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Chemical Modifications on 4-Arylpiperazine-Ethyl Carboxamide Derivatives Differentially Modulate Affinity for 5-HT_{1A}, D4.2, and α_{2A} Receptors: Synthesis and In Vitro Radioligand Binding Studies

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A series of substituted 4-aryl-piperazine-ethyl heteroarylcarboxamides were prepared and tested in in vitro radioligand binding studies. The presence of a quinoxaline has a favourable impact in terms of serotonin 5-HT_{1A} versus dopamine D4.2 receptor selectivity. Compounds with a 3-CF_3 group at the distal phenyl ring are the most effective in terms of affinity and selectivity for 5-HT_{1A} versus D4.2 receptors. A 4-phenyl-1,2,3,6-tetrahydropyridine in place of the corresponding 4-phenyl-piperazine side chain is also favourable not only for the affinity for 5-HT_{1A} and D4.2 receptors but also in some cases for α_{2A}-adrenoceptors.

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Introduction

Medicinal chemistry research is often focussed on either the discovery of a pharmacological tool for exploring a specific target or the development of a new drug based on a new therapeutic strategy. In the first case, selective agents are generally required for studying the role of the corresponding target. In the second case, drugs acting on several sites have also great interest.[1] Recently, multireceptor affinity strategy was put forward as an innovative approach to the discovery of new drug candidates.[1–3] This is clearly the case of clozapine (Fig. 1). Partially owing to its toxicological potential, but also because its unique therapeutic benefit for schizophrenic patients is important, clozapine has inspired the development of numerous medicinal chemistry programs. In parallel, clozapine's biological potential was extensively explored. The hypothesis of an adequate ratio of affinity for serotonin 5-HT_{2A} receptors versus dopamine D2 receptors (high affinity for serotonin 5-HT_{2A} receptors combined with a low affinity for dopamine D2 receptors)[4] led to the development of the second generation of antipsychotic drugs while, in parallel, other interaction sites of the molecule (e.g. dopamine D4 receptors) were the targets for extensive development programs.[5] Importantly, in vivo microdialysis studies and radioligand binding studies have demonstrated the beneficial combination of several neuronal interactions.[1] Thus, for instance, serotonin 5-HT_{1A} partial agonism is likely involved in the ability of clozapine and other atypical antipsychotic drugs to increase dopamine release in several important brain areas such as the hippocampus[6] and prefrontal cortex.[7,8] The highest density of 5-HT_{1A} receptors in rat brain is found in the hippocampus, followed by the medial prefrontal cortex. The interaction of various atypical antipsychotic drugs with 5-HT_{1A} receptors leading to the modulation of external dopamine concentrations has been proposed to be beneficial for improving negative symptoms and cognition in patients with schizophrenia.[9] Alternatively, α_2-adrenergic receptor antagonism has also been proposed as an explanation for the atypical antipsychotic potential of clozapine. Thus, the combination of raclopride a D2 antagonist and idazoxan an α_2-antagonist also produces a comparable effect on dopamine release in the prefrontal cortex.[10] Thus, selective or mixed ligands for these receptors (5-HT_{1A} and D4.2 receptors, and α_{2A}-adrenoceptors) would be of great interest.

In continuation of our work on a series of naphthalene carboxamides,[11,12] we observed that the replacement of the naphthalene ring by nitrogen-containing aromatic heterocycles was differentially favourable for the affinity for D4.2 receptors (J.-F. Liégeois, pers. comm.). The naphthalene moiety represents a particularly lipophilic group and appears in several medicinal programs. *N*-[2-(4-phenylpiperazin-1-yl)ethyl]-2-naphthyl carboxamide **1** (Fig. 1) is not structurally so far from these molecules and is claimed to be a 5-HT_{1A} ligand.[13] In our hands, this compound possesses effectively a high affinity for 5-HT_{1A} receptors (affinity for the receptor, $K_i = 14 \pm 4$ nM) but also a high affinity for dopamine D4.2 receptors ($K_i = 8 \pm 1$ nM) (J.-F. Liégeois, pers. comm.). Similarly, WAY100635 (Fig. 1),

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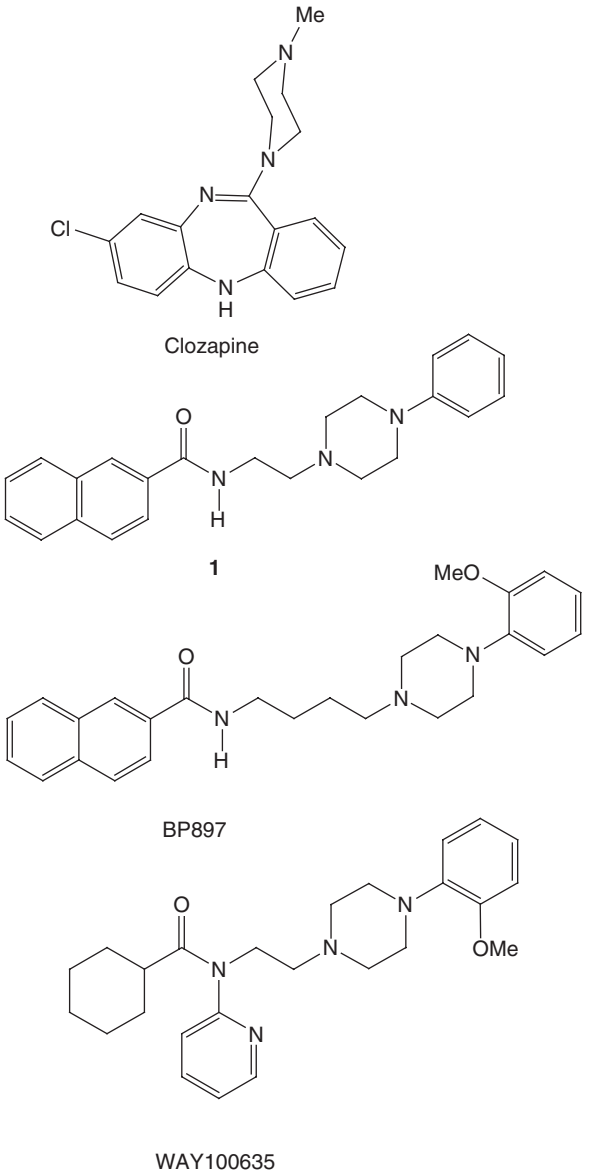


Fig. 1. Chemical structure of different dopaminergic and serotonergic ligands.

a classical 5-HT_{1A} ligand frequently used in many pharmacological investigations, has also been reported to possess a high potency for dopamine D4 receptors.[14] Otherwise, BP897 (Fig. 1), with a butyl linker between the naphthamide and the basic nitrogen, described as a dopamine D3 receptor partial agonist or as an antagonist,[15,16] was also found to have a high 5-HT_{1A} affinity ($K_i = 3 \pm 0$ nM). This fact was also recently reported by others.[17] Thus, we were interested in developing less lipophilic compounds related to compound **1** (Fig. 1) and then in examining the impact of moieties of lesser lipophilicity on the affinity for several receptors such as 5-HT_{1A} and D4.2 receptors and α_{2A}-adrenoceptors. In the present work, nitrogen-containing aromatic heterocycles were used to replace the carbon ring and we also explored different chemical modifications on the distal aromatic ring. The last one was monosubstituted by atoms or groups with different electronic, steric, or lipophilic properties. Analogues possessing a tetrahydropyridine instead of a piperazine nucleus were also prepared in order to evaluate the impact of a steric constraint. Biological evaluation was done by in vitro radioligand binding studies with human cloned receptors.

Chemistry

The target compounds were synthesized by reaction of the appropriate primary amine with the appropriate acyl chloride (2-quinoline, 3-quinoline, or 2-quinoxaline) as described in Scheme 1. The crude amines were obtained following a Gabriel procedure using the appropriate *N*-substituted phthalimides, which were synthesized by reaction of an adequate *N*-phenylpiperazine with *N*-(2-bromoethyl)phthalimide in the presence of potassium carbonate. The *N*-arylpiperazine derivatives were obtained from commercial sources, whereas *N*-(2-bromoethyl)phthalimide was purchased or prepared in house following classical methods and further characterized. Most *N*-substituted phthalimides are known. Nevertheless, they were used after purification and crystallization followed by a classical analytical characterization (e.g. ^{1}H NMR, elemental analysis). This information is summarized separately in the Accessory Publication. Target compounds were mainly isolated as the base and further characterized.

Receptor Binding Studies

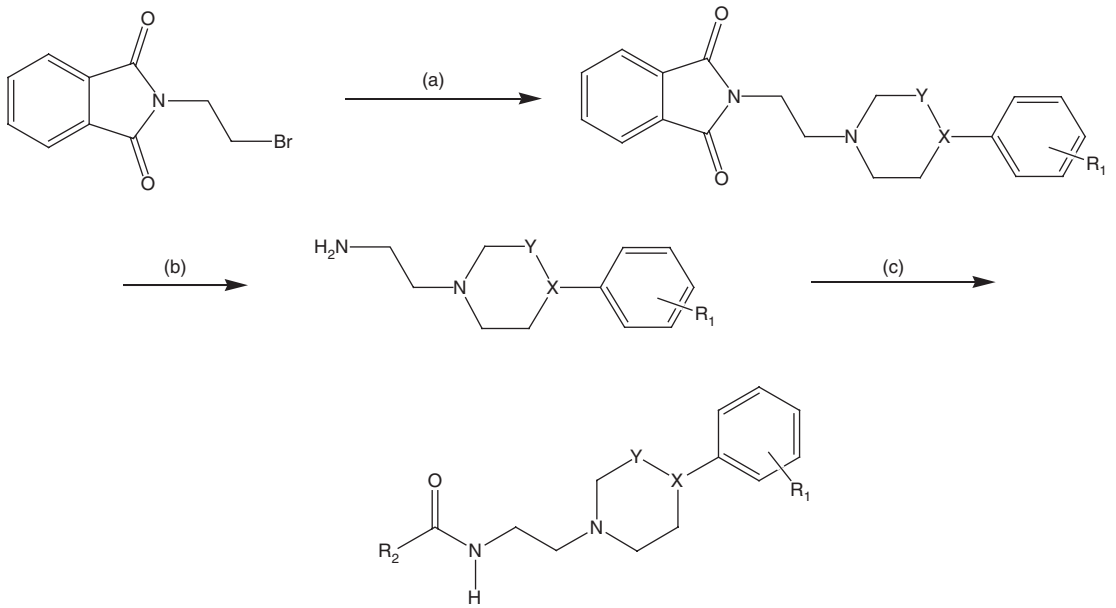
In vitro binding experiments were conducted on human cloned receptors expressed in appropriate cells and used as membrane preparations. The radioligands used were [^{3}H]-8-OH-DPAT (0.25 nM), [^{3}H]-MK912 (0.7 nM), and [^{3}H]-YM-09151–2 (0.2 nM) for 5-HT_{1A}, α_{2A}, and D4.2 receptors, respectively. Experimental procedures for filtration and radioactivity counting used previously described methodology[18] and are summarized below in the Experimental section.

