The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor. 2: 2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione Analogues

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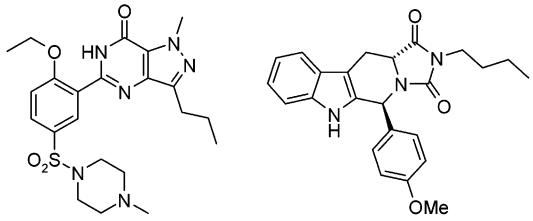
Modification of the hydantoin ring in the previously described lead compound **2a** has led to the discovery of compound **12a**, tadalafil, a highly potent and highly selective PDE5 inhibitor. The replacement of the hydantoin in compound **2a** by a piperazinedione ring led to compound *cis*-**11a** which showed similar PDE5 inhibitory potency. Introduction of a 3,4-methylenedioxy substitution on the phenyl ring in position 6 led to a potent PDE5 inhibitor *cis*-**11c** with increased cellular potency. Optimization of the chain on the piperazinedione ring led to the identification of the racemic *cis*-*N*-methyl derivative **11i**. High diastereospecificity for PDE5 inhibition was observed in the piperazinedione series with the *cis*-(6*R*,12a*R*) enantiomer displaying the highest PDE5 inhibitory activity. The piperazinedione **12a,** tadalafil (GF196960), has been identified as a highly potent PDE5 inhibitor (IC_{50} = 5 nM) with high selectivity for PDE5 vs PDE1−4 and PDE6. Compound **12a** displays 85-fold greater selectivity vs PDE6 than sildenafil **1**. **12a** showed profound and long-lasting blood pressure lowering activity (30 mmHg/ >7 h) in the spontaneously hypertensive rat model after oral administration (5 mg/kg).

Introduction

Inhibition of cyclic nucleotide phosphodiesterase type 5 (PDE5) as a therapeutic target has received considerable attention in recent years, particularly for the treatment of cardiovascular diseases, e.g., angina, hypertension, and congestive heart failure.[1,2] Research in this area was refocused and stimulated by the demonstration of the role of PDE5 in penile erection and the recognition that PDE5 inhibition would be useful in treating male erectile dysfunction (MED).[3] After these discoveries, sildenafil **1** (Viagra)[4] was approved for the treatment of MED.[5,6] Despite the efficacy of sildenafil, clinically significant adverse effects have been noted,[7] and it has been proposed that some of these side effects may be due to a lack of selectivity for PDE5.[8] Notably, visual disturbances could stem from inhibition of the retina-specific PDE enzyme, namely, PDE6, involved in vision signal transduction. We describe the discovery of a structurally different series of PDE5 inhibitors that show greatly enhanced PDE5 selectivity, most significantly vs PDE1 and PDE6.

Previously,[9] we described the discovery of a series of hydantoins and the identification of butyl hydantoin **2a** as a potent and selective inhibitor of PDE5 (Chart 1). This compound was found to be highly potent on PDE5 enzyme, selective versus the other phosphodiesterases, and capable of increasing intracellular cGMP levels in rat smooth muscle cells (RSMC assay). However, hydantoin **2a** displayed poor hypotensive activity in spontaneously hypertensive rats after oral administration (30 mg/kg). The objective of our research in the early 1990s was to identify a novel chemical series of potent and selective inhibitors of PDE5, especially vs PDE1 and PDE6, with improved pharmacokinetic and pharmacological profiles.

Chart 1



In the present paper, we describe the results we obtained by modification of the hydantoin ring in compound **2a** to discover piperazinedione **12a** (GF 196960, tadalafil), a highly potent, selective, efficacious, and orally bioavailable inhibitor of PDE5.

Chemistry

Racemic compounds bearing structural modifications of the hydantoin ring were prepared from key intermediates **3a,c** (*cis* or *trans*), as presented in Scheme 1. The hydantoin *cis*-**2a** was prepared as described in the previous paper[9] by treatment of *cis*-aminoester **3a** with butyl isocyanate in refluxing 2-butanone. Reduction of the carbonyl groups of **2a** with a large excess of lithium aluminum hydride in THF according to the literature procedure[10] led to the formation of the imidazolidine derivative **4**. Treatment of *cis*-**3c** with a large excess of methylamine in methanol[11] gave the corresponding amide **5**. Reduction of the amide **5** with lithium aluminum hydride in refluxing THF, followed by cyclization

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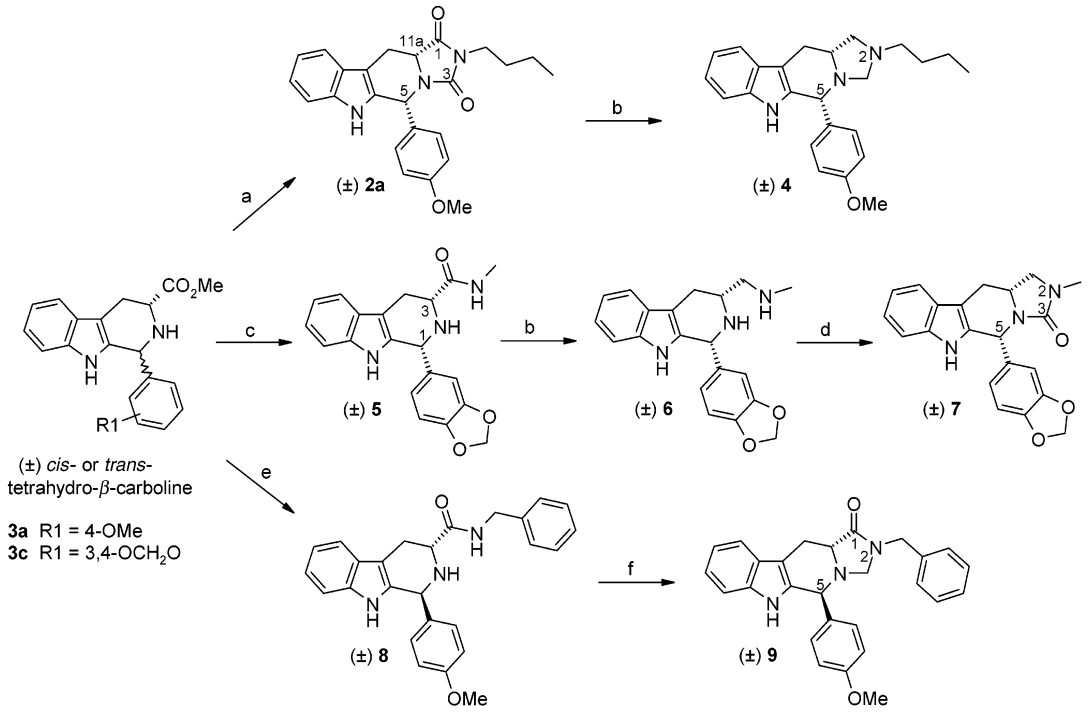
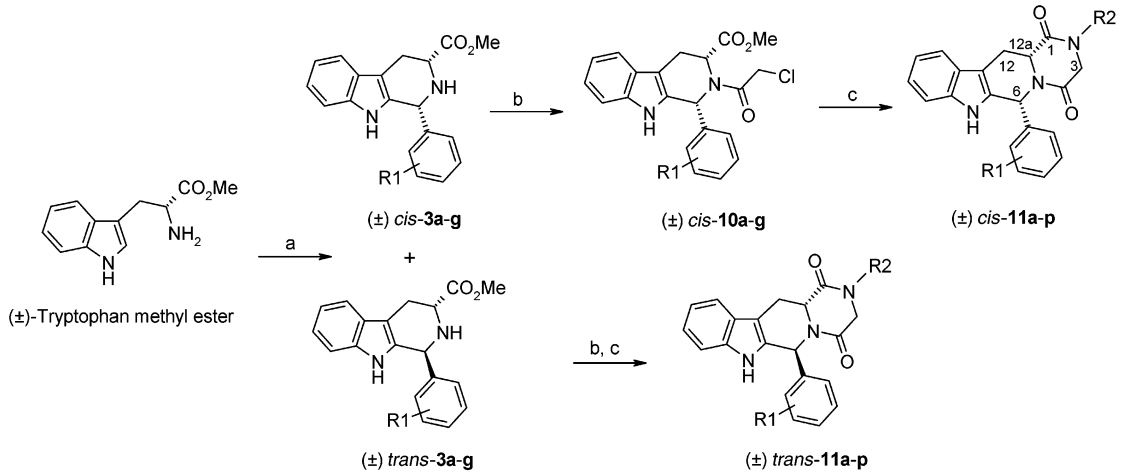
Scheme 1[a]



[a] Conditions: (a) Bu-NCO, 2-butanone, reflux; (b) $LiAlH_4$, THF, 40 °C; (c) Me-NH_2, MeOH; (d) triphosgene, CH_2Cl_2; (e) $PhCH_2NH_2$; (f) $(HCHO)_n$, toluene.

Scheme 2[a]



[a] Conditions: (a) R1-Ph-CHO, CF_3CO_2H, CH_2Cl_2; (b) chloroacetyl chloride, Et_3N, CH_2Cl_2 or $NaHCO_3$, $CHCl_3$; (c) R2−NH, MeOH, reflux.

