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Structure-Activity Relationships of Substituted 2,3,4,4a,5,10b-Hexahydro-benz[h]isoquinoline-6(1H)-ones as 5-HT_{2C} Receptor Antagonists

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Abstract: A series of *cis* and *trans* configured 2,3,4,4a,5,10b-hexahydro-benz[h]isoquinoline-6(1H)-ones **2** were studied with respect to the binding affinity to the 5-HT_2 subtype receptors. The influence of substituents in positions 7 (R^1), 8 (R^2) and 9 (R^3) on affinity and selectivity to 5-HT_{2A} and 5-HT_{2C} receptors and the preference of one diastereoisomer is discussed.

Keywords: 5-HT_{2C} receptor antagonists · *O*-Methylasparvenone · Pharmaceutical chemistry · Serotonin · Stereoselective synthesis

Introduction

There is considerable interest in the development of 5-HT_{2C} receptor agonists for depression, obsessive-compulsive disorder and obesity as well as 5-HT_{2C} receptor antagonists for anxiety disorders, schizophrenia and Parkinson's disease [1–4]. In the course of our work on 5-HT_{2C} receptor ligands we have identified the high affinity antagonist **1** [5], which is based on the nitrogen-free lead structure *O*-methylasparvenone [6].

For SAR studies we evaluated the affinity of the parent ring system **2** (R^1 = R^2 = R^3 = H) [7] and were surprised to find higher affinity and selectivity for the 5-HT_{2C} receptor relative to the 5-HT_{2A} receptor for the *cis*-compound as opposed to the trisubstituted derivative **1**. The indolo-naphthyridin SDZ SER-082 (**3**), a 5-$HT_{2C/2B}$ receptor antagonist with low 5-HT_{2A} receptor affinity [8], resembles structure **2** with a tertiary aromatic amino group in place of a carbonyl group as a possible binding site. For this compound the Sandoz group reported the *cis*-isomer to be the selective compound with a pK_D (5-HT_{2C}) of 7.8.

This prompted us to study the influence of the different substituents at the phenyl ring of **1** on the affinity and selectivity of the diastereoisomers of **2**.

Chemistry

All compounds could be synthesized using the same general protocol described previously for **1** [5], which is summarized in Scheme 1.

The different substituted phenylacetic acids or esters used as starting materials were either commercially available (**4a, 4b, 4d**) or could be easily prepared (**4c**) by the method described by Ogura *et al.* [9] from 4-ethylbenzaldehyde. The synthesis has, however, some serious drawbacks when synthesizing larger amounts of the desired compounds. In the hydrogenation step (*e*) a mixture of *cis*- and *trans*-isomers was obtained with a ratio of 4:1 favoring the *cis*-isomer and in the cyclisation step (*f*) the 7-monosubstituted methoxy compounds **11** were only minor

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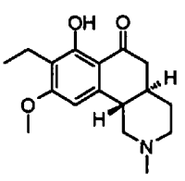

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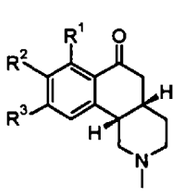

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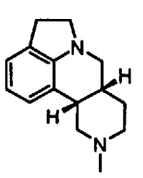