The experimental data for quinoxaline, 2-quinoline, and 3-quinoline derivatives are reported in Tables 1–3 respectively.

Impact of Modifications on Serotonin 5-HT_{1A} Receptor Affinity

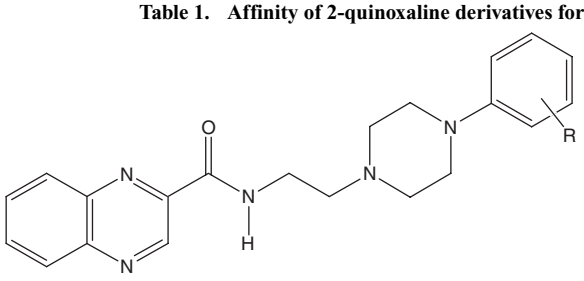
Most of the compounds tested in this work possess a significant affinity for 5-HT_{1A} receptors, although the presence of a nitrogen heterocycle compared with a naphthalene moiety significantly reduces the lipophilicity. Indeed, when measuring the log k'_{IAM}, a high-performance liquid chromatography (HPLC) approach for experimental lipophilicity measurement,[19–21] the determined values were 3.39, 2.49, 2.66, and 2.94 for the naphthalene (**1**), the quinoxaline (**2**), the 3-quinoline (**32**), and the 2-quinoline (**17**) derivatives, respectively. This parameter is quite important in the context not only of a drug development in terms of bioavailability but also in the context of pharmacological investigation when aqueous solutions are required. In a series of dopamine D3 ligands reported in the literature, the replacement of the naphthalene ring by a nitrogen-containing aromatic heterocycle led to a decrease in lipophilicity parallel to a significant reduction in affinity for this receptor.[22] In fact, the affinity was reduced by 10, 30, and 36 times for the 3-quinoline, the 2-quinoxaline, and the 2-quinoline, respectively.[22] In the present work, compared with the naphthalene analogue (**1**), the affinity was reduced by 23, 2, and 2 times for the 3-quinoline (**32**), the 2-quinoxaline (**2**), and the 2-quinoline (**17**), respectively. Therefore, the impact of such modulations leads to significant variations depending on the receptor that cannot be readily generalized.

Otherwise, we observe that the impact of the nitrogen position on the affinity for 5-HT_{1A} receptors is somewhat different. Although possessing two nitrogens and thus having a reduced



Scheme 1. Reagents and conditions: (a) *N*-(un)substituted-4-arylpiperazine (or 4-phenyl-1,2,3,6-tetrahydropyridine), K_2CO_3, reflux; (b) NH_2NH_2, EtOH, reflux; (c) acyl chloride, Et_3N, EtOAc, rt. R_1: H, 2-Cl, 3-Cl, 4-Cl, 2-F, 3-F, 4-F, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 3-CF_3. R_2: 2-quinolinyl, 3-quinolinyl, 2-quinoxalinyl. X–Y: N–CH_2 or C=CH.

Table 1. Affinity of 2-quinoxaline derivatives for human cloned 5-HT_{1A}, α_{2A}, and D4.2 receptors



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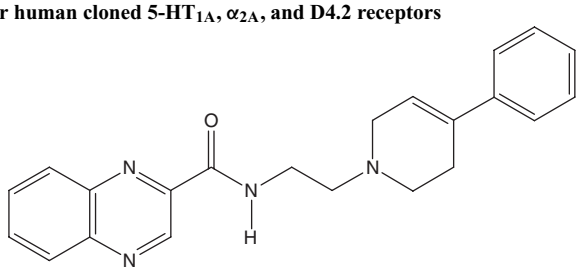


16

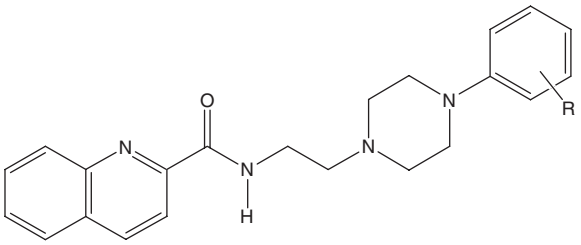
Compound	R	5-HT_{1A} affinity	α_{2A} affinity	D4.2 affinity	Selectivity[B]
2	H	28 ± 9	18[A]	41[A]	>18
3	2-F	13 ± 1	49[A]	53[A]	>38
4	3-F	11 ± 1	36[A]	27[A]	>45
5	4-F	37 ± 6	4[A]	55[A]	>14
6	2-Cl	25 ± 15	51[A]	180 ± 3	8
7	3-Cl	3.3 ± 1	11[A]	44[A]	>150
8	4-Cl	33 ± 4	15[A]	53[A]	>15
9	2-Me	11 ± 1	55[A]	244 ± 71	22
10	3-Me	3 ± 1	21[A]	32[A]	>167
11	4-Me	28 ± 0.9	10[A]	45[A]	>18
12	3-CF_3	2 ± 1	3[A]	28[A]	>250
13	2-OMe	3 ± 0	48[A]	163 ± 2	51
14	3-OMe	7 ± 3	9[A]	10[A]	>71
15	4-OMe	329 ± 91	8[A]	0[A]	1.5
16	–	4 ± 1	316 ± 3	53[A]	>125

[A] K_i (in nM, mean ± s.d.; $n \geq 2$ if unspecified) or percentage of inhibition at 1 μM.
[B] Selectivity is obtained by dividing K_i D4.2 by K_i 5-HT_{1A}. A value of 500 nM was chosen for compounds having low affinity and thus the selectivity is superior to the mentioned value.

lipophilicity, the quinoxaline derivatives have higher affinity for 5-HT_{1A} receptors. A significant difference is observed between both quinoline isomers. The 2-substituted derivatives possess generally a higher affinity than the 3-substituted ones.

Otherwise, the nature and the position of the substituent on the distal aromatic ring differentially influence the binding to the 5-HT_{1A} receptor sites. An electron-withdrawing atom or group is better tolerated in position 3 than 2 and 4. Nevertheless, in the latter position, a fluorine atom leads to a significant affinity

Table 2. Affinity of 2-quinoline derivatives for human cloned 5-HT$_{1A}$, α_{2A}, and D4.2 receptors



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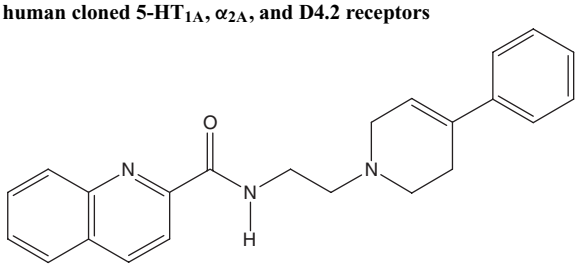


31

Compound	R	5-HT$_{1A}$ affinity	α_{2A} affinity	D4.2 affinity	Selectivity[A]
17	H	31 ± 6	46[A]	112 ± 12	3.6
18	2-F	29 ± 4	244 ± 26	85 ± 0.7	2.9
19	3-F	23 ± 1	51[A]	50[A]	>22
20	4-F	170 ± 37	16[A]	67 ± 12	0.4
21	2-Cl	19 ± 11	384 ± 63	77 ± 9	4
22	3-Cl	12 ± 3	27[A]	32[A]	>42
23	4-Cl	282 ± 40	17[A]	61 ± 6	0.2
24	2-Me	16 ± 3	339 ± 55	65 ± 19	4
25	3-Me	9 ± 1	39[A]	138 ± 27	15.9
26	4-Me	185 ± 57	11[A]	82 ± 1	0.4
27	3-CF_3	8 ± 2	17[A]	58[A]	>63
28	2-OMe	5 ± 1	291 ± 23	78 ± 46	16.7
29	3-OMe	13 ± 5	24[A]	54[A]	>38
30	4-OMe	614 ± 78	15[A]	19[A]	<1
31	–	10 ± 1	150 ± 21	61 ± 17	6.3

[A] K_i (in nM, mean ± s.d.; $n \geq 2$ if unspecified) or percentage of inhibition at 1 μM.
[B] Selectivity is obtained by dividing K_i D4.2 by K_i 5-HT$_{1A}$. A value of 500 nM was chosen for compounds having low affinity and thus the selectivity is superior to the mentioned value.

in the quinoxaline series (**5**). The presence of a group with steric hindrance has also a favourable impact on the affinity for 5-HT$_{1A}$ receptors. A methyl group is more favourable in position 3 (**10**, **25**, **40**) than 2 (**9**, **24**, **39**) and 4 (**11**, **26**, **41**). Regarding the methoxy group, the presence in position 2 (**13**, **28**, **43**) and 3 (**14**, **29**, **44**) is significantly more favourable than in position 4 (**15**, **30**, **45**). In another study, such an electron-withdrawing group decreases binding to 5-HT1A and D2 receptors.[23] In the present series, a slight advantage in terms of affinity is observed for the 2-substituted analogues (**13**, **28**, **43**). In position 3, the compromise of an electron-withdrawing character and steric hindrance found in the CF_3 group (**12**, **27**, **42**) increase the affinity for 5-HT$_{1A}$ receptors.

Interestingly, the presence of the 1,2,3,6-tetrahydropyridine ring instead of the piperazine moiety is highly favourable for 5-HT$_{1A}$ affinity, particularly for the quinoxaline (**16**) and the 3-quinoline (**32**) analogues. Compared with the phenylpiperazine analogues, the affinity is 7, 3, and 11 times higher for the quinoxaline (**2** versus **16**), the 2-quinoline (**17** versus **31**), and the 3-quinoline (**32** versus **46**) analogues respectively. In the literature, a study on a series of D3 ligands reported no significant difference between both chains in terms of affinity for the studied receptors.[24] The rigidity conferred on this part of the molecule must facilitate some interactions in the receptor sites that compensate for the negative impact of the nitrogen-containing heterocycle. The replacement of the sp^3 nitrogen by an sp^2 carbon leads to spatial constraints without a huge impact in terms of basicity. The nitrogen close to the aromatic ring is not sufficiently basic to be protonated at physiological pH and the electron lone pair is not sufficiently available for hydrogen bonding.

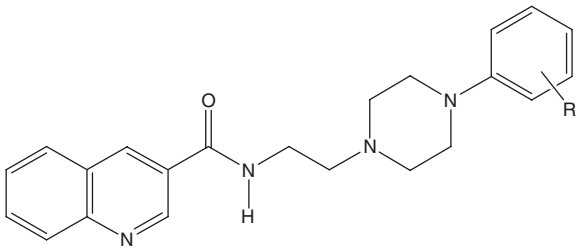
Impact of Modifications on α_2-Adrenoceptor Affinity

A weak interaction appears in the three groups in piperazine series when a substituent, whatever its steric or electronic character, is at position 2. In this series, contrary to the interaction for 5-HT$_{1A}$ receptors, the quinoxaline analogues present less affinity than the 2- and 3-quinoline derivatives. Otherwise, the presence of the tetrahydropyridine side chain (**16**, **31**, **46**) increases the interaction for these sites compared with the corresponding phenylpiperazine analogues (**2**, **17**, **32**) but the impact is less pronounced in the quinoxaline (**2** versus **16**) series than in the 2- (**17** versus **31**) and 3-quinoline (**32** versus **46**) series.

