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1,2,5-Thiadiazole Derivatives Are Potent and Selective Ligands at Human 5-HT_{1A} Receptors

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Abstract—Amino acid derivatives of 1,2,5-thiadiazol-3-yl-piperazine related to (+)-WAY-100135 and WAY-100635 are potent 5-HT_{1A} receptor agonists and antagonists, which have selective affinity for 5-HT_{1A} receptors versus α_1 and dopamine (D_2, D_3, and D_4) receptors.

The serotonin 5-HT_{1A} receptor has been implicated in the regulation of cognition, psychosis, feeding/satiety, temperature regulation, anxiety, depression, sleep, pain perception, and sexual activity. The development of non-benzodiazepine anxiolytics, such as buspirone **1**, a partial agonist at 5-HT_{1A} receptors, has substantiated the correlation between serotonin and anxiety. In addition, there has been a recent report that flesinoxan **2**, a 5-HT_{1A} full agonist, is effective in generalized anxiety disorder in humans. On the contrary, the 5-HT_{1A} receptor antagonists, (+)-WAY-100135 **3** and WAY-100635 **4**, show limited anxiolytic activity. Instead these compounds have demonstrated robust activity in a number of preclinical models of cognitive impairment associated with Alzheimer's disease. Harder et al.[1] reported that WAY-100635 alleviates impairments caused by dizocilipine (MK-801), a noncompetitive NMDA antagonist, in monkeys. Similarly, Boast et al.[2] found that WAY-100635 significantly reduced the cognitive impairment caused by MK-801, in a delayed nonmatch to sample radial arm maze task in rats. Furthermore, Carli et al.[3] showed that post-training administration of WAY-100635 was able to reverse a learning deficit induced in rats by administration of scopolamine, a cholinergic antagonist, in an autoshaping learning task (Fig. 1).

In an effort to discover novel 5-HT_{1A} receptor antagonists in the arylpiperazine family having improved bioavailability and a longer biological half-life than (+)-WAY-100135 and WAY-100635, it was proposed that compounds containing a 1,2,5-thiadiazolepiperazine would serve as a bioisosteric replacement for those containing the *ortho*-methoxyphenylpiperazine (OMPP) moiety and hence retain 5-HT_{1A} affinity. It was also reasoned that such compounds would be less susceptible to oxidative metabolism of the thiadiazole ring than the metabolism typically seen with those containing OMPP. We now report that unlike OMPP, 1,2,5-thiadiazolepiperazine, itself, has no affinity for the human 5-HT_{1A} receptor transfected into Chinese hamster ovary (CHO) cells. However, amino acid 2-aryl substituted ethylamide derivatives of 1,2,5-thiadiazol-3-yl-piperazines are potent 5-HT_{1A} receptor agonists and antagonists, which demonstrate selective affinity for 5-HT_{1A} receptors versus α_1 and dopamine (D_2, D_3, and D_4) receptors.

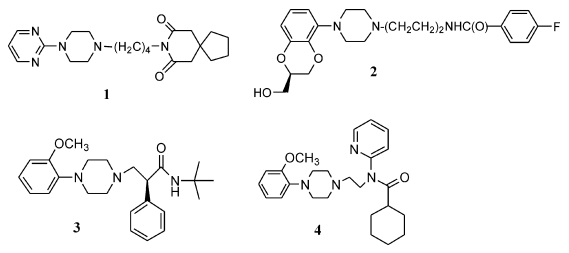

Figure 1. Known 5-HT_{1A} partial agonsits, agonists, and antagonists.

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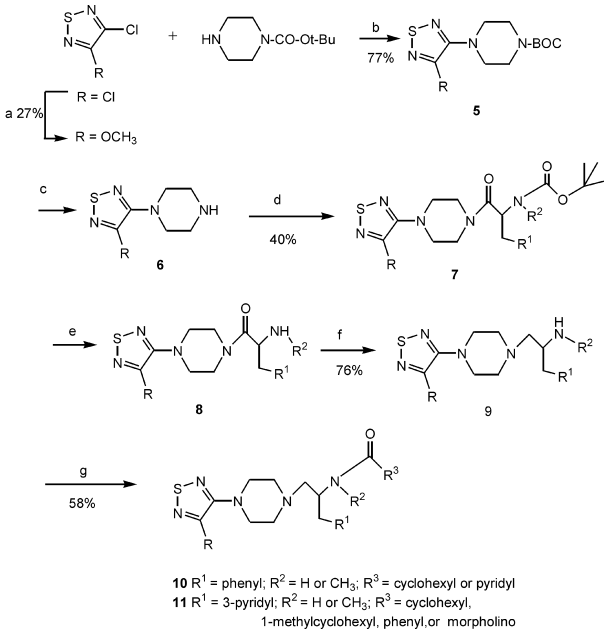
In this paper we describe the synthesis and structure–activity relationships of a series of phenylalanine and 3-pyridylalanine derivatives of 4-substituted [1,2,5]thiadiazolepiperazines and discuss their structure–activity relationships in relation to their affinity and intrinsic activity at human 5-HT_{1A} receptors. In addition, the selectivity versus α_1 and dopamine receptors for specific compounds will be reported.

