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Design, synthesis and biological evaluation of piperazine analogues as CB1 cannabinoid receptor ligands

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Abstract—After the CB1 receptor antagonist SR141716 (rimonabant) was previously reported to modulate food intake, CB1 antagonism has been considered as a new therapeutic target for the treatment of obesity. Several series of urea, carbamate, amide, sulfonamide and oxalamide derivatives based on 1-benzhydrylpiperazine scaffold were synthesized and tested for CB1 receptor binding affinity. The SAR studies to optimize the CB1 binding affinity led to the potent urea derivatives. After the additional SAR studies to optimize the substituents of diphenyl rings, the combination of 2-chlorophenyl and 4-chlorophenyl turned out to be the most potent scaffold. The CB2 binding affinity assay as well as functional assay was also conducted on these compounds. Herein we wish to introduce several novel CB1 antagonists with IC_{50} values less than 100 nM for the CB1 receptor binding.

1. Introduction

In recent years, obesity has become a major health problem for many postindustrial societies. The number of deaths per year attributable to obesity is about 30,000 in the UK and nearly 400,000 in the United States, where obesity is set to overtake smoking as the main preventable cause of illness and premature death.[1–3] The total direct and indirect costs of obesity was estimated to be approximately €32,800 million per year in the EU and $99.2 billion per year in the USA.[3,4] Obesity poses a major health risk for serious diet-related chronic disease, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and some of cancers.[1] For these reasons, the World Health Organization declared obesity a global epidemic[5,6] and obesity is now considered as disease that needs pharmacological treatments.[7–9]

Numerous studies on causes of obesity have been made to identify new potential targets that could be exploited to create novel type of anti-obesity drugs. At last it was discovered that modulation of endocannabinoid system by specifically blocking the cannabinoid receptor 1 (CB1) in both the brain and periphery can provide a novel target for the treatment of obesity.[10] The endocannabinoid system includes endogenous ligands (such as anandamide and 2-AG) and two cannabinoid receptor subtypes (CB1 and CB2). These receptors (CB1 and CB2) belong to the G-protein coupled receptor superfamily and were first cloned in 1990 and 1993, respectively.[11–13] The CB1 receptors are mainly expressed in several brain areas including the limbic system (amygdala, hippocampus), hypothalamus, cerebral cortex, cerebellum, and basal ganglia. It has been known that CB1 receptors, especially in the limbic system-hypothalamus axis cannabinoids, have an important role in the control of appetite.[14,15] By contrast, CB2 receptors are almost exclusively expressed in cells of the immune system.[15,16]

The physiological role of both CB receptors is not yet completely understood, although they seem to be involved in certain pathophysiological processes. In particular, the physiological role of CB1 receptors has been

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of interest, since the impressive clinical results of rimonabant, the first CB1 antagonist, were reported for the treatment of obesity and metabolic disorders in 2001. Accordingly antagonism of CB1 receptor has been pursued as a highly promising strategy for the treatment of obesity.[17] Even though rimonabant (Acomplia™) is currently launched by Sanofi–Aventis in the European Union, many research groups, including major pharmaceutical companies, are still searching for novel CB1 antagonists with improved physicochemical properties or reduced psychiatric adverse effects, such as depression or anxiety.[1,18,19]

Most analogues, reported as novel CB1 antagonists, are derived from the structure of rimonabant (Fig. 1A).[16] In most cases, either the central pyrazole core or the carbonyl moiety of rimonabant is substituted by either other aromatic rings or other hydrogen bonding acceptors, respectively. However, there was an interesting moiety distinguished by a diphenyl group geminally coupled to the central core (Fig. 1B).[16,17] It was identified by Aventis Pharma and Vernalis Research that some series of analogues with a 1,1-diphenyl methylene group, which might mimic the 1,5-diphenyl motif of rimonabant, could act as CB1 antagonists.[20,21] Indeed, these derivatives were previously described for the treatment of CNS disorders,[21] such as anxiety or depression which is a serious adverse effect of rimonabant. Compound **2** (AVE1625, Fig. 1B) is in phase II clinical trials for obesity and cognitive disorder (THOMSON Pharma®). We envisioned that some derivatives with this intriguing moiety can divert the psychiatric adverse effect of rimonabant, while retaining its good in vitro and in vivo biological activity. We thought that the central azetidine moiety could be replaced by simple six-membered heterocyclic scaffolds, such as piperazine, while keeping carbonyl moiety to maintain the pivotal hydrogen-bonding with backbone of the protein.[22] Herein we wish to unveil synthetic details and structure–activity studies for the various derivatives with 1,1-diphenyl methylene groups geminally coupled to the central piperazine ring, possessing good in vitro CB1 receptor binding affinity and selectivity of CB1 over CB2 in addition to good functional activity.

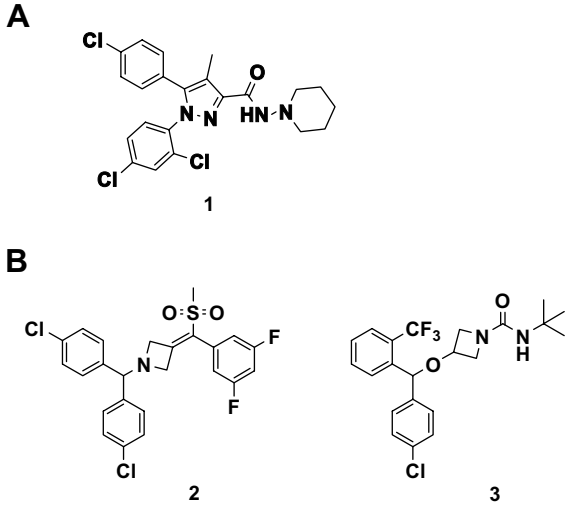


Figure 1. (A) The structure of rimonabant (**1**, SR141716). (B) Analogs with benzhydryl moiety connected to the central azetidine core. These analogs are reported by Aventis Pharma (**2**, AVE1625) and Vernalis Research (**3**).

2. Results and discussion

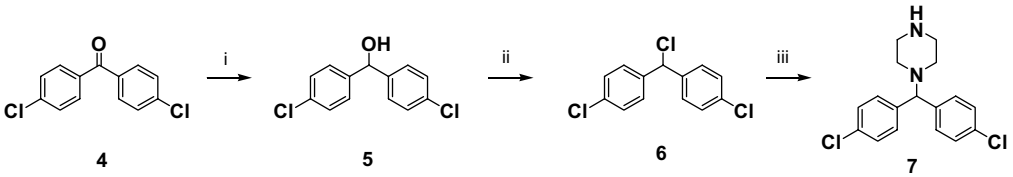
2.1. Chemistry

The synthesis of compounds **13**–**23** commenced with the preparation of the requisite intermediate **7** or **12a**–**e**. The key piperazines **7** and **12a**–**e** were prepared as displayed in Schemes 1 and 2, respectively. As shown in Scheme 1, 4,4′-dichlorobenzophenone, the commercially available starting material, was reduced by sodium borohydride to prepare the symmetrical diphenylmethanol **5**.[23] The compound **5** was treated with thionyl chloride to provide the corresponding chloromethylene intermediate **6** which was subsequently refluxed with piperazine in acetonitrile to give 1-(bis(4-chlorophenyl)methyl)piperazine (**7**).[24]

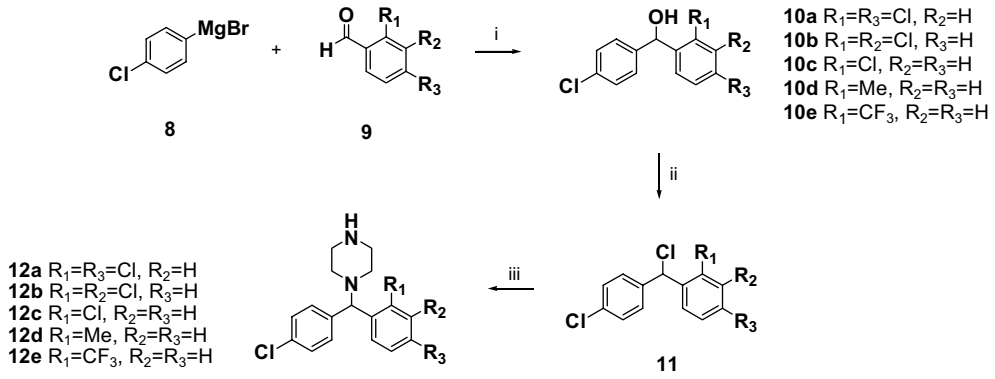
The other key intermediates **12a**–**e** were also prepared by the method outlined in Scheme 2. Grignard reactions of 4-chlorophenylmagnesium bromide (**8**) with substituted benzaldehydes **9** in tetrahydrofuran (THF) provided the corresponding diphenylmethanols **10a**–**e**.[24] Compounds **10a**–**e** were then treated with thionyl chloride followed by refluxing with piperazine in acetonitrile to provide **12a**–**e**. As shown in Scheme 3, the target compounds **13**–**18** were prepared by the coupling reaction between key intermediates (compounds **7** or **12a**–**e**) and the corresponding isocyanates in the presence of triethylamine.[25]

The amide bond formations of compounds **7** or **12a**–**e** with required acids produced compounds **19** or **20** by the use of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in *N*,*N*-dimethylformamide (DMF).[26] The reaction of compounds **7** with chloroformates in the presence of triethylamine gave the corresponding carbamate derivatives **21**.[27] The compounds **22**, containing a sulfonamide group, were prepared by the reaction of compounds **7** with required sulfonyl chlorides.[28] A piperazine intermediate **12c** was reacted with excess oxalyl chloride (more than 10 equivalents) at low temperature and the resulting intermediates were successively treated with required amines to provide a series of target compounds **23**.[27]

Meanwhile, a series of bromo-substituted phenyl group such as compounds **29** was prepared by reactions of amine compound **28** with the corresponding isocyanates, as described in Scheme 4. The condensation of 2-chlorobenzaldehyde (**25**) with 1,4-dibromobenzene (**24**) in the presence of *n*-BuLi produced the corresponding alcohol **26**.[29] The resulting alcohol **26** was transformed into compound **28** by the treatment of thionyl chloride followed by refluxing with piperazine in acetonitrile in an analogous fashion as previously described. The coupling reaction of intermediate **28** and the corre-



Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, THF, 0 °C → rt; (ii) $SOCl_2$, DCM, rt; (iii) piperazine, MeCN, reflux.



Scheme 2. Reagents and conditions: (i) THF, rt; (ii) $SOCl_2$, DCM, rt; (iii) piperazine, MeCN, reflux.

