Communications to the Editor

(5a*R*,11b*S*)-4,5,5a,6,7,11b-Hexahydro-2-propyl-3-thia-5-azacyclopent-1-ena[*c*]-phenanthrene-9,10-diol (A-86929): A Potent and Selective Dopamine D1 Agonist That Maintains Behavioral Efficacy following Repeated Administration and Characterization of its Diacetyl Prodrug (ABT-431)

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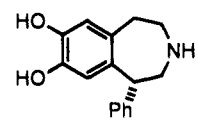
Dopamine (DA) receptors can be classified into either the D1-like or D2-like family of subtypes based on their pharmacological differences.[1] Recent evidence from molecular cloning techniques shows a greater heterogeneity of DA receptors, with the D1-like family consisting of the D1 and D5 subtypes and the D2-like family further delineated into the D2, D3, and D4 subtypes.[2]

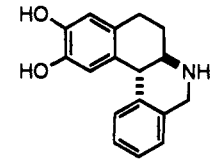
Parkinson's disease (PD) is characterized by the degeneration of DA-secreting neurons in the nigrostriatal pathway.[3] This loss of DA is believed to be responsible for the symptomology of the disease. Clinically effective agents used to treat PD include L-Dopa, which is endogenously converted to DA, and is the most effective therapy, and direct-acting D2-selective agonists (bromocriptine, lisuride, pergolide).[4] Long-term treatment with L-Dopa is associated with the induction of drug-related side effects, e.g. dyskinesia, while the D2 agonists are predominantly used as cotherapy.

Initial results with the prototypical D1 agonist SKF-38393 (1) showed lack of efficacy in both the MPTP-lesioned primate model of PD and in clinical trials.[5] However, since SKF-38393 possesses only low *in vitro* intrinsic activity (ca. 10% relative to dopamine) in primate tissues,[6] the therapeutic potential of a fully efficacious D1-selective agonist in PD has not been fully explored. Recent findings with the D1 full agonists dihydrexidine (**2**)[7] and A-77636 (**3**)[8] indeed demonstrate their *acute* efficacy in the MPTP-lesioned primate models of PD. A D1 agonist may also have advantages over L-Dopa and D2 agonists in terms of an improved side-effect profile.[9]

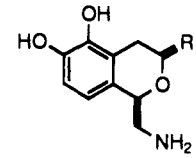
Development of **3** as a preclinical candidate for the treatment of PD was precluded because of the significant behavioral tolerance observed in both rodent and primate models of PD upon repeated administration.[10] Compound 4 (A-68930), another isochroman D1-selective agonist with a similar *in vitro* profile to **3**, was also examined in the 6-hydroxy-DA-lesioned rodent model. While **4** produced a robust response on the first day of treatment, a nearly complete loss of responsiveness was observed by the second day of treatment.[11]



1 SKF-38393



2 Dihydrexidine



3 R = 1-Adamantyl
A-77636

4 R = Ph
A-68930

A new class of dopamine agonists has been developed, and from these efforts compound **5** [(−)-(5a*R*,11b*S*)-4,5,-5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol, A-86929] has been identified as a novel D1-selective agonist that maintains efficacy upon repeated administration in the rat rotation model. Its diacetyl prodrug derivative **6** (ABT-431) was shown to have improved long-term solid-state stability.

