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Short communication

The synthesis and pharmacological evaluation of indole congeners of the calcium entry blocker verapamil

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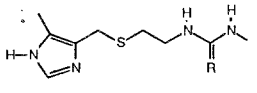
Summary – Based on the notion of a bioisosteric relationship between catechol-(phenol-) and indole-amines, indole congeners of the calcium entry blocker verapamil were synthesized and examined as calcium entry blockers and as alpha$_1$-adrenoceptor antagonists in isolated tissue preparations and as antihypertensive agents in the spontaneously hypertensive rat. Indole **27** exhibited potent calcium entry blockade *in vitro* and displayed antihypertensive activity, albeit slightly less than verapamil. Indole **23** possessed both calcium entry blockade and potent alpha$_1$-adrenoceptor activity *in vitro* but *in vivo* was less active than verapamil as an antihypertensive agent.

Résumé – **Synthèse et évaluation pharmacologique d'analogues indoliques de l'antagoniste du calcium, vérapamil.** *En considération de la notion de bioéquivalence indole-phénol (ou catéchol), des analogues indoliques du vérapamil ont été synthétisés et évalués comme antagonistes du calcium et des adrénorécepteurs alpha$_1$* in vitro, *et pour leurs propriétés antihypertensives* in vivo. *Le dérivé indolique* ***27*** *a démontré des activités intéressantes comme antagoniste du calcium* in vitro *et comme antihypertenseur. Ces effets cependant ont été moins prononcés que dans le cas du vérapamil. L'analogue indolique* ***23*** *s'est avéré très actif comme antagoniste du calcium et des adrénorécepteurs alpha$_1$ in vitro, mais n'a pas produit une activité anti-hypertensive supérieure à celle du vérapamil* in vivo.

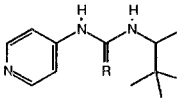
phenol-indole bioisosterism / calcium entry blocker / verapamil analogs

Introduction

The concept of bioisosterism has played a pivotal role in drug design [1, 2]. Such a rationale led in part to the discovery of the antiulcer drug cimetidine **2** [3] and the antihypertensive agent pinacidil **4** [4] in which a thiourea moiety was replaced with an *N*-cyanoguanidine bioisostere.



1. R = S: metiamide
2. R = NCN: cimetidine



3. R =S
4. R = NCN; pinacidil

In recent years phenol-indole bioisosterism has been exploited in the identification of more potent and selective pharmacologically active catechol-, phenol-, and indole-amines and in the elucidation of such ligand-receptor interactions. For example, potent indole congeners of the dopamine agonist **5** [5] and the antihypertensive agent labetolol **7** [6] (Fig. 1) were synthesized based on the premise of a bioisofunctionality between the phenolic hydroxyl and the indolic NH, in that both serve as hydrogen bond donors at the receptor site.

On the other hand, the activities of phenols **9** and **10**, which are related to the dopaminergic indoles pergolide **11** and CQP 201-403 **12** as well as to apomorphine **13**, were ascribed to a rigid pyrrole ethyl amine and phenol ethyl amine pharmacophore of the same absolute stereochemical sense, respectively, rather than phenol-indole bioisofunctionality [7]. In this pharmacophoric model, the phenolic OH and the indolic NH are not coincidental, although it has been noted that the phenolic OH is a critical feature of the dopaminergic pharmacophore [8].

That one aspect of phenol-indole bioisosterism may be related to electronic similarities of these aromatic nuclei is seen in comparing both *in vitro* (5-HT$_2$ receptor binding assay) and *in vivo* (rat and human behavioral tests) correlations of phenethylamines and tryptamines with experimentally measured ionization potentials [9–14]. In this regard, the enhanced potency of tryptamine **15** *vs.* 3,4-

