

# Molecular Design Based on 3D Pharmacophores. Applications to 5-HT<sub>7</sub> Receptors

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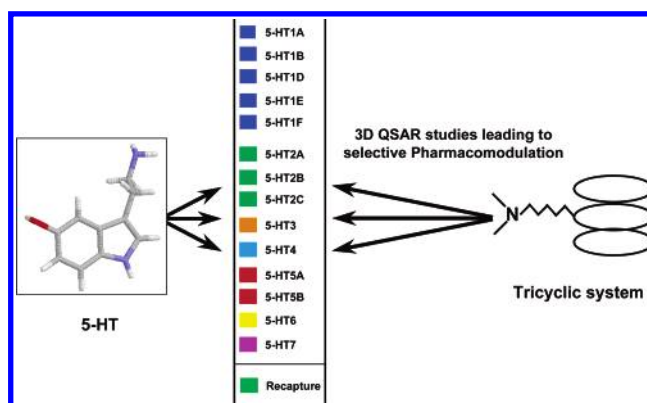
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A definition of a pharmacophore for the 5-HT<sub>7</sub> antagonists was carried out by searching the common chemical features of selective antagonists from the literature. A molecular design is described by analyzing the differences between this new pharmacophore and three other 3D serotonin pharmacophores previously described. This comparison led to the synthesis of a new series of potent 5-HT<sub>7</sub> antagonists.

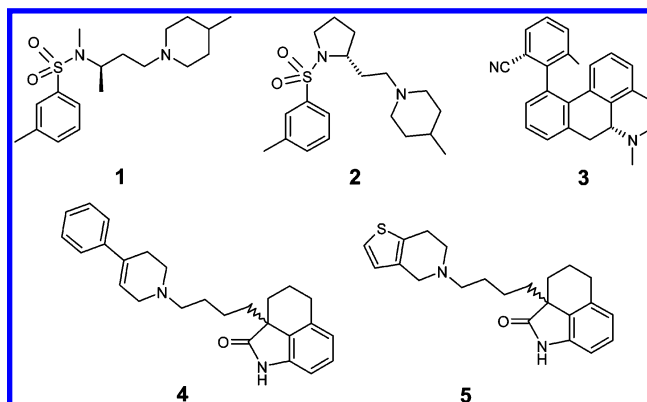
## INTRODUCTION

The pharmacophore<sup>1–4</sup> classically determines the fundamental characteristics, in terms of the nature and disposition of chemical groups (topologic and topographic patterns), required for a biological affinity. 3D-QSAR software such as Catalyst<sup>5</sup> allowed a pharmacophore to be obtained among active compounds in a multiconformation structure database. Within the framework of the cationic neurotransmitters, such as serotonin (5-HT), which can interact with a series of subtype receptors<sup>6–8</sup> (Figure 1), 3D-QSAR data could provide us the elements explaining the existing relations linking these receptor subtypes (analogies, differences between the pharmacophores). Consequently, molecular design based on a 3D pharmacophore could be carried out to obtain new ligands with a unique or a multiple controlled affinity for one or more receptor subtypes. Previous studies were carried out on 5-HT<sub>3</sub> ligands,<sup>9</sup> 5-HT<sub>4</sub> ligands,<sup>10</sup> and 5-HT reuptake inhibitors.<sup>11</sup> We demonstrated that the structural modifications of a tricyclic feature linked to an aminoalkyl side chain (Figure 1) could be controlled to obtain selective ligands toward these three receptors.