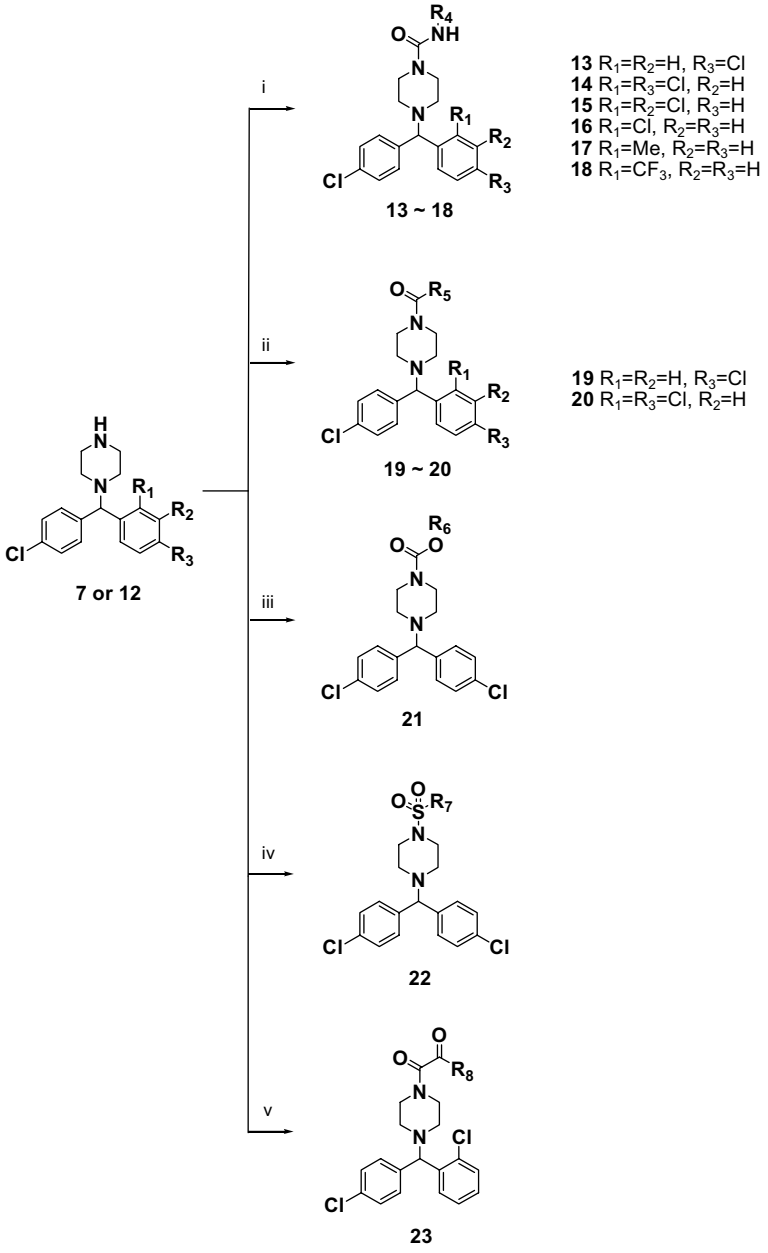
sponding isocyanates in the presence of triethylamine produced the desired compounds **29**.

2.2. Structure–activity relationship studies

A symmetrical diphenylmethylene template attached to piperazine was used to construct various target compounds bearing a strong hydrogen-bonding acceptor for the initial SAR study. As mentioned earlier, the crucial receptor–ligand interaction is recognized to be a hydrogen bond between a hydrogen-bonding acceptor such as the carbonyl group of rimonabant and the Lys192-Asp366 residue of the CB1 receptor. Using the piperazine compound **7**, several functional groups acting as hydrogen-bonding acceptor were investigated. As shown in Scheme 3, urea **13**, amide **19**, carbamate **21** and sulfonamide **22** derivatives were synthesized, and subsequently biological activities of these compounds were evaluated via a rat CB1 binding assay.[30] Even though most of the derivatives had over 2 μM of IC_{50} value at CB1 receptor, a urea derivative **13a**, displayed the potent CB1 receptor binding affinity while some of amide derivatives (**19a**, **19c** and **19h**) showed slightly weaker activities. Thus, additional urea **14** and amide **20** derivatives with chlorine at the ortho position (R_1 in Scheme 3) were prepared for the further SAR study. The chlorine substituents at both ortho and *para* positions were reminiscent of counterparts from rimonabant. The introduction of chlorine atom to the ortho position resulted in significant improvement in binding affinity at CB1 receptor. Especially compound **14a**, in which a chlorine was introduced to the ortho position of compound **13a**, was found to result in an approximate gain of CB1 binding affinity by one order of magnitude. Among numerous ureas tested in this series, compound **14b** containing *N*-cycloheptyl carboxamide moiety demonstrated the most potent binding affinity. In case of the amide derivatives, the insertion of chlorine at the ortho position also showed the slightly improved binding affinity (**20j**), with *n*-hexanoyl moiety as lipophilic pharmacophore. Except **20j**, all other amide derivatives demonstrated $IC_{50} > 1$ μM values, indicating the superiority of urea functionality to amide counterpart for CB1R binding affinity.

Further SAR study was performed on 2,4-dichlorophenyl moiety of urea derivatives (compound **14** series). In order to evaluate the requirement of chlorine at the *para* position, chlorine position was either switched from R_3 to R_2 (Scheme 3) or completely removed. When chlorine position was switched from the *para* position to the meta position (compound **15** series), there was a moderate loss of CB1 binding affinity. For example, compound **14b** is compared with the corresponding compound **15b**. On the other hand, removing the chlorine at the *para* position slightly increased binding affinity for the CB1 receptor as exemplified by either compound **14a** versus compound **16a** or compound **14b** versus compound **16b**. Based on this SAR study, it is suggested that the chlorine at the ortho position (R_1 position in Scheme 3) is essential for CB1 receptor binding affinity.

A few of substituents at the ortho position were also explored in order to determine the optimal group at the ortho position. The chlorine at the ortho position was replaced by the methyl (compound **17** series) or trifluoromethyl (compound **18** series) group. However, these replacements led to a mild decrease in CB1R binding affinity. For example, methyl derivative **17b** or trifluoromethyl derivative **18b** proved to slightly lose binding affinity compared with compound **16b**. According to this result, the chlorine was selected as the best substituent at the ortho position. In order to explore further,

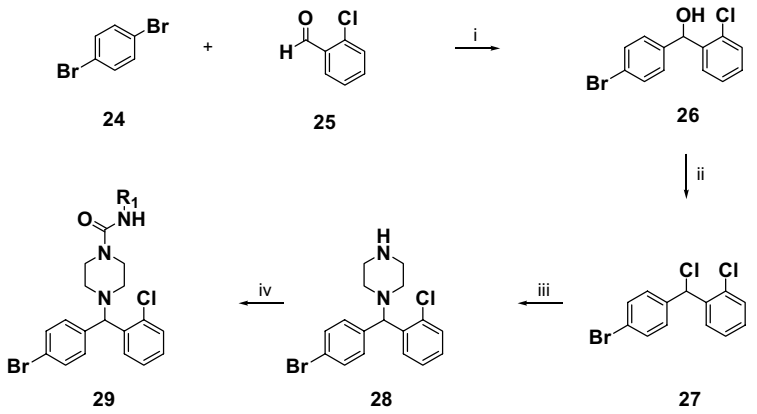


Scheme 3. Reagents and conditions: (i) R_4-NCO, TEA, DCM, rt; (ii) R_5-COOH, DCC, HOBT, DMF, rt; (iii) R_6-OCOCl, TEA, DCM, 0 °C → rt; (iv) R_7-SO_2Cl, TEA, DCM, rt; (v) $(COCl)_2$, TEA, R_8-NH_2, DCM, 0 °C → rt.

compound **23** series was prepared by exchanging the urea group of compound **16** series into the 2-oxoacetamide group (Scheme 3). Initially, these derivatives were hoped to improve CB1 receptor binding affinity, because additional carbonyl group might be able to act as a supplementary hydrogen-bonding acceptor. However, it was found that 2-oxoacetamide group was about threefold less active than the urea counterpart in terms of CB1R binding affinity.

Finally, 4-chlorophenyl group was replaced with 4-bromophenyl group as shown in Scheme 4. The introduction of 4-bromophenyl group provided a comparable activity in CB1 binding affinity. Thus, it appears that despite the alteration of chlorine to bromine atom at the *para* position, both **29b** and **16b** proved to be effective in binding CB1 receptor.

The interesting urea compounds were further evaluated in a functional assay using hCB1R expressed in Chinese hamster ovary (CHO) cells in the presence of forskolin.[35] Two compounds (**29a** and **29b**) exhibited better functional activities than **1** in in-house functional assay. Binding affinities were also measured for the CB2 receptor expressed in CHO cells and employing [^{3}H]WIN-55,212-2 as a radio-ligand.[32] Almost all compounds were devoid of activity in this CB2 binding assay, indicating a great selectivity for CB1 over CB2 of the piperazine analogues. Selected examples of the above derivatives are summarized in Tables 1 and 2.



Scheme 4. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C → rt; (ii) $SOCl_2$, DCM, rt; (iii) piperazine, MeCN, reflux; (iv) R_1-NCO, TEA, DCM, rt.

3. Conclusion

Piperazine derivatives as CB1 receptor–ligands were designed, synthesized and evaluated via in vitro cannabinoid CB1 and CB2 binding assays. In general, urea derivatives linked to 1-((2-chlorophenyl)(4-chlorophenyl)methyl)piperazine showed the modest CB1 binding affinities and extremely weak CB2 binding affinities. Especially, compound **16a** or **16b** appeared to be the most potent among compounds tested (IC_{50} = 72.8 nM and 66.5 nM, respectively) in terms of rat CB1R binding affinity, while compound **29a** or **29b** showed the better functional activities (IC_{50} = 62.8 nM and 49.4 nM, respectively) than rimonabant in cell lines expressing hCB1R. Despite slightly weaker CB1 binding affinities compared to the affinity of rimonabant, there is no doubt that the benzhydrylpiperazine urea derivatives are active as cannabinoid CB1 receptor antagonists. Indeed the benzhydryl moiety differs from the usually reported moieties of CB1 receptor antagonists, which have two phenyl pharmacophores linked to an aromatic central core. Currently, only two companies reported the benzhydryl moiety linked to azetidine for the CB1 receptor antagonists and while this research was being finished, AstraZeneca published a patent (WO2007018459), which claimed similar derivatives to ours. However, they have not reported any detailed CB1 and CB2 binding affinity data or functional assay data. To the best of our knowledge, AstraZeneca has not also published the main derivatives (**14a**, **14b**, **16a**, **16b**) described in this research. Since the derivatives in this study showed significant CB1 antagonistic characters and virtually no CB2 binding affinities, further studies should be undertaken to optimize the CB1 binding affinity. Additional PK and in vivo efficacy studies in addition to further SAR studies will be the subject of future investigations.

