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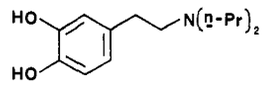
Communications to the Editor

4-(Aminoalkyl)-7-hydroxy-2(3*H*)-indolones, a Novel Class of Potent Presynaptic Dopamine Receptor Agonists

Sir:

In our search for peripheral dopamine receptor agonists that would produce specific renal vasodilatation, we have prepared and examined a number of molecules, including *N,N*-di-*n*-propyldopamine (**1**)[1] and 6-chloro-7,8-di-



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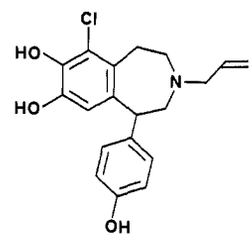


2 (SK&F 85174)

hydroxy-1-(4-hydroxyphenyl)-3-(2-propen-1-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**2**, SK&F 85174),[2] that produced hypotension and bradycardia in a preliminary canine assay and in subsequent testing in spontaneously hypertensive rats.[3] The pharmacological profile of hypotension accompanied by frank bradycardia is somewhat unique. Clonidine and α-methyl-β-(3,4-dihydroxyphenyl)-L-alanine (α-Me-Dopa) are examples of clinically useful antihypertensive agents that produce hypotension and bradycardia. It is generally believed that these agents cause a reduced sympathetic outflow by a central mechanism of action.[4]

We set as a worthwhile medicinal chemical goal the development of a peripherally acting dopaminergic agent that would decrease sympathetic neurotransmission. One of our synthetic approaches was directed to the preparation

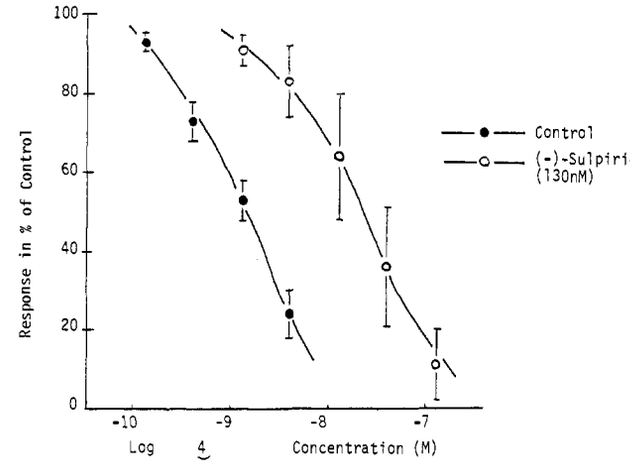
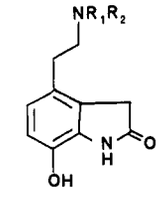


Figure 1. Blockade by (–)-sulpiride of the neuroinhibitory action of **4**. Concentration–effect curves for **4** were determined in the absence and presence of (–)-sulpiride in the same artery; each point represents the mean from four such experiments. Receptor dissociation constant (K_B) for (–)-sulpiride calculated from these averaged concentration–effect curves = 8.8 nM.

of catechol-replacement analogues of dopamine and *N,N*-di-*n*-propyldopamine, as illustrated by the indolones **3** and



3, $R_1 = R_2 = H$ (SK&F 88827)
4, $R_1 = R_2 = n$-Pr (SK&F 89124)

4.[5] While this synthetic effort was in progress, further study of SK&F 85174 (**2**) revealed that its mechanism of action includes a peripheral presynaptic dopaminergic component.[2] Recent work by Cavero and co-workers provides evidence that *N,N*-di-*n*-propyldopamine may also lower blood pressure by activation of presynaptic dopamine receptors.[6,7] We now report the syntheses of indolones

(1) Cannon, J. G.; Hsu, F. L.; Long, J. P.; Flynn, J. R.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1978**, *21*, 248. Kohli, J. D.; Goldberg, L. I.; Volkman, P. H.; Cannon, J. G. *J. Pharmacol. Exp. Ther.* **1978**, *207*, 16. This compound was prepared in our laboratories by Mark Schwartz.

(2) Blumberg, A. L.; Hieble, J. P.; McCafferty, J.; Hahn, R. A.; Smith, Jr., J. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1982**, *41*, 1345, Abstract 6281. SK&F 85174 was originally prepared in our laboratories by Dr. Martin Brenner.

