ACS Medicinal Chemistry Letters

Letter

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# Enhancing a CH−$\pi$ Interaction to Increase the Affinity for 5-HT$_{1A}$ Receptors

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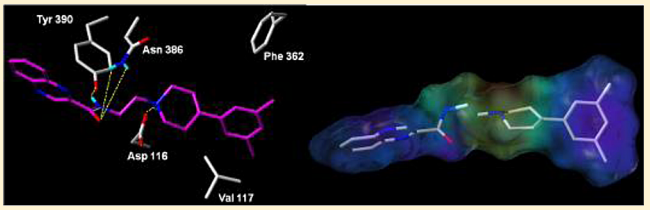
Supporting Information

**ABSTRACT:** An electrostatic interaction related to a favorable position of the distal phenyl ring and a phenylalanine residue in the binding pocket would explain the higher 5-HT$_{1A}$ affinity of a 4-phenyl-1,2,3,6-tetrahydropyridine (THP) analogue compared to the corresponding 4-phenylpiperazine analogue. To explore a possible reinforcement of this interaction to increase the affinity for 5-HT$_{1A}$ receptors, different 4-substituted-phenyl analogues were synthesized and tested. The most important increase of affinity is obtained with two electron-donating methyl groups in positions 3 and 5.

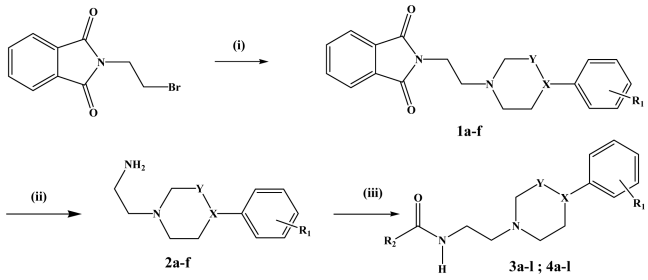



**KEYWORDS:** *CH−$\pi$ interaction, quinoxaline, carboxamide, arylpiperazine, electron-donating, docking*

Recently, we reported that a 4-phenyl-1,2,3,6-tetrahydropyridine (THP) analogue was shown to be favorable compared to the corresponding 4-phenyl-piperazine one in terms of affinity for 5-HT$_{1A}$ receptors in a series of 4-arylpiperazine-ethyl carboxamides.[1] An electrostatic interaction between the distal benzene ring of the molecule and a phenylalanine residue (Phe 6.52) particularly in the 5-HT$_{1A}$ receptor binding pocket was suggested by molecular modeling approaches.[2] The almost coplanar orientation of both rings displayed in the 4-phenyl-THP compound appeared as an important spatial requirement for an optimal interaction with the 5-HT$_{1A}$ receptor in the present series. This orientation should stabilize the ligand binding by an edge-to-face CH−$\pi$ interaction between the phenyl ring of the 4-phenyl-THP compounds and the phenyl ring of the Phe 6.52 residue.[2] This would explain why the chemical modification of the piperazine ring into THP is favorable for receptor affinity.

The electron donating/withdrawing properties of an aromatic substituent is an important factor for the electron density of the aromatic ring and consequently for the capacity of these rings to be involved in aromatic stacking interactions.[3] Some studies have already shown the impact of the electronic properties of the substituents on the stability of these interactions in ligand−receptor binding.[4,5] Therefore, by increasing the electronic density with an electron-donating group, we expected to reinforce the interaction between the distal benzene ring and the Phe 6.52 residue. The substituents were positioned either in position 4 or positions 3 and 5 of the distal ring in order to avoid a sterical constraint if present in position 2 or 6. To explore a possible opposite effect linked to the electronic properties of the substituents, electron-withdrawing atoms were also introduced. The THP derivatives were tested, in parallel with the corresponding arylpiperazine derivatives, for their affinity for 5-HT$_{1A}$ receptors. The intrinsic activity of six selected compounds was also investigated using an electrophysiological approach.

**Scheme 1**[a]




[a]Reagents and conditions: (i) *N*-(un)substituted-4-phenylpiperazine (or (un)substituted-4-phenyl-THP), $K_2CO_3$, ACN, reflux; (ii) $NH_2NH_2$, EtOH, reflux; (iii) acyl chloride, $Et_3N$, EtOAc, rt. $R_1$: H, 4-F, 4-Cl, 4-Me, 3,5-diF, 3,5-diMe. $R_2$: 2-naphthyl (**3a−l**), 2-quinoxalinyl (**4a−l**). X−Y: N−$CH_2$ or C═CH.

