Synthesis and Structure−Affinity Relationships of 1-[ω-(4-Aryl-1-piperazinyl)alkyl]-1-aryl Ketones as 5-HT$_7$ Receptor Ligands

Roberto Perrone,* Francesco Berardi, Nicola A. Colabufo, Enza Lacivita, Marcello Leopoldo, and Vincenzo Tortorella

Dipartimento Farmaco-Chimico, Università degli Studi di Bari, via Orabona, 4, 70126, Bari, Italy

Received July 12, 2002

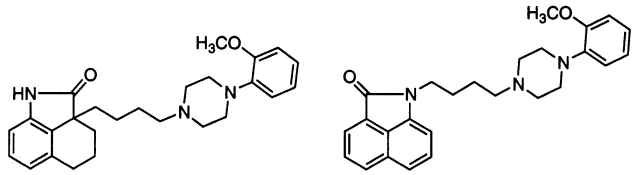
Structural requirements for 5-HT$_7$ receptor affinity and selectivity over that for the 5-HT$_{1A}$ receptor were studied on a series of 1-[ω-(4-aryl-1-piperazinyl)alkyl]-1-aryl ketones. The presence of a hydroxy or methoxy substituent on aryl ketone moiety, alkyl chain length, and the nature of *N*-1-piperazine substituent were explored. 6-[4-(3-Benzisoxazolyl)-1-piperazinyl]-1-(2-hydroxyphenyl)-1-hexanone (**40**) and its methoxy analogue **43** exhibited high 5-HT$_7$ receptor affinities (K_i = 2.93 nM and 0.90 nM, respectively) and agonist properties when tested for 5-HT$_7$ receptor-mediated relaxation of substance P-induced guinea-pig ileum contraction.

Serotonin (5-HT) is involved in various physiological and pathological processes by interaction with seven classes of receptors (5-HT$_{1-7}$), containing 14 distinct receptors grouped on the basis of amino acid sequence, pharmacology, and signal transduction pathways.[1,2] The 5-HT$_7$ receptor was found by the application of molecular cloning and has been identified in rat,[3−5] mouse,[6] human,[7] and guinea pig.[8] Although the biological functions of the 5-HT$_7$ receptor are poorly understood, preliminary evidence suggests that it may be involved in depression,[9,10] control of circadian rhythms,[11] and relaxation of vascular smooth muscle.[12,13] Clearly, the 5-HT$_7$ receptor may be a valuable novel drug target. To examine this possibility, the development of potent and selective ligands for the 5-HT$_7$ receptor is highly desired. To date a limited number of papers dealing with the research of selective 5-HT$_7$ ligands has been published.[14−21] Kikuchi[15,21] and Lopez-Rodriguez[16] reported some arylpiperazine derivatives sharing some structural features with "long-chain" arylpiperazines, a well-known class of 5-HT$_{1A}$ receptor ligands. In particular, 1-(2-methoxyphenyl)piperazine derivatives **1**[15] and **2**[16] (Chart 1) were reported as 5-HT$_7$ receptor ligands (K_i = 5.1 nM and K_i = 63 nM, respectively). These findings have prompted us to test on a rat cloned 5-HT$_7$ receptor several derivatives previously studied[22−26] as 5-HT$_{1A}$ or D$_4$ ligands, characterized by a 1-(2-methoxyphenyl)piperazinyl group joined by a spacer to an aromatic structure. In this way, we have identified compounds **3** and **4**[26] (Table 1) possessing moderate 5-HT$_7$ receptor affinities (K_i = 109 nM and K_i = 85 nM, respectively). Unfortunately, they proved to be high-affinity 5-HT$_{1A}$ receptor ligands (K_i = 0.78 nM and K_i = 3.4 nM, respectively). Therefore, we developed novel compounds by modifying the structure of **4**, having as a primary goal the improvement of the 5-HT$_7$ receptor affinity.

