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N,N-6-BIS-[2-(3,4-DIHYDROXYBENZYL)PYRROLIDINYL]HEXANE, A POTENT, SELECTIVE, ORALLY ACTIVE DOPAMINE ANALOG WITH HYPOTENSIVE AND DIURETIC ACTIVITY[1]

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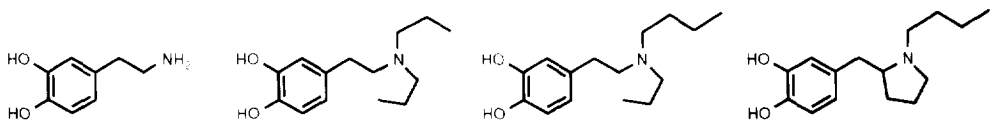
Abstract: The D-1 and D-2 affinities, *in vivo* femoral and renal vasodilatory effects, oral antihypertensive and diuretic effects and syntheses of selected dopamine congeners are described.

Several dopamine analogs have been reported[2] to be selective peripheral D-2 dopamine receptor agonists, while the benzazepin, fenoldopam, is known to be a potent peripheral D-1 receptor agonist.[3] A series of 4-(2-aminoethyl)-2(3*H*) indolones has been reported to be highly active as peripheral DA-receptor agonists in the isolated perfused rabbit ear artery.[4-6] Dopamine receptor activity of some 5-(2-aminoethyl)carbostyril[7], 4-(2-aminoethyl)indole derivatives[8,9] and a series of *N,N*-di-*n*-propyldopamine congeners containing phenolic bioisosteres[10] with activity at D-1 and D-2 receptors has been reported. However, to date, no reports of therapeutically useful peripherally acting dopamine analogs with combined D-1 and D-2 receptor activity have appeared.[11]

A single chemical entity combining selective peripheral D-1 and D-2 dopamine receptor affinity[12] whose *in vivo* activity is consistent with peripheral D-1 and D-2 stimulation might provide a useful treatment for hypertension, acute and chronic renal failure, and congestive heart disease.[13,14] This is based upon findings that the stimulation of peripheral D-2 dopamine receptors prejunctionally inhibit release of norepinephrine (NE) from postganglionic noradrenergic nerves, thereby reducing the postjunctional effects of NE on the vasculature and myocardium. This leads to passive systemic vasodilation, a decrease in blood pressure and a reduction in heart rate. Further, stimulation of peripheral D-1 dopamine receptors (located primarily in the renal and mesenteric vascular beds and on renal tubular cells) leads to renal vasodilation, increased renal blood flow and diuresis.[3]

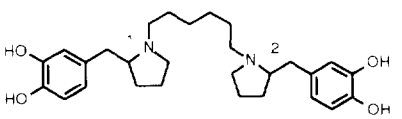
Our goal was to identify such a chemical entity. The structure activity relationship of derivatives of dopamine (**1**)[2,3,11] and the dopamine receptor agonist activity of **2**, *N,N*-dipropyl dopamine (DPDA)[12] and **3**, *N*-butyl-*N*-propyl dopamine)[13] prompted us to synthesize a number of analogs of **1** and evaluate their activity at D-1 and D-2 receptors. Those compounds showing activity at D-1 and D-2 receptors were then evaluated *in vivo*.[14-16]



