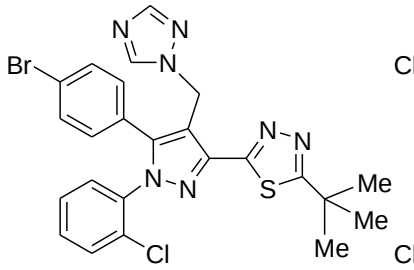
(**51**)

Seo et al.[134] replaced methyl group with 1,2,4-triazolylmethyl moiety at 4th position of the pyrazole ring which yielded compound (**51**) showing excellent CB1 receptor binding affinity and good selectivity (IC_{50} = 1.1 nM; CB2/CB1 = 1627).

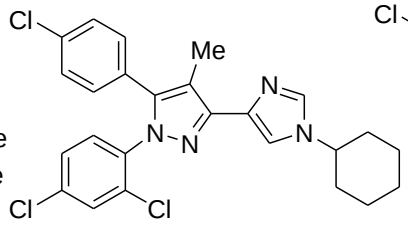
Lee et al.[135] reported novel diaryl pyrazolylthiadiazole derivatives having 1,2,4-triazolylmethyl moiety at 4th position of the pyrazole ring offering compound (**52**) having IC_{50} value of 0.681 nM with good CB1 selectivity (CB2/CB1 = 807). The compound (**52**) was considered for preclinical studies as it showed excellent *in vivo* efficacy and favourable pharmacokinetic and toxicological profile. The high fat diet induced obese (DIO) mice were used to evaluate the compound (**52**) at 10 mg/kg dose. It was observed that the compound (**52**) reduced the body weight (32.55 %) more efficiently than compounds (**1** and **2**) showing 18.02 % and 29.55 % body weight reduction respectively.

On the basis of bioisosteric approach, Dow et al.[136] replaced the hydrazide moiety of rimonabant with the isosteric imidazole-based moiety. This replacement was logically carried out to preserve the hydrogen bond acceptor feature. The *N*-3 nitrogen atom of imidazole of compound (**53**) preserves the hydrogen bond acceptor role by forming hydrogen bond with Lys192. Thus, cyclohexylimidazole derivative (**53**) and isopropyl substituted compound (**54**) showed K_i values of 8.6 nM and 5.3 nM respectively.

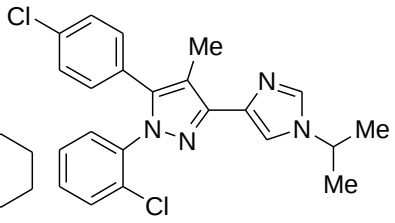
Kang et al.[137] reported tetrazole containing diarylpyrazole derivatives as CB1 receptor antagonists. Replacement of amide moiety of rimonabant was carried out by a tetrazole as a bioisostere. The cyclopentyltetrazole (**55**) showed good activity (IC_{50} = 11.6 nM) with good CB1 selectivity (CB2/CB1 = 366). The 1,3,4-oxadiazole group was also used as a bioisostere of the amide moiety as in compound (**56**) which showed IC_{50} value of 0.57 nM with CB1 selectivity (CB2/CB1 = 1842).



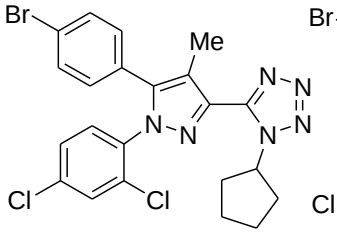
(**52**)



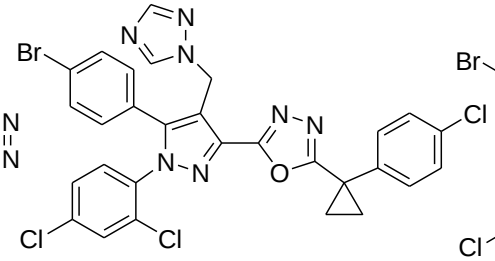
(**53**)



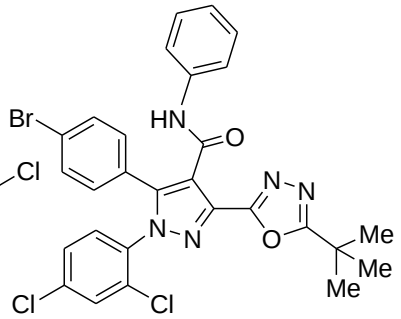
(**54**)



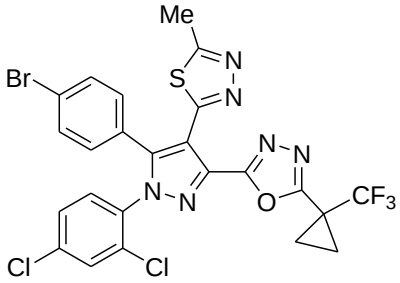
(**55**)



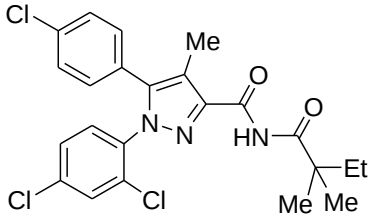
(**56**)



(**57**)



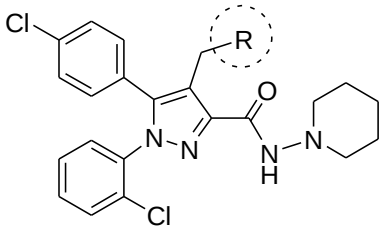
(**58**)



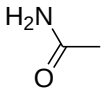
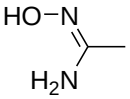
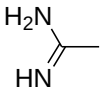
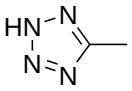
(**59**)

The 4th position of the pyrazole ring was further modified by placing more polar amide groups because this region has a capability of embracing substituents of various functionalities, size and polarity. Compounds (**57**) showed good binding affinity (IC_{50} = 1.35 nM) and good CB1 selectivity (CB2/CB1 = 286).[138] Further, Lee et al.[139] replaced the polar amide group at 4th position of pyrazole by using its bioisostere pentacyclic rings. Introduction of 1,3,4-thiadiazole at 4th position of pyrazole ring resulted in compound (**58**) having high binding affinity (IC_{50} = 1.72 nM) and good CB1R selectivity (CB2/CB1= 142). Song et al.[140] from the same group introduced imide, sulfonamide, *N*-methylimide and methylenediamide moieties in place of *N*-piperidinylcarboxamide group of rimonabant. Out of them, the imide linked to diaryl pyrazole moiety in compound (**59**) showed significant CB1 binding affinity (IC_{50} = 21.2 nM).

Cooper et al.[141] planned to increase the polar surface area (PSA) and lower the lipophilicity to limit the BBB permeation. Hence, replacement of 4-methyl group of pyrazole ring by a more polar nitrile group was further functionalized into various polar groups such as amides, amidoximes, amidines, carboxylic acids and tetrazoles. The nitrile containing compound (**60**) showed comparable CB1 antagonist activity to rimonabant (IC_{50} = 7.5 and 4.5 nM respectively), and lowered lipophilicity (clogP = 4.9 and 6.4 respectively) and increased PSA (73.9 and 50.2 $Å^2$ respectively).

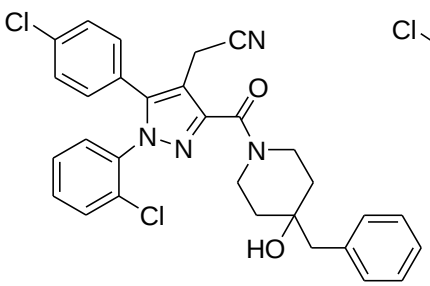


(**60**)

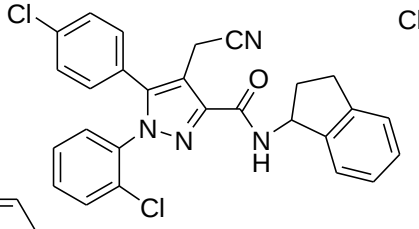
R	clogP (PSA)	R	clogP (PSA)
	-1.11 (+ 19.4)		-0.21 (+34.9)
	-1.06 (+26.1)		-0.18 (+30.7)
	-0.15 (+13.6)		

Further modifications in the amide component resulted in compound (**61**) showing IC_{50} value of 3.4 nM and clogP of 4.8 whereas the most potent compound (**62**) showed IC_{50} value of 0.41 nM but unfortunately the lipophilicity got increased (clogP = 6.0). The nitrile group was further replaced by more polar amide, amidoxime and amidine functional groups.[142] The amide derivative (**63**) showed IC_{50} value of 0.19 nM with lower lipophilicity (logD = 2.8) and improved plasma/brain ratio of 10.2. It was

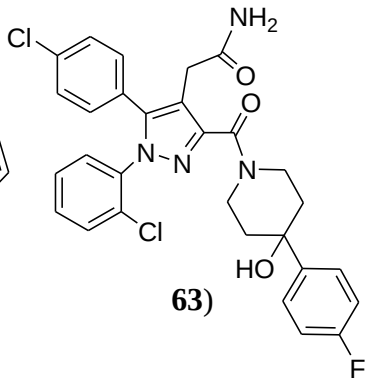
obsereved that the replacement of methyl group by more polar groups showed increased PSA and lowered clogP value.[141]



(**61**)

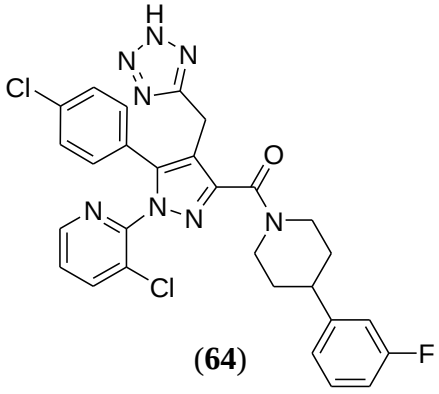


(**62**)

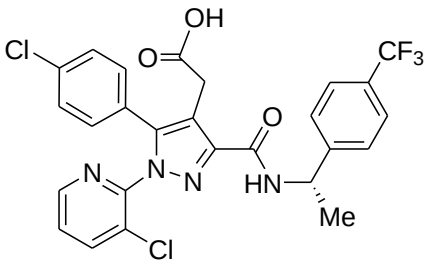


63)

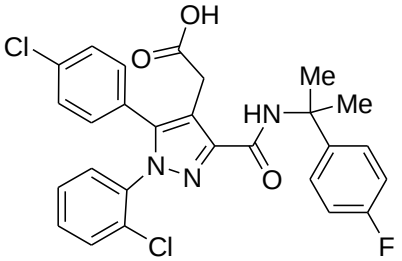
Cooper et al.[143] from 7TM Pharma replaced phenyl ring at 1st position of rimonabant by the pyridine ring and methyl group at 4th position by tetrazole or carboxylic acid to obtain compounds (**64** and **65**) respectively. This kind of modification makes the compounds more polar and useful for the designing of peripherally acting CB1 receptor antagonists. Further, Cooper et al.[144] reported CB1 modulators having reduced central action. Carboxylic acid derivative (**66**) and tetrazole containing compound (**67**) showed IC_{50} values less than 0.30 μM.



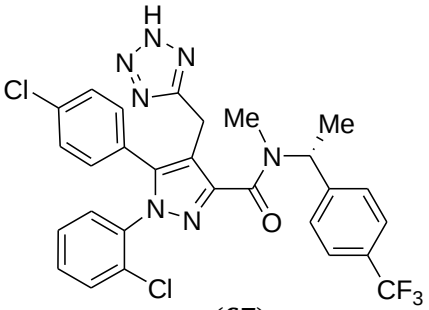
(**64**)



(**65**)



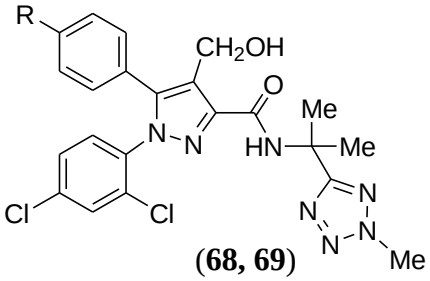
(**66**)



(**67**)

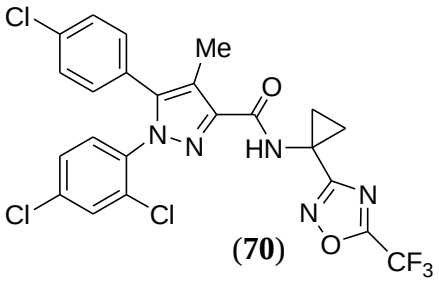
Sasmal et al.[145] reported novel peripherally restricted pyrazole-3-carboxamide as CB1 receptor antagonists. This kind of compounds having higher PSA and lower lipophilicity do not cross the BBB hence avoid serious psychiatric disorders. The

hydrazide functionality was replaced by an amide and polar moieties at 3rd, 4th and 5th positions of pyrazole ring were introduced to reduce CNS exposure. Compound (**68**) was considered as a lead molecule having significant CB1 receptor binding affinity (IC_{50} = 8 nM) with high tPSA value (105.3 Å^2). A significant weight loss (12 % in 15 days) was observed at 10 mg/kg, q.d. on oral administration. The most potent compound (**69**) showed IC_{50} value of 0.5 nM and high CB1 selectivity (> 1000 fold) with tPSA value of 148.6 Å^2. Further, Sasmal et al.[146] reported oxadiazole containing compound (**70**) exhibiting excellent potency (IC_{50} = 0.1 nM) with good oral PK profile. Compound (**70**) showed dose dependent weight reduction in acute food intake evaluated at 10 and 30 mg/kg po in Swiss Albino Mice (SAM) model. Rimonabant exhibited better effect at 10 mg/kg po dose than the compound (**70**) at 30 mg/kg po dose indicating that rimonabant was having more pronounced central effect than the compound (**70**). At 30 mg/kg po dose, rimonabant and compound (**70**) showed brain to plasma ratio of 3.64 and 0.21 respectively after 1 hr. A significant 11 % weight loss in 15 days was observed for compound (**70**) at 10 mg/kg, q.d. on oral administration.



