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SOME BENZENESULFONAMIDO-SUBSTITUTED VALEROPHENONES THAT ARE SELECTIVE ANTAGONISTS FOR THE 5-HT_{2C} RECEPTOR

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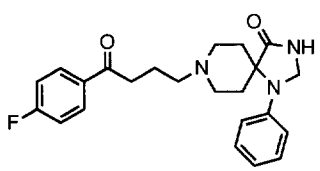
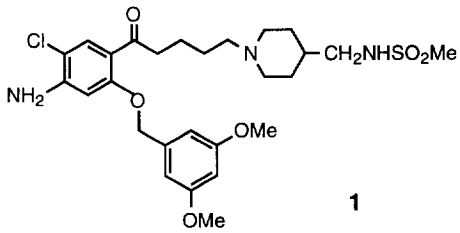
Abstract: Substituted benzenesulfonyl derivatives of *m*-aminovalerophenones bearing a 1,3,8-triazaspiro[4.5]decane-2,4-dione at the alkyl terminus are the first known, selective ligands for the 5-HT_{2C} receptor. A brief structure-activity relationship of this series is outlined. Copyright © 1996 Elsevier Science Ltd

The classification of serotonin (5-HT) receptors is an ongoing proccess that has resulted in the recognition of seven classes of serotonin receptors, several of which are comprised of multiple subtypes.[1] The 5-HT_2 class is subdivided into the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes on the basis of their close structural similarity and common second messenger transductional system. All three receptors have been cloned. The 5-HT_{2C} receptor, originally classified as 5-HT_{1C},[1] has been found to be present in the brain; however, its functional role is not known. Potential therapeutic targets of 5-HT_{2C} antagonists have been identified[2] from clinical observations and animal testing[3] of nonselective 5-HT_{2C} antagonists and include migraine, anxiety, obsessive compulsive disorders, and other diseases.[1,2,3] Efforts to elucidate the function of the 5-HT_{2C} receptor have been hampered by the lack of selective ligands. However, there have been some recent reports on the discovery of agents that have affinities for both the 5-HT_{2B} and 5-HT_{2C} receptors, but are selective in regard to the 5-HT_{2A} receptor.[4] We now wish to report the synthesis and receptor binding properties of RS-102221 (**18**), a 5-HT_{2C} antagonist with nanomolar affinity and ca. hundredfold selectivity over the 5-HT_{2A} and 5-HT_{2B} receptor subtypes.



Spiperone



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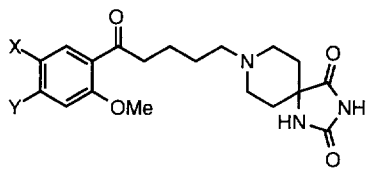
At the outset of this work it was known that spiperone was a potent 5-HT_{2A} antagonist that also possessed some, although rather minimal, affinity for the 5-HT_{2C} receptor. Earlier efforts in the area of 5-HT_4 antagonists had led to a series of compounds that, like spiperone, was also based on an alkanophenone skeleton that was substituted with a piperidine at the alkyl terminus, as is exemplified by **1**.[5] It appeared feasible to produce compounds within a series of piperidino-substituted alkanophenones that would possess enhanced 5-HT_{2C} antagonist properties by modifying some of the salient features of spiperone as well as those of the 5-HT_4 antagonists. These modifications included elimination of the N-phenyl group of spiperone while retaining the 1,3,8-triazaspirodecane moiety in the form of a 2,4-dione. Some of the substituents that were known to be beneficial to the series of 5-HT_4 antagonists, such as 4-amino and 2-benzyloxy, were also deleted or changed. Some of the results of these initial efforts are summarized in Table I.

