Atropisomeric Derivatives of 2′,6′-Disubstituted (*R*)-11-Phenylaporphine: Selective Serotonin 5-HT$_7$ Receptor Antagonists

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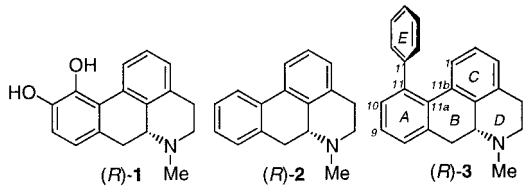
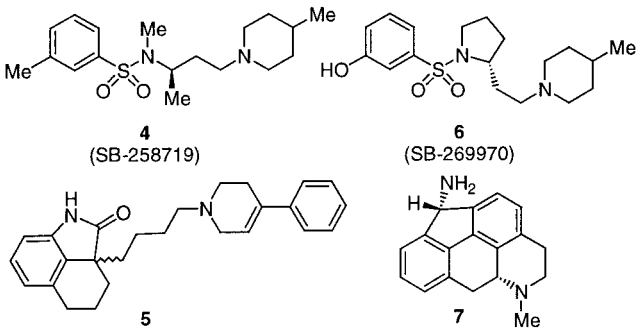
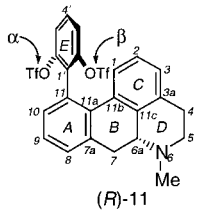
Introduction. The most well-known aporphine derivative, (*R*)-apomorphine [(*R*)-**1**], is a prototypic dopaminergic agonist.[1] In contrast, (*R*)-aporphine [(*R*)-**2**] itself is less potent as a dopamine (DA) receptor agonist and displays predominantly serotonergic activity.[2] Recently, we described that introduction of a C11-phenyl substituent in (*R*)-**2**, producing (*R*)-**3**, increases the affinity for serotonin 5-HT$_{1A}$ receptors more than 40-fold, thus leading to a potent 5-HT$_{1A}$ receptor ligand.[3] On expanded profiling of (*R*)-**3**, we observed that it also is a relatively potent 5-HT$_7$ receptor[4] ligand (Table 1).



No selective 5-HT$_7$ receptor agonists and only a few putatively selective antagonists, **4**−**7** (Table 1), have been reported to date.[5] The relatively high affinity of (*R*)-**3** for 5-HT$_7$ receptors provided an opportunity to derive potent and selective 5-HT$_7$ receptor ligands by structural modification of (*R*)-**3**. Therefore, we initiated a synthetic program targeting analogues of (*R*)-**3**. Initially, we focused on variations of the substitution pattern in the C11-phenyl ring. Herein, we describe the introduction of substituents in the ortho positions of the C11-phenyl group. The 2′-CN,6′-Me-substituted analogue (6a*R*,a*S*)-**14** is the most interesting of the novel derivatives as it is a potent 5-HT$_7$ receptor antagonist which exhibits selectivity versus 5-HT$_{1A}$ and D$_{2A}$ receptors. Furthermore, the stable atropisomers[6] (6a*R*,a*S*)- and (6a*R*,a*R*)-**14** display pharmacological stereoselectivity. This is one of the few instances in which stereoisomers with axial chirality have been demonstrated to interact in a stereoselective fashion with G-protein-coupled receptors.[7]



Chemistry. The key intermediate for the synthesis of the atropisomeric aporphine derivatives, ditriflate (*R*)-**11**, was prepared from the known triflate (*R*)-**8**[3] using the three-step sequence shown in Scheme 1. A Suzuki coupling reaction[8] of (*R*)-**8** and 2,6-dimethoxyphenylboronic acid gave (*R*)-**9**. Demethylation of (*R*)-**9** gave resorcinol (*R*)-**10**, which was treated with *N*-phenyltrifluoromethanesulfonimide to afford (*R*)-**11**.



