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SYNTHESIS AND DOPAMINERGIC ACTIVITY OF THE ENANTIOMERS OF 6-METHYL-4,5,5a,6,7,8-HEXAHYDROTHIAZOLO[4,5-f]QUINOLIN-2-AMINE (PD 128483).

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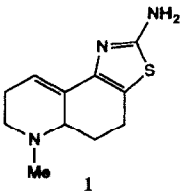
Abstract. The enantiomers of the dopamine (DA) agonist PD 128483 (1) have been synthesized and characterized biochemically (D_1, D_2 receptor binding, effects on rat brain DA synthesis), electrophysiologically (inhibition of DA neuron firing) and behaviorally (effects on rat exploratory locomotor activity). While R-(+)-1 is a potent D_2 agonist that stimulates both pre- and postsynaptic DA receptors, S-(-)-1 is a weak partial DA agonist able to stimulate only the more sensitive presynaptic DA receptors (DA autoreceptors).

Dopamine (DA) agonists hold promise for the treatment of a number of pathological conditions. DA D_2 receptors in the anterior pituitary gland inhibit prolactin secretion; because of this, D_2 agonists are effective therapy for conditions associated with hyperprolactinaemia, such as unwanted puerperal lactation, galactorrhea, and some cases of amenorrhea, anovular infertility, and impotence.[1] Prolactinomas, although a cause of hyperprolactinaemia rather than a consequence of it, can be shrunk by D_2 agonists with remarkable speed.[2] Acromegaly, which results from an excessive secretion of growth hormone from the pituitary, can also be treated successfully with D_2 agonists.[3] In the brain, dopamine has been postulated to play a central role in modulating thought and motor processes, based on the termination of dopaminergic pathways in cortical and subcortical brain regions.[4] Thus, stimulation of striatal D_2 receptors provides well-documented symptomatic relief to Parkinson's disease patients.[5] The potential use of selective DA autoreceptor agonists in the treatment of schizophrenia is currently one of the more interesting hypotheses in psychiatry.[6]

Three main requirements for clinically useful psychotherapeutic DA agonists are: (1) good CNS penetration, (2) acceptable oral activity, and (3) a reasonable duration of action. Even though most DA agonists meet the first requirement, many of these compounds do not satisfy the last two, usually due to their phenolic character, which leads to large first-pass effects and short in vivo half-lives.[7] Our research group has been interested for some time in the design of CNS-active DA agonists, with special interest in selective DA autoreceptor agonists. PD 128483 (1),

a racemic compound, has been described by us as an orally active D_2 agonist with selective activity at presynaptic DA autoreceptors and potent behavioral efficacy in rodent and primate preclinical tests predictive of antipsychotic activity.[8] The N-propyl analogue of PD 128483 (**2**) has also been described recently.[9] The R-(+)-enantiomer of **2** is a DA agonist that stimulates both pre- and postsynaptic D_2 receptors, while the S-(-)-enantiomer is a weak partial DA agonist with weak presynaptic activity. This paper describes the synthesis of the enantiomers of PD 128483 and their evaluation as dopaminergic agents.



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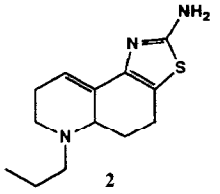