4. Experimental

4.1. General synthetic methods

^{1}H NMR spectra were recorded on either a Jeol ECX-400, or a Jeol JNM-LA300 spectrometer for solution in $CDCl_3$. Chemical shifts were expressed in parts per million (ppm, δ units) downfield from the signal for TMS. 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), and br (broad). Mass spectra were obtained with either a Micromass, Quattro LC Triple Quadruple Tandem Mass Spectrometer or Agilent, 1100LC/MSD system equipped with XTerra®MS C18 3.5 μm 2.1 × 50 mm column with a 9 min gradient from 30% CH_3CN to 90% CH_3CN in H_2O.

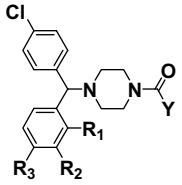
For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of DMSO or MeOH onto a SunFire™ Prep C18 OBD 5 μm 19 × 100 mm column with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O. Flash chromatography was carried using Merck silica gel 60 (230–400 mesh). Most of the reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light.

4.2. Chemistry

4.2.1. 1-(Bis(4-chlorophenyl)methyl)piperazine (7). 4,4′-Dichlorobenzophenone (12.56 g, 50 mmol) was dissolved in a mixture of methanol (100 mL) and THF (150 mL) and cooled to 0 °C. $NaBH_4$ (1.89 g, 50 mmol) was added to the above solution at 0 °C. After additional 10 min at 0 °C, the reaction mixture was subsequently stirred at room temperature for 2 h. The reaction mixture was diluted with water (200 mL), and the product was extracted with diethyl ether (400 mL). The organic phase was washed with 1 N HCl, followed by a saturated $NaHCO_3$ and finally with water. It was dried over $MgSO_4$ and evaporated under vacuum to provide 4,4′-dichlorobenzhydrol (**5**, 12.05 g, 47.6 mol, 95%). The crude product was used in the following steps without further purification.

The alcohol (**5**, 5.06 g, 20 mmol) was dissolved in DCM (50 mL) and $SOCl_2$ (1.6 mL, 22 mmol) was added to the solution. The reaction mixture was stirred at room temperature overnight and the solvent was evaporated un-

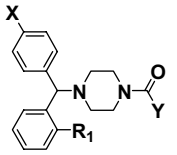
Table 1. Structures and binding affinities of selected ligands to rat CB1 and human CB2 receptors, and human CB1 functional activities of the ligands



Ligand	R_1	R_2	R_3	Y	Receptor affinity[a] (IC_{50}, nM)		hCB1 functional activity[a] (IC_{50}, nM)
					rCB1	hCB2	
1 (rimonabant)					1.9	1760	120
13a	H	H	Cl	–NH-Cyclohexyl	914	—	—
14a	Cl	H	Cl	–NH-Cyclohexyl	104	>10,000	367
14b	Cl	H	Cl	–NH-Cycloheptyl	89.2	>10,000	729
14c	Cl	H	Cl	–NH-Cyclohexylmethyl	262	>10,000	1040
14d	Cl	H	Cl	–NH-*tert*-Butyl	2000	—	—
15a	Cl	Cl	H	–NH-Cyclohexyl	186	>10,000	441
15b	Cl	Cl	H	–NH-Cycloheptyl	158	>10,000	424
15c	Cl	Cl	H	–NH-Cyclohexylmethyl	2000	—	—
15d	Cl	Cl	H	–NH-*tert*-Butyl	783	>10,000	316
19a	H	H	Cl	–Cyclohexyl	1390	—	—
19c	H	H	Cl	–Cyclobutyl	1070	—	—
19h	H	H	Cl	–Pentyl	1150	—	—
20j	Cl	H	Cl	–Pentyl	257	—	—

[a] These data were obtained by single determinations.

Table 2. Structures and binding affinities of selected ligands to rat CB1 and human CB2 receptors, and human CB1 functional activities of the ligands



Ligand	X	R_1	Y	Receptor affinity[a] (IC_{50}, nM)		hCB1 functional activity[a] (IC_{50}, nM)
				rCB1	hCB2	
16a	Cl	Cl	–NH-Cyclohexyl	72.8	>10,000	128
16b	Cl	Cl	–NH-Cycloheptyl	66.5	>10,000	226
16c	Cl	Cl	–NH-Cyclohexylmethyl	189	>10,000	273
16d	Cl	Cl	–NH-*tert*-Butyl	122	4820	443
17a	Cl	Me	–NH-Cyclohexyl	248	>10,000	195
17b	Cl	Me	–NH-Cycloheptyl	151	>10,000	163
17c	Cl	Me	–NH-Cyclohexylmethyl	291	>10,000	340
17d	Cl	Me	–NH-*tert*-butyl	680	>10,000	334
18a	Cl	CF_3	–NH-Cyclohexyl	163	>10,000	186
18b	Cl	CF_3	–NH-Cycloheptyl	141	>10,000	204
18c	Cl	CF_3	–NH-Cyclohexylmethyl	526	>10,000	798
18d	Cl	CF_3	–NH-*tert*-Butyl	2050	—	—
23a	Cl	Cl	–CO–NH-Cyclohexyl	226	—	—
23b	Cl	Cl	–CO–NH-Cycloheptyl	229	—	—
29a	Br	Cl	–NH-Cyclohexyl	103	>10,000	62.8
29b	Br	Cl	–NH-Cycloheptyl	82.3	>10,000	49.4
29c	Br	Cl	–NH-Cyclohexylmethyl	127	>10,000	146
29d	Br	Cl	–NH-*tert*-Butyl	237	4950	286

[a] These data were obtained by single determinations.

der vacuum. The crude residue was dissolved in MeCN (100 mL) and piperazine (17.23 g, 200 mmol) was added. The mixture was refluxed at 90 °C for 16 h. The solvent was removed under vacuum. The residue was dissolved in DCM (150 mL) and washed with water followed by 1 M HCl (100 mL). The organic phase was evaporated

under vacuum and the crude residue was dissolved in the mixture of 1 M HCl (100 mL) and diethyl ether (100 mL). The diethyl ether layer was discarded and to the remaining water layer was added 1 M NaOH (200 mL). The aqueous solution was extracted with DCM (200 mL). The DCM layer was washed successively with water, dried over $MgSO_4$ and evaporated under vacuum to provide the title compound (4.75 g, 14.8 mmol, 74%). $[M+H]^+$: 321.

4.2.2. 4-(Bis(4-chlorophenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (13a). To a solution of the compound **7** (161 mg, 0.50 mmol) in DCM (5 mL) was added cyclohexylisocyanate (63 mg, 0.50 mmol) and triethylamine (51 mg, 0.50 mmol). The reaction mixture was subsequently stirred at room temperature overnight. The mixture was poured into 1 M HCl solution (10 mL) and extracted with DCM (2× 20 mL). The combined DCM was washed successively with water, dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by prep HPLC to provide the title compound (98 mg, 0.22 mmol, 44%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.7 Hz, 4H), 4.22 (s, 1H), 4.20 (s, 1H), 3.62 (m, 1H), 3.32 (t, J = 5.2 Hz, 4H), 2.35 (t, J = 4.8 Hz, 4H), 1.95–1.90 (m, 2H), 1.71–1.57 (m, 3H), 1.41–1.29 (m, 2H), 1.19–1.01 (m, 3H). $[M+H]^+$: 446, HPLC: t_R = 5.4 min.

4.2.3. *N*-Benzyl-4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxamide (13b). The procedure described for the synthesis of **13a** was applied to **7** and benzylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (m, 13H), 4.67 (t, J = 5.2 Hz, 1H), 4.41 (d, J = 5.5 Hz, 2H), 4.20 (s, 1H), 3.37 (t, J = 5.2 Hz, 4H), 2.36 (t, J = 4.8 Hz, 4H). $[M+H]^+$: 454.

4.2.4. 4-(Bis(4-chlorophenyl)methyl)-*N*-phenylpiperazine-1-carboxamide (13c). The procedure described for the synthesis of **13a** was applied to **7** and phenylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (m, 12H), 7.02 (t, J = 7.2 Hz, 1H), 6.30 (s, 1H), 4.23(s, 1H), 3.48 (t, J = 5.2 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H). $[M+H]^+$: 440.

4.2.5. 4-(Bis(4-chlorophenyl)methyl)-*N*-(4-chlorophenyl)-piperazine-1-carboxamide (13d). The procedure described for the synthesis of **13a** was applied to **7** and 4-chlorophenylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.21 (m, 12H), 6.30 (s, 1H), 4.23(s, 1H), 3.48 (t, J = 5.2 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H). $[M+H]^+$: 474.

4.2.6. 4-(Bis(4-chlorophenyl)methyl)-*N*-*tert*-butylpiperazine-1-carboxamide (13e). The procedure described for the synthesis of **13a** was applied to **7** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.7 Hz, 4H), 7.25 (d, J = 8.2 Hz, 4H), 4.24 (s, 1H), 4.19 (s, 1H), 3.30 (t, J = 4.8 Hz, 4H), 2.34 (t, J = 4.4 Hz, 4H), 1.33 (s, 9H). $[M+H]^+$: 420.

4.2.7. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-(cyclohexyl)methanone (19a). To a solution of the compound **7** (161 mg, 0.5 mmol) and cyclohexanecarboxylic acid (70 mg, 0.55 mmol) in DMF (5 mL), were added DCC (113 mg, 0.55 mmol) and HOBT (74 mg, 0.55 mmol). The resulting solution was stirred at room temperature overnight. The precipitate was filtered off and the filtrate was evaporated to remove DMF. The residue was dissolved in DCM (40 mL), washed with 1 M HCl (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by prep HPLC to provide the title compound (134 mg, 0.31 mmol, 62%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 4H), 7.26 (d, J = 8.6 Hz, 4H), 4.19 (s, 1H), 3.60 (t, J = 5.1 Hz, 2H), 3.49 (t, J = 4.4 Hz, 2H), 2.49–2.38 (m, 1H), 2.35 (m, 4H), 1.81–1.75 (m, 2H), 1.70–1.65 (m, 3H), 1.55–1.43 (m, 2H), 1.25–1.18 (m, 3H). $[M+H]^+$: 431, HPLC: t_R = 6.2 min.

4.2.8. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-(cyclopentyl)methanone (19b). The procedure described for the synthesis of **19a** was applied to **7** and cyclopentylcarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.8 Hz, 4H), 7.26 (d, J = 8.8 Hz, 4H), 4.19 (s, 1H), 3.62 (t, J = 4.8 Hz, 2H), 3.51 (t, J = 4.8 Hz, 2H), 2.88–2.78 (m, 1H), 2.33 (m, 4H), 1.87–1.64 (m, 6H), 1.60–1.49 (m, 2H). $[M+H]^+$: 417.

