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NOVEL CONFORMATIONALLY RESTRICTED AROMATIC PIPERIDINES AS SELECTIVE SIGMA RECEPTOR LIGANDS[1]

Gary A. Cain*, Thomas E. Christos, Charles J. Eyermann, Paul J. Gilligan, Dimitri E. Grigoriadis, Alexander L. Johnson, S. William Tam

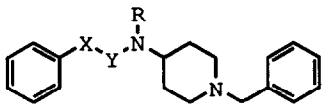
The DuPont Merck Pharmaceutical Company, P.O. Box 80402, Wilmington, Delaware 19880-0402

Abstract. A series of novel conjugated aromatic 4-amino- and 4-amido-piperidines which are potent sigma receptor ligands are described. These ligands exhibit good to excellent selectivities for binding at sigma versus D_2 and 5-HT_2 receptors.

Schizophrenia and related psychoses are diseases for which there remains a great unmet medical need. Traditional dopamine D_2 antagonist drugs are effective against the positive symptoms of schizophrenia, but suffer from several adverse side effects.[2] Clozapine,[3] an atypical antipsychotic, is active against both the positive and negative symptoms of schizophrenia, and does not produce the extrapyramidal symptoms caused by D_2 antagonists. Clozapine does, however, have side effects of its own, such as agranulocytosis and seizures. The shortcomings of all current antipsychotic drugs have led to an urgent need for better therapies.

The sigma (σ) receptor has been the focus of a considerable amount of research in the past few years because of its possible role in psychosis.[4] Much of this research has centered around the hypothesis that a sigma receptor ligand which blocks the action of (+)-*N*-allylnormetazocine ((+)-SKF-10,047), which is known to produce psychotomimetic effects in animals, could become an antipsychotic drug with a novel mode of action and a superior side effect profile.

Recently,[5] we presented a model describing the structural requirements of a series of novel piperidines which were selective, high affinity ligands for the [^{3}H]-(+)-SKF-10,047 subtype of σ receptors. Several of these compounds also exhibited activity in antipsychotic animal models. The compounds of our previous study possessed aromatic rings tethered to the piperidine 4-position by a flexible hydrocarbon chain containing a polar functional group. In that study, the optimal distance between the piperidine nitrogen and the distal aromatic group was proposed to be 6 ± 2 Angstroms. As a follow-up to that study, we have prepared a series of new piperidines, represented by structure **1**, wherein the tether contains alkene or alkyne groups conjugated to the aromatic ring. By introducing conformational constraints in this fashion, we expected to refine our σ receptor ligand model.



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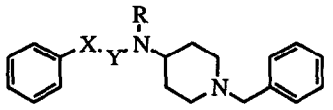
X = trans CH=CH, C≡C
Y = CH_2, CO

The new compounds of this study were evaluated for sigma, dopamine D_2, and serotonin 5-HT_2 receptor binding, with the results shown in Table 1. The σ and D_2 receptor binding assays were performed

according to the method of Tam,[6] using [^{3}H]-(+)-SKF-10,047 and [^{3}H]-spiperone as radioligands in the respective assays. The 5-HT$_2$ receptor binding was performed following the method of Wander,[7] using [^{3}H]-ketanserin as radioligand.

Table 1. Comparative receptor binding data.



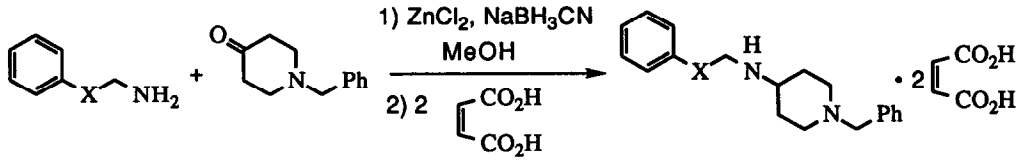
Ex.	X	Y	R	Salt	m.p. °C	Sigma K_i, nM	D_2 IC_{50}, nM	5-HT$_2$ K_i, nM
2	CH=CH[a]	CH_2	H	•2 MA[b]	196-198	16	>10,000	4600
3	CH=CH	CH_2	Me	•2 MA	187-189	2.6	>10,000	840
4	CH=CH	CH_2	Ph	•MA	ca. 50	1500	>10,000	>10,000
5	CH=CH	CH_2	trans PhCH=CHCH$_2$	•2 MA	190-192	7	>10,000	550
6	CH=CH	CO	H	•MA	163-164	15	4700	100
7	CH=CH	CO	Me	•MA	179.5-180.5	5	7100	1500
8	CH=CH	CO	Ph	•MA	195-196	58	>10,000	4200
9	C≡C	CH_2	H	•2 MA	156-159	2.5	>10,000	3300
10	C≡C	CH_2	Me	•2 MA	187-188	5	4100	320
11	C≡C	CH_2	Ph	•MA	137-138	22	890	280
12	C≡C	CO	H	•MA	183-183.5	8	2500	280
13	C≡C	CO	Me	•MA	163.5-164.5	4	4900	1700
14	C≡C	CO	Ph	•MA	158-161	6	1500	3100

(a) all CH=CH double bonds are trans
(b) MA = maleic acid

The new compounds of this study[8] were readily prepared in straightforward fashion. The precursor for the synthesis of examples **2**, **5**, **6**, **9**, and **12**, 4-amino-1-benzylpiperidine (**15**), was purchased from the Aldrich Chemical Company (Milwaukee, WI). The intermediate for the synthesis of **3**, **7**, **10**, and **13**, 4-(methylamino)-1-benzylpiperidine (**16**), was prepared by reductive amination of 1-benzyl-4-piperidone