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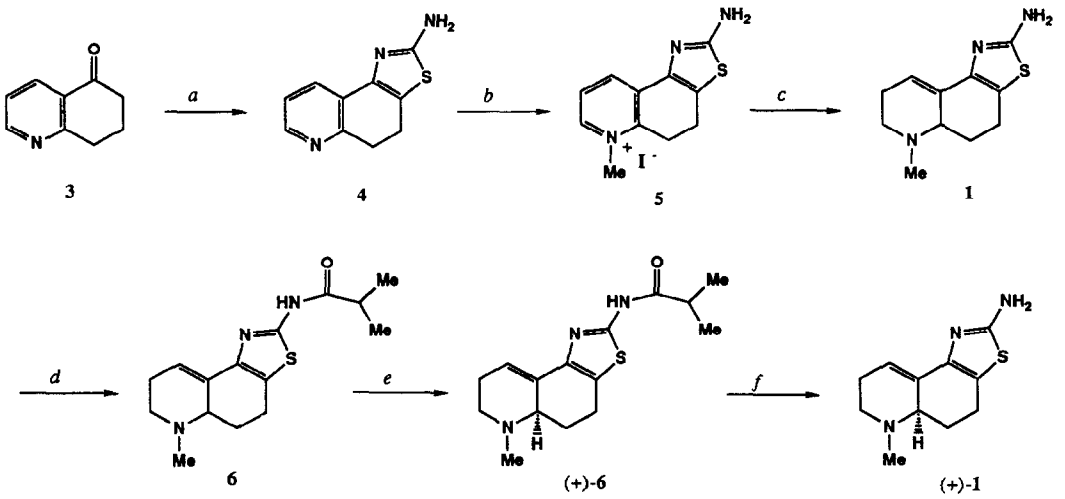
As outlined in Scheme 1, methylation of **4**[9,10] to give pyridinium salt **5**[10], followed by $NaBH_4$ reduction provided racemic **1** in good overall yield. All attempts to resolve **1** directly via diastereomeric salt formation with chiral acids failed to provide optically enriched material. It was postulated that decreasing the basicity of the aminothiazole moiety by converting the free amine group into an amide would help in maximizing the interaction of the chiral acid with the tetrahydropyridine nitrogen. A number of amides were prepared, and it was found that resolution of isobutyramide **6** with either (+)- or (-)-ditoluoyltartaric acid readily provided (-)- and (+)-**6**, respectively, in about 98% ee (determined by chiral HPLC). Acid hydrolysis of (-)- and (+)-**6** provided (-)- and (+)-**1**, respectively. The absolute stereochemistry shown in Scheme 1 was derived from single crystal X-ray diffraction experiments performed on the (S)-mandelate salt of (-)-**1**.

The affinity of these compounds for D_1 and D_2 receptors in rat striatal membranes was determined in vitro using the D_1 antagonist [^{3}H]SCH23390 and the D_2 antagonist [^{3}H]spiperone, respectively, as ligands. Binding experiments were also performed with the D_1/D_2 agonist [^{3}H]N-propylnorapomorphine. Activation of D_2 autoreceptors on the soma of substantia nigra DA neurons (as well as other brain dopaminergic projections) is known to inhibit the spontaneous firing of these neurons.[11] The synthesis of DA in mesolimbic and nigrostriatal DA neurons is also under the inhibitory control of D_2 autoreceptors.[12] Thus, inhibition of the spontaneous firing of substantia nigra DA neurons in anesthetized rats and reversal of the gamma-butyrolactone (GBL)-induced increase in the rate of L-dihydroxyphenylalanine (DOPA) synthesis in rat corpus striatum were used as neurophysiological and neurochemical indices of DA autoreceptor agonist efficacy, respectively. In the latter test, the use of GBL blocks neuronal activity, thus isolating the presynaptic terminals from any postsynaptic influences via feed-back loops. Having established the ability of compounds to stimulate presynaptic DA receptors, the relative selectivity of compounds for pre- vs. postsynaptic DA receptors was assessed through their

effects on rat exploratory locomotor activity. Selective activation of DA autoreceptors results in the inhibition of locomotor activity, while postsynaptic DA stimulation increases exploratory locomotor behavior.[14]

Scheme 1



(a) i. Br_2, 48% HBr; 88%. ii. Thiourea, water; 63%. (b) MeI, CH_3CN; 80%. (c) $NaBH_4$, MeOH, H_2O; 69%. (d) $(^iPrCO)_2O$, $^iPrCOONa$; 91%. (e) (-)-Ditoluoyl-L-tartaric acid, EtOH; 55%. (f) 10%HCl, reflux; 94%.

