Bioorganic & Medicinal Chemistry 18 (2010) 1149–1162

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and structure–activity relationship of 1,2,4-triazole-containing diarylpyrazolyl carboxamide as CB1 cannabinoid receptor–ligand

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ARTICLE INFO

Article history:
Received 12 October 2009
Revised 11 December 2009
Accepted 15 December 2009
Available online 22 December 2009

Keywords:
CB1 receptor
Rimonabant
Triazole
Pyrazole
Carboxamide

ABSTRACT

Numerous research groups have been engaged in searching for novel CB1 receptor antagonists, since SR141716A (rimonabant), a CB1 receptor antagonist, proved to be efficacious in human for the treatment of obesity. In the present study, a series of 1,2,4-triazole-containing diarylpyrazolyl carboxamides based on the 1,5-diarylpyrazole template of rimonabant, was synthesized and tested for CB1 receptor binding affinity. The structure–activity relationship studies demonstrated that incorporation of 1,2,4-triazole ring onto the pyrazole scaffold via a methylene linker led to a significant improvement for CB1 receptor binding affinity. Importantly, these analogues also exhibited excellent selectivity for CB1 receptor over CB2 receptor.

1. Introduction

The prevalence of obesity is rapidly increasing globally. Obesity has reached epidemic proportions in developed countries. It is now widely accepted that obesity is not a cosmetic issue, but is a major health issue. At last, the World Health Organization (WHO) officially declared obesity a disease in 1998.[1,2] Obesity has received significant attention due to its high prevalence and association with serious health risks, especially metabolic syndrome including insulin resistance, hypertension, and heart disease.[3–5] Obesity is defined as a body mass index of more than 30 kg/m.[2] This index gives a measure of weight and body fat in relation to height. Moreover, obesity is included in the pathogenesis of metabolic syndrome, which can lead to cardiovascular diseases and type II diabetes. Currently only two drugs are approved by FDA in the United States for the long-term treatment of obesity, that is, sibutramine and orlistat. However, both of these agents suffer from variable efficacy or undesirable side effects that have restricted their therapeutic potential. Accordingly, there are still unmet medical needs for novel target developments for antiobesity drug.[1,6,7]

Under these circumstances, the endocannabinoid system provided the good clue for a new approach to the antiobesity drug development. This endogenous signaling system has been known to play a key role in the regulation of food intake, fat accumulation, and energy balance. The over activation of the endocannabinoid system appears to be closely related to the abdominal obesity and the development of the metabolic syndrome.[8] The particular interest has been focused on the characteristic role of CB1 receptor, which could effectively modulate endocannabinoid system. The down-regulation of the endocannabinoid system by the specific blockage of CB1 receptors could induce body weight reduction. Accordingly, a number of research groups have attempted to find clinically useful CB1 receptor antagonists and eventually, rimonabant, the first commercial CB1 receptor antagonist, was identified by Sanofi-Aventis. Since then, antagonism against CB1 receptor has been regarded as a highly promising strategy for the treatment of obesity and various CB1 receptor antagonists have been discovered and developed by many pharmaceutical companies.[9–11] Although several CB1 receptor inverse agonists or antagonists including rimonabant (**1**),[12] taranabant (**2**),[13] and otenabant (**3**)[14] were recently withdrawn from clinical development, many research groups and pharmaceutical companies are still searching for novel CB1 antagonists such as ibipinabant (**4**) or AVE-1625 (**5**), bearing improved physicochemical properties and decreased adverse effects involving depression, anxiety or suicidality (Fig. 1).

The main objective of this study was the search for novel CB1 receptor antagonists. A pharmacophore model for the binding of a low energy conformation of rimonabant in the CB1 receptor has been well-documented.[15a,15b] The key receptor–ligand interaction is reported to be a hydrogen bond between the carbonyl group of rimonabant and the Lys192-Asp366 residue of the CB1 receptor, thereby exerting a stabilizing effect on the Lys192-Asp366 salt bridge as shown in Figure 2.[15a]

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doi:10.1016/j.bmc.2009.12.040

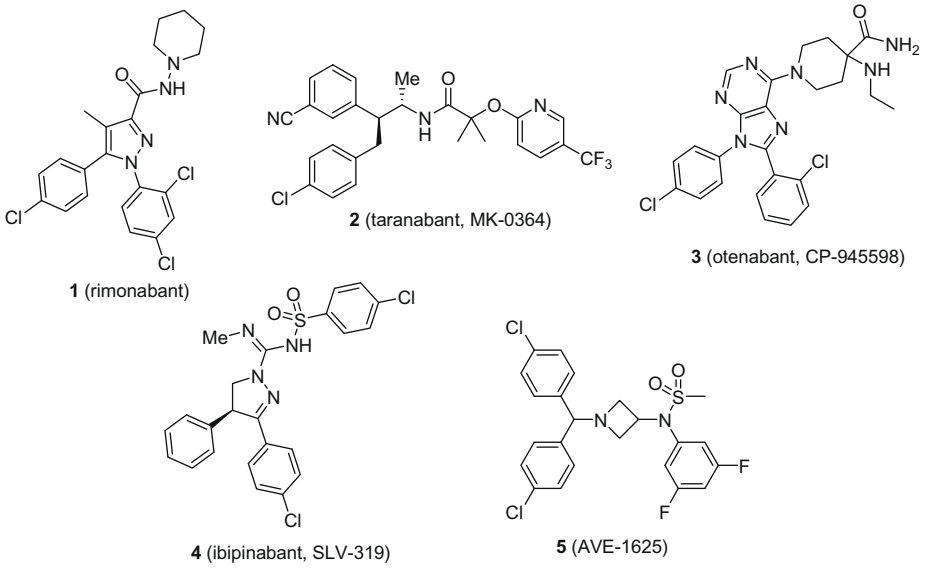


Figure 1. Structures of CB1R antagonists or inverse agonists.

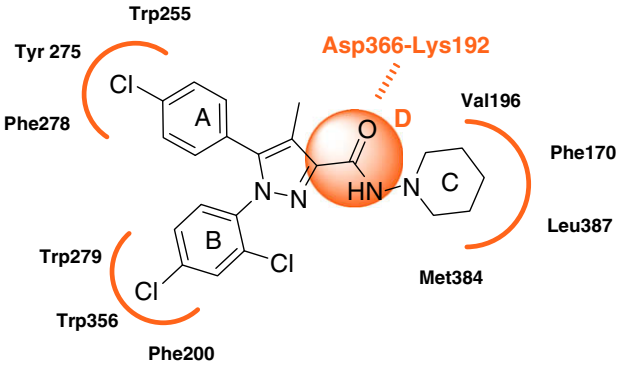


Figure 2. Rimonabant and its receptor–ligand interaction.

In our previous studies,[17,18] we investigated a series of diarylpyrazolyl oxadiazole derivatives as antagonists for the cannabinoid CB1 and CB2 receptors. A few of compounds (e.g., **6**, Fig. 3) in this series exhibited better binding affinity of known CB1 antagonists, validating the hypothesis that a 1,3,4-oxadiazole[16,17] could act as a CB1 bioisostere of the amide moiety in rimonabant (**1**). Along the line, both imidazole[23] and tetrazole[24] replacements for the amide functionality have been reported. Subsequently, we introduced a triazolyl ring onto the C4 methyl group of the pyrazole scaffold via a methylene linker (**7**, Fig. 3) leading to a potent CB1 receptor antagonist with a significant antiobesity effect in animal model. A subsequently conducted modeling study revealed that the N2 of triazole substituent forms a bidentate H-bond with side chain OH and backbone NH of Thr 197, which is an exclusive interaction observed in the binding model of **7** (GCC2469).[17]

As shown in Figure 4, we envisioned that incorporation of 1,2,4-triazolylmethyl moiety onto the pyrazole 3-carboxamide could lead to more potent CB1 receptor antagonists based on the encouraging observation made in our previous study.[17] In this article, we describe the synthesis and biological evaluation of 1,2,4-triazole-containing diarylpyrazolyl carboxamides as novel CB1 receptor–ligands. Through a process of lead optimization, we successfully identified a promising compound showing strong binding affinity for CB1 receptor (IC_{50} = 1.1 nM).

2. Chemistry

The synthetic pathway toward a series of 1,2,4-triazole-containing diarylpyrazolyl carboxamide is outlined in Scheme 1. The compounds containing 1,2,4-triazole were obtained by a reaction sequence involving key intermediate bromide **11**. Thus, the generic ester **10**[12] underwent a benzylic bromination-type reaction (NBS, catalytic amount AIBN)[19] to produce **11**, which was reacted with triazole in the presence of cesium carbonate to generate **12**. Hydrolysis of ester **12** with lithium hydroxide, activation of acid **13**, followed by coupling with an amine in the presence of triethylamine provided the corresponding target carboxamide **9**. Alternatively, acid **13** was directly coupled with requisite amines by use of coupling reagents such as EDCI, HOBt, NMM in a suitable solvent such as DMF or CH_2Cl_2 to generate **9**.

3. Results and discussion

The target 1,2,4-triazole-containing diarylpyrazolyl carboxamides were evaluated in vitro at a rat CB1 binding assay,[21,26] and ini-

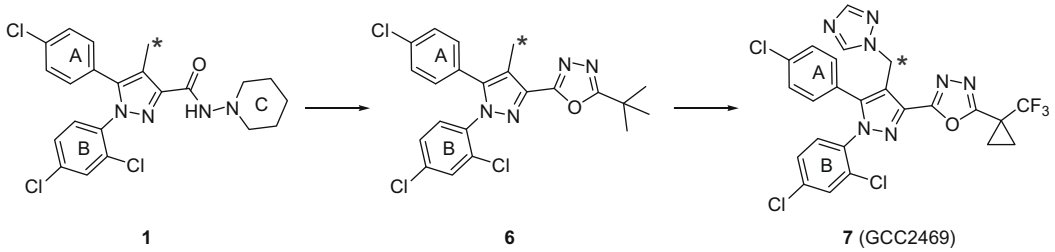


Figure 3. Rimonabant **1**, its bioisostere compound **6**, and compound **7** evolved from earlier form **6** (* = C4 methyl group).

