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Preliminary evaluation of 4-(2-*N*,*N*-dialkylaminoethyl)indoles as potential dopamine agonists

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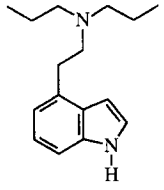
Introduction

The selective dopamine autoreceptor stimulant 4-(2-*N*,*N*-di-*n*-propylaminoethyl)indole (DPAI, **1**) was designed independently by our group [1–3] and by Cannon *et al* [4] as part of a project to determine the pharmacophore of the ergolines responsible for dopamine receptor stimulation. In our studies, an assay measuring the inhibition of serum prolactin was used as a first screen for dopaminergic activity [5]. Although DPAI was active in this assay, it was only one tenth as potent as the ergoline pergolide.



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In an effort to develop structure–activity relationships for DPAI-congeners, we have synthesized and evaluated a series of 4-(2-*N*,*N*-dialkyl-substituted-aminoethyl)indoles. The compounds synthesized and their biological data are presented in table I.

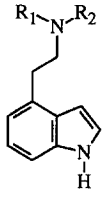

Table I. Ability of test compounds to affect rat serum prolactin levels.

Compound No	R_1	R_2	*Dose (mg/kg)*	*% Change*	P*
1 (DPAI)	nPr	nPr	5	−84	< 0.001
			2	−69	< 0.001
			1	−43	< 0.01
2	H	nPr	5	−57	< 0.001
3	CH_3	nPr	2	−55	< 0.001
4	nPr	nBu	5	−73	< 0.001
5	nBu	nBu	2	+45	NS
6	nPr	allyl	2	−59	< 0.002
7	H	phenethyl	2	+ 5	NS
8	nPr	phenethyl	2	−69	< 0.001
9	CH_3	CH_3	5	−86	< 0.001
10	$-CH_2(CH_2)_3CH_2-$		2	+91	< 0.05
11	$-(CH_2)_2-O-(CH_2)_2-$		2	+23	< 0.05
12	$-(CH_2)_4-$		2	−60	< 0.001

[a]Percent change from control value, measured 1 h after ip injection. *Statistical level of significance of change; NS = not significantly different.

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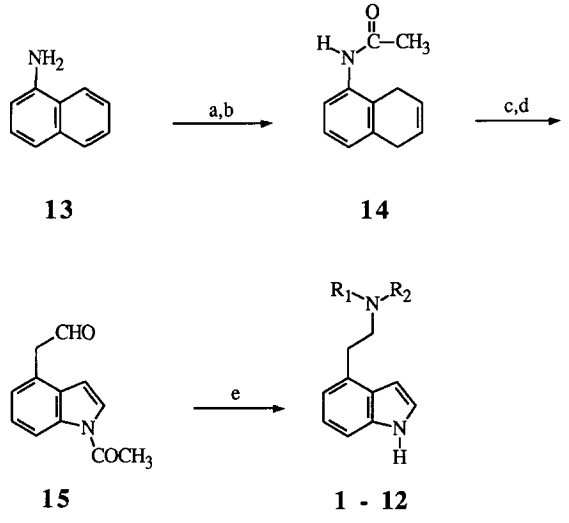
Chemistry

The compounds were prepared as shown in scheme 1. Aldehyde **15** was an attractive precursor to the series of DPAI congeners. The literature procedure for the preparation of **15** was based on oxidation of **14** [6]. An improvement in yield was achieved by substituting OsO_4/IO_4^- for ozonolysis. Reductive amination of **15** with appropriate amines and $NaCNBH_3$ led to symmetric as well as nonsymmetric N-substituted isotryptamines. These intermediates were N-deprotected by treatment with sodium ethoxide. The oxalate salts of the amines were characterized and had physical and spectral data consistent with the expected structures.

Results and Discussion

The target compounds were screened at 2 or 5 mg/kg using the prolactin inhibition model of Clemens *et al* [2] as a general screen for dopamine D-2 receptor activity. The results are summarized in table I. DPAI (**1**) is included for purposes of comparison. Compounds **2**, **3**, **4**, **6**, **8**, **9** and **12** show activity comparable to DPAI as prolactin inhibitors. The lack of activity in the 6-membered cyclic analogs parallels results reported by McDermed *et al* [7] for non-indolic dopamine agonists. Introduction of a second basic atom into the ring (*ie* 4-methylpiperazinyl; data not shown) also failed to give an active compound.

