Pyrroloquinolone PDE5 Inhibitors with Improved Pharmaceutical Profiles for Clinical Studies on Erectile Dysfunction

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We previously reported a series of potent and selective pyrimidinyl pyrroloquinolone PDE5 inhibitors such as **2a** for potential use in male erectile dysfunction (MED) (Sui, Z.; Guan, J.; Macielag, M. J.; Jiang, W.; Zhang, S.; Qiu, Y.; Kraft, P., Bhattacharjee, S.; John, T. M.; Craig, E.; Haynes-Johnson, D.; Clancy, J. *J. Med. Chem.* **2002**, *45*, 4094−4096). Unfortunately, the low aqueous solubility and poor oral bioavailability rendered them undesirable development candidates. To address this issue, we designed a series of analogues using two approaches: increasing the overall basicity and reducing molecular weight of the lead. Through earlier SAR studies, we discovered that the PDE5 potency of the pyrroloquinolones is insensitive to substitution on the pyrrole nitrogen. Basic functional groups such as pyridines and benzimidazoles were appended via the aromatic ring connected to the pyrrole nitrogen. Several truncated analogues were also designed and synthesized to improve oral absorption. These modifications allowed us to identify analogues with good oral bioavailability in rats, dogs, and monkeys while the high potency against PDE5 and desirable selectivity versus other PDE isozymes were maintained. Compounds ***R*-11e** and ***R*−11l** were selected as development candidates for MED and other indications.

Introduction

Male erectile dysfunction (MED or ED)[1] was a largely unmet medical need prior to the introduction of sildenafil in 1998. Sildenfil, a potent inhibitor of phosphodiesterase type 5 (PDE5),[2] was originally studied for the treatment of angina before its effectiveness in treating ED was serendipitously discovered.[3] Despite its success, sildenafil has several notable side effects, such as headache, nausea, cutaneous flushing, and visual disturbances. These side effects may be attributed to the limited selectivity of sildenafil versus other PDE isozymes, most notably PDE1 and PDE6. Thus, the need exists for PDE5 inhibitors possessing improved PDE isozyme selectivities and therefore demonstrating fewer side effects, as evidenced by the recent launches of tadalafil[4] and vardenafil.[5,6] In addition, the potential use of PDE5 inhibitors in other indications such as pulmonary hypertension, stroke, and cardiac protection is also fueling interest in this field.

PDE5 belongs to the superfamily of phosphodiesterases that catalyze hydrolysis of the cyclic phosphate bond in the second messengers cAMP and cGMP.[2c] To date, the 21 mammalian PDE genes cloned thus far are organized into 11 families on the basis of their sequence homology and biochemical properties.[7] Among the 11 families, PDE5, initially discovered in lung tissues, is the first recognized cGMP-binding PDE. In the human corpus carvernosum, PDE5 is the major enzyme to facilitate the hydrolysis of cGMP to GMP, thus playing an important role in penile erection.[6b] Upon sexual stimulation, release of nitric oxide from nonadrenergic, noncholinergic neurons activates soluble guanylyl cyclase, which catalyzes the cyclization of guanosine triphosphate (GTP), generating cGMP. Increased cGMP levels eventually cause a decrease in intracellular calcium concentration, leading to relaxation of smooth muscle in the corpus cavernosum. This allows increased arterial blood flow to the penis, resulting in tumescence. PDE5 inhibition blocks cGMP degradation, facilitating cGMP accumulation.

Previously, we described the discovery of a series of pyrimidine pyrroloquinolones as potent and selective inhibitors of PDE5.[8a] The lead compound (**2a**, Chart 1) was a highly potent inhibitor of PDE5, selective versus other phosphodiesterases, capable of increasing intracellular cGMP levels in RFL-6 cells, and efficacious in a dog model for erectile dysfunction. However, its physical and chemical properties proved unsuitable for clinical studies. The poor aqueous solubility of the compound not only affected the pharmacokinetic profile but also significantly increased the difficulty in creating formulations. Systematic modifications of this lead were successful in achieving suitable pharmacokinetic (PK) properties and solubility profile for clinical development while the potency against PDE5 and selectivity versus other PDE isozymes were maintained.

Chemistry

Pyrimidinyl pyrroloquinolones were synthesized either via Winterfeldt oxidation[9] of β-carboline precursors (Scheme 1) or via coupling reactions of the key pyrroloquinolone precursor **1a** (Scheme 2). Compounds **11a**, **11b**, **11c**, and **11d** were respectively synthesized from β-carbolines **10a**, **10b**, **10c**, and **10d** by oxidation with $KOtBu/O_2$ (Scheme 1). The β-carboline intermediates **8a** and **10a** were synthesized through coupling of β-carbolines **6a** with chloropyrimidine **7a** and of β-carboline **6b**

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Scheme 1. Pyrroloquinolones via Winterfeldt Oxidations of β-Carbolines

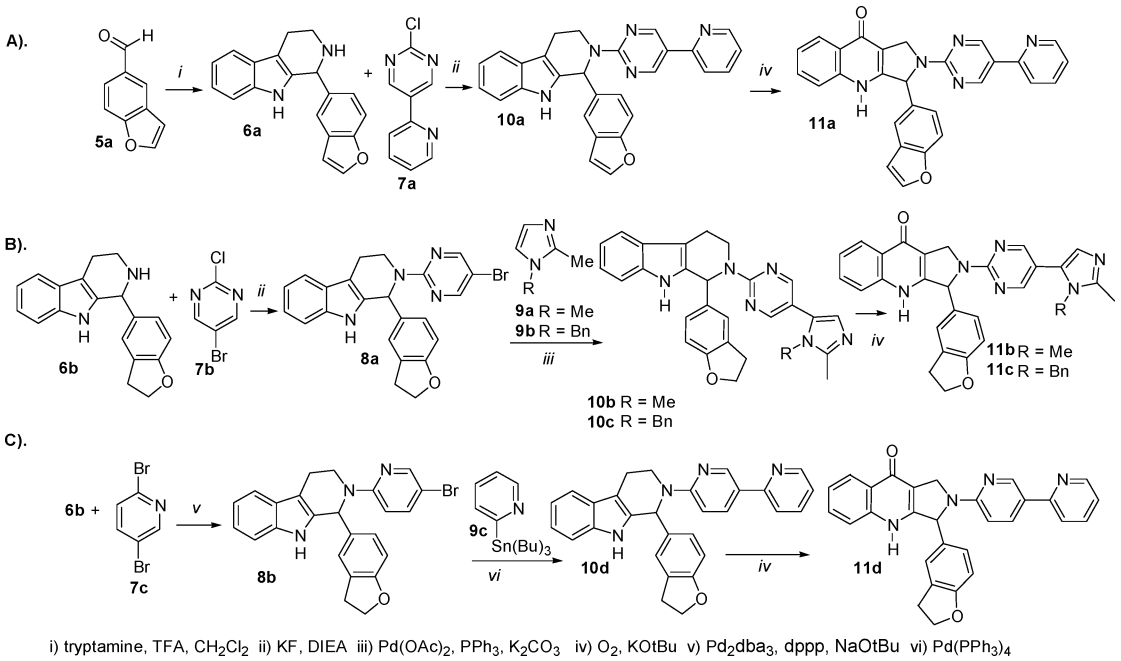
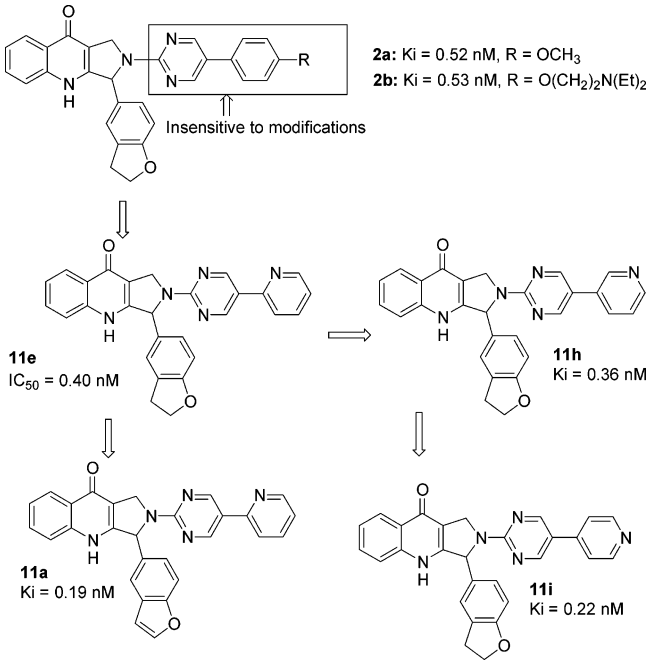