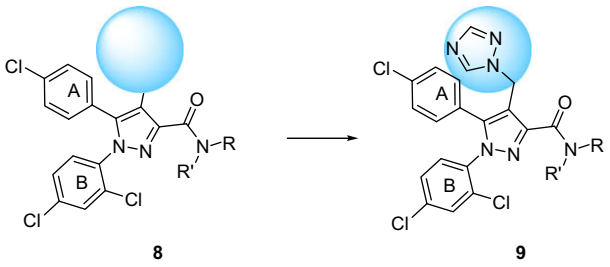
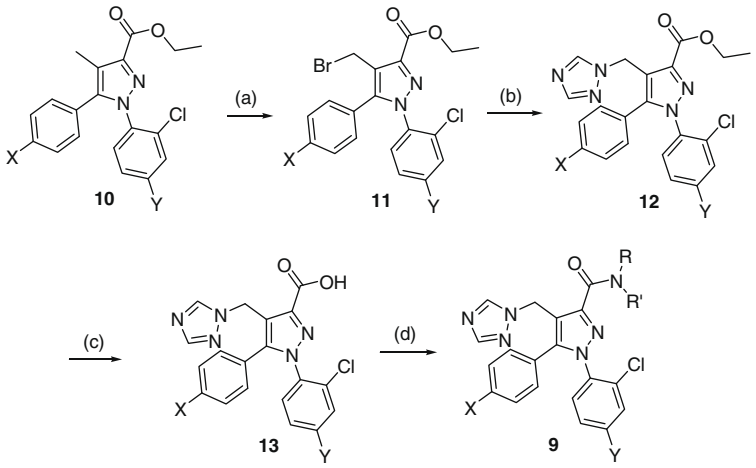


Figure 4. Exploration of 1,2,4-triazole-containing diarylpyrazolyl carboxamide series **9.**

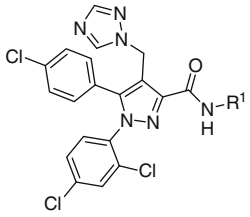
tial results are shown in Table 1. The structure–activity relationship (SAR) work presented in Table 1 was performed with the 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide. Initial SAR studies were performed with alkyls, carbocycles, and piperidine derivatives. Aryl or heteroaryl groups were not attempted for the region, since our previous study exhibited that a phenyl or heteroaryls such as furan, thiophene, pyridine or pyrazine did not appear to be tolerated, showing dramatic decrease in binding affinity to rCB1 receptor.[17] Substitution of the NH_2 with piperidin-1-yl resulted in a slight improvement over rimonabant (**1**) in binding affinity against a rat CB1 receptor (IC_{50} = 3.83 nM for **19a** vs. IC_{50} = 4.53 nM for **1**), implying that there might be indeed promising structure–activity relationship (SAR) potential via incorporation of 1,2,4-triazolylmethyl moiety onto the pyrazole 3-carboxamide. For cyclic analogues, the size of the carbocycle appears to affect binding affinity. Thus, six-membered ring (**21a**) is slightly more potent than the corresponding five- or seven-membered carbocycle (**20a** and **22a**). Addition of methyl group alpha to cyclohexyl ring diminished binding affinity to rCB1 receptor in sixfold (**23a**, IC_{50} = 22.8 nM vs **21a**, IC_{50} = 3.77 nM), suggesting that there might be a size requirement for the alkyl carboxamide region to bind with high affinity to the rCB1 receptor. Introduction of methyl group or dimethyl group on cyclohexyl or piperidinyl moiety has a three- to fivefold impact on rCB1 binding affinities (**24**–**28**). Moreover, hydroxycyclohexyl **29** demonstrated a 16-fold loss of activity, implying that polar functionality in the region is not tolerated. For acyclic analogues, branched aliphatic chains were prepared and evaluated, since our prior work showed that branched aliphatic chains are usually more potent than the corresponding non-branched counterparts.[17] Substitution with *tert*-butyl **30a** or *tert*-pentyl **31a** exhibited nanomolar activity against rCB1 receptor (IC_{50} = 4.9 nM for **30a** and IC_{50} = 3.01 nM for **31a**). As the size of the carbon chain is increased, a slight decrease in binding affinity is observed (**32** and **33**). Similarly, 1-(trifluoromethyl)cyclopropyl **34a** or 1-(trifluoromethyl)cyclobutyl **35a** which possibly acts as a *gem*-dimethyl surrogate, also showed nanomolar level of activity against rCB1 receptor (IC_{50} = 4.5 nM for **34a** and IC_{50} = 4.67 nM for **35a**). Trifluoromethylcyclopropyl **34a** should confer lower lipophilicity and possibly enhanced water solubility. Acylhydrazides **36**, **37** only showed modest rCB1 receptor binding affinity, respectively, indicating that additional carbonyl functionality in **36**, **37** does not appear to be well tolerated. Moreover, substitution with (1-ethylpyrrolidin-2-yl)methyl **38** demonstrated a dramatic loss of activity, suggesting that isolated amine functionality in the region is not tolerated. Additionally, substitution with polar piperidine moiety[14] **39** demonstrated loss of activity in two orders of magnitude against rCB1 receptor (IC_{50} = 3.83 nM for **19a** and IC_{50} = 878 nM for **39a**), indicating the importance of lipophilicity at this region for the improvement of in vitro activity.

It was encouraging to observe that significant rCB1 receptor binding affinity was already evident in this series. At this juncture, we proceeded to explore the effect of halogen atoms on diphenyl rings connected to the pyrazole against rCB1 receptor binding affinities. We focused on branched alkyls, trifluoromethylcyclopropyl, trifluoromethylcyclobutyl and cyclic moieties including cyclohexyl, cycloheptyl or piperidine for the SAR studies as shown in Table 2. First, the compounds lacking the para chlorine atom at the N-1 pyrazole phenyl substituent were prepared and evaluated. Comparison of des-chloro analogues **34b** (IC_{50} = 4.75 nM) and **35b** (IC_{50} = 5.14 nM) with **34a** (IC_{50} = 4.5 nM) and **35a** (IC_{50} = 4.67 nM), respectively, exhibited that there would be little impact on their in vitro profiles. Next, in order to explore the effect of substitution of 5-(4-chlorophenyl)pyrazole with the corresponding 5-(4-bromophenyl)pyrazole, a small set of bromo dichloro analogues were prepared. Comparison of bromo dichloro analogues **34c** (IC_{50} = 3.31 nM) and **35c** (IC_{50} = 3.87 nM) with **34a** (IC_{50} = 4.5 nM) and **35a** (IC_{50} = 4.67 nM), respectively, demonstrated a marginally improved binding affinity against rCB1 receptor. Subsequently, bromo des-chloro (R^1 = Br, R^2 = H in Table 2) analogues were prepared and evaluated. The structure–activity relationship in this set of analogues was less obvious, but branched chains (**34d**, **35d**) appear to diminish rCB1 receptor binding affinity, while cyclic analogue **19c** retains similar level of binding affinity (IC_{50} = 5.23 nM). Interestingly, the best result for bromo des-chloro analogues was obtained when cyclohexyl was substituted (**21d**, IC_{50} = 1.6 nM), indicating that cyclohexyl moiety in this analogue binds optimally to a hydrophobic pocket consisting of residues Phe174, Phe177, Phe189, Val263, Tyr365 and Phe379.[17,18b]



Scheme 1. Reagents: (a) NBS, AIBN, CCl_4; (b) 1,2,4-triazole, Cs_2CO_3, DMF; (c) LiOH, THF–H_2O; (d) (i) $(COCl)_2$, (ii) NHRR′, Et_3N, CH_2Cl_2.

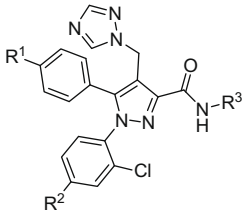
Table 1
Structures and binding affinities of selected ligands to rat CB1 receptors[a,b]



Compound	R^1	Receptor affinity (IC_{50}, nM) rCB1
1		4.53
6		7.59
19a	Piperidin-1-yl	3.83
20a	Cyclopentyl	6.9
21a	Cyclohexyl	3.77
22a	Cycloheptyl	11.2
23a	Cyclohexylmethyl	22.8
24	(2,6-Dimethyl)piperidin-1-yl	11.4
25	*cis*-4-Methylcyclohexyl	17.1
26	*trans*-4-Methylcyclohexyl	14.2
27	*cis*-2-Methylcyclohexyl	18.3
28	*trans*-2-Methylcyclohexyl	12.9
29	*trans*-2-Hydroxycyclohexyl	60.7
30a	*t*-Butyl	4.9
31a	*t*-Pentyl	3.01
32a	3,3-Dimethylbutan-2-yl	8.44
33	2-Ethylhexyl	20.2
34a	1-(Trifluoromethyl)cyclopropyl	4.5
35a	1-(Trifluoromethyl)cyclobutyl	4.67
36	Cyclohexylcarboxamido	189
37	Trifluoromethylcyclopropylcarboxamido	126
38	1-Ethylpyrrolidinylmethyl	4020
39	(4-Carboxamido-4-ethylamino)piperidin-1-yl	878

[a] These data were obtained by single determinations.
[b] Compound **1** was evaluated to have CB1 binding affinity via in-house assay.

Table 2
Structures and binding affinities of selected ligands to rat CB1 receptors[a,b]



Compound	R^1	R^2	R^3	Receptor affinity (IC_{50}, nM) rCB1
1				4.53
21b	Cl	H	Cyclohexyl	6.6
22b	Cl	H	Cycloheptyl	9.7
23b	Cl	H	Cyclohexylmethyl	12.2
34b	Cl	H	1-(Trifluoromethyl)cyclopropyl	4.75
35b	Cl	H	1-(Trifluoromethyl)cyclobutyl	5.14
31b	Cl	H	t-Pentyl	11.9
32b	Cl	H	3,3-Dimethylbutan-2-yl	6.22
19b	Br	Cl	Piperidin-1-yl	5.11
40	Br	Cl	Homopiperidin-1-yl	8.23
21c	Br	Cl	Cyclohexyl	4.38
22c	Br	Cl	Cycloheptyl	8.49
23c	Br	Cl	Cyclohexylmethyl	20.5
34c	Br	Cl	1-(Trifluoromethyl)cyclopropyl	3.31
35c	Br	Cl	1-(Trifluoromethyl)cyclobutyl	3.87
30b	Br	Cl	*t*-Butyl	2.9
31c	Br	Cl	*t*-Pentyl	3.67
32c	Br	Cl	3,3-Dimethylbutan-2-yl	4.1
19c	Br	H	Piperidin-1-yl	5.23
21d	Br	H	Cyclohexyl	1.6
22d	Br	H	Cycloheptyl	2.7
34d	Br	H	1-(Trifluoromethyl)cyclopropyl	9.15
35d	Br	H	1-(Trifluoromethyl)cyclobutyl	7.48
30c	Br	H	*t*-Butyl	7.9
31d	Br	H	*t*-Pentyl	8.99
32d	Br	H	3,3-Dimethylbutan-2-yl	6.0
41	Br	H	1-Cyanocyclopropyl	19.6

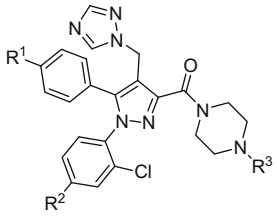
[a] These data were obtained by single determinations.
[b] Compound **1** was evaluated to have CB1 binding affinity via in-house assay.