Growing efforts are being made to understand the physiological role of the 5-HT<sub>7</sub> receptor. Recent findings have implicated the 5-HT<sub>7</sub> receptor in the pathogenesis of migraine, depression, schizophrenia, and cardiovascular disease.<sup>12–14</sup> Since only a few putative antagonists have been reported to date, the design of new antagonists of 5-HT<sub>7</sub> receptors will be studied with the same approach described above. This one includes the definition of a pharmacophore from selective 5-HT<sub>7</sub> ligands, comparison with other pharmacophores (5-HT<sub>3</sub> receptor, 5-HT<sub>4</sub> receptor, and 5-HT transporter), and finally the definition of the structural modifications. Only one 5-HT<sub>7</sub> pharmacophore appeared in the literature. The main difference from this work is the nature of the training set composed by selective and nonselective 5-HT<sub>7</sub> ligands.<sup>15</sup>



**Figure 1.** General representation of the pharmacomodulation program.



**Figure 2.** 5-HT<sub>7</sub> ligands considered in the training set.

## MATERIALS AND METHODS

**Training Set and Conformational Analysis.** For the definition of the 5-HT<sub>7</sub> pharmacophore, five selective antagonists previously described in the literature<sup>16–20</sup> were considered in the training set (Figure 2). These compounds belonged to three different chemical families<sup>21</sup> (Table 1).

The geometry of each compound was built with the Catalyst builder and optimized by using the CHARMM-like force field implemented in the program.<sup>22</sup> A stochastic

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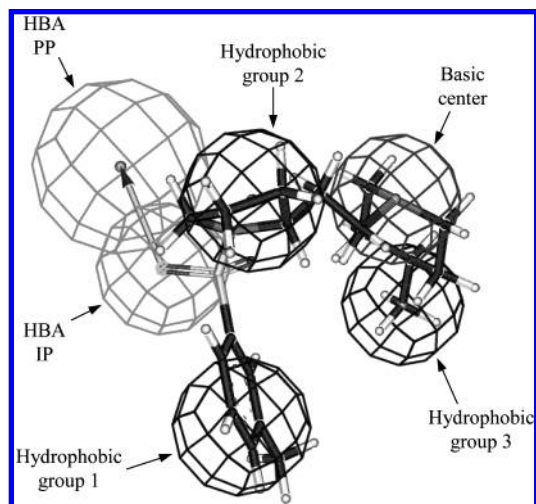
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**Table 1.** Chemical Similarity Values between the Compounds Used in the Training Set<sup>a</sup>

compd	1	2	3	4	5
1	1				
2	0.95	1			
3	0.31	0.30	1		
4	0.31	0.32	0.35	1	
5	0.29	0.30	0.37	0.66	1

<sup>a</sup> Tanimoto coefficient from a 2D search with UNITY molecular fingerprint.

**Figure 3.** Representation of the selected hypothesis (alignment of 2 with this hypothesis).

research coupled to a poling method<sup>23</sup> was applied to generate conformers for each compound of the training set (20 kcal/mol maximum compared to the energy of the most stable conformer).

**Definition of the Pharmacophore.** The definition of the pharmacophore was based on a common features alignment approach. In this algorithm, the program identifies common three-dimensional spatial arrangements of chemical features. The weight, assigned to each chemical function, was set to 1. As functions of the chemical structures, a hydrogen bond acceptor, an ionizable group (basic amine), and hydrophobic features (aromatic or aliphatic) were considered as potentially present in this pharmacophore. The interfeature distance was kept to 3 Å.

## RESULTS AND DISCUSSION

**Selection of One Hypothesis.** Ten hypotheses were generated by the program. All of them were described as the same five-feature models. The variation concerns the 3D position of two hydrophobic features named hydrophobic groups 2 and 3 (see Figure 3). The superimposition between the compounds and the hypotheses led to the definition of fit values. The selected hypothesis had the best fit values for all the compounds (Table 2) and the best rank according to the program.

**Characteristics of the Pharmacophore.** The 3D pharmacophore (Figure 3) consists of one basic center, three hydrophobic groups, and one hydrogen bond acceptor. The distances between the chemical features are recapitulated in Table 3.