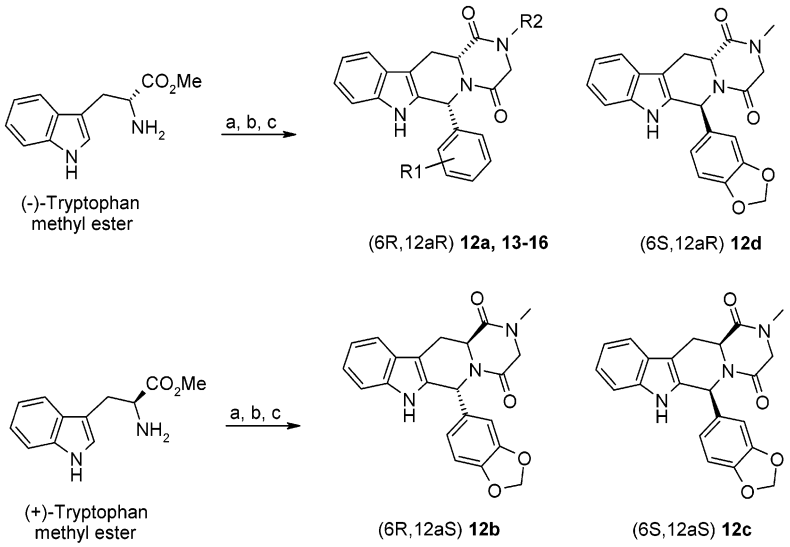
of the diamine intermediate **6** in the presence of triphosgene or 1,1′-carbonyldiimidazole,[12] led to the formation of 3-oxo-derivative **7**. The benzyl amide **8**, obtained by heating *trans*-**3a** with benzylamine, was cyclized to give imidazolidinone derivative **9** using paraformaldehyde in refluxing toluene.

Piperazinedione derivatives *cis*- and *trans*-**11a**−**p** were prepared via the elaboration of key intermediate **3a**−**g** as illustrated in Scheme 2. The modified Pictet−Spengler reaction, starting from racemic tryptophan methyl ester, was used to generate the *cis*- and *trans*-tetrahydro-*β*-carbolines **3a**−**g** as described in the previous paper.[9] Chloroacetylation of the *cis*- or *trans*-*β*-carbolines **3a**−**g**, in the presence of triethylamine or sodium hydrogen carbonate as base, provided, respectively, the *cis*- and the *trans*-chloroacetyl derivatives **10a**−**g** in good yield. The piperazinedione derivatives *cis*- and *trans*-**11a**−**p** were then obtained by ring closure of the *cis*- or *trans*-chloroacetyl derivatives **10a**−**g** in the presence of primary amines in refluxing methanol. Chiral derivatives **12a**, **12d**, **13**−**16** and **12b**, **12c** were prepared using the same route as shown in Scheme 2 but starting from, respectively, D-(−) and L-(+) tryptophan methyl ester as starting materials (Scheme 3). The piperazinedione **12a** was subjected to chiral HPLC analysis, and no trace of diastereoisomers **12b**−**d** was detected, indicating that no racemization occurred during the process.

Results and Discussion

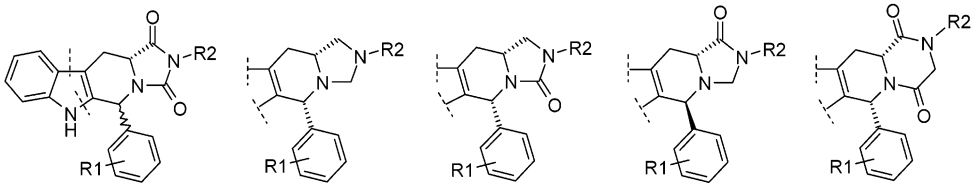
Compounds were evaluated in an in vitro assay for inhibitory activity against bovine PDE5. Each compound was evaluated in two steps. The first step was the

Scheme 3[a]



[a] Conditions: (a) R1−Ph-CHO, CF_3CO_2H, CH_2Cl_2; (b) chloroacetyl chloride, $NaHCO_3$, $CHCl_3$; (c) R2−NH_2, MeOH, reflux.

Table 1. PDE5 Inhibition and Cellular Activity: Modification of the Hydantoin Ring



			PDE5	RSMC
compd	R1	R2	IC_{50} (μM)[a]	EC_{50} (μM)
cis-**2a**	4-OMe	butyl	0.008	0.7
cis-**4**	4-OMe	butyl	>10	nd[b]
cis-**2b**	4-OMe	methyl	0.010	1
cis-**7**	3,4-OCH_2O	methyl	0.060	>10
trans-**2c**	4-OMe	benzyl	0.018	>10
trans-**9**	4-OMe	benzyl	0.060	>10
trans-**2d**	3,4-OCH_2O	benzyl	0.006	3
cis-**11a**	4-OMe	butyl	0.005	1.5

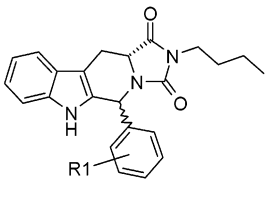
[a] IC_{50} values were reproducible to ±25%. [b] Not determined.

determination of the percentage of inhibition at 10 μM performed in triplicate. For compounds displaying a percentage of inhibition greater than 50% at 10 μM, the IC_{50} was determined from a concentration−response curve using concentrations of 1 nM, 10 nM, 100 nM, 1 μM, and 10 μM, each tested in duplicate. IC_{50} values were reproducible to ±25%. Selectivity toward other PDEs was evaluated using similar assays. Rat PDE5 was not available at the time, but it was known that there is 94.3% homology between rat and bovine PDE5.[13] We therefore made the assumption that our PDE5 inhibitors would exhibit similar potency against the rat enzyme as against bovine. Selected compounds were then tested in a cellular assay using atrial natriuretic factor treated rat aortic smooth muscle cells (RSMC). This assay is designed to reveal the ability of the tested compound to increase intracellular cGMP concentration in cells. In this assay the EC_{50} values were determined as the concentration giving half-maximal increase of cGMP observed with saturating compound concentration. Finally, spontaneously hypertensive rat model (SHR) was used to measure blood pressure lowering ability of the best compounds.

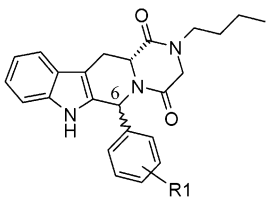
Compounds were initially prepared in racemic form. Both *cis*- and *trans*-isomers were synthesized since we had previously shown that in the hydantoin series[9] the isomers gave equivalent potency of PDE5 inhibition.

Modification of the Hydantoin Ring. Modification of the fused hydantoin ring system led to the following general conclusions (Table 1): Deletion of the two carbonyl groups (*cis*-**2a** vs *cis*-**4**) led to a marked decrease in potency, whereas removal of the lower carbonyl group (*trans*-**2c** vs t*rans*-**9**) was only marginally deleterious. The analogue lacking the upper carbonyl group (*cis*-**2b** vs *cis*-**7**) also showed slightly decreased potency (the 4-methoxy substituent on the pendant phenyl group was essentially equivalent to the 3,4-methylenedioxy group *trans*-**2c** vs *trans*-**2d**). As noted previously,[9] there was little difference in potency between the *cis*- and *trans*-hydantoin compounds (*cis*-**2a** vs *trans*-**2a**).

Table 2. PDE5 Inhibition and Cellular Activity: SAR on the Phenyl Ring in C-6 Position



Hydantoin Series **2**



Piperazinedione Series **11a-11g**

compd	R1	PDE5 IC_{50} (μM)[a]	RSMC EC_{50} (μM)
cis-**2a**	4-OMe	0.008	0.7
trans-**2a**	4-OMe	0.005	1
cis-**11a**	4-OMe	0.005	1.5
trans-**11a**	4-OMe	0.070	>10
cis-**11b**	H	0.091	>10
cis-**11c**	3,4-OCH_2O	0.005	0.6
trans-**11c**	3,4-OCH_2O	0.138	3.5
cis-**11d**	4-CN	0.758	nd[b]
cis-**11e**	4-Cl	0.015	>10
cis-**11f**	4-Me	0.026	0.35
cis-**11g**	3,4-OMe	62%[c]	nd[b]

[a] IC_{50} values were reproducible to ±25%. [b] Not determined. [c] % Inhibition at 10 μM.

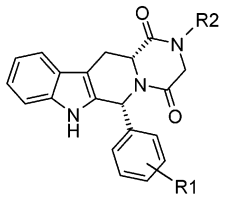
Since it appeared that retention of the two carbonyl groups was nevertheless beneficial, we decided to expand the hydantoin ring to the six-membered piperazinedione system. Gratifyingly, the piperazinedione *cis*-**11a** retained the PDE5 inhibitory potency of the corresponding hydantoin *cis*-**2a**, with a similar functional effect on the intracellular cGMP concentration in ANF-treated rat aortic smooth muscle cells (Table 1).