The [1,2,5]thiadiazol-3-yl-piperazine compounds shown in Tables 1–3 were prepared as outlined in Scheme 1.

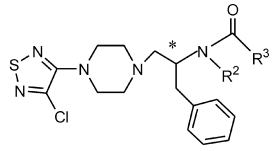


Scheme 1. 1-Benzyl-2-[4-chloro-[1,2,5]thiadiazol-3-yl-piperazin-1-yl]-ethylamides **10** and 3-pyridyl-2-[4-methoxy-[1,2,5-thiadiazol-3-yl]-ethylamides **11**.[4] (a) Na metal, MeOH, N_2, reflux; (b) DMF, N_2, reflux; (c) 4 N HCl, dioxane; (d) *N*-Boc-amino acid, TEA, DCC, HOBt, CH_2Cl_2; (e) 4 N HCl, dioxane; (f) 1 M BH_3 in THF; (g) R_3COCl or R_3COOH plus a coupling reagent. Intermediates **7**, **8**, and **9** can be used without purification. Yields are averages.

Commercially available 3,4-dichloro-[1,2,5]thiadiazole was treated with *N*-Boc-piperazine in refluxing DMF under a nitrogen atmosphere to provide the protected 4-chloro-3-piperazinyl-[1,2,5]thiadiazole **5**. Alternatively, treatment of 3,4-dichloro-[1,2,5]thiadiazole with sodium methoxide in methanol gave 3-chloro-4-methoxy-[1,2,5]thiadiazole. Reaction of this thiadiazole with *N*-Boc piperazine gave the corresponding compound **5** where R = OCH_3. Compound **5** was deprotected by stirring overnight at room temperature in 4 N HCl in dioxane. Coupling of [1,2,5]thiadiazolepiperazine **5** with *N*-Boc protected amino acids in methylene chloride at room temperature using the coupling agent, DCC, in the presence of triethylamine and 1-hydroxybenzotriazole hydrate gave amide **7**. Removal of the *N*-BOC protecting group with 4 N HCl in dioxane at room temperature gave amino amide **8**, which was reduced with 1 M BH_3 in THF to give amine **9**. Amine **9** was treated with a carboxylic acid chloride or with a carboxylic acid in the presence of a coupling reagent, such as DCC, to give [1,2,5]thiadiazolepiperazine derivatives **10** and **11**.

Compounds **10a–d** were prepared using *R* and *S* phenylalanine. The compounds were evaluated for 5-HT_{1A} binding affinity by measuring their ability to displace [^{3}H]8-OH-DPAT from CHO cells stably transfected with human 5-HT_{1A} receptors according to the procedure of Dunlop et al.[5] Their intrinsic activity was determined by measuring the compounds' ability to reverse the forskolin-stimulated turnover of cAMP in CHO cells.[5] (% $E_{max} = 0$ for antagonists in this assay) Results of these studies are summarized in Table 1.

Table 1. 5-HT_{1A} in vitro profile of 4-chloro[1,2,5]thiadiazol-3-yl piperazines

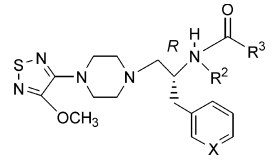


Compd	R^2	R^3	Stereo	5-HT_{1A} K_i (nM)	c-AMP %E_{max}
10a	H	Cyclohexyl	*S*	0.8	93.0 EC_{50} = 4.6 (nM)
10b	CH_3	Cyclohexyl	*R*	4.5	0 IC_{50} = 49.3 (nM)
10c	H	4-Pyridyl	*S*	425	NT[a]
10d	H	2-Pyridyl	*S*	47%@1 (μM)	NT

[a]NT = not tested.

Compounds **11a–d** were prepared using *N*-Boc-*N*-methyl-*R*-phenylalanine or *N*-Boc-*R*-3-pyridylalanine. Results of their evaluation for 5-HT_{1A} binding affinity and intrinsic activity are summarized in Table 2.

Table 2. 5-HT_{1A} affinity and antagonist activity of 4-methoxy[1,2,5]-thiadiazol-3-yl piperazines

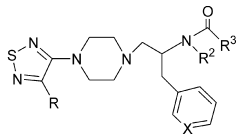


Compd	R^2	R^3	X	5-HT_{1A} K_i (nM)	c-AMP %Emax
11a	CH_3	Cyclohexyl	CH	1.5	0 IC_{50} = 72.7 (nM)
11b	CH_3	Phenyl	CH	9.9	0 IC_{50} = 6.4 (nM)
11c	CH_3	*N*-Morpholino	CH	46%@1 (μM)	NT[a]
11d	H	1-Methylcyclohexyl	N	3.0	0 IC_{50} = 113 (nM)

[a]NT = not tested.