Impact of Modifications on Dopamine D4.2 Receptor Affinity

The higher affinity for these receptor sites is found in the 2- and 3-quinolinyl series. Contrary to the 5-HT$_{1A}$ receptors, the quinoxaline analogues present lesser affinity than the 2- and 3-quinoline derivatives. In the quinoxaline series, only compounds possessing a substituent with steric hindrance such as a chlorine (**6**), a methyl (**9**), or a methoxy (**13**) at position 2 of the distal phenyl ring have medium affinity. In the quinoline series, it appears that a chlorine in position 4 (**23**, **38**) is well tolerated. This observation can also be found in the literature.[25] A subtle difference appears between the 2- and 3-quinoline analogues, generally in favour of the latter. The electronic and steric parameters together seem involved because the methyl group has a less favourable impact on D4.2 receptor affinity. A substituent in position 3 is less well tolerated in both series except for the presence of a methyl group. Similarly to the presence of a substituent

Table 3. Affinity of 3-quinoline derivatives for human cloned 5-HT$_{1A}$, α_{2A}, and D4.2 receptors



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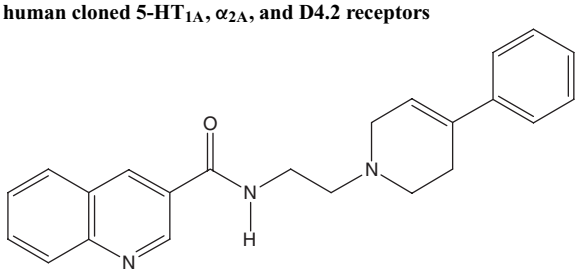

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Compound	R	5-HT$_{1A}$ affinity	α_{2A} affinity	D4.2 affinity	Selectivity[B]
32	H	315 ± 72	23[A]	104 ± 13	0.3
33	2-F	63 ± 23	202 ± 24	58 ± 2.4	0.9
34	3-F	66 ± 4	47[A]	82 ± 9.7	1.3
35	4-F	320 ± 5	10[A]	45 ± 4	0.1
36	2-Cl	49 ± 10	256 ± 21	33 ± 2.8	0.7
37	3-Cl	22 ± 5	25[A]	120 ± 2	5
38	4-Cl	215 ± 55	21[A]	28 ± 7.5	0.1
39	2-Me	46 ± 18	200 ± 6	42 ± 10	1.6
40	3-Me	14 ± 5	33[A]	59 ± 17	4.1
41	4-Me	217 ± 15	10[A]	132 ± 5	0.6
42	3-CF_3	15 ± 4	22[A]	341 ± 48	23
43	2-OMe	15 ± 5	350 ± 16	25 ± 3.5	1.7
44	3-OMe	40 ± 3	24[A]	316 ± 24	7.9
45	4-OMe	2019 ± 561	12[A]	31[A]	–
46	–	23 ± 9	173 ± 6	34 ± 5	1.5

[A] K_i (in nM, mean ± s.d.; $n \geq 2$ if unspecified) or percentage of inhibition at 1 μM.
[B] Selectivity is obtained by dividing K_i D4.2 by K_i 5-HT$_{1A}$. A value of 500 nM was chosen for compounds having low affinity and thus the selectivity is superior to the mentioned value.

in position 4, the 3-quinolinyl analogues have a higher affinity than the 2-quinoline analogues. The presence of a substituent in position 2 is also favourable compared with the unsubstituted analogues. Regarding these receptor sites, the favourable impact of a tetrahydropyridine side chain is less pronounced compared with the 5-HT$_{1A}$ receptors except for the 2-quinoline (**31**) and 3-quinoline (**46**) derivatives.

Selectivity of Serotonin 5-HT$_{1A}$ versus Dopamine D4.2 Receptors

To evaluate this parameter, it is necessary to fix a limit for compounds that present a low affinity for a receptor. In this discussion, we have chosen a value of 500 nM for compounds with no precisely determined affinity. In the quinoxaline series (Table 1), it thus appears that the most selective compounds for 5-HT$_{1A}$ receptors possess in position 3 of the phenyl ring an electron-withdrawing atom or group (chlorine (**7**) or trifluoromethyl (**12**)) or a methyl group (**10**). In the 2-quinoline series (Table 2), the highest selectivity for 5-HT$_{1A}$ receptors, although lower than in the quinoxaline series, is also found with compounds substituted with a group in position 3 (**19**, **22**, **25**, **29**) of the distal phenyl ring. In the three series, the most selective compound for 5-HT$_{1A}$ versus D4.2 receptors possess a CF_3 group in position 3 (**12**) of the distal phenyl ring. Otherwise, in these series, some compounds (**20**, **23**, **26**) present a slight selectivity for D4.2 receptors versus 5-HT$_{1A}$ receptors. In the 3-quinoline series (Table 3), compounds substituted with a group in position 3 of the phenyl ring (**37**, **40**, **42**, **44**) present a weak selectivity for 5-HT$_{1A}$ receptors versus D4.2 receptors in comparison with the two other series. In this series, at least two compounds (**34**, **38**) being 10 times more selective for D4.2 receptors versus 5-HT$_{1A}$ receptors are observed. Regarding the tetrahydropyridine derivatives, the selectivity for 5-HT$_{1A}$ receptors versus D4.2 receptors is 125, 6.3, and 1.5 times greater for the quinoxaline (**16**), the 2-quinoline (**31**), and the 3-quinoline (**46**) derivatives, respectively, and thus superior to those found with derivatives possessing a 4-phenyl-piperazine side chain.

Preliminary in vitro experiments for determining the intrinsic activity were done according to previously described procedures.[26] Compounds were assessed at 10 μM for stimulation of [^{35}S]GTPγS binding to membrane fractions from D4 receptor- and 5-HT$_{1A}$ receptor-expressing cells. Of the 45 compounds tested for D4 receptor agonism, only one (**43**) repeatedly exhibited more than 20% activity (baseline [^{35}S]GTPγS binding = 0%, [^{35}S]GTPγS binding in the presence of 10 μM dopamine = 100%). Several compounds exhibited less than −20% activity, suggesting that these compounds might behave as inverse agonists of [^{35}S]GTPγS binding; additional studies are necessary to confirm and characterize this. Among the 45 compounds tested for 5-HT$_{1A}$ agonism, five repeatedly demonstrated more than 20% activity: **7** (74 ± 10%), **12** (73 ± 14%), **27** (81 ± 8%), **37** (54 ± 23%), and **42** (82 ± 16%). In contrast to our observations of activity at D4 receptors, none of the compounds exhibited less than −20% activity at 5-HT$_{1A}$ receptors.

Conclusion

The 5-HT$_{1A}$ versus D4 selectivity is significantly increased when the nitrogen-containing aromatic heterocycle replaces the naphthalene moiety. The presence of a quinoxaline moiety yielded compounds not only with a high affinity for 5-HT$_{1A}$ receptors but also with higher selectivity for 5-HT$_{1A}$ versus D4.2 receptors and with a concomitant decrease in lipophilicity. In the

quinoline series, some derivatives possessed significant affinities for D4.2 receptors whereas the affinity for 5-HT_{1A} receptors was reduced. The 3-CF_3-substituted derivatives are the most potent and selective compounds for 5-HT_{1A} versus D4.2 receptors. The presence of a 4-phenyl-1,2,3,6-tetrahydropyridine is an interesting alternative to replace the phenylpiperazine moiety without increased lipophilicity. Finally, this tetrahydropyridine ring is also favourable in terms of affinity for α_{2A}-adrenoceptors. Such information will be useful for further medicinal chemistry programs.

Experimental

General

Melting points were determined on a Büchi-Tottoli capillary melting point apparatus in open capillaries and are uncorrected. NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 MHz. For ^{13}C NMR, DEPT135 (Distortionless Enhancement by Polarization Transfer) and APT (Attached Proton Test) experiments were used for detecting on the one hand CH_3, CH_2, and CH and on the other hand C. In fluorine containing derivatives, spectra are more complicated probably due to carbon-fluorine coupling. IR spectra were performed on a Perkin–Elmer Fourier-transform (FT)IR-1750 spectrometer using KBr discs. Only significant bands from IR are reported. Low resolution mass spectrometry (LRMS) was carried out using an Ultima Triple Quadrupole instrument (Micromass, Manchester, UK) operating under *MassLynx 4.1* and configured with a Z-Spray electrospray ionization source. Elemental analyses were performed using a Carlo-Erba elemental analyzer CHNS-O model EA1108 and the results are within 0.4% of the theoretical values. All starting materials and reagents were obtained from Aldrich Chemical Co. and Acros Chemical Co. and were used without further purification. When necessary, separations by column chromatography were carried out using Merck Kieselgel 60 (230–400 mesh). Concentration and evaporation refer to removal of volatile materials under reduced pressure (10–15 mmHg at 30–50°C) on a Büchi-Rotavapor.

General Method for the Preparation of Primary Amines

The corresponding *N*-[2-(4-phenylpiperazin-1-yl)ethyl] phtalimide (2.2 mmol) was refluxed in absolute EtOH (10 mL) with an excess of hydrazine hydrate (0.22 g, 4.4 mmol) for 1 h. After cooling and dilution with CH_2Cl_2 (50 mL), the suspension was filtered and the resulting solution was washed with water (10 mL), then with a saturated aqueous NaCl solution (2 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The oily residue was diluted in ethyl acetate (20 mL) and triethylamine (3.16 mL, 22 mmol) was added. This solution was then used without further purification in the following step.

*General Method for the Preparation of Amide Derivatives **2**–**46***

The appropriate carboxylic acid (2.2 mmol) was refluxed in an excess of thionyl chloride (3.17 mL, 44 mmol) for 3 h. The solution was evaporated under reduced pressure. The residue was solubilized in ethyl acetate (20 mL) and the resulting solution was added dropwise to the solution of the appropriate primary amine (see above). The mixture was stirred for 15 h. The suspension was then evaporated under reduced pressure. The residue was stirred with a 10% aqueous K_2CO_3 solution (20 mL) and CH_2Cl_2 (40 mL) was added. The organic layer was washed with a 10% aqueous K_2CO_3 solution (2 × 20 mL). Then the organic layer was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized in the corresponding solvent. Overall yields are between 50 and 70%.