The activity pattern of the open-chain series of isotryptamines parallels a series of *N,N*-di-substituted dopamine derivatives prepared by Ginos *et al* [8].



Scheme 1. (a) Na°, EtOH, xylene; (b) $(CH_3CO)_2O$; (c) OsO_4, $NaIO_4$; (d) oxalic acid, H_2O, heat; (e) R_1R_2NH, $NaCNBH_3$, EtOH, Na°.

Examples of active analogs common to both series include the *N,N*-di-*n*-propyl, *N,N*-dimethyl, and *N*-2-phenethyl-*N*-*n*-propyl. The *N,N*-dibutyl analog is inactive in both series. The observation that dopaminergic activity is high when one of the *N*-substituents is an *n*-propyl is also consistent with observations in other series of dopamine agonists [9].

Experimental protocols

Thin layer chromatography (TLC) was performed using EM Labs Silica Gel 60 F-254 plates. Chromatograms were visualized using an ultraviolet lamp and/or Van Urk's spray reagent; final compounds were purified to chromatographic homogeneity, and all had spectral data (IR, NMR, MS) consistent with the expected structures.

*2-[(1-Acetyl)-4-indolyl]acetaldehyde **15***

To a solution of 1-acetamido-5,8-dihydronaphthalene **14** (10.0 g, 0.053 mol) in 225 ml of dioxane was added water (75 ml) and osmium tetroxide solution (1 molar %, 0.53 mmol, 5.3 ml of a 0.10 M solution in diethyl ether). After 10 min the clear black solution was treated with sodium metaperiodate (22.88 g, 0.107 mol) over a 30 min period, and then stirred for another 90 min. The tan suspension was filtered, and the filtrate was diluted with water and methanol (200 ml each). Oxalic acid (20 g) was added and the solution was heated on a steam bath for 1 h, at which time the color had turned black. The reaction mixture was allowed to cool to room temperature and was extracted with benzene (5 x 200 ml), dried (Na_2SO_4), filtered and concentrated to yield a black solid. This was dissolved in benzene, filtered through a pad (100 g) of silica gel and the silica was washed with 4 x 100 ml of ethyl acetate. The organic filtrates were combined, the solvent was evaporated, and the bisulfite adduct was formed by shaking the suspension with saturated $NaHSO_3$ solution for 24 h. Liberation of the compound from the adduct with cold saturated sodium carbonate solution, followed by extraction into ethyl acetate, drying (Na_2SO_4) and concentration yielded a tan solid (2.58 g, 24%) mp 64°C (lit [6] mp = 64°C), mass spectrum: MH^+ (CI) = 202; IR (salt plates) 1700 cm^{-1}.

General method for isotryptamines

To a solution of 40 mM of *N*-acetylindolyl-4-acetaldehyde **15** in 40 ml ethanol were added 10 equivalents of the appropriate primary or secondary amine and 2 equivalents of $NaBH_3CN$. The pH was maintained at 6 with dropwise addition of acetic acid. The reaction was stirred for several h at room temperature and monitored by TLC for disappearance of starting material. Sodium metal (4 mM) was then added to create an approximately 0.1 M ethoxide concentration and the reaction was stirred at room temperature for several h. Most of the EtOH was removed by rotary evaporation and the residue was partitioned between ether and 2% aqueous acetic acid. The aqueous layer was basified with NH_4OH and extracted with ethyl ether. The ether layers were combined, dried, filtered and concentrated to yield the free base either as an oil or a solid. Oxalate salts were prepared by dissolving the free base in a minimum amount of hot EtOH and adding 1 equivalent of oxalic acid in ethanol. The salt usually crystallized upon cooling.

Determination of prolactin inhibitory activity

Adult male Sprague-Dawley rats were used, and each rat was injected ip with an aqueous suspension of reserpine (15 mg/kg) 18 h before administration of test compounds. The rats were decapitated 1 h after drug injection. Blood was collected, allowed to clot, and 150 µl aliquots of serum were assayed for prolactin by radioimmunoassay. The results were expressed as ng of NIAMD-prolactin-RP-1 per ml serum, the activity of the compounds as percent above or below the control value.

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