Ditriflate (*R*)-**11** contains diastereotopic triflate groups (α and *β*, Scheme 2) and could therefore be utilized for stereoselective palladium-catalyzed coupling reactions. A cyano and a methyl substituent were stereoselectively introduced into the C11-aryl substituent of (*R*)-**11** yielding 90% and 60% de of (6a*R*,a*R*)-**12** and (6a*R*,a*R*)-**13**, respectively. In both reactions, 4−10% of the di-coupled product was also formed. The stereoselectivity obtained in these reactions is probably due to a preferred attack by a palladium species on the least sterically hindered triflate group; triflate α is positioned away from the aporphine skeleton, while triflate *β* is situated above it (for comparison, see the solid-state conformation of (6a*R*,a*R*)- and (6a*R*,a*S*)-**14** in Figure 1). Therefore, the conformation of (*R*)-**11** makes triflate α more accessible for attack by a palladium species. The pure monotriflates (6a*R*,a*R*)-**12** and (6a*R*,a*R*)-**13** were then converted into the atropisomeric (6a*R*,a*S*)- and (6a*R*,a*R*)-**14** by palladium-catalyzed methylation and cyanation, respectively. For these second coupling reactions stronger conditions were required. For example, introduction of the methyl group in (6a*R*,a*R*)-**12** required the more reactive and less sterically hindered tetramethylstannane instead of tributylmethylstannane and also a longer reaction time (5 h), compared with the methylation of (*R*)-**11** (40 min) vide supra. For the introduction of the cyano group in (6a*R*,a*R*)-**14** microwave heating was utilized in order to shorten the

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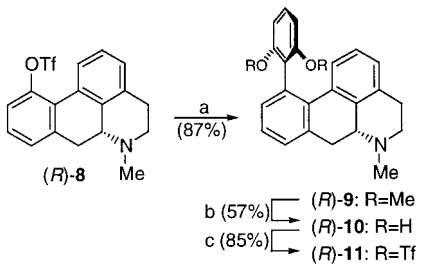
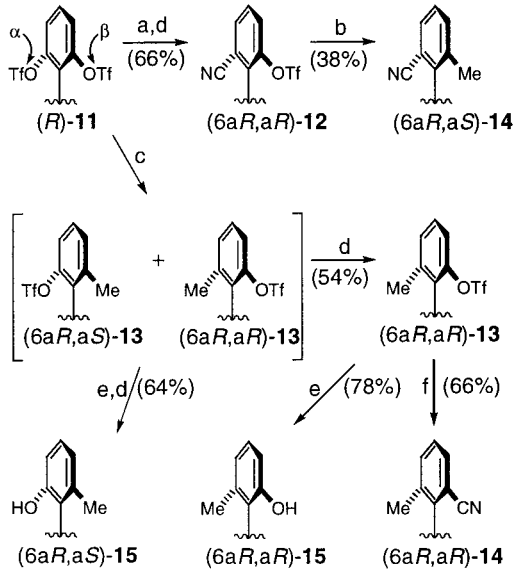
Scheme 1[a]



[a] Reagents: (a) $(Ph_3P)_4Pd$, 2,6-$(OMe)_2PhB(OH)_2$, K_2CO_3, DMF; (b) aq HBr (48%); (c) K_2CO_3, Et_3N, $(CF_3SO_2)_2NPh$, CH_2Cl_2.

Scheme 2[a]



[a] Reagents: (a) $(Ph_3P)_4Pd$, $Zn(CN)_2$, DMF; (b) $Pd(OAc)_2$, dppf, LiCl, Me_4Sn, DMF; (c) $Pd(OAc)_2$, dppf, $CoCl_3$, $MeSnBu_3$, DMF; (d) separation of isomers; (e) K_2CO_3, EtOH, H_2O; (f) $(dba)_3Pd_2$, dppf, $Zn(CN)_2$, DMF.

reaction time.[9] Hydrolysis of the triflate group in (6a*R*,a*R*)-**13** gave phenol (6a*R*,a*R*)-**15**. The isomeric phenol (6a*R*,a*S*)-**15** was obtained by hydrolysis of a mixture of (6a*R*,a*S*)- and (6a*R*,a*R*)-**13** (8:2)[10] followed by separation of the isomers.