Chart 1. Identification of Lead Compound **11e**



with chloropyrimidine **7b** using the KF/DIEA condition. Compound **8b** was synthesized by palladium-catalyzed coupling reaction of **6b** with bromopyridine **7c**. To install the imidazole functionality in **11b** and **11c**, β-carboline intermediates **10b** and **10c** were synthesized by a modified literature protocol[10] through coupling reactions of either *N*-methyl (**9a**) or *N*-benzylimidazole (**9b**) to bromide **8a**. Intermediate **10d** was synthesized by Stille coupling reaction of 2-tributylstannanylpyridine **9c** with bromide **8b**.

In some cases, the Winterfeldt oxidation of fully elaborated β-carbolines proceeded with relatively low yield. To address this problem, we utilized a more divergent synthetic route via unsubstituted pyrroloquinolones **1a** and **1b** for further analogue synthesis (Scheme 2). Pyrimidinyl pyrroloquinolones **11e**, **11f**, and **11g** were respectively synthesized by direct substitution of pyrroloquinolone **1a** with chloropyrimidines **7a**, **7b**, and **7d** in the presence of KF/DIEA; analogous treatment of **1b** produced **11p**. Pyrroloquinolone **11f** was converted to **11h** and **11i** by Suzuki coupling reactions of the appropriate boronic acids. Buchwald amination of the pyrrole nitrogen of **1a** utilizing a combination of $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl as the catalyst system delivered compounds **11j** and **11k**. A different catalyst mixture (Pd_2dba_3/BINAP) proved more efficient when amine **1a** was coupled with 2-bromopyridine. For relatively unreactive substrates **7h** and **7i**, a more active, bulkier ligand 2-(dicyclohexylphosphino)-biphenyl was used to prepare compounds **11m**, **11n**, and **11o** from **1a** or **1b**, respectively (Scheme 2).

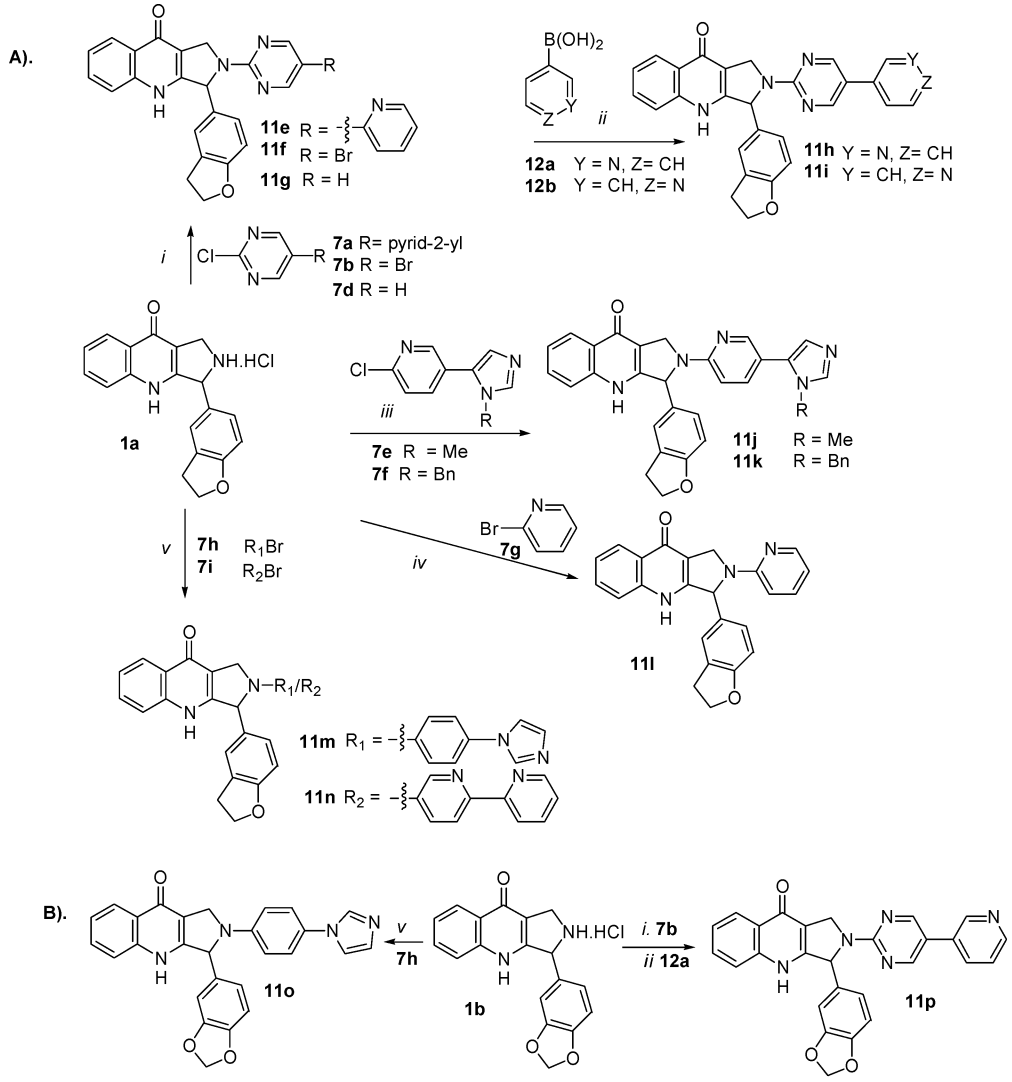
Enantiomers **(*R*)-11e** and **(*R*)-11l** were synthesized via the same route as racemic **11e** and **11l**, starting from enantiomerically pure **(*R*)-1a**.[8b]

Results and Discussion

In general, compounds in this series were found to be extremely potent and selective PDE5 inhibitors. They exhibit excellent selectivities versus PDE1−4/PDE5 and good selectivity versus PDE6 (Table 1). It is worth mentioning that, consistent with our earlier observation, both potency and PDE6/5 selectivity are sensitive to the *C*-1 aromatic substituents, and dihydrobenzofuranyl at this position is more selective than methylenedioxyphenyl.[8a] For example, compound **11h** and **11m** are more selective than **11p** and **11o**, respectively. Furthermore, replacing dihydrobenzofuran in **11e** with benzofuran (**11a**) did not have profound effects on potency.

Identification of Lead Compound 11e. Although our previous lead compound phenylpyrimidine pyrroloquinolone derivative **(*R*)-2a** (JNJ-10258859)[8c] showed very good potency against PDE5, superior selectivity in the in vitro studies, and demonstrated in vivo efficacy in the dog model for erectile dysfunction, its poor solubility precluded its further development (Chart 1). During our systematic SAR studies, we identified that

Scheme 2. Pyrroloquinolones via Coupling Reactions of Pyrroloquinolone Precursor 1



i) KF, DIEA, 60°C, ii) $Pd(dppf)(OAc)_2$, Et_3N; iii) $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, NaOtBu; iv) Pd_2dba_3, BINAP, NaOtBu; v) Pd_2dba_3, 2-(di-t-butylphosphino)biphenyl, NaOtBu;

the right portion of the molecule tolerates a wide range of substituents on the pyrrole nitrogen. We took advantage of this finding to improve the physical and chemical properties by modifying this area of the scaffold through introduction of solubilizing groups such as the basic chain in **2b**. While the PDE5 inhibition and isozyme selectivity were maintained, these analogues were not orally bioavailable. We reasoned that the increase in molecular weight of **2b** relative to **2a** might have decreased the absorption. Other approaches such as replacing the methoxy group in **2a** with carboxylic acid and hydroxy groups proved unsuccessful in improving bioavailability, possibly due to increased in vivo conjugation. We then focused our efforts on pyridine analogues with molecular weight similar to **2a**. While the potency against PDE5 slightly increased, the PDE6/5 selectivity remained the same. Moving the pyridine nitrogen from ortho (**11e**) to meta (**11h**) or to para (**11i**) did not significantly impact the PDE5 potency. Even though PDE6/5 selectivity of **11h** seems to be better than that of **11e** and **11i**, we selected **11e** as the lead compound, since the steric environment of the *o*-pyridine might render it less prone to P450 oxidation.