4.2.9. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-(cyclobutyl)methanone (19c). The procedure described for the synthesis of **19a** was applied to **7** and cyclobutylcarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.8 Hz, 4H), 7.26 (d, J = 8.8 Hz, 4H), 4.18 (s, 1H), 3.61 (t, J = 4.8 Hz, 2H), 3.34 (t, J = 5.0 Hz, 2H), 3.26–3.14 (m, 1H), 2.38–2.25 (m, 6H), 2.15–2.04 (m, 2H), 2.00–1.78 (m, 2H). $[M+H]^+$: 403, HPLC: t_R = 5.5 min.

4.2.10. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-(cyclopropyl)methanone (19d). The procedure described for the synthesis of **19a** was applied to **7** and cyclopropylcarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.6 Hz, 4H), 7.26 (d, J = 8.6 Hz, 4H), 4.21 (s, 1H), 3.65 (m, 4H), 2.37 (m, 4H), 1.72–1.65 (m, 1H), 0.99–0.90 (m, 2H), 0.76–0.70 (m, 2H). $[M+H]^+$: 389.

4.2.11. 1-(4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-2-ethylbutan-1-one (19e). The procedure described for the synthesis of **19a** was applied to **7** and 2-ethylbutanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.6 Hz, 4H), 7.27 (d, J = 8.2 Hz, 4H), 4.18 (s, 1H), 3.67 (t, J = 5.0 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 2.50–2.40 (m, 1H), 2.34 (m, 4H), 1.72–1.57 (m, 2H), 1.52–1.38 (m, 2H), 0.84 (t, J = 7.5 Hz, 6H). $[M+H]^+$: 419.

4.2.12. 1-(4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)butan-1-one (19f). The procedure described for the synthesis of **19a** was applied to **7** and butanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4 Hz, 4H), 7.26 (d, J = 8.6 Hz, 4H), 4.20 (s, 1H), 3.61 (t, J = 4.6 Hz, 2H), 3.46 (t, J = 4.7 Hz, 2H), 2.33

(m, 4H), 2.26 (t, J = 7.3 Hz, 2H), 1.69–1.57 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 391.

4.2.13. 1-(4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-2-methylpropan-1-one (19g). The procedure described for the synthesis of **19a** was applied to **7** and isobutanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4 Hz, 4H), 7.26 (d, J = 8.6 Hz, 4H), 4.20 (s, 1H), 3.62 (t, J = 4.4 Hz, 2H), 3.50 (t, J = 4.5 Hz, 2H), 2.78–2.69 (m, 1H), 2.35 (m, 4H), 1.10 (d, J = 6.8 Hz, 6H). $[M+H]^+$: 391.

4.2.14. 1-(4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-hexan-1-one (19h). The procedure described for the synthesis of **19a** was applied to **7** and hexanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4 Hz, 4H), 7.26 (d, J = 8.6 Hz, 4H), 4.20 (s, 1H), 3.61 (t, J = 4.8 Hz, 2H), 3.45 (t, J = 4.6 Hz, 2H), 2.33 (m, 4H), 2.27 (t, J = 7.3, 2H), 1.65–1.57 (m, 2H), 1.32–1.28 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H). $[M+H]^+$: 419, HPLC: t_R = 6.2 min.

4.2.15. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)(furan-2-yl)methanone (19i). The procedure described for the synthesis of **19a** was applied to **7** and 2-furanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 7.33 (d, J = 8.6 Hz, 4H), 7.27 (d, J = 8.6 Hz, 4H), 6.97 (d, J = 3.5 Hz, 1H), 6.45 (m, 1H), 4.23 (s, 1H), 3.80 (m, 4H), 2.42 (t, J = 5.0 Hz, 4H). $[M+H]^+$: 415.

4.2.16. (4-(Bis(4-chlorophenyl)methyl)piperazin-1-yl)-(thiophen-2-yl)methanone (19j). The procedure described for the synthesis of **19a** was applied to **7** and thiophene-2-carboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42(d, J = 5.1 Hz, 1H), 7.32 (d, J = 8.4 Hz, 4H), 7.27–7.24 (m, 5H), 7.01 (m, 1H), 4.23 (s, 1H), 3.75 (t, J = 4.8 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H). $[M+H]^+$: 431.

4.2.17. Benzyl 4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxylate (21a). To a solution of the compound **7** (161 mg, 0.5 mmol) and TEA (0.077 mL, 0.55 mmol) in DCM (4 mL) was added dropwise benzylchloroformate (94 mg, 0.55 mmol) in DCM (1 mL) at 0 °C. The resulting mixture was subsequently stirred at room temperature overnight. 1 M HCl (20 mL) was poured into the reaction mixture and extracted with DCM (2× 20 mL). The combined DCM was washed successively with water, dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by prep HPLC to yield the title compound (160 mg, 0.35 mmol, 70%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 13H), 5.11 (s, 2H), 4.20 (s, 1H), 3.50 (t, J = 5.0 Hz, 4H), 2.33 (m, 4H). $[M+H]^+$: 455.

4.2.18. Phenyl 4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxylate (21b). The procedure described for the synthesis of **21a** was applied to **7** and phenylchloroformate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 10H), 7.20–7.16 (m, 1H), 7.10–7.06 (m, 2H), 4.26 (s, 1H), 3.62 (m, 4H), 2.42 (t, J = 5.1 Hz, 4H). $[M+H]^+$: 441.

4.2.19. Neopentyl 4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxylate (21c). The procedure described for the synthesis of **21a** was applied to **7** and neopentylchloroformate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 4H), 7.26 (d, J = 8.8 Hz, 4H), 4.20 (s, 1H), 3.76 (s, 2H), 3.49 (t, J = 5.1 Hz, 4H), 2.34 (t, J = 5.1 Hz, 4H), 0.91 (s, 9H). $[M+H]^+$: 435.

4.2.20. *tert*-Butyl 4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxylate (21d). The procedure described for the synthesis of **21a** was applied to **7** and *tert*-butylchloroformate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 7.8 Hz, 4H), 7.25 (d, J = 6.9 Hz, 4H), 4.19 (s, 1H), 3.41 (t, J = 5.2 Hz, 4H), 2.31 (t, J = 4.4 Hz, 4H), 1.43 (s, 9H). $[M+H]^+$: 421.

4.2.21. Butyl 4-(bis(4-chlorophenyl)methyl)piperazine-1-carboxylate (21e). The procedure described for the synthesis of **21a** was applied to **7** and butylchloroformate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 4H), 7.25 (d, J = 8.6 Hz, 4H), 4.20 (s, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 5.0 Hz, 4H), 2.32 (t, J = 5.0 Hz, 4H), 1.63–1.54 (m, 2H), 1.42–1.25 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 421.

4.2.22. 1-(Bis(4-chlorophenyl)methyl)-4-(ethylsulfonyl)-piperazine (22a). To a solution of 1-(bis(4-chlorophenyl)methyl)piperazine (257 mg, 0.8 mmol) and ethanesulfonyl chloride (103 mg, 0.8 mmol) in DCM (5 mL) was added dropwise TEA (0.123 mL, 0.88 mmol) at room temperature. The resulting mixture was subsequently stirred at room temperature overnight. 1 M HCl (20 mL) was poured into the reaction mixture and extracted with DCM (2× 20 mL). The combined DCM was washed successively with water, dried over $MgSO_4$ and evaporated under vacuum. The residue was further purified by prep HPLC to yield the title compound (141 mg, 0.34 mmol, 43%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.4 Hz, 4H), 7.26 (d, J = 8.8 Hz, 4H), 4.25 (s, 1H), 3.30 (t, J = 4.8 Hz, 4H), 2.95 (q, J = 7.5 Hz, 2H), 2.45 (t, J = 4.8 Hz, 4H), 1.38 (t, J = 7.5 Hz, 3H). $[M+H]^+$: 441.

4.2.23. 1-(Bis(4-chlorophenyl)methyl)-4-(isopropylsulfonyl)piperazine (22b). The procedure described for the synthesis of **22a** was applied to **7** and isopropanesulfonyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.7 Hz, 4H), 7.26 (d, J = 8.7 Hz, 4H), 4.24 (s, 1H), 3.36 (t, J = 4.8 Hz, 4H), 3.17 (m, 1H), 2.42 (t, J = 4.8 Hz, 4H), 1.34 (d, J = 6.9 Hz, 6H). $[M+H]^+$: 427.

4.2.24. 1-(Bis(4-chlorophenyl)methyl)-4-(butylsulfonyl)-piperazine (22c). The procedure described for the synthesis of **22a** was applied to **7** and butanesulfonyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.24 (m, 8H), 4.25 (s, 1H), 3.29 (m, 4H), 2.91 (t, J = 7.5 Hz, 2H), 2.45 (m, 4H), 1.85–1.75 (m, 2H), 1.51–1.39 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). $[M+H]^+$: 441.

4.2.25. 1-(Bis(4-chlorophenyl)methyl)-4-(octylsulfonyl)piperazine (22d). The procedure described for the synthesis of **22a** was applied to **7** and octanesulfonyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.8 Hz, 4H), 7.26 (d, J = 8.8 Hz, 4H), 4.24 (s, 1H), 3.28 (t, J = 4.4 Hz, 4H), 2.89 (t, J = 8.1 Hz, 2H), 2.45 (t, J = 4.4 Hz, 4H), 1.86–1.76 (m, 2H), 1.45–1.35 (m, 2H), 1.35–1.20 (m, 8H), 0.89 (t, J = 0.66 Hz, 3H). $[M+H]^+$: 497.

4.2.26. 1-(Bis(4-chlorophenyl)methyl)-4-tosylpiperazine (22e). The procedure described for the synthesis of **22a** was applied to **7** and tosyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.22 (s, 8H), 4.19 (s, 1H), 3.00 (t, J = 4.0 Hz, 4H), 2.47 (s, 3H), 2.44 (t, J = 4.4 Hz, 4H). $[M+H]^+$: 475.

4.2.27. 1-(Bis(4-chlorophenyl)methyl)-4-(4-chlorophenylsulfonyl)piperazine (22f). The procedure described for the synthesis of **22a** was applied to **7** and 4-chlorophenylsulfonyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.23 (s, 8H), 4.20 (s, 1H), 3.01 (t, J = 4.0 Hz, 4H), 2.44 (t, J = 4.4 Hz, 4H). $[M+H]^+$: 495.