Compound **5** was synthesized as shown in Scheme 1. The 6,7-dimethoxytetralone **7** was converted to the dihydronaphthalene **8**, as previously described by sequential reduction and acid-catalyzed elimination of the intermediate alcohol.[12] Reaction of **8** with tetranitromethane and pyridine in acetone afforded the nitro olefin **9**.[13] Michael addition of the dilithio derivative of 5-allyl-2 thiophene carboxylic acid *N-tert*-butylamide (**10**) afforded a 1-to-1 mixture of *cis* and *trans* adducts in 70% yield.[14] Equilibration of this crude mixture with triethylamine in acetonitile gave the thermodynamically favored *trans* adduct **11** in greater than 15:1 ratio. Reduction of the nitro group with zinc in HCl followed by hydrogenation of the double bond and subsequent acid-mediated cyclization of the resulting amino amide gave an intermediate lactam. Lactam reduction with borane afforded the amine **12** (50% overall yield from **11**). The racemic amine **12** was then separated on a preparative Chiracel OD column to resolve the enantiomers to >99% ee, as determined by analytical HPLC.[15] Deprotection of the methyl ethers with BBr_3 gave the corresponding catecholamines **5** and **13** in quantitative yield.[16] The solid-state stability of **5** is problematic due to the lability of the catechol to undergo air oxidation. Although **5** can be stored as a solid at −5 °C for up to 60 days with no appreciable loss, 50% degradation is observed under conditions used to simulate long-term stability (storage for 6 days at 60 °C). Thus, **5** was converted to the diacetyl prodrug **6** via treatment with acetyl chloride in TFA followed by basic workup and

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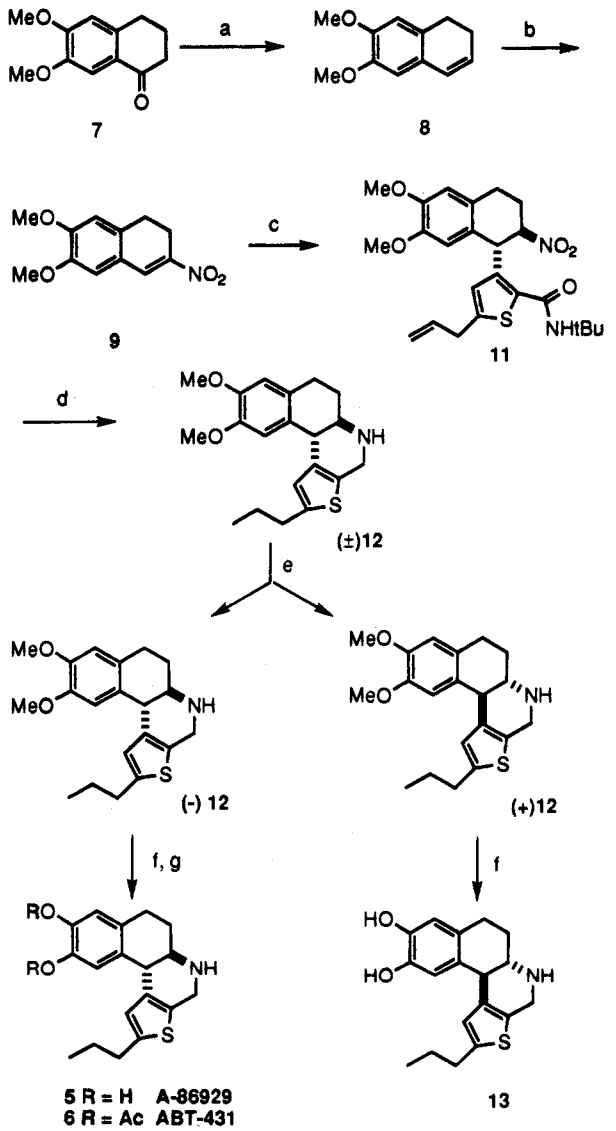
Table 1. *In Vitro* Pharmacology[a]

compound	D1			D2		
	K_i, nM	EC_{50}, nM	IA (%)[b]	K_i, nM	EC_{50}, nM	IA (%)
5·HCl	49 ± 4.6	9 ± 1.8	125 ± 3.1	710 ± 79.7	3900 ± 831	80 ± 5.9
(A-86929)	(32)	(29)	(29)	(52)	(21)	(21)
13·HCl	3050 ± 338	1700 ± 550	126 ± 15	4020 ± 1058	>10000	3 ± 3 at 10 μM
	(3)	(3)	(3)	(3)	(5)	(5)
DA	130 ± 21.1	100 ± 10.3	100	260 ± 88.3	170 ± 28.4	100
	(9)	(32)	(32)	(11)	(24)	(24)
3	21 ± 4.0	3 ± 0.6	142 ± 10.5	1550 ± 143.1	>4000	18 ± 9 at 10 μM
(A77636)	(18)	(9)	(9)	(22)	(4)	(4)
2	33 ± 1.7	14 ± 5.1	121 ± 7.4	1520 ± 526.5	1610 ± 408.8	80 ± 7.3
(dihydrexidine)	(6)	(6)	(6)	(5)	(3)	(3)
1	56 ± 4.7	59 ± 12.2	57 ± 9	4670 ± 1360	>5000	no
(SKF 38393)	(12)	(5)	(5)	(10)	(5)	activity