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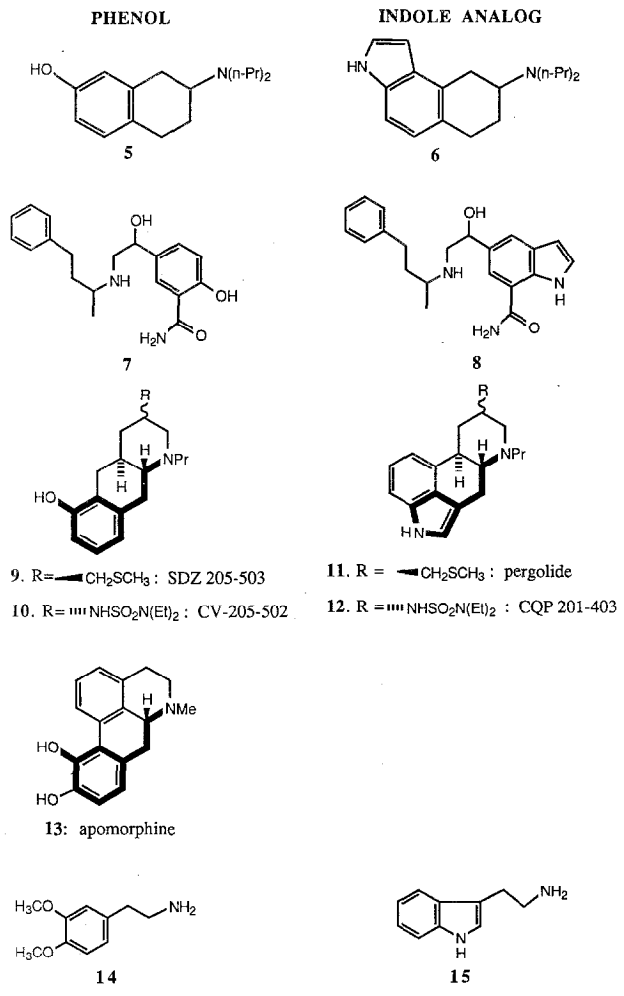
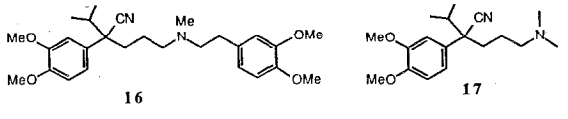


Fig. 1.

dimethoxyphenethylamine **14** may be explained in terms of the lower ionization potential of **15** as compared to **14** [9]. These results support the view that the electronic characteristic of the aromatic moiety may play a crucial role in receptor mediated pharmacological events of many of these phenethylamine derived compounds.

It was within this context that we became interested in a bioisosteric replacement of the phenethylamine portion of the phenylalkylamine class of calcium entry blockers, typified by verapamil **16** [15–19]. Previous structure–activity relationship studies on verapamil have focussed primarily on the chiral quaternary center, the amino moiety and substituent effects about the phenyl ring closest to the quaternary site [20–24]. It is known, however, that the phenethylamine nucleus is essential for calcium entry blockade. Thus, D619 **17** is inactive as a calcium entry blocker [21].



It was anticipated that designing such bioisosteric analogs of verapamil would not only probe phenol-indole bioisosterism further, but would serve as potential approach to the identification of novel potent calcium entry blockers of the phenethylamine class with an enhanced receptor selectivity [25–30] and an improved *in vivo* profile.

We wish to report the synthesis and pharmacological evaluation of two novel indole congeners of verapamil.

Chemistry

The synthesis of indoles **23** and **27** is outlined in Scheme 1. 5-Bromoindole **18** was elaborated to aldehyde **21** according to the sequence: (a) *N*-silylation of the anion of **18** with triisopropylsilyl trifluoromethanesulfonate; (b): metal-halgen exchange with *n*-butyllithium followed by either a boron trifluoride [31] mediated- or copper catalyzed-opening [32] of ethylene oxide to alcohol **20**; and (c) Dess–Martin periodinane [33] oxidation of **20** to aldehyde **21**. Reductive amination of **21** with amine **28** [34] under Borch conditions [35] provided coupled product **22**. Desilylation to **23** was effected with tetra-*n*-butylylammonium fluoride.