TABLE 1. Pharmacological Evaluation of Dopamine Agonists.

Compd	[^{3}H]SPIP[a] IC_{50}, nM	[^{3}H]NPA[b] IC_{50}, nM	[^{3}H]SCH23390 IC_{50}, nM	Inh DOPA Synthesis, ED_{50}[c]	% Inh DA Neuron Firing[d]
(+)-1	376	127 ± 19	> 20,000	0.5	99 ± 1
(-)-1	768	464 ± 57	> 20,000	>10	67 ± 9
(+)-2	860	138 ± 29	> 15,000	4.8	91 ± 6
(-)-2	2243	295 ± 21	> 15,000	>10	22 ± 8
APO[e]	24.1	1.7 ± 0.2	384 ± 8	(100%)[f]	100 ± 0[g]

[a]SPIP = Spiperone; Assays were performed in duplicate. [b]NPA = N-propylnorapomorphine; Assays were performed in triplicate. [c]Shown is the ED_{50} (mg/kg ip) for reversal of the increase in rat striatum DOPA accumulation produced by pretreatment with GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip). Endogenous levels of DA were not affected by the test compounds. [d]At 2.5 mg/kg ip. [e]APO = Apomorphine. [f]At 2.0 mg/kg ip. [g]At 0.25 mg/kg ip.

As can be seen in Table 1, (+)-1 and (-)-1 selectively bind to the D_2 receptor with no detectable affinity for the D_1 receptor. While (+)-1 is extremely potent in reversing the GBL-induced DOPA accumulation in rat striatum (ED_{50} = 0.5 mg/kg ip) and completely inhibits DA neuronal firing, (-)-1 is relatively weak in the GBL test, up to the highest dose tested (38% inhibition at 10 mg/kg ip), and is only partially able to inhibit DA neuronal firing. These results suggest that while (+)-1 is an efficacious agonist at DA autoreceptors, (-)-1 is unable to efficiently stimulate these receptors. A similar situation was described for the enantiomers of **2**.[9] A comparison between the enantiomers of these two compounds (see Table 1) reveals that while (+)-1 and (+)-**2** possess similar affinities for D_2 receptors, (+)-1 is about ten times more potent in vivo (GBL test). This difference suggests that (+)-1 has greater intrinsic activity at DA autoreceptors than (+)-**2**. Alternatively, different pharmacokinetic profiles of (+)-1 and (+)-**2** may account for this difference in potency.

Figure 1 illustrates the effects of (+)-1 and (-)-1 on exploratory locomotor activity in rats. At doses ranging from 0.1 to 1.0 mg/kg po, (+)-1 produced a dose-dependent inhibition of locomotor activity. Between 1.0 and 10 mg/kg, a pronounced dose-related stimulation of locomotor activity was observed. This biphasic profile is characteristic of DA agonists that selectively stimulate DA autoreceptors at low doses and activate both pre- and postsynaptic DA receptors at higher doses.[14] In comparison, (-)-1 produced only inhibition of locomotor activity over a similar dose range. This would imply that the weak DA agonist activity of (-)-1 is not sufficient to stimulate postsynaptic DA receptors.

In spite of the identification of at least six distinct molecular subtypes of mammalian CNS DA receptors (D_1, D_{2long}, D_{2short}, D_3, D_4, and D_5), none of these has been characterized as being exclusively localized on intrinsic DA neurons. Thus, there is presently no evidence to suggest that DA D_2 autoreceptors differ from postsynaptic D_2 receptors at the molecular level. Instead, current thinking holds that pre- and postsynaptic D_2 receptors represent the same molecular entity with different levels of sensitivity.[15] It has been hypothesized that DA autoreceptors may not be localized in the immediate vicinity of the DA synapse; thus, they may normally be exposed to a much smaller dopaminergic tone than postsynaptic DA receptors, which must be localized near the synaptic connection in order to fulfill their signal-sensing role. This lesser exposure of DA autoreceptors to DA may make these receptors more sensitive to dopaminergic activation than postsynaptic DA receptors.[15] Another way of rationalizing the increased sensitivity of DA autoreceptors is based on receptor reserve. DA neurons are thought to possess large numbers of spare autoreceptors that allow even partial DA agonists to produce a maximal response.[16] In contrast, the presumably low percentage of spare postsynaptic DA receptors requires agonists with greater intrinsic efficacy for a full response. Thus, agents with low intrinsic efficacy, such as (-)-3-PPP, can activate presynaptic DA receptors but appear as antagonists at postsynaptic DA receptors.[17]