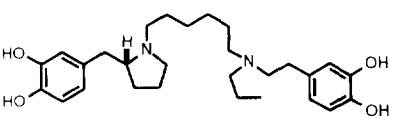
1 2 3 4

RATIONALE

"Cyclization" of **3** led to butyl-(2-(3,4-dihydroxybenzyl)pyrrolidine (**4**), an early lead. It possessed relatively high affinities at the D-1 (pKi = 8.1) and D-2 (pKi = 8.5) receptors but exhibited poor oral activity. Interestingly, a straightforward "dimerization" of **4**[17a] via linkage of the two benzylpyrrolidinyl pharmacophores by an alkyl chain retained the dopamine receptor D-1 and D-2 affinity of **4** while conferring oral activity to **5a**[17b] (Table III). It is not clear whether the change in size or the combination of two active pharmacophores in one chemical entity resulted in oral activity. However, in life studies have indicated that metabolism and excretion of **5a** is slower than **4**. Analog **5a**, the *R,R* isomer, possessed the highest D-1 and D-2 receptor affinity and the greatest *in vivo* activity (Table II). *S,S* compound **5b** exhibited lower affinity at the D-1 and D-2 receptors. Predictably, **5b** was also less effective *in vivo*. *Meso* compound **5c** (absolute configuration *R* at one chiral center, *S* at the other) showed intermediate D-2 affinity and *in vivo* activity with respect to **5a** and **5b**. Based on this intermediate activity, we also explored the SAR of "unsymmetrical" compounds of which **6**[15] is an example. The D-1 and D-2 affinity and *in vivo* data exhibited by **5a** and **6** led us to examine their ability to affect blood pressure and diuresis in saline loaded spontaneously hypertensive rats.[18]



Absolute Configuration
5a 1=R, 2=R
5b 1=S, 2=S
5c 1=R, 2=S



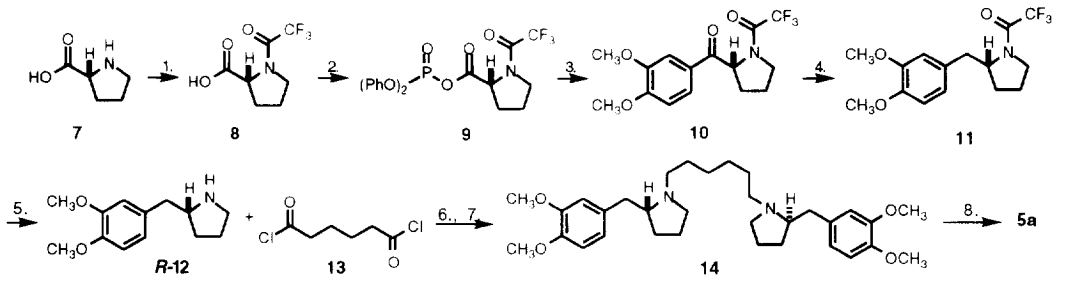
6

CHEMISTRY

The common chiral subunit **12** (see Scheme I) was synthesized via *N*-trifluoroacetylation of *D*-proline (**7**) with ethyl trifluoroacetate, acyl group activation of the acid with diphenyl chlorophosphate, and treatment of this mixed anhydride with the Grignard's reagent derived from 4-bromoveratrole to give ketone **10** (42%, mp 122-124 °C). The reduction of this ketone to the benzyl trifluoroamide **11** was accomplished with triethylsilane and boron trifluoride etherate. Hydrolysis of the trfluoroacetamide proceeded under either acidic or basic conditions to yield *R*-**12** (17% from **7**, oil, $[\alpha]_D$ -18.3° *c* 0.6, methanol). The optical purity of *R*-**12** (>95%) was established via ^{1}H-NMR of its alpha-*S*- methylbenzyl urea derived from *S*-methyl benzylisocyanate.

Dimer **5a** (Scheme I) (mp 281-283 °C, di-hydrobromide salt, isopropanol-ether, $[\alpha]_D$ -12.5° *c* 0.5, methanol) was produced via reaction of two equivalents of *R*-**12** with adipoyl chloride followed by successive treatment of diamide **14** with diborane and excess boron tribromide.