Next, we decided to investigate piperazine analogues as carboxamide substituents since it has structural similarity to piperidine or cyclohexyl moiety and presents a cyclic motif which has convenient synthetic access to a variety of analogues. The distal nitrogen atom (4 N) of the piperazine ring provided the desired site for SAR work in Table 3. Substitution of NH in piperazine with small alkyl such as methyl or ethyl showed a dramatic lost of binding potency against rCB1 (**42b**, IC_{50} = 961 nM; **48a**, IC_{50} = 1050 nM). However, substitution with a phenyl group as in **43b** (IC_{50} = 11.5 nM) significantly altered the in vitro profile of the simple *N*-alkylamines. Replacement of a phenyl with a substituted phenyl even increased binding potency against rCB1 receptor as displayed in 3-chlorophenyl **44b** (IC_{50} = 4.08 nM) or 2,3-dimethylphenyl **46b** (IC_{50} = 6.09 nM). Substitution of the NH in piperazine with heterocycle such as 2-pyrimidyl did not improve the binding potency against rCB1 receptor (**47a**, IC_{50} = 56.0 nM), implying the importance of non-polar moiety in order to optimally bind to a hydrophobic area of rCB1 receptor. The in vitro profile of the piperazine-based ligands was quite sensitive to the changes in both steric and electronic environments. Among the compounds tested in this piperazine series, bromophenyl des-chlorophenyl compounds **44d**, **45c**, and **46d** showed the best binding affinity against rCB1 in this particular series to date (IC_{50} = 2.07–2.28 nM).

Following the prior examples in Table 1–3, we undertook substitution of NH with benzyl, or more lipophilic benzyl analogues such as methylbenzyl and *gem*-dimethylbenzyl groups as well as spiro-cyclopropylphenyl for the focused SAR studies around 1,2,4-triazole-containing diarylpyrazolyl carboxamide as shown in Table 4. Our previous studies illustrated usefulness of *gem*-dimethyl and spiro-cyclopropyl groups at the lipophilic region for the in vitro and in vivo profile of the CB1 ligands.[17] Substitution of benzyl with *gem*-dimethylbenzyl improved binding potency against rCB1 receptor in about threefold (IC_{50} = 7.4 nM for **50a**). Substitution of *gem*-dimethylbenzyl with 4-chloro-α,α-dimethylbenzyl **51a** ameliorated rCB1 receptor binding potency in twofold (IC_{50} = 3.3 nM). Spiro-cyclopropyl groups such as phenylcyclopropyl **54a** and (4-chlorophenyl)cyclopropyl **55a** did not significantly affect binding affinity against rCB1, respectively. Heteroaryl groups such as 2-pyridylmethyl **56a** diminished binding potency against rCB1 receptor, suggesting the importance of lipophilicity at the region.

Next, the des-chloro compounds on the N1 phenyl group in the series were prepared and evaluated. As shown in **52b** and **53b**, these ligands did not lead to any loss of affinity, but rather enhanced their binding potency (IC_{50} = 1.8 nM for **52b**; IC_{50} = 2.0 nM for **53b**). This phenomenon was observed in 5-(4-bromophenyl)-pyrazole series as well. Thus, 4-bromo-α-methylbenzyl **52d** demonstrated the best binding affinity in the series prepared to date (IC_{50} = 1.1 nM). Binding affinity was also measured for the CB2 cannabinoid receptor expressed in chinese hamster ovary (CHO) cells, employing [^{3}H]-WIN55,212-2 as a radioligand.[22] Virtually all of our triazole-containing diarylpyrazole carboxamides were devoid of noticeable activity in this hCB2, resulting in excellent selectivity for rCB1 over hCB2 for these analogues (i.e., **52c**, hCB2/rCB1 = 4629; **52d**, hCB2/rCB1 = 1627).

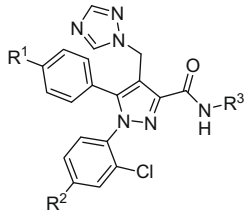
Table 3
Structures and binding affinities of selected ligands to rat CB1 and human CB2 receptors and hCB2/rCB1 selectivity of the ligands[a,b]



Compound	R^1	R^2	R^3	Receptor affinity (IC_{50}, nM)		hCB2/rCB1 selectivity
				rCB1	hCB2	
1				4.53	1760	389
21d				1.6	4060	2538
42a	Cl	Cl	Methyl	1420	—	—
43a	Cl	Cl	Phenyl	8.88	—	—
44a	Cl	Cl	3-Chlorophenyl	7.33	—	—
45a	Cl	Cl	2,3-Dichlorophenyl	5.50	—	—
46a	Cl	Cl	2,3-Dimethylphenyl	11.5	—	—
47a	Cl	Cl	2-Pyrimidyl	56.0	—	—
42b	Cl	H	Methyl	961	—	—
48a	Cl	H	Ethyl	1050	—	—
43b	Cl	H	Phenyl	11.5	—	—
44b	Cl	H	3-Chlorophenyl	4.08	—	—
46b	Cl	H	2,3-Dimethylphenyl	6.09	—	—
42c	Br	Cl	Methyl	1340	—	—
48b	Br	Cl	Ethyl	285	—	—
43c	Br	Cl	Phenyl	12.5	—	—
44c	Br	Cl	3-Chlorophenyl	7.22	—	—
45b	Br	Cl	2,3-Dichlorophenyl	5.74	—	—
46c	Br	Cl	2,3-Dimethylphenyl	3.8	—	—
47b	Br	Cl	2-Pyrimidyl	27.7	—	—
42d	Br	H	Methyl	901	—	—
48c	Br	H	Ethyl	303	—	—
43d	Br	H	Phenyl	8.01	—	—
44d	Br	H	3-Chlorophenyl	2.28	296	130
45c	Br	H	2,3-Dichlorophenyl	2.22	582	262
46d	Br	H	2,3-Dimethylphenyl	2.07	547	264
47c	Br	H	2-Pyrimidyl	22.3	—	—

[a] These data were obtained by single determinations.
[b] Compound **1** was evaluated to have CB1 binding affinity via in-house assay.

Table 4
Structures and binding affinities of selected ligands to rat CB1 and human CB2 receptors and hCB2/rCB1 selectivity of the ligands[a,b]



Compound	R^1	R^2	R^3	Receptor affinity (IC_{50}, nM)		hCB2/rCB1 selectivity
				rCB1	hCB2	
1				4.53	1760	389
49a	Cl	Cl	Benzyl	19.2	—	—
50a	Cl	Cl	α,α-Dimethylbenzyl	7.4	—	—
51a	Cl	Cl	4-Chloro-α,α-dimethylbenzyl	3.33	—	—
52a	Cl	Cl	4-Bromo-α-methylbenzyl	2.6	—	—
53a	Cl	Cl	2,4-Dichloro-α-methylbenzyl	2.6	—	—
54a	Cl	Cl	Phenylcyclopropyl	5.1	—	—
55a	Cl	Cl	(4-Chlorophenyl)cyclopropyl	5.09	—	—
56a	Cl	Cl	2-Pyridylmethyl	74.8	—	—
57	Cl	Cl	(4-Chlorophenyl)cyclopropyl-carboxamido	44.5	—	—
49b	Cl	H	Benzyl	14.1	—	—
50b	Cl	H	α,α-dimethylbenzyl	12.9	—	—
51b	Cl	H	4-Chloro-α,α-dimethylbenzyl	7.70	—	—
52b	Cl	H	4-Bromo-α-methylbenzyl	1.8	3510	1950
53b	Cl	H	2,4-Dichloro-α-methylbenzyl	2.0	3330	1665
54b	Cl	H	Phenylcyclopropyl	5.81	—	—
55b	Cl	H	(4-Chlorophenyl)cyclopropyl	9.03	—	—
49c	Br	Cl	Benzyl	13.0	—	—
51c	Br	Cl	4-Chlroro-α,α-dimethylbenzyl	2.99	—	—
52c	Br	Cl	4-Bromo-α-methylbenzyl	1.4	6480	4629
53c	Br	Cl	2,4-Dichloro-α-methylbenzyl	2.2	—	—
54c	Br	Cl	Phenylcyclopropyl	7.86	—	—
55c	Br	Cl	(4-Chlorophenyl)cyclopropyl	2.8	—	—
50c	Br	H	α,α-Dimethylbenzyl	6.1	—	—
52d	Br	H	4-Bromo-α-methylbenzyl	1.1	1790	1627
53d	Br	H	2,4-Dichloro-α-methylbenzyl	2.2	2420	1100
54d	Br	H	Phenylcyclopropyl	1.98	3200	1616
55d	Br	H	(4-Chlorophenyl)cyclopropyl	1.7	2570	1512
56b	Br	H	2-Pyridylmethyl	63.4	—	—

[a] These data were obtained by single determinations.
[b] Compound **1** was evaluated to have CB1 binding affinity via in-house assay.

The analogues **52c**, **52d** were also shown to be highly potent in the CHO-hCB1R-luciferase assay,[27,28] with IC_{50} values being 28.2 nM, 2.51 nM, respectively (for comparison, IC_{50} = 108 nM for rimonabant), thus demonstrating inverse agonism activity of this series. In vivo efficacy was evaluated on DIO (diet-induced obesity) mice in order to confirm proof-of-concept on animal model of the current scaffold.[25] Male C57BL/6 J mice weighing over 38 g were housed one per cage on a 12-/12-h light/dark cycle, had free access to food (rodent sterilized diet) and water, and were experimentally native before testing. Mice were allowed at least 7 days to habituate to the experimental room prior to testing, and testing was conducted during the light period. Mice were maintained and experiments were conducted in accordance with the Institutional Animal Care. The selected compounds **52c** and **52d** were prepared fresh daily by dissolving it in de-ionized water containing 10% DMSO. By oral administration, animals received at a volume of 10 mL/kg for 7 days. All control animals received 10% DMSO dissolved in de-ionized water. The vehicles 10% DMSO-treated groups were comprised of five mice in oral test. There were five mice in each of the other experimental groups (n = 5 in each group). By oral administration, the losing weight was checked everyday for the drug treated group and the control group.[17,18b]

Figure 5 shows chronic effects of compounds **52c** and **52d** in DIO mice. Body weight change from day 0 was observed on all days at 10 mg/kg of example **52c** compound, at 10 mg/kg of example **52d** compound. Each value is the mean ± S.E.M. of 5 mice. $^*P$ <0.05 versus corresponding vehicle (ANOVA with Dunnett's test). Figure 5 shows that compound **52d** is substantially more efficacious in in vivo efficacy study on the DIO mice model (15.04 ± 2.00% reduction in body weight after 7 days), while **52c** reduces body weight moderately (7.99 ± 0.98%). This is a notable piece of information that this series of compounds are indeed CB1 receptor antagonists or inverse agonists.