Chemistry

The preparation of the final compounds (Scheme 1) required the key intermediate ω-haloalkylphenyl ketones **9**−**22**. Derivatives **9**−**12** were prepared from benzaldehydes **5a**,**b** that were reacted with the appropriate Grignard reagent to give benzyl alcohols **6a**,**b** and **7a**,**b**. Oxidation of these latter compounds with Jones reagent afforded ketones **9**−**12**.[27] Ketone **13** was obtained following a previously reported procedure.[27] Aldehyde **5a** was reacted with trimethylsilyl cyanide to give the trimethylsilyl cyanohydrin **8**. This latter compound was transformed into its anion with lithium diisopropylamide (LDA) and then was alkylated with 1-bromo-3-chloropropane. The protected cyanohydrin so obtained gave ketone **13** by treating with dilute HCl. Phenolic derivatives **14**−**18** were prepared from the corresponding methoxy derivatives **9**−**13** by cleavage of the ether bond with concentrated HBr. Phenyl or 4-hydroxyphenyl ketones **19**−**22** were prepared according to literature methods by a Friedel−Crafts acylation.[28] Final compounds **23**−**43** were achieved by reacting ω-haloalkyl ketones **10**, **12**, and **14**−**22** with the appropriate 1-substituted piperazine. These latter intermediates were obtained from commercial sources or were prepared by literature methods as detailed in the Experimental Section (see Supporting Information).

Chart 1



1 2

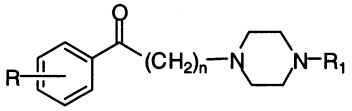
Results and Discussion

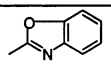
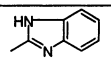
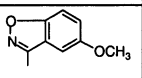
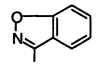
The results of the binding assays on 5-HT$_7$ and 5-HT$_{1A}$ receptors are listed in Table 1. The first modification of **4** was the elongation of the intermediate alkyl chain from four to five methylenes (compound **23**). 5-HT$_7$ affinity values of compounds **3**, **4**, and **23** showed that affinity was increased by alkyl chain elongation. This result suggested that the alkyl chain length of these compounds is important in determining the affinity for

* To whom correspondence should be addressed. Phone: +39-080-5442752. Fax: +39-080-5442231. E-mail: perrone@farmchim.uniba.it.

10.1021/jm020994z CCC: $25.00
Published on Web 01/18/2003

Table 1. Binding Affinities of Final Compounds[a]