Modification at the C-6 Position. Having shown that a hydantoin ring can be replaced by a piperazinedione heterocycle, we turned our attention to the exploration of the SAR around the C-6 aryl substituent. A series of substituted phenyl groups was incorporated at C-6 position and the results are shown in Table 2.

Substitution on the C-6 aromatic ring with electron-donating groups generally increased inhibitory potency compared with the unsubstituted compound **11b**. The best results were obtained with the 4-methoxy (*cis*-**11a**) and 3,4-methylenedioxy substituents (*cis*-**11c**) where an 18-fold improvement in PDE5 inhibitory potency was observed, compared to the unsubstituted analogue **11b**. In contrast, introduction of strong electron-withdrawing groups such as cyano (*cis*-**11d**) at the 4-position of the phenyl ring resulted in a marked decrease in PDE5 inhibitory activity. Introduction of the weaker electron-withdrawing chlorine atom in the para position (*cis*-**11e**) retained the PDE5 inhibitory activity but totally lost functional activity in the cellular assay. Substitution at the 4-position with a methyl group (*cis*-**11f**) also resulted in improved potency vs PDE5 compared with the unsubstituted compound **11b**. Disubstitution of the phenyl ring at positions 3 and 4 by methoxy groups (*cis*-**11g**) led to a complete loss in activity on PDE5. Interestingly, the conformationally constrained 3,4-methylenedioxy analogue, *cis*-**11c**, retained good PDE5 inhibitory potency, suggesting that 3,4-substitution needs to be sterically compact.

We next investigated the stereochemical requirements for PDE5 inhibitory activity in the piperazinedione series. As shown in Table 2, the *cis*-diastereoisomers were found to be significantly more potent than the corresponding *trans*-diastereoisomers (cf. *cis*-**11a**, **-11c** vs *trans*-**11a**, **-11c**). These results are in marked contrast to the results previously obtained in the hydantoin series where the *cis*- and *trans*-isomers **2a** showed equivalent PDE5 inhibitory potencies.[9]

Table 3. PDE5 Inhibition and Cellular Activity: SAR on the Piperazinedione Ring



Piperazinediones **11h-p**

compd	R1	R2	PDE5 IC_{50} (μM)[a]	RSMC EC_{50} (μM)
cis-**11a**	4-OMe	butyl	0.005	1.5
cis-**11c**	3,4-OCH_2O	butyl	0.005	0.6
cis-**11h**	3,4-OCH_2O	hydrogen	0.012	0.6
cis-**11i**	3,4-OCH_2O	methyl	0.005	0.5
cis-**11j**	4-OMe	methyl	0.041	0.2
cis-**11k**	4-OMe	ethyl	0.009	0.5
cis-**11l**	3,4-OCH_2O	c.hexyl	0.005	0.3
cis-**11m**	3,4-OCH_2O	i-propyl	0.006	0.5
cis-**11n**	4-OMe	CH_2-c.propyl	0.006	0.5
cis-**11o**	4-Me	CH_2-c.propyl	0.023	0.6
cis-**11p**	3,4-OCH_2O	benzyl	0.003	0.8

[a] IC_{50} values were reproducible to ±25%.

N-Substitution of the 1,4-Piperazinedione. Retaining the best 6-aryl substituents (4-MeO, 3,4-OCH_2O, and 4-Me) and the *cis*-relative stereochemistry, different N-substituted piperazinedione derivatives were evaluated for their impact on PDE5 inhibition and functional activity. Results are shown in Table 3. It is apparent that a wide range of N-alkyl groups is tolerated on the piperazinedione ring, similar to what has been observed in the hydantoin series.[9]

Absolute Stereochemical Requirement for PDE5 Inhibition. The two pairs of enantiomers **12a,c** and **12b,d** were prepared and evaluated for PDE5 inhibitory potency (Table 4). In the *cis*-isomer series the (6*R*,12a*R*) diastereoisomer **12a** was the more potent PDE5 inhibitor, while in the enantiomeric *cis*-compound of (6*S*,12a*S*) absolute configuration **12c** was inactive at concentrations up to 10 μM. Of the two *trans*-compounds the (6*R*,12a*S*) enantiomer **12b** was significantly more potent than the (6*S*,12a*R*) isomer **12d**. Compound **12a** was found to be 18-fold more potent than **12b** and 1200-fold more potent than **12d** on PDE5, demonstrating the critical stereochemical requirement at position-6 for a R absolute configuration to display strong PDE5 inhibitory activities in this piperazinedione series.

Table 4. PDE5 Inhibition and Absolute Configuration

compd	configuration	PDE5 IC_{50} (μM)[a]
12a	(6*R*,12a*R*)	0.005
12b	(6*R*,12a*S*)	0.090
12c	(6*S*,12a*S*)	>10
12d	(6*S*,12a*R*)	6

[a] IC_{50} values were reproducible to ±25%.

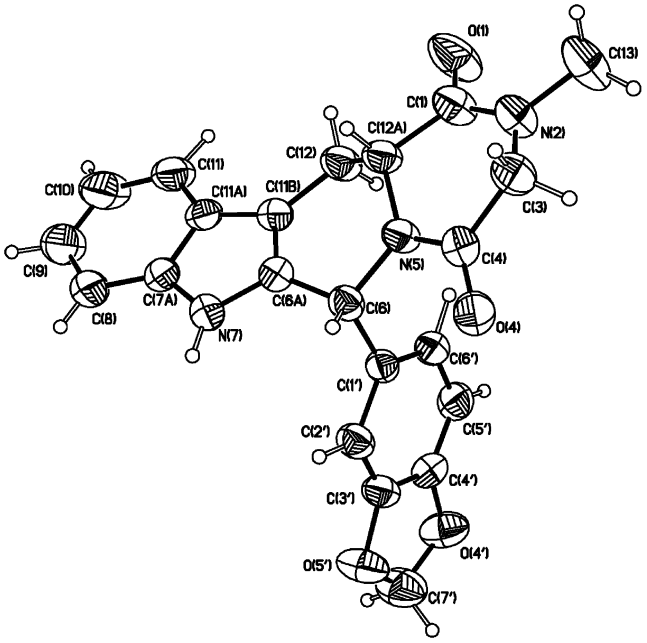
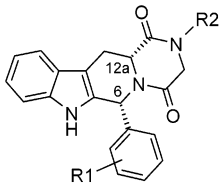


Figure 1. X-ray Crystal Structure for Compound **12a**.

Table 5. PDE5 Inhibition and Cellular Activity: (6*R*,12a*R*) Enantiomers of Selected Piperazinediones



(6R,12aR)-Piperazinediones **12a,13-16**

compd	R1	R2	PDE5 IC_{50} (μM)[a]	RSMC EC_{50} (μM)
12a	3,4-OCH_2O	methyl	0.005	0.15
13	3,4-OCH_2O	butyl	0.003	1
14	3,4-OCH_2O	i-propyl	0.008	0.15
15	4-OCH_3	c.pentyl	0.017	0.2
16	3,4-OCH_2O	hydrogen	0.011	0.3

[a] IC_{50} values were reproducible to ±25%.

The relative stereochemistry of compound **12a** was confirmed by crystal X-ray structure determination as illustrated in Figure 1.

The stereochemically preferred (6*R*,12a*R*) isomers of a selection of the most potent racemic *cis*-compounds were prepared (Table 5). Compound **12a** was chosen for further study based on its potency vs PDE5 and in the RSMC assay.

Phosphodiesterase Selectivity. As shown in Table 6, compound **12a** is highly selective for PDE5 vs PDE1−4. More significantly, compound **12a** shows considerably greater selectivity vs PDE6 compared to sildenafil **1**. Furthermore, these two compounds displayed the same IC_{50} against both bovine and human recombinant PDE5 (data not shown).

Acute Effects of Compound 12a on Blood Pressure. Compound **12a** was evaluated in the conscious spontaneously hypertensive rat model (SHR), which is generally considered as a reference model for antihypertensive drug evaluation. As shown in Figure 2, compound **12a** (5 mg/kg) reduced mean blood pressure by 30 mmHg within the first 30 min, and the fall in blood pressure was maintained for at least 7 h after oral administration.

Consistent with the in vivo activity observed, a pharmacokinetic study (Table 7) demonstrated that compound **12a** has an excellent pharmacokinetic profile in the rat with a bioavailability of 63% and a low plasma clearance, indicative of a high metabolic stability.

Conclusion

The hydantoin lead **2a** is a potent and specific PDE5 inhibitor which shows moderate antihypertensive activity in SHR model. A medicinal chemistry program based on the hydantoin series has led to the discovery of the piperazinedione **12a** (GF196960), a potent inhibitor of phosphodiesterase type 5, which shows a high degree of selectivity for PDE5 vs PDE1−4 and PDE6. Compound **12a** displays profound and long-lasting blood pressure lowering activity in the spontaneously hypertensive rat model after acute treatment. GF196960, **12a** was selected as a clinical development candidate for the treatment of hypertension and congestive heart failure and is now approved for the treatment of male erectile dysfunction (INN, tadalafil; Trademark, Cialis).