4. Conclusion

We investigated a series of 1,2,4-triazole-containing diarylpyrazolyl carboxamides based on the 1,5-diarylpyrazole template of rimonabant for their binding affinity against rCB1 and hCB2 receptors. We have identified a novel series of small molecule rCB1 ligands that demonstrate binding affinity superior to that of reported rCB1 antagonists. Several compounds in this series exhibited potent rCB1 receptor binding affinities, confirming the hypothesis that incorporation of 1,2,4-triazolylmethyl moiety onto the pyrazole 3-carboxamide could lead to more potent CB1 receptor antagonists. Of note is **52d** was shown to possess the highest

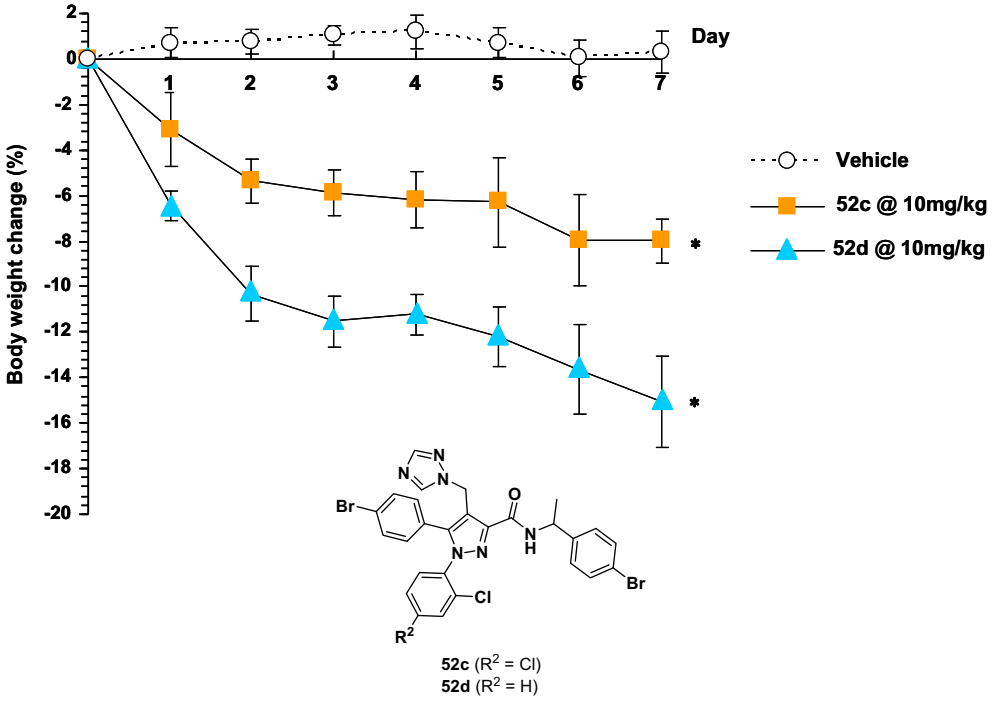


Figure 5. In vivo efficacy study of compounds **52c** and **52d** on DIO mice.

binding affinity with a significant antiobesity effect in this 1,2,4-triazole-containing diarylpyrazolyl carboxamide series prepared to date. Importantly, these analogues also demonstrate excellent selectivity for rCB1 over hCB2. The analogue **52d** was shown to be highly potent in the CHO-hCB1R-luciferase assay, with IC_{50} value being 2.51 nM, thus demonstrating inverse agonism activity of this series. Therefore, diarylpyrazolyl carboxamide class of compounds bearing a triazolylmethyl as the optimal side chain possesses a therapeutic potential as a CB1 receptor antagonist or inverse agonist for the treatment of obesity. The structural unit of triazolylmethyl might be considered to be included in new design of CB1 receptor antagonists based on diarylpyrazole scaffold.

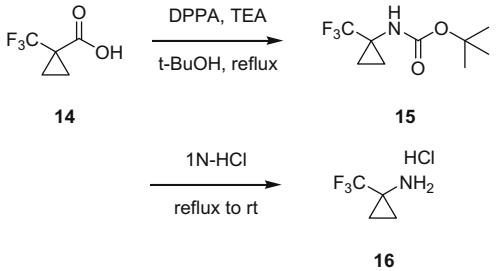
5. Experimental

5.1. General methods

All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated. Microwave reaction was conducted with a Biotage Initiator™ microwave reactor. ^{1}H NMR spectra were recorded on 400 MHz Fourier Transform-Nuclear Magnetic Resonance; Varian, 400-MR. Chemical shifts were expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Mass spectra were obtained with either a Micromass, Quattro LC Triple Quadruple Tandem Mass Spectometer, ESI or Agilent, 1200LC/MSD, system equipped with XTerra® MS C_{18} 3.5 μm 2.1 × 50 mm column with a 12 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O with 0.05% TFA. For preparative HPLC, ca 100 mg of a product was injected in 1 mL of DMSO onto a SunFire™ Prep C_{18} OBD 5 μm 19 × 100 mm Column with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O. Biotage® SP1 Flash purification system or Biotage® Isolera™ Flash purification system was used for normal phase column chromatography with ethyl acetate and hexane. Flash chromatography was carried using Merck Silica Gel 60 (230–400 mesh). Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck Silica Gel plates (60F-254), visualized with UV light using a 5% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution.

5.2. Chemistry

5.2.1. Preparation of amines[20]

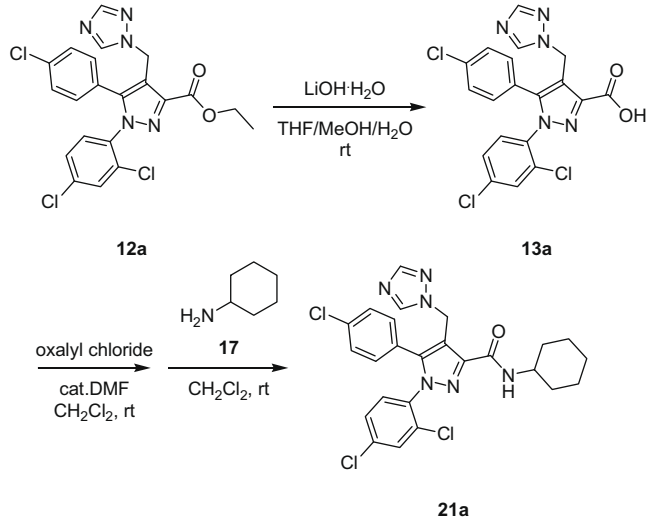


14 **15** **16**

5.2.1.1. *tert*-Butyl 1-(trifluoromethyl)cyclopropylcarbamate (15). To a solution of 1-(trifluoromethyl)cyclopropanecarboxylic acid (**14,** 3.26 g, 21.1 mmol), triethylamine (2.95 mL, 21.1 mmol) in *t*-BuOH (12.5 mL) was added dropwise diphenylphosphoryl azide (5.05 mL, 23.3 mmol) at room temperature. The reaction mixture was stirred at 83 °C for 12 h and then added diethyl ether (50 mL). The mixture was stirred for 2 h and filtered to give a biphasic solution. The ether layer was isolated, and the oily liquid was extracted with ether (25 mL × 4). The combined ether phase was washed with 5% citric acid (25 mL), saturated $NaHCO_3$ solution (15 mL × 2) and saturated NaCl solution (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The obtained product (3.4 g, white solid) was used for the next step without purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (s, 9H), 1.12–1.11 (m, 2H), 0.98–0.96 (m, 2H).

5.2.1.2. 1-(Trifluoromethyl)cyclopropanamine hydrochloride (16). To a mixture of *tert*-butyl 1-(trifluoromethyl)cyclopropylcarbamate (**15**, 3.3 g, 14.65 mmol) in 1 N-HCl (120 mL) was stirred at 100 °C for 2 h and then at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with acetone (25 mL) at 0 °C, and filtered affording 800 mg (23%) of title compound **16** as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (br s, 1H), 1.43–1.39 (m, 2H), 1.29–1.22 (m, 2H); MH+ 126.

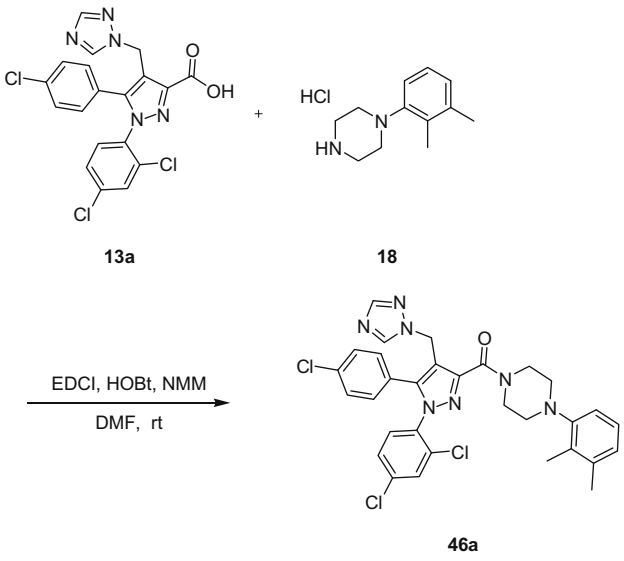
5.2.2. General method I



5.2.2.1. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid (13a). To a solution of ethyl 4-((1*H*-1,2,4-triazol-1-yl)-methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylate[17] (**12a**, 2.37 g, 4.97 mmol) and LiOH·H_2O (625 mg, 14.91 mmol) in THF/CH_3OH/H_2O (20/20/2 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 1 N-HCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The obtained product (2.2 g, white solid) was used for the next step without purification. MH+ 448.

5.2.2.2. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-cyclohexyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (21a). To a mixture of 4-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid (**13a**, 200 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (77 μL, 0.88 mmol) and the catalytic amount of DMF at room temperature and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue (acyl chloride) was diluted with CH_2Cl_2 (10 mL), to which cyclohexylamine (**17**, 150 μL, 1.32 mmol) was added and stirred for 1 h at room temperature. The resultant was concentrated under reduced pressure, diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by preparative HPLC (purification system, Gilson) to provide the title compound (157 mg, 67%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.45–7.40 (m, 3H), 7.36–7.32 (m, 2H), 7.30–7.25 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 5.49 (s, 2H), 3.96–3.87 (m, 1H), 2.01–1.98 (m, 2H), 1.77–1.74 (m, 2H), 1.66–1.60 (m, 2H), 1.45–1.37 (m, 2H), 1.29–1.13 (m, 2H); MH+ 529.

5.2.3. General method II



5.2.3.1. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dimethylphenyl)piperazin-1-yl)methanone (46a). To a mixture of 4-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxylic acid (**13a**, 150 mg, 0.33 mmol), 1-(2,3-dimethylphenyl)piperazine hydrochloride (**18**, 84 mg, 0.43 mmol), EDCI (96 mg, 0.50 mmol) and HOBt (54 mg, 0.40 mmol) in anhydrous DMF (2 mL) was added NMM (221 μL, 2.01 mmol). The reaction mixture was stirred at room temperature for 15 h. The mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, and washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by preparative HPLC (purification system, Gilson) to provide the title compound (150 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (s, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.36–7.34 (m, 2H), 7.30–7.23 (m, 4H), 7.10–7.06 (t, J = 8.0 Hz, 1H), 6.90 (dd, J = 18.0, 8.0 Hz, 2H), 5.40 (s, 2H), 3.92 (m, 4H), 2.91 (m, 2H), 2.75 (m, 2H), 2.25 (d, J = 14.4 Hz, 6H); MH+ 620.