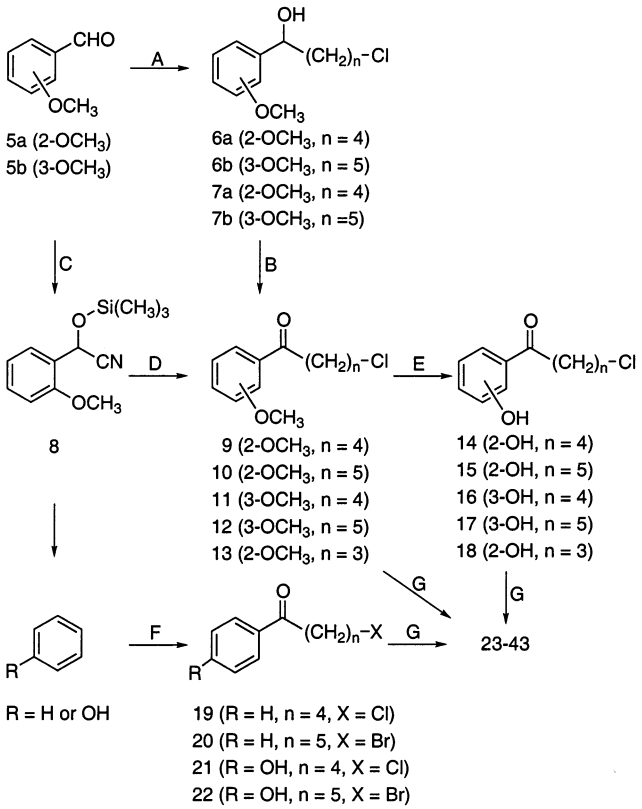


				K_i ± S.E.M., nM	
cpd	**R**	**n**	**R_1**	**5-HT_7**	**5-HT_{1A}**
3	3-OCH_3	3	2-CH_3O-Ph	109 ± 27	0.78 ± 0.02
4	3-OCH_3	4	2-CH_3O-Ph	85 ± 5	3.4 ± 0.4
23	3-OCH_3	5	2-CH_3O-Ph	46 ± 4	3.4 ± 0.6
24	3-OH	4	2-CH_3O-Ph	15 ± 3	3.7 ± 0.6
25	H	4	2-CH_3O-Ph	43.5 ± 8.0	7.0 ± 0.4
26	3-OH	5	2-CH_3O-Ph	26.8 ± 2.3	24.0 ± 2.5
27	H	5	2-CH_3O-Ph	28.4 ± 6.2	6.4 ± 1.1
28	2-OH	4	2-CH_3O-Ph	16.4 ± 2.5	4.1 ± 0.7
29	4-OH	4	2-CH_3O-Ph	59.1 ± 8.2	20 ± 4
30	2-OH	5	2-CH_3O-Ph	5.8 ± 0.1	5.8 ± 0.3
31	4-OH	5	2-CH_3O-Ph	23.7 ± 3.0	14.0 ± 1.5
32	2-OH	5	CH_3	>1000 (23%)[b]	>850 (31%)
33	2-OH	5	cyclohexyl	>800 (29%)	>850 (13%)
34	2-OH	5	2-Py	105 ± 15	56 ± 9
35	2-OH	5	Ph	43 ± 4	137 ± 20
36	2-OH	5	3-CF_3-Ph	384 ± 12	282 ± 25
37	2-OH	5		148 ± 20	1459 ± 125
38	2-OH	5		682 ± 35	>850 (7%)
39	2-OH	5		462 ± 45	389 ± 18
40	2-OH	5		2.93 ± 0.22	189 ± 12
41	2-OH	3		19.5 ± 3.0	1061 ± 220
42	2-OH	4		52 ± 4	919 ± 110
43	2-OCH_3	5		0.90 ± 0.05	175 ± 20
5-CT				0.51 ± 0.01	
8-OH-DPAT					1.2 ± 0.2

[a] Receptors and radioligand used in binding assays: 5-HT_7 (rat cloned receptors in HEK-293 cells; [^{3}H]LSD); 5-HT_{1A} (rat hippocampus membranes, [^{3}H]-8-OH-DPAT). [b] Full K_i not obtained, percentage inhibition at the concentration shown given in parentheses.

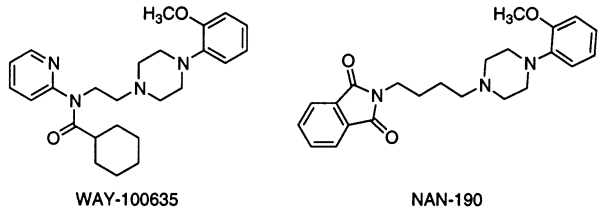
the 5-HT_7 receptor. Therefore, the next modifications were limited to compounds having $n = 4$ or $n = 5$. Then, an initial investigation on the nature of the substituent required on the aromatic ring attached to the carbonyl function was accomplished by removal or demethylation of methoxy substituent (compounds **24**−**27**). Both modifications resulted in a slight increase in 5-HT_7 affinity, but did not give any insight on the role of those substituents on the aromatic ring. However, 3-hydroxy derivative **24** displayed higher 5-HT_7 receptor affinity than the corresponding 3-methoxy derivative **4** and, for this reason, we also investigated the 2- and 4-hydroxy-substituted derivatives **28**−**31**. The position of the hydroxy substituent seems to have a marginal role on

Scheme 1[a]



[a] Reagents: (A) Bromo(4-chlorobutyl)magnesium or bromo(5-chlorobutyl)magnesium; (B) Jones reagent; (C) trimethylsilyl cyanide, ZnI_2; (D) i. LDA; ii. 1-bromo-3-chloropropane; iii. 2 N HCl; (E) 48% HBr; (F) ω-haloacyl chloride, $AlCl_3$; (G) 1-substituted piperazine.