The weak fit values observed for three compounds out of five (only one chemical family was correctly associated) were

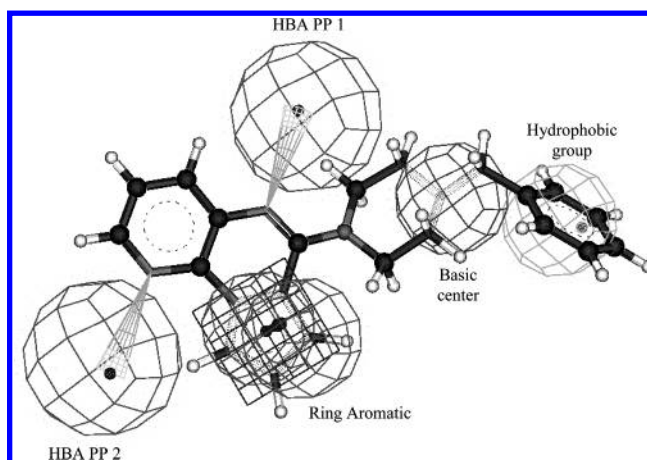
**Table 2.** 5-HT<sub>7</sub> Receptor Affinity and Fit Value for the Compounds Used in the Training Set

compd	5-HT <sub>7</sub> affinity (pK <sub>i</sub> )	fit value	
		selected hypothesis	modified hypothesis
1	7.5	4	3.8
2	8.5	5	4
3	8.4	0.8	2.8
4	8.7	2.4	2.8
5	8.2	1.3	2.6

**Table 3.** Matrix Distances (Å) for the Characteristics of the Selected Hypothesis<sup>a</sup>

	HBA (IP)	HBA (PP)	hydrophobic			basic center
			group 1	group 2	group 3	
HBA (IP)						
HBA (PP)	3					
hydrophobic group 1	4.7	7.8				
hydrophobic group 2	4.5	5.7	5.7			
hydrophobic group 3	7.6	8.9	7.7	8.8		
basic center	6.3	7.2	7.3	5.4	4.3	

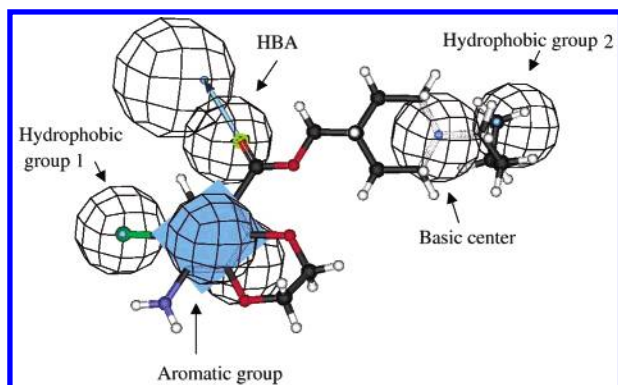
<sup>a</sup> IP = initial point for the ligand; PP = projected point on the receptor.

**Figure 4.** Representation of the 5-HT<sub>3</sub> partial agonist pharmacophore.

in relation with a poor fit with hydrophobic group 3. The values increase strongly when this function is suppressed (Table 2). Moreover, for this function, the fits of compounds 1 and 2 were carried out by the axial position of a methyl group on nitrogen (Figure 3). These two problems, i.e., a poor fit for three compounds and nonfavorable conformations for the two others, led us to set aside this hydrophobic group.

Consequently, on the basis of a four-feature model, the first 10 hypotheses now differ only by the position of one feature (hydrophobic group 2). Moreover, the three common features are found in the 5-HT<sub>7</sub> pharmacophore previously described in the literature by Lopez-Rodriguez et al.<sup>15</sup> if we consider an equivalence between the aromatic ring of their pharmacophore and hydrophobic group 1 (the distances between these three features are very close).