The target compounds were prepared by reaction of the appropriate primary amine with the appropriate acyl chloride (2-naphthoyl chloride or 2-quinoxaline chloride) as reported in Scheme 1. The crude amines were synthesized following a Gabriel procedure using the appropriate *N*-substituted phthalimide analogues, which were obtained by reaction of an adequate substituted *N*-phenylpiperazine (or substituted 4-

**Received:** November 26, 2013
**Accepted:** January 29, 2014
**Published:** January 29, 2014

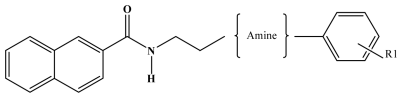
   dx.doi.org/10.1021/ml4004843 | *ACS Med. Chem. Lett.* 2014, 5, 358−362

phenyl-THP) with *N*-(2-bromoethyl)phthalimide in the presence of potassium carbonate.

Most *N*-arylpiperazine derivatives were obtained from commercial sources and used without further purification. Phthalimide derivatives are characterized and tested in parallel in the in vitro binding model. Most substituted 4-aryl-THP derivatives have been prepared by a Grignard reaction between the adequate substituted-phenyl magnesium bromide and commercially available *N*-Boc-4-piperidone according to similar protocols as those reported in the literature.[6−8] For 3,5-difluoro and 3,5-dimethyl analogues, Grignard reagents were prepared in the laboratory, while 4-methyl and 4-fluoro analogues were purchased. After reaction, the *N*-Boc-piperidinol analogue is dehydrated and deprotected by treatment with trifluoroacetic acid in methylene chloride to give the appropriate THP derivatives. With the 3,5-difluoro derivative, unexpectedly, the hydroxyl group was not eliminated, and the piperidinol was obtained with this procedure. Another approach using a mixture of HBr and acetic acid led to the appropriate analogue. Target compounds (**3a−l** and **4a−l**) were isolated as the base and further characterized before biological evaluation.

In vitro binding experiments were conducted on human cloned 5-$HT_{1A}$ receptors expressed in CHO cells and used as membrane preparations. The radioligand used was [$^3$H]-8-OH-DPAT. Experimental procedures for filtration and radioactivity counting are the same used in our previous studies.[1,9,10] Details can be found in the Supporting Information. Values of affinity for naphthyl (**3a−l**) and quinoxaline (**4a−l**) derivatives are reported in Tables 1 and 2, respectively.

**Table 1. Affinity for 5-$HT_{1A}$ Receptors and Physicochemical Characteristics of Naphthalene Carboxamide Derivatives (3a−l)**

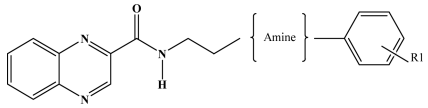



| compd | amine | $R_1$ | $K_i$[a] | p$K_a$ | log *P* |
|---|---|---|---|---|---|
| **3a** | piperazine | H | 24.7 ± 3.6 | 7.21 | 4.42 |
| **3b** | THP | H | 6.1 ± 0.9 | 8.06 | 4.95 |
| **3c** | piperazine | 4-F | 54.3 ± 6.9 | 7.15 | 4.66 |
| **3d** | THP | 4-F | 33.5 ± 18.5 | 8.02 | 4.96 |
| **3e** | piperazine | 4-Cl | 50.7 ± 14.9 | 7.12 | 5.23 |
| **3f** | THP | 4-Cl | 42.5 ± 11.8 | 7.98 | 5.53 |
| **3g** | piperazine | 4-Me | 221.4 ± 19.3 | 7.41 | 4.84 |
| **3h** | THP | 4-Me | 31.6 ± 5.1 | 8.38 | 5.32 |
| **3i** | piperazine | 3,5-diF | 28.95 ± 3.2 | 7.06 | 4.86 |
| **3j** | THP | 3,5-diF | 7.29 ± 1.07 | 7.90 | 5.1 |
| **3k** | piperazine | 3,5-diMe | 21.0 ± 1.7 | 7.55 | 4.34 |
| **3l** | THP | 3,5-diMe | 8.06 ± 0.35 | 8.43 | 5.82 |

[a]$K_i$ in nM; mean ± SEM $n \geq 3$.