The solid-state conformation and the relative axial stereochemistry of each of the atropisomers (6a*R*,a*R*)- and (6a*R*,a*S*)-**14** were established by single-crystal X-ray diffraction techniques.[11] Thermal ellipsoid plots of the solid-state conformations are shown in Figure 1. The torsion angle τ_1[C11a−C11−C1′−C2′] is −68.0(6)° and 119.6(5)° in (6a*R*,a*R*)- and (6a*R*,a*S*)-**14**, respectively, giving conclusive evidence for the relative axial configuration a*R* in (6a*R*,a*R*)-**14** and a*S* in (6a*R*,a*S*)-**14**. The relative stereochemistry of the other two atropisomers was unambiguously assigned by chemical correlation with the two epimers above.[12] The solid-state conformations of the two epimers are very similar and a best fit of all C and N atoms gave a root-mean-square (rms) value of 0.11 Å, the main deviation being observed in the C11-aryl group. We have previously shown that the torsion angle between the aromatic A- and C-rings, τ_2-[C11−C11a−C11b−C1], in a calculated idealized (*R*)-aporphine skeleton is approximately −24°.[5d] In (6a*R*,a*R*)- and (6a*R*,a*S*)-**14**, however, τ_2 is −28.7(7)° and −30.2(7)°, respectively. This widened angle probably results from the proximity in space of the C11-substituent and the (*R*)-aporphine skeleton.[13]

Since the presence of atropisomerism in the compounds described here is due to hindered rotation about the C11−C1′ bond, the stability[14] of two isomers toward isomerization was determined: although the neutral (6a*R*,a*S*)- and (6a*R*,a*R*)-**14** were left in H_2O (pH 7.4) at 100 °C and the corresponding hydrochloride salts were dissolved in DMSO and kept at 150 °C for 24 h, no isomerization was detected by HPLC, demonstrating that these atropisomers are stable toward isomerization at temperatures <100 °C for at least 24 h.

Biological Results and Discussion. The receptor affinities of the novel derivatives were evaluated in vitro at 5-HT_7, 5-HT_{1A}, and D_{2A} receptors, essentially as described before.[5d,15] Compounds (*R*)-**1**−**7** are included for comparative purposes. The efficacy of the atropisomers, (*R*)-**3**, (*R*)-**9**, and (*R*)-**10** at 5-HT_7 receptors was studied in CHO cells expressing rat 5-HT_7 receptors by measuring the cAMP formation with and/or without pretreatment with the endogenous ligand 5-HT. In this assay, the ability of a compound to fully or partially reverse the 5-HT-stimulated production of cAMP is a measurement of antagonism or partial agonism. The results are presented in Table 1.

The present and previous[3] results indicate that a C11-phenyl group is beneficial for the interaction of (*R*)-aporphines with both the 5-HT_{1A} and the 5-HT_7 receptor subtypes. The profile of these derivatives may, however, be modified by the introduction of symmetrically diortho-substituted C11-phenyl groups such as in (*R*)-**9** [$(OMe)_2$], (*R*)-**10** [$(OH)_2$], and (*R*)-**11** [$(OTf)_2$]. The affinities of these derivatives for D_{2A}, 5-HT_{1A}, and 5-HT_7 receptors were decreased with the largest decrease observed at 5-HT_{1A} receptors. This resulted in compounds with selectivity for the 5-HT_7 receptor, the dimethoxy derivative (*R*)-**9** being the most selective and also the most potent analogue. It displays a 42- and 156-fold selectivity for 5-HT_7 receptors versus 5-HT_{1A} and D_{2A} receptors, respectively. Also the introduction of unsymmetrical diortho-substituted phenyl groups gives compounds with selectivity for the 5-HT_7 receptor. Only one derivative, (6a*R*,a*S*)-**15**, showed moderate affinity for 5-HT_{1A} receptors while the other atropisomers were weaker. The atropisomer (6a*R*,a*S*)-**14**, substituted with a cyano and a methyl group, is the most potent and selective atropisomer displaying a K_i value of 3.79 nM at the 5-HT_7 receptors and 37- and 131-fold selectivity for 5-HT_7 versus 5-HT_{1A} and D_{2A} receptors, respectively. The atropisomeric (6a*R*,a*R*)-**14** showed the same selectivity for 5-HT_7 receptors as (6a*R*,a*S*)-**14** but was about 5 times less potent. This indicates that both a methyl and a cyano group are tolerated by the 5-HT_7 receptor although the receptor−ligand interaction appears more optimal for (6a*R*,a*S*)-**14** than for (6a*R*,a*R*)-**14**. Atropisomers (6a*R*,a*R*)- and (6a*R*,a*S*)-**15**, being substituted with a methyl and a hydroxy group, are less selective and/or less potent at 5-HT_7 receptors as compared to (6a*R*,a*S*)- and (6a*R*,a*R*)-**14**.