**Comparison with Other Pharmacophores.** 5-HT<sub>3</sub> partial agonist<sup>9</sup> (Figure 4), 5-HT<sub>4</sub> antagonist<sup>10</sup> (Figure 5), and 5-HT<sub>7</sub> antagonist (Figure 3) pharmacophores have three common features: an aromatic or aliphatic hydrophobic group, a hydrogen bond acceptor, and a basic center.



**Figure 5.** Representation of the 5-HT<sub>4</sub> antagonist pharmacophore.

**Table 4.** 5-HT<sub>7</sub> Receptor Affinity of Compounds **6** and **7**

compd	5-HT <sub>7</sub> (% inhibition <sup>25</sup> )	
	10 <sup>-6</sup> M	10 <sup>-8</sup> M
<b>6</b>	96	32
<b>7</b>	52	8

**Table 5.** Binding Properties of Compound **6**

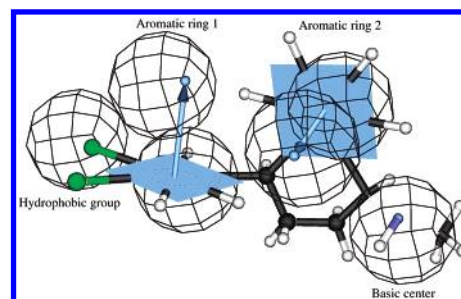
5-HT <sub>1A</sub> <sup>a</sup>	5-HT <sub>1B</sub> <sup>a</sup>	5-HT <sub>2C</sub> <sup>a</sup>	5-HT <sub>3</sub> <sup>a</sup>	5-HT <sub>4</sub> <sup>b</sup>
7.23	7.86	7.46	7.92	18% at 10 <sup>-6</sup> M 10% at 10 <sup>-8</sup> M

<sup>a</sup> Experimental affinity [ $-(\log IC_{50})$ ]. <sup>b</sup> Experimental affinity (percent inhibition at 10<sup>-6</sup> and 10<sup>-8</sup> M).

Hydrophobic group and basic center distances are close for 5-HT<sub>3</sub> and 5-HT<sub>7</sub> pharmacophores (6.6 vs 7.3 Å) contrary to the 5-HT<sub>4</sub> pharmacophore (8.5 Å). The spatial position of the hydrogen bond acceptor toward the basic center was different between the 5-HT<sub>3</sub> (partial agonists) and 5-HT<sub>7</sub> (antagonists) pharmacophores (4.9 vs 6.3 Å).

The analogies between the 5-HT<sub>3</sub> and 5-HT<sub>7</sub> pharmacophores are well represented by compounds **6** and **7** (Table 4). Indeed, compound **6**, previously described as a 5-HT<sub>3</sub> partial agonist ( $-(\log IC_{50}) = 7.92$ ) and considered as a first lead for our 5-HT<sub>3</sub> ligands,<sup>24</sup> showed a high affinity toward the 5-HT<sub>7</sub> receptor<sup>25</sup> (96% inhibition at 10<sup>-6</sup> M, 32% at 10<sup>-8</sup> M). This is a nonselective compound since it presents comparable affinities toward the 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>2C</sub> receptors (Table 5). Besides these data, compound **6** has no affinity for the 5-HT<sub>4</sub> receptor (Table 5), confirming the differences between the 5-HT<sub>3</sub> and 5-HT<sub>4</sub> pharmacophores.<sup>10</sup> The equivalent double affinity for the 5-HT<sub>3</sub> receptor and 5-HT transporter<sup>11</sup> for compound **7** could be understood by the relationship between the 5-HT<sub>3</sub> partial agonist and 5-HT reuptake inhibitor (Figure 6) pharmacophores.<sup>11</sup> Like compound **6**, compound **7** also has an affinity for the 5-HT<sub>7</sub> receptor (52% inhibition at 10<sup>-6</sup> M).

These first analyses enabled us to define the relationships between these different pharmacophores. From these data, the structural modifications were fixed.