N-*[2-(4-Phenylpiperazin-1-yl)ethyl]-2-quinoxaline Carboxamide **2***

Mp 123–124°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.28 (t, *J* 4.9, 4H), 3.7 (q, *J* 6.0, 2H), 6.87 (t, *J* 7.3, 1H), 6.96 (d, *J* 8.0, 2H), 7.28 (m, 2H), 7.84 (m, 2H), 8.10 (d, *J* 1.1, 1H), 8.11 (d, *J* 1.4, 1H), 8.4 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.28, 49.29, 53.04, 56.64; (CH) 116.07, 119.81, 129.17, 129.52, 129.80, 130.76, 131.52, 143.95; (C) 140.33, 143.65, 143.89, 151.26, 163.35. ν_{max}(KBr)/cm^{-1} 3385, 2824, 1672, 1234, 756. *m/z* [MH^+] 362.4. (Calc. for $C_{21}H_{23}N_5O$ (361.440): C 69.78, H 6.41, N 19.38 Found: C 69.82, H 6.48, N 19.14%.)

N-*{2-[4-(2-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide **3***

Mp 109–110°C. δ_H (500 MHz, $CDCl_3$) 2.76 (m, 6H), 3.19 (t, *J* 4.6, 4H), 3.70 (q, *J* 6.1, 2H), 6.92–7.09 (m, 4H), 7.85 (m, 2H), 8.13 (dd, *J* 1.4, 8.2, 1H), 8.19 (dd, *J* 1.4, 8.4, 1H), 8.40 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.22, 50.52, 53.11, 56.71, (CH) 116.10, 116.27, 118.96, 122.53, 122.59, 124.45, 124.48, 129.53, 129.78, 130.76, 131.54, 143.94, (C) 140.01, 140.08, 140.32, 143.66, 143.87, 154.75, 156.71, 163.36. ν_{max}(KBr)/cm^{-1} 3355, 2817, 1684, 1501, 1236, 748. *m/z* [MH^+] 380.3. (Calc. for $C_{21}H_{22}FN_5O$ (379.431): C 66.47, H 5.84, N 18.46 Found: C 66.17, H 5.90, N 18.30%.)

N-*{2-[4-(3-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide **4***

Mp 153–154°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.27 (t, *J* 5.0, 4H), 3.70 (q, *J* 6.0, 2H), 6.54 (m, 1H), 6.61 (m, 1H), 6.69 (dd, *J* 2.1, 8.3, 1H), 7.19 (m, 1H), 7.85 (m, 2H), 8.10 (dd, *J* 1.3, 8.1, 1H), 8.18 (dd, *J* 1.3, 8.3, 1H), 8.39 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.24, 48.71, 52.82, 56.65, (CH) 102.61, 102.81, 105.88, 106.05, 111.17, 129.52, 129.77, 130.12, 130.20, 130.79, 131.56, 143.92. ν_{max}(KBr)/cm^{-1} 3393, 2833, 1671, 1495, 776. *m/z* [MH^+] 380.3. (Calc. for $C_{21}H_{22}FN_5O$ (379.431): C 66.47, H 5.84, N 18.46 Found: C 66.28, H 6.07, N 18.54%.)

N-*{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide **5***

Mp 132–133°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.19 (t, *J* 4.9, 4H), 3.70 (q, *J* 6.2, 2H), 6.90 (m, 2H), 6.97 (m, 2H), 7.84 (m, 2H), 8.10 (m, 1H), 8.18 (dd, *J* 1.3, 8.2, 1H), 8.39 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.18, 50.12, 53.02, 56.65, (CH) 115.50, 115.68, 117.90, 117.96, 129.52, 129.78, 130.79, 131.57, 143.91, (C) 140.32, 143.60, 147.85, 156.29, 158.19, 163.41. ν_{max}(KBr)/cm^{-1} 3376, 2824, 1655, 1511, 1234, 818, 754. *m/z* [MH^+] 380.3. (Calc. for $C_{21}H_{22}FN_5O$ (379.431): C 66.47, H 5.84, N 18.46 Found: C 66.70, H 5.72, N 18.44%.)

N-*{2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide **6***

Mp 119–120°C. δ_H (500 MHz, $CDCl_3$) 2.77 (m, 6H), 3.15 (brs, 4H), 3.70 (q, *J* 6.1, 2H), 6.98 (m, 1H), 7.08 (dd, *J* 1.4, 8.0, 1H), 7.23 (m, 1H), 7.37 (dd, *J* 1.4, 8.0, 1H), 7.86 (m, 2H), 8.13 (dd, *J* 1.8, 8.3, 1H), 8.19 (dd, *J* 1.7, 8.2, 1H), 8.40 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.32, 51.27, 53.22, 56.73,

(CH) 120.38, 123.76, 127.60, 129.55, 129.77, 130.72, 130.74, 131.51, 143.98, (C) 128.80, 140.34, 143.68, 143.90, 149.19, 163.37. ν_{max}(KBr)/cm^{-1} 3356, 2837, 2815, 1679, 1526, 772. *m/z* [MH$^+$] 396.2. (Calc. for $C_{21}H_{22}ClN_5O$ (395.885): C 63.71, H 5.60, N 17.69 Found: C 63.62, H 5.74, N 17.81%.)

N-*{2-[4-(3-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***7***

Mp 128–129°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.27 (t, *J* 5.0, 4H), 3.70 (q, *J* 6.1, 2H), 6.81 (m, 2H), 6.90 (t, *J* 2.1, 1H), 7.17 (t, *J* 8.1, 1H), 7.85 (m, 2H), 8.10 (dd, *J* 1.4, 8.6, 1H), 8.18 (dd, *J* 1.2, 8.3, 1H), 8.39 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.25, 48.78, 52.82, 56.64, (CH) 113.96, 115.80, 119.42, 129.51, 129.75, 130.04, 130.75, 131.50, 143.92, (C) 134.97, 140.31, 143.61, 143.89, 152.30, 163.34. ν_{max}(KBr)/cm^{-1} 3396, 2832, 1672, 1237, 777. *m/z* [MH$^+$] 396.2. (Calc. for $C_{21}H_{22}ClN_5O$ (395.885): C 63.71 H, 5.60, N 17.69 Found: C 63.44, H 5.68, N 17.90%.)

N-*{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***8***

Mp 174–175°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.23 (t, *J* 5, 4H), 3.69 (q, *J* 6.0, 2H), 6.86 (m, 2H), 7.21 (m, 2H), 7.84 (m, 2H), 8.10 (dd, *J* 1.3, 8.2, 1H), 8.18 (dd, *J* 1.2, 8.3, 1H), 8.39 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.28, 49.27, 52.86, 56.63, (CH) 117.20, 128.96, 129.52, 129.73, 130.74, 131.51, 143.92, (C) 124.57, 140.31, 143.62, 143.89, 149.88, 163.35. ν_{max}(KBr)/cm^{-1} 3314, 2821, 1652, 1544, 1495, 812. *m/z* [MH$^+$] 396.2. (Calc. for $C_{21}H_{22}ClN_5O$ (395.885): C 63.71, H 5.60, N 17.69 Found: C 63.95, H, 5.87, N 17.71%.)

N-*{2-[4-(2-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***9***

Mp 98–99°C. δ_H (500 MHz, $CDCl_3$) 2.32 (s, 3H), 2.76 (m, 6H), 3.01 (t, *J* 4.7, 4H), 3.70 (q, *J* 5.2, 2H), 7.00 (m, 1H), 7.06 (d, *J* 7.7, 1H), 7.18 (t, *J* 7.5, 2H), 7.86 (m, 2H), 8.14 (m, 1H), 8.19 (m, 1H), 8.42 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 17.91, (CH_2) 36.36, 51.85, 53.55, 56.74, (CH) 118.92, 123.16, 126.55, 129.52, 129.77, 130.72, 131.11, 131.47, 143.96, (C) 132.61, 140.35, 143.71, 143.89, 151.45, 163.35. ν_{max}(KBr)/cm^{-1} 3350, 2836, 1676, 1526, 776. *m/z* [MH$^+$] 376.3. (Calc. for $C_{22}H_{25}N_5O$ (375.467): C 70.38, H 6.71, N 18.65 Found: C 70.00, H 6.76, N 18.55%.)

N-*{2-[4-(3-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***10***

Mp 114–115°C. δ_H (500 MHz, $CDCl_3$) 2.33 (s, 3H), 2.73 (m, 6H), 3.26 (t, *J* 4.9, 4H), 3.70 (q, *J* 6.1, 2H), 6.69 (d, *J* 8.4, 1H), 6.76 (m, 2H), 7.17, (t, *J* 7.7, 1H), 7.84 (m, 2H), 8.10 (dd, *J* 1.4, 8.2, 1H), 8.18, (dd, *J* 1.3, 8.3, 1H), 8.42 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 21.78, (CH_2) 36.16, 49.21, 53.04, 56.63, (CH) 113.27, 117.00, 120.84, 129.01, 129.49, 129.81, 130.76, 131.54, 143.89, (C) 138.80, 140.31, 143.62, 143.86, 151.28, 163.37. ν_{max}(KBr)/cm^{-1} 3363, 2819, 1678, 1531, 778. *m/z* [MH$^+$] 376.3. (Calc. for $C_{22}H_{25}N_5O$ (375.467): C 70.38, H 6.71, N 18.65 Found: C 70.78, H 6.76, N 18.82%.)

N-*{2-[4-(4-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***11***

Mp 151–152°C. δ_H (500 MHz, $CDCl_3$) 2.28 (s, 3H), 2.74 (m, 6H), 3.22 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.1, 2H), 6.87 (d, *J* 8.4, 2H), 7.08 (d, *J* 8.4, 2H), 7.84 (m, 2H), 8.10 (dd, *J* 1.3, 8.2, 1H), 8.18 (dd, *J* 1.3, 8.2, 1H), 8.42 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 20.42, (CH_2) 36.27, 49.83, 53.04, 56.60, (CH) 116.37, 129.49, 129.66, 129.77, 130.72, 131.47, 143.92, (C) 129.28, 140.33, 143.66, 143.88, 149.19, 163.33. ν_{max}(KBr)/cm^{-1} 3318, 2813, 1652, 1545, 1519, 808, 753. *m/z* [MH$^+$] 376.3. (Calc. for $C_{22}H_{25}N_5O$ (375.467): C 70.38, H 6.71, N 18.65 Found: C 70.67, H 6.95, N 18.68%.)

N-*{2-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***12***

Mp 111–112°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.31 (t, *J* 5.0, 4H), 3.70 (q, *J* 6.0, 2H), 7.08 (d, *J* 8.1, 2H), 7.14 (s, 1H), 7.36 (t, *J* 8.0, 1H), 7.84 (m, 2H), 8.10 (dd, *J* 1.3, 8.2, 1H), 8.18 (dd, *J* 1.2, 8.3, 1H), 8.39 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 48.33, 52.78, 56.69, (CH) 119.05, 129.50, 129.68, 129.83, 130.84, 131.65, 143.84, (C) 140.37, 143.28, 143.94, 150.69, 163.91. ν_{max}(KBr)/cm^{-1} 3310, 2825, 1652, 1112, 754. *m/z* [MH$^+$] 430.3. (Calc. for $C_{22}H_{22}F_3N_5O$ (429.438): C 61.53, H 5.16, N 16.31 Found: C 61.77, H 5.18, N 16.23%.)