Experimental Section

All starting materials were commercially available and used without further purification. All reactions were carried out with the use of standard techniques under an inert atmosphere (Ar or N_2). Organic extracts were routinely dried over anhydrous Na_2SO_4. Solvent removal refers to rotary evaporation under reduced pressure at 30−40 °C. The analytical thin-layer chromatography (TLC) was carried out on E. Merck 60-F_{254} precoated silica gel plates and components were usually visualized using UV light, iodine vapor, or Dragendorff preparation. Flash column chromatography was performed on silica gel 60 (E. Merck, 230−400 mesh). Melting points were determined on a hit-stage Kofler apparatus and are uncorrected. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were recorded at ambient temperature on a Bruker Avance 300 DPX spectrometer using tetramethylsilane as internal standard, and proton chemical shifts are expressed in ppm in the indicated solvent. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quadruplet, dd = double doublet, m = multiplet. Mass spectra were determined using a Hewlett-Packard 5890 and 5971 series. The elemental analyses were performed by Wolff Laboratories and are within ±0.4% of the theoretical value, unless stated otherwise. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1-dm cell in the indicated solvent.

Methyl 1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3c). Representative example: Racemic tryptophan methyl ester (13 g, 59.5 mmol, 1 equiv) and 1,3-benzodioxole-5-carboxaldehyde (9.7 g, 64.66 mmol, 1.08 equiv) were dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C with an ice bath. To this solution was added dropwise TFA (9 mL), and the mixture was stirred at room temperature for 24 h. The reaction mixture was then basified with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The organic layer was washed with water, brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH, 99/1, to give first the *cis*-isomer **3c** as white crystals (6.5 g, 31%), mp 90−93 °C after recrystallization from methanol; ^{1}H NMR ($CDCl_3$) δ 7.51 (m, 2H), 7.29−7.08 (m, 3H), 6.91−6.75 (m, 3H), 5.94 (s, 2H), 5.16 (s, 1H, C_1−H), 3.95 (dd, 1H, J = 11.2, 4.2 Hz, C_3−H), 3.80 (s, 3H), 3.21 (dd, 1H, J = 15.2, 4.3 Hz, C_4−H), 2.99 (dd, 1H, J = 15.1, 11 Hz, C_4−H), 2.30 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 173.8, 148.8, 148.5, 136.8, 135.3, 135.2, 127.8, 122.6, 120.3, 118.9,

Table 6. PDE5 Activity and Selectivity of **12a** on PDE Isoforms

	IC_{50} (μM)[d]						IC_{50} ratio	IC_{50} ratio
compd	PDE1[a]	PDE2[b]	PDE3[a]	PDE4[b]	PDE5[a]	PDE6[c]	PDE1/5	PDE6/5
12a	>10	>10	>10	>10	0.005	5.1	>2000	1000
sildenafil **1**	1.1	>10	9.2	7.8	0.006	0.074	180	12

[a] Bovine aorta PDE. [b] Human recombinant PDE. [c] Bovine retina PDE. [d] IC_{50} values were reproducible to ±25%.

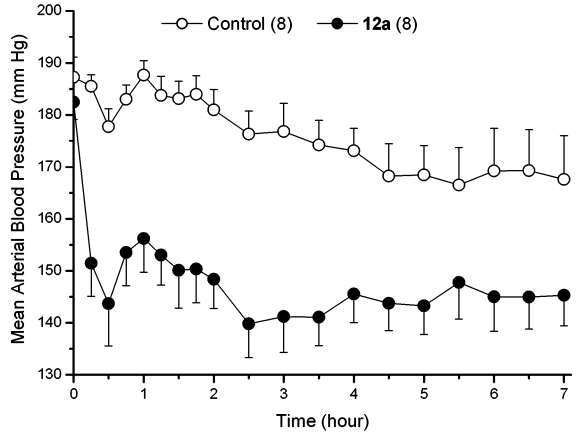


Figure 2. Acute effects of **12a** on blood pressure in SHR model. Time course of the changes in mean arterial blood pressure produced by **12a** (●) or its vehicule (○) after oral administration (5 mg/kg) to spontaneously hypertensive rats (SHR). Statistical analysis carried out at time 1, 4, and 7 h revealed a highly significant difference between treated and control group at 1 and 3 h ($p < 0.01$) and a significant difference ($p < 0.005$) at 7 h on blood pressure.

Table 7. Pharmacokinetic Parameters of **12a** in Rats

compd	F[a] (%)	Vd[b] (l/kg)	Cl[c] (ml/min/kg)	$t_{1/2}$ [d] (h)
12a	63	5.2	5.1	2.4

[a] Oral bioavailability. [b] Volume of distribution. [c] Clearance. [d] Half-life.

111.6, 109.5, 109.4, 108.9, 101.9, 59 (C_1), 57.5 (C_3), 52.9, 26.3; ^{1}H-^{13}C HMQC ($CDCl_3$) δ_H (δ_C) 5.16 (59, C_1), 3.95 (57.5, C_3), followed by the *trans*-isomer **3c** as white crystals (6.4 g, 30%), mp 170 °C after recrystallization from toluene; ^{1}H NMR ($CDCl_3$) δ 7.61 (br s, 1H), 7.54 (d, 1H, J = 7 Hz), 7.31−7.09 (m, 3H), 6.75 (s, 3H), 5.92 (s, 2H), 5.34 (s, 1H, C_1−H), 3.98 (t, 1H, J = 5.8 Hz, C_3−H), 3.71 (s, 3H), 3.26 (dd, 1H, J = 15.4, 5.4 Hz, C_4−H), 3.12 (dd, 1H, J = 15.6, 6.6 Hz, C_4−H), 2.35 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 174.8, 148.7, 148.1, 133.8, 136.6, 133.9, 127.6, 122.6, 122.4, 120.1, 118.9, 111.6, 109.3, 108.9, 108.8, 101.8, 55.3 (C_1), 53.2 (C_3), 52.8, 25.2; ^{1}H-^{13}C HMQC ($CDCl_3$) δ_H (δ_C) 5.34 (55.3, C_1), 3.98 (53.2, C_3).

The following compounds were prepared using a similar procedure with appropriate aldehydes.

Ethyl 1-(4-Methylphenyl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3f). The title compounds were prepared from tryptophan ethyl ester and 4-methylbenzaldehyde. The crude residue was purified by flash column chromatography eluting with CH_2Cl_2/MeOH, 95/5, to give first *cis*-**3f** as a white solid (2.45 g, 39.8%), mp 148 °C, followed by *trans*-**3f** as a white solid (1.3 g, 21.1%), mp 180 °C.

Methyl 1-(3,4-Dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3g). The title compounds were prepared from racemic tryptophan methyl ester and 3,4-dimethoxybenzaldehyde. The crude residue was purified by flash column chromatography eluting with CH_2Cl_2/MeOH, 99/1, to give first *cis*-**3g** as a white solid (5.5 g, 64%), mp 174−176 °C (MeOH), followed by *trans*-**3g** as a white solid (1.5 g, 18%), mp 194−196 °C (toluene/ hexane).

(1*R*,3*R*)- and (1*S*,3*R*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3h). The title compounds were prepared from d-tryptophan methyl ester and 1,3-benzodioxole-5-carboxaldehyde to afford the *cis*-isomer (1*R*,3*R*) **3h** as a white solid (17.4 g, 42%), mp 154−155 °C (2-propanol), and the *trans*-isomer (1*S*,3*R*) **3h** as a white solid (11.4 g, 27%), mp 188−190 °C (CH_2Cl_2).

(1*R*,3*S*)- and (1*S*,3*S*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3i). The title compounds were prepared from l-tryptophan methyl ester and 1,3-benzodioxole-5-carboxaldehyde to afford the *cis*-isomer (1*S*,3*S*) **3i** as a white solid (1.31 g, 36%), mp 154 °C (Et_2O/hexane), and the *trans*-isomer (1*R*,3*S*) **3i** as a white solid (1.29 g, 35%), mp 187−189 °C (MeOH).

(1*R*,3*R*)- and (1*S*,3*R*)-Methyl 1-(4-Methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-3-carboxylate (*cis*- and *trans*-3j). The title compounds were prepared from d-tryptophan methyl ester and 4-methoxybenzaldehyde to afford the *cis*-isomer (1R,3R) **3j** as a pale yellow solid (3.2 g, 41%), mp 117−119 °C (petroleum ether), and the *trans*-isomer (1*S*,3*R*) **3j** as a white solid (2 g, 25%), mp 219−222 °C (CH_2Cl_2/AcOEt).