(**68, 69**)

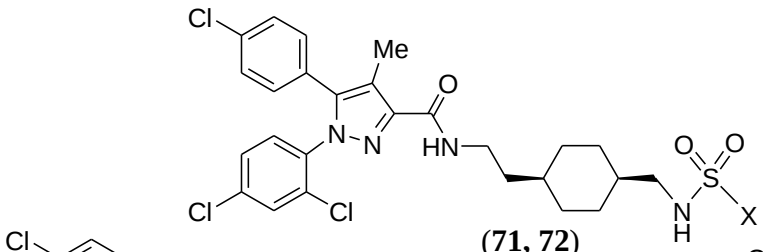
68: R = Cl
69: R = OSO_2Pr



(**70**)

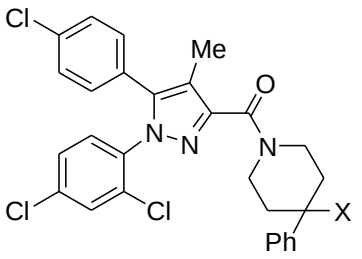
Fulp et al.[147] designed some charged compounds with the aim that such compounds would not cross the BBB but unfortunately, these compounds showed poor activity in the calcium flux assay. Further, they designed sulfonamide derivatives with increased PSA for lower penetration into the CNS. The most potent compounds (**71** and **72**) showed dissociation equilibrium constant (K_e) values of 0.030 and 0.093 μM having tPSA (101 and 127 Å^2 respectively). They showed better transport from apical to basal side (less than 1%) compared to rimonabant and otenabant (15 % and 90 % transport respectively) indicating their poor brain penetration. Further, Fulp et al.[148] replaced the sulfonamide group with carboxamide at 3th position of the pyrazole ring. Compound (**73**) was obtained as a potent and selective CB1 receptor antagonist (K_e = 0.44 nM; CB2/CB1 = 1600). Urea derivative (**74**) was found to be potent (K_e = 2.4 nM) and selective (CB2/CB1 = 426) CB1 receptor antagonist with little or no CNS penetration.

Manca et al.[149] reported peripherally acting neutral CB1 receptor selective antagonists having reduced side effects. By avoiding hydrogen bonding with K3.28(192), a neutral CB1 receptor antagonist (**75**) was designed.[150] An alcohol derivative (±)-**76** and fluorovinyl derivative (*Z*-**77**) exhibited significant efficacy having K_i values of 175 nM and 25.8 nM respectively in the control of food intake. Compounds (**76** and **77**) showed no adverse effects at doses up to 20 mg/kg whereas rimonabant showed psychiatric side effects at this dose.[149] Alvarado et al.[151] reported novel fatty acid amide analogs of LH21 as anti-obesity agents. The results obtained showed that the pyrazole derivative (**78**) had higher affinity and selectivity towards CB2 receptors.



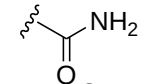
(**71, 72**)

71: X = Me
72: X = NH_2

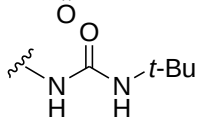


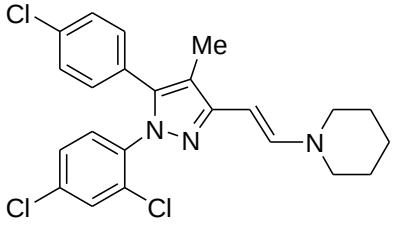
(**73**, **74**)

73: X =

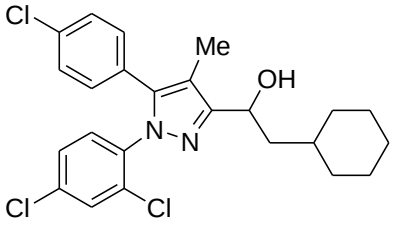


74: X =

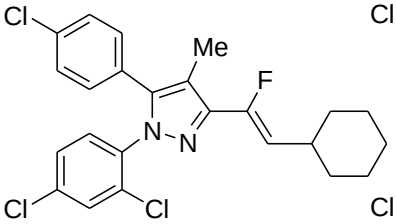




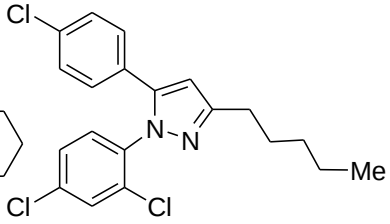
(**75**)



(**76**)



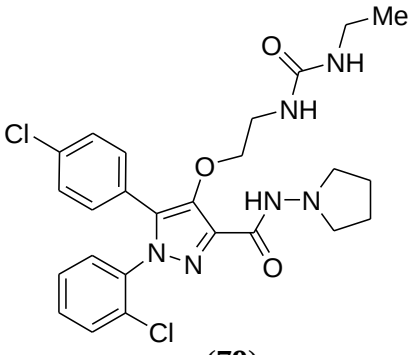
(**77**)



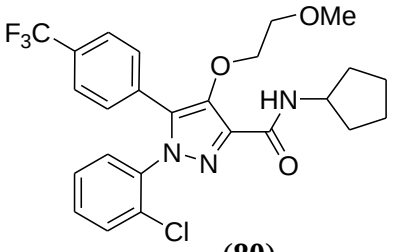
(**78**)

At the same time, Moritani et al.[152] reported novel pyrazole containing potent CB1 receptor antagonists. Substitution with *N*-ethylureidoethoxy group at 4th position of pyrazole ring yielded compound (**79**) having IC_{50} value between 0.1 μM to 0.5 μM whereas substituents like 2-methoxyethoxy and methoxy groups at the same place offered compounds (**80** and **81**) having IC_{50} values between 0.01 μM to 0.1 μM. Further, replacement with difluoromethoxy group at 4th position and difluoropiperidinyl group attached at 3rd position of the pyrazole yielded the most active compound (**82**) having IC_{50} value less than 10 nM. Ahlqvist et al.[153] from AstraZeneca Limited patented novel

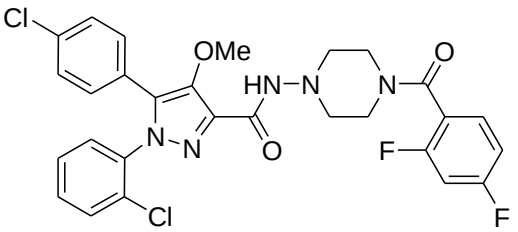
sulphonate esters (**83** and **84**) attached to the phenyl ring at 5th position of pyrazole scaffold which exhibited IC_{50} values of less than 0.2 μM.



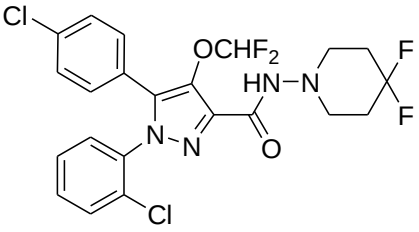
(**79**)



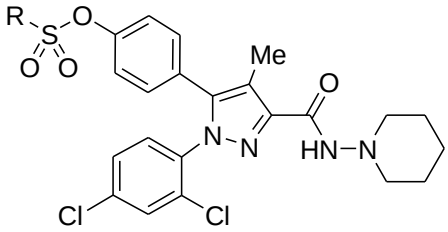
(**80**)

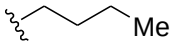


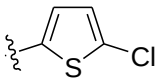
(**81**)



(**82**)

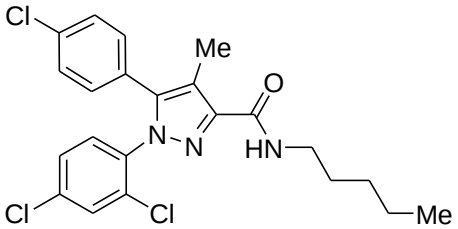


83: R = 

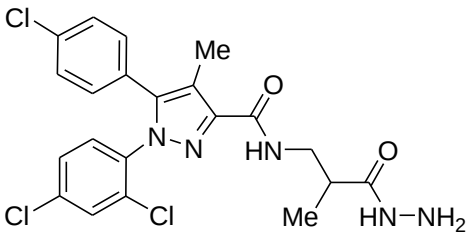
84: R = 

(**83**, **84**)

Thomas et al.[154] patented some novel amide and hydrazide derivatives as CB1 receptor antagonists. The amide derivative (**85**) containing pentyl group attached at 3rd position of pyrazole exhibited good activity (EC_{50} = 5.27 μM) in GTP-γ-[^{35}S] in whole rat brain. The 2-methylpropanoylhydrazide containing compound (**86**) at the 3rd position of pyrazole offered decreased activity (EC_{50} = 73.58 μM).



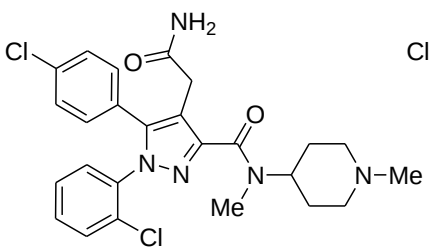
(**85**)



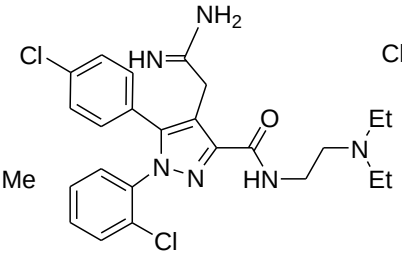
(**86**)

Receveur et al.[155] replaced methyl group of rimonabant at 4th position by more polar groups such as amide, imide and hydroxyamidine. Polar groups at 4th position were

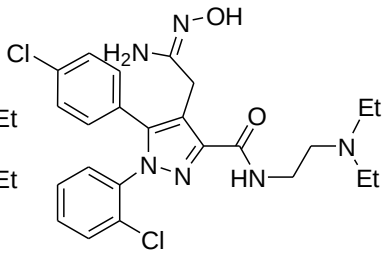
found beneficial for modulating the peripheral CB1 receptor antagonistic activity with reduced propensity to induce psychiatric side effects. Compounds (**87**-**89**) containing substituents such as amide, imide and hydroxyamidine at 4th position respectively showed IC_{50} values in the range of 0.5 μM to 5 μM. Further, substituents such as 4-cyanobenzyl, 4-fluorophenyl and piperidinyl groups attached to carboxmide at the 3rd position of the pyrazole ring yielded compounds (**90**-**92**) having IC_{50} values less than 0.5 μM. Receveur et al.[156] attached five membered ring systems like oxadiazolinone, triazolinone, imidazolidinedione etc. at 4th position of the pyrazole ring yielding compounds (**93**-**95**) as peripherally acting CB1 receptor antagonists ($IC_{50} < 0.5$ μM).



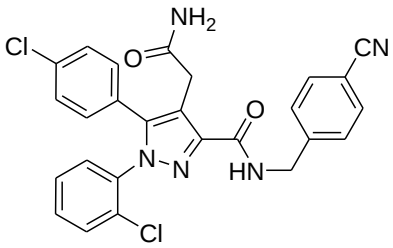
(**87**)



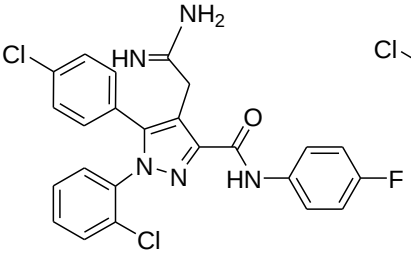
(**88**)



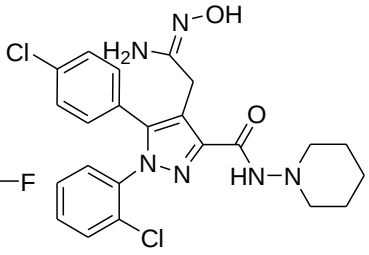
(**89**)



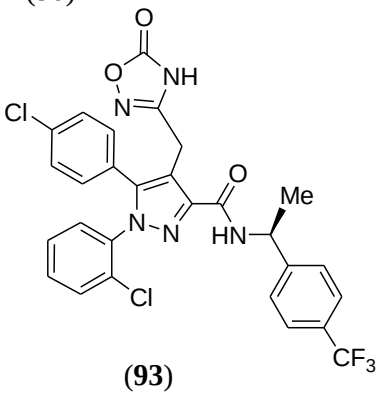
(**90**)



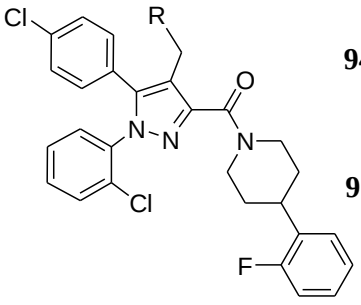
(**91**)



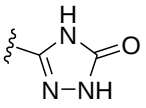
(**92**)



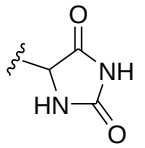
(**93**)



94: R =



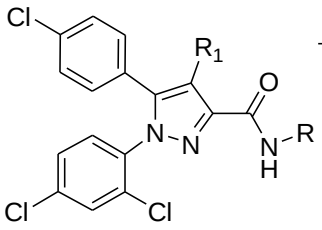
95: R =



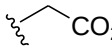
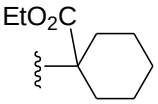
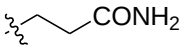
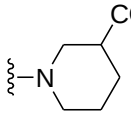
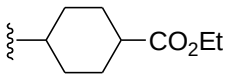
(**94**, **95**)

In the development of peripherally acting CB1 receptor antagonists having less or no CNS side effects, McElroy et al.[157] introduced ethyl group at 4th position as well as polar groups such as ester, amide and piperidine on the carboxamide at 3rd position of the pyrazole ring to offer compounds (**96**-**98**). Compounds (**99** and **100**) having cyclohexyl ring and methyl group at 3rd and 4th positions of the pyrazole ring were also reported as

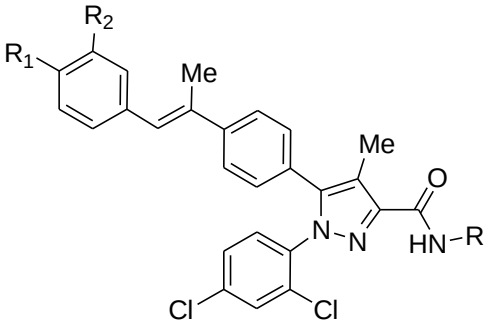
peripherally acting CB1 receptor antagonists. All these compounds showed IC_{50} values of less than 10 μM.