N-*{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***13***

Mp 123–124°C. δ_H (500 MHz, $CDCl_3$) 2.76 (m, 6H), 3.17 (brs, 4H), 3.70 (q, *J* 6.1, 2H), 3.88 (s, 3H), 6.88 (dd, *J* 1.2, 8.0, 1H), 6.92–7.03 (m, 3H), 7.85 (m, 2H), 8.12 (m, 1H), 8.18 (dd, *J* 1.4, 8.2, 1H), 8.42 (brs, 1H), 9.69 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.39, (CH_2) 36.32, 50.79, 53.25, 56.70, (CH) 111.28, 118.37, 121.05, 123.35, 129.47, 129.90, 130.79, 131.59, 143.85, (C) 140.35, 141.31, 143.72, 143.88, 152.30, 163.34. ν_{max}(KBr)/cm^{-1} 3313, 2814, 1651, 1500, 1242, 748. *m/z* [MH$^+$] 392.3. (Calc. for$C_{22}H_{25}N_5O_2$ (391.466): C 67.50, H 6.44, N 17.89 Found: C 67.24, H 6.66, N 17.53%.)

N-*{2-[4-(3-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***14***

Mp 91–92°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.27 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.1, 2H), 3.80 (s, 3H), 6.43 (dd, *J* 2.1, 8.1, 1H), 6.50 (t, *J* 2.2, 1H), 6.57 (d, *J* 2.1, 8.2, 1H), 7.19 (t, *J* 8.2, 1H), 7.85 (m, 2H), 8.10 (m, 1H), 8.18 (dd, *J* 1.3, 8.2, 1H), 8.42 (brs,1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.21, (CH_2) 36.09, 48.96, 52.95, 56.65, (CH) 102.66, 104.68, 108.96, 129.49, 129.83, 129.87, 130.78, 131.56, 143.91, (C) 140.32, 143.65, 143.88, 152.67, 160.62, 163.33. ν_{max}(KBr)/cm^{-1} 3374, 2816, 1677, 1534, 1202, 774. *m/z* [MH$^+$] 392.3. (Calc. for $C_{22}H_{25}N_5O_2$ (391.466): C 67.50, H 6.44, N 17.89 Found: C 67.37, H 6.80, N 17.89%.)

N-*{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoxaline Carboxamide* ***15***

Mp 143–144°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.17 (t, *J* 4.8, 4H), 3.69 (q, *J* 6.1, 2H), 3.78 (s, 3H), 6.85 (m, 2H), 6.92 (m, 2H), 7.84 (m, 2H), 8.10 (dd, *J* 1.8, 7.7, 1H), 8.18 (dd, *J* 1.3, 8.3, 1H), 8.41 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.58, (CH_2) 36.28, 50.72, 53.13, 56.62, (CH) 114.48, 118.16, 129.51, 129.77, 130.74, 131.51, 143.93, (C) 140.33, 143.67, 143.89, 145.68, 153.84, 163.34. ν_{max}(KBr)/cm^{-1} 3316, 2818, 1654, 1514, 1252, 817. *m/z* [MH$^+$] 392.3. (Calc. for $C_{22}H_{25}N_5O_2$ (391.466): C 67.50, H 6.44, N 17.89 Found: C 67.40, H 6.72, N 17.72%.)

N-*[2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)ethyl]-2-quinoxaline Carboxamide* ***16***

Mp 102–104°C. δ_H (500 MHz, $CDCl_3$) 2.64 (m, 2H), 2.83 (m, 4H), 3.30 (q, *J* 2.7, 2H), 3.74 (q, *J* 6.2, 2H), 6.12 (m, 1H), 7.25 (m, 1H), 7.34 (m, 2H), 7.42 (m, 2H), 7.81 (m, 1H), 7.85 (m, 1H), 8.11 (m, 1H), 8.17 (dd, *J* 1.2, *J* 8.4, 1H), 8.37 (brs, 1H), 9.68 (s, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 27.99, 36.80, 50.34, 53.20, 56.70, (CH) 121.53, 124.87, 127.11, 128.36, 129.49, 129.79, 130.72, 131.48, 143.96, (C) 135.05, 140.34, 140.64, 143.67, 143.86, 163.48. ν_{max}(KBr)/cm^{-1} 3404, 3390, 2823, 1670, 1527, 750. *m/z* [MH^+] 359.3. (Calc. for $C_{22}H_{22}N_4O$ (358.436): C 73.72, H 6.19, N 15.63 Found: C 73.63, H 6.44, N 15.56%.)

N-*[2-(4-Phenylpiperazin-1-yl)ethyl]-2-quinoline Carboxamide* ***17***

Mp 158–159°C. δ_H (500 MHz, $CDCl_3$) 2.75 (m, 6H), 3.28 (t, *J* 4.9, 4H), 3.70 (q, *J* 6, 2H), 6.87 (t, *J* 7.3, 1H), 6.96 (d, *J* 7.9, 2H), 7.28 (m, 2H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.5, 8.2, 1H), 8.09 (d, *J* 8.4, 1H), 8.31 (s, 2H), 8.64 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.41, 49.28, 53.08, 56.87, (CH) 116.07, 118.88, 119.74, 127.74, 127.87, 129.15, 129.85, 130.06, 137.43, (C) 129.29, 146.54, 149.95, 151.32, 164.58. ν_{max}(KBr)/cm^{-1} 3386, 2834, 1668, 1497, 774. *m/z* [MH^+] 361.3. (Calc. for $C_{22}H_{24}N_4O$ (360.452): C 73.31, H 6.71, N 15.54 Found: C 73.15, H 7.06, N 15.69%.)

N-*{2-[4-(2-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***18***

Mp 84–85°C. δ_H (500 MHz, $CDCl_3$) 2.76 (m, 6H), 3.19 (t, *J* 4.7, 4H), 3.70 (q, *J* 6.3, 2H), 6.93–7.09 (m, 4H), 7.62 (m, 1H), 7.76 (m, 1H), 7.88 (dd, *J* 0.5, 8.2, 1H), 8.10 (d, *J* 8.5, 1H), 8.32 (s, 2H), 8.63 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.42, 50.67, 53.14, 56.91, (CH) 116.06, 116.23, 118.90, 118.93, 122.41, 124.44, 127.75, 127.86, 129.80, 130.04, 137.44, (C) 129.32, 140.13, 140.19, 146.56, 149.99, 154.79, 156.75, 164.60. ν_{max}(KBr)/cm^{-1} 3355, 2822, 1682, 1501, 1243, 780. *m/z* [MH^+] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80 Found: C 69.69, H 6.30, N 14.82%.)

N-*{2-[4-(3-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***19***

Mp 153–154°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.28 (t, *J* 5.0, 4H), 3.69 (q, *J* 6.2, 2H), 6.53 (m, 1H), 6.61 (m, 1H), 6.69 (dd, *J* 2.1, 8.3, 1H), 7.19 (dd, *J* 8.2, 15.3, 1H), 7.61 (m, 1H), 7.76 (m, 1H), 7.88 (d, *J* 8.2, 1H), 8.09 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.62 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.41, 48.77, 52.87, 56.87, (CH) 102.56, 102.76, 105.76, 105.93, 111.13, 118.88, 127.76, 127.90, 129.81, 130.09, 130.17, 137.47, (C) 129.32, 146.55, 149.93, 152.93, 153.01, 162.93, 164.61, 164.86. ν_{max}(KBr)/cm^{-1} 3384, 2839, 1667, 1497, 777. *m/z* [MH^+] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80 Found: C 69.56, H 6.56, N 14.88%.)

N-*{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***20***

Mp 163–164°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.19 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.2, 2H), 6.90 (m, 2H), 6.97 (m, 2H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.6, 8.2, 1H), 8.09 (d, *J* 8.09, 1H), 8.31 (s, 2H), 8.62 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.40, 50.25, 53.07, 56.86, (CH) 115.46, 115.63, 117.81, 117.87, 118.89, 127.76, 127.90, 129.80, 130.08, 137.47, (C) 129.29, 146.53, 147.98, 147.99, 149.94, 156.20, 158.10, 164.57. ν_{max}(KBr)/cm^{-1} 3388, 2834, 1668, 1517, 1236, 811. *m/z* [MH^+] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80 Found: C 70.09, H 5.91, N 14.90%.)

N-*{2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***21***

Mp 106–107°C. δ_H (500 MHz, $CDCl_3$) 2.77 (m, 6H), 3.16 (brs, 4H), 3.70 (q, *J* 6.2, 2H), 6.98 (m, 1H), 7.08 (dd, *J* 1.4, 8.0, 1H), 7.23 (m, 1H), 7.36 (dd, *J* 1.4, 8.0, 1H), 7.62 (m, 1H), 7.77 (m, 1H), 7.88 (dd, *J* 0.5, 8.2, 1H), 8.12 (d, *J* 8.5, 1H), 8.32 (s, 2H), 8.62 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.48, 51.34, 53.25, 56.94, (CH) 118.93, 120.40, 123.69, 127.59, 127.78, 128.87, 129.80, 130.06, 130.70, 137.46, (C) 128.80, 129.30, 146.55, 149.31, 150.01, 164.56. ν_{max}(KBr)/cm^{-1} 3364, 2817, 1678, 781. *m/z* [MH^+] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19. Found: C 66.84, H 6.15, N 14.26%.)

N-*{2-[4-(3-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***22***

Mp 160–161°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.27 (t, *J* 5, 4H), 3.69 (q, *J* 6.2, 2H), 6.81 (m, 2H), 6.90 (t, *J* 2.1, 1H), 7.17 (t, *J* 8.1, 1H), 7.61 (m, 1H), 7.76 (m, 1H), 7.87 (dd, *J* 0.6, 8.2, 1H), 8.09 (d, *J* 8.4, 1H), 8.31 (s, 2H), 8.62 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.39, 48.82, 52.88, 56.86, (CH) 113.93, 115.78, 118.88, 119.33, 127.76, 127.90, 129.82, 130.05, 130.09, 137.47, (C) 129.32, 135.00, 146.55, 149.92, 152.36, 164.61. ν_{max}(KBr)/cm^{-1} 3381, 2839, 1667, 1496, 778. *m/z* [MH^+] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19 Found: C 66.72, H 5.45, N 14.36%.)

