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NOVEL 4,5,6,7-TETRAHYDROBENZOTHIAZOLE DOPAMINE AGONISTS DISPLAY VERY LOW STEREOSELECTIVITY IN THEIR INTERACTION WITH DOPAMINE RECEPTORS.

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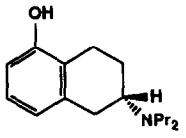
Abstract. The synthesis and resolution of 4,5,6,7-tetrahydro-6-[4-(2-pyridinyl)-1-piperazinyl]-2-benzothiazolamine (**7**), a centrally active dopamine (DA) agonist, are described. Unlike the structurally related 2-aminotetralins, both enantiomers of this compound possess comparable dopaminergic efficacy.

Although the neurotransmitter dopamine (DA) contains no elements of chirality, the majority of the compounds known to mimic DA possess at least one asymmetric center. The interaction of these compounds with DA receptors is highly stereospecific.[1] In most cases their DA agonist activity resides primarily in one enantiomer while the other one may be inactive, a weaker partial DA agonist, or even a DA antagonist. To the best of our knowledge, there have been no reports of a pair of enantiomers with almost identical ability to activate DA receptors. We describe here such a pair of compounds.

Hydroxylated aminotetralins (e.g. **1**)[2] constitute one of the simplest types of DA agonists. Recently, the 2-aminothiazole ring system has been introduced as a bioisosteric replacement for the catechol ring, leading to compounds such as **2**.[3] In both cases, dopaminergic activity resides mainly in the **S** enantiomer. Since it is well established that changes in the amine moiety dramatically affect the biological activity of these compounds, and having identified the 4-(2-pyridinyl)piperazine group as optimal for DA agonist activity in a different series,[4] compound **7** was designed as a potential DA agonist.



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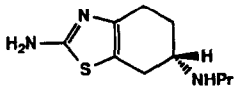
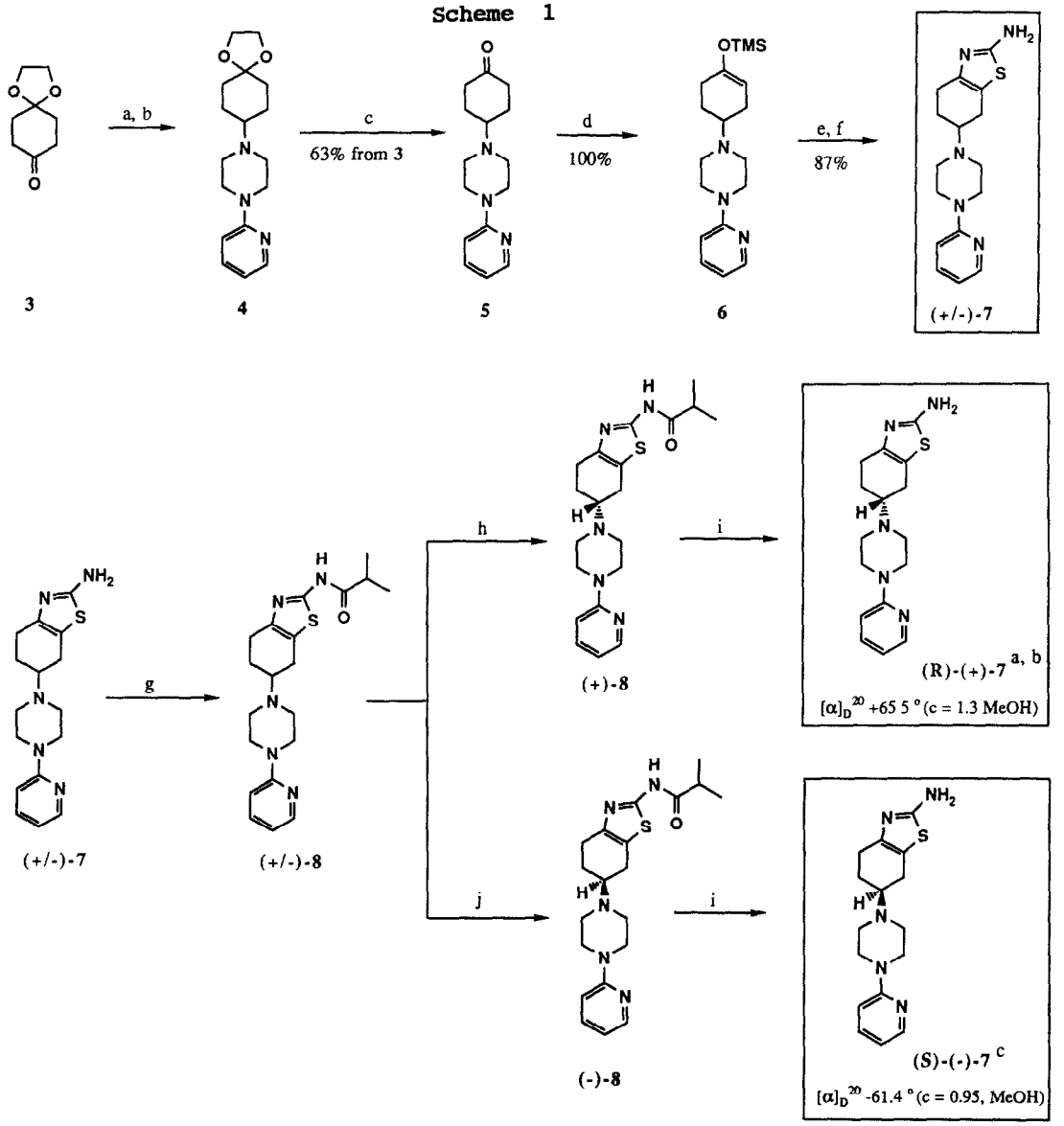