The high affinity and the preference for 5-HT_7 receptors of the novel derivatives are of interest since only a few antagonists (**4**−**7**) with putative selectivity for 5-HT_7 have been reported.[5] Therefore, we decided to further characterize the pharmacology of the novel compounds;

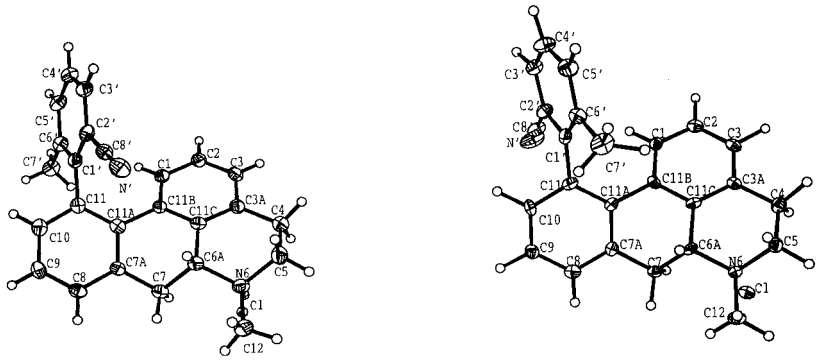
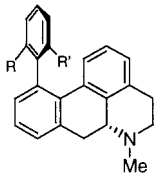


Figure 1. Perspective view (ORTEP) of the solid-state molecules of (6a*R*,a*R*)-**14**·HCl (left) and (6a*R*,a*S*)-**14**·HCl (right). Displacement ellipsoids are represented at the 40% probability level.

Table 1. Effects of the Novel Derivatives on 5-HT_7-Mediated Stimulation of cAMP Production in CHO Cells Expressing Rat 5-HT_7 Receptors and In Vitro Binding Affinities to 5-HT_7, 5-HT_{1A} and D_{2A} Receptors Labeled by [^{3}H]5-HT, [^{3}H]8-OH-DPAT, and [^{3}H]Raclopride



			cAMP production				K_i (nM)[a]		
			% stimulation		% inhib of 5-HT-induced stimulation				
compd	R	R′	concn (nM)	%[b]	concn (nM)	%[b]	[^{3}H]5-HT (5-HT_7)	[^{3}H]8-OH-DPAT (5-HT_{1A})	[^{3}H]Raclopride (D_{2A})
(*R*)-**1**			NT[c]		NT		188 ± 17[d]	296 ± 1[e,f]	41.9 ± 4.7[f]
(*R*)-**2**			NT		NT		88.0 ± 3.7[d]	80.0 ± 2.3[e,f]	527 ± 296[f]
(*R*)-**9**	OMe	OMe	*g*	NA[h]	NT		13.0 ± 0.15	554 ± 58	2030 ± 345
(*R*)-**10**	OH	OH	*g*	NA	NT		36.2 ± 12	139 ± 3.2	>1000
(*R*)-**11**	OTf	OTf	NT		NT		708 ± 282	>10000	2260 ± 660
(*R*)-**3**	H	H	*i*	NA	1	23 ± 5	9.78 ± 0.82	1.8 ± 0.4[e,f]	233 ± 3[f]
					100	30 ± 4			
					10000	100			
(6a*R*,a*R*)-**14**	Me	CN	*i*	NA	1	21 ± 0	20.8 ± 2.1	778 ± 105	2470 ± 220
					100	42 ± 1			
					10000	100			
(6a*R*,a*S*)-**14**	CN	Me	*i*	NA	1	33 ± 3	3.79 ± 0.99	142 ± 24	498 ± 98
					100	97 ± 3			
					10000	100			
(6a*R*,a*R*)-**15**	Me	OH	*i*	NA	1	21 ± 5	43.1 ± 10	319 ± 54	3380 ± 300
					100	43 ± 5			
					10000	100			
(6a*R*,a*S*)-**15**	OH	Me	*i*	NA	1	11 ± 1	23.0 ± 3.4	48.8 ± 8.4	2500 ± 390
					100	72 ± 0			
					10000	100			
4[j]							31.6	>7943	3981
5[k]							3.31	170	105
6[l]							1.26	>10000	316
7[m]							18.0 ± 1.2	355 ± 32	2250 ± 550