All naphthyl analogues possess a significant affinity for 5-$HT_{1A}$ receptors. Except for halogenated analogues (**3c−f**), the THP derivatives (**3b**, **3d**, **3f**, **3h**, **3j**, **3l**) present a higher affinity than the piperazine ones (**3a**, **3c**, **3e**, **3g**, **3i**, **3k**). This increase is approximately four times. In this series, the impact of the substitution of the distal phenyl ring is limited except for the 4-halogenated derivatives (**3c−f**) and the methyl derivatives (**3g**, **3h**), which possess a lower affinity than the unsubstituted derivatives (**3a**, **3b**). For the 4-fluorine analogues (**3c**, **3d**), the electron-withdrawing effect of the fluorine on the electronic density of the benzene ring might also reduce the interaction with the residue in the binding pocket by more than a deleterious sterical effect contrary to the chlorine or methyl substituent in other derivatives. For the 3,5-difluoro analogues (**3i**, **3j**) and the 3,5-dimethyl analogues (**3k**, **3l**), the affinity is quite similar to that of the corresponding unsubstituted derivatives (**3a**, **3b**).

**Table 2. Affinity for 5-$HT_{1A}$ Receptors and Physicochemical Characteristics of Quinoxaline Carboxamide Derivatives (4a−l)**




| compd | amine | $R_1$ | $K_i$[a] | p$K_a$ | log *P* |
|---|---|---|---|---|---|
| **4a** | piperazine | H | 30.0 ± 5.8 | 6.98 | 3.66 |
| **4b** | THP | H | 3.76 ± 0.24 | 7.84 | 4.18 |
| **4c** | piperazine | 4-F | 63.3 ± 15.1 | 6.92 | 3.89 |
| **4d** | THP | 4-F | 14.0 ± 2.1 | 7.79 | 4.19 |
| **4e** | piperazine | 4-Cl | 27.0 ± 3.6 | 6.89 | 4.46 |
| **4f** | THP | 4-Cl | 9.30 ± 0.89 | 7.75 | 4.76 |
| **4g** | piperazine | 4-Me | 27.3 ± 4.5 | 7.18 | 4.08 |
| **4h** | THP | 4-Me | 7.55 ± 1.84 | 8.15 | 4.55 |
| **4i** | piperazine | 3,5-diF | 11.1 ± 0.7 | 6.83 | 4.09 |
| **4j** | THP | 3,5-diF | 2.62 ± 0.53 | 7.67 | 4.34 |
| **4k** | piperazine | 3,5-diMe | 3.67 ± 0.38 | 7.33 | 4.57 |
| **4l** | THP | 3,5-diMe | 1.10 ± 0.16 | 8.20 | 5.05 |

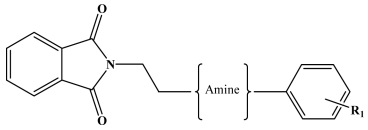
[a]$K_i$ in nM; mean ± SEM $n \geq 3$.

In the quinoxaline series, it appears that the unsubstituted analogues (**4a**, **4b**) possess a similar affinity as that of the naphthyl congeners (**3a**, **3b**). Substituted THP analogues (**4b**, **4d**, **4f**, **4h**, **4j**, **4l**) have a higher affinity than the corresponding piperazine derivatives (**4a**, **4c**, **4e**, **4g**, **4i**, **4k**). The presence of a fluorine in position 4 (**4c**, **4d**) reduces the affinity in both THP and piperazine series, and this might be related to the electron-withdrawing properties of the fluorine. The presence of a methyl group (**4g**, **4h**) and a chlorine (**4e**, **4f**) in the same position leads to a smaller decrease of affinity in THP series in comparison with the unsubstituted analogues (**4a**, **4b**). The presence of two substituents in positions 3 and 5 leads to an increase of the affinity for the corresponding THP (**4j**, **4l**) and piperazine (**4i**, **4k**) derivatives. The highest affinity is observed for the 3,5-dimethyl derivative (**4l**), while the most important increase is observed for the piperazine analogue (**4k**).

In parallel, the affinity of phthalimide derivatives (**1a−l**) is also determined (Table 3), as some reports indicated a biological effect of these compounds.[11] Except for some analogues, the affinity is weak as also reported separately for compound **1a**.[12] Like for the other two groups of molecules, it appears that the THP analogues (**1b**, **1d**, **1f**, **1h**, **1j**, **1l**) have a higher affinity than the corresponding piperazine analogues (**1a**, **1c**, **1e**, **1g**, **1i**, **1k**). In THP series, the presence of a substituent in position 4 of the distal phenyl ring has no or minimal impact in terms of affinity, e.g., the unsubstituted derivatives (**1b**) and the 4-chloro analogue (**1f**) have a similar affinity of 706 and 631 nM, respectively. However, the presence of two substituents in positions 3 and 5 leads to an increase of affinity of 425 and 105 nM for the 3,5-difluoro analogue (**1j**) and the 3,5-dimethyl analogue (**1l**), respectively. The 3,5-dimethyl derivatives are four (**1k**) and seven (**1l**) times more potent on these receptor sites in comparison with the unsubstituted analogue (**1b**).