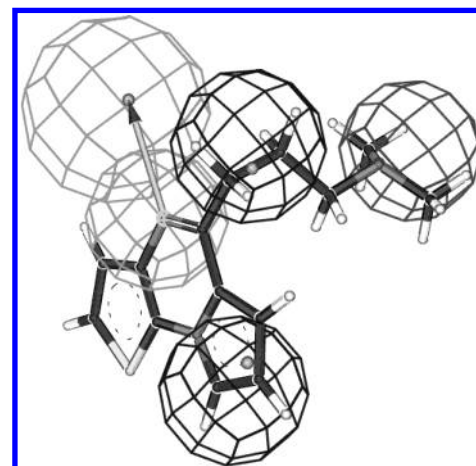


**Figure 6.** Representation of the 5-HT reuptake inhibitor pharmacophore.

**Table 6.** Evolution of the 5-HT<sub>7</sub> Affinity as a Function of the Pharmacomodulations

				5-HT <sub>7</sub> (% inhibition <sup>25</sup> )		pK <sub>i</sub>
compd	X	R <sub>1</sub>	R <sub>2</sub>	10 <sup>-6</sup> M	10 <sup>-8</sup> M	

<b>8</b>	CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	77	48	
<b>9</b>	O	CH <sub>3</sub>	CH <sub>3</sub>	71	4	
<b>10</b>	O	H	H	84	9	
<b>11</b>	NH	H	H	89	19	7.46
<b>12</b>	S	H	H	90	88	9.05
<b>13</b>	S	CH <sub>3</sub>	H	93	80	9.05
<b>14</b>	S	CH <sub>3</sub>	CH <sub>3</sub>	100	72	8.25



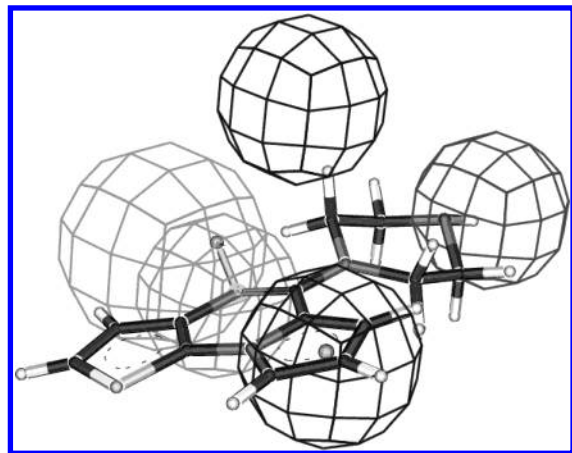
**Figure 7.** Alignment between **8** and the 5-HT<sub>7</sub> antagonist pharmacophore.

## STRUCTURAL MODIFICATIONS

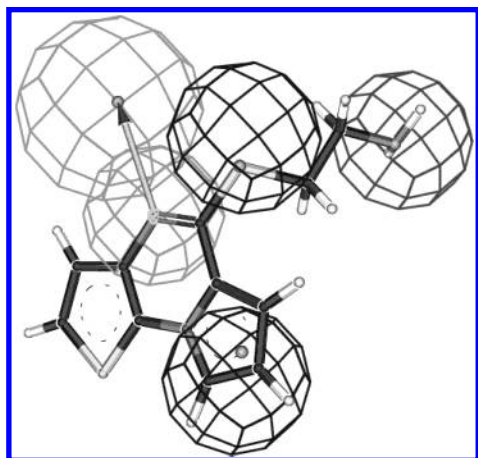
From the tricyclic feature (two characteristics of the pharmacophores) associated with compound **6**, the correct position of the basic center can be reached. For this target, an aminoalkyl chain was chosen the first time (flexible chain). A chain length corresponding to  $n = 3$  (compound **8**, Table 6) for this derivative allowed a correct fit (1.8 for the value) between the basic center and the amine to be obtained (Figure 7). The affinity of compound **8** toward the 5-HT<sub>7</sub> receptor (Table 6) was slightly superior compared to that of **6** (77% inhibition at 10<sup>-6</sup> M, 48% at 10<sup>-8</sup> M).