[a] The K_i values are means ± standard errors of 2−4 experiments. [b]All values are given as percent of the stimulation produced by 100 nM 5-HT. The EC_{50} value for 5-HT is 4.1 ± 0.7 nM. The stimulation produced by 5-HT at 100 nM is 95 ± 5% of that at 1 μM. [c]NT = not tested. [d]From ref 5d. [e]Data obtained from competition experiments with rat brain 5-HT_{1A} receptor recognition sites. [f]From ref 3. [g]The concentrations tested were 10, 100, and 1000 nM. [h]NA = no activity. [i]The concentrations tested were 1, 10, 100, 1000, and 10000 nM. [j]From ref 5a. [k]From ref 5b. [l]From ref 5c. [m]From ref 5d.

the four atropisomers and (*R*)-**3**, (*R*)-**9**, and (*R*)-**10** were tested in a functional assay in order to determine their efficacy at 5-HT_7 receptors. None of the analogues were able to stimulate the cAMP production in CHO cells transfected with rat 5-HT_7 receptors, and thus, none of the tested compounds appear to be able to stimulate 5-HT_7 receptors. The atropisomers and (*R*)-**3** dose-dependently inhibited the 5-HT-stimulated cAMP production and therefore behaved as 5-HT_7 receptor antagonists. In agreement with results from the binding studies, (6a*R*,a*S*)-**14** was the most potent antagonist. The pharmacological profiles of these novel derivatives make them interesting as structural leads for future medicinal chemistry efforts aiming at highly selective 5-HT_7 receptor ligands. Preliminary results of (*R*)-11-(2,6-dimethylphenyl)aporphine and (*R*)-11-(2,6-dicyanophenyl)aporphine indicate that also these derivatives display potency and/or selectivity for 5-HT_7 receptors.[16]

In conclusion, we have prepared stable atropisomeric biaryl derivatives of (*R*)-aporphine. These structurally well-characterized derivatives interact in a stereoselective fashion with 5-HT_7, 5-HT_{1A}, and D_{2A} receptors.

The novel derivatives show a preference for the 5-HT_7 receptor subtype and have been characterized as 5-HT_7 receptor antagonists. (6a*R*,a*S*)-**14** is a particularly selective and potent 5-HT_7 receptor antagonist. This will make it useful as a pharmacological tool in 5-HT research.

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, and anisotropic displacement parameters for (6a*R*,a*R*)- and (6a*R*,a*S*)-**14**·HCl; experimental, physical, and spectroscopic data for (6a*R*,a*R*)- and (6a*R*,a*S*)-**14**·HCl and (6a*R*,a*R*)- and (6a*R*,a*S*)-**15**·HCl; and experimental details for the pharmacological evaluation and the single-crystal X-ray diffraction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Microwave heating was carried out with a MicroWell 10 single-mode microwave cavity from Labwell AB, Uppsala, Sweden.

(10) The 8:2 mixture of (6a*R*,a*S*)- and (6a*R*,a*R*)-**13** was a residue from the reaction mixture that was purified to give pure (6a*R*,a*R*)-**13**.