4.2.28. 1-(Bis(4-chlorophenyl)methyl)-4-(thiophen-2-ylsulfonyl)piperazine (22g). The procedure described for the synthesis of **22a** was applied to **7** and thiophen-2-ylsulfonyl chloride providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 5.2 Hz, 1H), 7.54 (d, J = 4.0 Hz, 1H), 7.24 (s, 8H), 7.18 (t, J = 4.0 Hz, 1H), 4.21 (s, 1H), 3.08 (t, J = 4.8 Hz, 4H), 2.47 (t, J = 4.8 Hz, 4H). $[M+H]^+$: 467.

4.2.29. (4-Chlorophenyl)(2,4-dichlorophenyl)methanol (10a). To the solution of 2,4-dichlorobenzaldehyde (17.5 g, 0.10 mol) in THF (400 mL) was added dropwise 4-chlorophenylmagnesium bromide (110 mL, 1.0 M solution in THF) at room temperature. After additional stirring for 5 h, NH_4Cl aqueous solution (1 M, 300 mL) and diethyl ether (300 mL) were added to the reaction mixture. The organic phase was removed under vacuum. The crude residue was dissolved in hexane/EtOAc (1:1, 500 mL), washed successively with brine (200 mL), dried over $MgSO_4$ and evaporated under vacuum. The further purification by flash chromatography (silica gel 60) afforded the title compound (11.2 g, 0.039 mol, 39%). $[M-H_2O+H]^+$: 266.

4.2.30. 1-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazine (12a). The procedure described for the synthesis of **7** was applied to **10a** instead of **5** providing the title product. $[M+H]^+$: 355.

4.2.31. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (14a). The procedure described for the synthesis of **13a** was applied to **12a** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.21(d, J = 7.7 Hz, 1H), 3.67–3.58 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.38–2.34 (m, 4H), 1.95–1.90 (m, 2H), 1.71–1.57 (m, 3H), 1.41–1.29 (m, 2H), 1.19–1.00 (m, 3H). $[M+H]^+$: 480, HPLC: t_R = 6.8 min.

4.2.32. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (14b). The procedure described for the synthesis of **13a** was applied to **12a** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.28 (d, J = 7.4 Hz, 1H), 3.88–3.78 (m, 1H), 3.31 (t, J = 5.1 Hz, 4H), 2.41–2.32 (m, 4H), 1.94–1.85 (m, 2H), 1.61–1.36 (m, 10H). $[M+H]^+$: 494, HPLC: t_R = 7.0 min.

4.2.33. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (14c). The procedure described for the synthesis of **13a** was applied to **12a** and cyclohexanemethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.43 (m, 1H), 3.34 (t, J = 5.0 Hz, 4H), 3.06 (t, J = 6.6 Hz, 2H), 2.39–2.32 (m, 4H), 1.72–1.60 (m, 5H), 1.46–1.38 (m, 1H), 1.28–1.10 (m, 3H), 0.94–0.83 (m, 2H). $[M+H]^+$: 494, HPLC: t_R = 7.1 min.

4.2.34. *N*-*tert*-Butyl-4-((4-chlorophenyl)(2,4-dichlorophenyl)-methyl)piperazine-1-carboxamide (14d). The procedure described for the synthesis of **13a** was applied to **12a** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.73 (s, 1H), 4.26 (s, 1H), 3.29 (t, J = 5.1 Hz, 4H), 2.42–2.30 (m, 4H), 1.33 (s, 9H). $[M+H]^+$: 454, HPLC: t_R = 6.4 min.

4.2.35. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (14e). The procedure described for the synthesis of **13a** was applied to **12a** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.15 (d, J = 7.1 Hz, 1H), 4.01–3.90 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.41–2.31 (m, 4H), 1.14 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 440.

4.2.36. *N*-Butyl-4-((4-chlorophenyl)(2,4-dichlorophenyl)-methyl)piperazine-1-carboxamide (14f). The procedure described for the synthesis of **13a** was applied to **12a** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.34 (t, J = 5.1 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.21 (q, J = 6.5 Hz, 2H), 2.42–2.31 (m, 4H), 1.52–1.43 (m, 2H), 1.39–1.27 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). $[M+H]^+$: 454.

4.2.37. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-hexylpiperazine-1-carboxamide (14g). The procedure described for the synthesis of **13a** was applied to **12a** and hexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.36 (m, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.24–3.17 (m, 2H), 2.41–2.34 (m, 4H), 1.55–1.40 (m, 2H), 1.39–1.20 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H). $[M+H]^+$: 482.

4.2.38. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-octylpiperazine-1-carboxamide (14h). The procedure described for the synthesis of **13a** was applied to **12a** and octylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.74 (s, 1H), 4.36 (t, J = 5.3 Hz, 1H), 3.33 (t, J = 5.1 Hz, 4H), 3.20 (q, J = 5.7 Hz, 2H), 2.39–2.32 (m, 4H), 1.48 (m, 2H), 1.39–1.20 (m, 10H), 0.88 (t, J = 6.4 Hz, 3H). $[M+H]^+$: 510.

4.2.39. *N*-Adamantyl-4-((4-chlorophenyl)(2,4-dichlorophenyl)methyl)piperazine-1-carboxamide (14i). The procedure described for the synthesis of **13a** was applied to **12a** and adamantylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.73 (s, 1H), 4.14 (s, 1H), 3.29 (t, J = 5.0 Hz, 4H), 2.40–2.31 (m, 4H), 2.06 (m, 3H), 1.97–1.95 (m, 6H), 1.66 (m, 6H). $[M+H]^+$: 532.

4.2.40. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-phenylpiperazine-1-carboxamide (14j). The procedure described for the synthesis of **13a** was applied to **12a** and phenylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.6 Hz, 1H), 7.37–7.24 (m, 10H), 7.06–6.99 (m, 1H), 6.31 (s, 1H), 4.77 (s, 1H), 3.47 (t, J = 4.9 Hz, 4H), 2.48–2.36 (m, 4H). $[M+H]^+$: 474.

4.2.41. *N*-Benzyl-4-((4-chlorophenyl)(2,4-dichlorophenyl)-methyl)piperazine-1-carboxamide (14k). The procedure described for the synthesis of **13a** was applied to **12a** and benzylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 11H), 4.74 (s, 1H), 4.68 (t, J = 5.3 Hz, 1H), 4.42 (d, J = 5.3 Hz, 2H), 3.36 (t, J = 5.0 Hz, 4H), 2.39–2.34 (m, 4H). $[M+H]^+$: 488.

4.2.42. 4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-*N*-(furan-2-yl)piperazine-1-carboxamide (14l). The procedure described for the synthesis of **13a** was applied to **12a** and 2-furanylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 7H), 6.32–6.30 (m, 1H), 6.21 (d, J = 3.1 Hz, 1H), 4.74 (s, 1H), 4.70 (t, J = 5.5 Hz, 1H), 4.40 (d, J = 5.3 Hz, 2H), 3.35 (t, J = 4.9 Hz, 4H), 2.41–2.31 (m, 4H). $[M+H]^+$: 464.

4.2.43. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(cyclohexyl)methanone (20a). The procedure described for the synthesis of **19a** was applied to **12a** and cyclohexanecarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.74 (s, 1H), 3.65–3.55 (m, 2H), 3.53–3.44 (m, 2H), 2.44–2.30 (m, 5H), 1.82–1.65 (m, 5H), 1.59–1.43 (m, 2H), 1.28–1.16 (m, 3H). $[M+H]^+$: 465.

4.2.44. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(cyclopentyl)methanone (20b). The procedure described for the synthesis of **19a** was applied to **12a** and cyclopentanecarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.74 (s, 1H), 3.65–3.50 (m, 2H), 3.54–3.47 (m, 2H), 2.89–2.78 (m, 1H), 2.49–2.30 (m, 4H), 1.83–1.65 (m, 6H), 1.60–1.50 (m, 2H). $[M+H]^+$: 451.

4.2.45. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(cyclobutyl)methanone (20c). The procedure described for the synthesis of **19a** was applied to **12a** and cyclobutanecarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.35–7.24 (m, 6H), 4.73 (s, 1H), 3.59 (q, J = 5.1 Hz, 2H), 3.34–3.31 (m, 2H), 3.26–3.15 (m, 1H), 2.41–2.27 (m, 6H), 2.16–2.05 (m, 2H), 2.00–1.79 (m, 2H). $[M+H]^+$: 437.

4.2.46. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(cyclopropyl)methanone (20d). The procedure described for the synthesis of **19a** was applied to **12a** and cyclopropanecarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 1H), 7.37–7.24 (m, 6H), 4.76 (s, 1H), 3.66–3.59 (m, 4H), 2.43–2.32 (m, 4H), 1.72–1.64 (m, 1H), 1.00–0.90 (m, 2H), 0.82–0.70 (m, 2H). $[M+H]^+$: 423.

4.2.47. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)-2-cyclopentylethanone (20e). The procedure described for the synthesis of **19a** was applied to **12a** and cyclopentylacetic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.74 (s, 1H), 3.63–3.57 (m, 2H), 3.50–3.43 (m, 2H), 2.41–2.30 (m, 6H), 2.28–2.15 (m, 1H), 1.87–1.77 (m, 2H), 1.64–1.49 (m, 6H), 1.20–1.06 (m, 2H). $[M+H]^+$: 465.

4.2.48. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)-2-cyclopropylethanone (20f). The procedure described for the synthesis of **19a** was applied to **12a** and cyclopropylacetic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.37–7.24 (m, 6H), 4.74 (s, 1H), 3.65–3.59 (m, 2H), 3.47–3.42 (m, 2H), 2.42–2.25 (m, 4H), 2.24 (d, J = 6.8 Hz, 2H), 1.25–0.94 (m, 1H), 0.59–0.47 (m, 2H), 0.23–0.12 (m, 2H). $[M+H]^+$: 437.

4.2.49. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)-2-methylpropan-1-one (20g). The procedure described for the synthesis of **19a** was applied to **12a** and isobutanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 1H), 7.37–7.24 (m, 6H), 4.74 (s, 1H), 3.65–3.57 (m, 2H), 3.53–3.47 (m, 2H), 2.78–2.69 (m, 1H), 2.41–2.32 (m, 4H), 1.10 (t, J = 6.8 Hz, 6H). $[M+H]^+$: 425.

4.2.50. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)-2-ethylbutan-1-one (20h). The procedure described for the synthesis of **19a** was applied to **12a** and 2-ethylbutanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.73 (s, 1H), 3.70–3.62 (m, 2H), 3.59–3.51 (m, 2H), 2.50–2.29 (m, 5H), 1.72–1.57 (m, 2H), 1.52–1.38 (m, 2H), 0.85 (t, J = 7.3 Hz, 6H). $[M+H]^+$: 453.