[a] Values represent the mean ±SEM, with the number of experiments in parentheses. Binding and adenylate cyclase assays were carried out in HEK and LTK cells transfected with the human D1[18] and D2[19] receptors, respectively. Binding ligands were as follows: D1, [^{125}I]SCH 23982; D2, [^{3}H]-spiperone. Binding K_i and cyclase EC_{50} values were determined as previously described.[8] [b] IA = Intrinsic activity, relative to dopamine.

Scheme 1[a]



[a] Reagents: (a) (1)$NaBH_4$, (2) TsOH, toluene; (b) $C(NO_2)_4$; (c) (1) 5-allyl-2-thiophenecarboxylic acid *N-tert*-butylamide (**10**), 2 equiv of nBuLi, THF, (2) Et_3N, CH_3CN; (d) (1) Zn, HCl, (2) H_2, Pd, (3) TsOH, toluene, (4) BH_3·THF; (e) chiral HPLC separation; (f) BBr_3; (g) AcCl, TFA.

treatment with ethereal HCl to give the hydrochloride salt.[17] Storage of **6** as a solid at 60 °C for 6 days resulted in no detectable degradation of **6**, thus demonstrating the greater solid-state long-term stability of **6** relative to **5**.

Compound **5** possesses high affinity for the cloned human D1 receptor exhibiting a K_i of 49 nM (Table 1). In addition, **5** is a potent D1 agonist exhibiting full intrinsic activity relative to DA in stimulating adenylate cyclase with an EC_{50} of 9 nM. The compound shows good selectivity over the cloned human D2 receptor in both binding (15-fold) and adenylate cyclase (>300-fold) assays. It also exhibits a high level of enantioselectivity in its interaction with the D1 receptor as the (+)-enantiomer is about 60 times weaker in both binding affinity and functional activity. **5** has weak affinity for adrenergic (β1, K_i = 1.5 μM; β2, K_i = 1.2 μM; α_1, α_2, K_i > 3 μM) and serotonergic ($5HT_{1c}$, K_i = 2.4 μM; $5HT_{1a}$ $5HT_2$ K_i > 3 μM) receptors.[20]

A rodent model of PD is produced by unilateral 6-hydroxydopamine injections that destroy the DA-secreting nigrostriatal neurons.[21] As a result of the loss of the dopaminergic tone, DA receptors on the lesioned side become supersensitive, and administration of a direct-acting DA agonist causes the animal to rotate away from (contralateral to) the lesioned side. Compound **5** was shown to produce robust rotation in the lesioned rat when administered subcutaneously (sc) (ED_{50} = 0.04 μmol/kg).[22] The diacetyl prodrug **6** produced a similar dose–response curve (ED_{50} = 0.02 μmol/kg), indicating rapid conversion to **5** upon sc administration.[23]

The conversion of **6** to **5** was also evaluated in various *in vitro* assays. Both *O*-acetyl groups are rapidly cleaved to give the parent in both rat blood and in rat liver or jejunal homogenates. The half-life for the conversion of **6** to **5** in these assays was less than 1 min. Both compounds are orally active, albeit at a much higher dose compared to sc administration (ED_{50} = 5.5–8 μmol/kg).