Chart 2



5-HT_7 affinity. Moreover, a clear trend was not shown, because when $n = 5$ the 2-hydroxy derivative **30** showed the higher 5-HT_7 affinity value, whereas when $n = 4$, the 2- and 3-hydroxy-substituted derivatives **28** and **24**, respectively, were equipotent. Although compounds **23**−**31** displayed improved 5-HT_7 affinity values (K_is ranging between 5.8 nM and 59.1 nM) compared to the starting compounds **3** and **4**, they all showed higher 5-HT_{1A} affinity than 5-HT_7 affinity, except compound **30** (K_i = 5.8 nM on both receptors). This latter compound was chosen for further structural modifications because it was the only one of this series showing nanomolar 5-HT_7 receptor affinity. The lack of selectivity over 5-HT_{1A} receptors of compounds **23**−**31** should be due to the 2-methoxyphenyl group linked to N-1 position of the piperazine ring. In fact, well-known 5-HT_{1A} receptor ligands such as WAY-100635 and NAN-190 (Chart 2) are 1-(2-methoxyphenyl)piperazine derivatives.[29] Therefore, we replaced the 2-methoxyphenyl group with a variety of substituents, including certain groups that were expected not to lead to 5-HT_{1A} ligands

Table 2. Extended Binding Screening of Compounds **40** and **43**[a]

receptor	$K_i \pm$ SEM, nM **40**	**43**
5-HT_7	2.93 ± 0.22	0.90 ± 0.05
5-HT_{1A}	189 ± 12	175 ± 20
5-HT_{2A}	7.97 ± 0.24	9.03 ± 0.71
D_{2L}	246 ± 15	78.1 ± 8.3
D_3	361 ± 25	54.9 ± 8.2
D_4	318 ± 20	3.94 ± 0.45
α_1	96 ± 5	0.41 ± 0.05
σ_1	61 ± 8	4295 ± 150
σ_2	182 ± 19	147 ± 18

[a] Receptors and radioligand used in binding assays: 5-HT_{2A} (rat cortex membranes; [^{3}H]ketanserin), D_{2L} (human cloned receptors in Sf9 cells; [^{3}H]spiroperidol); D_3 (rat cloned receptors in Sf9 cells; [^{3}H]spiroperidol); D_4 (human cloned receptors in CHO cells; [^{3}H]spiroperidol); α_1 (rat cortex membranes; [^{3}H]prazosin); σ_1 (guinea-pig brain membranes without cerebellum; [^{3}H]-(+)-pentazocine); σ_2 (rat liver membranes, [^{3}H]DTG).

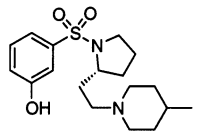
(i.e., 1,2-benzisoxazol-3-yl,[30] methyl,[31]cyclohexyl[31]). This modification was not tolerated. In fact, compounds **32**−**39** showed lower 5-HT_7 affinity than the 2-methoxyphenyl derivative **30**. In particular, the absence of an aromatic ring linked to the piperazine ring caused a complete loss of 5-HT_7 affinity (methyl and cyclohexyl derivatives **32** and **33**, respectively). The only exception was compound **40** that showed a slight increase in 5-HT_7 affinity as compared to **30**, along with the expected marked decrease in 5-HT_{1A} receptor affinity. Compound **40** was identified as a high-affinity 5-HT_7 receptor ligand (K_i = 2.93 nM), 65-fold selective over 5-HT_{1A} receptors. It is noteworthy that compound **39** differs from **40** by the presence of a methoxy in 5-position of the 1,2-benzisoxazole ring and this caused a drop in 5-HT_7 affinity. This unexpected result could suggest that this part of the molecule is quite sensitive to minimal structural changes. However, this hypothesis will be verified in future studies. Next, we evaluated the lower homologues of **40** (compounds **41** and **42**, having $n = 3$ and $n = 4$, respectively), and 5-HT_7 affinity data confirmed that a five-methylene chain was preferred. Encouraged by the high 5-HT_7 affinity of **40**, we also prepared the corresponding methoxy derivative **43** to obtain a potential PET radioligand, when ^{11}C labeled in the *O*-methyl position. Surprisingly, **43** showed higher 5-HT_7 affinity than the phenol **40**.