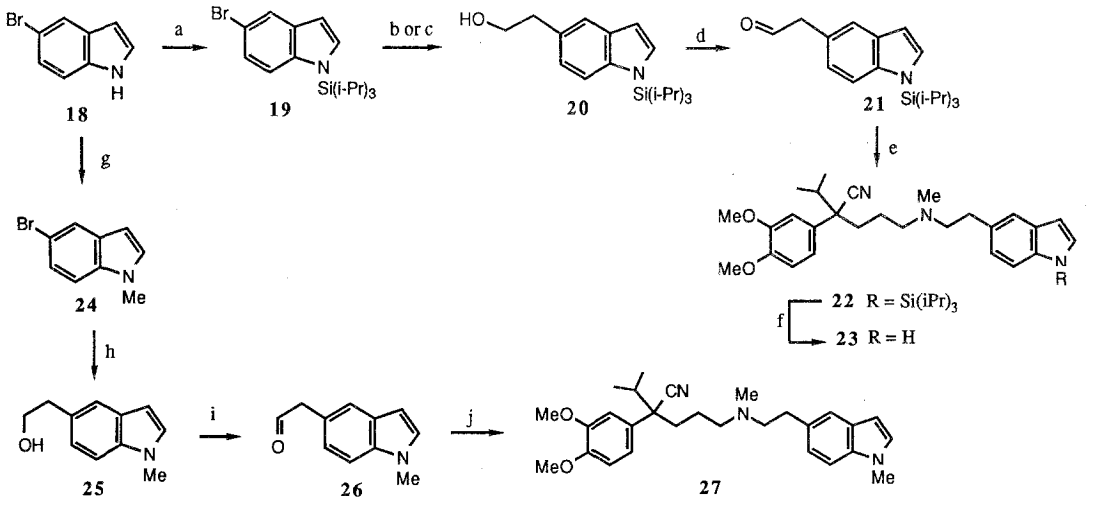
Indole **27** was prepared in an analogous fashion from 5-bromo-*N*-methylindole **24**.

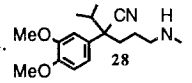
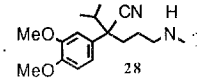
Pharmacology

The calcium entry blocking and alpha$_1$-adrenoceptor antagonist activities of indoles **23** and **27** were evaluated using their hydrochloride salts. Calcium entry blockade was determined by measuring the ability of the test compounds to reverse KCl-induced contractions of rabbit aortic strips [36]. Alpha$_1$-adrenoceptor antagonist activity was measured by determining the compound's ability to induce a rightward parallel shift of the concentration–response curve for phenylephrine-induced contractions of rabbit aortic strips [36].

Indole substitutions for the catechol group of verapamil resulted in compounds with calcium channel blocking activity identical to that of verapamil (Table I). Moreover, these substitutions enhanced alpha$_1$-adrenoceptor antagonist activity, since both **23** and **27** shifted the phenylephrine concentration–response curve rightward to a greater degree than did verapamil (Table I). That **23** is more potent than verapamil and **27** as an alpha$_1$-adrenoceptor antagonist might indicate some sensitivity towards steric bulk about that position of the aryl ring.

Indoles **23** and **27** were also assessed as antihypertensive agents in the spontaneously hypertensive rat (SHR). As shown in Table II both indoles **23** and **27** decreased blood pressure in the SHR maximally within 30–60 min after dosing. Indole **27** was more potent as an antihypertensive agent as compared to indole **23**; however, both indoles were less effective than verapamil in lowering blood pressure in the SHR. At the highest tested dose (25 mg/kg), indole **27** lowered blood pressure by 37% and did not



a. $LiN(TMS)_2$, THF, -78°, then triisopropylsilyl triflate, (100%). b. n-BuLi, THF, -78° to RT; -78°, $BF_3{\cdot}Et_2O$; ethylene oxide (58%).
c. n-BuLi, THF, -78° to RT; -78°; CuI and ethylene oxide (62%). d. Dess-Martin Periodinane, CH_2Cl_2 (76%).
e.  , $NaBH_3CN$, NaOAc, MeOH (86%). f. $N(Bu)_4F$, THF, RT. g. $LiN(TMS)_2$, THF, -78°, then MeI (53%).
h. n-BuLi, THF, 0°, 1 h; -65°, CuI and ethylene oxide, -65° to -40° (45%). i. Dess-Martin Periodinane, CH_2Cl_2 (61%).
j.  , NaOAc, $NaBH_3CN$, MeOH (74%).