5.2.3.2. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (19a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.89 (s, 1H), 7.72 (br s, 1H), 7.46–7.41 (m, 3H), 7.36–7.23 (m, 4H), 5.44 (s, 2H), 2.93–2.81 (m, 4H), 1.83–1.72 (m, 4H), 1.48–1.37 (m, 2H); MH+ 530

5.2.3.3. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (19b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.10 (br s, 1H), 7.93 (s, 1H), 7.63–7.41 (m, 2H), 7.45–7.42 (d, J = 1.8 Hz, 1H), 7.37–7.26 (m, 4H), 5.44 (s, 2H), 3.15–3.00 (m, 4H), 1.90–1.79 (m, 4H), 1.55–1.46 (m, 2H); MH+ 574.

5.2.3.4. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (19c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.89 (s, 1H), 7.67 (br s, 1H), 7.49–7.43 (m, 3H), 7.39–7.35 (m, 3H), 7.33–

7.29 (m, 2H), 5.47 (s, 2H), 2.83–2.81 (m, 4H), 1.79–1.74 (m, 4H), 1.44–1.42 (m, 2H); MH+ 540.

5.2.3.5. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-cyclopentyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.45 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.26 (m, 2H), 6.89 (d, J = 7.6 Hz, 1H), 5.49 (s, 2H), 4.38–4.33 (m, 1H), 2.09–2.04 (m, 2H), 1.72–1.48 (m, 6H); MH+ 515.

5.2.3.6. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-cyclohexyl-1*H*-pyrazole-3-carboxamide (21b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.44–7.37 (m, 4H), 7.36–7.30 (m, 4H), 6.87 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 3.94–3.91 (m, 1H), 2.02–1.98 (m, 2H), 1.77–1.74 (m, 2H), 1.43–1.37 (m, 2H), 1.29–1.16 (m, 4H); MH+ 495.

5.2.3.7. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-cyclohexyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (21c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.88 (s, 1H), 7.52–7.49 (m, 2H), 7.45 *d*, J = 2.4 Hz, 1H), 7.36–7.25 (m, 4H), 6.84 (d, J = 8.4 Hz, 1H), 5.49 (s, 2H), 3.96–3.87 (m, 1H), 2.17–1.99 (m, 2H), 1.97–1.73 (m, 2H), 1.66–1.63 (m, 2H), 1.47–1.36 (m, 2H), 1.29–1.13 (m, 2H); MH+ 573.

5.2.3.8. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-cyclohexyl-1*H*-pyrazole-3-carboxamide (21d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.49–7.43 (m, 3H), 7.40–7.36 (m, 1H), 7.35–7.30 (m, 4H), 6.88 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 3.96–3.89 (m, 1H), 2.05–1.98 (m, 2H), 1.77–1.73 (m, 2H), 1.66–1.63 (m, 2H), 1.51–1.36 (m, 2H), 1.28–1.13 (m, H); MH+ 539.

5.2.3.9. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-cycloheptyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (22a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.90 (s, 1H), 7.45 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.26 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 5.49 (s, 2H), 4.11–4.10 (m, 1H), 2.05–1.99 (m, 2H), 1.70–1.53 (m, 10H); MH+ 543.

5.2.3.10. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-cycloheptyl-1*H*-pyrazole-3-carboxamide (22b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.44–7.37 (m, 4H), 7.36–7.30 (m, 4H), 6.94 (d, J = 8.0 Hz, 1H), 5.51 (s, 2H), 4.10 (m, 1H), 2.05–1.99 (m, 2H), 1.70–1.53 (m, 10H); MH+ 509.

5.2.3.11. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-cycloheptyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (22c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 2.0 Hz, 1H), 7.35–7.25 (m, 4H), 6.91 (d, J = 8.4 Hz, 1H), 5.49 (s, 2H), 4.11–4.09 (m, 1H), 2.04–1.98 (m, 2H), 1.70–1.63 (m, 4H), 1.55–1.52 (m, 6H); MH+ 587.

5.2.3.12. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-cycloheptyl-1*H*-pyrazole-3-carboxamide (22d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92 (s, 1H), 7.51–7.42 (m, 3H), 7.40–7.38 (m, 1H), 7.36–7.29 (m, 4H), 6.94 (d, J = 8.0 Hz, 1H), 5.53 (s, 2H), 4.11–4.10 (m, 1H), 2.05–1.99 (m, 2H), 1.70–1.67 (m, 4H), 1.54–1.48 (m, 6H); MH+ 553.

5.2.3.13. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-(cyclohexylmethyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (23a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.90 (s, 1H), 7.42–7.40 (m, 1H), 7.36–7.34 (m, 2H), 7.32–7.25 (m, 2H), 7.03 (m, 1H), 5.50 (s, 2H), 3.26 (t, J = 6.4 Hz, 2H), 1.78–1.66 (m, 4H), 1.56–1.54 (m, 1H), 1.28–1.18 (m, 4H), 1.02–0.96 (m, 2H); MH+ 543.

5.2.3.14. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(cyclohexylmethyl)-1*H*-pyrazole-3-carboxamide (23b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.90 (s, 1H), 7.46–7.37 (m, 4H), 7.37–7.27 (m, 4H), 7.06 (m, 1H), 5.52 (s, 2H), 3.28–3.25 (m, 2H), 1.79–1.66 (m, 5H), 1.26–1.19 (m, 2H), 1.03–0.97 (m, 2H); MH+ 509.

5.2.3.15. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-(cyclohexylmethyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (23c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 (s, 1H), 7.53–7.49 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.36–7.24 (m, 5H), 7.02 (t, J = 6.4 Hz, 1H), 5.49 (s, 2H), 3.25 (t, J = 6.8 Hz, 2H), 1.78–1.65 (m, 4H), 1.57–1.50 (m, 2H), 1.29–1.11 (m, 3H), 1.02–0.92 (m, 2H); MH+ 587.

5.2.3.16. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(2,6-dimethylpiperidin-1-yl)-1*H*-pyrazole-3-carboxamide (24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.87 (s, 1H), 7.47 (m, 2H), 7.38–7.36 (m, 2H), 7.34–7.24 (m, 3H), 7.07 (m, 1H), 5.49 (s, 2H), 2.38 (m, 2H), 1.70–1.63 (m, 4H), 1.32 (m, 2H), 1.11 (d, J = 6.0 Hz, 6H); MH+ 558.

5.2.3.17. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1*S*,4*S*)-4-methylcyclohexyl)-1*H*-pyrazole-3-carboxamide (25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 (s, 1H), 7.46–7.40 (m, 3H), 7.36–7.27 (m, 3H), 7.06 (d, J = 8.0 Hz, 1H), 5.49 (s, 2H), 4.16–4.11 (m, 1H), 1.76–1.60 (m, 5H), 1.28–1.21 (m, 4H), 0.91 (d, J = 6.4 Hz, 3H); MH+ 543.

5.2.3.18. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1*R*,4*R*)-4-methylcyclohexyl)-1*H*-pyrazole-3-carboxamide (26). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.88 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.41–7.39 (m, 2H), 7.35–7.33 (m, 2H), 7.31–7.25 (m, 1H), 6.77 (d, J = 8.4 Hz, 1H), 5.48 (s, 2H), 3.90–3.80 (m, 1H), 2.04–2.01 (m, 2H), 1.75–1.72 (m, 2H), 1.36–1.30 (m, 1H), 1.28–1.18 (m, 2H), 1.14–1.04 (m, 2H), 0.90 (d, J = 6.4 Hz, 3H); MH+ 543.

5.2.3.19. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1*R*,2*S*)-2-methylcyclohexyl)-1*H*-pyrazole-3-carboxamide (27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.88 (s, 1H), 7.45 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.26 (m, 2H), 6.74 (d, J = 9.2 Hz, 1H), 5.49 (dd, J = 23.2 Hz, 2H), 3.64–3.61 (m, 1H), 2.03–2.00 (m, 1H), 1.80–1.67 (m, 4H), 1.40–1.33 (m, 2H), 1.25–1.12 (m, 3H), 0.95 (d, J = 6.8 Hz, 3H); MH+ 543.

5.2.3.20. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1*R*,2*R*)-2-methylcyclohexyl)-1*H*-pyrazole-3-carboxamide (28). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.45 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.25 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 5.49 (dd, J = 24 Hz, 2H), 4.24–4.20 (m, 1H), 2.00–1.88 (m, 1H), 1.77–1.46 (m, 6H), 1.37–1.26 (m, 3H), 0.91 (d, J = 6.8 Hz, 3H); MH+ 543.

5.2.3.21. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1*S*,2*S*)-2-hydroxycyclohexyl)-1*H*-pyrazole-3-carboxamide (29). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.89 (s, 1H), 7.46–7.40 (m, 3H), 7.36–7.32 (m, 2H), 7.30–7.26 (m, 2H), 6.95 (d, J = 7.6 Hz, 1H), 5.58 (d, J = 14.0 Hz, 1H), 5.56 (d, J = 14.4 Hz, 1H), 3.86–3.79 (m, 1H), 3.43 (td, J = 10.0, 4.4 Hz, 1H), 2.17–2.02 (m, 2H), 1.78–1.73 (m, 2H), 1.45–1.24 (s, 4H); MH+ 545.

5.2.3.22. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-*tert*-butyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (30a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.86 (s, 1H), 7.42 (m, 1H), 7.37–7.29 (m, 4H), 7.27–7.23 (m, 2H), 6.79 (s, 1H), 5.48 (s, 2H), 1.43 (s, 9H); MH+ 503.

5.2.3.23. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-*tert*-butyl-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (30b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.88 (s, 1H), 7.51–7.49 (m, 2H), 7.44 (d, J = 2.0 Hz, 1H), 7.33–7.29 (m, 2H), 7.27–7.25 (m, 2H), 6.81 (br s, 1H), 5.30 (s, 2H), 1.45 (s, 9H); MH+ 547.

5.2.3.24. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-*tert*-butyl-1-(2-chlorophenyl)-1*H*-pyrazole-3-carboxamide (30c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.88 (s, 1H), 7.48–7.42 (m, 3H), 7.40–7.34 (m, 1H), 7.33–7.30 (m, 4H), 6.84 (s, 1H), 5.51 (s, 2H), 1.46 (s, 9H); MH+ 513.

5.2.3.25. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-*tert*-pentyl-1*H*-pyrazole-3-carboxamide (31a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.86 (s, 1H), 7.42 (m, 1H), 7.37–7.29 (m, 4H), 7.27–7.23 (m, 2H), 6.71 (s, 1H), 5.47 (s, 2H), 1.81 (q, J = 7.6 Hz, 2H), 1.38 (s, 6H), 0.87 (t, J = 7.2 Hz, 3H); MH+ 517.

5.2.3.26. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-*tert*-pentyl-1*H*-pyrazole-3-carboxamide (31b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.42 (m, 1H), 7.40–7.30 (m, 7H), 6.77 (s, 1H), 5.51 (s, 2H), 1.83 (q, J = 7.6 Hz, 2H), 1.41 (s, 6H), 0.90 (t, J = 7.6 Hz, 3H); MH+ 483.