Consequently, compounds **40** and **43** were tested against a panel of receptors capable of binding 4-substituted-1-arylpiperazines (Table 2), but results were disappointing. Compounds **40** was found to have low affinity for D_2, D_3, D_4, and σ_2 receptors (K_is > 100 nM), moderate affinity for α_1 and σ_1 receptors (K_i = 96 nM and 61 nM, respectively), and high 5-HT_{2A} receptor affinity (K_i = 8.0 nM). σ_1 Receptor affinity could depend on some structural features shared with butyrophenones, a class of compounds reported to bind at σ_1 receptors.[32−34] 5-HT_{2A} receptor affinity could be explained by the presence of the 3-(1-piperazinyl)-1,2-benzisoxazole moiety which is closely related to the 3-(1-piperidinyl)-1,2-benzisoxazole moiety contained by the 5-HT_{2A} agent risperidone.[35] Compound **43** showed an even worse binding profile than **40**, being nonselective over 5-HT_{2A}, D_4, and α_1 receptors. For this reason **43** cannot be proposed as a potential PET radioligand.

Table 3. Comparison between Maximal Relaxation Effects Induced by 5-CT, **40**, and **43** on Substance P-stimulated Guinea Pig Ileum Contracture with or without 5-HT_7 Receptor Desensitization

compd	dose, μM	% relaxation (± SEM) 5-HT_7 nondesensitized	5-HT_7 desensitized
5-CT	3	39 ± 3	no response
40	3	43 ± 4	no response
43	3	38 ± 2	no response

Chart 3



SB-269970

Compounds **40** and **43** were tested for 5-HT_7 intrinsic activity in an isolated guinea-pig ileum preparation along with 5-HT_7 receptor agonist 5-CT [5-carboxamidotryptamine]. It has been reported that 5-HT_7 agonists can produce dose-dependent guinea-pig ileum relaxation of substance P-induced contraction.[36,37] EC_{50} values of 5-CT, **40**, and **43** were found to be 0.63 μM, 0.37 μM, and 0.18 μM, respectively. Compounds **40** and **43** behaved as 5-HT_7 competitive agonists such as 5-CT because (a) they did not induce relaxation when 5-HT_7 receptors were desensitized by 5-CT (Table 3); (b) the selective 5-HT_7 antagonist SB-269970 (Chart 3) was able to revert their effects by shifting to the right the corresponding concentration−response curve in a surmountable manner. The slope of Schild plots (95% confidence intervals) of 5-CT, **40**, and **43** were 1.2 (1.0−1.4), 1.1 (1.0−1.2), and 1.0 (0.9−1.1), respectively. pA_2 values of 5-CT, **40**, and **43** were 7.48 ± 0.12 (n = 12), 7.54 ± 0.24 (n = 12), and 7.62 ± 0.30 (n = 22), respectively.