To examine the behavioral effects following repeated administration, **5** was administered once daily for 10 consecutive days at doses that produce a robust response (0.25 and 0.5 μmol/kg). Behavioral responsivity was maintained across the 10-day period (Figure 1). As the duration of action is relatively short at these doses (3 h), multiple daily doses would likely be required for a clinical regimen. Thus, **5** was administered at 0.22 μmol/kg, sc, three-times daily at 3-h intervals for 10

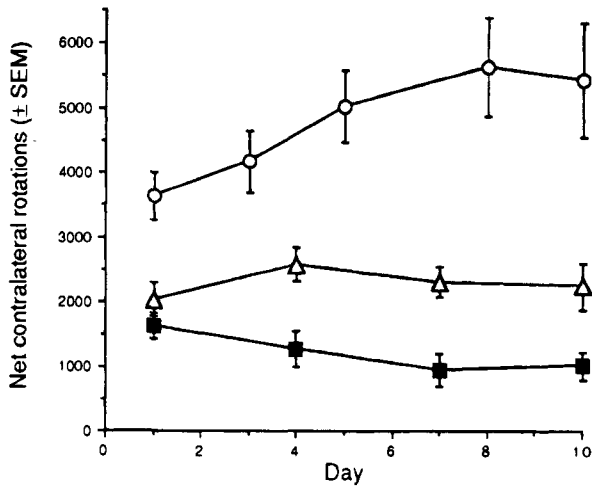


Figure 1. Effects of repeated administration (sc) of **5** on rotation: (■) 0.25 μmol/kg, once daily; (△) 0.5 μmol/kg, once daily; (○) 0.22 μmol/kg, three times daily). Values represent the mean (six animals in each test group) number of net contralateral rotations elicited over a 3-h and 9-h period, for the once-a-day and three times daily regimens, respectively.

consecutive days. Behavioral responsivity was maintained across the 10-day period (Figure 1). These results contrast sharply with our previous findings with the isochroman class of compounds, where significant reduction of the rotation response was seen as early as the second day of treatment.[10,11]

In conclusion, **5** represents a novel compound that is a potent and selective DA D1 agonist. The compound produces robust rotation in the unilaterally lesioned rat after both acute and *repeated* administration. Its diacetyl prodrug derivative **6** offers greater solid-state stability and is rapidly cleaved to the parent compound both *in vitro* and *in vivo*. Further work on the pharmacological characterization of **5** as well as the SAR of this class of compounds will be forthcoming.

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Supporting Information Available: Full experimental procedures, NMR data, and analytical data for the final products (8 pages). Ordering information is given on any current masthead page.

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(14) (a) Addition of the corresponding lithiated 5-*n*-propyl derivative of **10** proceeded in only 30% yield. (b) Thiophene **10** was prepared from 2-allylthiophene via lithiation and subsequent reaction with *tert*-butyl isocyanate.
(15) The analytical and preparative (50 mm × 500 mm) Chiracel OD columns were purchased from Chiral Technologies Inc., 730 Springdale Dr., Exton, PA.
(16) (a) All new compounds gave analytical and spectral data consistent with their structures. (b) The absolute stereochemistry has been assigned on the basis of the structural analogy to dihydrexidine. See: Knoerzer, T. A.; Nichols, D. E.; Brewster, W. K.; Watts, V. J.; Mottola, D.; Mailman, R. B. Dopaminergic Benzo[a]phenanthridines: Resolution and Pharmacological Evaluation of the Enantiomers of Dihydrexidine, the Full Efficacy D1 Dopamine Receptor Agonist. *J. Med. Chem.* **1994**, *37*, 2453–2460.
(17) Removal of the acetyl groups with methanolic HCl provided a convenient way for convering **5** and **13** from the hydrobromide to the hydrochloride salt, as the free base of **5** undergoes rapid decomposition.
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(22) ED_{50} is the dose at which half of the test group animals (6–8) will exhibit at least 50 net contralateral rotations (number of contralateral minus ipsilateral rotations) in a 30-min period.
(23) The 95% confidence limits for the ED_{50} values for **5** and **6** are 0.02–0.12 μmol/kg and 0.01–0.04 μml/kg, respectively, and are therefore not statistically different.

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