N-*{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***23***

Mp 161–162°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.23 (t, *J* 5, 4H), 3.69 (q, *J* 6.2, 2H), 6.86 (m, 2H), 7.22 (m, 2H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.7, 8.2, 1H), 8.08 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.61 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.40, 49.27, 52.92, 56.86, (CH) 117.25, 118.88, 127.76, 127.90, 128.98, 129.79, 130.09, 137.47, (C) 124.54, 129.32, 146.55, 149.95, 164.61. ν_{max}(KBr)/cm^{-1} 778, 1497, 1666, 2837, 3385. *m/z* [MH^+] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19 Found: C 66.91, H 5.85, N 13.99%.)

N-*{2-[4-(2-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***24***

Mp 69–70°C. δ_H (500 MHz, $CDCl_3$) 2.32 (s, 3H), 2.76 (m, 6H), 3.01 (t, *J* 4.6, 4H), 3.70 (q, *J* 6.3, 2H), 6.99 (m, 1H), 7.06 (d, *J* 7.4, 1H), 7.18 (t, *J* 7.2, 2H), 7.62 (m, 1H), 7.77 (m, 1H), 7.88 (dd, *J* 0.8, 8.2, 1H), 8.12 (d, *J* 8.5, 1H), 8.32 (s, 2H), 8.64 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 17.94, (CH_2) 36.51, 51.86, 53.61, 57.00, (CH) 118.92, 118.98, 123.14, 126.57, 127.76, 127.87, 129.83, 130.07, 131.11, 137.45, (C) 129.32, 132.63, 146.58, 150.02, 151.53, 164.62. ν_{max}(KBr)/cm^{-1} 3263, 2824, 1650, 1494, 1145, 769. *m/z* [MH^+] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.79, H 7.13, N 14.81%.)

N-*{2-[4-(3-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***25***

Mp 145–147°C. δ_H (500 MHz, $CDCl_3$) 2.33 (s, 3H), 2.73 (m, 6H), 3.27 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.2, 2H), 6.69 (d, *J* 7.4, 1H), 6.77 (m, 2H), 7.17 (t, *J* 7.7, 1H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.6, 8.2, 1H), 8.09 (d, *J* 8.4, 1H), 8.31 (s, 2H), 8.65 (brs, 1H).

δ_C (500 mHz, $CDCl_3$) (CH_3) 21.79, (CH_2) 36.39, 49.36, 53.10, 56.85, (CH) 113.19, 116.91, 118.87, 120.64, 127.72, 127.85, 128.97, 129.82, 130.04, 137.42, (C) 129.29, 138.80, 146.54, 149.95, 151.39, 164.57. ν_{max}(KBr)/cm^{-1} 3383, 2835, 1668, 1497, 772. *m/z* [MH^+] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.83, H 7.37, N 14.80%.)

N-*{2-[4-(4-Methylphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***26***

Mp 157–159°C. δ_H (500 MHz, $CDCl_3$) 2.28 (s, 3H), 2.74 (m, 6H), 3.23 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.2, 2H), 6.87 (d, *J* 8.5, 2H), 7.09 (d, *J* 8.5, 2H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.6, 8.1, 1H), 8.08, (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.65 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 20.42, (CH_2) 36.39, 49.83, 53.09, 56.85, (CH) 116.39, 118.86, 127.71, 127.85, 129.65, 129.82, 130.04, 137.41, (C) 129.14, 129.23, 146.49, 149.21, 149.93, 164.52. ν_{max}(KBr)/cm^{-1} 3384, 2836, 1668, 1521, 1498, 800. *m/z* [MH^+] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.69, H 6.68, N 15.31%.)

N-*{2-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***27***

Mp 128–129°C. δ_H (500 MHz, $CDCl_3$) 2.75 (m, 6H), 3.32 (t, *J* 5.0, 4H), 3.70 (q, *J* 6.2, 2H), 7.08 (dd, *J* 1.5, 7.9, 2H), 7.14 (s, 1H), 7.36 (t, *J* 8.0, 1H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (d, *J* 8.2, 1H), 8.09 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.62 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.38, 48.76, 52.86, 56.85, (CH) 112.19, 115.91, 118.78, 118.87, 127.76, 127.91, 129.57, 129.80, 130.09, 137.48, (C) 129.33, 146.56, 149.86, 151.34, 164.68. ν_{max}(KBr)/cm^{-1} 3382, 2841, 1668, 1498, 1170, 1112, 780. *m/z* [MH^+] 429.3. (Calc. for $C_{23}H_{23}F_3N_4O$ (428.450): C 64.48, H 5.41, N 13.08 Found: C 64.01, H 5.50, N 13.09%.)

N-*{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***28***

Mp 136–137°C. δ_H (500 MHz, $CDCl_3$) 2.76 (m, 6H), 3.17 (brs, 4H), 3.69 (q, *J* 6.2, 2H), 3.88 (s, 3H), 6.87 (dd, *J* 1.3, 7.9, 1H), 6.92–7.03 (m, 3H), 7.61 (m, 1H), 7.76 (m, 1H), 7.87 (dd, *J* 0.7, 8.2, 1H), 8.11 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.64 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.38, (CH_2) 36.44, 50.80, 53.30, 56.94, (CH) 111.24, 118.21, 118.89, 120.99, 122.92, 127.73, 127.83, 129.82, 130.03, 137.40, (C) 129.29, 141.37, 146.55, 150.01, 152.30, 164.57. ν_{max}(KBr)/cm^{-1} 3375, 2821, 1671, 1497, 1238, 754. *m/z* [MH^+] 391.3. (Calc. for $C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.76, H 7.12, N 14.41%.)

N-*{2-[4-(3-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***29***

Mp 131–132°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.27 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.2, 2H), 3.80 (s, 3H), 6.42 (dd, *J* 2.1, 8.2, 1H), 6.50 (t, *J* 2.3, 1H), 6.57 (dd, *J* 2.1, 8.2, 1H), 7.18 (t, *J* 8.2, 1H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.7, 8.2, 1H), 8.08 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.64 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.19, (CH_2) 36.39, 49.20, 53.02, 56.85, (CH) 102.48, 104.46, 108.86, 118.86, 127.72, 127.86, 129.80, 129.83, 130.06, 137.42, (C) 129.29, 146.54, 149.94, 152.72, 160.61, 164.58. ν_{max}(KBr)/cm^{-1} 3344, 2830, 1651, 1502, 1214, 777. *m/z* [MH^+] 391.3. (Calc. for $C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.63, H 6.66, N 14.48%.)

N-*{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-2-quinoline Carboxamide* ***30***

Mp 138–139°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.17 (t, *J* 4.9, 4H), 3.69 (q, *J* 6.3, 2H), 3.78 (s, 3H), 6.85 (m, 2H), 6.93 (m, 2H), 7.61 (m, 1H), 7.75 (m, 1H), 7.87 (dd, *J* 0.6, 8.2, 1H), 8.09 (d, *J* 8.5, 1H), 8.31 (s, 2H), 8.63 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.58, (CH_2) 36.34, 50.63, 53.17, 56.83, (CH) 114.48, 118.23, 118.86, 127.72, 127.87, 129.83, 130.06, 137.43, (C) 129.31, 145.57, 146.55, 149.87, 153.93, 164.67. ν_{max}(KBr)/cm^{-1} 3405, 2824, 1678, 1514, 1253, 777. *m/z* [MH^+] 391.3. (Calc. for $C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.78, H 6.61, N 14.53%.)

N-*[2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)ethyl]-2-quinoline Carboxamide* ***31***

Mp 139–140°C. δ_H (500 MHz, $CDCl_3$) 2.64 (m, 2H), 2.84 (m, 4H), 3.30 (q, *J* 2.8, 2H), 3.74 (q, *J* 6.4, 2H), 6.11 (m, 1H), 7.23 (m, 1H), 7.33 (m, 2H), 7.42 (m, 2H), 7.61 (m, 1H), 7.74 (m, 1H), 7.87 (dd, *J* 0.8, 8.2, 1H), 8.10 (d, *J* 8.5, 1H), 8.31 (m, 2H), 8.58 (brs, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 28.06, 36.96, 50.41, 53.24, 56.93, (CH) 118.90, 121.68, 124.91, 127.04, 127.71, 127.83, 128.32, 129.82, 130.02, 137.41, (C) 129.30, 135.06, 140.78, 146.55, 149.97, 164.69. ν_{max}(KBr)/cm^{-1} 3402, 2803, 1668, 1498, 745. *m/z* [MH^+] 358.3. (Calc. for $C_{23}H_{23}N_3O$ (357.448): C 77.28, H 6.49, N 11.76 Found: C 77.70, H 6.69, N 11.77%.)

N-*[2-(4-Phenylpiperazin-1-yl)ethyl]-3-quinoline Carboxamide* ***32***

Mp 165–166°C. δ_H (500 MHz, $CDCl_3$) 2.72 (m, 6H), 3.24 (t, *J* 4.9, 4H), 3.67 (q, *J* 5.5, 2H), 6.87 (t, *J* 7.3, 1H), 6.94 (d, *J* 8.0, 2H), 7.03 (brs, 1H), 7.28 (m, 2H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.1, 1H), 8.15 (d, *J* 8.4, 1H), 8.61 (d, *J* 2.0, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.45, 49.34, 52.93, 56.25, (CH) 116.19, 119.98, 127.53, 128.82, 129.17, 129.43, 131.22, 135.71, 148.08, (C) 127.00, 127.17, 149.25, 151.14, 165.50. ν_{max}(KBr)/cm^{-1} 3299, 2824, 1636, 1541, 754. *m/z* [MH^+] 361.3. (Calc. for $C_{22}H_{24}N_4O$ (360.452): C 73.31, H 6.71, N 15.54 Found: C 72.92, H 6.75, N 15.34%.)

N-*{2-[4-(2-Fluorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***33***

Mp 163–164°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.15 (t, *J* 4.6, 4H), 3.67 (q, *J* 6.1, 2H), 6.92–7.09 (m, 5H), 7.62 (m, 1H), 7.81 (m, 1H), 7.93 (d, *J* 8.1, 1H), 8.14 (d, *J* 8.4, 1H), 8.64 (d, *J* 1.9, 1H), 9.27 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.42, 50.64, 52.98, 56.29, (CH) 116.09, 116.26, 118.99, 122.63, 124.51, 127.52, 128.85, 131.23, 135.87, 148.03, (C) 127.07, 127.2, 139.86, 149.24, 154.78, 165.49. ν_{max}(KBr)/cm^{-1} 3304, 2817, 1631, 1540, 1241, 752. *m/z* [MH^+] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80 Found: C 69.36, H 6.35, H 14.80%.)