5.2.3.27. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-*tert*-pentyl-1*H*-pyrazole-3-carboxamide (31c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.53–7.50 (m, 2H), 7.45 (d, J = 2.0 Hz, 1H), 7.34–7.26 (m, 4H), 6.73 (br s, 1H), 5.50 (s, 2H), 1.83 (q, J = 7.6 Hz, 2H), 1.41 (s, 6H), 0.90 (d, J = 7.6 Hz, 3H); MH+ 561.

5.2.3.28. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-*tert*-pentyl-1*H*-pyrazole-3-carboxamide (31d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.90 (s, 1H), 7.49–7.42 (m, 3H), 7.34–7.27 (m, 4H), 6.77 (s, 1H), 5.51 (s, 2H), 1.84 (q, J = 7.2 Hz, 2H), 1.41 (s, 6H), 0.90 (t, J = 7.2 Hz, 3H); MH+ 527.

5.2.3.29. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(3,3-dimethylbutan-2-yl)-1*H*-pyrazole-3-carboxamide (32a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.86 (s, 1H), 7.43 (m, 1H), 7.40–7.38 (m, 2H), 7.34–7.32 (m, 2H), 7.29–7.23 (m, 2H), 6.84 (d, J = 10.0 Hz, 1H), 5.47 (dd, J = 24.8 Hz, 2H), 4.04–4.00 (m, 1H), 1.13 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H); MH+ 531.

5.2.3.30. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(3,3-dimethylbutan-2-yl)-1*H*-pyrazole-3-carboxamide (32b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.45–7.35 (m, 4H), 7.34–7.29 (m, 4H), 6.89 (d, J = 10.0 Hz, 1H), 5.51 (dd, J = 25.6 Hz, 2H), 4.09–4.01 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.95 (s, 9H); MH+ 497.

5.2.3.31. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(3,3-dimethylbutan-2-yl)-1*H*-pyrazole-3-carboxamide (32c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 (s, 1H), 7.51 (d, J = 7.2 Hz, 2H), 7.46 (br s, 1H), 7.35–7.25 (m, 4H), 6.86 (d, J = 10.0 Hz, 1H), 5.53 (d, J = 14.4 Hz, 1H), 5.47 (d, J = 14.0 Hz, 1H), 4.07–4.00 (m, 1H), 1.15 (d, J = 6.0 Hz, 3H), 0.94 (s, 9H); MH+ 575.

5.2.3.32. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(3,3-dimethylbutan-2-yl)-1*H*-pyrazole-3-carboxamide (32d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (s, 1H), 7.49–7.43 (m, 3H), 7.40–7.29 (m, 4H), 6.89 (d, J = 9.6 Hz, 1H), 5.54 (d, J = 14.0 Hz, 1H), 5.48 (d, J = 14.0 Hz, 1H), 4.09–4.02 (m, 1H), 1.15 (d, J = 6.4 Hz, 2H), 0.95 (s, 9H); MH+ 541.

5.2.3.33. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(2-ethylhexyl)-1*H*-pyrazole-3-carboxamide (33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 (s, 1H), 7.46 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.31–7.24 (m, 2H), 6.92–6.93 (m, 1H), 5.50 (s, 2H), 3.37–3.34 (m, 2H), 1.55–1.52 (m, 1H), 1.40–1.26 (m, 8H), 0.94–0.89 (m, 6H); MH+ 559.

5.2.3.34. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(trifluoromethyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (34a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.46–7.43 (m, 4H), 7.37–7.35 (m, 2H), 7.33–7.26 (m, 1H), 5.47 (s, 2H), 1.43–1.35 (m, 2H), 1.21 (m, 2H); MH+ 555.

5.2.3.35. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(1-(trifluoromethyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (34b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.89 (s, 1H), 7.46–7.41 (m, 4H), 7.36–7.32 (m, 4H), 5.48 (s, 2H), 1.35 (m, 2H), 1.21 (m, 2H); MH+ 521.

5.2.3.36. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(trifluoromethyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (34c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.42 (br s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 7.27 (d, J = 6.8 Hz, 1H), 5.46 (s, 2H), 1.43–1.39 (m, 2H), 1.26–1.25 (m, 2H); MH+ 599.

5.2.3.37. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-(trifluoromethyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (34d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.89 (s, 1H), 7.50–7.43 (m, 4H), 7.41–7.29 (m, 5H), 5.48 (s, 2H), 1.42–1.39 (m, 2H), 1.21–1.19 (m, 2H); MH+ 565.

5.2.3.38. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(trifluoromethyl)cyclobutyl)-1*H*-pyrazole-3-carboxamide (35a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.90 (s, 1H), 7.46–7.42 (m, 3H), 7.38–7.33 (m, 2H), 7.31–7.27 (m, 1H), 7.09 (s, 1H), 5.48 (s, 2H), 2.68–2.56 (m, 4H), 2.11–2.03 (m, 2H); MH+ 569.

5.2.3.39. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(1-(trifluoromethyl)cyclobutyl)-1*H*-pyrazole-3-carboxamide (35b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.90 (s, 1H), 7.45–7.37 (m, 4H), 7.34–7.30 (m, 4H), 5.49 (s, 2H), 2.68–2.56 (m, 4H), 2.11–2.02 (m, 2H); MH+ 535.

5.2.3.40. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(trifluoromethyl)cyclobutyl)-1*H*-pyrazole-3-carboxamide (35c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.89 (s, 1H), 7.53–7.50 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.37–7.27 (m, 4H), 7.08 (br s, 1H), 5.47 (s, 2H), 2.68–2.56 (m, 4H), 2.11–2.02 (m, 2H); MH+ 613.

5.2.3.41. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-(trifluoromethyl)cyclobutyl)-1*H*-pyrazole-3-carboxamide (35d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.89 (s, 1H), 7.49–7.47 (m, 2H), 7.47–7.43 (m, 1H), 7.41–

7.31 (m, 5H), 7.12 (br s, 1H), 2.68–2.56 (m, 4H), 2.10–2.02 (m, 2H); MH+ 579.

5.2.3.42. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*′-(cyclohexanecarbonyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carbohydrazide (36). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 9.17 (s, 1H), 8.60 (s, 1H), 8.26 (s, 1H), 7.44–7.27 (m, 7H), 5.53 (s, 2H), 2.39–2.22 (m, 1H), 1.96–1.63 (m, 5H), 1.59–1.19 (m, 6H); MH+ 572.

5.2.3.43. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*′-(1-(trifluoromethyl)cyclopropanecarbonyl)-1*H*-pyrazole-3-carbohydrazide (37). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 9.01 (s, 1H), 8.51 (s, 1H), 8.23 (s, 1H), 7.45–7.26 (m, 7H), 5.59 (s, 2H), 1.58–1.51 (m, 2H), 1.39–1.33 (m, 2H); MH+ 598.

5.2.3.44. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-((1-ethylpyrrolidin-2-yl)methyl)-1*H*-pyrazole-3-carboxamide (38). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (m, 1H), 7.40–7.34 (m, 4H), 7.29 (m, 2H), 5.47 (dd, *J* = 17.2, 2H), 3.75–3.70 (m, 1H), 3.49 (m, 2H), 3.00 (m, 2H), 2.60–2.48 (m, 2H), 1.85–1.74 (m, 4H), 1.18 (m, 3H); MH+ 558.

5.2.3.45. 1-(4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carbonyl)-4-(ethylamino)piperidine-4-carboxamide (39). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.92 (s, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.37–7.34 (m, 2H), 7.29–7.26 (m, 3H), 7.24–7.22 (m, 1H), 5.46 (d, *J* = 14.4 Hz, 1H), 5.29 (d, *J* = 14.8 Hz, 1H), 3.95–3.87 (m, 2H), 3.79–3.71 (m, 2H), 2.54 (q, *J* = 7.2 Hz, 2H), 1.94–1.88 (m, 4H), 1.13 (t, *J* = 6.8 Hz, 3H); MH+ 601.

5.2.3.46. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-(azepan-1-yl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.06 (br s, 1H), 7.88 (s, 1H), 7.53–7.49 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.39–7.37 (m, 2H), 7.32–7.20 (m, 2H), 5.47 (s, 2H), 3.13–3.11 (m, 4H), 1.75–1.72 (m, 4H), 1.68–1.62 (m, 4H); MH+ 588.

5.2.3.47. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-cyanocyclopropyl)-1*H*-pyrazole-3-carboxamide (41). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.88 (s, 1H), 7.48–7.42 (m, 4H), 7.39–7.23 (m, 4H), 5.46 (s, 2H), 1.61–1.59 (m, 2H), 1.34–1.31 (m, 2H); MH+ 522.

5.2.3.48. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (42a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.90 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.36–7.33 (m, 2H), 7.29–7.24 (m, 3H), 7.23–7.21 (m, 1H), 5.37 (s, 2H), 3.82–3.77 (m, 4H), 2.45–2.43 (m, 2H), 2.29 (s, 3H), 2.26–2.22 (m, 2H); MH+ 530.

5.2.3.49. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (42b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.92 (s, 1H), 7.46 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 (td, *J* = 8.0, 0.8 Hz, 1H), 7.34–7.30 (m, 2H), 7.28–7.24 (m, 4H), 5.39 (s, 2H), 2.80 (s, 3H); MH+ 496.

5.2.3.50. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (42c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.92 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.31–7.28 (m, 1H), 7.25–7.19 (m, 3H), 5.38 (s, 2H), 3.81–3.79 (m, 4H), 2.45 (t, *J* = 4.4 Hz, 2H), 2.30 (s, 3H), 2.25 (t, *J* = 4.4 Hz, 2H); MH+ 574.

5.2.3.51. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (42d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.92 (s, 1H), 7.49–7.43 (m, 3H), 7.39–7.34 (m, 1H), 7.32–7.28 (m, 2H), 7.21–7.18 (m, 2H), 3.83–3.79 (m, 4H), 2.45 (t, *J* = 4.8 Hz, 2H), 2.29 (s, 3H), 2.25 (t, *J* = 4.8 Hz, 2H); MH+ 540.

5.2.3.52. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-phenylpiperazin-1-yl)methanone (43a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.88 (s, 1H), 7.47 (m, 1H), 7.36–7.34 (m, 2H), 7.30–7.22 (m, 6H), 6.93–6.88 (m, 3H), 5.39 (s, 2H), 4.00–3.98 (m, 2H), 3.94–3.91 (m, 2H), 3.25–3.22 (m, 2H), 3.09–3.07 (m, 2H); MH+ 592.

5.2.3.53. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl)(4-phenylpiperazin-1-yl)methanone (43b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.89 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.40–7.35 (m, 1H), 7.34–7.25 (m, 8H), 6.93–6.88 (m, 3H), 5.40 (s, 2H), 4.03–4.01 (m, 2H), 3.95–3.92 (m, 2H), 3.25–3.23 (m, 2H), 3.11–3.08 (m, 2H); MH+ 558.