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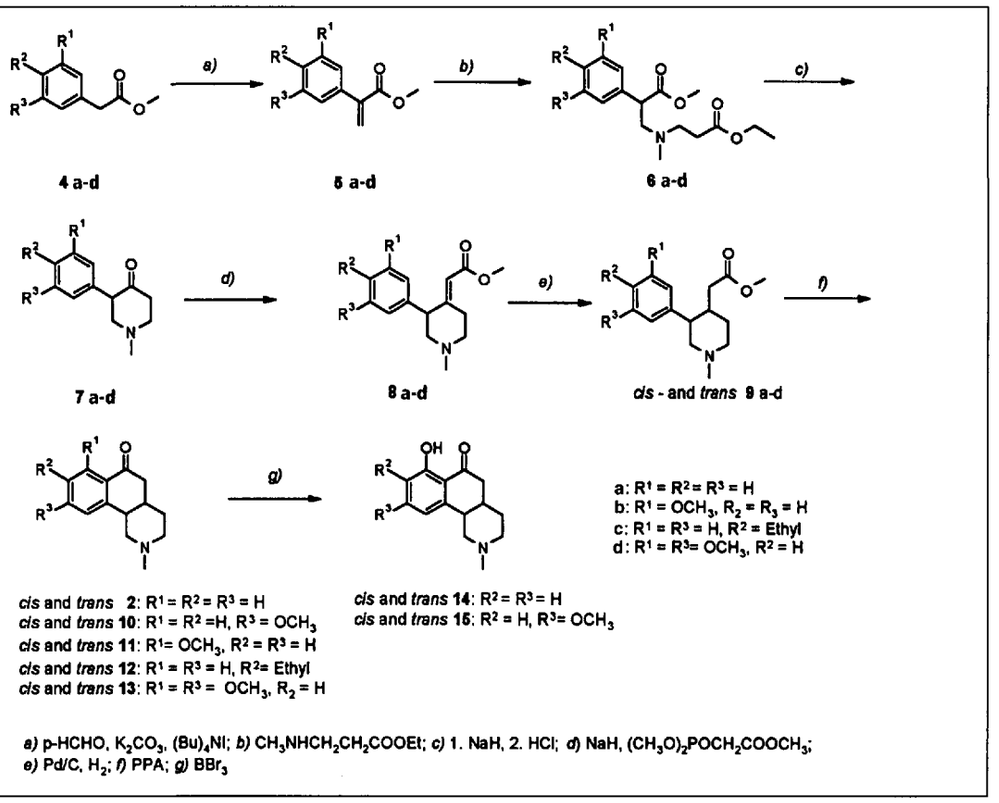
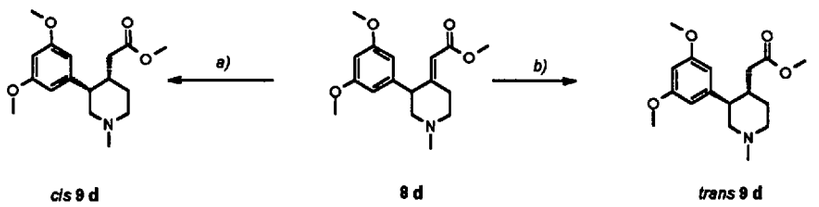
Scheme 1.



Scheme 2.



Scheme 3.

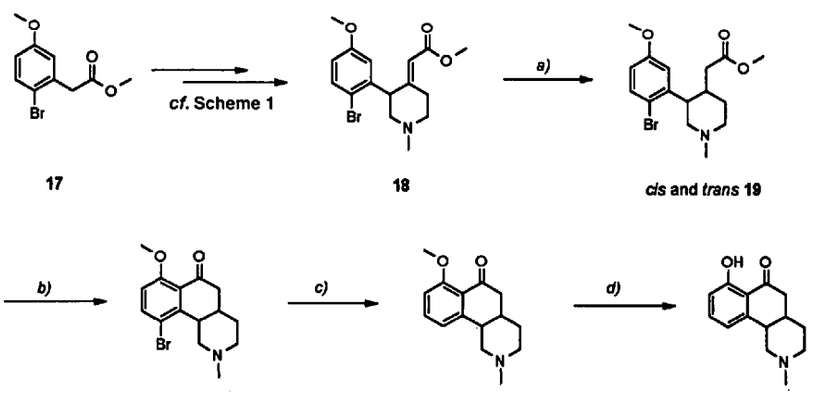


Table. Binding affinities (p*Ki*) for human 5-HT2 receptors

Entry	Compound	R^1	R^2	R^3	5-HT_{2C} (p*Ki*)	5-HT_{2A} (p*Ki*)	Selectivity (Δp*Ki*)
1	*trans*-**1**	OH	ethyl	OCH_3	8	6.9	1.1
2	*cis*-**1**	OH	ethyl	OCH_3	6.5	5.3	1.2
3	*trans*-**2**	H	H	H	6.8	5.6	1.2
4	*cis*-**2**	H	H	H	7.6	5.1	2.5
5	*trans*-**14**	OH	H	H	7.7	6.5	1.2
6	*cis*-**14**	OH	H	H	8.5	5.8	2.7
7	*trans*-**12**	H	ethyl	H	6.4	5.4	1.0
8	*cis*-**12**	H	ethyl	H	6.3	<5	>1.3
9	*trans*-**10**	H	H	OCH_3	6.8	<5	>1.8
10	*cis*-**10**	H	H	OCH_3	7.2	<5	>2.2
11	*trans*-**15**	OH	H	OCH_3	7.3	5.9	1.4
12	*cis*-**15**	OH	H	OCH_3	7.0	5.1	1.9

side products (less than 10%) and difficult to separate from their corresponding regioisomers **10**.