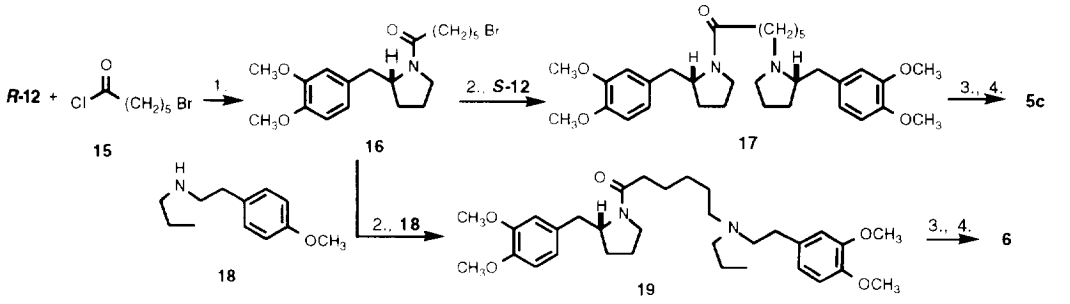
Scheme 1



1. CF_3CO_2Et , 1,1,3,3-Tetramethylguanidine 2. $ClP(O)(OPh)_2$, N-methylmorpholine. 3. 3,4-Dimethoxy phenylmagnesium bromide, 0 °C, THF. 4. BF_3-OEt_2, Et_3SiH, CH_2Cl_2 5. ^-OH or H^+ 6. Et_3N, CH_2Cl_2, 0 °C. 7. BH_3-DMS, THF, Reflux 4 h, then CH_3OH, CH_3OH-HCl. 8. BBr_3, CH_2Cl_2, -78 °C.,then CH_3OH.

Alternatively, *L*-Proline can be substituted for *D*-Proline to synthesize the *S,S*-isomer **5b** (mp 279-281 °C, di-hydrobomide salt, $[\alpha]_D$ +11.5 *c* 0.6, methanol). The *meso* compound is made according to Scheme 2. Thus *R*-**12** was treated with 6-bromohexanoyl chloride to give bromoamide **15.** Heating of **15** with *S*-**12** in DMF gave the mixed amide-amine **17.** Successive treatment of **17**, as in Scheme 1, with diborane and boron tribromide gave **5c** (mp 256-259 °C, di-hydrobromide salt, isopropanol-ether). The unsymmetrical diamine **6** (mp 166-168 °C, di-hydrobromide salt, $[\alpha]_D$ -6.4°; *c* 0.6, methanol) was synthesized in a similar manner from **16** and *N*-propyl-4-methoxyphenethyl amine (**18**),[19] (Scheme 2).

Scheme 2



1. Et_3N, CH_2Cl_2, 0 °C. 2. DMF, K_2CO_3, KI, 100 °C., 4h. 3. BH_3-DMS, THF, reflux, then CH_3OH, CH_3OH-HCl. 4. BBr_3, CH_2Cl_2, -78 °C., then CH_3OH

Biological Results

The relative affinities of **4**, **5a**, **5b**, **5c** and **6** for dopamine D-1 and D-2 receptors were determined in rat striatal membranes by competitive binding studies using displacement of 0.2 nM [^{3}H]SCH 23390[20] and 0.2 nM [^{3}H] spiperone,[21] respectively.[22] These results appear in Table I. The data generated from the spiperone labelled rat striatal membrane strongly suggest specificity for the D-2 receptor but do not preclude binding at the D-3, D-4 and D-5 receptors. (Nonspecific binding was defined in the presence of 1 mM (+) butaclamol). Affinity estimates at the α_1, α_2, β_1 and β_2 adrenoceptors were determined using literature methods.[23]

Table I. Radioligand Binding (Ligand Binding, pKi[a] (HC)[b])

Compound	D-1	D-2	α_1	α_2	β_1	β_2
5a	8.19 (0.83)	8.21 (0.58)	7.25 (1.21)	7.24 (0.93)	IA[c]	IA
5b	6.21 (0.82)	7.83 (0.64)	6.41 (1.34)	5.84 (0.93)	IA	IA
5c	6.24 (0.84)	8.05 (0.62)	6.24 (1.13)	6.03 (0.84)	IA	IA
6	7.73 (0.70)	8.49 (0.50)	6.41 (1.32)	6.52 (0.87)	IA	IA
dopamine	6.51 (0.58)	6.98 (0.38)	5.60 (1.12)	6.01 (0.87)		
DPDA	5.33 (0.69)	7.65 (0.37)	5.70 (1.13)	<5		
Fenoldopam	8.91 (0.93)	7.88 (0.42)	6.82 (1.20)	7.45 (0.79)		
Quinpirole	3.50 (0.69)	7.20 (0.34)				

[a]Values are means for at least three separate determinations. [b]Hill coefficients. [c]IA = inactive.