An essential difference between derivatives **6** and **8** is the incapacity of the first one to occupy a zone corresponding to hydrophobic group 2 of the 5-HT<sub>7</sub> pharmacophore (Figure





**Figure 8.** Alignment between **6** and the 5-HT<sub>7</sub> antagonist pharmacophore.



**Figure 9.** Alignment between **12** and the 5-HT<sub>7</sub> antagonist pharmacophore.

8). The biological importance of this group (Table 6) was underlined by replacing the methylene group (CH<sub>2</sub>) by polar fragments such as O or NH (compounds **9–11**). With the same idea, the replacement of CH<sub>2</sub> by stronger hydrophobic groups must improve the affinity. Sulfur is an interesting atom in this case. Indeed, the studies, in particular of Hansch<sup>26</sup> and Rekker,<sup>27</sup> clearly showed the reinforcement of the hydrophobicity by the incorporation of the sulfur atom compared with the polar groups (O, NH). On the other hand, the difference between CH<sub>2</sub> and S is in favor of the first one according to their studies (0.195 vs 0.03 for the contributions to  $C \log P^{28}$ ). However, a study carried out by Wang et al.<sup>29</sup> showed a higher hydrophobic contribution of S compared to CH<sub>2</sub> (1.07 vs 0.36). By default, the Catalyst software did not consider sulfur as hydrophobic. Therefore, the hydrophobic definition of the program was modified.

A series of new derivatives (**12–14**) was synthesized including the sulfur atom (Table 6). Compound **12** (Figure 9, 2.2 for the fit value) had a very high affinity and also selectivity for the 5-HT<sub>7</sub> receptor (Table 7). The affinity for the 5-HT<sub>3</sub> receptor was very low (39% inhibition at 10<sup>-5</sup> M), like that for the 5-HT<sub>4</sub> receptor (10% inhibition at 10<sup>-6</sup> M). However, the affinity of this new series of compounds for the 5-HT transporter was not so low (96% inhibition at 10<sup>-5</sup> M for compound **12**, 100% at 10<sup>-5</sup> M and 63% at 10<sup>-7</sup> M for compound **14**), confirming the analogies between the 5-HT<sub>7</sub> and 5-HT transporter pharmacophores.

**Table 7.** Binding Properties of Compounds **12** and **14**

compd	% inhibition		
	5-HT <sub>3</sub>	5-HT <sub>4</sub>	5-HT transporter
<b>12</b>	39 at 10 <sup>-5</sup> M	10 at 10 <sup>-6</sup> M 0 at 10 <sup>-8</sup> M	96 at 10 <sup>-5</sup> M
<b>14</b>	76 at 10 <sup>-5</sup> M 21 at 10 <sup>-7</sup> M	52 at 10 <sup>-6</sup> M 11 at 10 <sup>-8</sup> M	100 at 10 <sup>-5</sup> M 63 at 10 <sup>-7</sup> M

The pharmacological profile of **13** was studied on aldosterone secretion in rat glomerulosa cells in primary culture.<sup>30,31</sup> It displayed antagonist properties with a pK<sub>B</sub> of 7.37. The binding data on the rat 5-HT<sub>7</sub> receptor were 93% at 10<sup>-6</sup> M and 37% at 10<sup>-8</sup> M.

## CONCLUSION

This study initially defined a pharmacophore for 5-HT<sub>7</sub> antagonists on the basis of a common features alignment approach. The analysis of the differences between the 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and 5-HT transporter pharmacophores previously described and this new 5-HT<sub>7</sub> pharmacophore directed the synthesis toward a new series of potent 5-HT<sub>7</sub> antagonists. This successful molecular design based on a 3D pharmacophore shows the efficiency of this approach to design new selective ligands.