Table I. Receptor affinity for compds. **2-11**

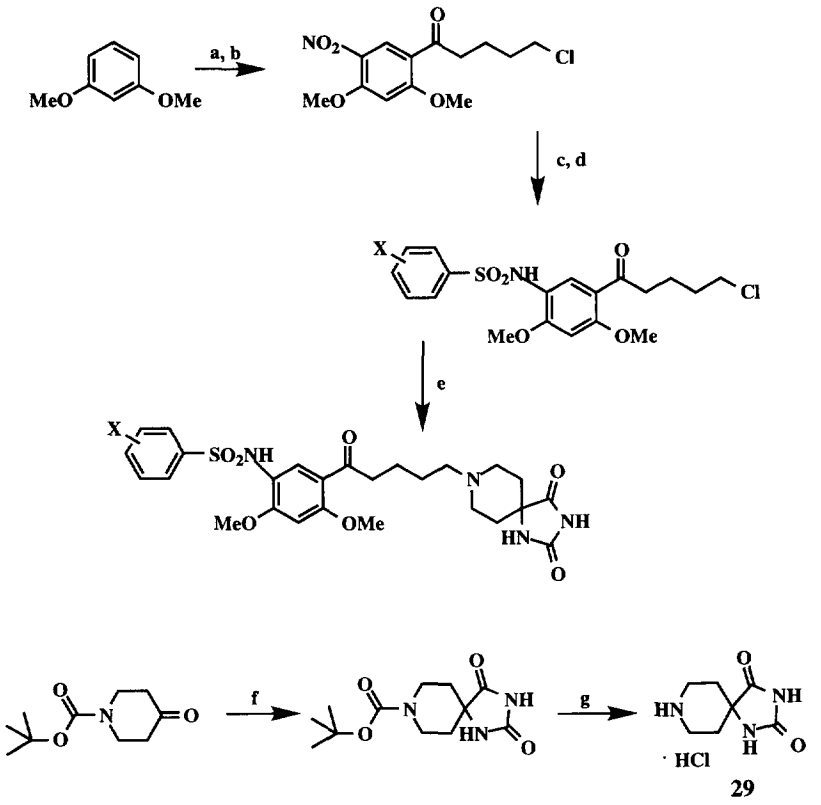


			Binding pK_i[a]		
compd.	X	Y	$5HT_{2A}$[b]	$5HT_{2B}$[c]	$5HT_{2C}$[d]
2	H	H	< 5	< 5	< 5
3	Cl	H	7.9 ± 0.1	7.3 ± 0.3	8.4 ± 0.3
4	OMe	H	7.7 ± 0.2	6.9 ± 0.3	8.5 ± 0.1
5	H	Cl	6.9 ± 0.1	6.7 ± 0.2	8.2 ± 0.1
6	Cl	OMe	8.3 ± 0 1[e]		9.2 ± 0.2[e]
7	Cl	Cl	8.2 ± 0.1	8.2 ± 0.1	9.6 ± 0.1
8	Ph	H	9.0 - 9.1[f]	8.0 ± 0.1	9.7 ± 0.1
9	Ph	OMe	6.4 ± 0.1	7.0 ± 0.1	8.0 ± 0.1
10	OPh	H	8.1 ± 0.1[e]		8.5 ± 0.1[e]
11	NH_2	OMe	6.9 ± 0.2[e]		7.4 ± 0.3[e]
Mesulergine			7.7 ± 0.1	8.7 ± 0.1	8.7 ± 0 1
Spiperone			8.8 ± 0.1	5.9 ± 0.2	6.2 ± 0.1

[a]Cloned human receptors(CHO cells), except where otherwise noted; n = 3. [b]Displacement of [^{3}H]ketanserin. [c]Displacement of [^{3}H]5-HT. [d]Displacement of [^{3}H]mesulergine. [e]Cloned rat receptors. [f]n = 2.

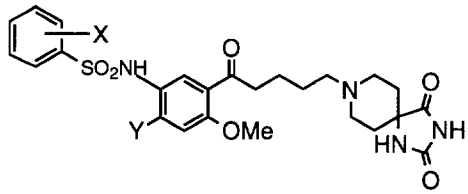
As can be seen from Table I, several analogs exhibited potent 5-HT_{2C} receptor affinity and some were also modestly selective in their binding profiles. The observation that placement of a large substituent in position 5 was not detrimental to receptor affinity (analogs **8**, **9**, and **10**) led to further exploration of the effects of substituents in that positon. A modification that appeared synthetically facile was the derivitization of a 5-amino group. Through synthetic efforts (Scheme I), it was found eventually that certain benzenesulfonamide derivatives of **11** possessed good affinities for the 5-HT_{2C} receptor and were selective in regard to the other 5-HT_2 receptors.

Scheme I



a: 5-chlorovaleryl chloride, $AlCl_3$, $ClCH_2CH_2Cl$; b: $Cu(NO_3)_2$, Ac_2O, 15-20 °C; c: Pt/H_2, EtOH-THF; d: $ArSO_2Cl$, Et_3N, THF, 50 °C, e: 29, Et_3N, NaI, DMF, 100 °C; f: $(NH_4)_2CO_3$, KCN, EtOH-H_2O, 60 °C; g: EtOH, HCl, 80 °C, 5 min.