5.2.3.54. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-phenylpiperazin-1-yl)methanone (43c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 (s, 1H), 7.52–7.51 (m, 2H), 7.50–7.47 (m, 1H), 7.31–7.24 (m, 4H), 7.22–7.18 (m, 2H), 6.93–6.88 (m, 3H), 3.99–3.98 (m, 2H), 3.92–3.91 (m, 2H), 3.23 (t, *J* = 5.2 Hz, 2H), 3.07 (t, *J* = 5.2 Hz, 2H); MH+ 636.

5.2.3.55. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-phenylpiperazin-1-yl)methanone (43d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.86 (s, 1H), 7.47–7.42 (m, 3H), 7.38–7.33 (m, 1H), 7.28–7.23 (m, 4H), 7.18–7.16 (m, 2H), 6.91–6.87 (m, 3H), 5.38 (s, 2H), 3.99 (t, *J* = 4.8 Hz, 2H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.22 (t, *J* = 4.8 Hz, 2H), 3.07 (t, *J* = 4.8 Hz, 2H); MH+ 602.

5.2.3.56. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(3-chlorophenyl)piperazin-1-yl)methanone (44a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.88 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.30–7.21 (m, 4H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.86–6.84 (m, 2H), 6.79–6.76 (m, 1H), 5.39 (s, 2H), 4.00–3.99 (m, 2H), 3.92–3.90 (m, 2H), 3.26–3.24 (m, 2H), 3.10–3.08 (m, 2H); MH+ 626.

5.2.3.57. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(3-chlorophenyl)piperazin-1-yl)methanone (44b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.89 (s, 1H), 7.47–7.45 (m, 1H), 7.40–7.36 (m, 1H), 7.33–7.25 (m, 8H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.87–6.83 (m, 2H), 6.77 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.40 (s, 2H), 4.02–4.00 (m, 2H), 3.93–3.90 (m, 2H), 3.26–3.23 (m, 2H), 3.11–3.08 (m, 2H); MH+ 592.

5.2.3.58. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(3-chlorophenyl)piperazin-1-yl)methanone (44c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.30–7.15 (m, 5H), 6.87–6.84 (m, 2H), 6.80–6.78 (m, 1H), 5.39 (s, 2H), 4.00–3.99 (m, 2H), 3.93–3.92 (m, 2H), 3.25 (t, *J* = 4.8 Hz, 2H), 3.09 (t, *J* = 4.8 Hz, 2H); MH+ 670.

5.2.3.59. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(3-chlorophenyl)piperazin-1-yl)methanone (44d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.88 (s, 1H), 7.49–7.44 (m, 3H), 7.40–7.35 (m, 1H), 7.33–

7.28 (m, 2H), 7.21–7.15 (m, 3H), 6.87–6.83 (m, 2H), 6.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.40 (s, 2H), 4.01 (t, *J* = 4.8 Hz, 2H), 3.91 (t, *J* = 4.8 Hz, 2H), 3.24 (t, *J* = 4.8 Hz, 2H), 3.09 (t, *J* = 4.8 Hz, 2H); MH+ 636.

5.2.3.60. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methanone (45a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.90 (s, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.37–7.34 (m, 2H), 7.30–7.25 (m, 2H), 7.22–7.13 (m, 4H), 6.92 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.40 (s, 2H), 3.96–3.95 (m, 4H), 3.08–3.06 (m, 2H), 2.90–2.88 (m, 2H); MH+ 660.

5.2.3.61. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methanone (45b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.90 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24–7.13 (m, 5H), 6.93 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.39 (s, 2H), 3.97–3.95 (m, 4H), 3.07 (t, *J* = 4.8 Hz, 2H), 2.88 (t, *J* = 4.8 Hz, 2H); MH+ 704.

5.2.3.62. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dichlorophenyl)piperazin-1-yl)methanone (45c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.92 (s, 1H), 7.50–7.45 (m, 3H), 7.41–7.37 (m, 1H), 7.32–7.31 (m, 2H), 7.23–7.15 (m, 4H), 6.94 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.42 (s, 2H), 4.00–3.96 (m, 4H), 3.10–3.07 (m, 2H), 2.91–2.89 (m, 2H); MH+ 670.

5.2.3.63. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dimethylphenyl)piperazin-1-yl)methanone (46b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.92 (s, 1H), 7.45–7.43 (m, 1H), 7.39–7.34 (m, 1H), 7.33–7.25 (m, 8H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.41 (s, 2H), 3.94 (m, 4H), 2.91 (m, 2H), 2.76 (m, 2H), 2.25 (d, *J* = 13.6 Hz, 6H); MH+ 586.

5.2.3.64. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dimethylphenyl)piperazin-1-yl)methanone (46c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.34–7.19 (m, 4H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.39 (s. 2H), 3.96–3.91 (m, 4H), 2.93–2.91 (m, 2H), 2.75–2.74 (m, 2H), 2.27 (s, 3H), 2.23 (s, 3H); MH+ 664.

5.2.3.65. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(2,3-dimethylphenyl)piperazin-1-yl)methanone (46d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.92 (s, 1H), 4.48–4.43 (m, 3H), 7.39–7.33 (m, 1H), 7.31–7.29 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.40 (s, 2H), 3.95–3.93 (m, 4H), 2.92–2.90 (m, 2H), 2.76–2.74 (m, 2H). 2.27 (s, 3H), 2.23 (s, 3H); MH+ 630.

5.2.3.66. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (47a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2H), 8.29 (s, 1H), 7.89 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.36–7.34 (m, 2H), 7.29–7.25 (m, 3H), 7.23–7.21 (m, 1H), 6.53 (t, *J* = 4.8 Hz, 1H), 5.39 (s, 2H), 3.93–3.83 (m, 6H), 3.76–3.74 (m, 2H); MH+ 543.

5.2.3.67. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (47b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 4.8 Hz, 2H), 8.28 (s, 1H), 7.87 (s, 1H), 7.49 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.27–7.24 (m, 1H), 7.21–7.17 (m, 3H), 6.52 (t, *J* = 4.8 Hz, 1H), 5.37 (s, 2H), 3.91–3.81 (m, 6H), 3.75–3.72 (m, 2H); MH+ 638.

5.2.3.68. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (47c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.8 Hz, 2H), 8.33 (s, 1H), 7.90 (s, 1H), 7.49–7.44 (m, 3H), 7.40–7.35 (m, 1H), 7.32–7.27 (m, 2H), 7.21–7.19 (m, 2H), 6.58 (t, *J* = 4.8 Hz, 1H), 5.40 (s, 2H), 3.95–3.92 (m, 4H), 3.87–3.81 (m, 4H); MH+ 604.

5.2.3.69. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl)(4-ethylpiperazin-1-yl)methanone (48a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.90 (s, 1H), 7.43 (m, 1H), 7.39–7.34 (m, 1H), 7.32–7.24 (m, 6H), 5.38 (s, 2H), 3.85–3.79 (m, 4H), 2.49–2.47 (m, 2H), 2.41 (q, *J* = 7.2 Hz, 2H), 2.31–2.28 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); MH+ 510.

5.2.3.70. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-yl)(4-ethylpiperazin-1-yl)methanone (48b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (s, 1H), 7.52–7.49 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.30–7.27 (m, 2H), 7.24–7.18 (m, 2H), 5.37 (s, 2H), 3.82–3.79 (m, 4H), 2.48 (t, *J* = 4.8 Hz, 2H), 2.42 (q, *J* = 7.2 Hz, 2H), 2.28 (t, *J* = 4.8 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); MH+ 588.

5.2.3.71. (4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)(4-ethylpiperazin-1-yl)methanone (48c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.91 (s, 1H), 7.49–7.43 (m, 3H), 7.40–7.34 (m, 1H), 7.32–7.29 (m, 2H), 7.21–7.18 (m, 2H), 5.38 (s, 2H), 3.85–3.78 (m, 4H), 2.48 (t, *J* = 4.8 Hz, 2H), 2.42 (q, *J* = 6.8 Hz, 2H), 2.28 (t, *J* = 4.8 Hz, 2H), 1.08 (t, *J* = 6.8 Hz, 3H); MH+ 554.

5.2.3.72. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-benzyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (49a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.90 (s, 1H), 7.43–7.40 (m, 2H), 7.36–7.31 (m, 6H), 7.30–7.22 (m, 4H), 5.51 (s, 2H), 4.60 (d, *J* = 6.0 Hz, 2H); MH+ 537.

5.2.3.73. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-benzyl-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxamide (49b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.43–7.40 (m, 4H), 7.39–7.26 (m, 9H), 5.53 (s, 2H), 4.60 (d, *J* = 5.6 Hz, 2H); MH+ 509.

5.2.3.74. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-benzyl-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (49c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.90 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.36–7.33 (m, 5H), 7.29–7.23 (m, 4H), 5.51 (s, 2H), 4.61 (d, *J* = 6.0 Hz, 2H); MH+ 581.

5.2.3.75. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrazole-3-carboxamide (50a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.86 (s, 1H), 7.46–7.34 (m, 9H), 7.34–7.25 (m, 4H), 5.45 (s, 2H), 1.79 (s, 6H); MH+ 565.

5.2.3.76. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrazole-3-carboxamide (50b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.87 (s, 1H), 7.46–7.44 (m, 3H), 7.41–7.30 (m, 10H), 5.46 (s, 2H), 1.79 (s, 6H); MH+ 531.

5.2.3.77. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrazole-3-carboxamide (50c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.87 (s, 1H), 7.49–7.43 (m, 4H), 7.41–7.32 (m, 8H), 7.28–7.24 (m, 1H), 5.46 (s, 2H), 1.79 (s, 6H); MH+ 575.

5.2.3.78. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-(2-(4-chlorophenyl)propan-2-yl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (51a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.87 (s, 1H), 7.47 (m, 1H), 7.41–7.31 (m, 10H), 5.44 (s, 2H), 1.76 (s, 6H); MH+ 599.

5.2.3.79. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazole-3-carboxamide (51b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.87 (s, 1H), 7.46–7.44 (m, 1H), 7.41–7.32 (m, 6H), 7.31–7.29 (m, 5H), 5.45 (s, 2H), 1.75 (s, 6H); MH+ 565.

5.2.3.80. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-(2-(4-chlorophenyl)propan-2-yl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (51c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.86 (s, 1H), 7.52–7.50 (m, 2H), 7.46–7.40 (m, 1H), 7.38–7.26 (m, 8H), 5.43 (s, 2H), 1.75 (s, 6H); MH+ 643.

5.2.3.81. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-(1-(4-bromophenyl)ethyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (52a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.89 (s, 1H), 7.48–7.45 (m, 3H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.24 (m, 3H), 7.19–7.17 (m, 1H), 5.56 (d, J = 14.4 Hz, 1H), 5.37 (d, J = 14.4 Hz, 1H), 5.24–5.20 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H); MH+ 509.

5.2.3.82. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-*N*-(1-(4-bromophenyl)ethyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxamide (52b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.90 (s, 1H), 7.48–7.46 (m, 2H), 7.43–7.36 (m, 4H), 7.34–7.26 (m, 4H), 7.25–7.21 (m, 2H), 5.58 (d, J = 14.0 Hz, 1H), 5.39 (d, J = 14.0 Hz, 1H), 5.27–5.20 (m, 1H), 1.55 (d, J = 7.2 Hz, 3H); MH+ 509.