dx.doi.org/10.1021/ml4004843 | ACS Med. Chem. Lett. 2014, 5, 358−362

**Table 3. Affinity for 5-HT$_{1A}$ Receptors and Physicochemical Characteristics of Phthalimide Derivatives (1a−l)**




| compd | amine | $R_1$ | $K_i$[a] | p$K_a$ | log $P$ |
|---|---|---|---|---|---|
| **1a** | piperazine | H | 82% | 6.81 | 3.47 |
| **1b** | THP | H | 706 ± 119 | 7.66 | 3.99 |
| **1c** | piperazine | 4-F | 80.4% | 6.74 | 3.69 |
| **1d** | THP | 4-F | 76.83% | 7.61 | 3.99 |
| **1e** | piperazine | 4-Cl | 97.36% | 6.71 | 4.26 |
| **1f** | THP | 4-Cl | 631 ± 54 | 7.57 | 4.56 |
| **1g** | piperazine | 4-Me | 97% | 7.01 | 3.87 |
| **1h** | THP | 4-Me | 80% | 7.98 | 4.35 |
| **1i** | piperazine | 3,5-diF | 79.56% | 6.66 | 3.89 |
| **1j** | THP | 3,5-diF | 425 ± 59 | 7.50 | 4.13 |
| **1k** | piperazine | 3,5-diMe | 496 ± 113 | 7.15 | 4.37 |
| **1l** | THP | 3,5-diMe | 105 ± 11 | 8.03 | 4.85 |

[a] $K_i$ in nM; mean ± SEM $n \geq 3$ (or for compounds with low affinity, the screening value expressed in % of residual specific radioactivity at 1 $\mu$M is mentioned).

Besides the affinity, calculated p$K_a$ and lipophilicity have been examined. Procedures used are indicated in the Supporting Information section. The presence of a basic nitrogen is an important element in terms of interactions with such GPCR. Therefore, the hydrogen bond between an aspartate in the binding pocket and this nitrogen is reinforced when this nitrogen is charged. In all series, an increase of p$K_a$ and lipophilicity is observed for the THP analogues in comparison with the piperazine analogues (Tables 1−3). Nevertheless, the affinity is not systematically increased in parallel. Indeed, in the naphthyl series, the unsubstituted analogues (**3a**, **3b**) and the 3,5-dimethyl analogues (**3k**, **3l**) have a similar affinity, while physicochemical parameters are increased for the substituted derivatives (**3k**, **3l**). In the quinoxaline series, the affinity is increased in parallel to the physicochemical parameters when comparing piperazine and THP analogues. Regarding the 3,5-difluoro analogues (**4i**, **4j**), the higher affinity is associated to a slightly reduced p$K_a$ value and a higher lipophilicity parameter than the unsubstituted analogues (**4a**, **4b**), while for the 3,5-dimethyl analogues (**4k**, **4l**) the highest affinity, p$K_a$, and lipophilicity values are observed in this series.

Complementary to binding studies, some electrophysiological experiments were devoted to the determination of the intrinsic activity of selected compounds (**4a**, **4b**, **4i**, **4j**, **4k**, **4l**) on the firing rate of presumed serotonergic neurons of the dorsal raphe nucleus (DR) recorded on rat brain slices according to previously reported procedures.[13] Indeed, several studies have shown that the firing of these neurons is inhibited by 5-HT$_{1A}$ agonists such as 8-OH-DPAT.[14] This effect is blocked or reversed by 5-HT$_{1A}$ antagonists such as WAY-100635.[15] The six compounds tested induced a concentration-dependent decrease in the firing rate of DR presumed serotonergic neurons. Concentration−response curves are illustrated in the Supporting Information. The IC$_{50}$s were, respectively, 1683 ± 783 nM for compound **4a**, 460 ± 72 nM for compound **4b**, 1140 ± 660 nM for compound **4i**, 95 ± 70 nM for compound **4j**, 383 ± 196 nM for compound **4k**, and 172 ± 85 nM for compound **4l**. The inhibitory effect of all four compounds was reversed by the simultaneous application of WAY-100635 (100 nM). One experiment performed with compound **4b** is illustrated in the Supporting Information. The six compounds thus behave as 5-HT$_{1A}$ agonists. The order of potency, **4j** > **4l** > **4k** > **4b** > **4i** > **4a**, is in good agreement with binding affinities obtained on cloned receptors.