The ability of the compounds to induce dilation of dog femoral artery when given iv (a D-2 receptor mediated effect)[13,24] was measured as changes in blood flow and the results were normalized to vasodilator effects to DPDA.[25] Blockade of renal artery dilation by the D-2 antagonist SCH23390 was measured and is expressed as percent reversal of compound induced dilation. Changes in renal artery blood flow (a D-1 receptor mediated effect) were measured and are presented as normalized to vasodilator effects of dopamine.[26] Blockade of renal artery dilation by the D-2 antagonist domperidone was measured and is expressed as percent reversal of compound induced dilation (Table II).

Table II. Dog Renal and Femoral Blood Flow Results

Compound	Renal Artery[b]	% Blockade[c] (SCH23390)	Femoral Artery[d]	% Blockade[e] (Domperidone)
5a	12	100	359	70
5b	1.2	100	0.3	0
5c	9.4	100	80	20
6	6	100	382	70
1	1	100	-	
2	-		1	80
Fenoldopam	8	100	0.2	20

[a]N is at least 4. [b]Values are potency versus dopamine. [c]0.05-0.1 mg/kg, iv. [d]Values are potency versus DPDA. [e]10-60 mg/kg, iv.

Effects on urine output after oral administration of **5a** and **6** were monitored in conscious, saline loaded spontaneously hypertensive rats (SHR)[27] and effects on blood pressure were monitored in the restrained SHR.[27] These test results are presented in Table III.

Table III. Urine Output and Blood Pressure Effects in Conscious SHR, 30 mg/kg, PO, 3 Hours Post Administration

	Decrease in Mean Blood Pressure	Cumulative Urine Volume
Control	8.8 ± 2.1	6 ± 2
5a	22.4 ± 1.8	17 ± 9
6	18.6 ± 2.8	24 ± 9
1	9.4 ± 3.2	4 ± 2
Fenoldopam[b]	14.2 ±2.1	16 ± 3

[a]Saline loaded SHR. ± indicates standard error of the mean. [b]IV administration, 0.03 mg/kg.

The data indicate that **5a**, **5c**, and **6** display higher affinity for dopamine receptors than dopamine. However, although the Hill coefficient for fenoldopam, **5a**, **5c**, and **6** were not significantly different from unity,

the vasodilatory effect in the renal arterial bed, the blockade of this activity by the D-1 antagonist SCH23390 and their diuretic activity indicated that they are probably dopamine D-1 receptor agonists.[28] These data may indicate that they were agonists of low affinity or that dopamine receptors in the CNS and periphery differ.

The compounds were highly potent with respect to dopamine in their ability to dilate the femoral arterial bed (Table II). This activity was partially blocked by the D-2 antagonist domperidone. These data, coupled with high dopamine D-2 receptor affinity, low Hill slopes, and blood pressure lowering effects of **5a**, **5c**, and **6** also indicated that they are likely to act as dopamine D-2 receptor agonists.[3] Analogs **5a** and **6** also induced diuresis and decreased blood pressure upon *oral* administration (Table III) and these effects were still present three hours after oral administration. Based upon these data, **5a** and **6** can be described as potent, orally active, peripheral, nonselective dopamine analogs with activity consistent with D-1 and D-2 receptor agonism in the dog and the rat.

Both **5a** and **6** were studied in several bioassays designed to detect CNS activity. In all of these assays (hexabarbitol induced sleep, neurological defect, pentalene tetrazole induced seizures, electroshock induced seizures and general mice behavior), **5a** and **6**, were inactive up to and including 30 mg/kg p. o. Studies in dogs (Table III) indicate that the desirable therapeutic effects of **5a** and **6** occur at dose levels below those which cause meaningful emesis in the dog. Compound **5a**, for example, showed a significant 40 % decrease in mean arterial blood pressure at 30 mg/kg p.o. whereas the onset of significant emetic episodes occurred at 120 mg/kg p. o. These compounds may have clinical applications for the treatment of hypertension, acute and chronic renal failure, and congestive heart failure based on their potent peripheral, nonselective dopamine D-1 and D-2 agonist activity.

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