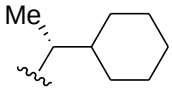
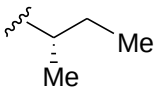
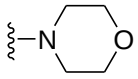
(**96**-**100**)

Comp	R	R_1	Comp	R	R_1
96		Et	**99**		Me
97		Et			
98		Et	**100**		Me

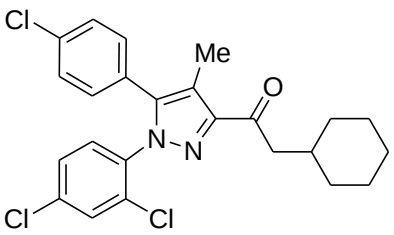
Xia et al.[158] patented novel 5-vinylphenyl-1-phenylpyrazole derivatives. The *S*-cyclohexylethyl group attached to carboxamide at 3rd position of pyrazole ring formed compound (**101**) exhibiting very poor inhibition (0.02 %) of CB1 receptor whereas introduction of *S-sec*·butyl group at the same position yielded compound (**102**) showing 52 % inhibition at 0.2 μM concentration. Introduction of morpholine ring formed compound (**103**) having 53 % inhibition of CB1 receptors at 1 μM concentration.



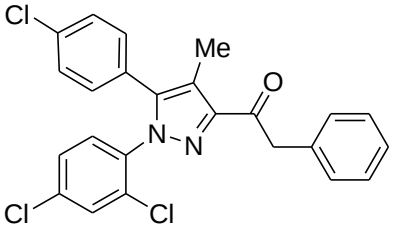
(**101**-**103**)

Comp	R	R_1	R_2
101		Cl	H
102		Cl	H
103		H	Cl

Greig et al.[159] patented 1,5-diaryl pyrazole derivatives as neutral CB1 receptor antagonists. Replacement of amide functional group at 3rd position of rimonabant by a ketone resulted in formation of neutral antagonists from inverse agonists/antagonists. In [^{35}S] GTPγS functional assay, compounds (**104** and **105**) exhibited K_D values of 0.0014 and 0.0023 μM respectively.

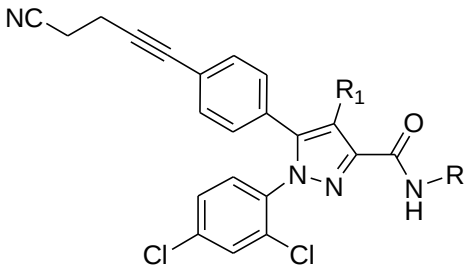


(**104**)

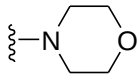
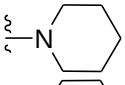
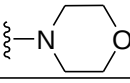


(**105**)

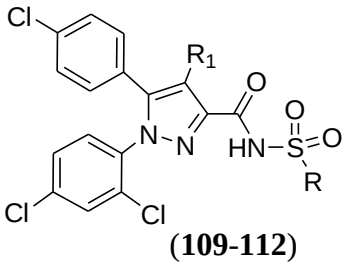
Makriyannis et al.[160] also patented neutral CB1 receptor antagonists showing good peripheral activity. Morpholine containing compound (**106**) having hydroxymethyl and cyanobutynylphenyl groups at 4th and 5th positions of the pyrazole ring exhibited a K_i value of 0.007 μM in [^{3}H]CP55,940 competitive binding assay with good CB1R selectivity (CB2/CB1 = 240). After 15 min post i.v. dose, compound (**106**) and rimonabnt showed 0.6 %/g and 1.8 %/g entery into the brain suggesting that the compound (**106**) exhibited low penetration into the brain. Further, Makriyannis et al.[161] introduced piperidino and methyl groups at 3rd and 4th positions of pyrazole ring offering compound (**107**) showing a K_i value of 0.00035 μM. In the same period, Makriyannis et al.[162] replaced the piperidino ring of compound (**107**) by morpholino ring yielding compound (**108**) which showed K_i value of 0.00089 μM with CB1 selectivity (CB2/CB1 = 100).



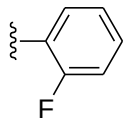
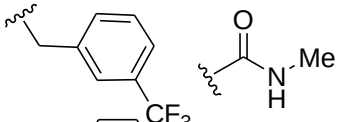
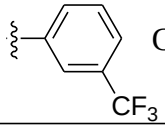
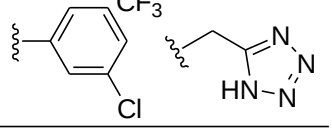
(**106**-**108**)

Comp	R	R$_1$
106		CH_2OH
107		Me
108		Me

Barth et al.[163] reported a series of sulfonamide derivatives as CB1 receptor antagonists. Polar functional groups such as cyano, methoxy, hydroxyl, hydroxymethyl, amide and tetrazole were introduced at 4th position as well as aryl sulfonamide groups at 3rd position of the pyrazole ring. These compounds (**109**-**112**) showed IC_{50} values less than 0.5 μM.

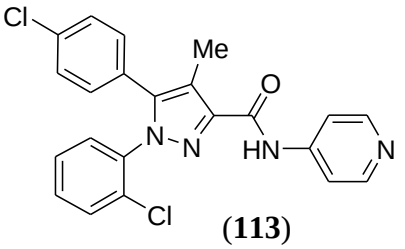


(**109**-**112**)

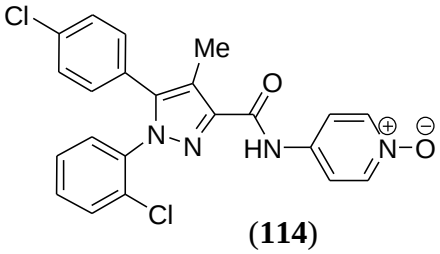
Comp	R	R$_1$	Comp	R	R$_1$
109		CN	**111**		
110		CH_2OH	**112**		

Fulp et al.[164] from Research Triangle Institute, USA patented peripherally restricted CB1 receptor antagonists devoid of CNS penetration. Infact, higher the PSA of a compound, lower the CNS penetration. Polar substituents such as sulfonamide, pyridine *N*-oxide and piperidine enhanced PSA of the compounds. Inroduction of pyridine ring at

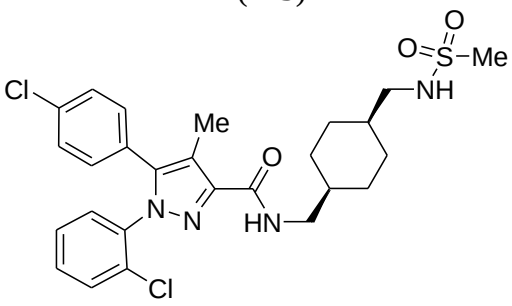
3rd position of the pyrazole ring yielded compound (**113**) having K_i value of 0.056 μM with CB1 selectivity (CB2/CB1 = 31). Pyridine *N*-oxide, a charged group containing compound (**114**) showed K_i value of 0.294 μM with decreased CB1 selectivity (CB2/CB1 = 15). The sulfonamide derivative (**115**) having increased PSA = 101 $Å^2$ exhibited a K_i value of 0.036 μM. The piperidino derivative (**116**) showed higher potency (K_i = 3.44 nM) and excellent CB1 selectivity (CB2/CB1 = 1600).



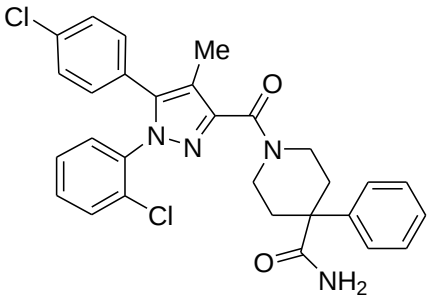
(**113**)



(**114**)

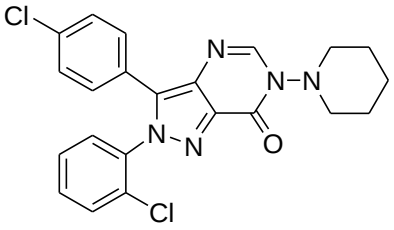


(**115**)

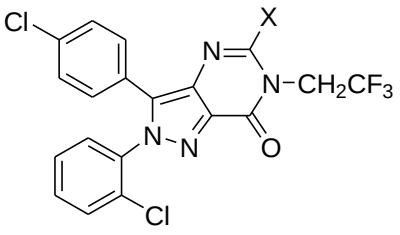


(**116**)

Carpino et al.[165] reported a novel series of conformationally constrained bicyclic derivatives of rimonabant. 2,6-Dihydropyrazolo[4,3-*d*]pyrimidin-7-one derivative (**117**) (K_i = 12 nM) was found to be slightly less active than rimoanabant (K_i = 2.1 nM). Compounds (**118** and **119**) were the most active compounds in the series (K_i = 0.3 and 0.6 nM respectively).



(**117**)



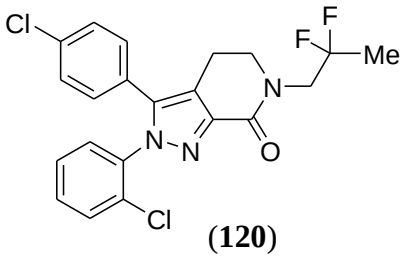
(**118**, **119**)

118: X = H

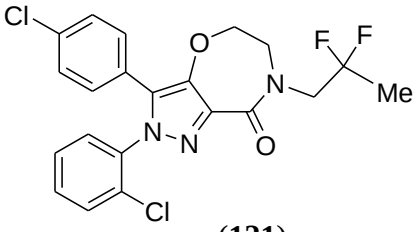
119: X = Me

The most potent compounds (**120** and **121**) showed K_i values of 0.7 and 1.0 nM respectively. On the basis of good *in vitro* activity and pharmacokinetic profiles in rat (1 mg/kg i.v., 5 mg/kg p.o., F = 42 %, $T_{1/2}$ 3.5 h, V_{ss} = 2.6 L/kg), compound (**121**) was selected for further evaluation. In diet-induced obese mice model in 7 days, compound (**121**) showed better reduction in food intake (23 %) at 1 mg/kg dose whereas rimonabant (**1**) showed 21 % reduction at 3 mg/kg of oral dose. A significant reduction in weight

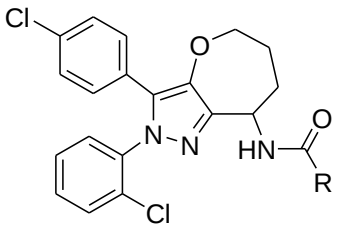
gain of 5.9 % and 5.2 % was observed for compounds (**121** and **1**) respectively, at a dose of 1 mg/kg and 3 mg/kg respectively.[166]



(**120**)



(**121**)



(**122-125**)

122: R = Me
123: R = *iso*-Propyl (*R*)
124: R = 1,2,5-Oxadiazol-3-yl
125: R = CH_2SO_2Me

Further, Dow et al.[167] reported peripherally restricted CB1 receptor antagonists having reduced CNS side effects. Compound (**122**) showed slightly higher PSA as compared to **1** (PSA = 56.1, 50.4 $Å^2$ respectively). Compound (**123**) showed functional antagonistic activity (K_i = 0.14 nM) for CB1 receptors. Compound (**123**) showed statistically significant reduction in cumulative food intake for three different doses (0.3, 1, 3 mg/kg) at 0.5 and 2 h. The most potent compounds (**124** and **125**) were obtained by introduction of more polar substituents showing K_i values of 1.7 and 0.54 nM having PSA values of 95.1 and 98.7 $Å^2$ respectively.

2.1.1.4 Imidazole derivatives

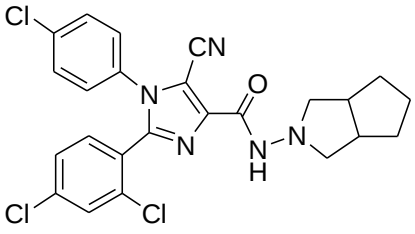
Dyck et al.[168] reported diaryl imidazolecarboxamide derivatives similar to rimonabant (**1**). The bicyclic hydrazide substituted compound (**126**) having cyano group offered the most potent compound (**126**, K_i = 9 nM) in the series. It was observed in this study that high CB1 affinity of the compounds relied on the nature of the side chain rather than on the type of the heterocyclic ring itself.

Bioisosteric replacement of the pyrazole motif of rimonabant by other bioisosteres such as imidazole, thiazole and triazole was carried by Lange et al.[169] Lange et al.[111] targeted 5th position of the 1,2-diaryl imidazole-4-carboxamides. Higher selectivity (840-fold) was observed in compound (**127**) by placing methylsulfonyl group at 5th position. Substitution with more polar groups formed compounds (**127** and **128**)

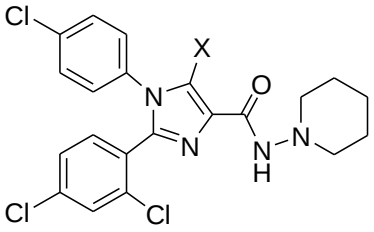
displaying limited brain exposure of P-glycoprotein substrates with *A*log*P* values of 5.3 and 5.2 respectively, which were better than that of rimonabant (*A*log*P* = 6.6).

Smith et al.[170] introduced hydroxyl group into the cyclohexyl ring for increasing the oral availability of the designed compounds (**129**) having K_i value of 3.7 nM with a significant hypophagic effect in Wistar rat model and in Zucker rat model in which a dose-dependent reduction in body weight gain was observed. Further, Kim et al.[171] introduced thiadiazole as a bioisosteric replacement in compound (**130**) exhibiting good potency (IC_{50} =1.91 nM) for CB1 receptor antagonism.

For the identification of potential leads as CB1 receptor antagonists, Plummer et al.[172] carried out high-throughput screening (HTS) by using Merck samples collection. A 4,5-diaryl imidazole containing compound (**131**) was identified having moderate affinity (IC_{50} = 7 μM) for CB1 receptor. Further modifications in compound (**131**) offered 4-(2,4-dichlorophenyl)-5-(4-chlorophenyl) derivatives (**132** and **133**) having good IC_{50} values of 6.1 and 4.0 nM respectively in the series.