(3) The cardiovascular properties of di-*n*-propyldopamine have been studied in spontaneously hypertensive rats by Cavero and co-workers (see ref 6). Similar studies carried out independently in our laboratories by R. Hahn and J. Stefankiewicz are in agreement with the results of Cavero et al.

(4) See, for instance, Kobinger, W. In "Regulation of Blood Pressure by the Central Nervous System"; Onesti, G.; Fernandes, M.; Kim, K. E., Eds.; Grune & Stratton: New York, 1976; pp 283–292.

(5) Huffman, W. F.; Wilson, J. W. U.S. Patent 4 314 944, 1982; *Chem. Abstr.* **1982**, *96*, 181146c. Catechol-replacement analogues of sympathomimetic amines (α and β) have been prepared using a carbostyril nucleus. See Yoshizaki, S.; Tanimura, K.; Tamada, S.; Yabuuchi, Y.; Nakagawa, K. *J. Med. Chem.* **1976**, *19*, 1138. A recent Japanese patent also discloses the use of 7-hydroxy-2(3*H*)-indolones as catechol replacements for similar sympathomimetic amines. See Yoshizaki, S.; Sato, T.; Nakagawa, K. Japanese Patent 3018562, 1978; *Chem. Abstr.* **1978**, *89*, 24145q.

(6) Cavero, I.; Lefevre-Borg, F.; Gomeni, R. *J. Pharmacol. Exp. Ther.* **1981**, *218*, 515; **1981**, *219*, 510.

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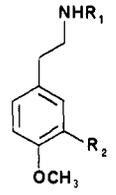
Table I. Biological Activity

compd[a]	dose, μg/kg, iv	cardiovascular act. (in vivo dog): % change[b] MAP	HR	dopamine agonist act. (in vitro rabbit ear artery): EC_{50}, nM
1	3	−4.7	+1.5	80 ± 17 (N = 12)[c]
	30	−17.7[d]	−3.0	
	300	−21.9[d]	−9.2[d]	
2	0.3	−3.5	0	122 ± 33 (N = 12)
	3	−14.4[d]	+0.5	
	30	−16.9[d]	−8.7[d]	
3	3	−10.6[d]	−2.9	116 ± 43 (N = 8)
	30	−16.1[d]	−2.9	
	300	+62.6[d]	−15.8[d]	
4	0.3	−5.1	+3.6	1.8 ± 0.3 (N = 10)
	3	−24.7[d]	−11.2[d]	
	30	+28.4[d]	−6.9[d]	

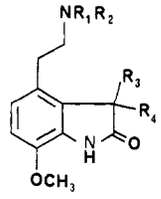
[a] Tested as the hydrobromide salts. [b] Percent change from control value recorded just prior to infusion. [c] Reference 15. [d] Statistically significant from corresponding control response ($p < 0.05$) for N = 2 dogs.

3 and 4 and their ability to act in a potent and selective fashion at peripheral dopamine receptors. The di-*n*-propyl derivative 4 produces potent hypotension with concommitant bradycardia in preliminary in vivo studies.

The preparation of indolones 3 and 4[8] takes advantage of the well-known Sandmeyer isatin synthesis.[9] The appropriately substituted aniline 8 was prepared from *p*-methoxyphenethylamine (5) in three steps. Trifluoro-



5, $R_1 = R_2 = H$
6, $R_1 = COCF_3$; $R_2 = H$
7, $R_1 = COCF_3$; $R_2 = NO_2$
8, $R_1 = COCF_3$; $R_2 = NH_2$
9, $R_1 = COCF_3$; $R_2 = NHCOCH{=}NOH$