The binding mode of the ligands with higher affinity (**4k**, **4l**) was explored by molecular docking simulations and compared to that of the corresponding unsubstituted (**4a**, **4b**) analogues (for experimental details, see Supporting Information).

Four main interactions known to be important for the receptor affinity[16] are found for all the compounds (Figure 1).

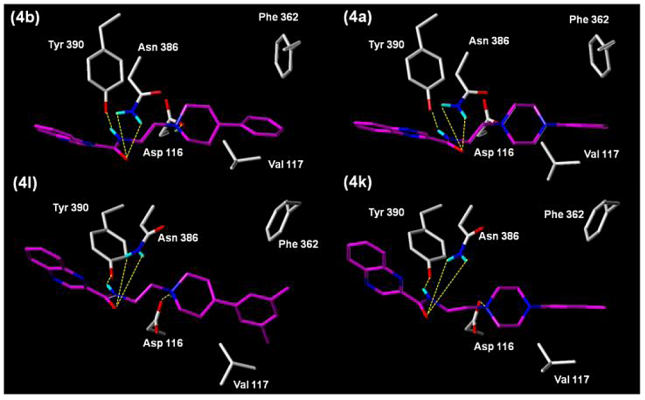



**Figure 1.** Binding mode of compounds **4a**, **4b**, **4k**, and **4l** (C, N, O, and H atoms in magenta, blue, red, and cyan, respectively) in a human 5-HT$_{1A}$ receptor agonist model. The hydrogen bonds are indicated by yellow dashed lines.

The first key binding feature is the protonated amine, which forms hydrogen bonds with Asp 116 (Asp 3.32 according to the Ballesteros and Weinstein numbering),[17] a specific residue for ligand binding among all mammalian biogenic amine receptors.[18] Two other hydrogen bonds are also observed. Indeed, a hydrogen bond is detected between the hydrogen atom of the amide group and the hydroxyl group of Tyr 390 (Tyr 7.43). An interaction with this residue was also demonstrated in the ligand binding of other aryl piperazine derivatives.[19] Then a bifurcated hydrogen bond is observed between the carbonyl oxygen atom and the amide group of Asn 386 (Asn 7.39). This is consistent with site directed mutagenesis data showing that the valine substitution for Asn 7.39 induces a reduction in the binding affinity of 5-HT$_{1A}$ ligands.[20]

The last key binding feature is the distal phenyl ring interacting with Phe 362 (Phe 6.52).[2,19] Contrary to the hydrogen bonds, the geometrical parameters of this interaction are shown to be altered following the presence of a THP or a piperazine group (Figure 1). Indeed, as suggested in previous work,[2] in the THP analogues (**4b** and **4l**), the phenyl ring preferentially adopts an almost coplanar orientation relative to the THP moiety, which appears to be favorable for an edge-to-face CH−$\pi$ interaction with Phe 362. The dihedral angle measured between the ring planes (86° and 91° for **4b** and **4l**, respectively) is very close to the optimal value of 90°.[21] In contrast, for piperazine analogues, the perpendicular orientation of the phenyl ring seems to be less favorable for the CH−$\pi$ interaction with dihedral angle values of 65° and 56° for **4a** and **4k**, respectively. This finding could be one of the keys for


dx.doi.org/10.1021/ml4004843 | ACS Med. Chem. Lett. 2014, 5, 358−362

explaining the different affinities observed between THP and piperazine compounds.

The influence of 3,5-dimethyl substituent as an electron-donating group is difficult to observe in the docking results. To measure this impact, the electrostatic potential of each compound was evaluated according to quantum calculations (see Supporting Information for experimental details). The presence of 3,5-dimethyl substituent appears to cause an electron enrichment of the phenyl ring (Figure 2), which is

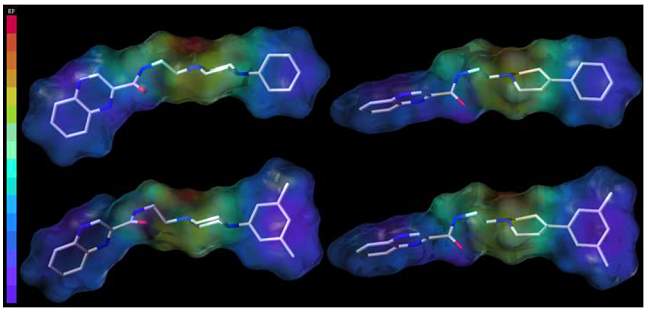


**Figure 2.** Electrostatic potential of compounds **4a** (top left), **4b** (top right), **4k** (bottom left), and **4l** (bottom right). The electrostatic map shows the electron-rich (purple) to the electron-deficient (red) regions of the compounds.