N-*{2-[4-(3-Fluorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***34***

Mp 158–159°C. δ_H (500 MHz, $CDCl_3$) 2.72 (m, 6H), 3.24 (t, *J* 4.9, 4H), 3.67 (q, *J* 5.6, 2H), 6.54 (m, 1H), 6.59 (m, 1H), 6.67 (dd, *J* 2.1, 8.3, 1H), 7.01 (brs, 1H), 7.19 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.2, 1H), 8.14 (d, *J* 8.4, 1H), 8.62 (d, *J* 1.8, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.43, 48.76, 52.72, 56.31, (CH) 102.71, 102.91, 106.05, 106.22, 111.22, 127.55, 128.83, 129.42, 130.15, 130.23, 131.25, 135.77, 148.05, (C) 127.02, 127.17, 149.26, 152.74, 152.81, 162.90,

164.84, 165.60. ν_{max}(KBr)/cm^{-1} 3314, 2827, 1630, 1543, 1494, 764. *m/z* [MH$^+$] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80 Found: C 69.48, H 6.52, N 14.85%.)

N-*{2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***35***

Mp 184–185°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.16 (t, *J* 4.9, 4H), 3.67 (q, *J* 5.6, 2H), 6.89 (m, 2H), 6.97 (m, 2H), 7.02 (brs, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.1, 1H), 8.14 (d, *J* 8.5, 1H), 8.62 (d, *J* 1.9, 1H), 9.25 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.42, 50.28, 52.91, 56.26, (CH) 115.50, 115.68, 117.94, 118.00, 127.54, 128.84, 129.40, 131.25, 135.81, 148.04, (C) 127.03, 127.07, 147.71, 149.25, 156.42, 158.32, 165.56. ν_{max}(KBr)/cm^{-1} 3291, 2822, 1637, 1510, 1230, 816. *m/z* [MH$^+$] 379.3. (Calc. for $C_{22}H_{23}FN_4O$ (378.443): C 69.82, H 6.13, N 14.80. Found: C 69.74, H 6.33, N 14.95%.)

N-*{2-[4-(2-Chlorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***36***

Mp 151–152°C. δ_H (500 MHz, $CDCl_3$) 2.75 (m, 6H), 3.12 (brs, 4H), 3.67 (q, *J* 5.5, 2H), 6.98 (m, 1H), 7.05 (dd, *J* 1.5, 8.0, 1H), 7.07 (brs, 1H), 7.23 (m, 1H), 7.36 (dd, *J* 1.5, 7.9, 1H), 7.63 (m, 1H), 7.81 (m, 1H), 7.94, (d, *J* 8.2, 1H), 8.15 (d, *J* 8.5, 1H), 8.65 (d, *J* 2, 1H), 9.27, (d, *J* 2.0, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.43, 51.34, 53.05, 56.19, (CH) 120.42, 123.86, 127.49, 127.61, 128.81, 129.37, 130.67, 131.17, 135.85, 148.00, (C) 127.05, 127.24, 128.80, 149.06, 149.22, 165.44. ν_{max}(KBr)/cm^{-1} 3239, 2828, 1631, 1558. *m/z* [MH$^+$] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19 Found: C 67.16, H 6.23, N 14.29%.)

N-*{2-[4-(3-Chlorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***37***

Mp 144–145°C. δ_H (500 MHz, $CDCl_3$) 2.70 (m, 6H), 3.24 (t, *J* 4.9, 4H), 3.67 (q, *J* 5.6, 2H), 6.80 (m, 2H), 6.88 (d, *J* 1.8, 1H), 6.99 (brs, 1H), 7.17 (t, *J* 8.1, 1H), 7.62 (t, *J* 7.5, 1H), 7.81 (t, *J* 7.3, 1H), 7.92 (d, *J* 8.2, 1H), 8.15 (d, *J* 8.4, 1H), 8.61 (d, *J* 1.8, 1H), 9.26 (d, *J* 1.8, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.43, 48.80, 52.76, 56.48, (CH) 114.03, 115.94, 119.63, 127.55, 128.84, 129.34, 130.10, 131.28, 135.83, 148.11, (C) 127.00, 127.14, 134.97, 149.25, 152.17, 165.53. ν_{max}(KBr)/cm^{-1} 3284, 2816, 1636, 760. *m/z* [MH$^+$] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19 Found: C 66.79, H 5.67, N 14.39%.)

N-*{2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***38***

Mp 204–205°C. δ_H (500 MHz, $CDCl_3$) 2.71 (m, 6H), 3.20 (t, *J* 4.9, 4H), 3.66 (q, *J* 5.6, 2H), 6.84 (m, 2H), 7.00 (brs, 1H), 7.21 (m, 2H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.1, 1H), 8.14 (d, *J* 8.4, 1H), 8.62 (d, *J* 1.9, 1H), 9.25 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.41, 49.29, 52.76, 56.28, (CH) 117.36, 127.54, 128.82, 129.01, 129.41, 131.25, 135.80, 148.01, (C) 124.86, 127.02, 127.08, 149.26, 149.70, 165.52. ν_{max}(KBr)/cm^{-1} 3298, 2825, 1631, 1546, 1498, 814. *m/z* [MH$^+$] 395.3. (Calc. for $C_{22}H_{23}ClN_4O$ (394.897): C 66.91, H 5.87, N 14.19 Found: C 66.63, H 6.10, N 14.23%.)

N-*{2-[4-(2-Methylphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***39***

Mp 126–128°C. δ_H (500 MHz, $CDCl_3$) 2.32 (s, 3H), 2.73 (m, 6H), 2.98 (t, *J* 4.5, 4H), 3.66 (q, *J* 5.6, 2H), 6.99 (m, 1H), 7.03 (d, *J* 7.7, 1H), 7.10 (brs, 1H), 7.18 (t, *J* 7.5, 2H), 7.63 (m, 1H), 7.81 (m, 1H), 7.93 (d, *J* 8.1, 1H), 8.15 (d, *J* 8.5, 1H), 8.65 (d, *J* 1.8, 1H), 9.28 (d, *J* 2.1, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 17.88, (CH_2) 36.46, 51.83, 53.43, 56.34, (CH) 119.03, 123.32, 126.62, 127.52, 128.86, 129.40, 131.12, 131.22, 135.88, 148.08, (C) 127.08, 127.23, 132.64, 149.25, 151.26, 165.50. ν_{max}(KBr)/cm^{-1} 3290, 2820, 1632, 1552, 758. *m/z* [MH$^+$] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.66, H 7.17, N 14.74%.)

N-*{2-[4-(3-Methylphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***40***

Mp 143–144°C. δ_H (500 MHz, $CDCl_3$) 2.33 (s, 3H), 2.72 (m, 6H), 3.23 (t, *J* 4.9, 4H), 3.67 (q, *J* 5.6, 2H), 6.70 (d, *J* 7.4, 1H), 6.76 (m, 2H), 7.04 (brs, 1H), 7.16 (t, *J* 7.7, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.1, 1H), 8.14 (d, *J* 8.5, 1H), 8.61 (d, *J* 1.8, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 21.77, (CH_2) 36.43, 49.43, 52.95, 56.26, (CH) 113.35, 117.07, 120.91, 127.50, 128.81, 128.99, 129.41, 131.20, 135.71, 148.08, (C) 127.01, 127.15, 138.84, 149.24, 151.20, 165.51. ν_{max}(KBr)/cm^{-1} 3278, 2816, 1642, 1556, 1249, 748. *m/z* [MH$^+$] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.72, H 7.19, N 14.77%.)

N-*{2-[4-(4-Methylphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***41***

Mp 172–174°C. δ_H (500 MHz, $CDCl_3$) 2.28 (s, 3H), 2.72 (m, 6H), 3.19 (t, *J* 4.9, 4H), 3.66 (q, *J* 5.6, 2H), 6.85 (d, *J* 9.5, 2H), 7.03 (brs, 1H), 7.07 (d, *J* 9.5, 2H), 7.62 (m, 1H), 7.80 (m, 1H), 7.91 (d, *J* 8.0, 1H), 8.14 (d, *J* 8.5, 1H), 8.61 (d, *J* 1.9, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 20.43, (CH_2) 36.44, 49.85, 52.95, 56.30, (CH) 116.51, 127.49, 128.81, 129.38, 129.68, 131.19, 135.71, 148.11, (C) 127.01, 127.14, 129.53, 149.01, 149.23, 165.53. ν_{max}(KBr)/cm^{-1} 3302, 2942, 2812, 1642, 1538, 1518, 809, 745. *m/z* [MH$^+$] 375.3. (Calc. for $C_{23}H_{26}N_4O$ (374.479): C 73.77 H 7.00, N 14.96 Found: C 73.89, H 7.27, N 15.21%.)

N-*{2-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***42***

Mp 172–174°C. δ_H (500 MHz, $CDCl_3$) 2.73 (m, 6H), 3.28 (t, *J* 5.0, 4H), 3.68 (q, *J* 5.6, 2H), 6.99 (brs, 1H), 7.07 (m, 2H), 7.12 (s, 1H), 7.35 (t, *J* 8.0, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 8.2, 1H), 8.14 (d, *J* 8.4, 1H), 8.61 (d, *J* 1.9, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 36.38, 48.79, 52.72, 56.33, (CH) 112.34, 116.22, 118.93, 127.53, 128.79, 129.40, 129.59, 131.23, 135.71, 148.03, (C) 127.01, 127.15, 131.34, 131.59, 149.26, 151.25, 165.55. ν_{max}(KBr)/cm^{-1} 3277, 2829, 1662, 1308, 1153, 1110. *m/z* [MH$^+$] 429.3. (Calc. for $C_{23}H_{23}F_3N_4O$ (428.450): C 64.48, H 5.41, N 13.08 Found: C 64.58, H5.49, N 13.13%.)

N-*{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***43***

Mp 150–151°C. δ_H (500 MHz, $CDCl_3$) 2.74 (m, 6H), 3.13 (brs, 4H), 3.66 (q, *J* 5.6, 2H), 3.88 (s, 3H), 6.87 (dd, *J* 1.0, 7.8, 1H), 6.94 (m, 2H), 7.01 (m, 1H), 7.12 (brs, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.93 (d, *J* 8.1, 1H), 8.15 (d, *J* 8.5, 1H), 8.64 (d, *J* 1.9, 1H), 9.27 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.40, (CH_2) 36.41, 50.75, 53.13, 56.31, (CH) 111.26, 118.25, 121.03, 123.12, 127.49, 128.84, 129.39, 131.19, 135.89, 148.09, (C) 127.06, 127.21, 141.08, 149.24, 152.28, 165.47. ν_{max}(KBr)/cm^{-1} 3339, 2824, 1636, 1542, 1499, 1241, 746. *m/z* [MH$^+$] 391.3. (Calc. for

$C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.76, H 7.18, N 14.41%.)