Scheme 1.

Table I. Calcium entry blocking and alpha$_1$-adrenoceptor antagonist activities of verapamil, **23** and **27**.

Compound	Activity			
	Calcium entry blocking		Alpha$_1$-adrenoceptor antagonist	
	$(-\log IC_{50})$	*N*	$(-\log K_b)$	*N*
Verapamil HCl	6.5 ± 0.1	3	5.8 ± 0.1	3
23 HCl	6.5 ± 0.1	5	7.5 ± 0.1	3
27 HCl	6.6 ± 0.1	4	6.1 ± 0.1	3

affect heart rate. Verapamil, at the same dose, lowered blood pressure by 47% and significantly depressed heart rate (−16%). Despite potent calcium entry blockade and enhanced alpha$_1$-adrenoceptor antagonist activities *in vitro,* indole **23** lowered blood pressure in the SHR by only 25% at 25 mg/kg; this may be due to a lesser bioavailability of the compound relative to either verapamil or **27.**

In summary, bioisosteric replacement of the catecholamine nucleus of the calcium entry blocker verapamil with an indole equivalent retained potent pharmacological activity both *in vitro* and *in vivo*. These results reinforce further the notion of a phenol−indole bioisosteric relationship based upon electronic similarities of the aromatic nuclei. Such a concept continues to be of value in the design of novel pharmacologically active agents.

Experimental protocols

Pharmacology

In vitro *studies*
Thoracic aortas isolated from male New Zealand white rabbits (1.3–3.0 kg) were cut spirally to yield 3 × 15 mm strips, and equilibrated in an organ bath containing a physiological salt solution as previously described [36]. Calcium entry blocking activity was assessed by measuring the ability of cumulatively-increasing concentrations of a test compound to reverse tonic KCl (80 mM)-induced aortic contractions [36]. The potency of each compound was expressed as the −log of the concentration (M) that inhibited the KCl-induced contraction by 50% $(-\log IC_{50})$ (Table I).

Alpha$_1$-adrenoceptor antagonist activity was measured by assessing the ability of a 1×10^{-5} M concentration of each compound to induce a parallel rightward shift of the phenylephrine concentration−contraction-response curve on the rabbit aorta. The potency of each compound is expressed as its $-\log K_b$ [36] (Table I).

In vivo *studies*
Spontaneously hypertensive rats ranging in weight from 295–360 g, obtained from Charles River (Lakeview, MA) were used for the study. Each rat was anesthetized with halothane, and the left femoral artery was cannulated with polyethylene tubing (PE50). The rats were placed in Bollman cages, and the arterial cannula was connected to a Gould–Statham pressure transducer (Model P23Db), which in turn was attached to a polygraph to record mean arterial blood pressure and heart rate.

Table II. Maximal changes in mean arterial blood pressure and heart rate induced by oral administration of **23, 27**, verapamil, or control vehicle (0.5% methylcellulose) to SHR.

Compound	Dose mg/kg *p.o.*	*N*	Mean arterial pressure		Heart rate	
			Pretreatment[a] (mmHg)	Max % change from pretreatment	Pretreatment beats/min	Max % change from pretreatment
23 HCl	25	4	171 ± 3	−25[c]	466 ± 2	− 6
27 HCl	25	4	186 ± 5	−37[c]	437 ± 6	− 5
	5	4	179 ± 3	−10	397 ± 27	− 4
Verapamil	25	4	185 ± 6	−47[c]	441 ± 10	−16[c]
HCl	10	4	180 ± 3	−25[c]	378 ± 13	+ 8
	5	4	168 ± 3	−12[b]	375 ± 17	+ 9
Control 0.5% methyl-cellulose	0	4	183 ± 3	− 3	400 ± 20	+ 7

[a]Pretreatment values are means ± SEM.
[b]$P<0.05$.
[c]$P<0.01$ when compared to control group using Dunnett's *t*-test for multiple comparisons.