***cis*-2-Butyl-5-(4-methoxyphenyl)-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole (4).** To a well-stirred dispersion of lithium aluminum hydride (0.75 g, 19.9 mmol) in THF (20 mL) and cooled at 0 °C was added dropwise a solution of butyl hydantoin **2a** (1 g, 2.48 mmol) in THF (20 mL). The resulting mixture was then heated at 40 °C for 2 h, cooled at 0 °C, and water carefully added. The precipitated salts were removed by filtration and washed thoroughly with THF. The filtrate was then evaporated to dryness under reduced pressure, and the crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH, 95/5, to give **4** as a white solid (0.35 g, 38%) after crystallization from 2-propanol/H_2O, mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.53−7.48 (m, 1H), 7.37−7.27 (m, 3H), 7.20−7.05 (m, 3H), 6.88 (d, 2H, J = 8.6 Hz), 4.5 (s, 1H), 3.81 (s, 3H), 3.62 (d, 1H, J = 4.9 Hz), 3.36 (d, 1H, J = 4.9 Hz), 3.24−3.10 (m, 2H), 3.04−2.94 (m, 1H), 2.91−2.72 (m, 2H), 2.62−2.48 (m, 2H), 1.49−1.23 (m, 4H), 0.88 (t, 3H, J = 7.2 Hz). GCMS *m*/*z* 375; Anal. ($C_{24}H_{29}N_3O$) C, H, N.

***cis*-1-(1,3-Benzodioxol-5-yl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (5).** To a suspension of *cis*-**3c** (2 g, 5.7 mmol) in methanol (100 mL) was added a 33% solution of methylamine in ethanol (2.7 mL, 28.5 mmol), and the mixture was heated at 50 °C in a sealed pressure flask for 48 h. The solution was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH, 97/3, to give **5** as a white solid (1.7 g, 86%) after crystallization from AcOEt/pentane, mp 216−218 °C; ^{1}H NMR ($CDCl_3$) δ 7.58−7.48 (m, 2H), 7.27−7.07 (m, 3H), 6.99 (br s, 1H), 6.84−6.79 (m, 2H), 6.76 (s, 1H), 5.95 (s, 2H), 5.13 (s, 1H), 3.74 (dd, 1H, J = 11.1, 4.4 Hz), 3.38 (dd, 1H, J = 15.6, 4.5 Hz), 2.90−2.77 (m, 4H), 1.72 (br s, 1H).

***cis*-1-[1-(1,3-Benzodioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-yl]-*N*-methylmethanamine (6).** To a stirred solution of 1 M lithium aluminum hydride in THF (24 mL, 24 mmol) was added at room temperature a solution of **5** in dry THF (40 mL), and the mixture was heated to reflux for 24 h. After cooling at 0 °C, water was carefully added and the precipitated salts were removed by filtration and washed thoroughly with THF. The filtrate was then evaporated to dryness under reduced pressure, and the crude residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH, 80/20, to give **6** as a colorless oil (0.5 g, 37%); ^{1}H NMR ($CDCl_3$) δ 7.6−7.45 (m, 2H), 7.35−7.10 (m, 3H), 6.95−6.75 (m, 3H), 5.95 (s, 2H), 5.1 (s, 1H), 3.35−3.15 (m, 1H), 2.95−2.55 (m, 5H), 2.5 (s, 3H); GCMS *m*/*z* 335.

***cis*-5-(1,3-Benzodioxol-5-yl)-2-methyl-1,2,5,6,11,11a-hexahydro-3*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indol-3-one (7).** To a solution of **6** (0.5 g, 1.49 mmol) in CH_2Cl_2 (20 mL) was added dropwise triphosgene (0.15 g, 0.49 mmol) at 0 °C. The mixture was stirred at the same temperature for 0.5 h and was then poured into ice water. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the resulting organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH, 99/1, to give **7** as a white solid (0.22 g, 42%) after crystallization from CH_2Cl_2/Et_2O, mp 309−312 °C; ^{1}H NMR ($CDCl_3$) δ 7.55−7.45 (m, 2H), 7.22−7.05 (m, 3H), 6.92 (d, 1H, J = 7.9 Hz), 6.78−6.73 (m, 2H), 5.89 (s, 2H), 5.46 (s, 1H), 3.97−3.82 (m, 1H), 3.57 (t, 1H, J = 7.4 Hz), 3.26−3.12 (m, 2H), 2.87 (dd, 1H, J = 14.7, 10.7 Hz), 2.79 (s, 3H); GCMS *m*/*z* 361; Anal. ($C_{21}H_{19}N_3O_3$) C, H, N.

***trans*-1-(4-Methoxyphenyl)-*N*-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (8).** A solution of *trans*-**3a** (4 g, 11.90 mmol) in (phenylmethyl)amine (5 mL) was heated at 80 °C for 24 h. After cooling at room temperature, diethyl ether was added and the resulting precipitate was filtered and recrystallized from ethanol to give the benzylamide **8** as a white solid (3.8 g, 78%), mp 199 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 7.58 (d, 1H, J = 7 Hz), 7.37−7.06 (m, 11H), 6.81 (d, 2H, J = 8.7 Hz), 5.20 (s, 1H), 4.50 (dd, 1H, J = 14.9, 6.4 Hz), 4.34 (dd, 1H, J = 14.9, 5.4 Hz), 3.76 (s, 3H), 3.70 (dd, 1H, J = 9.4, 4.9 Hz), 3.33 (dd, 1H, J = 16, 5.1 Hz), 2.96 (dd, 1H, J = 16, 9.4 Hz), 2.17 (br s, 1H).

***trans*-5-(4-Methoxyphenyl)-2-(phenylmethyl)-2,3,5,6,-11,11a-hexahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indol-1-one (9).** A mixture of **8** (0.41 g, 1 mmol) and paraformaldehyde (40 mg) in anhydrous toluene (25 mL) was heated to reflux with a Dean−Stark apparatus for 48 h. The solvent was then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with toluene/AcOEt, 80/20, to give **9** as a pale yellow solid (100 mg, 23%) after crystallization from MeOH/H_2O, mp 116−120 °C; ^{1}H NMR ($CDCl_3$) δ 7.6−7.5 (m, 2H), 7.4−7 (m, 8H), 6.9 (d, 2H, J = 8.7 Hz), 6.8 (d, 2H, J = 8.7 Hz), 5.05 (s, 1H), 4.75 (d, 1H, J = 14.3 Hz), 4.1−3.95 (m, 2H), 3.85−3.75 (m, 2H), 3.7 (s, 3H), 3.25 (dd, 1H, J = 16, 5 Hz), 2.95 (dd, J = 16, 9.5 Hz); Anal. ($C_{27}H_{25}N_3O_2$) C, H, N.

***cis*-Methyl 1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10c). Representative example:** To a stirred solution of *cis*-**3c** (2 g, 5.7 mmol, 1 equiv) and $NaHCO_3$ (0.575 g, 6.89 mmol, 1.2 equiv) in $CHCl_3$ (40 mL) was added dropwise chloroacetyl chloride (1.09 mL, 13.69 mmol, 2.4 equiv) under ice cooling. The mixture was then stirred at room temperature under a nitrogen atmosphere for 1 h. The mixture was diluted with CH_2Cl_2, washed with a solution of $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated under reduced pressure. The oily residue was then crystallized from diethyl ether to give *cis*-**10c** as a pale yellow solid (2 g, 82%), mp 215−218 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (br s, 1H), 7.46 (d, 1H, J = 7.1 Hz), 7.34−6.97 (m, 3H), 6.93−6.38 (m, 4H), 5.76 (s, 2H), 4.80 (br s, 1H), 4.36−3.99 (m, 2H), 3.55 (d, 1H, J = 16 Hz), 3.06 (m, 4H).

The following compounds were prepared using a similar procedure with appropriate tetrahydro-β-carbolines.

***cis*-Methyl 2-(Chloroacetyl)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10a).** The title compound was obtained from *cis*-**3a** as a pale yellow solid in 75% yield, mp 188 °C (Et_2O/hexane).

***trans*-Methyl 2-(Chloroacetyl)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*trans*-10a).** The title compound was obtained from *trans*-**3a** as a beige solid in 75% yield, mp 138−142 °C (Et_2O/hexane).

***cis*-Methyl 2-(Chloroacetyl)-1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10b).** The title compound was obtained from *cis*-**3b** as a pale yellow solid in 90% yield, mp 204 °C (hexane).

***trans*-Methyl 1-(Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*trans*-10c).** The title compound was obtained from *trans*-**3c** as a pale yellow solid in 76% yield, mp 118 °C (Et_2O/hexane).

***cis*-Methyl 2-(Chloroacetyl)-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10g).** The title compound was obtained from *cis*-**3g** as a pale yellow solid in 87% yield, mp 228 °C (hexane).

(1*R*,3*R*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10h). The title compound was obtained from *cis*-**3h** as a pale yellow solid in 93% yield, mp 232−234 °C (Et_2O).

(1*S*,3*R*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*trans*-10h). The title compound was obtained from *trans*-**3h** as a white solid in 72% yield, mp 209 °C (Et_2O).

(1*S*,3*S*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10i). The title compound was obtained from *cis*-**3i** as a beige solid in 78% yield, mp 233 °C (Et_2O/hexane).

(1*R*,3*S*)-Methyl 1-(1,3-Benzodioxol-5-yl)-2-(chloroacetyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*trans*-10i). The title compound was obtained from *trans*-**3i** as a pale yellow solid in 72% yield, mp 208 °C (Et_2O).

(1*R*,3*R*)-Methyl 2-(Chloroacetyl)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate (*cis*-10j). The title compound was obtained from *cis*-**3j** as a pale yellow solid in 78% yield, mp 223−225 °C (Et_2O).