In conclusion, structural modifications on known D_4 ligands (compounds **3** and **4**) led to the identification of several 1-[ω-[4-(2-methoxyphenyl)-1-piperazinyl)alkyl]-1-aryl ketones having good 5-HT_7 receptor affinity, but poor selectivity over 5-HT_{1A} receptor. Further modifications led to 6-[4-(3-benzisoxazolyl)-1-piperazinyl]-1-(2-hydroxyphenyl)-1-hexanone (**40**) and 6-[4-(3-benzisoxazolyl)-1-piperazinyl]-1-(2-methoxyphenyl)-1-hexanone (**43**) that exhibited high 5-HT_7 receptor affinity (K_i = 2.93 nM and 0.90 nM, respectively). Although **40** and **43** showed good selectivity over 5-HT_{1A} receptor, they were poorly selective over 5-HT_{2A} receptor. Moreover, derivatives **40** and **43** displayed agonist properties such as 5-CT when tested for 5-HT_7 receptor-mediated relaxation of substance P-induced guinea-pig ileum contraction.

Acknowledgment. This study was supported by Research Grant No. 2001037552-003 from Università degli Studi di Bari and MURST (Italy) for the scientific program in CO7X field (2002−2003).

Supporting Information Available: Physical and spectral data of all the synthesized compounds; experimental procedure for synthesis and biological evaluation. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Uphouse, L. Multiple serotonin receptors: too many, not enough, or just the right number? *Neurosci. Biobehav. Rev.* **1997**, *21*, 679−698.

(2) Saxena, P. R. Serotonin receptors: subtypes, functional responses and therapeutic relevance. *Pharmacol. Ther.* **1995**, 339−368.

(3) Shen, Y.; Monsma, F. J.; Metcalf, M. A.; Jose, P. A.; Hamblin, M. W.; Sibley, D. R. Molecular cloning and expression of a 5-HT_7 serotonin receptor subtype. *J. Biol. Chem.* **1993**, *268*, 18200−18204.

(4) Lovenberg, T. W.; Baron, B. M.; de Lecea, L.; Miller, J. O.; Prosser, R. A.; Rea, M. A.; Foye, P. E.; Rucke, M.; Slone, A. L.; Siegel, B. W.; Danielson, P. E.; Sutcliffe, J. G.; Erlander, M. G. A novel adenyl cyclase-activating serotonin receptor (5-HT_7) implicated in the regulation of mammalian circadian rhythms. *Neuron* **1993**, *11*, 449−458.

(5) Ruat, M.; Traiffort, E.; Leurs, R.; Tardivel-Lacombe, J.; Diaz, J.; Arrang, L. M.; Schwartz, J. C. Molecular cloning, characterization and localization of a high-affinity serotonin receptor (5-HT_7) activating cAMP formation. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8547−8551.

(6) Plassat, J.-L.; Amlaiky, N.; Hen, R. Molecular cloning of a mammalian serotonin receptor that activates adenylate cyclase. *Mol. Pharmacol.* **1993**, *44*, 229−236.

(7) Bard, J. A.; Zgombick, J.; Adham, N.; Vaysse, P.; Branchek, T. A.; Weinshank, R. L. Cloning of novel human serotonin receptor (5-HT_7) positively linked to adenylate cyclase. *J. Biol. Chem.* **1993**, *268*, 23422−23426.

(8) Tsou, A.-p.; Kosaka, A.; Bach, C.; Zuppan, P.; Yee, C.; Tom, L.; Alvarez, R.; Ramsey, S.; Bonhaus, D. W.; Stefanich, E.; Jakeman, L.; Eglen, R. M.; Chan, H. W. Cloning and expression of a 5-hydroxytryptamine$_7$ receptor positively coupled to adenylyl cyclase. *J. Neurochem.* **1994**, *63*, 456−464.

(9) Yau, J. L.; Noble, J.; Widdowson, J.; Seckl, J. R. Impact of adrenalectomy on 5-HT_6 and 5-HT_7 receptor gene expression in the rat hippocampus. *Brain Res. Mol. Brain Res.* **1997**, *45*, 182−186.

(10) Shimizu, M.; Nishida, A.; Zensho, H.; Yamawaki, S. Chronic antidepressant exposure enhances 5-hydroxytryptamine$_7$ receptor-mediated cyclic adenosine monophosphate accumulation in rat frontocortical astrocytes. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 1551−1558.