Biological studies demonstrated that **11e** has excellent potency and selectivity in our in vitro studies and 31% oral bioavailibility in male rats with a half-life about 6 h, though its bioavailability in monkeys was poor. Even though the aqueous solubility of **11e** was sufficient for developing suitable formulations for further development, we decided to further modify the nonpharmacorphore part of the molecule in order to improve the PK profile across different species. Pharmacokinetic and in vitro metabolism studies on **(*R*)-11e** indicated that neither fast metabolite formation nor rapid elimination is the major reason for its relatively moderate bioavailability. We decided to focus on improving the absorption of this series by two approaches: adjusting the pK_a and decreasing the molecular weight (MW).

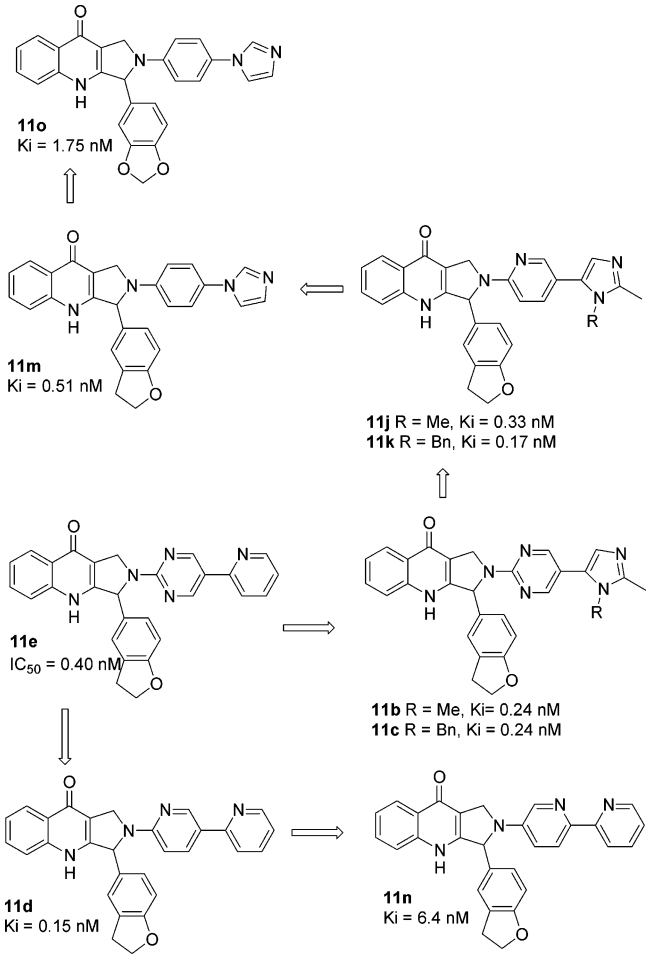
Modification of 11e. The acidic quinolone proton in **(*R*)-11e** has a pK_a of 9.24, and the pyridine has a basic pK_a of 4.43. Earlier studies indicated that the quinolone proton is essential for PDE5 inhibition,[8d] so we focused our efforts on increasing the basic pK_a without increasing the molecular weight. First, we replaced pyridine with more basic imidazole moieties (**11b** and **11c**, pK_a

Table 1. PDE5 Inhibition and Selectivity versus Other PDE Isozymes

compd	K_i[a](SD) for PDE5 (nM)	PDE1/5	PDE2/5	PDE3/5	PDE4/5	PDE6/5 cone	PDE6/5 rod
sildenafil	1.80(0.15)	180	12 750	12 790	2 920	9.0	3.2
tadalafil	5.00	>2 000	>2 000	>2 000	>2 000	1 000	–
11a	0.19(0.06)	>15 000	>15 000	>15 000	>2 500	22.3	22.6
11b	0.24(0.03)	>15 000	>15 000	>15 000	>2 500	219.4	236.8
11c	0.24(0.04)	>15 000	>15 000	>15 000	>2 500	359.2	366.2
11d	0.15(0.07)	>15 000	>15 000	>15 000	>2 500	69.2	93.0
11e[b]	0.40	>15 000	>15 000	>15 000	>2 500	–	–
11f[b]	1.90	>15 000	>15 000	>15 000	>2 500	39.2	35.7
11g	1.05(0.09)	>15 000	>15 000	>15 000	>2 500	309.9	754.7
11h	0.36(0.06)	>15 000	>15 000	>15 000	>2 500	66.5	127.2
11i	0.22(0.06)	>15 000	>15 000	>15 000	>2 500	12.1	10.5
11j	0.33(0.17)	>15 000	>15 000	>15 000	>2 500	10.3	2.6
11k	0.17(0.09)	>15 000	>15 000	4 560	>2 500	68.9	57.6
11lc	0.65	>15 000	>15 000	>15 000	>2 500	237	219
11m	0.51(0.04)	>15 000	>15 000	>15 000	>2 500	1837	499
11n	6.43(2.45)	>15 000	>15 000	>15 000	>2 500	148.7	328.6
11o[b]	1.75	>15 000	4 870	10 270	>2 500	13.2	20.1
11p	0.29(0.15)	>15 000	>15 000	>15 000	>2 500	7.6	9.3
(*R*)-**11e**	0.019	>15 000	>15 000	>15 000	>2 500	67	99
(*R*)-**11l**	0.12	>15 000	>15 000	>15 000	>2 500	106	173

[a] K_i was the mean of three tests for PDE5 and at least two tests for PDE1−4 and PDE6 (cone/rod). [b] IC_{50} was used. [c] K_i was tested one time. [d] Reference 4b,c.

Chart 2. Increasing Basic pK_a of **11e**



6−7, Chart 2). To our delight, while the potency against PDE5 was maintained, the selectivity versus PDE6 was improved about 20-fold (Table 1). However, some imidazole analogues were not orally bioavailable, e.g. compound **11b** has 0% bioavailability in rats. Other imidazole-containing derivatives such as phenylimidazole analogues (**11o** and **11m**) and pyridinylimidazole analogues (**11j** and **11k**) did not show desirable potency (**11o**, K_i = 1.75 nM) or selectivity (**11j** showed lower PDE6/5 selectivity than **11e**; **11k** showed lower PDE3/5 selectivity than **11e**). Another approach to increasing the basic pK_a was to replace the pyrrolopyrimidine (pK_a ∼ 3) with pyrrolopyridine (pK_a ∼ 6). First, pyrrolopyridine derivative **11d** was synthesized for direct comparison with pyrimidine derivative **11e**. While the potency was maintained and the PDE 6/5 selectivity slightly improved (3-fold), we were encouraged to note that compound **11d** showed slightly improved oral bioavailability (39%), though not statistically significant.

To decrease the molecular weight, compound **11e** was truncated and two analogues, **11g** and **11l**, were generated with about 17% molecular weight (MW) reduction (Chart 3). Both pyrimidinylpyrroloquinolone **11g** and pyridinylpyrroloquinolone **11l** showed excellent potency and PDE 6/5 selectivity. The slight increase in basicity from **11g** (pK_a = 4.4) to **11l** (pK_a ∼ 5) had a big influence on their bioavailability. Compound **11l** had an oral bioavailability of 38% in male rats, while **11g** had only 12% in a parallel study. The more active enantiomer, compound **(*R*)-11l** was taken to male beagle dogs and male cynomogolous monkeys for pharmacokinetic studies. To our delight, it was found to be 69% orally bioavailable in dogs and 40% in monkeys, a significant improvement in PK compared to **(*R*)-11e**. Thus, **(*R*)-11l** was selected as one of the development candidates for our PDE5 program.