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## REFERENCES AND NOTES

- (1) Korolkovas, A. *Essentials of Molecular Pharmacology, Background for drug design*; Interscience: New York, 1970.
- (2) Gund, P. Three-dimensional pharmacophore pattern searching. In *Progress in Molecular and Subcellular Biology*; Hahn, F. E., Ed.; Springer-Verlag: Berlin, 1977; Vol. 5, p 117.
- (3) Gund, P. Pharmacophoric pattern searching and receptor mapping. *Annu. Rep. Med. Chem.* **1979**, *14*, 299–308.
- (4) Humblet, C.; Marshall, G. R. Pharmacophore identification of receptor mapping. *Annu. Rep. Med. Chem.* **1980**, *15*, 267–276.
- (5) Catalyst version 4.5 software, Accelrys Inc., San Diego, CA, 2001.
- (6) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Harting, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin). *Pharmacol. Rev.* **1994**, *46*, 157–203.
- (7) Zifa, E.; Fillion, G. 5-Hydroxytryptamine Receptors. *Pharmacol. Rev.* **1992**, *44*, 401–458.
- (8) Peroutka, S. J. 5-Hydroxytryptamine receptor subtypes. In *Serotonin receptors and their ligands*; Olivier, B., Van Wijnngaarden, I., Soudijn, W., Eds.; Elsevier (pharmacochemistry library): Amsterdam, 1997; Vol. 27, pp 3–13.
- (9) Daveu, C.; Bureau, R.; Baglin, I.; Prunier, H.; Lancelot, J. C.; Rault, S. Definition of a Pharmacophore for Partial Agonists of Serotonin 5-HT<sub>3</sub> Receptors. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 362–369.
- (10) Bureau, R.; Daveu, C.; Lemaître, S.; Dauphin, F.; Landelle, H.; Lancelot, J. C.; Rault, S. Molecular Design Based on 3D-Pharmacophore. Application to 5-HT<sub>4</sub> Receptor. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 962–967.
- (11) Bureau, R.; Daveu, C.; Lancelot, J. C.; Rault, S. Molecular Design Based on 3D-Pharmacophore. Application to 5-HT Subtypes Receptors. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 429–436.
- (12) Pouzet, B. SB-258741: a 5-HT<sub>7</sub> receptor antagonist of potential clinical interest. *CNS Drug Rev.* **2002**, *8*, 90–100.
- (13) Wood, M. D.; Thomas, D. R.; Watson, J. M. Therapeutic potential of serotonin antagonists in depressive disorders. *Expert Opin. Invest. Drugs* **2002**, *11*, 457–467.