The animals were allowed 1 h to recover from anesthesia. Then the test compounds, all suspended in a solution of 0.5% methylcellulose were administered orally in a vol of 5 ml/kg to SHR. Four rats were used for each dose of each compound. A solution of methylcellulose was similarly administered to a group of 4 rats that served as vehicle-treated controls. Mean arterial blood pressure (MABP) and heart rate (HR) were recorded prior to and for 240 min after drug administration.

Maximum changes in MABP and HR produced by the test compound or the control vehicle were compared using Dunnett's *t*-test for multiple comparisons and the differences were considered significant if $P<0.05$.

Chemistry

Melting points were determined in open capillary tubes on a Thomas–Hoover apparatus and are uncorrected. IR spectra were taken on a Beckman Aculab 2 or on a Perkin–Elmer 291 spectrophotometer. ^{1}H NMR spectra were obtained at 200 MHz on a Varian XL-200 instrument, using $CDCl_3$ as solvent unless stated otherwise and tetramethylsilane as an internal standard. Chemical shifts are reported δ units, and coupling constants are in Hertz. Mass spectra were recorded on a Hewlett–Packard 9876A spectrometer. Flash chromatography refers to the technique described by Still [37]. Thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was effected with UV light and one of the following stains: 10% phosphomolybdic acid in ethanol, ceric ammonium sulfate (100 mg/10 ml of 35% sulfuric acid), or anisaldehyde (1 ml/1 ml sulfuric acid/18 ml ethanol). R_f refers to the ratio of the distance of the spot from the origin to that of the solvent front. Solvents for TLC are indicated. CHN analyses were measured on a Perkin–Elmer 240 analyzer. Anhydrous ether and THF were distilled from sodium/benzophenone. Dry methylene chloride was distilled from calcium hydride.

*5-Bromo-1-[tris(1-methylethyl)silyl]-1*H*-indole* ***19***

To 3.00 g (15.8 mmol) of 5-bromoindole **18** in dry THF (150 ml) at −78° was added slowly 24.5 ml (24.5 mmol) of lithium bis(trimethylsilyl)-amide (1.0 M in THF). Triisopropylsilyl trifluoromethanesulfonate (7.62 ml, 28.3 mmol) was then added. The cold bath was removed and stirring was continued for 1 h. The reaction mixture was decanted into a mixture of 100 ml of pH 7 buffer and 100 ml of brine and then was extracted into ether. The combined etheral extracts were washed with 0.1 M HCl and twice with brine. Drying ($MgSO_4$) followed by flash chromatography (petroleum ether) provided 5.48 g (100%) of the product as a colorless oil: R_f (hexane) 0.40; ^{1}H NMR δ 7.75 (d, 1H, J = 1.9 Hz), 7.38 (d, 1H, J = 8.9 Hz), 7.25 (dd, 1H, J = 3.2 Hz), 7.22 (dd, 1H, J = 1.9, 8.9 Hz), 6.57 (dd, 1H, J = 0.6, 3.2 Hz), 1.68 (septet, 3H, J = 7.6 Hz), and 1.14 ppm (d, 18H, J = 7.6 Hz); mass spectrum, m/e 353, 351, 308, 310 and 229. Anal. ($C_{17}H_{26}NBrSi$) C, H, N.