2

The synthesis of racemic **7** is outlined in Scheme 1. Ketone **5** was synthesized in 63% yield from **3**. Although more direct methods for the incorporation of the aminothiazole ring were explored, the most efficient route involved the synthesis of silyl enol ether **6**, in quantitative yield, followed by an extremely mild bromination of **6** with NBS in THF, and in situ reaction of the intermediate bromoketone with thiourea. The desired aminothiazole (+/-)-**7** was obtained in 87% yield. The direct resolution of (+/-)-**7** with optically active acids was unsuccessful. However,

Scheme 1



Reagents: (a) 1-(2-Pyridyl)piperazine, pTsOH, benzene [Dean-Stark]; (b) $NaCNBH_3$, HCl, MeOH; (c) 10% HCl, acetone; (d) $^iPr_2NLi$, TMSCl, THF, -78 °C; (e) NBS, THF, 0 °C; (f) Thiourea, THF, reflux; (g) $(Me_2CHCO)_2O$, $Me_2CHCOONa$, 100 °C; (h) (+)-di-p-toluoyl-D-tartaric acid, (EtOH, 2X); (i) 10% HCl, reflux; (j) (-)-di-p-toluoyl-L-tartaric acid, (EtOH, 2X).

Footnotes: (a) HPLC analysis on a Chiracel OD column (mobile phase: hexane:^{i}PrOH:Et_2NH, 80:20:0.1) showed this sample to contain 2.1% of the (-)-isomer; (b) Stereochemical assignments were based on experiments that showed that enantioselective deprotonation of prochiral ketone **5** with the lithium amide derived from (*S*)-(-)-N-isopropyl-α-methylbenzylamine gave enriched (+)-**6**, which was converted into enriched (+)-7 (50% ee). Based on Koga's work with 4-substituted cyclohexanones (*J. Am. Chem. Soc.* **1989**, *108*, 543), we have assigned the (R)-configuration to (+)-7; (c) Chiral HPLC (see footnote a) showed this product to contain 0.7% of the (+)-isomer.

once the basicity of the aminothiazole was diminished by conversion into its isobutyramide, (+/-)-**8**, optically pure materials could be obtained after only two recrystallizations of its (+)- or (-)-ditoluoyltartaric acid salts from ethanol. Acid hydrolysis of (+)-**8** and (-)-**8** yielded (R)-(+)-**7** and (S)-(-)-**7**, respectively.

The affinity of these compounds for DA D_2 receptors in rat striatal membranes was determined in vitro with the DA antagonist [^{3}H]spiperone[5] and the DA agonist [^{3}H]N-propylnorapomorphine[6] as ligands. DA D_1 binding was determined using the D_1 antagonist [^{3}H]SCH23390 as ligand.[7] Two in vivo mechanistic tests were used to assess the dopaminergic activity of the compounds. In the first one, the reversal of the gamma-butyrolactone (GBL)-induced increase in the rate of L-dihydroxyphenylalanine (DOPA) synthesis in rat corpus striatum was used as an indirect measure of the ability of DA agonists to inhibit DA synthesis in this DA rich brain area.[8] In the second one, inhibition of spontaneous DA neuronal firing in the substantia nigra of anesthetized rats was used as a direct indicator of DA agonist activity.[9]

TABLE 1. Pharmacological Evaluation of Dopamine Agonists.