- (14) Pouzet, B.; Didriksen, M. Effects of the 5-HT<sub>7</sub> receptor antagonist SB-258741 in animal models for schizophrenia. *Pharmacol., Biochem., Behav.* **2002**, *71*, 655–665.
- (15) Lopez-Rodriguez, M. L.; Porras, E.; Benhamu, B.; Ramos, J. A.; Morcillo, M. J.; Lavandera, J. L. First Pharmacophoric Hypothesis for 5-HT<sub>7</sub> Antagonism. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1097–1100.
- (16) Forbes, I. T.; Dabs, S.; Duckworth, D. M.; Jennings, A. J.; King, F. D.; Lovell, P. J.; Brown, A. M.; Collin, M.; Hagan, J. J.; Middlemiss, D. N.; Riley, G. J.; Thomas, D. R.; Upton, N. (R)-3,N-dimethyl-N-[1-methyl-3-(4-methyl-piperidin-1-yl)propyl]benzenesulfonamide: the First Selective 5-HT<sub>7</sub> Receptor Antagonist. *J. Med. Chem.* **1998**, *41*, 655–657.
- (17) Lovell, P. J.; Bromidge, S. M.; Dabs, S.; Duckworth, D. M.; Forbes, I. T.; Jennings, A. J.; King, F. D.; Middlemiss, D. N.; Rahman, S. K.; Saunders, D. V.; Collin, M.; Hagan, J. J.; Riley, G. J.; Thomas, D. R. a Novel, Potent and Selective 5-HT<sub>7</sub> Antagonist: (R)-3-(2-(4-methylpiperidin-1-yl)-ethyl)pyrrolidine-1-sulfonylphenol (SB-269970). *J. Med. Chem.* **2000**, *43*, 342–345.
- (18) Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A. Atropisomeric Derivatives of 2',6'-disubstituted (R)-11-phenylaporphine: Selective Serotonin 5-HT<sub>7</sub> Receptor Antagonists. *J. Med. Chem.* **2001**, *44*, 1337–1340.
- (19) Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. Tetrahydrobenzindoles: Selective Antagonists of the 5-HT<sub>7</sub> Receptor. *J. Med. Chem.* **1999**, *42*, 533–535.
- (20) Kikuchi, C.; Hiranuma, T.; Koyama, M. Tetrahydrothienopyridylbutyl-tetrahydrobenz indoles: New Selective Ligands of the 5-HT<sub>7</sub> Receptor. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549–2552.
- (21) Sybyl 6.9, Tripos Inc., St. Louis, MO, 2003.
- (22) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; Sates, D. J.; Swaninathan, S.; Karplus, M. CHAMM: A program for macromolecular energy, minimization, and dynamics calculations. *J. Comput. Chem.* **1983**, *4*, 187–217.
- (23) Smellie, A.; Teig, S. L.; Towbin, P. Poling: Promoting Conformational Variation. *J. Comput. Chem.* **1995**, *16*, 171–187.
- (24) Rault, S.; Lancelot, J. C.; Prunier, H.; Robba, M.; Renard, P.; Delagrang, P.; Pfeiffer, B.; Caignard, D. H.; Guardiola-Lemaître, B.; Hamon, M. Novel Selective and partial agonists of 5-HT<sub>3</sub> receptors. Part 1. Synthesis and biological evaluation of piperazinopyrrol-thienopyrazines. *J. Med. Chem.* **1996**, *39*, 2068–2080.
- (25) Shen, Y.; Monsma, F. J.; Metcalf, M. A.; Jose, P. A.; Hamblin, M. W.; Sibley, D. R. Molecular cloning and expression of a 5-hydroxytryptamine<sub>7</sub> serotonin receptor subtype. *J. Biol. Chem.* **1993**, *268*, 18200–18204.
- (26) Hansch, C.; Leo, A. *Exploring QSAR*; American Chemical Society: Washington, DC, 1995.
- (27) Rekker, R. F.; Mannhold, R. *Calculation of Drug Lipophilicity*; VCH: New York, 1992.
- (28) Hansch, C.; Leo, A. Calculation of Octanol-Water Partition Coefficients by Fragments. *Exploring QSAR*; American Chemical Society: Washington, DC, 1995; p 125.
- (29) Wang, R.; Fu, Y.; Lai, L. a New Atom-Additive Method for Calculating Partition Coefficients. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 615–621.
- (30) Contesse, V.; Lenglet, S.; Grumolato, L.; Anouar, Y.; Lihmann, I.; Lefebvre, H.; Delarue, C.; Vaudry, H. Pharmacological and Molecular Characterization of 5-Hydroxytryptamine<sub>7</sub> Receptors in the Rat Adrenal Gland. *Mol. Pharmacol.* **1999**, *56*, 552–561.
- (31) Lenglet, S.; Louiset, E.; Delarue, C.; Vaudry, H.; Contesse, V. Activation of 5-HT<sub>7</sub> Receptor in Rat Glomerulosa Cells is Associated with an Increase in Adenylyl Cyclase Activity and Calcium Influx through T-Type Calcium Channels. *Endocrinology* **2002**, *143*, 1748–1760.

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