Pharmacokinetic Studies

Phamacokinetic studies were conducted in male Sprague−Dawly rats, male beagle dogs, and male rhesus monkeys. Animals were separated into two groups for oral (po) and intravenous (iv) dosing with three animals per group. The oral group was dosed at 30 mg/kg using 0.5% methylcellulose as vehicle, while the intravenous group was dosed at 3.0 mg/kg using 20% cyclodextrin (HPBCD) as vehicle. The blood samples were collected at 0, 0.5, 1, 2, 4, 6, and 24 h after the administration of the drug. The plasma levels of the drug were quantitatively determined by LC/MS. The results were calculated using WinNonlin Pro version 2.1. The average

Chart 3. Truncated Analogues of **11e**

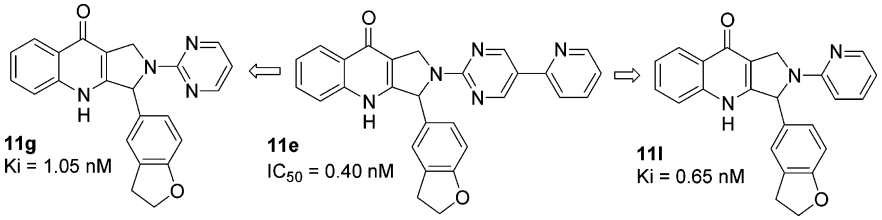


Table 2. Oral Bioavailability of Selected Compounds

compd	**11b**	**11d**	**11e**	**11g**	**11l**	(*R*)-**11l**	(*R*)-**11l**
oral bioavailability, %	0	39.0	31.3	12.0	38.0	69.0	40.0
standard deviatons, %	0	43.0	13.9	5.0	17.5	17.9	16.8
animal species	rat	rat	rat	rat	rat	dog	monkey

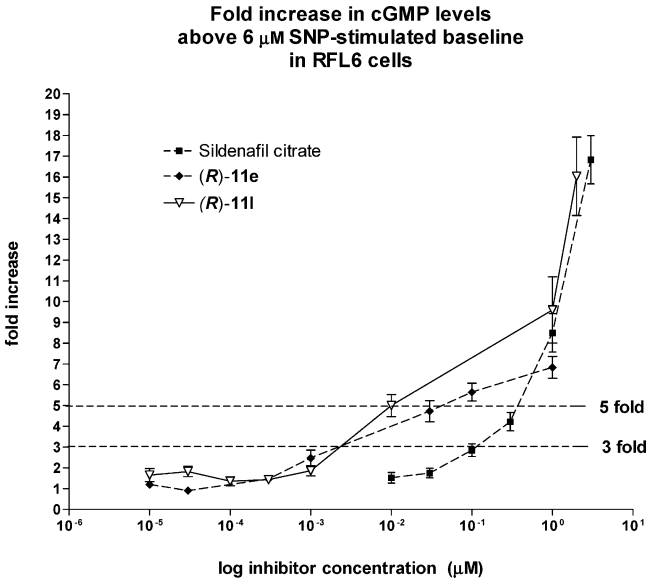


Figure 1. RFL-6 cell-based functional assay on **(*R*)-11e** and **(*R*)-11l**.

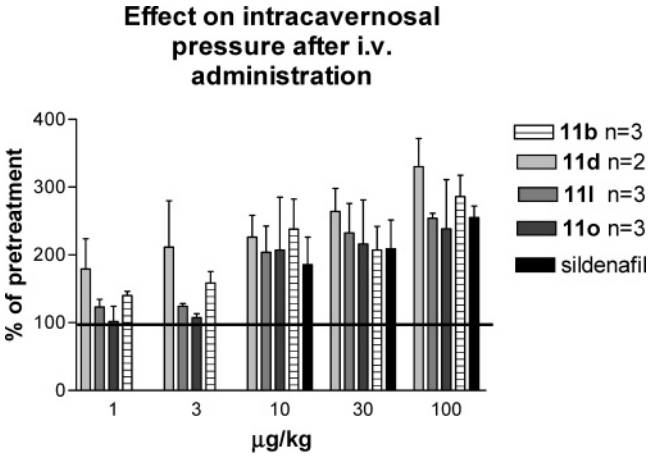


Figure 2. Effect on intracavernosal pressure after iv administration.

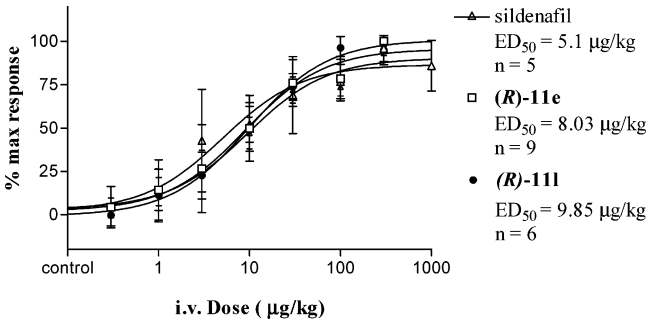


Figure 3. Efficacy for **(*R*)-11e** and **(*R*)-11l**.

value and standard deviation of bioavailability of the tested compounds from three animal species are reported in Table 2.

Cell-Based Functional Assay. To further evaluate the compounds, we tested selected compounds in vitro in rat fetal lung fibroblast (RFL-6) cells. This assay uses sodium nitroprusside-treated RFL-6 cells as a baseline to facilitate the measurement of a compound's ability to elevate intracellular cGMP levels. Inhibition of PDE5 in these cells should raise cGMP levels in a dose-dependent manner. As shown in Figure 1, both **(*R*)-11e** (K_i = 0.050 nM) and **(*R*)-11l** (K_i = 0.12 nM) induced a 5-fold increase in intracellular cGMP concentration at lower concentrations than sildenafil.

In Vivo Efficacy. Selected analogues were studied in the canine models in anesthetized male beagle dogs[8c] (Figures 2 and 3). The intracavernosal blood pressure (ICP) of the electrically stimulated dogs was measured after administering the drug by the intravenous route. PDE5 inhibitors increase ICP in this model as a result of elevated cGMP levels and the subsequent engorged penis. Figure 2 demonstrated that at dosage range of 1−100 μg/kg, many of our compounds (**11b**, **11d**, **11l**, and **11o**) showed comparable efficacy as sildenafil. Moreover, the more active enantiomers, **(*R*)-11e** and **(*R*)-11l**, showed excellent in vivo efficacy in this model (Figure 3).

Conclusion

We have identified a series of heterocyclic analogues of our earlier phenyl pyrimidine pyrroloquinolone PDE5 inhibitors. Most of the derivatives in this series are extremely potent against PDE5 and highly selective versus PDE1−4. Many analogues also showed very good selectivity versus PDE6. Through adjusting pK_a and decreasing molecular weight, we were able to improve the physical and chemical properties of the series. As a consequence, preclinical pharmacokinetic studies on these compounds showed that selected compounds such as **11e**, **11d**, and **11l** have oral bioavailibity of more than 30% in male rats. Among these compounds, **(*R*)-11l** has very good bioavailability in dogs and monkeys. The in vivo efficacy studies in anesthetized canines demonstrated that many analogues are as efficacious in vivo as sildenafil. Clinical studies of selected compounds are ongoing and will be reported in due course.