Table II. Receptor affinity for benzenesulfonamides



			Binding pK_i [a]		
comdp.	X	Y	$5HT_{2A}$ [b]	$5HT_{2B}$ [c]	$5HT_{2C}$ [d]
12	H	H	7.7 ± 0.1 [e]		8.2 ± 0.1 [e]
13	H	OMe	5.5 ± 0.1	6.2 ± 0.1	7.5 ± 0.1
14	4 - Cl	H	8.1 ± 0.2 [e]		8.7 ± 0.2 [e]
15	4 - Cl	OMe	6.1 ± 0.1	7.1 ± 0.1	8.3 ± 0.1
16	3 - Cl	OMe	5.7 ± 0.2	6.7 ± 0.3	7.3 ± 0.1
17	2 - Cl	OMe	<5	6.4 ± 0.2	6.4 ± 0.1
18	4 - CF_3	OMe	6.2 ± 0.2	6.5 ± 0.2	8.7 ± 0.1
19	3 - CF_3	OMe	6.1 ± 0.2 [e]		7.0 ± 0.3 [e]
20	4 - F	OMe	< 5	6.9 ± 0.2	8.0 ± 0.1
21	4 - Me	OMe	5.6 ± 0.2	6.5 ± 0.1	8.0 ± 0.1
22	4 - *i* - Pr	OMe	5.9 ± 0.3	5.9 ± 0.3	8.8 ± 0.4
23	4 - OCF_3	OMe	6.0 ± 0.2	6.4 ± 0.2	8.8 ± 0.1
24	4 - OMe	OMe	5.7 ± 0.2	5.9 ± 0.1	7.7 ± 0.4
25	4 - Ac	OMe	< 5	6.6 ± 0.2	7.4 ± 0.1
26	4 - NHAc	OMe	< 5	6.5 ± 0.1	7.4 ± 0.2
27	4 - SO_2NH_2	OMe	< 5	5.5 ± 0.1	7.1 ± 0.1
28	4 - CN	OMe	6.1 ± 0.2	6.4 ± 0.3	8.1 ± 0.1

[a]Cloned human receptors(CHO cells), except where otherwise noted; n = 3. [b]Displacement of [^{3}H]ketanserin. [c]Displacement of [^{3}H]5-HT. [d]Displacement of [^{3}H]mesulergine. [e]Cloned rat receptors.

The affinity for the 5-HT_{2C} receptor appeared to correlate most to the lipopilicity of a *para*-substituent (X) in the benzenesulfonyl moiety, as can be seen from the data in Table II. It is of interest to note the beneficial effects exerted upon receptor selectivity by the presence of the 4-methoxy (Y) substituent.

Additional findings not tabulated indicated that benzamide, phenylurea, 3-pyridylsulfonamide, methanesulfonamide, and 1-piperidinesulfonamide derivatives of **11** were essentially devoid of desirable

receptor affinities. An analog of **15**, where the methoxy (Y) and sulfonamide moieties had been transposed, and an analog of **18**, that was lacking the hydantoin ring exhibited pK_i's of <6.5.

The 5-carbon pentanoyl chain was the optimal connector between the benzene ring and the 1,3,8-triazaspirodecane moiety. Finally, additional substitution of the 6-aryl position by methoxy or N-methylation of the 3-position of the 1,3,8-triazaspironedecane moiety of **18** resulted in compounds with similar affinity as their parent.

The synthesis of compound **18** predated that of the closely related analogs **22** and **23** and therefore it was targeted for a more thorough receptor profile investigation. The analog **18**, RS-102221, was thousandfold selective over other 5-HT; adrenergic-alpha and -beta and muscarinic receptors, and hundredfold selective over the adrenergic-$alpha_{2A}$ receptor (pK_i of 6.5 ± 0.2). Further evaluation of the analog **18** showed that it was a functional 5-HT_{2C} antagonist as determined by a cytosensor assay.[6] An account detailing the pharmacological actions of **18** and the methods used in their determinations will be published elsewhere.

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6. The agonist or antagonist nature of RS-102221 was determined using the transfected CHO-K1 cells expressing the human cloned receptors and a Molecular Devices Cytosensor.[7] Cells stably expressing human 5-HT_{2A}, 5-$HT_{2B,}$ or 5-HT_{2C} receptors were transfered to 6.5 mm transwell capsule plates (3 micron pore size) and allowed to adhere overnight. The cell plating density on these disks was approximately 3 x 10^5 cells per disk. The disks were placed into the flow chambers and allowed to equilibrate to the perfusion buffer (Dulbecco's Minimal Essential Medium, DMEM with the sodium bicarbonate replaced by 44 mM NaCl). After baseline acidification rates stabilized, concentration response curves were generated in the presence or absence of antagonist. In a typical experiment, eight concentrations of agonist and at least three concentrations of antagonist were tested. The cells were perfused with the antagonist for at least thirty minutes prior to generating the agonist response curve. The cells were exposed to agonist for 30 seconds periods and at least 45 min were allowed for the washout of drug between each determination. Each curve was generated with quadruplicate measures at each concentration point.

   EC_{50} and maximum response values were determined by nonlinear regression analysis of the concentration response curves. pA_2 values for antagonists were determined by Schild regression analysis. Similar assays were also conducted using cells expressing rat cloned 5-HT_{2A} and 5-HT_{2C} receptors.

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