Compd	[^{3}H]Spip[a] IC_{50},[b] nM	[^{3}H]NPA[c] IC_{50},[b] nM	[^{3}H]SCH23390 IC_{50}, nM	Inh DOPA Synthesis,[d] ED_{50}, mg/kg ip	% Inh DA Neuron Firing[e]
(+/-)-**7**	320 (124-550)	100 (80-119)	> 15,000	4.4	97 ± 2
(+)-**7**	440 (270-500)	105 (70-150)	> 15,000	7.0	85 ± 6
(-)-**7**	800 (580-1050)	280 (204-360)	> 15,000	4.8	100 ± 0
APO[f]	24.1 (20-29)	1.7 (1.4-1.9)	384 ± 8	(100% @ 2 mg/kg)	100 ± 0[g]
(-)-**2**[h]	4700	---	---	(53% @ 1 mg/kg)	---

[a]Spip = Spiperone. [b]95% confidence limits in parentheses. [c]NPA = N-propylnorapomorphine. [d]Shown are the percent reversal of the increase in rat striatum DOPA accumulation produced by pretreatment with GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg). Endogenous levels of DA were not affected by the test compounds. [e]At 2.5 mg/kg ip. [f]APO = Apomorphine. [g]At 0.25 mg/kg ip. [h]Data taken fron Ref 3.

As shown in Table 1, the profiles of (+)-**7** and (-)-**7** are quite similar. Both compounds selectively bind to D_2 vs. D_1 DA receptors and, as expected of D_2 agonists, their affinity for DA receptors is greater for displacing NPA than spiperone.[4] The mechanistic tests clearly verify that both compounds are D_2 agonists. Shown in Figure 1 is the dose-related reversal of DOPA accumulation produced by these compounds. Even though (+)-**7** exhibits a slightly higher affinity than (-)-**7** for D_2 receptors, both compounds have the ability to inhibit brain DA synthesis and DA neuron firing in the same dose range. In sharp contrast to this, (R)-**1** and (R)-**2** are reported to possess almost no dopaminergic activity.[2,3] Thus, the finding of dopaminergic activity in both enantiomers of **7** is indeed an unexpected one.

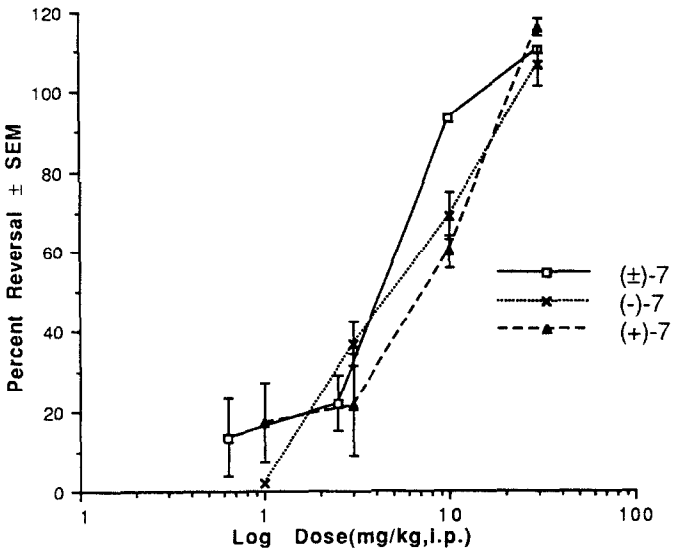


Figure 1. Reversal of the GBL-induced increase in DOPA synthesis (n = 4-8 per dose group).

Our results suggest that one or both enantiomers of **7** bind to the D_2 receptor at a site different from the one that recognizes DA agonists like (S)-**1** and (S)-**2** (the "DA site"). We have postulated the existence of an "arylpiperazine" binding site on the D_2 receptor.[4] If such a site exists, the lack of stereoselectivity displayed by (+)-**7** and (-)-**7** suggests that its stereochemical requirements are quite different from those of the "DA site". Additional asymmetric DA agonists containing the arylpiperazine moiety are needed to further explore this possibility, and this will be the subject of future publications.

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