*1-[Tris(1-methylethyl)silyl]-1*H*-indole-5-ethanol* ***20***

Procedure A. To 575 mg (1.63 mmol) of **19** in anhydrous ether (13 ml) at −78° was added *n*-butyllithium (20 ml, 4.0 mmol; 2.0 M in hexane). The bath was removed and stirring was continued for 1 h at room temperature. The reaction mixture was recooled to −78° and was treated with boron trifluoride etherate (200 μl, 3.2 mmol) followed immediately by rapid cannulation of a precooled (−78°) solution of ethylene oxide (1.5 g, 40 mmol) in ether (10 ml). After 15 min, the reaction mixture was decanted into brine and was extracted into ethyl-acetate (3 ×). The combined organic extracts were washed with brine (3 ×), dried ($MgSO_4$), and flash chromatographed (CH_2Cl_2) to provide 300 mg (58%) of the product as a colorless oil: R_f (CH_2Cl_2) 0.30; ^{1}H NMR δ 7.48 (s, 1H, J = 9.2 Hz), 7.25 (d, 1H, J = 3.2 Hz), 7.00 (dd, 1 H, J = 1.9, 8.7 Hz), 6.58 (d, 1H, J = 3.2 Hz), 3.91 (q, 2H, J = 6 Hz), 2.96 (t, 1H, J = 6.7 Hz), 1.70 (septet 3H, J = 7 Hz), and 1.15 ppm (d, 18H, J = 7 Hz); IR ($CHCl_3$) 3600 cm^{-1} (OH); mass spectrum, m/e 317, 286, and 274. Anal. ($C_{19}H_{31}NOSi$) C, H, N.

Procedure B. To 11.6 g (50 mmol) of **19** in THF at −78° was added dropwise 62.5 ml of *n*-butyllithium (125 mmol; 2.0 M in hexane). The bath was removed and stirring was continued for 1 h. The reaction mixture was recooled to −78° and was cannulated into a suspension of copper(I) iodide (1.90 g, 20 mmol) in a solution of ethylene oxide (*ca.* 50 g) in THF at −78°. After stirring at −40° for 2 h, pH 7 buffer (250 ml) was added dropwise. The resulting mixture was diluted with brine (100 ml), filtered through Celite, and washed successively with ammonium hydroxide (200 ml; 3 M) and then brine (3 × 200 ml), dried ($MgSO_4$), and then flashed chromatographed (CH_2Cl_2) to afford 9.88 g (62%) of the title compound.

*1-[Tris(1-methylethyl)silyl]-1*H*-indole-5-acetaldehyde* ***21***

To a solution of 140 mg (0.44 mmol) of **20** in dry CH_2Cl_2 was slowly added a solution of Dess–Martin Periodinane (243 mg, 0.57 mmol) in CH_2Cl_2. After 45 min, the reaction mixture was directly flash-chromatographed (CH_2Cl_2) to afford 106 mg (76%) of the product as a pale yellow oil. The material obtained in this fashion is somewhat unstable and is used directly in the next reaction. In larger runs (5.9 g of crude **21**) the yield of the product dropped to 42%: R_f (50% CH_2Cl_2–petroleum ether) 0.66; ^{1}H NMR δ 9.78 (t, 1H, J = 2.54 Hz), 7.50 (d, 1H, J = 7.9 Hz), 7.48 (s, 1H), 7.27 (d, 1H, J = 3.5 Hz), 6.97 (dd, 1H, J = 1.6, 8.6 Hz), 6.60 (d, 1H, J = 3.2 Hz), 3.74 (d, 2H, J = 3.2 Hz), 1.7 (septet, 3H,

J = 7.6 Hz), and 1.15 ppm (d, 18H, J = 7.6 Hz); IR ($CHCl_3$) 1720 cm^{-1} (C=O); mass spectrum, m/e 315, 272. Anal. ($C_{19}H_{29}NOSi$) C, H; N: Calcd. 4.44; Found 5.12.

α-[3-[[2-(1H-Indol-5yl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)benzeneacetonitrile ***23*** *hydrochloride*

A solution of amine **28** (93 mg, 0.32 mmol) and aldehyde **21** (101 mg, 0.32 mmol) in methanol (10 ml) containing 52.5 mg (0.64 mmol) of sodium acetate was stirred at room temperature for 30 min. To the reaction mixture was added sodium cyanoborohydride (20.1 mg, 0.32 mmol). After stirring overnight at room temperature, the reaction mixture was quenched with 10 ml of 1 M sodium hydroxide solution, and was extracted into ether (3 × 25 ml). The combined organic extracts were washed with brine (3 × 40 ml), dried, and flash chromatographed (97:3 $CHCl_3$/MeOH) to give 162 mg (86%) of **22** as an oil: R_f ($CHCl_3$/MeOH 97:3) 0.28; ^1H NMR δ 7.4 (m, 2H), 7.21 (d, 1H, J = 3.2 Hz), 6.8–7.0 (m, 4H), 6.54 (d, 1H, J = 3.2 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 2.2–2.8 (m, 6H), 2.21 (s, 3H), 1.9–2.2 (m, 4H), 1.68 (septet, 3H), 1.18 (d, 3H), and 0.78 ppm (d, 3H); mass spectrum, m/e 589 and 303.