4.2.51. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)butan-1-one (20i). The procedure described for the synthesis of **19a** was applied to **12a** and butanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.6 Hz, 1H), 7.36–7.25 (m, 6H), 4.74 (s, 1H), 3.64–3.56 (m, 2H), 3.48–3.42 (m, 2H), 2.39–2.31 (m, 4H), 2.27 (t, J = 7.3 Hz, 2H), 1.70–1.57 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 425.

4.2.52. 1-(4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)hexan-1-one (20j). The procedure described for the synthesis of **19a** was applied to **12a** and hexanoic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 1H), 7.36–7.24 (m, 6H), 4.74 (s, 1H), 3.65–3.54 (m, 2H), 3.46–3.42 (m, 2H), 2.42–2.31 (m, 4H), 2.28 (t, J = 7.5 Hz, 2H), 1.65–1.55 (m, 2H), 1.36–1.25 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H). $[M+H]^+$: 453, HPLC: t_R = 7.6 min.

4.2.53. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(furan-2-yl)methanone (20k). The procedure described for the synthesis of **19a** was applied to **12a** and 2-furanylcarboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 1H), 7.44–7.43 (m, 1H), 7.38–7.24 (m, 6H), 6.98 (d, J = 7.3 Hz, 1H), 6.46 (q, J = 1.7 Hz, 1H), 4.78 (s, 1H), 3.85–3.74 (m, 4H), 2.49–2.38 (m, 4H). $[M+H]^+$: 449.

4.2.54. (4-((4-Chlorophenyl)(2,4-dichlorophenyl)methyl)-piperazin-1-yl)(thiophen-2-yl)methanone (20l). The procedure described for the synthesis of **19a** was applied to **12a** and thiophene-2-carboxylic acid providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 1H), 7.43–7.41 (m, 1H), 7.37–7.24 (m, 7H), 7.03–6.99 (m, 1H), 4.78 (s, 1H), 3.74 (t, J = 4.9 Hz, 4H), 2.45–2.38 (m, 4H). $[M+H]^+$: 465.

4.2.55. (4-Chlorophenyl)(2,3-dichlorophenyl)methanol (10b). The procedure described for the synthesis of **10a** was applied to 2,3-dichlorobenzaldehyde instead of 2,4-dichlorobenzaldehyde providing the title product. $[M-H_2O+H]^+$: 269.

4.2.56. 1-((4-Chlorophenyl)(2,3-dichlorophenyl)methyl)-piperazine (12b). The procedure described for the synthesis of **7** was applied to **10b** instead of **5** providing the title product. $[M+H]^+$: 355.

4.2.57. 4-((4-Chlorophenyl)(2,3-dichlorophenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (15a). The procedure described for the synthesis of **13a** was applied to **12b** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 1H), 7.37–7.32 (m, 3H), 7.27–7.20 (m, 3H), 4.81 (s, 1H), 4.22 (d, J = 7.5 Hz, 1H), 3.71–3.58 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.44–2.30 (m, 4H), 1.98–1.87 (m, 2H), 1.75–1.52 (m, 3H), 1.45–1.24 (m, 2H), 1.20–1.00 (m, 3H). $[M+H]^+$: 480, HPLC: t_R = 6.6 min.

4.2.58. 4-((4-Chlorophenyl)(2,3-dichlorophenyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (15b). The procedure described for the synthesis of **13a** was applied to **12b** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 1H), 7.37–7.32 (m, 3H), 7.27–7.20 (m, 3H), 4.81 (s, 1H), 4.30 (d, J = 7.1 Hz, 1H), 3.86–3.78 (m, 1H), 3.32 (t, J = 5.1 Hz, 4H), 2.43–2.30 (m, 4H), 1.96–1.86 (m, 2H), 1.64–1.33 (m, 10H). $[M+H]^+$: 494, HPLC: t_R = 6.9 min.

4.2.59. 4-((4-Chlorophenyl)(2,3-dichlorophenyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (15c). The procedure described for the synthesis of **13a** was applied to **12b** and cyclohexylmethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 1H), 7.37–7.32 (m, 3H), 7.27–7.20 (m, 3H), 4.81 (s, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.34 (t, J = 5.0 Hz, 4H), 3.06 (t, J = 6.0 Hz, 2H), 2.44–2.30 (m, 4H), 1.75–1.63 (m, 5H), 1.51–1.37 (m, 1H), 1.28–1.11 (m, 3H), 0.95–0.83 (m, 2H). $[M+H]^+$: 494, HPLC: t_R = 7.0 min.

4.2.60. *N*-*tert*-Butyl-4-((4-chlorophenyl)(2,3-dichlorophenyl)-methyl)piperazine-1-carboxamide (15d). The procedure described for the synthesis of **13a** was applied to **12b** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 1H), 7.38–7.32 (m, 3H), 7.27–7.20 (m, 3H), 4.81 (s, 1H), 4.26 (s, 1H), 3.30 (t, J = 5.1 Hz, 4H), 2.43–2.30 (m, 4H), 1.33 (s, 9H). $[M+H]^+$: 454, HPLC: t_R = 6.3 min.

4.2.61. 4-((4-Chlorophenyl)(2,3-dichlorophenyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (15e). The procedure described for the synthesis of **13a** was applied to **12b** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.7 Hz, 1H), 7.38–7.32 (m, 3H), 7.27–7.21 (m, 3H), 4.81 (s, 1H), 4.16 (d, J = 7.1 Hz, 1H), 4.01–3.90 (m, 1H), 3.32 (t, J = 5.1 Hz, 4H), 2.44–2.30 (m, 4H), 1.14 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 440.

4.2.62. *N*-Butyl-4-((4-chlorophenyl)(2,3-dichlorophenyl)-methyl)piperazine-1-carboxamide (15f). The procedure described for the synthesis of **13a** was applied to **12b** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.7 Hz, 1H), 7.38–7.32 (m, 3H), 7.27–7.21 (m, 3H), 4.81 (s, 1H), 4.38 (t, J = 5.1 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.21 (q, J = 7.0 Hz, 2H), 2.44–2.30 (m, 4H), 1.52–1.43 (m, 2H), 1.39–1.27 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H). $[M+H]^+$: 454.

4.2.63. (2-Chlorophenyl)(4-chlorophenyl)methanol (10c). The procedure described for the synthesis of **10a** was applied to 2-chlorobenzaldehyde instead of 2,4-dichlorobenzaldehyde providing the title product. $[M-H_2O+H]^+$: 235.

4.2.64. 1-((2-Chlorophenyl)(4-chlorophenyl)methyl)piperazine (12c). The procedure described for the synthesis of **7** was applied to **10c** instead of **5** providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.29–7.21 (m, 4H), 7.12 (t, J = 7.2 Hz, 1H), 4.82 (s, 1H), 2.98 (t, J = 5.2 Hz, 4H), 2.51–2.42 (m, 4H). $[M+H]^+$: 321.

4.2.65. 4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (16a). The procedure described for the synthesis of **13a** was applied to **12c** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.31–7.23 (m, 4H), 7.13 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.22 (d, J = 7.8 Hz, 1H), 3.68–3.58 (m, 1H), 3.32 (t, J = 5.5 Hz, 4H), 2.43–2.32 (m, 4H), 1.97–1.89 (m, 2H), 1.72–1.56 (m, 3H), 1.43–1.29 (m, 2H), 1.19–1.01 (m, 3H). $[M+H]^+$: 446, HPLC: t_R = 5.7 min.

4.2.66. 4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (16b). The procedure described for the synthesis of **13a** was applied to **12c** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.31–7.23 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.29 (d, J = 7.3 Hz, 1H), 3.87–3.78 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.43–2.32 (m, 4H), 1.96–1.88 (m, 2H), 1.64–1.33 (m, 10H). $[M+H]^+$: 460, HPLC: t_R = 6.0 min.

4.2.67. 4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (16c). The procedure described for the synthesis of **13a** was applied to **12c** and cyclohexylmethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.31–7.23 (m, 4H), 7.14 (t, J = 7.4 Hz, 1H), 4.81 (s, 1H), 4.46 (t, J = 5.5 Hz, 1H), 3.34 (t, J = 5.0 Hz, 4H), 3.06 (t, J = 6.0 Hz, 2H), 2.44–2.33 (m, 4H), 1.74–1.65 (m, 5H), 1.49–1.38 (m, 1H), 1.27–1.11 (m, 3H), 0.95–0.83 (m, 2H). $[M+H]^+$: 460, HPLC: t_R = 6.1 min.

4.2.68. *N*-*tert*-Butyl-4-((2-chlorophenyl)(4-chlorophenyl)-methyl)piperazine-1-carboxamide (16d). The procedure described for the synthesis of **13a** was applied to **12c** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.31–7.23 (m, 4H), 7.13 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.25 (s, 1H), 3.29 (t, J = 5.5 Hz, 4H), 2.43–2.32 (m, 4H), 1.33 (s, 9H). $[M+H]^+$: 420, HPLC: t_R = 5.2 min.

4.2.69. 4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (16e). The procedure described for the synthesis of **13a** was applied to **12c** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.31–7.23 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.16 (d, J = 7.3 Hz, 1H), 4.0–3.91 (m, 1H), 3.32 (t, J = 5.5 Hz, 4H), 2.43–2.32 (m, 4H), 1.14 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 406.

4.2.70. *N*-Butyl-4-((2-chlorophenyl)(4-chlorophenyl)methyl)-piperazine-1-carboxamide (16f). The procedure described for the synthesis of **13a** was applied to **12c** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.31–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.38 (t, J = 5.0 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.22 (q, J = 6.9 Hz, 2H), 2.43–2.32 (m, 4H), 1.51–1.43 (m, 2H), 1.38–1.28 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 420.

4.2.71. 4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-*N*-hexylpiperazine-1-carboxamide (16g). The procedure described for the synthesis of **13a** was applied to **12c** and hexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.31–7.23 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.37 (t, J = 5.0 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.21 (q, J = 6.4 Hz, 2H), 2.43–2.32 (m, 4H), 1.51–1.44 (m, 2H), 1.34–1.25 (m, 6H), 0.88 (t, J = 7.4 Hz, 3H). $[M+H]^+$: 448.

4.2.72. (4-Chlorophenyl)(*o*-tolyl)methanol (10d). The procedure described for the synthesis of **10a** was applied to *o*-tolualdehyde instead of 2,4-dichlorobenzaldehyde providing the title product. $[M-H_2O+H]^+$: 215.

4.2.73. 1-((4-Chlorophenyl)(*o*-tolyl)methyl)piperazine (12d). The procedure described for the synthesis of **7** was applied to **10d** instead of **5** providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 9.2 Hz, 2H), 7.24–7.16 (m, 3H), 7.12–7.03 (m, 2H), 4.46 (s, 1H), 3.05–2.99 (m, 2H), 2.57–2.54 (m, 2H), 2.47–2.40 (m, 4H), 2.29 (s, 3H). $[M+H]^+$: 301.