6-(1,3-Benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11c). Representative example: A solution of *cis*-**10c** (0.6 g, 1.4 mmol, 1 equiv) and butylamine (0.28 mL, 2.8 mmol, 2 equiv) in methanol (25 mL) was heated to reflux under a nitrogen atmosphere for 16 h. The reaction mixture was cooled at room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2, and the organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was then purified by flash column chromatography eluting with toluene/AcOEt, 80/20, to give *cis*-**11c** as a white solid (370 mg, 61%) after recrystallization from MeOH/H_2O, mp 241−243 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.58 (m, 1H), 7.29−7.10 (m, 3H), 6.82 (d, 1H, J = 8.1 Hz), 6.71 (s, 1H), 6.66 (d, 1H, J = 8.1 Hz), 6.17 (s, 1H), 5.84 (d, 2H, J = 6.4 Hz), 4.27 (dd, 1H, J = 11.2, 4.3 Hz), 4.06 (d, 1H, J = 17.5 Hz), 3.90 (d, 1H, J = 17.5 Hz), 3.73 (dd, 1H, J = 16.1, 4.6 Hz), 3.65−3.53 (m, 1H), 3.37−3.28 (m, 1H), 3.20 (dd, 1H, J = 16.1, 11.6 Hz), 1.61−1.48 (m, 2H), 1.40−1.26 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{25}N_3O_4$) C, H, N.

The following compounds were prepared using a similar procedure with appropriate chloroacetyl derivatives and primary amines.

6-(1,3-Benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*trans*-11c). The title compound was obtained from *trans*-**10c** and butylamine as a white solid in 55% yield, mp 243 °C (toluene);^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.52 (d, 1H, J = 7.5 Hz), 7.36−7.09 (m, 3H), 6.95 (s, 1H), 6.79 (s, 1H), 6.70 (s, 2H), 5.92 (s, 2H), 4.32 (dd, 1H, J = 11.8, 4.2 Hz), 4.12 (d, 1H, J = 17.7 Hz), 3.96 (d, 1H, J = 17.7 Hz), 3.61−3.48 (m, 2H), 3.23 (m, 1H), 2.92 (dd, 1H, J = 15.5, 11.9 Hz), 1.61−1.48 (m, 2H), 1.41−1.26 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{25}N_3O_4$) C, H, N.

2-Butyl-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11a). The title compound was obtained from *cis*-**10a** and butylamine as a white solid in 35% yield, mp 157 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.59 (m, 1H), 7.28−7.12 (m, 5H), 6.75 (d, 2H, J = 8.7 Hz), 6.21 (s, 1H), 4.29 (dd, 1H, J = 11.7, 4.3 Hz), 4.07 (d, 1H, J = 17.3 Hz), 3.89 (d, 1H, J = 17.3 Hz), 3.80−3.52 (m, 2H), 3.70 (s, 3H), 3.35−3.15 (m, 2H), 1.66−1.47 (m, 2H), 1.39−1.26 (m, 2H), 0.93 (t, 3H, J = 7.4 Hz); Anal. ($C_{25}H_{27}N_3O_3 \cdot 0.5H_2O$) C, H, N.

2-Butyl-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*trans*-11a). The title compound was obtained from *trans*-**10a** and

butylamine as a white solid in 75% yield, mp 212−214 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H), 7.64 (m, 1H), 7.41−7.22 (m, 5H), 7.07 (s, 1H), 6.88 (d, 2H, J = 8.7 Hz), 4.40 (dd, 1H, J = 11.9, 4.2 Hz), 4.18 (d, 1H, J = 17.5 Hz), 4.03 (d, 1H, J = 17.5 Hz), 3.85 (s, 3H), 3.67−3.60 (m, 2H), 3.37−3.23 (m, 1H), 3.02 (dd, 1H, J = 15.2, 11.8 Hz), 1.70−1.56 (m, 2H), 1.50−1.38 (m, 2H), 1.05 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{27}N_3O_3$) C, H, N.

2-Butyl-6-phenyl-2,3,6,7,12,12a-hexahydropyrazino-[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11b). The title compound was obtained from *cis*-**10b** and butylamine as a white solid in 89% yield, mp 243−245 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.58 (m, 1H), 7.34−7.11 (m, 8H), 6.26 (s, 1H), 4.30 (dd, 1H, J = 11.5, 4.5 Hz), 4.06 (d, 1H, J = 17.4 Hz), 3.90 (d, 1H, J = 17.4 Hz), 3.75 (dd, 1H, J = 16, 4.5 Hz), 3.65−3.51 (m, 1H), 3.37−3.19 (m, 2H), 1.62−1.50 (m, 2H), 1.39−1.25 (m, 2H), 0.93 (t, 3H, J = 7.2 Hz); Anal. ($C_{24}H_{25}N_3O_2$) C, H, N.

The following piperazinediones *cis*-**11d**, **-11e**, **-11f** were obtained by a two-step procedure starting from tetrahydro-β-carboline: *cis*-**3d**, **-3e,** and **-3f,** respectively without isolation of their chloroacetyl derivative.

2-Butyl-6-(4-cyanophenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11d). The title compound was obtained from *cis*-**3d** with an overall yield of 24.7% as a white solid, mp 246 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.68−7.05 (m, 8H), 6.20 (s, 1H), 4.28 (dd, 1H, J = 11.3, 4.5 Hz), 4.06 (d, 1H, J = 17.5 Hz), 3.88 (d, 1H, J = 17.5 Hz), 3.76 (dd, 1H, J = 16.2, 4.5 Hz), 3.64−3.47 (m, 1H), 3.36−3.12 (m, 2H), 1.62−1.45 (m, 2H), 1.38−1.22 (m, 2H), 0.91 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{24}N_4O_2\cdot 1H_2O$) C, H, N.

2-Butyl-6-(4-chlorophenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11e). The title compound was obtained from *cis*-**3e** with an overall yield of 35% as a white solid, mp 164−166 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H), 7.59 (m, 1H), 7.31−7.13 (m, 7H), 6.21 (s, 1H), 4.29 (dd, 1H, J = 11.5, 4.6 Hz), 4.07 (d, 1H, J = 17.5 Hz), 3.89 (d, 1H, J = 17.5 Hz), 3.76 (dd, 1H, J = 16, 4.5 Hz), 3.64−3.52 (m, 1H), 3.39−3.06 (m, 2H), 1.66−1.48 (m, 2H), 1.41−1.25 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); Anal. ($C_{24}H_{24}ClN_3O_2$) C, H, N.

2-Butyl-6-(4-methylphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11f). The title compound was obtained from *cis*-**3f** with an overall yield of 57.7% as a white solid, mp 194 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.59 (m, 1H), 7.30−6.98 (m, 7H), 6.22 (s, 1H), 4.29 (dd, 1H, J = 11.5, 4.5 Hz), 4.06 (d, 1H, J = 17.3 Hz), 3.88 (d, 1H, J = 17.3 Hz), 3.74 (dd, 1H, J = 16, 4.7 Hz), 3.64−3.50 (m, 1H), 3.38−3.17 (m, 2H), 2.25 (s, 3H), 1.66−1.48 (m, 2H), 1.39−1.25 (m, 2H), 0.93 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{27}N_3O_2\cdot 0.5H_2O$) C, H, N.

2-Butyl-6-(3,4-dimethoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11g). The title compound was obtained from *cis*-**10g** and butylamine as a white solid in 75% yield, mp 154−156 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.58 (m, 1H), 7.29−7.06 (m, 3H), 6.84 (s, 1H), 6.80 (d, 1H, J = 8.3 Hz), 6.68 (d, 1H, J = 8.3 Hz), 6.21 (s, 1H), 4.26 (dd, 1H, J = 11.5, 4.7 Hz), 4.05 (d, 1H, J = 17.3 Hz), 3.88 (d, 1H, J = 17.3 Hz), 3.75 (s, 3H), 3.73 (s, 3H), 3.73−3.66 (m, 1H), 3.60−3.49 (m, 1H), 3.38−3.13 (m, 2H), 1.57−1.45 (m, 2H), 1.39−1.21 (m, 2H), 0.91 (t, 3H, J = 7.4 Hz); Anal. ($C_{26}H_{29}N_3O_4$) C, H, N.

6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11h). The title compound was obtained from *cis*-**10c** and a 2 M solution of ammonia in methanol as a white solid in 50% yield, mp 283−285 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1H), 7.59 (m, 1H), 7.31−7.12 (m, 3H), 6.89−6.83 (m, 3H), 6.19 (s, 1H), 6.02 (s, 1H), 5.87 (d, 2H, J = 6.9 Hz), 4.35 (dd, 1H, J = 11.5, 4.5 Hz), 4.14−3.99 (m, 2H), 3.72 (dd, 1H, J = 16.2, 4.7 Hz), 3.21 (dd, 1H, J = 16.2, 11.9 Hz); Anal. ($C_{21}H_{17}N_3O_4$) C, H, N.