Experimental Section

General Information for Chemistry. NMR spectra were obtained at 400 and 300 MHz on a Bruker AVANCE300 and AVANCE400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Thin-layer chromatography was carried out using 2.5 × 7.5 -cm silica gel 60 (250 mM layer) plates with UV detection. Magnesium sulfate was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM science silical gel 60 (230−400 mesh). Standard solvents from J. T. Baker were used as received. Anhydrous solvents from J. T. Baker or Aldrich and all other commercially available reagents were used without further purification. Melting points were taken using a Thomas-Hoover MelTemp apparatus without any correction. Quantitative Technologies Inc., Whitehouse, NJ, delivered the results of elemental analysis. Mass spectra were obtained on a Hewlett-Packard 5989A quadrupole mass spectrometer. Silica gel (E. Merck, 230−400 mesh) was used for all flash chromatography. Thin-layer chromatography was performed on Analtech silica gel GF prescored plates (250 μm). HPLC analysis was carried on Agilent 1100 Series LC/MSD equipment.

Benzofuran-5-carbaldehyde (5a) was synthesized in four steps in 24% overall yield according to the procedure reported by Hiroya et al. (*Heterocycles* **1994**, *38*, 2463−2472).

1-Benzofuran-5-yl-2,3,4,9-tetrahydro-1*H*-*β*-carboline (6a). Benzofuran-5-carbaldehyde (**5a**) (0.096 g, 0.657 mmol) and tryptamine (0.106 g, 0.661 mmol) were stirred in dichloromethane (5 mL) with trifluoroacetic acid (0.090 mL) for 48 h. The reaction mixture was concentrated to a brown oil. The crude mixture was purified by silica gel column (5% methanol/chloroform) to provide product as an off-white solid (0.157 g, 83%): ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H), 7.08−7.59 (m, 7H), 6.61 (s, 1H), 5.22 (s, 1H), 2.71−3.23 (m, 4H); MS (*m/z*) 289 (MH^+), 287 (MH^-).

1-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (6b) was prepared the same as **6a** in 82% yield starting from 2,3-dihydrobenzofuran-5-carbaldehyde.

1-Benzofuran-5-yl-2-(5-pyridin-2-ylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (**10a**). A mixture of chloropyrimidine **7a** (0.175 g, 0.913 mmol) and KF (0.194 g, 3.33 mmol) in DMF (2 mL) was stirred at 90 °C for 2 h. A solution of β-carboline (**6a**) (0.24 g, 0.833 mmol), DIEA (0.31 mL, 1.77 mmol), and DMF (2 mL) was added and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was partitioned between water and dichloromethane (40 mL/40 mL). The organic layer was washed with water (2 × 100 mL), dried, and concentrated. The residue was purified by silica gel column (1% methanol/dichloromethane) to provide product as off-white solid (0.36 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.08−9.21 (m, 14H), 6.68 (s, 1H), 5.08 (m, 1H), 3.48−2.81 (m, 4H); MS (*m/z*) 444 (MH^+), 442 (MH^-).

3-Benzofuran-5-yl-2-(5-pyridin-2-ylpyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11a). β-Carboline **10a** (300 mg, 0.68 mmol) was mixed with KO*t*Bu (129 mg) in DMF (6 mL) at room temperature. The reaction mixture was stirred under constant oxygen bubble for 10 h. The reaction mixture was partitioned between ethyl acetate and water (50 mL/50 mL). The organic layer was washed with aqueous HCl (1 N) solution (50 mL) and brine (50 mL) and then dried and concentrated. The crude product was purified on a silica gel column (5% methanol/dichloromethane) to provide product as an off-white solid (120 mg, 38%): ^{1}H NMR (CD_3OD) δ 8.87 (m, 2H), 8.59 (br s, 1H), 8.37 (br s, 1H), 7.21−7.79 (m, 10H), 6.80 (m, 1H), 6.60 (m, 1H), 5.21 (m, 2H); MS (*m/z*) 458(MH^+), 456 (MH^-); HRMS calcd MH^+ for $C_{28}H_{19}N_5O_2$ 458.1617, found 458.1606.

2-(5-Bromopyrimidin-2-yl)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (8a) was prepared the same as **10a** in 24% yield starting from β-carboline **6b** and chloropyrimidine **7b**. ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 2H), 7.12−7.55 (m, 7H), 6.83 (m, 1H), 4.87 (m, 1H), 4.55 (t, 2H, J = 8.0 Hz), 2.82−3.32 (m, 5H); MS (*m/z*) 447 (MH^-).

1-(2,3-Dihydrobenzofuran-5-yl)-2-[5-(2,3-dimethyl-3*H*-imidazol-4-yl)-pyrimidin-2-yl]-2,3,4,9-tetrahydro-1*H*-*β*-carboline (10b).[10] Bromide **8a** (0.45 g, 1.00 mmol), 1,2-dimethyl-1*H*-imidazole (0.18 g, 1.87 mmol), $Pd(OAc)_2$ (12 mg, 0.050 mmol), PPh_3 (26.0 mg, 0.10 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) was stirred in DMF (3.5 mL) at 140 °C for 14 h. The mixture was poured into 10% aqueous NaOH solution (50 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), dried, and concentrated. The crude product was purified by preparative TLC (ethyl acetate/hexane 3:7 and then 5% methanol/dichloromethane) to provide product as a yellow powder (0.167 g, 36%); ^{1}H NMR ($CDCl_3$) δ 6.68−7.61 (m, 10 H), 4.91 (m, 1H), 4.52 (t, 2H, J = 8.8 Hz), 3.35 (m, 1H), 3.10 (t, 2H, J = 8.8.Hz), 2.90 (m, 2H), 2.35 (s, 3H), 2.21 (s, 3H); MS (*m/z*) 463 (MH^+), 461 (MH^-); HRMS calcd MH^+ for $C_{28}H_{26}N_6O$ 463.2246, found 463.2233.

2-[5-(3-Benzyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-yl]-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (10c) was prepared the same as **10b** in 40% yield starting from 1-benzyl-2-methyl-1*H*-imidazole: ^{1}H NMR ($CDCl_3$) δ 6.65−7.60 (m, 10 H), 4.92 (m, 1H), 4.52 (t, 2H, J = 9.0 Hz), 2.85−3.45 (m, 7H), 2.21 (s, 3H); MS (*m/z*) 539 (MH^+), 537 (MH^-).

3-(2,3-Dihydrobenzofuran-5-yl)-2-[5-(2,3-dimethyl-3*H*-imidazol-4-yl)pyrimidin-2-yl]-1,2,3,4-tetrahydropyrrolo-[3,4-*b*]quinolin-9-one (11b) was prepared the same as **11a** in 24% yield starting from **10b**: ^{1}H NMR (CD_3OD) δ 8.35 (m, 3H), 7.53 (s, 2H), 7.31 (m, 1H), 7.19 (m, 2H), 6.84 (s, 1H), 6.63 (m, 1H), 6.24 (s, 1H), 5.02 (br s, 2H), 4.42 (t, 2H, J = 9.5 Hz), 3.50 (s, 3H), 3.28 (s, 3H), 3.08 (t, 2H, J = 9.5 Hz); MS (*m/z*) 477, (MH^+), 475 (MH^-); HRMS calcd MH^+ for $C_{28}H_{24}N_6O_2$ 477.2039, found 477.2026.

2-[5-(3-Benzyl-2-methyl-3*H*-imidazol-4-yl)pyrimidin-2-yl]-3-(2,3-dihydro-benzofuran-5-yl)-1,2,3,4-tetrahydro-pyrrolo[3,4-*b*]quinolin-9-one (11c) was prepared the same as **11a** in 15% yield starting from **10c**: ^{1}H NMR (CD_3OD) δ 8.85−6.61 (m, 15H), 6.15 (s, 1H), 5.12 (m, 2H), 4.48 (t, 2H, J = 8.8 Hz), 3.12 (t, 2H, J = 8.8 Hz), 2.21 (s, 2H), 1.90 (s, 3H); MS (*m/z*) MH^+ (553), MH^- (551); HRMS calcd MH^+ for $C_{34}H_{28}N_6O_2$ 553.2352, found 553.2357.