To 3.03 g (5.14 mmol) **22** in THF (50 ml) at 0° was added 6.2 ml (6.2 mmol) of tetrabutylammonium fluoride (1 M in THF). After stirring at 0° for 20 min, the reaction mixture was concentrated and directly flash-chromatographed (CH_2Cl_2/NEt_3 9:1) to provide 2.35 g of **23** as a colorless oil. ^1H NMR ($CDCl_3$) δ 8.1 (bs, 1H), 7.41 (s, 1H), 7.30 (d, 1H, J = 8.3 Hz), 7.17 (t, 1H, J = 3.2 Hz), 6.98 (dd, 1H, J = 1.3, 8.3 Hz), 6.7–6.9 (m, 3H), 6.47–6.49 (m, 1H), 3.85 (s, 6H), 2.20 (m, 5H), 1.5–2.2 (m, 5H), 1.16 (d, 3H), and 0.77 ppm (s, 3H); IR ($CHCl_3$) 3480 cm^{-1}; mass spectrum, m/e 303.

The product was dissolved in ethanol (7 ml) and was treated with 2.1 ml of 2.4 M ethanolic HCl. Evaporation of ethanol and recrystallization of the residue from ether/ethanol provided 2.02 g (83%) of the title compound as colorless crystals (mp 84–88°): ^1H NMR (DMSO) δ 11.2 (bs, 1H), 10.8 (d, 1H), 7.3–7.35 (m, 3H), 6.9–6.70 (m, 4H), 6.35 (m, 1H), 3.79, 3.77, 3.75, 3.73 (4 singlets, 6H), 1.11 (d, 3H), and 0.69 ppm (d, 3H); IR (KBr) 3480, 3200, and 2500 cm^{-1}. Anal. ($C_{27}H_{36}ClN_3O_2$) H, N; C: Calcd. 68.99; Found 67.97.

5-Bromo-1-methyl-1H-indole ***24***

At −78° to 49 g (0.25 mol) of **18** in anhydrous THF (1 l) was added lithium bis(trimethylsilyl)amide (400 ml, 0.4 mol; 1.0 M in THF). Methyl iodide (29 ml, 1.85 equiv.) was added and the reaction was warmed to room temperature overnight. The mixture was decanted into brine (1000 ml) and was extracted into ethyl acetate (3 × 250 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was combined with crude product obtained from a similar run of 19.6 g of **18** and purified by flash chromatography (hexane/ethyl acetate 19:1) and recrystallization from hexane to provide 39.6 g (53%) of the title compound, mp 42–43°: R_f (CH_2Cl_2/hexane 1:1) 0.77; ^1H NMR δ 7.74 (d, 1H, J = 1.9 Hz), 7.26 (dd, 1H, J = 8.6, 1.6 Hz), 7.18 (d, 1H, J = 8.6 Hz), 7.05 (d, 1H, J = 3.2 Hz), 6.41 (d, 1H, J = 3.2 Hz) and 3.77 ppm (s, 3H); IR ($CHCl_3$) 3000 cm^{-1}; mass spectrum, m/e 209 and 211. Anal. (C_9H_8BrN) C, H, N.