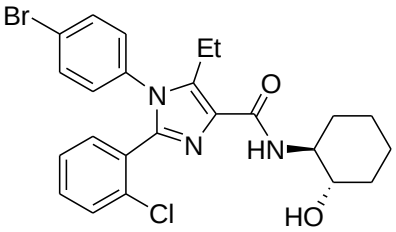


(**126**)



127: X = SO_2Me
128: X = SOMe

(**127**, **128**)



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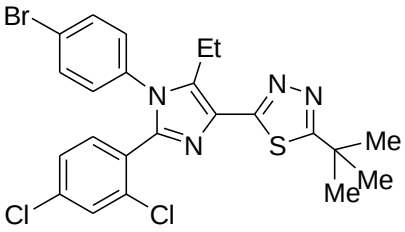
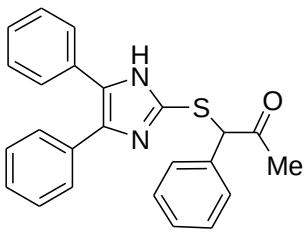


(**130**)



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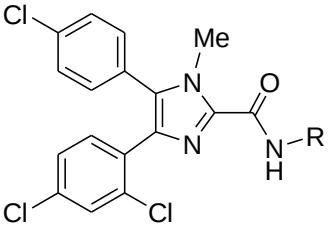
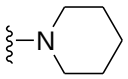
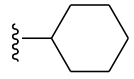


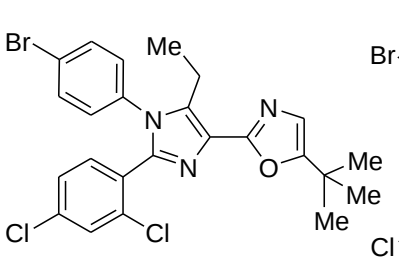
132: R = 

133: R = 

(**132**, **133**)

Lee et al.[173] also reported similar kind of compounds but they mainly focused at 4th position of the imidazole ring by substituting oxazole, oxadiazole, thiazole and thiadiazole groups and substituting various alkyl/heteroalkyl groups at 5th position.

Oxazole ring containing compound (**134**) showed an IC_{50} value of 0.00898 μM. Further, antagonistic activity was increased by introduction of triazolylmethyl at 5th position yielding compounds (**135** and **136**) having thiadiazole and oxadiazole rings repectively at 4th position giving IC_{50} values of 0.00170 μM and 0.00114 μM respectively.



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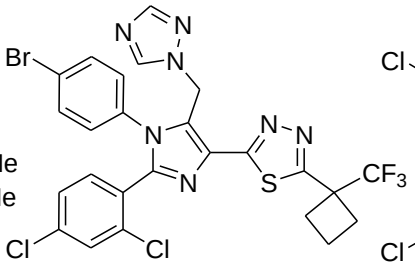

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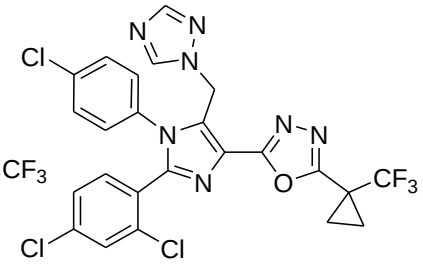
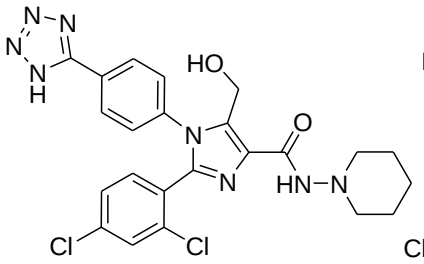


(**136**)

Makriyannis et al.[174] introduced tetrazole ring at 4th position of the phenyl ring attached to the imidazole ring to yield compound (**137**) showing poor K_i value of 5.8 μM. Further, iodo and 3-azidopropyne groups were attached to the 4th position of the phenyl ring, and methyl group at 5th position of the imidazole forming compounds (**138** and **139**) having good activity (K_i = 0.0012 and 0.001 μM respectively). Compound (**139**) showed some selectivity towards CB1 receptor (CB2/CB1 = 82).



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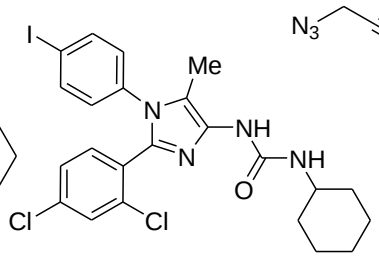

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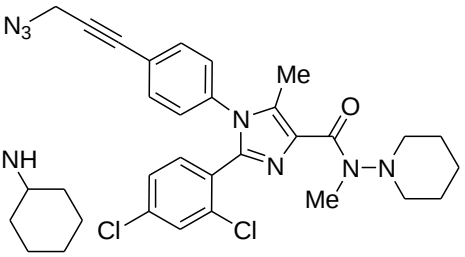


(**139**)

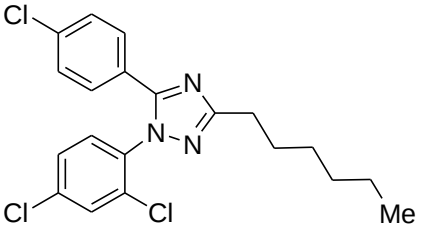
2.1.1.5 Triazole derivatives

Jagerovic et al.[175] reported silent cannabinoid antagonists having 1,2,4-triazole scaffold. In radioligand displacement assay, compound (**140**) (LH-21) showed moderate affinity (K_i = 855.6 nM and 748.0 nM) in rat cerebellar membranes using [^{3}H]-SR141716A and [^{3}H]-WIN 55,212-2 respectively as labelled ligands. Hence, compound (**140**) could be recognized as a silent lead molecule in the designing of CB1 receptor antagonists.

Shu et al.[176] replaced the pyrazole ring of rimonabant (**1**) with its bioisostere 1,2,3-triazole to offer compound (**141**) having enhanced bioavailability and lowered

lipophilicity as compared to rimonabant (*C*log*P* = 5.33 and 6.26 respectively). Further modifications led to enhanced affinity of compounds (**142** and **143**) having K_i values of 4.6 nM and 11 nM respectively while rimonabant showed K_i value of 11.5 nM. But, unfortunately the compounds (**142** and **143**) showed similar lipophilicity as rimonabant.

Hou et al.[177] reported 1,2,3-triazole derivatives as CB1 receptor antagonists. A methylene linker was introduced between the central triazole ring and carbonyl side chain enhancing the *in vitro* activity. The most potent benzylamide containing compounds (**144** and **145**) showed IC_{50} values of 11.6 nM and 19.3 nM respectively with excellent selectivity for CB1 receptors (CB2/CB1 > 1000).



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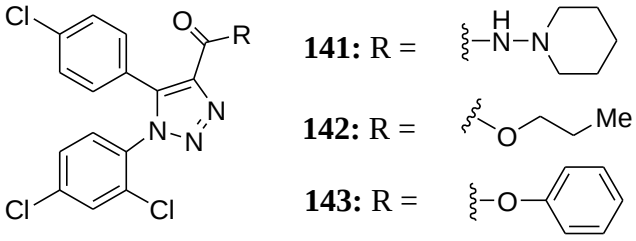
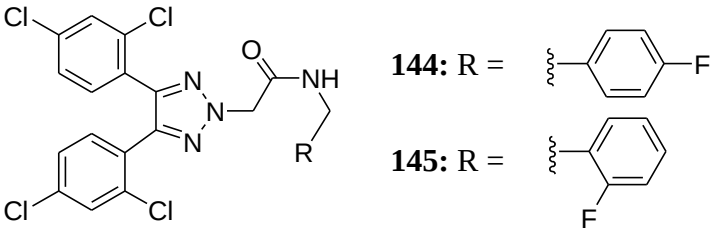
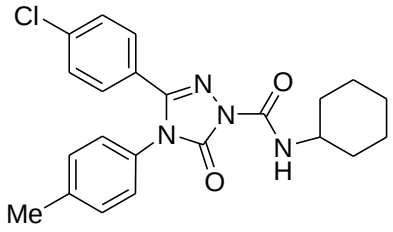


(**141-143**)



(**144**, **145**)

Han et al.[178] reported 1,2,4-triazolone derivatives based on scaffold hoping and privileged structure-oriented approaches. The designed compound (**146**) containing *p*-tolyl group showed an IC_{50} value of 222 nM and higher selectivity towards CB1 receptor.

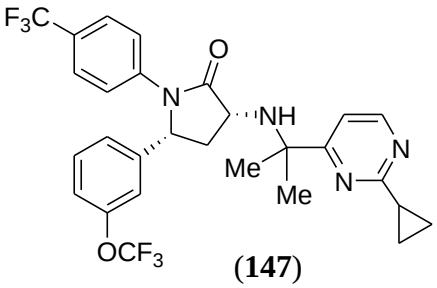


(**146**)

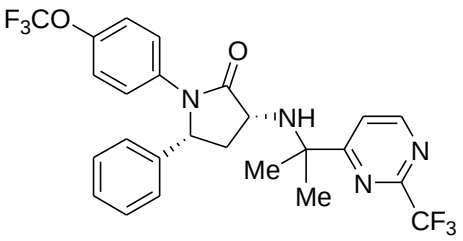
2.1.1.6 Pyrrolidine derivatives

Schaus et al.[179] reported 1,5-diphenylpyrrolidin-2-one derivatives in which phenyl ring at 1st and 5th positions of the pyrolidine ring contained groups like cyano, chloro, trifluoromethyl, trifluoromethoxy etc. Compounds containing pyrimidine ring with

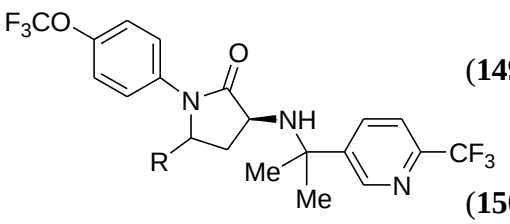
cyclopropyl (**147**) and trifluoromethyl (**148**) groups showed antagonistic activity having equilibrium dissociation constant (K_b) values of 0.000644 and 0.00083 μM respectively with higher selectivity towards CB1 receptors (CB2/CB1 >1000). The 1,5-diphenylpyrrolidin-2-one series was further extended by Coffey et al.[180] in which (3*S*, 5*S*)-isomer (**149**) and (3*S*, 5*R*)-form (**150**) having K_b values of 0.107 μM and 0.0727 μM respectively indicated that the 5*R*-isomer was more potent than the 5*S*-form. Further, the highest activity was found in (3*R*, 5*R*)-form (**151**) having K_b value of 0.00071 μM and excellent selectivity (CB2/CB1 >9000). The trifluoromethyl group at 4th position of the phenyl ring of compound (**151**) was replaced with chloro group resulting into compound (**152**) showing K_b value of 0.00091 μM with increased CB1 selectivity (CB2/CB1 > 15000).



(**147**)



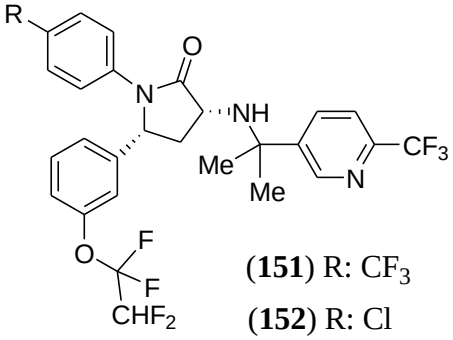
(**148**)



(**149**) R:

(**150**) R:

(**149**, **150**)



(**151**) R: CF_3

(**152**) R: Cl

(**151**, **152**)

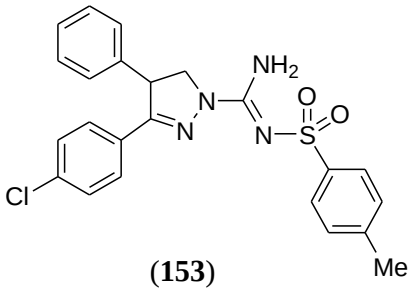
2.1.1.7 Pyrazoline derivatives

Lange et al.[96] reported a new series of 3,4-diaryl pyrazolines as CB1 receptor antagonists. Compound (**153**) with a K_i value of 197 nM was considered as the lead molecule. The most potent compounds (**154** and **5**) in the series were having K_i values of 35.9 and 7.8 nM respectively. Further, Lange et al.[181] lowered the lipophilicity by replacing the aryl sulfonyl group by a dialkyl aminosulfonyl moiety yielding compound (**155**) with a logP value of 4.8 whereas rimonabant and SLV319 showed logP values of 5.5 and 5.1 respectively. The most potent compound (**156**) in this series was having K_i value of 24 nM with 147 fold higher CB1 selectivity.

In the development of peripherally acting CB1 receptor antagonists, Wittgen et al.[182] reported a series of 3,4-diaryl pyrazoline derivatives. The 1,1-dioxothiomorpholino compound (**157**) was developed as peripherally acting compound having logP value of 3.00 and PSA value of 112 $Å^2$ with moderate activity (K_i = 830 nM). In the *in vivo* study on rats, compound (**157**) offered significantly lower brain/plasma concentration than rimonabant (0.4 ± 0.1 vs 6.2 ± 1.6, $p < 0.001$ respectively). Hence, peripherally acting CB1 receptor antagonists could be developed by considering compound (**157**) as a potential starting lead.

With the aim of reducing CNS side effect, Chorvat et al.[183] reported ibipinabant (**5**) analogs having poor penetration into the brain. Two lead compounds (**158**, JD-5006) and (**159**, JD-5037) showed IC_{50} values of 18 and 2 nM respectively having little brain presence in tissue distribution and receptor occupancy studies.

Srivastava et al.[184] reported diaryl dihydropyrazole-3-carboxamide analogs. The highest affinity (K_i = 0.150 μM) towards CB1 receptors was showed by compound (**160**) having significant body weight reduction in the *in vivo* studies. Further, Lange et al.[185] reported 1,3,5-trisubstituted 4,5-dihydropyrazole derivatives (**161** and **162**) exhibiting good CB1 receptor affinities having K_i values of 2.0 and 9.2 nM respectively.