10, $R_1 = H$; $R_2 = COCF_3$; $R_3 + R_4 = O$
11, $R_1 = H$; $R_2 = COCF_3$; $R_3 + R_4 = SCH_2CH_2S$
12, $R_1 = H$; $R_2 = COCF_3$; $R_3 = R_4 = H$
13, $R_1 = R_2 = R_3 = R_4 = H$
14, $R_1 = R_2 = n$-Pr; $R_3 = R_4 = H$

acetylation (TFAA, CH_2Cl_2, 0–25 °C, 2 h) resulted in amide 6 (88%; mp 84 °C), which was nitrated (HNO_3, TFA, 0–25 °C, 2.5 h) to afford the light-sensitive nitro derivative 7 (84%; mp 92.5–93.0 °C). Catalytic hydrogenation (10% Pd/C, EtOH, 53 psi, 1 h) afforded aniline 8, which was used directly in the Sandmeyer synthesis [$Cl_3CCH(OH)_2$, $(H_2NOH)_2H_2SO_4$, H_2O, H_2SO_4, reflux, 4 min] to provide the desired oxime intermediate 9 (68%; mp 197–198 °C). Cyclization of 9 was effected with concentrated sulfuric acid (80 °C, 6 min) to give the isatin 10 (64%; mp 236.5–238.5 °C) as a red solid. Conversion to oxindole was accomplished by preparation of the thioketal 11 (85%; mp 163–165 °C; $HSCH_2CH_2SH$, CH_2Cl_2, BF_3 etherate, 25 °C, 16 h) and subsequent Raney nickel reduction (Ra-Ni, EtOH, 25 °C, 2 h) to afford 2(3*H*)-indolone 12 (82%; mp 178–179 °C). Hydrolysis and demethylation of 12 was accomplished in one step with constant-boiling HBr (reflux, 3 h) to afford the desired amine 3 (83%; HBr, 250 °C dec). Treatment of 12 with HCl (6.0 N HCl, EtOH, 90 °C, 10 h) resulted in only amide hydrolysis to give amine 13 as the hydrochloride salt (87%; mp 258–260.5 °C). The free amine 13 was liberated by ion-exchange chromatography and treated with propionaldehyde under reductive amination conditions (Pd/C, AcOH, 55 psi, 25 °C, 1 H), and the product was converted to the HBr salt (0 °C, CH_3OH–HBr) to provide the di-*n*-propyl-2(3*H*)-indolone 14 (21%; mp 222–223 °C). Demethylation with constant-boiling HBr (reflux, 3 h) afforded the indolone 4 (75%; HBr, mp 252–254 °C).

A preliminary evaluation of the cardiovascular effects of indolones 3 and 4 was made in anesthetized dogs (Table I).[10] Intravenous infusion of 3 produced significant hypotension at dose levels of 3 and 30 (μg/kg)/min without any significant change in heart rate. The di-*n*-propyl analogue 4, however, produced significant hypotension accompanied by bradycardia at a dose level of 3 (μg/kg)/min. Both compounds 3 and 4 became pressor in this assay as the dose levels were raised to 300 and 30 (μg/kg)/min, respectively. In order to evaluate the ability of these indolones to activate presynaptic dopamine receptors, they were tested in the isolated perfused rabbit ear artery preparation[11] along with di-*n*-propyldopamine (1) and SK&F 85174 (2) (Table I). It was gratifying to find that both indolones displayed agonist activity in the ear artery preparation, with the di-*n*-propyl derivative being

(7) After the completion of our work, Cannon and co-workers reported the preparation and presynaptic dopaminergic activity of 4-[2-(di-*n*-propylamino)ethyl]indole. Cannon, J. G.; Demopoulos, B. J.; Long, J. P.; Flynn, J. R.; Sharobi, F. M. *J. Med. Chem.* **1981**, *24*, 238.

(8) All new compounds gave satisfactory analyses for C, H, and N, and were further characterized by IR, NMR, and in most cases by MS spectra, which were consistent with the assigned structures.

(9) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234.

(10) These effects were evaluated in pentobarbital-anesthetized dogs as described by Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wardell, Jr., J. R.; Tobia, A. J.; Setler, P. E.; Sarau, H. M.; Ridley, P. T. *J. Med. Chem.* **1980**, *23*, 973. Heart rate was recorded by means of a cardiotachometer triggered by a lead II electrocardiogram. In the test procedure used, the following changes were determined to be the minimum necessary to be considered significant for N = 2 dogs ($p < 0.05$): mean arterial blood pressure (MAP), ±5.2%; heart rate (HR), ±5.7%.