favorable for an edge-to-face CH−$\pi$ interaction with Phe 362. However, another explanation can be considered for the favorable impact of the substitution. This is the generation of additional favorable interactions with the receptor, namely, hydrophobic contacts between one methyl and the residue Val 117 (Val 3.33) (Figure 1). This residue is known to be also important for the binding of 5-$HT_{1A}$ agonists.[16]

In the exploration of 5-$HT_{1A}$ receptor−ligand recognition, several studies have been carried out,[19,22,23] but no one, in our knowledge, further examined the CH−$\pi$ interaction described in the current work. As the binding pocket of different GPCRs presents some homology, it will be interesting in the continuation of this work to evaluate this concept with other targets. Nevertheless, although homology concerns some amino acid residues are quite well conserved, the key residue Asn 7.39 is found to be replaced in other receptors (i.e., Val in 5-$HT_{2A}$-5-$HT_{2C}$R; Phe in $\alpha_{1A}$-$\alpha_{2A}$R; Thr in $D_2$-$D_4$R). As mentioned above, Val mutation in the sequence of 5-$HT_{1A}$ receptors[20] has shown a decrease of affinity for tested compounds. Moreover, quinoxaline analogues previously described[1] present low affinity for $\alpha_{2A}$ or $D_4$ receptors. Otherwise, 1,2,3,6-tetrahydropyridine moiety is used in the medicinal chemistry field[24] as reviewed,[25,26] although some health hazards are observed with MPTP analogues.[25] Because these compounds are structurally related to MPTP, they could be tested in the context of a structure−toxicity relationship.

In the present work, a significant increase of affinity is observed when electron-donating groups are present in the distal benzene ring (compound **4l**) leading to a possible reinforcement of the interaction observed in docking studies and previously seen with the unsubstituted analogue **4b** from a conformational analysis.[2] A favorable impact of the lipophilicity and p$K_a$ of the compound cannot be excluded, but the corresponding naphthyl analogue **3l** has a lower affinity despite a higher lipophilicity and p$K_a$. In the present work, the presence of the electronegative fluorine leads to a reduced affinity when located in position 4 (related to its electron-withdrawing character) and an increase of affinity when located in positions 3 and 5 in the quinoxaline series. Inductive and mesomeric electronic effects of halogen atoms can be sometimes in competition, and in these molecules, the mesomeric effect increasing the electronic density of the phenyl ring could explain the increase of affinity in comparison with the unsubstituted analogue. Fluorine is also quite different than other halogens as reported with the so-called $\sigma$-hole in the context of halogen bonding.[27] In case of a reduced affinity would be wanted, but this is not the priority in this program, other electron-withdrawing groups should be introduced taking into account a possible deleterious sterical impact. In these conditions, a trifluoromethyl group could be most appropriate.

In conclusion, substitution of the distal phenyl ring by two electron-donating methyl groups has permitted to obtain the highest increase of affinity for 5-$HT_{1A}$ receptors in both naphthyl and quinoxaline series. This is also observed for the intermediate phthalimide analogues. Although THP analogue **4l** is the most potent, the most important impact of the current strategy is observed with compound **4k** compared to **4a**. Examining the affinity and the physicochemical parameters of the corresponding compounds, the increase of affinity seems to be related to the increase of electronic density on the distal benzene ring. Finally, a possible extension of this work would be the biological and theoretical evaluation on other receptors to see whether the consequences of the current strategy can also be observed.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental details regarding synthesis, characterization of compounds, in vitro binding procedure, electrophysiological experiments, and molecular modeling studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Funding

Supported in part by grants of the F.R.S.-FNRS (Belgium) and the Fonds Spéciaux pour la Recherche of the University of Liège (Belgium).


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS


The technical assistance of S. Counerotte, J. Widart, C. Gillissen, and L. Massotte for elemental analyses, mass spectra, in vitro binding experiments, and electrophysiological recordings, respectively, is gratefully acknowledged. J.-F.L. is Research Director of the F.R.S.-FNRS. S.D. was supported financially by a postdoctoral fellowship of the F.R.S.-FNRS and a collective grant of the University of Liège.