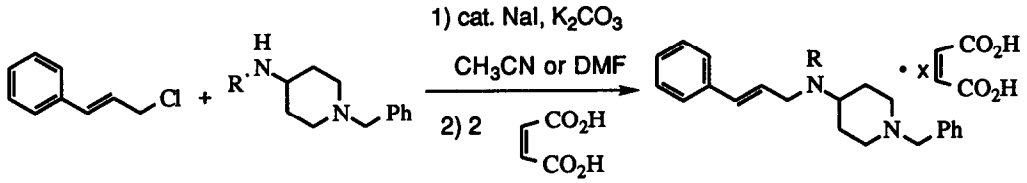
(Aldrich) with methylamine hydrochloride in the presence of zinc chloride and sodium cyanoborohydride in methanol according to the method of Kim et al.[9] The precursor to examples **4**, **8**, **11**, and **14**, 4-(anilino)-1-benzylpiperidine (**17**), was prepared by the known[10] two-step reductive amination procedure (imine formation followed by $NaBH_4$ reduction).

Examples **2** and **9** were synthesized from 1-benzyl-4-piperidone by the same Kim[9] reductive amination procedure as for **16**, using cinnamylamine and 3-phenylpropargylamine, respectively. These and all subsequent amine products were converted to the final salts by adding a THF solution of the appropriate number of equivalents of maleic acid to a chloroform solution of the amine, followed by dilution with diethyl ether to induce crystallization. The resulting salts were collected by filtration, and dried under high vacuum. Overall yields for all examples are given in the schemes.



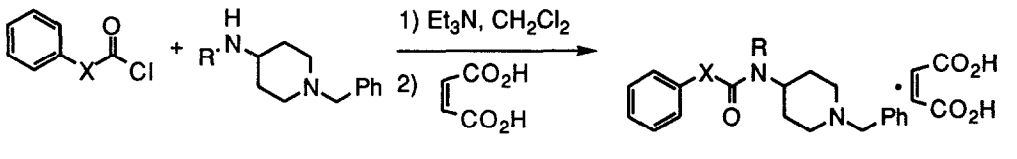
2	X =	trans CH=CH	46%
9		C≡C	69%

Examples **3** and **4** were prepared by alkylation of 4-aminopiperidines **16** and **17** with cinnamyl chloride in acetonitrile or DMF in the presence of K_2CO_3 and catalytic NaI. Bis-cinnamyl amine adduct **5** was prepared by double alkylation of **15** with cinnamyl chloride in acetonitrile as just described.



16	R = Me	**3**	R = Me	14%
17	Ph	**4**	Ph	18%
15	H	**5**	trans CH_2CH=CHPh	22%

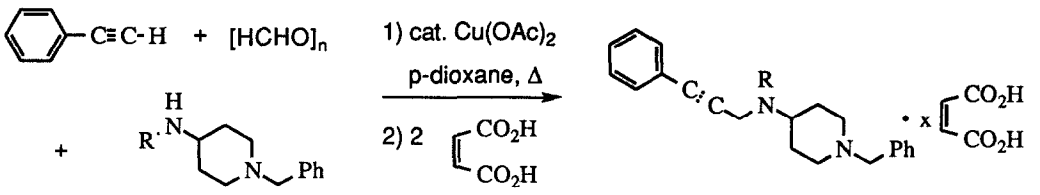
All the amide examples, **6-8** and **12-14** were prepared by reaction of cinnamoyl chloride or phenylpropionyl chloride with the appropriate 4-aminopiperidine in CH_2Cl_2 from 0 °C to 20 °C in the presence of a slight excess of Et_3N.



15-17

	X	R	
6	CH=CH	H	59%
7	CH=CH	Me	91%
8	CH=CH	Ph	93%
12	C≡C	H	66%
13	C≡C	Me	72%
14	C≡C	Ph	34%

Phenylpropargylamine examples **10** and **11** were synthesized under the Mannich condensation conditions reported by Brandsma,[11] wherein the secondary amine **16** or **17** was treated with phenylacetylene and paraformaldehyde in *p*-dioxane at reflux in the presence of catalytic $Cu(OAc)_2$.



16, 17

10	R = Me	93%
11	Ph	76%

It is readily apparent from the sigma binding results in the table that placing the distal aromatic rings in conjugation with double or triple bonds so as to impose more rigid, extended conformations yielded compounds

which possess very good to excellent affinities for the sigma receptor. The energetically allowed distances from the piperidine nitrogen to the centroid of the distal aromatic ring of these compounds has been determined using systematic search techniques.[12] All rotatable bonds were sampled at 30 degree increments and all conformers within 3kcal/mole of the lowest energy conformer were saved.[13] For Example **13**, the most rigid compound, the distance between the piperidine nitrogen and the distal aromatic ring centroid is constrained to 10.6Å. For Example **7**, containing an ethylene bridge, the distance between the piperidine nitrogen and the distal aromatic ring centroid can vary between 8.2Å and 10.6Å. Thus, for this series of conformationally restricted aromatic piperidines, the distance between the piperidine nitrogen and the distal aromatic ring centroid varies between 8.2Å and 10.6Å. This distance range is at the upper limit of the 6 ± 2Å range predicted in our initial model derived using flexible linkers. Taken together, the compounds with flexible and rigid linkers suggest optimum sigma binding is achieved if the piperidine nitrogen and the distal aromatic ring centroid is constrained to between 8.2Å and 10.6Å.

These new compounds all exhibit good to excellent selectivities for binding at the sigma receptor versus D_2 and 5-HT_2 receptors. The behavioral pharmacology of members of these series will be reported in due course.

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