4.2.74. 4-((4-Chlorophenyl)(*o*-tolyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (17a). The procedure described for the synthesis of **13a** was applied to **12d** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.3 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.26–7.20 (m, 3H), 7.13–7.05 (m, 2H), 4.41 (s, 1H), 4.20 (d, J = 7.3 Hz, 1H), 3.68–3.58 (m, 1H), 3.36–3.28 (m, 4H), 2.47–2.38 (m, 2H), 2.31–2.25 (m, 5H), 1.97–1.90 (m, 2H), 1.73–1.56 (m, 3H), 1.42–1.30 (m, 2H), 1.19–1.01 (m, 3H). $[M+H]^+$: 426, HPLC: t_R = 4.3 min.

4.2.75. 4-((4-Chlorophenyl)(*o*-tolyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (17b). The procedure described for the synthesis of **13a** was applied to **12d** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.26–7.20 (m, 3H), 7.14–7.05 (m, 2H), 4.41 (s, 1H), 4.28 (d, J = 7.8 Hz, 1H), 3.87–3.78 (m, 1H), 3.35–3.28 (m, 4H), 2.45–2.38 (m, 2H), 2.31–2.24 (m, 5H), 1.96–1.88 (m, 2H), 1.64–1.33 (m, 10H). $[M+H]^+$: 440, HPLC: t_R = 5.1 min.

4.2.76. 4-((4-Chlorophenyl)(*o*-tolyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (17c). The procedure described for the synthesis of **13a** was applied to **12d** and cyclohexylmethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.26–7.18 (m, 3H), 7.13–7.04 (m, 2H), 4.45–4.40 (m, 2H), 3.38–3.29 (m, 4H), 3.06 (t, J = 6.4 Hz, 2H), 2.47–2.38 (m, 2H), 2.33–2.26 (m, 5H), 1.74–1.62 (m, 5H), 1.49–1.38 (m, 1H), 1.27–1.11 (m, 3H), 0.95–0.83 (m, 2H). $[M+H]^+$: 440, HPLC: t_R = 5.2 min.

4.2.77. *N*-*tert*-Butyl-4-((4-chlorophenyl)(*o*-tolyl)methyl)piperazine-1-carboxamide (17d). The procedure described for the synthesis of **13a** was applied to **12d** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.26–7.20 (m, 3H), 7.13–7.05 (m, 2H), 4.41 (s, 1H), 4.24 (s, 1H), 3.32–3.27 (m, 4H), 2.46–2.38 (m, 2H), 2.31–2.25 (m,5H), 1.33 (s, 9H). $[M+H]^+$: 400, HPLC: t_R = 3.0 min.

4.2.78. 4-((4-Chlorophenyl)(*o*-tolyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (17e). The procedure described for the synthesis of **13a** was applied to **12d** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.27–7.20 (m, 3H), 7.14–7.06 (m, 2H), 4.41 (s, 1H), 4.14 (d, J = 7.3 Hz, 1H), 4.01–3.91 (m, 1H), 3.35–3.26 (m, 4H), 2.46–2.37 (m, 2H), 2.31–2.25 (m, 5H), 1.14 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 386.

4.2.79. *N*-Butyl-4-((4-chlorophenyl)(*o*-tolyl)methyl)piperazine-1-carboxamide (17f). The procedure described for the synthesis of **13a** was applied to **12d** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.26–7.20 (m, 3H), 7.14–06 (m, 2H), 4.41 (s, 1H), 4.34 (t, J = 5.5 Hz, 1H), 3.36–3.29 (m, 4H), 3.22 (q, J = 6.8 Hz, 2H), 2.46–2.38 (m, 2H), 2.31–2.26 (m, 5H), 1.53–1.42 (m, 2H), 1.38–1.28 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 400.

4.2.80. 4-((4-Chlorophenyl)(*o*-tolyl)methyl)-*N*-hexylpiperazine-1-carboxamide (17g). The procedure described for the synthesis of **13a** was applied to **12d** and hexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.26–7.18 (m, 3H), 7.14–7.05 (m, 2H), 4.41 (s, 1H), 4.34 (t, J = 5.0 Hz, 1H), 3.38–3.28 (m, 4H), 3.21 (q, J = 6.4 Hz, 2H), 2.47–2.39 (m, 2H), 2.31–2.25 (m, 5H), 1.51–1.43 (m, 2H), 1.35–1.24 (m, 6H), 0.88 (t, J = 7.4 Hz, 3H). $[M+H]^+$: 428.

4.2.81. (4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methanol (10e). The procedure described for the synthesis of **10a** was applied to 2-(trifluoromethyl)benzaldehyde instead of 2,4-dichlorobenzaldehyde providing the title product. $[M-H_2O+H]^+$: 269.

4.2.82. 1-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)piperazine (12e). The procedure described for the synthesis of **7** was applied to **10e** instead of **5** providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.31–7.22 (m, 3H), 4.69 (s, 1H), 2.91 (t, J = 4.8 Hz, 4H), 2.44–2.31 (m, 4H). $[M+H]^+$: 355.

4.2.83. 4-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (18a). The procedure described for the synthesis of **13a** was applied to **12e** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34–7.22 (m, 3H), 4.67 (s, 1H), 4.22 (d, J = 7.6 Hz, 1H), 3.65–3.54 (m, 1H), 3.36–3.27 (m, 4H), 2.45–2.35 (m, 2H), 2.33–2.24 (m, 2H), 1.97–1.88 (m, 2H), 1.73–1.55 (m, 3H), 1.42–1.29 (m, 2H), 1.19–1.01 (m, 3H). $[M+H]^+$: 480, HPLC: t_R = 6.4 min.

4.2.84. 4-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (18b). The procedure described for the synthesis of **13a** was applied to **12e** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.34–7.23 (m, 3H), 4.67 (s, 1H), 4.29 (d, J = 7.6 Hz, 1H), 3.87–3.76 (m, 1H), 3.35–3.25 (m, 4H), 2.45–2.37 (m, 2H), 2.33–2.23 (m, 2H), 1.95–1.85 (m, 2H), 1.66–1.33 (m, 10H). $[M+H]^+$: 494, HPLC: t_R = 6.7 min.

4.2.85. 4-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (18c). The procedure described for the synthesis of **13a** was applied to **12e** and cyclohexylmethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.34–7.23 (m, 3H), 4.67 (s, 1H), 4.45 (t, J = 5.2 Hz, 1H), 3.31 (t, J = 5.2 Hz, 4H), 3.05 (t, J = 6.4 Hz, 2H), 2.44–2.37 (m, 2H), 2.32–2.25 (m, 2H), 1.74–1.61 (m, 5H), 1.49–1.37 (m, 1H), 1.27–1.10 (m, 3H), 0.95–0.82 (m, 2H). $[M+H]^+$: 494, HPLC: t_R = 6.8 min.

4.2.86. *N*-*tert*-Butyl-4-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxamide (18d). The procedure described for the synthesis of **13a** was applied to **12e** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.34–7.24 (m, 3H), 4.67 (s, 1H), 4.25 (s, 1H), 3.27 (t, J = 4.8 Hz, 4H), 2.43–2.36 (m, 2H), 2.31–2.25 (m,2H), 1.33 (s, 9H). $[M+H]^+$: 454, HPLC: t_R = 6.1 min.

4.2.87. 4-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (18e). The procedure described for the synthesis of **13a** was applied to **12e** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.35–7.24 (m, 3H), 4.68 (s, 1H), 4.16 (d, J = 6.8 Hz, 1H), 4.0–3.91 (m, 1H), 3.35–3.26 (m, 4H), 2.45–2.36 (m, 2H), 2.32–2.25 (m, 5H), 1.13 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 440.

4.2.88. *N*-Butyl-4-((4-chlorophenyl)(2-(trifluoromethyl)phenyl)methyl)piperazine-1-carboxamide (18f). The procedure described for the synthesis of **13a** was applied to **12e** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34–7.25 (m, 3H), 4.67 (s, 1H), 4.37 (t, J = 5.5 Hz, 1H), 3.31 (t, J = 4.8 Hz, 4H),

3.21 (q, J = 7.2 Hz, 2H), 2.44–2.37 (m, 2H), 2.31–2.26 (m, 2H), 1.50–1.43 (m, 2H), 1.38–1.28 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H). $[M+H]^+$: 454.

4.2.89. 4-((4-Chlorophenyl)(2-(trifluoromethyl)phenyl)-methyl)-*N*-hexylpiperazine-1-carboxamide (18g). The procedure described for the synthesis of **13a** was applied to **12e** and hexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34–7.24 (m, 3H), 4.67 (s, 1H), 4.38 (t, J = 5.0 Hz, 1H), 3.31 (t, J = 5.2 Hz, 4H), 3.20 (q, J = 6.8 Hz, 2H), 2.44–2.37 (m, 2H), 2.32–2.27 (m, 2H), 1.51–1.43 (m, 2H), 1.35–1.23 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H). $[M+H]^+$: 482.

4.2.90. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-*N*-cyclohexyl-2-oxoacetamide (23a). Oxalyl chloride (857 mg, 6.8 mmol) was added to DCM (10 mL) with TEA (0.17 mL, 1.25 mmol) at 0 °C under nitrogen. After stirring for 10 min at 0 °C, 1-((2-chlorophenyl)(4-chlorophenyl)methyl)piperazine (**12c**, 0.2 g, 0.62 mmol) in DCM (2 mL) was added to the solution. The resulting solution was allowed to warm to room temperature, stirred overnight and evaporated under vacuum. The residue was dissolved in DCM (5 mL) and cyclohexylamine (185 mg, 1.87 mmol) in DCM (1 mL) was added to the above solution. After stirring at room temperature overnight, the reaction mixture was poured into 1 M HCl (20 mL) and extracted with DCM (2× 20 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was further purified by prep HPLC to provide the title compound (100 mg, 0.21 mmol, 34%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.31–7.24 (m, 4H), 7.17–7.11 (m, 2H), 4.83 (s, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.85–3.62 (m, 3H), 2.53–2.39 (m, 4H), 1.95–1.85 (m, 2H), 1.79–1.57 (m, 3H), 1.42–1.05 (m, 5H). $[M+H]^+$: 474, HPLC: t_R = 6.7 min.