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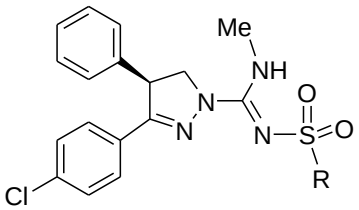
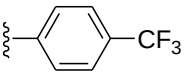
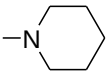
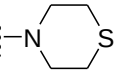
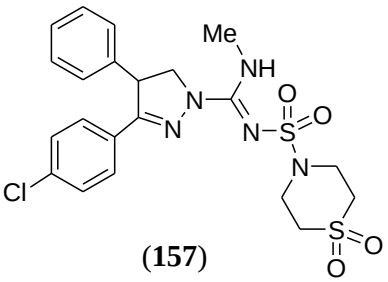


(**154-156**)

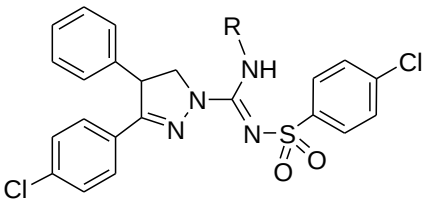
(**154**) R: 

(**155**) R: 

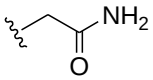
(**156**) R: 

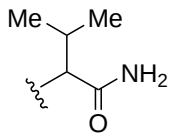


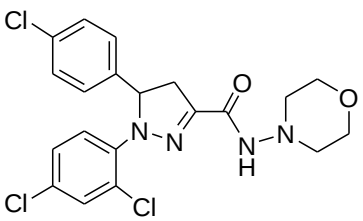
(**157**)



(**158**, **159**)

(**158**) R: 

(**159**) R: 



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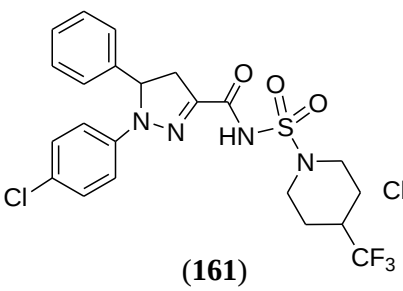

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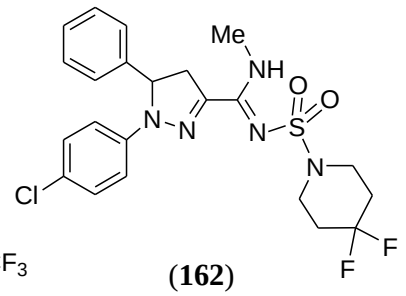
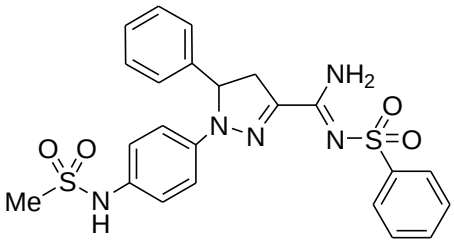
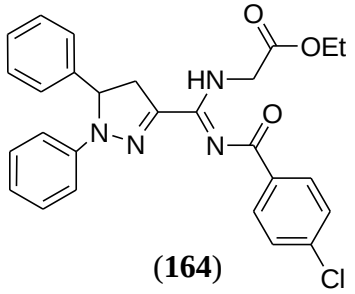


(**162**)

McElroy et al.[186] have been actively engaged in the development of novel sulfonamide and carboxamide containing pyrazolines (**163** and **164**) as peripherally acting CB1 receptor antagonists with reduced CNS exposure.

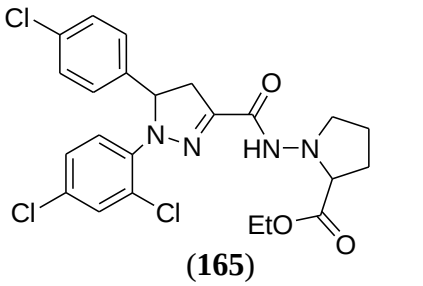


(**163**)



(**164**)

McElroy et al.[187] patented peripherally targeted CB1 receptors in which various ester groups were introduced at different positions of the pyrazolines ring yielding compounds (**165-167**) showing CB1 receptor antagonistic activity (IC_{50} <10 μM). Further, McElroy et al.[188] reported some peripherally acting compounds (**168**, **169**) having lowered CNS exposure with inability or limited ability to CNS permeation through active transport system.



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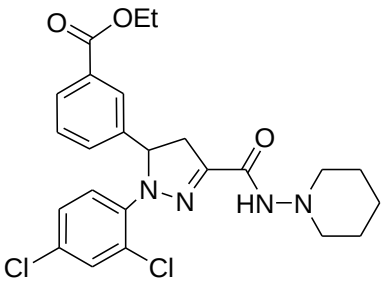

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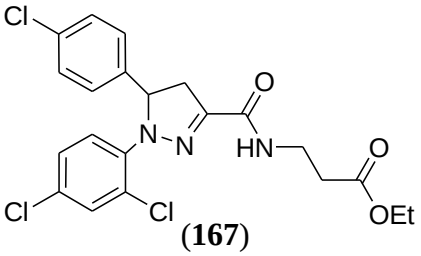
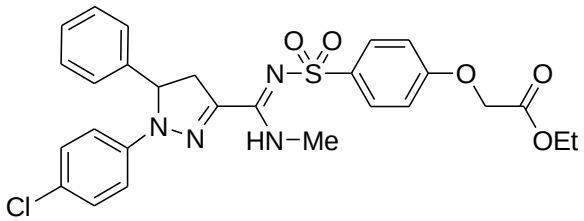
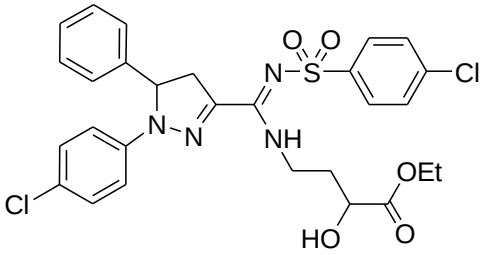


(**167**)

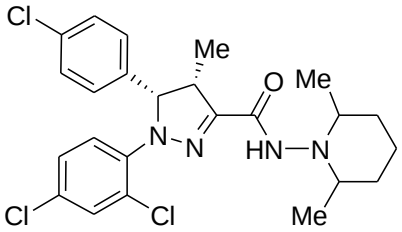


(**168**)



(**169**)

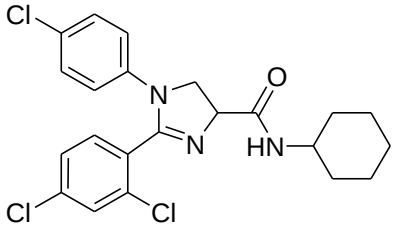
Vela et al.[189] patented some novel 4-methyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide derivatives as neutral CB1 receptor antagonists. These compounds acted either on CNS or peripheral nervous system or both but these were designed to reduce appetite without inducing the CNS side effects. The compound 2,6-dimethylpiperidin-1-yl containing *S*-isomer (**170**) exhibited an IC_{50} value of 0.00752 μM.



(**170**)

2.1.1.8 Imidazoline derivatives

Lange et al.[190] reported novel 1,2,4-trisubstituted imidazoline derivatives as CB1 receptor antagonists. Carboxamide derivative (**171**) showed *in vitro* antagonistic activity with a pA_2 value of 7.7.

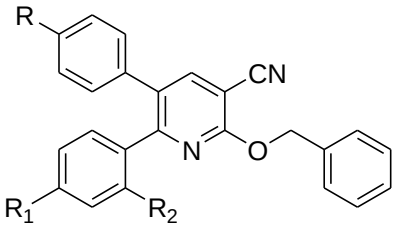


(**171**)

2.1.2 Six membered heterocycles

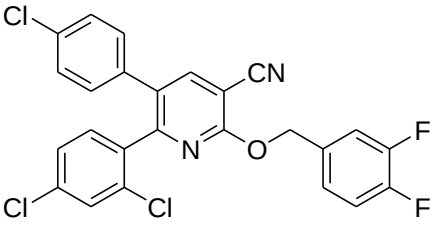
2.1.2.1 Pyridine derivatives

Meurer et al.[191] carried out HTS of the Merck samples collection in which 5,6-diaryl pyridine derivative (**172**) was found to have a moderate affinity for CB1 receptors (IC_{50} = 530 nM). The compound (**172**) was considered as a lead molecule for further development of CB1 receptor antagonists. The 6-(4-chlorophenyl) substituted pyridine derivative (**173**) exhibited poor *h*CB1 binding affinity (IC_{50} = 2800 nM). Additional chlorination on the phenyl moiety offered compound (**174**) showing an IC_{50} value of 11 nM with more than 200-fold higher selectivity for CB1 over CB2 receptors. The 3-cyano-2-(3,4-difluorobenzyloxy)pyridine derivative (**175**) and the 3-(*N*-propylcarboxamido) derivative (**176**) exhibited good *h*CB1 receptor antagonism (IC_{50} = 1.3 and 1.7 nM respectively) with CB1 selectivity (CB2/CB1 = 400).

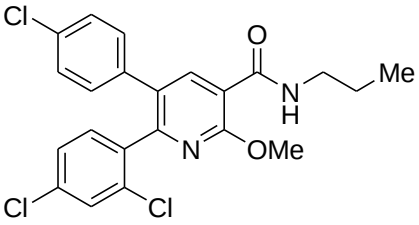


Comp	R	R_1	R_2
172	OMe	Cl	H
173	H	Cl	H
174	Cl	Cl	Cl

(**172-174**)



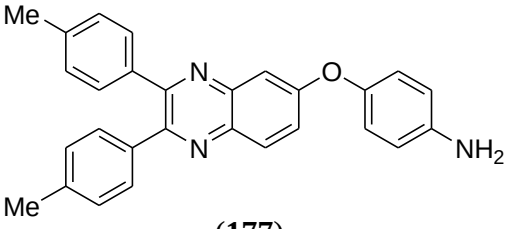
(**175**)



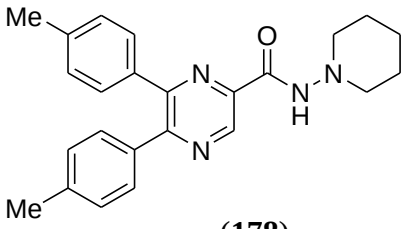
(**176**)

2.1.2.2 Pyrazine derivatives

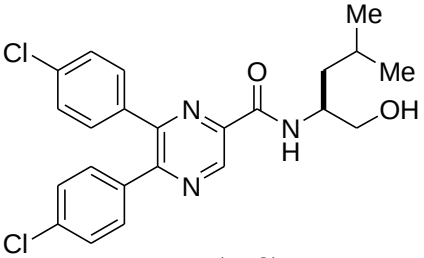
Ellsworth et al.[192] carried out HTS programme and identified compound (**177**) having K_i value of 650 nM which was considered as a lead molecule. Incorporation of carboxamide group resulted in compound (**178**) having K_i value of 52 nM. Further, incorporation of polar hydroxyl group in compound (**179**) showed K_i value of 14 nM with improved physicochemical and PK properties. Wustrow et al.[193] reported pyrazine derivative (**180**) which showed similar inhibiton of food intake and weight loss at 1 mg/kg dose of compound (**180**) as compared to 5 mg/kg dose of rimonabant. At 5 mg/kg dose, compound (**180**) induced approximately double weight loss as compared to 5 mg/kg dose of rimonabant after 18 days of dosing.



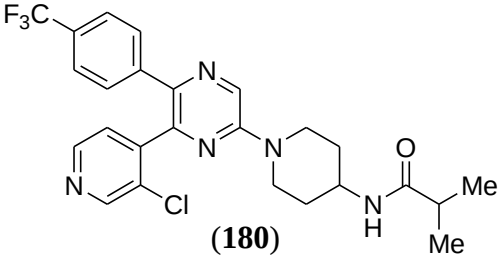
(**177**)



(**178**)

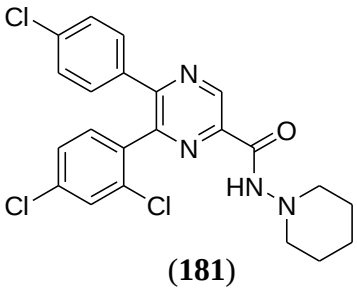


(**179**)

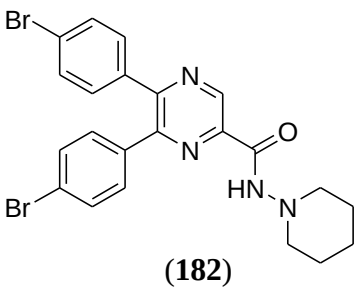


(**180**)

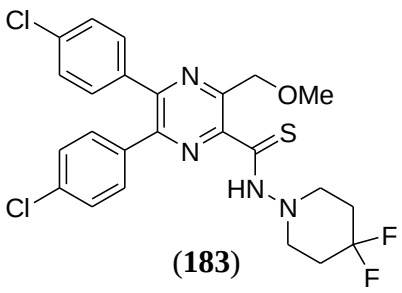
Bostrom et al.[194] designed diaryl heterocyclic compounds with the aim of retaining the global shape of rimonabant. Compound (**181**) was virtually identified having quite similar shape to rimonabant. The most potent compound (**182**) contains bromine atoms at both of the *para* positions of phenyl rings having IC_{50} value of 1 nM. Further, Bostrom et al.[195] replaced the carboxamide linker with thioamide linker in compound (**183**) showing IC_{50} value of 2.4 nM and caused significant reduction in body weight in cafeteria diet obese mice.



(**181**)



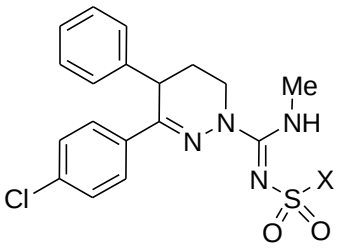
(**182**)



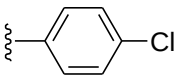
(**183**)

2.1.2.3 1,4,5,6-Tetrahydropyridazine derivatives

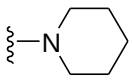
Lange et al.[196] applied bioisosteric approach in which the 4,5-dihydropyrazole moiety of ibipinabant was replaced with a 1,4,5,6-tetrahydropyridazine scaffold. Compounds (**184-186**) showed good CB1 receptor antagonistic activity (K_i = 43, 74 and 47 nM) respectively with significant selectivity towards CB1 receptor.