Consequently some modifications were necessary. To obtain the *cis*-isomers **9** only (*cf.* Scheme 2 for the preparation of *cis*- and *trans*-**9d**), the double bond in **8** was first isomerized with sodium methanolate in methanol and subsequently hydrogenated, whereas for the synthesis of the *trans*-isomers the double bond was reduced with magnesium in methanol [10], which yielded the *trans*-isomers (together with about 10–20% *cis*-isomer depending on the substitution pattern on the aromatic ring, Scheme 2).

The assignment of the stereochemistry is based on the coupling constants (two axial (J = 10 Hz each) couplings for the *trans* isomer) of the benzylic protons of compounds **9** as described in [5]. For the synthesis of the 7-monohydroxylated compounds **14**, position 2 of the aromatic ring was temporarily blocked by introducing a bromine atom in **4b** to give **17** as the starting material [11]. This directs the methoxy group in the cyclisation step exclusively into the desired peri-position. Cleavage of the methoxy group with BBr_3, followed by hydrogenation to remove the bromine atom yielded the desired compounds **14** in reasonable yields (Scheme 3).

Pharmacology

The affinity of the compounds for human 5-HT receptors was assessed using displacements of [^{3}H]-DOB (5-HT_{2A}) and [^{3}H]-5HT (5-HT_{2C}) [12]. In the phosphoinositol turnover model of 5-HT_{2C} receptor activation in the choroid plexus of the rat [6], the ligands behave as antagonists, displaying no intrinsic activity.

The binding data obtained for human 5-HT_2 receptors from these *in vitro* assays are displayed in the Table.

As already mentioned, it was found that for the parent ring system **2** the *cis*-diastereomer shows the higher affinity towards the 5-HT_{2C}-receptor than the corresponding *trans*-diastereomer by about a factor of 6, while also being the more selective one. Addition of a hydroxy group in position 7 increases the affinity 8-fold for both isomers, resulting in *cis*-**14** with high affinity (p*Ki* (5-HT_{2C}) = 8.5) and excellent selectivity (factor 400). The methoxy group in position 7 has a negative effect on the affinity for the 5-HT_{2C} receptor, which is more pronounced in the *cis*-series than in the *trans*-series, which can be seen by comparing *cis*- and *trans*-**2** with *cis*- and *trans*-**10** as well as *cis*- and *trans*-**14** with *cis*- and *trans*-**15**. The substituent which is responsible that *trans*-**1** has the higher affinity than *cis*-**2** is clearly the ethyl group in position 8. Whereas in the *cis*-series the ethyl group has a detrimental effect on the affinity (20-fold) (*cis*-**12** *vs.* *cis*-**2**), which is translated into the trisubstituted compound *cis*-**1** (p*Ki* = 6.5 (5-HT_{2C}), in the *trans*-series (*trans*-**12** vs. *trans*-**2**) the difference is only a factor of 2.5. However in contrast to the *cis*-series this difference not only is not translated to the trisubstituted compound *trans*-**1**, but now the addition of an ethyl group to *trans*-**15** increases the affinity giving rise to a compound with p*Ki* = 8 (5-HT_{2C}). The influence of the different substituents on the selectivity (5-HT_{2C} *vs.* 5-HT_{2A}) is less spectacular as the selectivity is more or less determined by the stereochemistry of the ring system, *cis* being in general more selective than *trans*, less pronounced for *cis*- and *trans*-**1**.

In summary we have studied the influence of different substituents, originated from *O*-methylasparvenone, on affinity and selectivity of the phenone **2**, leading to potent and selective 5-HT_{2C} receptor antagonists *trans*-**1** and *cis*-**14**.

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