2-(5-Bromopyridin-2-yl)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (8b). 1-(2,3-Dihydro-5-benzofuranyl)-2,3,4,9-tetrahydro-1*H*-β-carboline **6b** (2.90 g, 10.0 mmol), 2,5-dibromopyridine **7c** (2.63 g, 11.0 mmol), Pd_2-dba_3 (0.367 g, 0.40 mmol), dppp (0.33 g, 0.80 mmol), and NaO*t*Bu (1.35 g, 14 mmol) were stirred in DMF (60 mL) at 80 °C until the starting material was consumed, as monitored by HPLC−MS. The reaction mixture was then filtered through a plug of Celite with dichloromethane. The solution was washed with brine (3 × 50 mL), dried with $MgSO_4$ and filtered. The filtrate was concentrated to a brown oil and then loaded on silica gel column (110 g of silica gel) and eluted with ethyl acetate/hexane (3:7). The product crystallized out in test tubes. The fractions containing product were combined, concentrated, and then recrystallized from THF to provide yellow crystals as product (2.01 g, 45%): ^{1}H NMR (THF-d_8) δ 8.12 (s, 1H), 6.28 (s, 1H), 5.72 (m, 1H), 5.58 (m, 1H), 5.38 (m, 2H), 5.10 ∼5.28 (m, 4H), 5.02 (d, 1H, J = 7.6 Hz), 4.75 (d, 1H, J = 7.6 H), 2.60 (t, 2H, J = 9.5 Hz), 2.31 (m, 1H), 1.60 (m, 1H), 1.25 (t, 2H, J = 9.5 Hz), 1.15 (m, 1H), 0.91 (m, 1H); MS (*m/z*) 446, 448 (MH^+), 444, 446 (MH^-).

2-[2,3′]Bipyridinyl-6′-yl-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (10d). Bromide **8b** (0.446 g, 1.0 mmol), 2-tributylstannanylpyridine **9c** (0.70 g, 1.90 mmol), and $Pd(PPh_3)_4$ (0.115 g, 0.10 mmol) were stirred in 1,4-dioxane (3 mL) at 90 °C for 20 h. The reaction mixture was filtered through a plug of Celite, washed with dichloromethane, and then concentrated to a small volume. Preparative TLC (3:7 ethyl acetate/hexane; then 5% methanol/dichloromethane) yielded the product (0.185 g, 42%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 6.85 (d, 1H, J = 7.6 Hz), 6.71 (d, 1H, J = 7.6 Hz), 4.53 (t, 2H, J = 9.5 z), 4.31 (m, 1H), 3.58 (m, 1H), 3.10 (m, 3H), 2.82 (m, 1H); MS (*m/z*) 445, (MH^+), 443 (MH^-).

2-[2,3′]Bipyridinyl-6′-yl-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11d) was prepared the same as **11a** in 11% yield starting from **10d**: ^{1}H NMR ($CDCl_3$) δ 8.70−6.60 (15 H), 6.12 (s, 1H), 5.20−4.98 (m, 2H), 4.43 (t, 2H, J = 9.5 Hz), 3.16 (t, 2H, J = 9.5 Hz); MS (*m*/*z*) 459 (MH^+), 457 (MH^-); HRMS calcd MH^+ for $C_{29}H_{22}N_4O_2$ 459.1821, found 459.1819.

1,2,3,4-Tetrahydro-2-[5-(2-pyridinyl)pyrimidin-2-yl]-3-(3,4-dihydrobenzofuranyl)-9*H*-pyrrolo[3,4-*b*]quinolin-9-one (11e). Anhydrous KF (1.80 g, 0.031 mmol), chloropyrimidine **7a** (1.60 g, 8.36 mmol), and DMF (8.3 mL) was stirred at 80 °C for 3 h. After cooling, a solution of amine **1a** (2.60 g, 7.60 mmol) and DIEA (2.9 mL, 0.017 mmol) in DMF (11 mL) was added. After stirring at 55 °C for 4 h, the reaction mixture was partitioned between ethyl acetate and water (220 mL/220 mL). While the solid was collected, the organic layer was washed with water (2 × 220 mL), dried, and concentrated. The residue was combined with the solid obtained before and the mixture was triturated with ethyl acetate to yield the product as a white solid (2.61 g, 75%): mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1 H), 9.12 (s, 2 H), 8.98 (s 1H), 8.60 (d, J = 4.5 Hz, 1 H), 8.16 (d, J = 7.9 Hz, 1 H), 7.91 (d, J = 7.7 Hz, 1 H), 7.84 (d, J = 7.1 Hz, 1 H), 7.59 (t, J = 8.6 Hz, 2 H), 7.31 (m, 4H), 6.73 (d, J = 8.1 Hz, 1H), 6.34 (s, 1H), 4.91 (m, 2H), 4.46 (t, J = 8.5 Hz, 2H), 3.11 (t, J = 8.5 Hz, 2H); MS (*m*/*z*) 460 (MH^+), 458 (MH^-); HRMS calcd MH^+ for $C_{28}H_{21}N_5O_2$ 460.1774, found 460.1785.

(*R*)-1,2,3,4-Tetrahydro-2-[5-(2-pyridinyl)pyrimidin-2-yl]-3-(3,4-dihydrobenzofuranyl)-9*H*-pyrrolo[3,4-*b*]quinolin-9-one [(*R*)-11e] was prepared the same as **11e** in 85% yield starting from **(*R*)-1a:** mp 231−233 °C; $[\alpha]^{22}_D$ −237.9 ° (*c* 0.1883, methanol). Anal. Calcd for $C_{28}H_{21}N_5O_2.CH_4O_3S\cdot 1.5H_2O$: C, 59.78; H, 4.84; N, 12.02; S, 5.50. Found: C, 59.50; H, 4.78; N, 11.87; S, 5.19.

2-(5-Bromopyrimidin-2-yl)-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11f) was prepared the same as **11e** in 41% yield starting from **7b**: ^{1}H NMR (DMSO-d_6) δ 12.05 (s, 1H), 8.81−7.29 (sets of m, 9H), 6.82 (s, 1H), 6.36 (s, 1H), 4.92 (m, 2H), 4.62 (t, 2H, J = 8.0 Hz), 3.21 (t, 2H, J = 8.0 Hz); HRMS calcd MH^+ for $C_{23}H_{17}BrN_4O_2$ 461.0613, found 461.0616.

3-(2,3-Dihydrobenzofuran-5-yl)-2-pyrimidin-2-yl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11g) was prepared the same as **11e** in 24% yield starting from 2-chloropyrimidine **7d:** ^{1}H NMR ($CDOD_3$) δ 8.38−6.59 (m, 10 H), 6.31 (s, 1H), 4.95 (m, 2H), 4.48 (t, 2H, J = 9.0 Hz), 3.12 (t, 2H, J = 9.0 Hz); MS (*m*/*z*) 383 (MH^+), 381 (MH^-); HRMS calcd MH^+ for $C_{23}H_{18}N_4O_2$ 383.1508, found 383.1506.

3-(2,3-Dihydrobenzofuran-5-yl)-2-(5-pyridin-3-ylpyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11h). A stirred mixture of $Pd(OAc)_2$ (13.6 mg, 0.061 mmol) and dppf (42.1 mg, 0.076 mmol) in DMF (5 mL) was warmed to 50 °C for 15 min. After cooling, pyrroloquinolone **11f** (350 mg, 0.76 mmol), 3-pyridine boronic acid **12a** (102 mg, 0.83 mmol), and Et_3N (0.15 mL, 1.6 mmol) were heated to 90 °C for 30 h. The reaction mixture was diluted with ethyl ether and filtered through a filter paper. The solution was washed by 10% aqueous ammonium, brine, and water. After being dried and concentrated, silica gel column chromatograph purification provided the product as off-white solid (80.2 mg, 23%): ^{1}H NMR ($CDCl_3$) δ 6.75−8.95 (sets of m, 13H), 6.31 (s, 1H), 4.92 (m, 2H), 4.54 (t, 2H, J = 8.0 Hz), 3.13 (t, 2H, J = 8.0 Hz); HRMS calcd MH^+ for $C_{28}H_{21}N_5O_2$ 460.1774, found 460.1753.