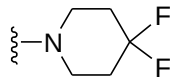
184: X =



185: X =



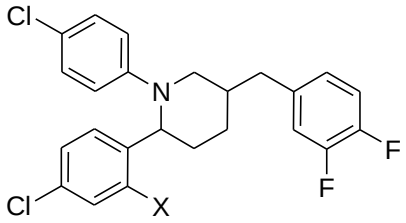
186: X =



(**184-186**)

2.1.2.4 Piperidine derivatives

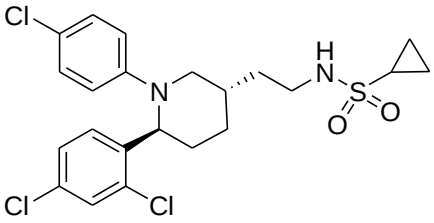
Scott et al.[197] reported piperidine derivative (**187**) having a K_i value of 72 nM. The 2,4-dichlorophenyl substituted compound (**188**) showed 6-fold improved binding affinity (K_i = 15 nM) compared to the compound (**187**). Introduction of sulfonamide group in compound (**189**) showed further improvement in the activity (K_i = 3.4 nM).



187: X = H

188: X = Cl

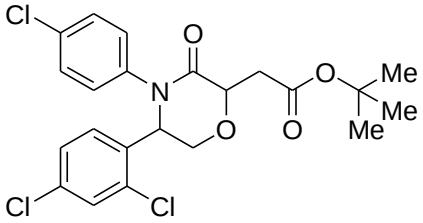
(**187**, **188**)



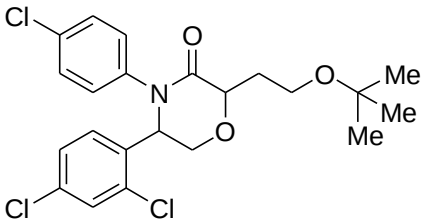
(**189**)

2.1.2.5 Morpholine derivatives

Scott et al.[198] patented novel diaryl morpholine derivatives as CB1 receptor antagonists. The *t*-butyl ester group at 2nd position and carbonyl group at 3rd position of the morpholine ring yielded compound (**190**) exhibiting a K_i value ≤ 0.8 μM. Removal of carbonyl group from the side chain resulted in compound (**191**) showing activity (K_i ≤ 0.055 μM).



(**190**)

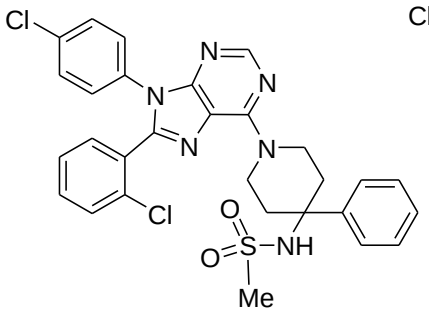


(**191**)

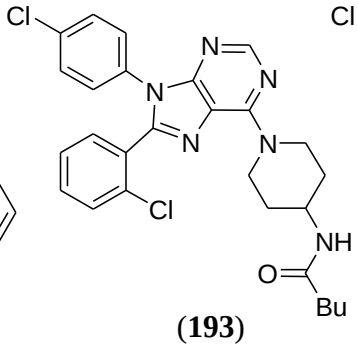
2.1.3 Fused diaryl heterocycles

2.1.3.1 Purine derivatives

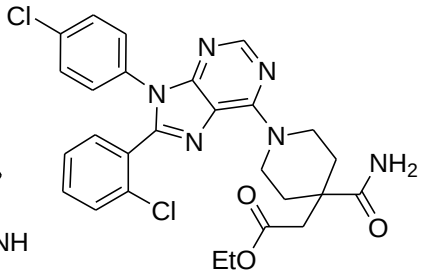
Griffith et al.[95] reported a novel series of purine derivatives as CB1 receptor antagonists. The sulfonamide derivative (**192**) showed good CB1 activity (K_e = 2.9 nM) with good CB1 selectivity (CB2/CB1 = 153) having higher tPSA (101 Å^2). After 8 h post dose, compound (**192)** showed brain to plasma ratio ranging from 0.05 to 0.11 at an oral dose of 10 mg/kg indicating its very poor brain penetration.[199] Further, Fulp et al.[200] reported compound (**193**) showing K_e value of 4.9 nM with good CB1 selectivity (CB2/CB1 = 50). Compound (**193**) showed higher plasma levels than compound (**192**) [C_{max} (1965 vs 1653 ng/mL) and after 8 h time point (1965 vs 914 ng/mL)]. Compound (**193**) having brain-to-plasma ratios from 0.01 to 0.07 indicated minimal or no CNS penetration. McElroy et al.[201] reported purine derivative (**194**) as CB1 receptor antagonists having antagonistic activity equal to or less than 10 μM.



(**192**)

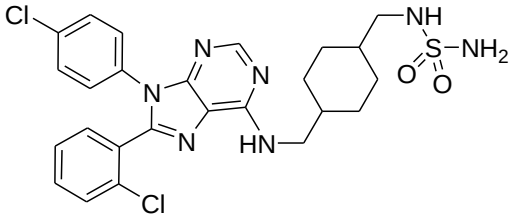


(**193**)

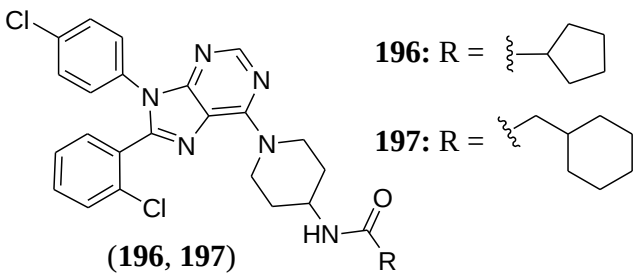


(**194**)

Maitra et al.[202] patented novel peripherally restricted diphenyl purine derivatives with minimal CNS-related side effects. Compound (**195**) showed a K_i value of 0.355 μM with CB1R selectivity (CB2/CB1 = 30.2). Introduction of a cyclopentyl group attached to the piperidine carboxamide at 4th position of the purine ring resulted into compound (**196**) having K_i value of 0.00154 μM with CB2/CB1 ratio of 39. Replacement of cyclopentyl group of compound (**196**) with cyclohexylmethyl offered compound (**197**) having K_i value of 0.00193 μM with increased CB1 selectivity (CB2/CB1 = 1223).



(**195**)



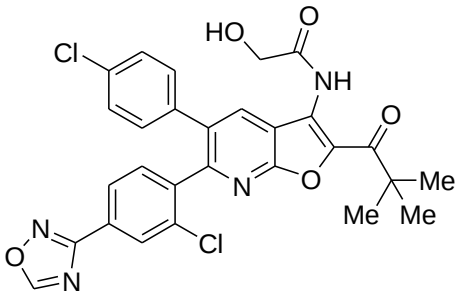
(**196**, **197**)

196: R =

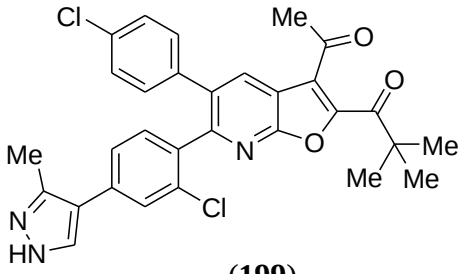
197: R =

2.1.3.2 Fused pyridine ring derivatives

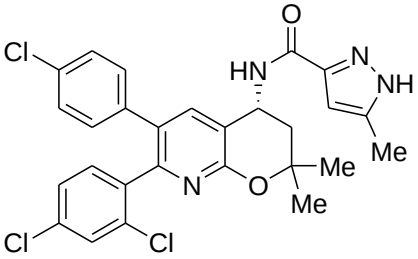
Clements et al.[203] invented novel furopyridine derivatives as CB1 receptor antagonists. Compounds (**198** and **199**) containing oxadiazole and pyrazole respectively at *para* position of the phenyl ring showed IC_{50} values of 0.0004 and 0.001 μM respectively. Further, Debenham et al.[204] patented substituted pyrano[2,3-*b*]pyridine derivatives. The most potent compound (**200**) with pyrano[2,3-*b*]pyridine ring showed an IC_{50} value of 0.001 μM.



(**198**)

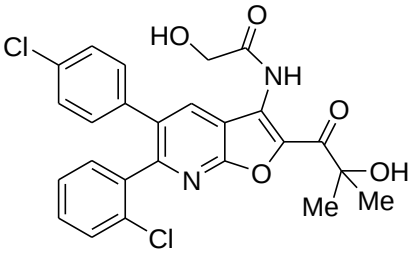


(**199**)

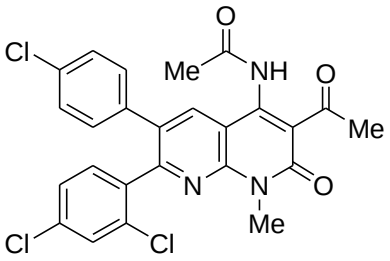


(**200**)

Debenham et al.[205] reported a novel series of furo[2,3-*b*]pyridine derivatives. Compounds (**201**) showed high affinity toward CB1 receptors (IC_{50} = 4.3 nM) and significantly decreased food intake and body weight gain. Further,[206] two pyridine rings were fused to design 1,8-naphthyridinone core system. Compound (**202**) was found to be orally active, highly potent (IC_{50} = 7.5 nM) with selectivity towards CB1 receptor (CB2/CB1 = 546).

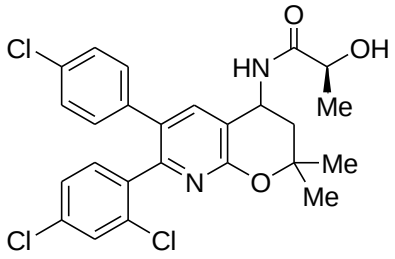


(**201**)

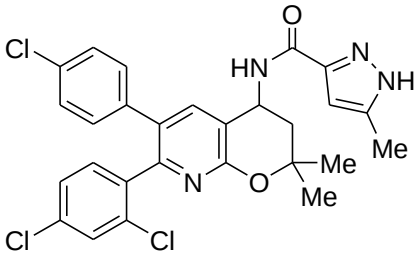


(**202**)

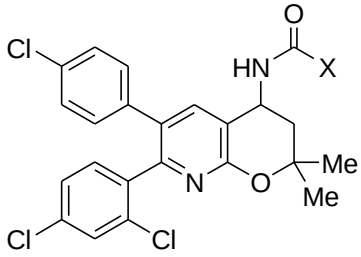
Yan et al.[207] reported pyranopyridine derivative (**203**) having an IC_{50} value of 4.8 nM which was considered as a lead molecule. Introduction of pyrazole ring yielded compound (**204**) having an IC_{50} value of 1.0 nM with higher CB1 selectivity (CB2/CB1 >1000). Further, from the same research group, Madsen-Duggan et al.[208] reported a series of dihydropyrano[2,3-*b*]pyridine and tetrahydro-1,8-naphthyridine bicyclic core scaffolds. Compounds (**205-207**) were obtained as orally active CB1 receptor antagonists which significantly modulated food intake and body weight in a rodent model having IC_{50} values of 1.7, 3.0 and 3.7 nM respectively. Compounds (**205** and **206**) exhibited more than 80 % oral bioavailability while compound (**207**) showed 25 % bioavailability.

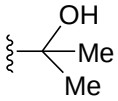


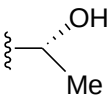
(**203**)



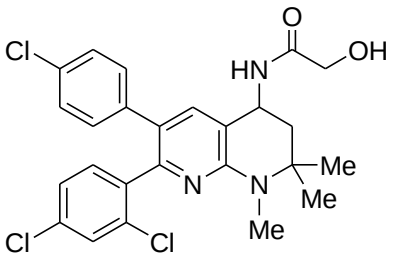
(**204**)



205: X = 

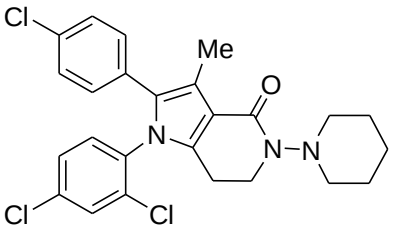
206: X = 

(**205**, **206**)

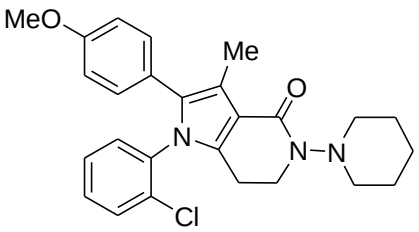


(**207**)

Smith et al.[209] reported a novel series of pyrrolopyridinones as constrained analogs of rimonabant. A 1,5,6,7-tetrahydro-4-*H*-pyrrolo[3,2-*c*]pyridin-4-one containing compound (**208**) was identified having K_i value of 2.2 nM. Replacement of chloro group with methoxy group at *para* position of the phenyl ring resulted into compound (**209**) showing K_i value of 20 nM with significant anorectic effect at 10 mg/kg p.o. dose in the fasted re-fed Wistar rat model with C_{max} = 0.62 μM and $AUC_{(0–2h)}$ = 0.58 μM·h.



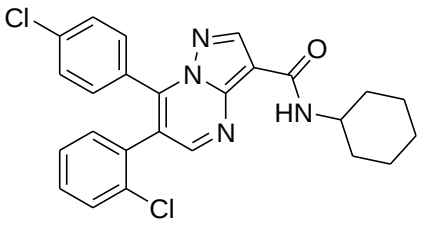
(**208**)



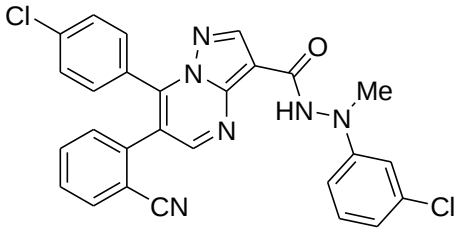
(**209**)

2.1.3.3 Fused pyrimidine derivatives

Moritani et al.[210] patented novel pyrazolo[1,5-*a*]pyrimidine derivatives as centrally acting CB1 receptor antagonists. Carboxamide derivative (**210**) showed IC_{50} value in between 0.01 to 0.1 μM whereas the acid hydrazide (**211**) exhibited IC_{50} value less than 0.01 μM.