5.2.3.83. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-(1-(4-bromophenyl)ethyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (52c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.88 (s, 1H), 7.52–7.45 (m, 4H), 7.35–7.24 (m, 6H), 7.18–7.16 (m, 1H), 5.55 (d, J = 14.0 Hz, 1H), 5.37 (d, J = 14.4 Hz, 1H), 5.26–5.18 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H); MH+ 673.

5.2.3.84. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-(1-(4-bromophenyl)ethyl)-1-(2-chlorophenyl)-1H-pyrazole-3-carboxamide (52d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.89 (s, 1H), 7.48–7.43 (m, 5H), 7.40–7.38 (m, 1H), 7.37–7.30 (m, 4H), 7.24–7.20 (m, 2H), 5.57 (d, J = 14.4 Hz, 1H), 5.39 (d, J = 14.4 Hz, 1H), 5.27–5.19 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H); MH+ 639.

5.2.3.85. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(2,4-dichlorophenyl)ethyl)-1*H*-pyrazole-3-carboxamide (53a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.87 (s, 1H), 7.46 (m, 1H), 7.42–7.40 (m, 3H), 7.36–7.26 (m, 6H), 7.24–7.22 (m, 1H), 5.56 (d, J = 14.4 Hz, 1H), 5.52–5.46 (m, 1H), 5.35 (d, J = 14.4 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H); MH+ 619.

5.2.3.86. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(1-(2,4-dichlorophenyl)ethyl)-1*H*-pyrazole-3-carboxamide (53b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.89 (s, 1H), 7.47–7.45 (m, 1H), 7.42–7.37 (m, 4H), 7.36–7.31 (m, 6H), 5.57 (d, J = 14.4 Hz, 1H), 5.53–5.48 (m, 1H), 5.37 (d, J = 14.4 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H); MH+ 585.

5.2.3.87. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-(2,4-dichlorophenyl)ethyl)-1*H*-pyrazole-3-carboxamide (53c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.87 (s, 1H), 7.52–7.50 (m, 2H), 7.47 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.35–7.29 (m, 5H), 7.23 (dd, J = 8.4, 2.4 Hz, 1H), 5.55 (d, J = 14.4 Hz, 1H), 5.51–5.46 (m, 1H), 5.35 (d, J = 14.4 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H); MH+ 663.

5.2.3.88. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-(2,4-dichlorophenyl)ethyl)-1*H*-pyrazole-3-carboxamide (53d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.88 (s, 1H), 7.49–7.45 (m, 3H), 7.42–7.38 (m, 2H), 7.34–7.31 (m, 5H), 7.24–7.21 (m, 1H), 5.56 (d, J = 14.4 Hz, 1H), 5.52–5.47 (m, 1H), 5.37 (d, J = 14.4 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H); MH+ 629.

5.2.3.89. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-phenylcyclopropyl)-1*H*-pyrazole-3-carboxamide (54a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.86 (s, 1H), 7.60 (s, 1H), 7.44–7.39 (m, 3H), 7.35–7.29 (m, 2H), 7.27–7.23 (m, 6H), 7.23–7.17 (m, 1H), 5.46 (s, 2H), 1.35 (m, 4H); MH+ 563.

5.2.3.90. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(1-phenylcyclopropyl)-1*H*-pyrazole-3-carboxamide (54b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.88 (s, 1H), 7.65 (s, 1H), 7.46–7.36 (m, 4H), 7.33–7.26 (m, 8H), 7.22–7.19 (m, 1H), 5.50 (s, 2H), 1.40–1.33 (m, 4H); MH+ 529.

5.2.3.91. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-*N*-(1-phenylcyclopropyl)-1*H*-pyrazole-3-carboxamide (54c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.87 (s, 1H), 7.61 (br s, 1H), 7.52–7.50 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.37–7.35 (m, 2H), 7.33–7.25 (m, 6H), 7.23–7.19 (m, 1H), 5.48 (s, 2H), 1.37–1.36 (m, 4H); MH+ 607.

5.2.3.92. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-phenylcyclopropyl)-1*H*-pyrazole-3-carboxamide (54d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.88 (s, 1H), 7.65 (br s, 1H), 7.49–7.43 (m, 3H), 7.41–7.28 (m, 9H), 7.22–7.18 (m, 1H), 5.49 (s, 2H), 1.40–1.33 (m, 4H); MH+ 573.

5.2.3.93. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*-(1-(4-chlorophenyl)cyclopropyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (55a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.86 (s, 1H), 7.57 (s, 1H), 7.44–7.39 (m, 3H), 7.34–7.32 (m, 2H), 7.28–7.24 (m, 3H), 7.23–7.19 (m, 3H), 5.45 (s, 2H), 1.35–1.30 (m, 4H); MH+ 597.

5.2.3.94. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-1-(2-chlorophenyl)-5-(4-chlorophenyl)-*N*-(1-(4-chlorophenyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (55b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.89 (s, 1H), 7.63 (m, 1H), 7.46–7.36 (m, 4H), 7.33–7.31 (m, 3H), 7.28–7.21 (m, 5H), 5.48 (s, 2H), 1.39–1.30 (m, 4H); MH+ 503.

5.2.3.95. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-*N*-(1-(4-chlorophenyl)cyclopropyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carboxamide (55c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.88 (s, 1H), 7.59 (br s, 1H), 7.53–7.50 (m, 2H), 7.46–7.45 (m, 1H), 7.37–7.34 (m, 2H), 7.32–7.21 (m, 6H), 5.47 (s, 2H), 1.39–1.30 (m, 4H); MH+ 641.

5.2.3.96. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(1-(4-chlorophenyl)cyclopropyl)-1*H*-pyrazole-3-carboxamide (55d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.89 (s, 1H), 7.63 (br s, 1H), 7.49–7.44 (m, 3H), 7.41–7.32 (m, 5H), 7.28–7.21 (m, 4H), 5.48 (s, 2H), 1.39–1.36 (m, 2H), 1.33–1.25 (m, 2H); MH+ 607.

5.2.3.97. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(pyridin-2-ylmethyl)-1*H*-pyrazole-3-carboxamide (56a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.93–7.90 (m, 1H), 7.87 (s, 1H), 7.65 (td, J = 7.6, 2.0 Hz, 1H), 7.43–7.38 (m, 3H), 7.34–7.27 (m, 6H), 7.19–7.16 (m, 1H), 5.49 (s, 2H), 4.72 (d, J = 5.6 Hz, 2H); MH+ 538.

5.2.3.98. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-*N*-(pyridin-2-ylmethyl)-1*H*-pyrazole-3-carboxamide (56b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58–8.57 (m, 1H), 8.55 (s, 1H), 8.02–7.98 (m, 1H), 7.91 (s, 1H), 7.99–7.76 (m, 1H), 7.50–7.28 (m, 9H), 5.52 (s, 2H), 4.81 (s, 2H); MH+ 548.

5.2.3.99. 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-5-(4-chlorophenyl)-*N*′-(1-(4-chlorophenyl)cyclopropanecarbonyl)-1-(2,4-dichlorophenyl)-1*H*-pyrazole-3-carbohydrazide (57). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.90 (d, J = 4.4 Hz, 1H), 8.16 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 7.48–7.29 (m, 11H), 5.46 (s, 2H), 1.74–1.68 (m, 2H), 1.19–1.13 (m, 2H); MH+ 640.

5.3. CB1 and CB2 receptor binding assay

For CB1 receptor binding studies, rat cerebellar membranes were prepared as previously described by the methods of Kuster et al.[21] Male Sprague Dawley rats (200–300 g) were sacrificed by decapitation and the cerebella rapidly removed. The tissue was homogenized in 30 volumes of TME buffer (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH = 7.4) using a Dounce homogenizer. The crude homogenates were immediately centrifuged (48,000*g*) for 30 min at 4 °C. The resultant pellets were resuspended in 30 volumes of TME buffer and protein concentration was determined by the method of Bradford and stored at −70 °C until use.

For CB2 receptor binding studies, CHO K-1 cells were transfected with human CB2 receptor as previously described, and cell membranes were prepared as described above.[22]

Competitive binding assays were performed as described. Briefly, approximately 10 μg of rat cerebella membranes (containing CB1 receptor) or cell membranes (containing CB2 receptor) were incubated in 96-well plate with TME buffer containing 0.5% essentially fatty acid free bovine serum albumin (BSA), 3 nM [3*H*]WIN55,212-2 {[3*H*] (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone]} (for CB2 receptor, NEN; specific activity 50–80 Ci/mmol) or 3 nM [3*H*]CP55,940 {[3*H*]2-[(1*S*,2*R*,5*S*)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol}, for CB1 receptor, NEN; specific activity 120–190 Ci/mmol) and various concentrations of the synthesized cannabinoid ligands in a final volume of 200 μL. The assays were incubated for 1 h at 30 °C and then immediately filtered over GF/B glass fibre fiber filter (Perkin–Elmer Life and Analytical Sciences, Boston, MA) that had been soaked in 0.1% PEI for 1 h by a cell harvester (PerkinElmer Life and Analytical Sciences, Boston, MA). Filters were washed five times with ice-cold TBE buffer containing 0.1% essentially fatty acid free BSA, followed by oven-dried for 60 min and then placed in 5 ml of scintillation fluid (Ultima Gold XR; PerkinElmer Life and Analytical Sciences, Boston, MA), and radioactivity was quantitated by liquid scintillation spectrometry. In CB1 and CB2 receptor competitive binding assay, nonspecific binding was assessed using 1 μM **1** and 1 μM WIN55,212-2, respectively. Specific binding was defined as the difference between the binding that occurred in the presence and absence of 1 μM concentrations of **1** or WIN55,212-2 and was 70–80% of the total binding. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM.

5.4. Measurements of in vivo activity analysis

Male C57BL/6J mice weighing over 38 g were housed one per cage on a 12 h/12 h light/dark cycle, had free access to food (rodent sterilizable diet) and water, and were experimentally native before testing. Mice were allowed 7 days to habituate to the experimental room prior to testing, and testing was conducted during the light period. Mice were maintained and experiments were conducted in accordance with the Institutional Animal Care. The compounds **52c** and **52d** were prepared daily by dissolving them in deionized water containing 10% DMSO. By oral administration, animals received a volume of 10 ml/kg for 7 days. All control animals received 10% DMSO dissolved in deionized water. The vehicles 10% DMSO treated group were comprised of five mice in oral test. There were five mice in each of the other experimental groups (n = 5 in each group). By oral administration, the losing weight was checked everyday for the drug treated group and the control group.

Acknowledgements

We thank Dr. Chong-Hwan Chang for his leadership in R&D at Green Cross Corporation (GCC). Also we are grateful to Dr. Eun Chul Huh, Mr. Jung Ho Kim, and Mr. Jung-Won Jeon at GCC Office of R&D planning and coordination for their supports and services.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.12.040.

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