3-Benzo[1,3]dioxol-5-yl-2-(5-pyridin-3-ylpyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11p) was prepared the same as **11h** in two steps in 40% and 23% yields starting from amine **1b**: ^{1}H NMR (DMSO-d_6) δ 8.45−8.95 (m, 4H); 8.12 (m, 2H), 7.28−7.62 (m, 4H), 6.95 (m, 3H), 6.31 (s, 1H), 5.95 (s, 2H), 4.91 (m, 2H); HRMS calcd MH^+ for $C_{27}H_{19}N_5O_3$ 462.1566, found 462.1593.

3-(2,3-Dihydrobenzofuran-5-yl)-2-(5-pyridin-4-ylpyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11i) was prepared the same as **11h** in 25% yield starting from 4-pyridine boronic acid **12b**: ^{1}H NMR ($CDCl_3$) δ 6.65−8.95 (sets of m, 13 H), 6.32 (s, 1H), 4.41 (t, 2H, J = 8.0 Hz), 3.12 (t, 2H, J = 8.0 Hz); HRMS calcd MH^+ for $C_{28}H_{21}N_5O_2$ 460.1774, found 460.1763.

3-(2,3-Dihydrobenzofuran-5-yl)-2-[5-(3-methyl-3*H*-imidazol-4-yl)pyridin-2-yl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-quinolin-9-one (11j). Pyrroloquinolone **1a** (0.127 g, 0.372 mmol), 2-chloro-5-(3-methyl-3*H*-imidazol-4-yl)pyridine **7e** [0.060 g, 0.31 mmol, prepared in 31% yield according to the procedure reported by Kondo et al. (*Org. Lett*. **2000**, *2*, 3111−3113)], $Pd(OAc)_2$ (3.5 mg, 0.0155 mmol), biphenyl-2-yldicyclohexylphosphane (5.43 mg, 0.0155 mmol), and NaO*t*Bu (0.104 g, 1.085 mmol) were stirred in 1,4-dioxane (0.6 mL) at 90 °C until the starting material was consumed as monitored by HPLC−MS. Ethyl acetate (50 mL) and water (50 mL) were added to the reaction mixture. The organic layer was separated, dried and concentrated. Purification by preparative TLC (5% methanol in dichloromethane) yielded the product as a yellow solid (18.8 mg, 12%): ^{1}H NMR (CD_3OD) δ 7.20−8.55 (m, 10 H), 6.70 (m, 2H), 6.08 (s, 1H), 5.12 (m, 2H), 3.60 (s, 3H), 3.50 (t, 2H, J = 8.0 Hz), 3.12 (t, 2H, J = 8.0 Hz); MS (*m*/*z*) MH^+ (462), MH^- (460); HRMS calcd MH^+ for $C_{28}H_{23}N_5O_2$ 462.1930, found 462.1917.

2-[5-(3-Benzyl-3*H*-imidazol-4-yl)pyridin-2-yl]-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-quinolin-9-one (11k) was prepared the same as **11j** in 14% yield starting from chloride **7f**: ^{1}H NMR (CD_3OD) δ 6.45−8.54 (m, 12H), 6.05 (s, 1H), 5.10 (m, 2H), 4.55 (t, 2H, J = 8.3 Hz), 3.60 (m, 2H), 3.12 (t, 2H, J = 8.3 Hz); MS (*m*/*z*) MH^+ (538), MH^- (536); 446123; HRMS calcd MH^+ for $C_{34}H_{27}N_5O_2$ 538.2243, found 538.2239.

3-(2,3-Dihydrobenzofuran-5-yl)-2-pyridin-2-yl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11l). Pyrroloquinolone·HCl (**1a**·HCl) (0.30 g, 0.88 mmol), 2-bromopyridine **7g** (2 mL), Pd_2dba_3 (0.23 g, 0.25 mmol), (±)-BINAP (0.47 g, 0.75 mmol), and NaO*t*Bu (0.66 g, 6.87 mmol) were stirred in 1,4-dioxane (4 mL) at 90 °C for 1 h. The resulting mixture was concentrated and then filtered on a plug of Celite with dichloromethane. Ethyl acetate (50 mL) and water (50 mL) were added to the reaction mixture. The organic layer was separated, dried and concentrated. Purification by preparative TLC (5% methanol/dichloromethane) yielded the product as a yellow solid (0.185 g, 55%): ^{1}H NMR (CD_3OD) δ 8.30 (d, 1H, J = 9.3 Hz), 8.02 (m, 1H), 7.35 (m, 4H), 7.10 (m, 3H), 6.55 (m, 2H), 4.85 (d, 1H, J = 22.0 Hz), 4.54 (d, 1H, J = 22.0 Hz), 4.40 (t, 2H, J = 9.5 Hz), 2.92 (t, 2H, J = 9.5 Hz); MS (*m*/*z*) 382, (MH^+), 380 (MH^-); HRMS calcd MH^+ for $C_{24}H_{19}N_3O_2$ 382.1556, found 382.1552.

(*R*)-(−)-3-(2,3-Dihydrobenzofuran-5-yl)-2-pyridin-2-yl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one [(*R*)-11l] was prepared the same as **11l** in 50% yield starting from **(*R*)-1a**. Karl Fisher analysis calcd %H_2O 0.66, found %H_2O 0.59; $[\alpha]^{22}_D$ −199.0° (*c* 0.31, methanol); mp 251.0−253.0 °C. Anal. Calcd for $C_{24}H_{19}N_3O_2\cdot 0.14H_2O$: C, 74.93; H, 5.05; N, 10.92. Found: C, 74.57; H. 5.21; N, 10.59.

3-(2,3-Dihydrobenzofuran-5-yl)-2-(4-imidazol-1-ylphenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11m).[11c,d] Pyrroloquinolone (**1a**) (34.1 mg, 0.1 mmol), 1-(4-bromophenyl)-1*H*-imidazole **7h** (22.3 mg, 0.10 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol), biphenyl-2-yldi-*tert*-butylphosphane (3.0 mg, 0.010 mmol), and NaO*t*Bu (14 mg, 0.14 mmol) were stirred in 1,4-dioxane (0.60 mL) at 89 °C for 17 h. Ethyl acetate (50 mL) and water (50 mL) were added to the reaction mixture. The organic layer was separated, dried and concentrated. Purification by preparative TLC (5% methanol/dichloromethane) provide product as yellow powder (12.3 mg, 24%): ^{1}H NMR (CD_3OD) δ 6.67−8.58 (sets of m), 5.89 (s, 1H), 5.05 (d, 1H, J = 16.0 Hz), 4.78 (d, 1H, J = 16.0 Hz), 4.50 (t, 2H, J = 8.0 Hz), 3.12 (t, 2H, J = 8.0 Hz); MS (*m*/*z*) MH^+ (447), MH^- (445); HRMS calcd MH^+ for $C_{28}H_{22}N_4O_2$ 447.1821, found 447.1816.

3-Benzo[1,3]dioxol-5-yl-2-(4-imidazol-1-ylphenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11o) was prepared the same as **11m** in 20% yield starting from amine **1b**: ^{1}H NMR (CD_3OD) δ 6.75−8.32 (m, 14H), 5.88 (s, 2H), 5.48 (s,

2H), 5.02 (d, 1H, J = 13.8 Hz), 4.70 (d, 1H, J = 13.8 Hz); MS (m/z) MH^+ (449), MH^- (447); HRMS calcd MH^+ for $C_{27}H_{20}N_4O_3$ 449.1614, found 449.1617.