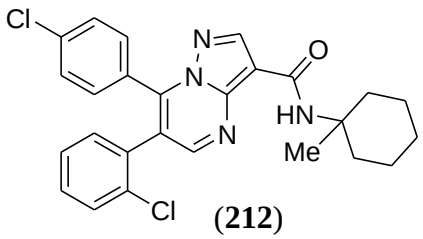


(**210**)

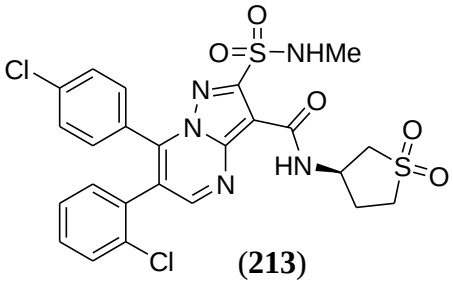


(**211**)

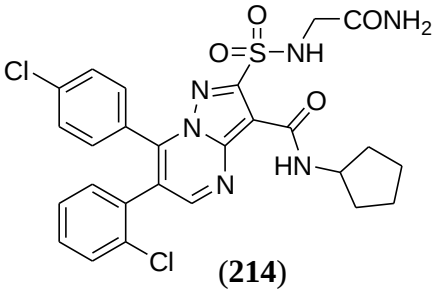
Tanimoto et al.[211] invented pyrazolo[1,5-*a*]pyrimidines as CB1 receptor antagonists. A cyclohexyl group attached to the carboxamide at 3rd position in compound (**212**) was having IC_{50} value in between 0.01 to 0.1 μM. Methylsulfamoyl containing compound (**213**) and acetamide group attached with sulfamoyl group in compound (**214**) showed IC_{50} values in between 0.01 to 0.1 μM. Sulfamoyl group only at 2nd position in compound (**215**) enhanced the activity (IC_{50} <0.01 μM). Introduction of 1,1-dioxotetrahydrothiopyran in compound (**216**) showed similar activity with more than 500 times greater CB1 selectivity over CB2 receptor. Further, compound (**217**) containing 2-hydroxyethoxy group and 1,1-dioxotetrahydrothiophene ring at 2nd and 3rd positions showed an IC_{50} value of less than 0.01 μM with CB1R selectivity (CB2/CB1 > 500).[212]



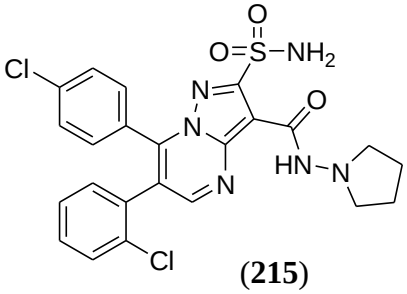
(**212**)



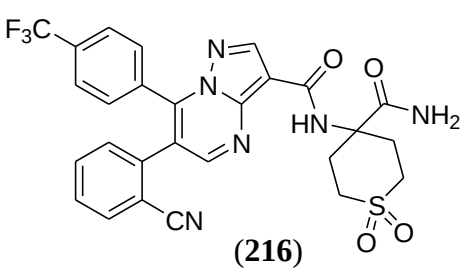
(**213**)



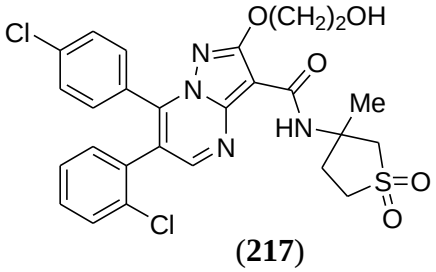
(**214**)



(**215**)

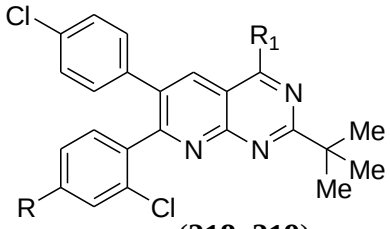


(**216**)



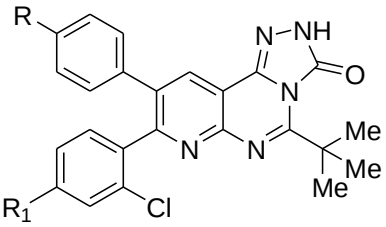
(**217**)

Debenham et al.[213] patented some novel pyridopyrimidine derivatives. Amine group at 4th position of the pyrimidine ring formed compound (**218**) showing an IC_{50} value of 0.011 μM. 4-Fluorophenyl group in place of amine in compound (**219**) showed better antagonistic activity (IC_{50} = 0.0006 μM). Further, Debenham et al.[214] invented novel pyridotriazolopyrimidine derivatives. Compound (**220**) containing oxadiazole ring at 4th position of the phenyl ring showed IC_{50} value of 0.011 μM. Replacement of the oxadiazole ring with Cl in compound (**220**) and cyano group at *para* position of the phenyl ring resulted in compound (**221**) having IC_{50} value of 0.001 μM.

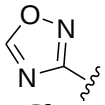


(**218**, **219**)

Comp	R	R1
218	Cl	NH_2
219	H	4F-Ph



(**220**, **221**)

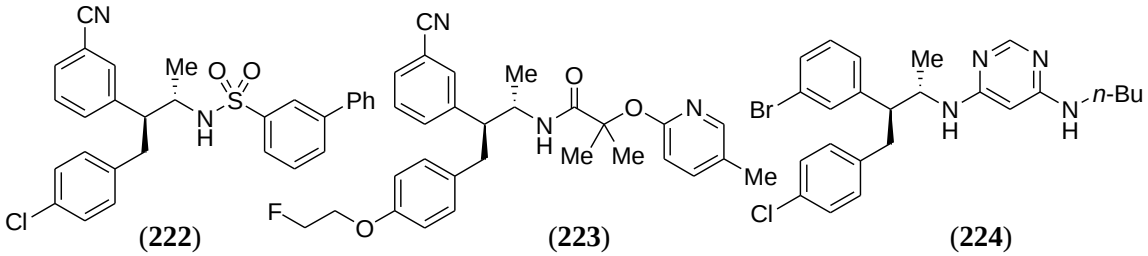
Comp	R	R1
220		H
221	Cl	CN

2.2 Non-vicinal diarayl containing compounds

2.2.1 Acyclic derivatives

Lin et al.[93] reported a novel series of acyclic amide CB1 inverse agonists. The most potent compound (**2**) showed IC_{50} value of 0.3 nM with high CB1 selelctivity (CB2/CB1 = 900). Armstrong et al.[215] reported sulfonamide analog of taranabant (**2**) in which compound (**222**) was observed to be the most potent one having an IC_{50} value of 2.8 nM. Compound (**222**) at 2 mg/kg oral dose showed plasma C_{max} of 343 nM, good distribution (V_d = 6.9 L/kg) and low clearance (Cl = 10.6 ml/min/kg). Further, compound (**222**) was utilized as a lead molecule by Liu et al.[216] with the aim to reduce the lipophilicity and increasing the CB1 affinity. The most potent compound (**223**) in the series showed IC_{50} value of 0.7 nM having low lipophilicity (logD = 4.0).

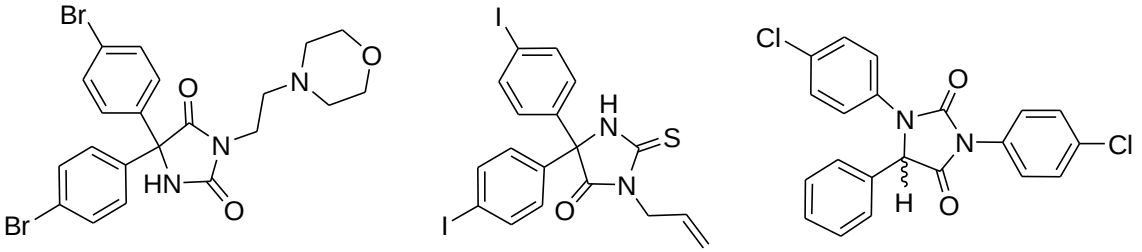
Kim et al.[217] introduced substituted pyrimidine ring in the basic chemical structure of taranabant (**2**). Unfortunately, the designed compounds exhibited less CB1 binding affinity as compared to the standard taranabant. The most potent compound (**224**) showed IC_{50} value of 16.3 nM with CB1 selectivity (CB2/CB1 = 181).



(**222**) (**223**) (**224**)

2.2.2 (Thio)hydantoin derivatives

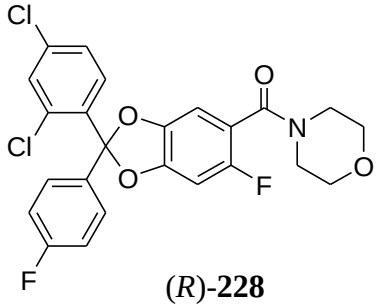
Ooms et al.[218] reported a novel series of diaryl hydantoins as neutral CB1 antagonists in which compound (**225**) showed K_i value of 70.3 nM with logP value of 3.86. Muccioli et al.[219] replaced the oxygen atom by sulphur atom at 2nd position of the hydantoin ring. But the designed compounds (**226**) showed less CB1 binding affinity (K_i = 589 nM) as compared to compound (**225**). Muccioli et al.[220] tried to design 1,5-diphenylimidazolidine-2,4-dione and 1,3,5-triphenylimidazolidine-2,4-dione series in which 1,5-diphenylimidazolidine-2,4-dione derivatives exhibited no CB1 binding affinity. The most active compound was obtained by substituting chloro group at *para* positions of the *N*1 and *N*3 phenyl rings in compounds (**227**) showing K_i value of 247 nM.



(**225**) (**226**) (**227**)

2.2.3 Benzodioxole derivatives

Alig et al.[221] reported a novel series of benzodioxole derivatives as CB1 receptor antagonists. In a 16 days diet-induced obesity (DIO) rat model, compound (**228**) exhibited high CB1 binding affinity (K_i = 4 nM) and a significant decrease in the body weight gain.

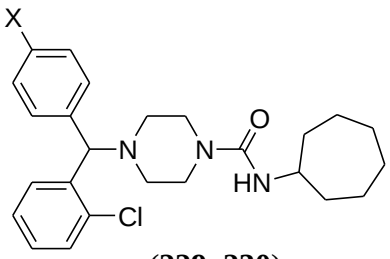


(*R*)-**228**

2.2.4 Benzhydrylpiperazine derivatives

Song et al.[222] reported a novel series of piperazine derivatives as CB1 receptor antagonists. Compound (**229**) showed IC_{50} value of 66.5 nM for CB1 receptor. Replacement of chloro group attached at *para* position of phenyl ring by bromo group resulted in compound (**230**) having IC_{50} value of 49.4 nM.

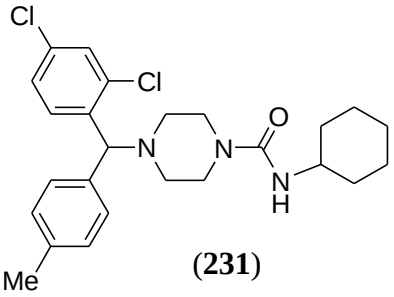
Further, Meng et al.[223] introduced a cyclohexylurea and a *p*-methyl substituent offering compound (**231**) showing K_i value of 0.15 nM and good CB1 selectivity (> 2000). At 10 mg/kg dose, compound (**231**) showed plasma-to-brain concentration ratios of 0.5 and 1.0 at 3 h and 12 h postdose respectively, while at the same dose and time rimonabant exhibited plasma-to-brain concentration ratios of 1.6 and 4.4 respectively, which indicates that compound (**231**) is a poor brain-entrant as compared to rimonabant. In DIO rats model, compound (**231**) at 10 mg/kg (p.o.) single dose suppressed 39 and 22 % food intake after 3 h and overnight (18 h) respectively.



229: X = Cl

230: X = Br

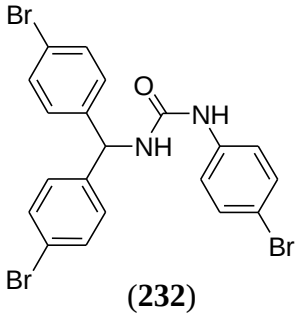
(**229**, **230**)



(**231**)

2.2.5 Benzhydryl derivatives

Muccioli et al.[224] reported a new series of 1-benzhydryl-3-phenylurea derivative (**232**) having a K_i value of 500 nM.



(**232**)

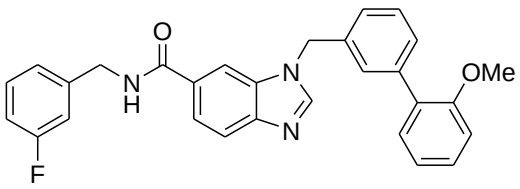
2.3 Miscellaneous compounds

2.3.1 Indole derivatives

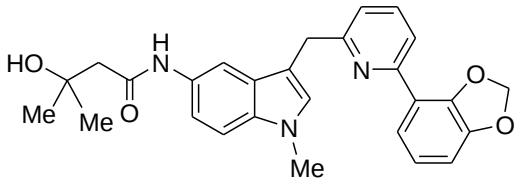
By using HTS programme, Letourneau et al.[225] identified different active structural hits. On the basis of physicochemical properties and potency, a benzimidazole-based compound **(233)** was selected. Isosteric replacement of benzimidazole scaffold by

indole ring resulted in compound (**234**) having an IC_{50} value of 0.005 μM with reduced logP value of 3.60 as compared to rimonabant (logP = 7.02).