(11) The following programs have been used: (a) SHELXS: Sheldrick, G. M. Phase annealing in *SHELX*-90: direct methods for larger structures. *Acta Crystallogr., Sect. A46* **1990**, 467−473. (b) SHELXL-93: Sheldrick, G. M. *SHELXL-93, Program for the Refinement of Crystal Structures;* University of Göttingen: Germany, 1993. (c) PLATON-92: Spek, A. L. *PLATON-92, Program for the Analysis of Molecular Geometry;* University of Utrecht: Utrecht, The Netherlands, 1992.

(12) The ^{1}H NMR chemical shift of the aromatic methyl group in epimers **13**−**15** could also be utilized for determination of the relative axial stereochemistry. For derivatives (6a*R*,a*S*)-**13**, (6a*R*,a*S*)-**14**, and (6a*R*,a*S*)-**15** a consistent upfield shift of the methyl protons was observed. This effect is most probably due to the induced field of the aromatic C-ring system, which causes the aromatic methyl group, positioned close in space to the C-ring, to be shifted upfield.

(13) Moreover, this sterical interaction is also likely to be the cause of an unusual deviation in the C11−C1′ bond. The carbon atom C1′ in (6a*R*,a*R*)- and (6a*R*,a*S*)-**14** is located 0.231(8) and 0.252(7) Å, respectively, out of a least-squares plane containing C7a, C8, C9, C10, C11, and C11a. In addition, the C11−C1′ bond deviates out of the aromatic plane of the A-ring, the torsion angles τ_3(C9−C10−C11−C1′) and τ_4(C7a−C11a−C11−C1′) in (6a*R*,a*R*)-**14** being −172° and 169°, respectively, and in (6a*R*,a*S*)-**14** they are $\tau_3 = -171°$ and $\tau_4 = 168°$. In (6a*R*,a*S*)-**14**, which has the slightly larger distortion, the bulky methyl group is positioned close to the aporphine skeleton, while (6a*R*,a*R*)-**14** has a cyano group in the equivalent position. This supports the idea of sterical interactions being the main factors causing the described changes in the solid-state conformations of these atropisomeric (*R*)-aporphines. Minimization (MM3)[17] of the two solid-state conformations in their nonprotonated form resulted in conformations in which the deviation of the C11−C1′ bond is smaller and the torsion angle between the A- and C-rings (τ_2) is slightly larger than in the solid-state conformations. Ab initio minimizations at the RHF/6-31G* level[18] of the solid-state conformation of (6a*R*,a*R*)- and (6a*R*,a*S*)-**14** gave similar C11−C1′ bond and torsion angles as found in the MM3 calculated conformations. Hence, the larger deviations of the C11−C1′ bond and the smaller τ_2 values observed in the solid-state conformations might be effects due to crystal packing.

(14) For stability of atropisomers, see for example: Eliel, E. L.; Wilen, S. H. *Stereochemisty of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1119−1190.

(15) (a) Malmberg, Å.; Jackson, D. M.; Eriksson, A.; Mohell, N. Unique Binding Characteristics of Antipsycotic Agents Interacting with Human Dopamine D_{2a}, D_{2b} and D_3 Receptors. *Mol. Pharmacol.* **1993**, *43*, 749−754. (b) Jackson, D. M.; Mohell, N.; Georgiev, J.; Bengtsson, A.; Larsson, L.-G.; Magnusson, O.; Ross, S. B. Time-Course of Bromocriptine Induced Excitation in the Rat: Behavioral and Biochemical Studies. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1995**, *351*, 146−155.

(16) Linnanen, T.; Nordvall, G.; Mohell, N.; Leonova, I.; Johansson, A. M. Studies of Selective Serotonergic Derivatives of (*R*)-11-Phenylaporphine. Manuscript in preparation.

(17) MacroModel, version 5.5. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. Macromodel − An Integrated Software System For Modeling Organic and Bioorganic Molecules Using Molecular Mechanics. *J. Comput. Chem.* **1990**, *11*, 440−467.

(18) SPARTAN 5.0.3; Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612; www.wavefun.com.

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