2-[2,2′]Bipyridinyl-5-yl-3-(2,3-dihydrobenzofuran-5-yl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]quinolin-9-one (11n). Pyrroloquinolone·HCl (**1a**·HCl) (0.034 g, 0.1 mmol), 5-bromo-[2,2′]bipyridinyl **7h** [23.5 mg, 0.10 mmol; prepared according to the procedure reported by Bomero and Ziessel (*Tetrahedron Lett.* **1995**, *36*, 6471−6474)], Pd_2dba_3 (4.6 mg, 0.005 mmol), biphenyl-2-yldi-*tert*-butylphosphane (3.0 mg, 0.01 mmol), and NaO*t*Bu (44 mg, 0.44 mmol) were stirred in 1,4-dioxane (0.6 mL) at 90 °C for 1 h. The resulting mixture was concentrated and filtered on a plug of Celite with dichloromethane. Purification by preparative TLC (5% methanol/dichloromethane) yielded the product as a yellow solid (10.0 mg, 22%): ^{1}H NMR (CD_3OD) δ 6.65−8.45 (sets of m, 14H), 5.92 (s, 1H), 5.10 (m, 2H), 4.45 (t, 2H, J = 8.0 Hz), 3.15 (t, 2H, J = 8.0 Hz); MS (m/z) 459 (MH^+), 457 (MH^-); HRMS (ESI) calcd MH^- for $C_{29}H_{22}N_4O_2$ 457.1665, found 457.1688.

Biological Assays. All assays used in this report were discussed in our previous publication.[8c]

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Supporting Information Available: A table listing the purity of **11a**−**p**; ^{1}H NMR of **6a,b**, **8a,b**, **10a**−**d**, and **11a**−**p**; and HPLC of **11a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For MED, see: (a) Lue, T. F. Erectile Dysfunction. *N. Engl. J. Med.* **2000**, *342*, 1802−1818. (b) Feldman, H. A.; Goldstein, I.; Hatzichristou, D. G.; Krane, R. J.; McKinlay, J. B. Impotence and Its Medical and Physiological Correlates: Results of the Massachusetts Male Aging Study. *J. Urol.* **1994**, *151*, 54−56.

(2) (a) Corbin, J. D.; Francis, S. H. Cyclic GMP Phosphodiesterase-5: Target of Sildenafil. *J. Biol. Chem.* **1999**, *274*, 13729−13732. (b) Soderling, S. H.; Beavo, J. A. Regulation of cAMP and cGMP signaling: New phosphodiesterases and new functions. *Curr. Opin. Cell Biol.* **2000**, *12*, 174−179. (c) Conti, M.; Jin, S.-L. C. The molecular Biology of Cyclic Nucleotide Phosphodiesterases. *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *65*, 1−52.

(3) For Viagra (sildenafil), see: Brook, G. Sildenafil Citrate (Viagra). *Drugs Today* **2000**, *36* (2−3), 125−134 and references therein.

(4) For Cialis (tadalafil), see: (a) Sorbera, L A.; Martin, L.; Leeson, P. A.; Casraner, J.; IC-351, Treatment of Erectile Dysfunction. Treatment of Female Sexual Dysfunction, Phosphodiesterase 5 Inhibitor. *Drugs Future* **2001**, *26* (1), 15−19 and references therein. For discovery of tadalafil, see: (b) Daugan, A.; Grondin, P.; Ruault, C.; Gouville, A.-C. L. M.; Coste, H.; Kirilovsky, J.; Hyafil, F.; Labaudiniere, R. The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor. 1: 5,6,11,11a-Tetrahydro-1*H*-imidazole[1′,5′:1,6]pyrido[3,4-b]indole-1, 3(2H)-dione Analogues. *J. Med. Chem.* **2003**, *46*, 4525−4532. (c) Daugan, A.; Grondin, P.; Ruault, C.; Gouville, A.-C. L. M.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudiniere, R. 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. *J. Med. Chem.* **2003**, *46*, 4533−4542.

(5) For Levitra (vardenafil), see: Sorbera, L. A.; Martin, L.; Rabasseda, J.; Castaner, J.; Vardenafil, Treatment of Erectile Dysfunction, Phosphodiesterase 5 Inhibitor. *Drugs Future* **2001**, *26* (2), 141−144 and references therein.

(6) For comparison of the three launched PDE5 inhibitors, see: (a) Gresser, U.; Gleiter, C. H. Erectile Dysfunction: Comparison of Efficacy and Side Effects of the PDE-5 Inhibitors Sildenafil, Vardenafil and Tadalafil. *Eur. J. Med. Res.* **2002**, *7*, 435−466. (b) Sui, Z.; Phosphodiesterase-5 Inhibitors for Male Erectile Dysfunction. *Expert Opin. Ther. Pat.* **2003**, *13* (9), 1373−1388.

(7) Fawcett, L.; Baxendale, R.; Stacey, P.; McGrouther, C.; Harrow, I.; Soderling, S.; Hetman, J.; Beavo, J. A.; Phillips, S. C.; Molecular cloning and characterization of a distinct human phosphodiesterase gene family: PDE11A. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 3702−07.

(8) (a) Sui, Z.; Guan, J.; Macielag, M. J.; Jiang, W.; Zhang, S.; Qiu, Y.; Kraft, P., Bhattacharjee, S.; John, T. M.; Craig, E.; Haynes-Johnson, D.; Clancy, J. Pyrimidinyl Pyrroloquinolones as Highly Potent and Selective PDE5 Inhibitors for Treatment of Erectile Dysfunction. *J. Med. Chem.* **2002**, *45*, 4094−4096. (b) Jiang, W.; Sui, Z.; Chen, X. Synthesis of Optically Pure Pyrroloquinolones via Pictet−Spengler and Winterfeldt Reactions. *Tetrahedron Lett.* **2002**, *43* (49), 8941−8945. (c) Qiu, Y.; Bhattacharjee, S.; Kraft, P.; John, T. M.; Craig, E.; Haynes-Johnson, D.; Guan, J.; Jiang, W.; Macielag, M.; Sui, Z.; Clancy, J.; Lundeen, S. Characterization of a novel phosphodiesterase type 5 inhibitor: JNJ-10258859. *Eur. J. Pharm.* **2003**, *472* (1−2), 73−80. (d) Lanter, J. C.; Walsh, S. P.; Sui, Z.; Macielag, M. J.; Jiang, W.; Fiordeliso, J. J.; Guan, J.; Qiu, Y.; Kraft, P.; Lombardi, E.; John, T. M.; Clancy, J. Structure−Activity Relationships of *N*-Acyl Pyrroloquinolone PDE-5 Inhibitors. *J. Med. Chem.* **2004,** *47,* 656−662.

(9) (a) Winterfeldt, E. Chinolon-Derivate durch autoxidation**.** *Liebigs Ann. Chem*. **1971**, *745*, 23−30. (b) Warneke, J.; Winterfeldt, E. Die autoxidative indol-chinolon-umwandlung eines camptothecin-modells. *Chem. Ber.* **1972**, *105*, 2120−2125. (c) Boch, M.; Korth T.; Nelke, J. M.; Pike, D.; Radunz, H.; Winterfeldt, E.; Die biogenetisch orientierte totalsynthese von DL-Camptoyhecin und 7-chlor-camptothecin. *Chem. Ber.* **1972**, *105,* 2126−2142. (d) Carniaux, J.-F.; Kan-Fan, C.; Royer, J.; Husson, H.-P. Synthesis of a Novel Fused Tricyclic Quinolone system via Oxidation of 1,2,3,4-Tetrahydro-β-Carbolines *Tetrahedron Lett.* **1997**, *38*, 2997−3000.

(10) Pivsa-Art, S.; Sato, T.; Kawamura, Y.; Miura, M.; Nomura, M. Palladium-Catalyzed Arylation of Azolation of Azole Compounds with Aryl Halides in the Presence of Alkali Metal Carbonates and the Use of Copper Iodides in the Reaction. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−73.

(11) (a) Wolfe, J. P.; Buchwald, S. L.; Palladium-Catalyzed Amination of Aryl Iodides, *J. Org. Chem.* **1996**, *61*, 1133−35. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L.; Efficient Palladium-Catalyzed N-arylation of Indoles, *Org. Lett.* **2000**, *2,* 1403−1406. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald. S. L. Simple, Efficient Catalyst System for the Palladium-Catalyzed Amination of Aryl Chlorides, Bromides, and Triflates. *J. Org. Chem.* **2000**, *65*, 1158−74. (d) Wolfe, J. P.; Buchwald, S. L. Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides. *J. Org. Chem*. **2000**, *65*, 1144−57.

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