(11) Hieble, J. P.; Pendleton, R. G. *Arch. Pharmacol.* **1979**, 309, 217.

particularly potent.[12] The activity of 4 could be blocked by (–)-sulpiride,[13] a selective dopaminergic antagonist, with a K_B of 8.8 nM (Figure 1). This K_B value is comparable to that obtained for this antagonist against dopamine in the same series of experiments (32 nM) and is essentially identical with the value of 9.3 nM reported for (–)-sulpiride as an antagonist of 6,7-ADTN in the ear artery.[14] Therefore, the activity of 4 in the rabbit ear artery is attributed to activation of presynaptic dopamine receptors. These results indicate that the di-*n*-propylindolone 4 is one of the most potent presynaptic dopamine receptor agonists reported to date.

Acknowledgment. We are grateful to James M. Smith, Jr., and Caleb A. Jervay for their expert assistance in conducting the biological experiments.

(12) Vasoconstriction was observed in the rabbit ear artery for both compounds 3 and 4 at doses on the order of 1000 nM. This result is consistent with the previously mentioned pressor effects exhibited by 3 and 4 at higher doses (Table I).
(13) Brown, R. A.; O'Connor, S. E. *Br. J. Pharmacol.* **1981**, *73*, 189P. The (–)-sulpiride was kindly supplied by Professor P. Fresia, Ravizza S.P.A., Milan, Italy.
(14) Steinsland, O. S.; Hieble, J. P. *Adv. Biosci.* **1979**, *18*, 93–97.
(15) An EC_{50} value of 110 nM in the rabbit ear artery has been reported (ref 13) for this compound.

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Articles

Neuroleptic Activity and Dopamine-Uptake Inhibition in 1-Piperazino-3-phenylindans

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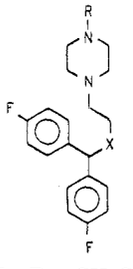
A series of 1-piperazino-3-phenylindans was synthesized and tested for neuroleptic and thymoleptic activity. Neuroleptic activity was found only in trans racemates and was associated with one of the enantiomers only. The potent and long-acting neuroleptic compound *trans*-4-[3-(4-fluorophenyl)-6-(trifluoromethyl)indan-1-yl]-1-piperazineethanol (Lu 18-012, tefludazine) was developed by systematic variation of structural components. Thymoleptic activity was optimized, especially with respect to dopamine-uptake inhibition. No geometrical stereoselectivity was found with regard to dopamine-uptake inhibition, but a high enantioselectivity could be demonstrated for both cis and trans racemates. The most potent compounds were 1-piperazino-3-(3,4-dichlorophenyl)indans with IC_{50} values of about 2 nM for inhibition of dopamine uptake.

Since the introduction of chlorpromazine as an antipsychotic drug many compounds with neuroleptic activity have been synthesized. These compounds include a diversity of chemical structures and are often categorized on the basis of a common "nucleus", i.e., phenothiazines, thioxanthenes, thiepins, butyrophenones, etc.[1] The piperazine ring is common to many of these compounds. This piperazine ring can either be part of a flexible piperazinopropyl(idene) side chain, as in perphenazine or flupentixol, or be attached directly to a tricyclic nucleus, as in clozapine or octoclothepin (4).

The butyrophenones have no polycyclic nucleus, but the related diphenylbutylamines, for example, penfluridol, have two phenyl rings that might interact with the dopamine (DA) receptor at the same site as the tricyclic nucleus.[2] The great majority of butyrophenones and diphenylbutylamines contain a 4-substituted piperidine ring as the amine part. If the diphenylbutyl part of penfluridol is combined with a piperazine base, compounds without neuroleptic activity are obtained. For example, 1 (VUFB



1, X = CH_2; R = CH_2CH_2OH
2, X = O; R = $CH_2CH{=}CH{-}C_6H_5$

10.674) is reported to have no central depressant activity.[3] We have also synthesized 1 (Lu 9-106) and also can report that we found no antistereotypic effect (methyl phenidate

(1) Kaiser, C.; Setler, P. E. "Burger's Medicinal Chemistry", Part III, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; p 859.
(2) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* **1981**, *24*, 1026.
(3) Rajšner, M.; Kopicovā, Z.; Holubek, J.; Svātek, E.; Metyš, J.; Bartošovā, M.; Mikšik, F.; Protiva, M. *Collect. Czech. Chem. Comm.* **1978**, *43*, 1760.

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