6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11i). The title compound was obtained from *cis*-**10c** and a 33% solution of methylamine in ethanol as a white solid in 94% yield, mp 253−255 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.60 (m, 1H), 7.28−7.12 (m, 3H), 6.81 (d, 1H, J = 7.9 Hz), 6.71 (s, 1H), 6.66 (d, 1H, J = 8.1 Hz), 6.12 (s, 1H), 5.83 (d, 2H, J = 6.6 Hz), 4.28 (dd, 1H, J = 11.5, 4.3 Hz), 4.08 (d, 1H, J = 17.5 Hz), 3.90 (d, 1H, J = 17.5 Hz), 3.77 (dd, 1H, J = 16.1, 4.3 Hz), 3.20 (dd, 1H, J = 16.1, 11.5 Hz), 3.02 (s, 3H); Anal. ($C_{22}H_{19}N_3O_4$) C, H, N.

6-(4-Methoxyphenyl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11j). The title compound was obtained from *cis*-**10a** and a 33% solution of methylamine in ethanol, as a white solid in 22% yield, mp 257−263 °C (2-propanol); ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 7.64 (m, 1H), 7.33−7.17 (m, 5H), 6.79 (d, 2H, J = 8.5 Hz), 6.23 (s, 1H), 4.34 (dd, 1H, J = 11.5, 4.3 Hz), 4.13 (d, 1H, J = 17.5 Hz), 3.94 (d, 1H, J = 17.5 Hz), 3.83 (dd, 1H, J = 16, 4.5 Hz), 3.75 (s, 3H), 3.27 (dd, 1H, J = 16, 11.5), 3.06 (s, 3H); Anal. ($C_{22}H_{21}N_3O_3$) C, H, N.

2-Ethyl-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11k). The title compound was obtained from *cis*-**10a** and a 2 M solution of ethylamine in methanol as a white solid in 67% yield, mp 245−255 °C (MeOH);^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.64 (m, 1H), 7.32−7.15 (m, 5H), 6.80 (d, 2H, J = 8.7 Hz), 6.26 (s, 1H), 4.31 (dd, 1H, J = 11.5, 4.6 Hz), 4.10 (d, 1H, J = 17.3 Hz), 3.92 (d, 1H, J = 17.3 Hz), 3.83−3.65 (m, 2H), 3.75 (s, 3H), 3.43−3.19 (m, 2H), 1.21 (t, 3H, J = 7.3 Hz); Anal. ($C_{23}H_{23}N_3O_3$) C, H, N.

6-(1,3-Benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11l). The title compound was obtained from *cis*-**10c** and cyclohexylamine as a white solid in 71% yield, mp 268−269 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.56 (m, 1H), 7.28−7.06 (m, 3H), 6.80−6.60 (m, 3H), 6.15 (s, 1H), 5.82 (d, 2H, J = 6.6 Hz), 4.49−4.31 (m, 1H), 4.24 (dd, 1H, J = 11.5, 4.5 Hz), 3.95 (d, 1H, J = 17.3 Hz), 3.82 (d, 1H, J = 17.3 Hz), 3.69 (dd, 1H, J = 16, 4.7 Hz), 3.17 (dd, 1H, J = 16, 11.5 Hz), 1.87−0.95 (m, 11H); Anal. ($C_{27}H_{27}N_3O_4$) C, H, N.

6-(1,3-Benzodioxol-5-yl)-2-isopropyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11m). The title compound was obtained from *cis*-**10c** and isopropylamine as a white solid in 65% yield, mp 248−250 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.59 (m, 1H), 7.35−7.07 (m, 3H), 6.90−6.65 (m, 3H), 6.18 (s, 1H), 5.85 (d, 2H, J = 5.8 Hz), 4.90−4.79 (m, 1H), 4.25 (dd, 1H, J = 11.3, 4.5 Hz), 3.95 (d, 1H, J = 17.3 Hz), 3.85 (d, 1H, J = 17.3 Hz), 3.73 (dd, 1H, J = 16.2, 4.7 Hz), 3.21 (dd, 1H, J = 16, 11.5 Hz), 1.17 (d, 6H, J = 6.1 Hz); Anal. ($C_{24}H_{23}N_3O_4$) C, H, N.

2-Cyclopropylmethyl-6-(4-methoxyphenyl)-2,3,6,7,12,-12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11n). The title compound was obtained from *cis*-**10a** and (cyclopropylmethyl)amine as a white solid in 69% yield, mp 180−185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.59 (m, 1H), 7.28−7.12 (m, 5H), 6.75 (d, 2H, J = 8.8 Hz), 6.23 (s, 1H), 4.30 (dd, 1H, J = 11.5, 4.6 Hz), 4.16 (d, 1H, J = 17.4 Hz), 4.02 (d, 1H, J = 17.4 Hz), 3.82−3.56 (m, 2H), 3.71 (s, 3H), 3.29−3.01 (m, 2H), 1.02−0.88 (m, 1H), 0.61−0.51 (m, 2H), 0.31−0.22 (m, 2H); Anal. ($C_{25}H_{25}N_3O_3\cdot 0.5H_2O$) C, H, N.

2-Cyclopropylmethyl-6-(4-methylphenyl)-2,3,6,7,12,-12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11o). The title compound was obtained from *cis*-**3f** with an overall yield of 30% as a white solid, mp 194 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.59 (m, 1H), 7.32−6.96 (m, 7H), 6.23 (s, 1H), 4.30 (dd, 1H, J = 11.3, 4.1 Hz), 4.15 (d, 1H, J = 17.4 Hz), 4.02 (d, 1H, J = 17.4 Hz), 3.83−3.54 (m, 2H), 3.29−3.02 (m, 2H), 2.24 (s, 3H), 1.02−0.88 (m, 1H), 0.61−0.51 (m, 2H), 0.31−0.22 (m, 2H); Anal. ($C_{25}H_{25}N_3O_2\cdot 1.1H_2O$) C, H, N.

6-(1,3-Benzodioxol-5-yl)-2-(phenylmethyl)-2,3,6,7,12,-12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (*cis*-11p). The title compound was obtained from *cis*-**10c** and (phenylmethyl)amine as a white solid in 80% yield, mp 285−287 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) δ 7.80 (s,

1H), 7.60 (m, 1H), 7.39−7.08 (m, 8H), 6.86−6.65 (m, 3H), 6.15 (s, 1H), 5.86 (d, 2H, J = 5.2 Hz), 4.90 (d, 1H, J = 14.5 Hz), 4.41 (d, 1H, J = 14.5 Hz), 4.35 (dd, 1H, J = 11.5, 4.8 Hz), 3.97−3.74 (m, 3H), 3.26 (dd, 1H, J = 16, 11.5 Hz); Anal. ($C_{28}H_{23}N_3O_4 \cdot 1H_2O$) C, H, N.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (12a). The title compound was obtained from *cis*-**10h** and a 33% solution of methylamine in ethanol as a white solid in 77% yield, mp 301−303 °C (CH_2Cl_2/hexane); $[\alpha]_D$ +71° (c = 1.13; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.60 (d, 1H, J = 7.6 Hz), 7.28−7.12 (m, 3H), 6.81 (d, 1H, J = 7.9 Hz), 6.71 (s, 1H), 6.66 (d, 1H, J = 8.1 Hz), 6.12 (s, 1H, C_6−H), 5.83 (d, 2H, J = 6.6 Hz), 4.28 (dd, 1H, J = 11.5, 4.3 Hz, C_{12a}-H), 4.08 (d, 1H, J = 17.5 Hz, C_3−H), 3.90 (d, 1H, J = 17.5 Hz, C_3−H), 3.77 (dd, 1H, J = 16.1, 4.3 Hz, C_{12}−H), 3.20 (dd, 1H, J = 16.1, 11.5 Hz, C_{12}−H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.5, 167.1, 148.5, 147.8, 137.2, 136, 133.5, 126.8, 123.2, 121.4, 120.8, 119.3, 111.9, 108.9, 108.1, 107.2, 101.8, 57.4 (C_6), 56.9 (C_{12a}), 52.8, 34.3, 24.5; ^{1}H-^{13}C HMQC ($CDCl_3$) δ_H (δ_C) 6.12 (57.4, C_6), 4.28 (56.9, C_{12a}); Anal. ($C_{22}H_{19}N_3O_4$) C, H, N.

(6*R*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (12b). The title compound was obtained from *trans*-**10i** and a 33% solution of methylamine in ethanol as a white solid in 81% yield, mp 287−289 °C (toluene); $[\alpha]_D$ −293° (c = 1.28; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.62 (m, 1H), 7.45−7.23 (m, 3H), 7.07 (s, 1H), 6.90 (s, 1H), 6.80 (s, 2H), 6.02 (s, 2H), 4.44 (dd, 1H, J = 11.8, 4.1 Hz), 4.23 (d, 1H, J = 17.7 Hz), 4.08 (d, 1H, J = 17.7 Hz), 3.64 (dd, 1H, J = 15.5, 4.2 Hz), 3.13−2.99 (m, 1H), 3.09 (s, 3H); Anal. ($C_{22}H_{19}N_3O_4 \cdot 0.25$ toluene) C, H, N.