4.2.91. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-*N*-cycloheptyl-2-oxoacetamide (23b). The procedure described for the synthesis of **23a** was applied to cycloheptylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.0 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.31–7.24 (m, 4H), 7.20–7.11 (m, 2H), 4.83 (s, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.95–3.82 (m, 1H), 3.65 (t, J = 5.0 Hz, 2H), 2.50–2.37 (m, 4H), 1.96–1.87 (m, 2H), 1.70–1.40 (m, 10H). $[M+H]^+$: 488, HPLC: t_R = 6.9 min.

4.2.92. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-2-oxo-*N*-(piperidin-1-yl)acetamide (23c). The procedure described for the synthesis of **23a** was applied to aminopiperidine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.31–7.24 (m, 4H), 7.14 (t, J = 7.7 Hz, 1H), 4.82 (s, 1H), 4.10 (t, J = 5.0 Hz, 2H), 3.63 (m, 2H), 2.82–2.62 (m, 4H), 2.51–2.38 (m, 4H), 1.76–1.59 (m, 4H), 1.50–46 (m, 2H). $[M+H]^+$: 475.

4.2.93. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-*N*-cyclopentyl-2-oxoacetamide (23d). The procedure described for the synthesis of **23a** was applied to cyclopentylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.32–7.23 (m, 4H), 7.20–7.11 (m, 2H), 4.83 (s, 1H), 4.18–4.09 (m, 3H), 3.65 (t, J = 5.0 Hz, 2H), 2.53–2.38 (m, 4H), 2.05–1.92 (m, 2H), 1.78–1.53 (m, 4H), 1.51–1.39 (m, 2H). $[M+H]^+$: 460.

4.2.94. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-*N*-cyclobutyl-2-oxoacetamide (23e). The procedure described for the synthesis of **23a** was applied to cyclobutylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 8.4 Hz, 3H), 7.31–7.24 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 4.82 (s, 1H), 4.40–4.20 (m, 1H), 4.14 (t, J = 5.0 Hz, 2H), 3.65 (t, J = 4.8 Hz, 2H), 2.51–2.40 (m, 4H), 2.39–2.20 (m, 2H), 2.10–1.86 (m, 2H), 1.81–1.67 (m, 2H). $[M+H]^+$: 446.

4.2.95. *N*-*tert*-Butyl-2-(4-((2-chlorophenyl)(4-chlorophenyl)-methyl)piperazin-1-yl)-2-oxoacetamide (23f). The procedure described for the synthesis of **23a** was applied to *tert*-butylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.31–7.24 (m, 4H), 7.14 (t, J = 7.7 Hz, 1H), 7.02 (s, 1H), 4.83 (s, 1H), 4.09 (t, J = 5.1 Hz, 2H), 3.63 (t, J = 5.1 Hz, 2H), 2.51–2.42 (m, 4H), 1.36 (s, 9H). $[M+H]^+$: 448.

4.2.96. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-2-oxo-*N*-(pentan-3-yl)acetamide (23g). The procedure described for the synthesis of **23a** was applied to pentan-3-amine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.31–7.24 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 4.83 (s, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.78–3.62 (m, 3H), 2.45 (q, J = 5.0 Hz, 4H), 2.52–2.38 (m, 4H), 1.63–1.51 (m, 2H), 1.48–1.33 (m, 2H), 0.89 (t, J = 7.3 Hz, 6H). $[M+H]^+$: 462.

4.2.97. *N*-Butyl-2-(4-((2-chlorophenyl)(4-chlorophenyl)-methyl)piperazin-1-yl)-2-oxoacetamide (23h). The procedure described for the synthesis of **23a** was applied to butylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.31–7.24 (m, 4H), 7.15 (t, J = 7.7 Hz, 1H), 4.83 (s, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.65 (t, J = 5.0 Hz, 2H), 3.26 (q, J = 6.2 Hz, 2H), 2.50–2.39 (m, 4H), 1.57–1.46 (m, 2H), 1.41–1.29 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). $[M+H]^+$: 448.

4.2.98. 2-(4-((2-Chlorophenyl)(4-chlorophenyl)methyl)-piperazin-1-yl)-*N*-hexyl-2-oxoacetamide (23i). The procedure described for the synthesis of **23a** was applied to hexylamine instead of cyclohexylamine providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.32–7.24

(m, 5H), 7.15 (t, J = 7.5 Hz, 1H), 4.83 (s, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.66 (t, J = 4.8 Hz, 2H), 3.25 (q, J = 6.8 Hz, 2H), 2.52–2.38 (m, 4H), 1.60–1.48 (m, 2H), 1.40–1.21 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H). $[M+H]^+$: 476.

4.2.99. (4-Bromophenyl)(2-chlorophenyl)methanol (26). 1,4-Dibromobenzene (11.8 g, 50 mmol) in THF (60 mL) was treated with *n*-BuLi (20 mL, 2.5 M solution in hexane) at −78 °C under nitrogen. After the mixture was stirred for 10 min, 2-chlorobenzaldehyde (7.03 g, 70 mmol) in THF (5 mL) was added dropwise and stirred at −78 °C for additional 1 h. The reaction mixture was allowed to warm to room temperature and stirred overnight. It was poured into water (200 mL) and extracted twice with MTBE (200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness (13.6 g, 45.8 mmol, 92%). The expected alcohol was used without further purification in the next step. $[M-H_2O+H]^+$: 281.

4.2.100. 1-((4-Bromophenyl)(2-chlorophenyl)methyl)piperazine (28). The procedure described for the synthesis of **7** was applied to **26** instead of **5** providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.0 Hz, 1H), 7.41–7.35(m, 2H), 7.33–7.21 (m, 4H), 7.15–7.08 (m, 1H), 4.86 (s, 1H), 3.07 (t, J = 4.8 Hz, 2H), 2.63–2.55 (m, 4H), 2.48–2.34 (m, 2H). $[M+H]^+$: 367.

4.2.101. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-cyclohexylpiperazine-1-carboxamide (29a). The procedure described for the synthesis of **13a** was applied to **28** and cyclohexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.34–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.22 (d, J = 7.4 Hz, 1H), 3.68–3.58 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.43–2.32 (m, 4H), 1.97–1.89 (m, 2H), 1.72–1.56 (m, 3H), 1.43–1.29 (m, 2H), 1.19–1.01 (m, 3H). $[M+H]^+$: 492, HPLC: t_R = 5.9 min.

4.2.102. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-cycloheptylpiperazine-1-carboxamide (29b). The procedure described for the synthesis of **13a** was applied to **28** and cycloheptylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.34–7.24 (m, 4H), 7.14 (t, J = 7.3 Hz, 1H), 4.79 (s, 1H), 4.28 (d, J = 7.3 Hz, 1H), 3.87–3.78 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.43–2.32 (m, 4H), 1.96–1.88 (m, 2H), 1.63–1.33 (m, 10H). $[M+H]^+$: 506, HPLC: t_R = 6.2 min.

4.2.103. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-(cyclohexylmethyl)piperazine-1-carboxamide (29c). The procedure described for the synthesis of **13a** was applied to **28** and cyclohexylmethylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.35–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.80 (s, 1H), 4.45 (t, J = 5.5 Hz, 1H), 3.34 (t, J = 5.0 Hz, 4H), 3.06 (t, J = 6.4 Hz, 2H), 2.44–2.33 (m, 4H), 1.74–1.62 (m, 5H), 1.48–1.38 (m, 1H), 1.27–1.11 (m, 3H), 0.95–0.83 (m, 2H). $[M+H]^+$: 506, HPLC: t_R = 6.3 min.

4.2.104. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-*tert*-butylpiperazine-1-carboxamide (29d). The procedure described for the synthesis of **13a** was applied to **28** and *tert*-butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.34–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.25 (s, 1H), 3.29 (t, J = 5.0 Hz, 4H), 2.40–2.32 (m, 4H), 1.33 (s, 9H). $[M+H]^+$: 466, HPLC: t_R = 5.4 min.

4.2.105. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-isopropylpiperazine-1-carboxamide (29e). The procedure described for the synthesis of **13a** was applied to **28** and isopropylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.34–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.16 (d, J = 7.4 Hz, 1H), 4.05–3.91 (m, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.43–2.32 (m, 4H), 1.14 (d, J = 6.4 Hz, 6H). $[M+H]^+$: 452.

4.2.106. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-butylpiperazine-1-carboxamide (29f). The procedure described for the synthesis of **13a** was applied to **28** and butylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.35–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.37 (t, J = 5.5 Hz, 1H), 3.33 (t, J = 5.0 Hz, 4H), 3.22 (q, J = 7.3 Hz, 2H), 2.43–2.32 (m, 4H), 1.51–1.43 (m, 2H), 1.38–1.28 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). $[M+H]^+$: 466.

4.2.107. 4-((4-Bromophenyl)(2-chlorophenyl)methyl)-*N*-hexylpiperazine-1-carboxamide (29g). The procedure described for the synthesis of **13a** was applied to **28** and hexylisocyanate providing the title product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.35–7.24 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 4.79 (s, 1H), 4.37 (t, J = 5.0 Hz, 1H), 3.33 (t, J = 5.5 Hz, 4H), 3.21 (q, J = 6.9 Hz, 2H), 2.44–2.33 (m, 4H), 1.52–1.44 (m, 2H), 1.34–1.24 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H). $[M+H]^+$: 494.

4.3. 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.[30] 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.[31]

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.[32]

Competitive binding assays were performed as described.[33] 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]CP55,940 (for CB1 receptor, NEN; specific activity 120–190 Ci/mmol) or 3 nM [^{3}H]WIN55,212-2 (for CB2 receptor, NEN; specific activity 50–80 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 filter (PerkinElmer 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-drying 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 SR141716A and 1 μM WIN 55,212-2, respectively. Specific binding was defined as the difference between the binding that occurred in the presence and absence of 1 μM concentrations of SR 141716 A or WIN55,212-2 and was 70–80% of the total binding. IC_{50} was determined by nonlinear regression analysis using GraphPad PRISM.

4.4. Luciferase assay

The CHO-K1 cell line expressing hCB1R and CRE-luc gene was obtained from KRICT (Korea Research Institute of Chemical Technology). Cells were seeded at 5×10^4 cells/well in white 96-well microplates for luminescence, in DMEM supplemented with 10% FBS. Twenty-four hours later, cells were co-treated for 4 h with various concentrations of cannabinoid receptor–ligands, 1 μM forskolin and 10 nM CP55,940. Four hours after, cells were washed twice with phosphate-buffered saline and lysed by the addition of Luciferase assay substrate from the Bright-Glo Luciferase assay system (Promega). Measurement of light emission was determined after the addition of reconstituted luciferase assay substrate following the supplier's instructions. Luminescence was detected by a CCD camera. The quantitation of light emission was made by accumulation of photon counting, and mean values from triplicate determinations were expressed as percentage of values from forskolin-stimulated cells.[34,35]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.01.023.

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