(11) Ying, S. W.; Rusak, B. 5-HT_7 receptors mediate serotonergic effects on light-sensitive suprachiasmatic nucleus neurons. *Brain Res.* **1997**, *755*, 246−254.

(12) Terron, J. A.; Falcon-Neri, A. Pharmacological evidence for the 5-HT_7 receptor mediating smooth muscle relaxation in canine cerebral arteries. *Br. J. Pharmacol.* **1999**, *127*, 609−616.

(13) De Vries, P.; De Visser, P. A.; Heiligers, J. P.; Villalon, C. M.; Saxena, P. R. Changes in systemic and regional haemodynamics during 5-HT_7 receptor-mediated depressor responses in rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1999**, *359*, 331−338.

(14) Forbes, I. T.; Dabbs, S.; Duckworth, D. M.; Jennings, A. J.; King, F. D.; Lovell, P. J.; Brown, A. M.; Collin, L.; Hagan, J. J.; Middlemiss, D. N.; Riley, G. J.; Thomas, D. R.; Upton, N. (*R*)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzenesulfonamide: the first selective 5-HT_7 receptor antagonist. *J. Med. Chem.* **1998**, *41*, 655−657.

(15) Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. Tetrahydrobenzindoles: selective antagonists of the 5-HT_7 receptor. *J. Med. Chem.* **1999**, *42*, 533−535.

(16) López-Rodríguez, M. L.; Porras, E.; Benhamú, B.; Ramos, J. A.; Morcillo, M. J.; Lavandera, J. L. First pharmacophoric hypothesis for 5-HT_7 antagonism. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1097−1100.

(17) Lovell, P. J.; Bromidge, S. M.; Dabbs, S.; Duckworth, D. M.; Forbes, I. T.; Jennings, A. J.; King, F. D.; Middlemiss, D. N.; Rahman, S. K.; Saunders, D. V.; Collin, L. L.; Hagan, J. J.; Riley, G. J.; Thomas, D. R. A novel, potent, and selective 5-HT_7 antagonist: (*R*)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulfonyl)phenol (SB-269970). *J. Med. Chem.* **2000**, *43*, 342−345.

(18) Linnanen, T.; Brisander, M.; Mohell, N.; Johansson, A. M. Serotonergic and dopaminergic activities of rigidified (*R*)-aporphine derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 367−370.

(19) Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A. M. Atropisomeric derivatives of 2′,6′-disubstituted (*R*)-11-phenylaporphine: selective serotonin 5-HT_7 receptor antagonists. *J. Med. Chem.* **2001**, *44*, 1337−1340.

(20) Rezaie, R.; Joseph, B.; Bremner, J. B.; Delagrange, P.; Kopp, C.; Misslin, R.; Pfeiffer, B.; Renard, P.; Guillaumet, G. 5-Substituted 3,4-dihydro-3-amino-2*H*-1-benzopyran derivatives: synthesis and interaction with serotoninergic receptors. *J. Pharm. Pharmacol.* **2001**, *53*, 959−668.

(21) Kikuchi, C.; Ando, T.; Watanabe, T.; Nagaso, H.; Okuno, M.; Hiranuma, T.; Koyama, M. 2a-[4-(Tetrahydropyridoindol-2-yl)-butyl]tetrahydrobenzindole derivatives: new selective antagonists of the 5-hydroxytryptamine$_7$ receptor. *J. Med. Chem.* **2002**, *45*, 2197−2206.

(22) Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Vanotti, E.; Govoni, S. Mixed 5-HT_{1A}/D-2 activity of a new model of arylpiperazine: 1-aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]piperazines. 1. Synthesis and structure−activity relationships. *J. Med. Chem.* **1994**, *37*, 99−104.

(23) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. High affinity and selectivity on 5-HT_{1A} receptor of 1-aryl-4-[(1-tetralin)alkyl]piperazines. 2. *J. Med. Chem.* **1995**, *38*, 942−949.