Studies using both *R* and *S* phenylalanine suggest that ligand binding to the 5-HT_{1A} receptor is not dependent upon stereochemistry in this series. However, even though both stereoisomers have potent affinity for the receptor, when R^2 is H, and R^3 is cyclohexyl (**10a**) the

Table 3. α_1 and dopamine affinity for selected compounds



Compd	R	R^2	R^3	X	Stereo	α_1 %inhib. @ 100 (nM)	IC_{50} (nM)		
							D_2	D_3	D_4
10a	Cl	H	Cyclohexyl	CH	S	17	NT[a]	NT	NT
10b	Cl	CH_3	Cyclohexyl	CH	R	0	NT	NT	NT
11a	OCH_3	CH_3	Cyclohexyl	CH	R	0	11%@100nM	NT	NT
11b	OCH_3	CH_3	Phenyl	CH	R	15	NT	NT	NT
11d	OCH_3	H	1-Me-Cyclohexyl	N	R		3516	489	1102

[a]NT = not tested.

compound is a partial agonist whereas when R^2 is methyl and R^3 is cyclohexyl (**10b**) the compound is an antagonist. In additon, it was observed that binding affinity is remarkably sensitive to the nature of the amide group as demonstrated by compounds **10c** and **10d**. Since it was our objective to develop potent and selective 5-HT_{1A} antagonists, we focused our SAR study on analogues of **10b** in which there was steric crowding around the amide portion of the molecule. The methoxy derivatives were selected for study, since both (+)-WAY-100135 and WAY-100635 contain a methoxyarylpiperazine group. Compounds **11a**,**b**,**d** demonstrate that either a methyl group at R^2 or a 1-methylcyclohexyl group at R^3 give potent 5-HT_{1A} antagonists. Compound **11b** shows that a phenyl amide but not pyridyl amides (**10c** and **10d**) are tolerated by the receptor. Compound **11c**, in which R^3 is morpholine, lost affinity for the 5-HT_{1A} receptor.

In order to evaluate the selectivity of compounds **10** and **11**, representatives of each type were tested in receptor binding assays for affinity at α_1[6] and dopamine (D_2, D_3, and D_4) receptors.[7] Results of these binding assays are summarized in Table 3. In each case examined, significant selectivity for the 5-HT_{1A} receptor versus α_1 and dopamine receptors was observed.

In summary, a series of phenylalanine and 3-pyridylalanine derivatives of 4-substituted [1,2,5]thiadiazole-piperazines was synthesized and evaluated for affinity and intrinsic activity at human 5-HT_{1A} receptors. Selectivity versus α_1 and dopamine receptors was also determined. Both *R* and *S* enantiomers of the phenylalanine derivatives had affinity for the 5-HT_{1A} receptor and selectivity versus α_1.

R enantiomers of the 3-pyridylalanine derivatives had affinity for the 5-HT_{1A} receptor and selectivity for both α_1 and dopamine receptors. (*S* enantiomers were not tested.) Steric crowding in the amide region of either series of molecules favored antagonism. The antagonist with the best profile is **11a** which has a $K_i = 1.5$ nM at the human 5-HT_{1A} receptor, functions as a full antagonist (no effect in the c-AMP assay), and has no affinity at α_1 and dopamine receptors.

References and Notes

1. Harder, J. A.; Ridley, R. M. *Neuropharmacology* **2000**, *39*, 547.
2. Boast, C.; Bartolomeo, A. C.; Morris, H.; Moyer, J. *Neurobiol. Learn. Mem.* **1999**, *71*, 259.
3. Carli, M.; Silva, S.; Balducci, C.; Samanin, R. *Neuropharmacology* **1999**, *38*, 1165.
4. All final compounds were characterized by C, H, and N microanalysis, NMR, IR, and mass spectrometry. For experimental details see Sabb, A. L.; Vogel, R. L.; Kelly, M. G.; Palmer, Y. L.; Childers, W. E. WO 0051999, 2000; *Chem. Abstr.* Number 133:222746 AN 2000:628129.
5. Dunlop, J.; Zhang, Y.; Smith, D. L.; Schechter, L. *J. Pharmacol. Tox. Meth.* **1998**, *40*, 47.
6. Morrow, A. L.; Creese, I. *Mol. Pharmacol.* **1986**, *29*, 321.
7. Mewshaw, R. E.; Nelson, J. A.; Shah, U. S.; Shi, X.; Mazandarani, H.; Coupet, J.; Marquis, K. L.; Brennan, J. A.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2593.