## ■ REFERENCES


(1) Graulich, A.; Léonard, M.; Résimont, M.; Huang, X.; Roth, B. L.; Liégeois, J.-F. Chemical modifications on 4-arylpiperazine-ethyl carboxamide derivatives differentially modulate affinity for 5-$HT_{1A}$, D4.2, and $\alpha_{2A}$ receptors: synthesis and in vitro radioligand binding studies. *Aust. J. Chem.* **2010**, *63*, 56−67.

(2) Dilly, S.; Graulich, A.; Liégeois, J.-F. Molecular modeling study of 4-phenylpiperazine and 4-phenyl-1,2,3,6-tetrahydropyridine deriva-

tives: a new step towards the design of high-affinity 5-$HT_{1A}$ ligands. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1118−23.
(3) Cockroft, S. L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S. E.; Low, C. M.; Vinter, J. G.; Lawson, K. R.; Urch, C. J.; Hunter, C. A. Substituent effects on aromatic stacking interactions. *Org. Biomol. Chem.* **2007**, *5*, 1062−80.
(4) Gallardo-Godoy, A.; Fierro, A.; McLean, T. H.; Castillo, M.; Cassels, B. K.; Reyes-Parada, M.; Nichols, D. E. Sulfur-substituted alpha-alkyl phenethylamines as selective and reversible MAO-A inhibitors: biological activities, CoMFA analysis, and active site modeling. *J. Med. Chem.* **2005**, *48*, 2407−19.
(5) Pettersson, F.; Svensson, P.; Waters, S.; Waters, N.; Sonesson, C. Synthesis, pharmacological evaluation and QSAR modeling of monosubstituted 4-phenylpiperidines and 4-phenylpiperazines. *Eur. J. Med. Chem.* **2013**, *62*, 241−55.
(6) Nakazato, A.; Kumagai, T.; Okubo, T.; Tanaka, H.; Chaki, S.; Okuyama, S.; Tomisawa, K. Design, synthesis and structure-affinity relationships of 4-methylidenepiperidine and 4-aryl-1,2,3,6-tetrahydropyridine derivatives as corticotropin-releasing factor1 receptor antagonists. *Bioorg. Med. Chem.* **2000**, *8*, 1183−93.
(7) Sikazwe, D. M.; Nkansah, N. T.; Altundas, R.; Zhu, X. Y.; Roth, B. L.; Setola, V.; Ablordeppey, S. Y. Synthesis and evaluation of ligands for D2-like receptors: the role of common pharmacophoric groups. *Bioorg. Med. Chem.* **2009**, *17*, 1716−23.
(8) Wimalasena, D. S.; Perera, R. P.; Heyen, B. J.; Balasooriya, I. S.; Wimalasena, K. Vesicular monoamine transporter substrate/inhibitor activity of MPTP/MPP+ derivatives: a structure−activity study. *J. Med. Chem.* **2008**, *51*, 760−8.
(9) Liégeois, J.-F.; Deville, M.; Dilly, S.; Lamy, C.; Mangin, F.; Résimont, M.; Tarazi, F. I. New pyridobenzoxazepine derivatives derived from 5-(4-methylpiperazin-1-yl)-8-chloro-pyrido[2,3-b][1,5]-benzoxazepine (JL13): chemical synthesis and pharmacological evaluation. *J. Med. Chem.* **2012**, *55*, 1572−82.
(10) Résimont, M.; Liégeois, J.-F. Synthesis and in vitro binding studies of piperazine-alkyl-naphthamides: impact of homology and sulphonamide/carboxamide bioisosteric replacement on the affinity for 5-$HT_{1A}$, $alpha_{2A}$, D4.2, D3 and D2L receptors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5199−202.
(11) Glennon, R. A.; Naiman, N. A.; Lyon, R. A.; Titeler, M. Arylpiperazine derivatives as high-affinity 5-$HT_{1A}$ serotonin ligands. *J. Med. Chem.* **1988**, *31*, 1968−71.
(12) Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Smith, J. D.; Ismaiel, A. M.; Titeler, M.; Lyon, R. A. *N*-(Phthalimidoalkyl) derivatives of serotonergic agents: a common interaction at 5-$HT_{1A}$ serotonin binding sites? *J. Med. Chem.* **1989**, *32*, 1921−6.