(24) Perrone, R.; Berardi, F.; Leopoldo, M.; Tortorella, V.; Lograno, M. D.; Daniele, E.; Govoni, S. 5-HT_{1A} and D-2 receptor affinity of *o*-methoxyphenylpiperazine derivatives with terminal benzamide fragment on N-4 alkyl chain. 2. *Farmaco* **1995**, *50*, 505−510.

(25) Perrone, R.; Berardi, F.; Leopoldo, M.; Tortorella, V.; Fornaretto, M. G.; Caccia, C.; McArthur, R. 1-Aryl-4-[(1-tetralinyl)alkyl]-piperazines: alkylamido and alkylamino derivatives. Synthesis, 5-HT_{1A} receptor affinity, and selectivity. 3. *J. Med. Chem.* **1996**, *39*, 3195−3202.

(26) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V. 1-(2-Methoxyphenyl)-4-alkylpiperazines: effect of the N-4 substituent on the affinity and selectivity for dopamine D_4 receptor. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1327−1330.

(27) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V. A structure-affinity relationship study on derivatives of *N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide, a high-affinity and selective D_4 receptor ligand. *J. Med. Chem.* **2000**, *43*, 270−277.

(28) Kawakita, T.; Kuriota, T.; Murozono, T.; Hakira, H.; Haga, K.; Ito, K.; Sonda, S.; Kawahara, T.; Asano, K. Preparation of 5-HT_4 agonist 4-amino-N-(piperidinylalkyl)benzamides and analogues as gastrointestinal drugs. US 5864039A, 1999.

(29) Cliffe, I. A.; Fletcher, A. Advances in 5-HT_{1A} antagonist research. *Drugs Future* **1993**, *18*, 631−642.

(30) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V. 1-Substituted-4-[3-(1,2,3,4-tetrahydro-5- or 7-methoxynaphthalen-1-yl)propyl]piperazines: influence of the *N*-1 piperazine substituent on 5-HT_{1A} receptor affinity and selectivity versus D_2 and α_1 receptors. 6. *Bioorg. Med. Chem.* **2000**, *8*, 873−881.

(31) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Abate, C.; Tortorella, V. *N*-aryl- or *N*-alkylpiperazine derivatives: the role of *N*-substituent on σ_1, σ_2, 5-HT_{1A} and D_2 receptor affinity. *Med. Chem. Res.* **2000**, *10*, 201−207.

(32) Glennon, R. A.; Ablordeppey, S. Y.; Ismaiel A. M.; El-Ashmawy M. B.; Fischer, J. B.; Burke Howie, K. Structural features important for σ_1 receptor binding. *J. Med. Chem.* **1994**, *37*, 1214−1219.

(33) Ablordeppey, S. Y.; Issa, H.; Fischer, J. B.; Burke Howie, K. J.; Glennon R. A. Synthesis and structure-affinity relationship studies of sigma ligands related to haloperidol. *Med. Chem. Res.* **1993**, *3*, 131−138.

(34) Jaen, J. C.; Caprathe, B. W.; Pugsley T. A.; Wise, L. D.; Akunne H. Evaluation of the effects of the enantiomers of reduced haloperidol, azaperol and related 4-amino-1-arylbutanols on dopamine and σ receptors. *J. Med. Chem.* **1993**, *36*, 3929−3936.

(35) Megens, A. A. H. P.; Kennis, L. E. J. Risperidone and related 5HT_2/D_2 antagonists: a new type of antipsychotic agent? *Prog. Med. Chem.* **1996**, *33*, 185−232.

(36) Carter, D.; Champney, M.; Hwang, B.; Eglen, R. M. Characterization of a postjunctional 5-HT receptor mediating relaxation of guinea-pig isolated ileum. *Eur. J. Pharmacol.* **1995**, *280*, 243−250.

(37) Lucchelli, A.; Santagostino-Barbone, M. G.; D'Agostino, G.; Masoero, E.; Tonini, M. The interaction of antidepressant drugs enteric 5-HT_7 receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 284−289.

JM020994Z