N-*{2-[4-(3-Methoxyphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***44***

Mp 137–139°C. δ_H (500 MHz, $CDCl_3$) 2.71 (m, 6H), 3.24 (t, *J* 4.9, 4H), 3.66 (q, *J* 5.6, 2H), 3.80 (s, 3H), 6.43 (dd, *J* 2.0, 8.0, 1H), 6.47 (t, *J* 2.2, 1H), 6.54 (dd, *J* 2.0, 8.2, 1H), 7.03 (brs, 1H), 7.18 (t, *J* 8.2, 1H), 7.62 (m, 1H), 7.80 (m,1H), 7.91 (d, *J* 8.1, 1H), 8.14 (d, *J* 8.5, 1H), 8.61 (d, *J* 1.7, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.20, (CH_2) 36.43, 49.23, 52.87, 56.27, (CH) 102.63, 104.70, 108.94, 127.51, 128.81, 129.42, 129.84, 131.21, 135.69, 148.08, (C) 127.02, 127.15, 149.26, 152.52, 160.61, 165.51. ν_{max}(KBr)/cm^{-1} 3292, 2819, 1641, 1549, 1210, 753. *m/z* [MH^+] 391.3. (Calc. for $C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.70, H 6.80, N 14.49%.)

N-*{2-[4-(4-Methoxyphenyl)piperazin-1-yl]ethyl}-3-quinoline Carboxamide* ***45***

Mp 172–174°C. δ_H (500 MHz, $CDCl_3$) 2.72 (m, 6H), 3.13 (t, *J* 4.8, 4H), 3.66 (q, *J* 5.6, 2H), 3.78 (s, 3H), 6.85 (m, 2H), 6.90 (m, 2H), 7.05 (brs, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.92 (d, *J* 7.9, 1H), 8.14 (d, *J* 8.5, 1H), 8.62 (d, *J* 1.8, 1H), 9.26 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_3) 55.57, (CH_2) 36.30, 50.63, 53.03, 56.35, (CH) 114.50, 118.40, 127.49, 128.86, 129.39, 131.21, 135.79, 148.15, (C) 126.99, 127.19, 145.53, 149.22, 153.92, 165.49. ν_{max}(KBr)/cm^{-1} 3304, 2818, 1638, 1513, 1251, 822. *m/z* [MH^+] 391.3. (Calc. for $C_{23}H_{26}N_4O_2$ (390.478): C 70.75, H 6.71, N 14.35 Found: C 70.84, H 6.89, N 14.00%.)

N-*[2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)ethyl]-3-quinoline Carboxamide* ***46***

Mp 173–175°C. δ_H (500 MHz, $CDCl_3$) 2.61 (m, 2H), 2.81 (m, 4H), 3.26 (q, *J* 2.9, 2H), 3.70 (q, *J* 5.5, 2H), 6.10 (m, 1H), 7.10 (brs, 1H), 7.24 (m, 1H), 7.33 (m, 2H), 7.40 (m, 2H), 7.60 (m, 1H), 7.79 (m, 1H), 7.90 (d, *J* 8.2, 1H), 8.13 (d, *J* 8.4, 1H), 8.60 (d, *J* 1.9, 1H), 9.27 (d, *J* 2.2, 1H). δ_C (500 mHz, $CDCl_3$) (CH_2) 27.92, 36.83, 50.12, 53.02, 56.21, (CH) 121.23, 124.84, 127.21, 127.42, 128.37, 128.80, 129.39, 131.13, 135.64, 148.33, (C) 126.96, 127.20, 135.09, 140.43, 149.21, 165.68. ν_{max}(KBr)/cm^{-1} 3299, 2920, 1638, 1540, 743. *m/z* [MH^+] 358.3. (Calc. for $C_{23}H_{23}N_3O$ (357.448): C 77.28, H 6.49, N 11.76 Found: C 77.39, H 6.71, N 11.77%.)

Lipophilicity Measurement (Log k'_{IAM})

The column was an IAM.PC.DD2 HPLC column (30 length × 4.6 mm internal diameter; particle size: 12 μm; pore diameter: 300 Å) from Regis Technologies (Morton Grove, IL, USA). The LC system consisted in a Merck-Hitachi L-6000 Pump, a Merck-Hitachi D-2000 Chromato-Integrator and a Rheodyne 7125 injector module equipped with a 20-μL loop (Rohnert Park, CA, USA). The column was maintained in a thermostatted water-bath Tectron 473–100 from Selecta (Barcelona, Spain), and detection was carried out with a Merck-Hitachi L-4000 UV detector. Prior to use, mobile phases were degassed for 15 min in a Branson 5510 ultrasonic bath (Branson Ultrasonics Corporation, Danbury, CT, USA). Buffer was adjusted to the expected pH values with a Radiometer Analytical pH meter, model ION check 10 (Villeurbanne, France). Each drug was dissolved in methanol (10.0 mL) at a concentration of 200 μg mL^{-1}. A 1-mL volume of this stock solution was then diluted with methanol in a 10-mL flask in order to obtain a daughter solution of each compound (20 μg mL^{-1}). These diluted solutions (20 μL) were injected. The flow rate was maintained at 1 mL min^{-1}. The temperature of the column was fixed at 25°C, and the ultraviolet absorption wavelength was set at 250 nm. The mobile phases were phosphate buffer (50 mM, pH 7.4) containing 10 to 60% methanol, according to the lipophilicity of the compounds. The increment of methanol between two mobile phases is 10%. All retention factors given represent the mean of three determinations of each sample solution. Retention times of the test compounds were transformed into capacity factors (k'_{IAM}) according to the following equation: $k'_{IAM} = \frac{(t_r - t_0)}{t_0}$, where t_r and t_0 are the retention time of the test compound and the column void volume time respectively. Capacity factors were expressed as a logarithm (log k'_{IAM}). The values reported in the text correspond to the extrapolation at 100% aqueous medium.

In Vitro Binding Procedures

5-HT$_{1A}$ Receptor Binding Assays

CHO cells expressing recombinant human serotonin receptors subtype 1A were used as membrane preparations (Perkin–Elmer 6110501). Briefly, incubations were carried out in 50 mM Tris-HCl buffer (pH 7.4) containing 10 mM $MgSO_4$, 0.5 mM EDTA, and 0.1% ascorbic acid. Binding assays were performed in 540 μL total volume divided in 500 μL diluted membranes, 20 μL radioligand ([^{3}H]-8-OH-DPAT at 0.25 nM) and 20 μL buffer, unlabelled ligand, or tested drugs. After 60 min at 27°C, incubations were terminated by rapid filtration on Whatman GF/C filters pre-soaked in 0.3% polyethylenimine followed by washing two times with ice-cold 50 mM TRIS-HCl (pH 7.4). Filters were placed in a vial containing 7.5 mL Ecoscint A. Radioactivity remaining on the filter was evaluated by liquid scintillation using a TRI-CARB 1600TR liquid scintillation analyzer. Non-specific binding was estimated in the presence of 10 μM WB4101. Affinities were determined at least in duplicate with eight concentrations in duplicate. A preliminary screening was made at 10^{-6} M. Compounds displacing more than 60% specific radioactivity were further tested for K_i determinations (K_d of the radioligand is 0.32 nM).

α$_{2A}$-Adrenoceptor Binding Assays

Sf9 cells expressing human cloned α_{2A}-adrenoceptors were used as membrane preparations (Perkin–Elmer 6110113). Briefly, incubations were carried out in 50 mM Tris-HCl buffer (pH 7.4) containing 12.5 mM $MgCl_2$ and 2 mM EDTA. Binding assays were performed in 540 μL total volume divided in 500 μL diluted membranes, 20 μL radioligand ([^{3}H]-MK912 at 0.7 nM), and 20 μL buffer, unlabelled ligand or tested drugs. After 60 min at 27°C, incubations were terminated by rapid filtration on Whatman GF/C filters followed by washing two times with ice-cold 50 mM Tris-HCl (pH 7.4). Filters were placed in a vial containing 7.5 mL Ecoscint A. Radioactivity remaining on the filter was evaluated by liquid scintillation using a TRI-CARB 1600TR liquid scintillation analyzer. Non-specific binding was estimated in the presence of 10 μM metergoline. Affinities were determined at least in duplicate with eight concentrations in duplicate. A preliminary screening was made at 10^{-6} M. Compounds displacing more than 60% specific radioactivity were further tested for K_i determinations (K_d of the radioligand is 0.75 nM).

D4.2 Receptor Binding Assays

Sf9 cells expressing human cloned D4.2 receptors were used as membrane preparations (Sigma D2439). Briefly, incubations were carried out in 50 mM Tris-HCl buffer (pH 7.4) containing 5 mM $MgCl_2$, 5 mM KCl, 1.5 mM $CaCl_2$, and 5 mM EDTA. Binding assays were performed in 540 μL total volume divided in 500 μL diluted membranes, 20 μL radioligand ([^{3}H]-YM-09151–2 at 0.2 nM) and 20 μL buffer, unlabelled ligand, or tested drugs. After 60 min at 27°C, incubations were terminated by rapid filtration on Whatman GF/C filters followed by washing two times with ice-cold 50 mM Tris-HCl (pH 7.4). Filters were placed in a vial containing 7.5 mL Ecoscint A. Radioactivity remaining on the filter was evaluated by liquid scintillation using a TRI-CARB 1600TR liquid scintillation analyzer. Non-specific binding was estimated in the presence of 10 μM clozapine. Affinities were determined at least in duplicate with eight concentrations in duplicate. A preliminary screening was made at 10^{-6} M. Compounds displacing more than 60% specific radioactivity were further tested for K_i determinations (K_d of the radioligand is 0.06 nM).

Intrinsic Activity Methods

Reference agonist (dopamine or serotonin) and test compounds were dissolved in assay buffer or DMSO according to solubility. Dilutions of the compounds were made in binding buffer at two times the assay concentration (final assay concentration: 10 μM). Crude D4 receptor- or 5-HT1A receptor-expressing membrane fractions (1.8 to 3.5 cm^2 per well) (prepared from 10-cm plates by harvesting PBS-rinsed monolayers, resuspending and lysing in chilled, hypotonic 50 mM Tris-HCl, pH 7.4, centrifuging at 20000*g* at 4°C, decanting the supernatant, and storing at −80°C) were resuspended in assay buffer (1.2 mL) containing 20 μM GDP, wheat germ agglutinin-coated scintillation proximity beads (2.4 mg), and [^{35}S]GTPγS (300 pM final). The suspension was then added (50 μL per well) to 50 μL of the 2× test or reference compounds (each concentration assayed in triplicate) in flexible transparent 96-well plates (Perkin–Elmer). The reaction plates were incubated for 90 min at room temperature, then centrifuged for 5 min at 216*g* at 4°C, and finally loaded into a Wallac MicroBeta TriLux counter. Non-specific [^{35}S]GTPγS binding was assessed in the presence of 10 μM antagonist (chlorpromazine or WAY100635). The background signal was measured at 10 μM reference agonist in the presence of 10 μM unlabelled GTPγS. Raw data (disintegration per min) representing total [^{35}S]GTPγS binding (i.e. specific + non-specific binding) were normalized such that [^{35}S]GTPγS binding in the presence of 10 μM reference agonist was 100% and non-specific [^{35}S]GTPγS binding was 0%.

Accessory Publication

The Accessory Publication contains analytical characterization data of phthalimide derivatives available on the Journal's website.

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