1-Methyl-1H-indole-5-ethanol ***25***

At 0° to a solution of **24** (21.1 g, 100 mmol) in 350 ml of anhydrous THF and ether (100 ml) *n*-butyllithium (125 ml, 0.25 mol; 2.0 M in hexane) was added. After stirring at room temperature for 90 min, the reaction mixture was cooled to −65° and cannulated over a 30-min period into a suspension of 3.8 g (0.2 equiv) of copper(I) iodide and ethylene oxide (*ca.* 20 g) in 120 ml of anhydrous ether at −65°. The reaction mixture was stirred at −40° for 3 h and then cooled to −65°. Aqueous citric acid (10%, 440 ml) was added slowly and mixture partitioned between ethyl acetate (200 ml) and brine (200 ml). The aqueous phase was further extracted into ethyl acetate (2 × 200 ml), dried ($MgSO_4$), and flash-chromatographed (CH_2Cl_2) to give 7.89 g of pure product (45%). An analytical sample was obtained as a waxy solid (mp 51–52°): R_f (ether) 0.69; ^1H NMR ($CDCl_3$) δ 7.45 (s, 1H), 7.28 (d, 1H), 7.10 (dd, 1H), 7.05 (d, 1H), 6.40 (d, 1H), 3.90 (q, 2H), 3.75 (s, 3H), 2.95 (t, 2H), and 1.42 ppm (1H); IR ($CHCl_3$) 3320 and 3190 cm^{-1}; mass spectrum, m/e 175 and 144. Anal. ($C_{11}H_{13}NO$) C, H, N.

1-Methyl-1H-indole-5-acetaldehyde ***26***

To a solution of 6.50 g (15.4 mmol) of Dess–Martin Periodinane in 70 ml of CH_2Cl_2 was added a solution of 2.07 g (11.8 mmol) of **25** in 200 ml of CH_2Cl_2. After 2.5 h, the reaction mixture was diluted with 100 ml of CH_2Cl_2, and was successively washed with aq. $NaHCO_3$ (2 × 100 ml) and brine (2 × 100 ml). Drying ($MgSO_4$) and flash chromatography (CH_2Cl_2) provided 1.24 g (61%) of the pure product as an oil. The product so obtained is unstable and is used directly in the next reaction: R_f (CH_2Cl_2) 0.4: ^1H NMR δ 9.75 (t, 1H), 7.48 (s, 1H), 7.35 (d, 1H), 7.05 (dd, 1H), 7.08 (s, 1H), 6.45 (d, 1H), 3.78 (s, 1H), and 3.75 ppm (d, 1H); IR ($CHCl_3$) 1710 cm^{-1}.

3,4-Dimethoxy-α-(1-methylethyl)-α-[3-[methyl[2-(1-methyl-1H-indol-5-yl)ethyl]amino]propyl]benzeneacetonitrile ***27*** *hydrochloride*

To a solution of amine **28** (HCl salt, 2.52 g, 0.31 mol) and aldehyde **26** (2.51 g, 7.7 mol) in methanol (15 ml) containing 2.52 g (31 mmol) of sodium acetate sodium cyanoborohydride (490 mg, 7.8 mmol) was added. After stirring at room temperature overnight, the reaction mixture was quenched with 25 ml of 1.0 M sodium hydroxide and was partitioned between brine (50 ml) and CH_2Cl_2 (50 ml). The aqueous layer was further extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried (K_2CO_3) and flash-chromatographed ($CHCl_3$/MeOH 97:3) to give pure amine (2.55 g, 74%) as a foam: R_f ($CHCl_3$/MeOH 9:1) 0.55; ^1H NMR δ 7.39 (s, 1H), 7.22 (d, 1H, J = 8.8 Hz), 6.99–7.1 (m, 2H), 6.7–6.9 (m, 3H), 6.4 (dd, 1H, J = 0.9, 2.9 Hz), 2.21 (s, 3H), 1.16 (d, 3H, J = 6.7 Hz), and 0.77 ppm (d, 3H, J = 6.7 Hz); mass spectrum, m/e 447 and 303.

The product was dissolved in ethanol (2.5 ml) and treated with 2.36 ml of ethanolic HCl. Evaporation to dryness and recrystallization from ether/ethanol gave 2.30 g of the title compound as a beige solid, mp 80–85°: ^1H NMR (DMSO) δ 7.3–7.4 (m, 3H), 6.9–7.0 (m, 4H), 6.35 (d, 1H), 2.69 (d, 3H), 1.11 (d, 3H), and 0.69 ppm (d, 3H); IR (KBr) 3430, and 2610 cm^{-1}; Anal. ($C_{28}H_{28}ClN_3O_2 \cdot 0.5\ H_2O$) C, H, N.

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