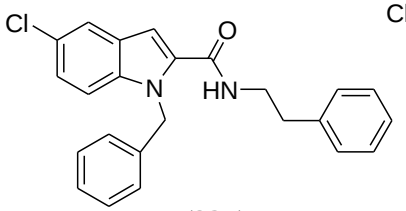
Cowley et al.[226] reported a series of indole-2-carboxamide derivatives as CB1 receptor antagonists. Compound (**235**), identified by performing medium throughput screening campaign as a lead molecule was having weak potency (IC_{50} = 0.42 μM) and higher lipophilicity (logP = 6.32). Further modifications led to the development of compound (**236**) having moderate potency (IC_{50} = 0.26 μM) with reduced lipophilicty (logP = 4.78). Introduction of a polar electron withdrawing nitrile group at 5th position of the indole ring resulted in compound (**237**) showing substantial increase in CB1 potency (IC_{50} = 1.8 nM). Introduction of methoxy group at benzyl ring resulted in compound (**238**) having higher potency (IC_{50} = 1.1 nM) and lower lipophilicity (logP = 4.76).



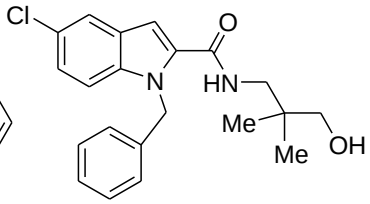
(**233**)



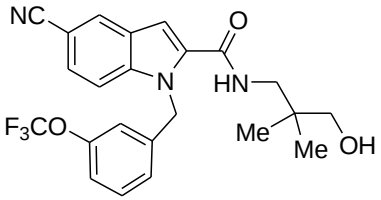
(**234**)



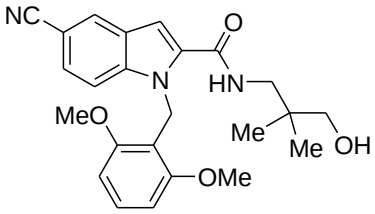
(**235**)



(**236**)



(**237**)

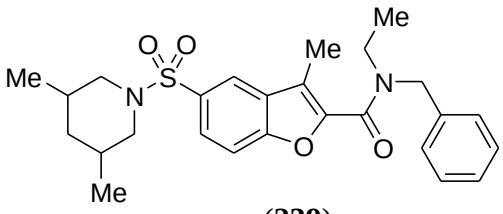


(**238**)

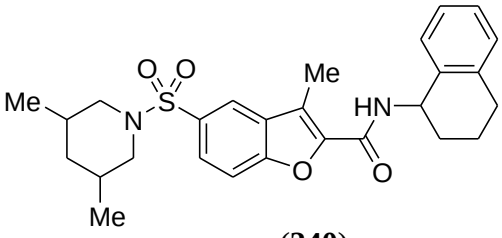
2.3.2 Benzofuran derivatives

By performing ligand-based virtual screening, Foloppe et al.[227] identified a new series of benzofurans as potent and selective CB1 receptor antagonists. Compound (**239**) fitted well in the developed pharmacophore model in which the benzyl and the furan moieties of compound (**239**) were matching with the aryl pharmacophore points and the sulfonamide group acted as hydrogen-bond acceptor. Compound (**239**) demonstrating K_i value of 91.6 nM with CB1 selectivity (CB2/CB1 = 34) was utilized as a lead molecule.

Further modifications led to the most potent compound (**240**) having a K_i value of 5 nM and high CB1 selectivity (CB2/CB1 = 4560).



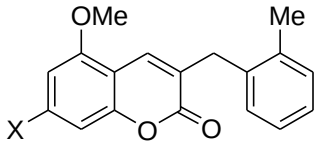
(**239**)



(**240**)

2.3.3 Coumarin derivatives

Behrenswerth et al.[228] reported a novel series of coumarins and related 2*H*-coumarins as CB1 receptor antagonists. The most potent compound (**241**) showed K_i value of 0.738 μM for CB1 receptor. Further, Rempel et al.[229] reported a series of 7-alkyl/aryl-3-benzylcoumarins as potent and selective CB1 receptor antagonist in which compound (**242**) showed K_i value of 0.022 μM with CB2/CB1 value of 18.



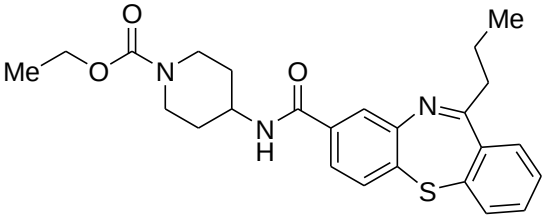
241: X = Me

242: X = Ph

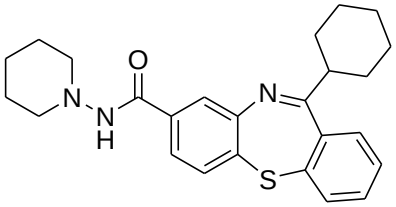
(**241**, **242**)

2.3.4 Dibenzothiazepine derivatives

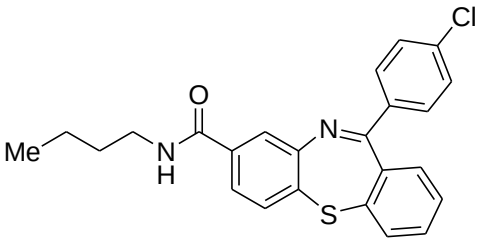
Pettersson, et al.[230] performed an HTS programm using a library of 270,000 compounds. Compound (**243**) was identified having CB1 affinity (pIC_{50} = 6.5). Introduction of cyclohexyl group in place of *n*-propyl group and acid hydrazide side chain resulted in compound (**244**) having pIC_{50} value of 7.6. Replacement of cyclohexyl group of compound (**244**) by 4-chlorophenyl and attachment of *n*-butyl group to the amide chain resulted in compound (**245**) having pIC_{50} value of 8.1. Introducing a 3,4-dihalogenated phenyl group in compound (**246**) improved the solubility (pIC_{50} = 8.4).



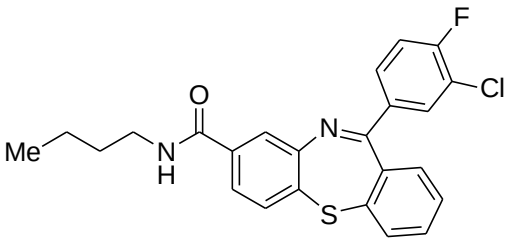
(**243**)



(**244**)



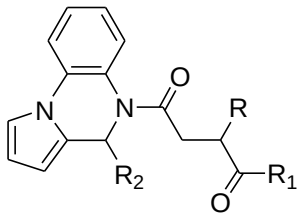
(**245**)



(**246**)

2.3.5 Pyrrolo[1,2-*a*]quinoxaline derivatives

By using a functional Ca^{2+} assay, Szabo et al.[231] performed HTS campaign to obtain hits having a pyrrolo[1,2-*a*]quinoxaline scaffold. Thus, compound (**247**) was utilized as a lead molecule having K_i value of 831 nM. Further modifications led to the development of compound (**248**) having K_i value of 45 nM.



(**247**, **248**)

Comp	R	R1	R2
247	$(CH_2)_3Me$	3,5-Dichlorophenyl	4-Mehoxyphenyl
248	$(CH_2)_3Me$	CH(Me)Cl	4-Chlorophenyl

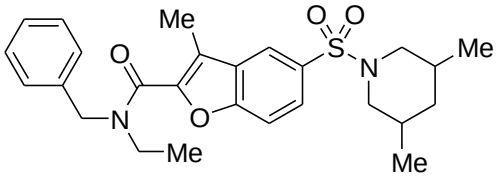
2.4 Molecular modeling studies

Molecular modeling studies have been performed by various research groups for the designing and optimization of CB1 receptor antagonists. Ligand based designing approaches such as 3D-QSAR, pharmacophore and virtual screening have been used as well as various structure based designing approaches such as homology modeling and docking studies have been reported in the literature.

Cichero et al.[232] perfomed 3D-QSAR studies using a dataset of 78 compounds. The electrostatic parameter exhibited higher importance in the established CoMFA model. This study defined that the *m*-substituent on the 1-phenyl ring of rimonabant containing cyano group or hydrogen acceptor group was favourable for higher CB1 receptor antagonistic activity. A pharmacophore modeling for identification of essential key features responsible for the biological activity was performed having three

pharmacophoric features including one hydrogen bond acceptor function (HA) and two hydrophobic-aromatic features (HY1 and HY2). HA feature involved the area where H-bond formed between the ligand and Lys192 residue as well as HY1 and HY2 feature showed important π-π stacking interactions of the ligand with the receptor.

Foloppe et al.[233] performed ligand-based virtual screening using a 3D pharmacophore model as one of the filter and identified thirty novel diverse CB1 receptor antagonists having drug-like properties. Among these lead compounds, compound (**249**) showed the highest affinity (K_i = 92 nM) with good selectivity over CB2 receptor (CB2/CB1 = 33.7).



(**249**)

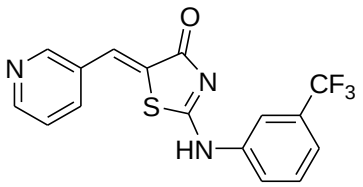
Ye et al.[234] developed Hologram QSAR (HQSAR) model using a series of 75 compounds of biaryl pyrazolyloxadiazole. It was observed from the contribution maps that 1,2,4-trizole and cyclopropane fragments play an important role in the biological activities.

Weber et al.[235] developed HQSAR and CoMFA models on 55 compounds of diaryl pyridines. It was observed from this study that the biological activity could be increased by balancing electrostatic and hydrophobic features in the substituents neighbouring the pyridine nitrogen. Modifications in the steric and electrostatic fields were also favourable for increasing the CB1 receptor antagonistic activity.

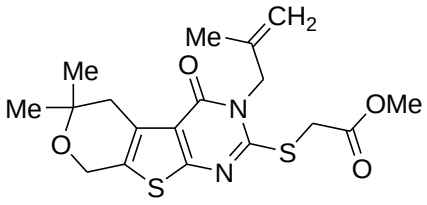
Kang et al.[236] developed pharmacophore model by using the Hip-Hop Refine algorithm. Receptor-aligned model from the docking pose and pharmacophore-aligned model from the HipHop Refine were used in this study. The oxygen of carbonyl group of rimonabant formed H-bond with K192 residue. The 2,4-dichlorophenyl ring was having interactions with the F200/W279/W356 residues, the 4-chlorophenyl ring showing interactions with W255/Y275/F278 residues and piperidine group of rimonabant fitted in the hydrophobic cavity composed of V196/F170/M385/L387 residues. Further, high throughput virtual screening was performed by using the obtained information.

For identification of new scaffold, virtual screening was performed by Lee et al.[237] Different filters such as pharmacophoric features, 3D-QSAR (CoMFA) model, physicochemical properties and docking interactions were used to obtain the new

scaffolds. Compounds (**250** and **251**) forming H-bonds with K192 and D366 residues were considered as lead compounds for CB1 receptor antagonist activity.

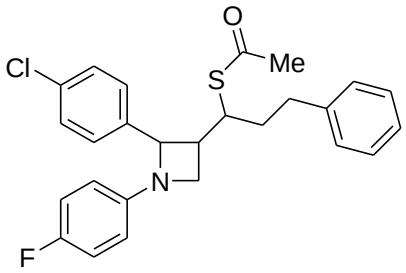


(**250**)



(**251**)

Wang et al.[238] developed a pharmacophore model using reported CB1 receptor antagonists, which was used to screen a database of half a million Schering-Plough compounds. The most potent compound (**252**) showed K_i value of 53 nM with (CB2/CB1 > 5).



(**252**)

Structure based drug designing is a very powerful tool for understanding the interactions of ligands with the receptors. Homology models of CB1 receptor were developed by various research groups. Homology model of cannabinoid receptor was developed by different templates such as bacteriorhodopsin,[239] bovine rhodopsin,[240-244] β_2-adrenergic receptor,[245,246] and A_{2A} adenosine receptor.[246,247] In case of CB1 receptor antagonists, rimonabant was located at the TMH3-4-5-6-7 region and bound to the similar aromatic microdomain as WIN55212-2. The binding site of this CB1 receptor model was composed of 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 Figure 2.1. 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 a bulky group was introduced on C7.42(386) residue.[246]

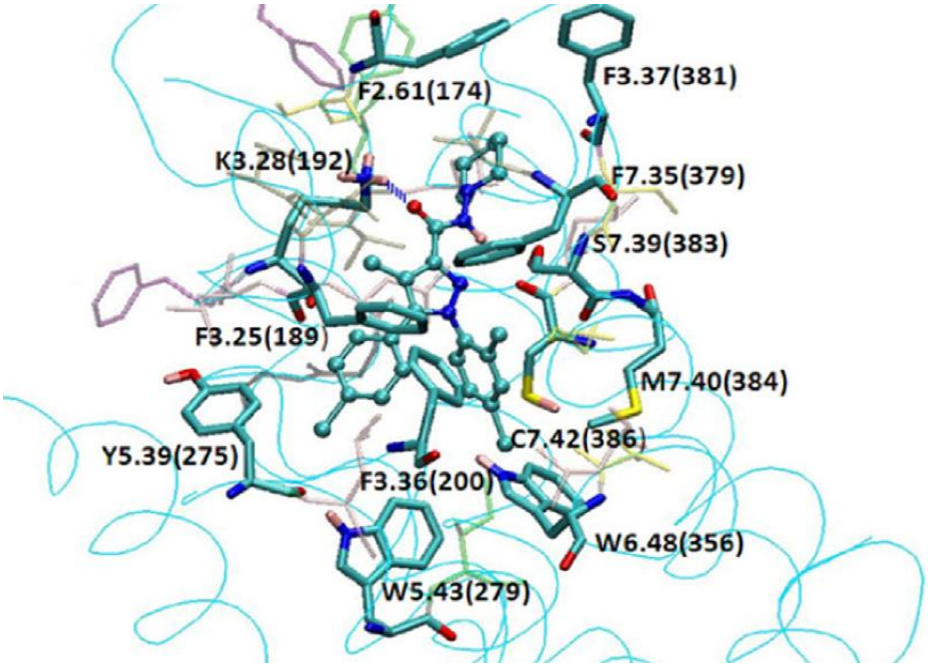


Fig. 2.1 Binding of SR141716A in the active site of CB1 receptor.[246]