In light of this, it will be of particular interest to study in more detail the intrinsic efficacy of (+)-1 and (-)-1 at D_2 receptors and how it correlates with pre- and postsynaptic D_2 receptor stimulation in vivo.

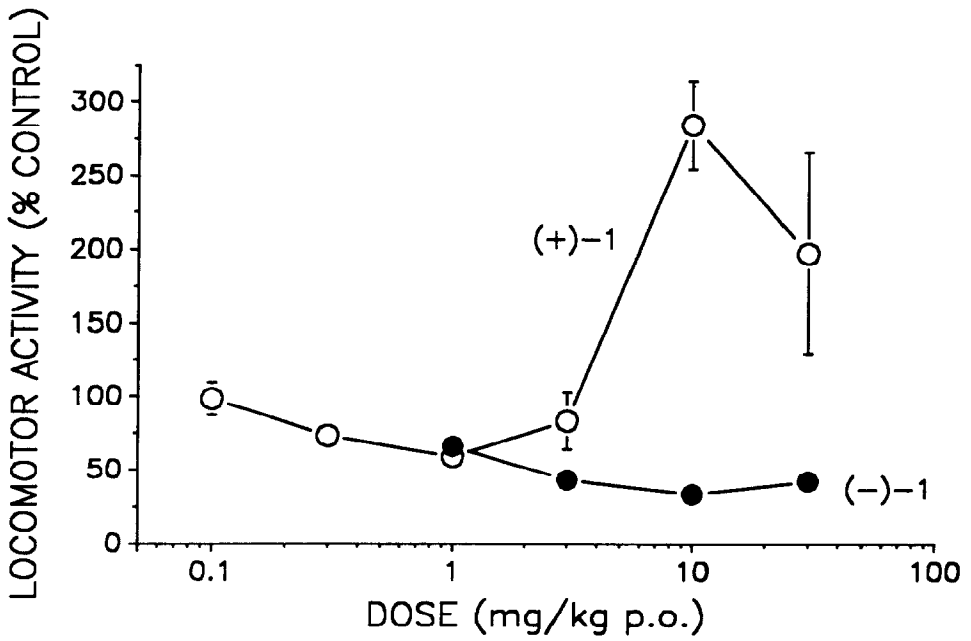


Figure 1. Effect of (+)-1 and (-)-1 on rat locomotor activity (n = 4-9 per dose).

In conclusion, R-(+)-1, the (+)-enantiomer of PD 128483, is a potent D_2 agonist. Unlike many DA agonists, (+)-1 possesses oral activity, as evidenced by its effects on rat locomotor activity following oral administration. In addition, (+)-1 readily crosses the blood-brain barrier, as evidenced by its pronounced effects on the electrophysiology and neurochemistry of brain dopaminergic neurons after systemic administration. The data presented in this communication indicate that (+)-1 stimulates, albeit in different dose ranges, pre- and postsynaptic DA receptors. Thus, (+)-1 might be useful in the treatment of Parkinson's disease or even schizophrenia. On the other hand, by comparison to R-(+)-1, S-(-)-1 is a weak DA agonist, able to stimulate DA autoreceptors but not postsynaptic DA receptors. As such, S-(-)-1 may prove useful in schizophrenia.[18] For the medicinal chemist, this work provides one more example of the high degree of stereoselectivity that characterizes the interactions between DA agonists and DA receptors.

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