(13) Defraiteur, C.; Plenevaux, A.; Scuvee-Moreau, J.; Rouchet, N.; Goblet, D.; Luxen, A.; Seutin, V. Characterization of 4-(2-hydroxyphenyl)-1-[2′-[*N*-(2″-pyridinyl)-*p*-fluorobenzamido]ethyl]-piperazine (*p*-DMPPF) as a new potent 5-$HT_{1A}$ antagonist. *Br. J. Pharmacol.* **2007**, *152*, 952−8.
(14) Aghajanian, G. K.; Sprouse, J. S.; Sheldon, P.; Rasmussen, K. Electrophysiology of the central serotonin system: receptor subtypes and transducer mechanisms. *Ann. N.Y. Acad. Sci.* **1990**, *600*, 93−103 discussion 103.
(15) Forster, E. A.; Cliffe, I. A.; Bill, D. J.; Dover, G. M.; Jones, D.; Reilly, Y.; Fletcher, A. A pharmacological profile of the selective silent 5-$HT_{1A}$ receptor antagonist, WAY-100635. *Eur. J. Pharmacol.* **1995**, *281*, 81−8.
(16) Prandi, A.; Franchini, S.; Manasieva, L. I.; Fossa, P.; Cichero, E.; Marucci, G.; Buccioni, M.; Cilia, A.; Pirona, L.; Brasili, L. Synthesis, biological evaluation, and docking studies of tetrahydrofuran-, cyclopentanone-, and cyclopentanol-based ligands acting at adrenergic alpha(1)- and serotonine 5-$HT_{1A}$ receptors. *J. Med. Chem.* **2012**, *55*, 23−36.
(17) Ballesteros, J.; Weinstein, H. Integrated methods for the construction of three-dimensional models and computational probing of structure-function relations in G protein coupled receptors. *Methods Neurosci.* **1995**, *25*, 366−428.
(18) Bywater, R. P. Location and nature of the residues important for ligand recognition in G-protein coupled receptors. *J. Mol. Recognit.* **2005**, *18*, 60−72.
(19) Nowak, M.; Kolaczkowski, M.; Pawlowski, M.; Bojarski, A. J. Homology modeling of the serotonin 5-$HT_{1A}$ receptor using automated docking of bioactive compounds with defined geometry. *J. Med. Chem.* **2006**, *49*, 205−14.
(20) Kuipers, W.; Link, R.; Standaar, P. J.; Stoit, A. R.; Van Wijngaarden, I.; Leurs, R.; Ijzerman, A. P. Study of the interaction between aryloxypropanolamines and Asn386 in helix VII of the human 5-hydroxytryptamine1A receptor. *Mol. Pharmacol.* **1997**, *51*, 889−96.
(21) Burley, S. K.; Petsko, G. A. Aromatic−aromatic interaction: a mechanism of protein structure stabilization. *Science* **1985**, *229*, 23−8.
(22) Chanda, P. K.; Minchin, M. C.; Davis, A. R.; Greenberg, L.; Reilly, Y.; McGregor, W. H.; Bhat, R.; Lubeck, M. D.; Mizutani, S.; Hung, P. P. Identification of residues important for ligand binding to the human 5-hydroxytryptamine1A serotonin receptor. *Mol. Pharmacol.* **1993**, *43*, 516−20.
(23) Ngo, T.; Nicholas, T. J.; Chen, J.; Finch, A. M.; Griffith, R. 5-$HT_{1A}$ receptor pharmacophores to screen for off-target activity of alpha1-adrenoceptor antagonists. *J. Comput.-Aided Mol. Des.* **2013**, *27*, 305−19.
(24) Schuster, D. I.; Pan, Y. P.; Singh, G.; Stoupakis, G.; Cai, B.; Lem, G.; Ehrlich, G. K.; Frietze, W.; Murphy, R. B. *N*-(1-Arylpropionyl)-4-aryltetrahydropyridines, a new class of high-affinity selective sigma receptor ligands. *J. Med. Chem.* **1993**, *36*, 3923−8.
(25) Mateeva, N. N.; Winfield, L. L.; Redda, K. K. The chemistry and pharmacology of tetrahydropyridines. *Curr. Med. Chem.* **2005**, *12*, 551−71.
(26) Okoroa, C. O.; Wilsonb, T. L.; Redda, K. K. Conformational analysis and molecular properties of *N*-(substituted phenyl-carbonylamino)-4-(1-hydroxymethylphenyl)-1,2,3,6-tetrahydropyridines. *Curr. Med. Chem.* **2003**, *10*, 313−20.
(27) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. Principles and applications of halogen bonding in medicinal chemistry and chemical biology. *J. Med. Chem.* **2013**, *56*, 1363−88.