(6*S*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (12c). The title compound was obtained from *cis*-**10i** and a 33% solution of methylamine in ethanol as a white solid in 71% yield, mp 283−287 °C (2-propanol); $[\alpha]_D$ −71° (c = 1.02; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.60 (m, 1H), 7.28−7.12 (m, 3H), 6.81 (d, 1H, J = 7.9 Hz), 6.71 (s, 1H), 6.66 (d, 1H, J = 8.1 Hz), 6.12 (s, 1H), 5.83 (d, 2H), 4.28 (dd, 1H, J = 11.5, 4.3 Hz), 4.08 (d, 1H, J = 17.5 Hz), 3.90 (d, 1H, J = 17.5 Hz), 3.77 (dd, 1H, J = 16.1, 4.3 Hz), 3.20 (dd, 1H, J = 16.1, 11.5 Hz), 3.02 (s, 3H); Anal. ($C_{22}H_{19}N_3O_4$) C, H, N.

(6*S*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (12d). The title compound was obtained from *trans*-**10h** and a 33% solution of methylamine in ethanol as a white solid in 70% yield, mp 285−287 °C (toluene); $[\alpha]_D$ +297° (c = 1.21; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.62 (m, 1H), 7.45−7.23 (m, 3H), 7.07 (s, 1H), 6.90 (s, 1H), 6.80 (s, 2H), 6.02 (s, 2H), 4.44 (dd, 1H, J = 11.8, 4.1 Hz), 4.23 (d, 1H, J = 17.7 Hz), 4.08 (d, 1H, J = 17.7 Hz), 3.64 (dd, 1H, J = 15.5, 4.2 Hz), 3.13−2.99 (m, 1H), 3.09 (s, 3H); Anal. ($C_{22}H_{19}N_3O_4 \cdot 0.3$ toluene) C, H, N.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (13). The title compound was obtained from *cis*-**10h** and butylamine as a white solid in 57% yield, mp 209−210 °C (toluene/hexane); $[\alpha]_D$ +50° (c = 0.53; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.58 (m, 1H), 7.29−7.10 (m, 3H), 6.82 (d, 1H, J = 8.1 Hz), 6.71 (s, 1H), 6.66 (d, 1H, J = 8.1 Hz), 6.17 (s, 1H), 5.84 (d, 2H, J = 6.4 Hz), 4.27 (dd, 1H, J = 11.2, 4.3 Hz), 4.06 (d, 1H, J = 17.5 Hz), 3.90 (d, 1H, J = 17.5 Hz), 3.73 (dd, 1H, J = 16.1, 4.6 Hz), 3.65−3.53 (m, 1H), 3.37−3.28 (m, 1H), 3.20 (dd, 1H, J = 16.1, 11.6 Hz), 1.61−1.48 (m, 2H), 1.40−1.26 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); Anal. ($C_{25}H_{25}N_3O_4$) C, H, N.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-isopropyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (14). The title compound was obtained from *cis*-**10h** and isopropylamine as a white solid in 69% yield, mp 290−293 °C (MeOH); $[\alpha]_D$ +52° (c = 1.14; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 1H), 7.59 (m, 1H), 7.32−7.09 (m, 3H), 6.88−6.65 (m, 3H), 6.17 (s, 1H), 5.84 (d, 2H, J = 4.5 Hz), 4.93−4.79 (m, 1H), 4.25 (dd, 1H, J = 11.4, 4.5 Hz), 3.96 (d, 1H, J = 17.3 Hz), 3.85 (d, 1H, J = 17.3 Hz), 3.72 (dd, 1H, J = 16, 4.7 Hz), 3.21 (dd, 1H, J = 16, 11.5 Hz), 1.17 (d, 6H, J = 6.8 Hz); Anal. ($C_{24}H_{23}N_3O_4$) C, H, N.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (15). The title compound was obtained from *cis*-**10j** and cyclopentylamine as a white solid in 77% yield, mp 210−211 °C (Et_2O); $[\alpha]_D$ +29° (c = 1.07; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.60 (m, 1H), 7.27−7.12 (m, 5H), 6.74 (d, 2H, J = 8.9 Hz), 6.22 (s, 1H), 4.98−4.86 (m, 1H), 4.26 (dd, 1H, J = 11.5, 4.8 Hz), 3.90 (s, 2H), 3.76−3.64 (m, 1H), 3.70 (s, 3H), 3.23 (dd, 1H, J = 16, 11.5), 1.94−1.42 (m, 8H); Anal. ($C_{26}H_{27}N_3O_3$) C, H, N.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (16). The title compound was obtained from *cis*-**10h** and a 2 M solution of ammonia in methanol as a white solid in 31% yield, mp 285−290 °C (MeOH); $[\alpha]_D$ +88° (c = 0.48; pyridine); ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1H), 7.59 (m, 1H), 7.31−7.12 (m, 3H), 6.89−6.83 (m, 3H), 6.19 (s, 1H), 6.02 (s, 1H), 5.87 (d, 2H, J = 6.9 Hz), 4.35 (dd, 1H, J = 11.5, 4.5 Hz), 4.14−3.99 (m, 2H), 3.72 (dd, 1H, J = 16.2, 4.7 Hz), 3.21 (dd, 1H, J = 16.2, 11.9 Hz); Anal. ($C_{21}H_{17}N_3O_4$) C, H, N.

Phosphodiesterase Preparations. PDE1, -3, and -5 were purified from bovine aorta as previously described in the literature.[14] Bovine PDE6 (ROS−PDE) was supplied by Dr. N. Virmaux (Inserm U338, Strasbourg, France). Human recombinant PDE2 and 4 were provided from Drs. Vince Florio and Tim Martins (ICOS Corporation, Bothell, WA).

Phosphodiesterase Assays. The PDE assay[14,15] was based on the use of Multiscreen plates (Millipore) and a vacuum manifold (Millipore). In such plates, both the reaction and the subsequent separation between substrates and products can be achieved. The assay (100 μL) contained 50 mM Tris pH 7.5, 5 mM Mg acetate, 1 mM EGTA, and 250 μg/mL snake venom nucleotidase. Fifty nanomolar [8-^{3}H]-cGMP (15 Ci/mmol; Amersham) or [8-^{3}H]-cGMP (25 Ci/mmol; Amersham) was added. Reactions were started by the addition of 25 μL of the diluted enzyme preparation. The assays were incubated for 30 min at 30 °C. Microcolumns were prepared by aliquoting 300 μL per well of QAE Sephadex previously swollen for 2 h in water (12 mL/g). At the end of the incubation, the total volume of the assays was loaded on microcolumn plate by filtration. The elution of free radioactivity was obtained by 200 μL of water from which 50 μL aliquots were analyzed by scintillation counting.

In this PDE assay, the substrate concentration never exceeded 30% of the K_m of the enzyme tested. Under such conditions, the IC_{50} obtained for any given compound closely corresponded to the K_i for such compound. In addition, all enzymes studies were performed under conditions of initial velocity (maximal substrate hydrolysis of 10−15%). Stock solutions of PDE inhibitors were prepared in dimethyl sulfoxide, and the final solvent concentration in each assay was 2% (v/ v).

Determination of cGMP Accumulation in RSMC. Rat aortic smooth muscle cells (RSMC) were prepared according to Chamley.[16] Cells were cultured in Dubelcco's modified Eagle medium (GIBCO) containing 10% fetal calf serum, 1% glutamine, and 1% penicillin−streptomycin at 37 °C in a 95% air−5% CO_2 humidified atmosphere.

Cells were seeded in 24-well culture dishes at a density of (2−5) × 10^4 cells/well. Experiments were performed after 3−5 days in culture when cells reached confluence. Media were aspired and replaced with 0.5 mL of PBS containing the PDE inhibitor. After 30 min at 37 °C, soluble or particular guanylate cyclase was stimulated by addition of atrial natriuretic factor (0.1 μM) for 10 min at 37 °C. At the end of the incubation, the medium was removed and stored at −20 °C for extracellular cyclic nucleotides determinations. Intracellular cyclic nucleotides were extracted by two ethanolic (65%) washes at 4 °C for 5 min. The ethanolic extracts were pooled, evaporated to dryness using a speed-Vac system, and stored at −20 °C. cGMP was measured by scintillation proximity immunoassay (Am-

ersham). In all cases, any given treatment with effectors was performed in triplicate wells. Stock solutions of PDE inhibitors were made in dimethyl sulfoxide. In the assays, the final concentration of dimethyl sulfoxide never exceeded 0.1% (v/v).

Effect on Blood Pressure of Conscious SHR After Acute Treatment. The experiments were performed in spontaneously hypertensive rats (SHR, Charles River, France) weighting 340−380 g. The day before experiment, the left carotid artery was catheterized under pentobarbital anesthesia. On the day of experiment, the catheter was connected to pressure transducers for blood pressure measurement. After an equilibration period of ca. 30 min, the product was dissolved in a mixture of 5% (v/v) DMF in olive oil. The concentration was adjusted in order to administer the compound per os in a volume of 1 mL. Arterial blood pressure was monitored continuously over 7 h.

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Supporting Information Available: X-ray crystallographic data for compound **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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