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# SAR development of polycyclic guanine derivatives targeted to the discovery of a selective PDE5 inhibitor for treatment of erectile dysfunction

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**Abstract**—Development of structure–activity relationship of cyclic guanines **I** lead us to discovery of a potent and selective series of phosphodiesterase 5 inhibitors **52**–**59** ($IC_{50}$ = 1.3–11.0 nM, PDE6/5 = 116–600).


Introduction of sildenafil (Viagra™) for the treatment of erectile dysfunction in 1998 has led to a fundamental shift in this therapeutic area. This effective, orally active drug has virtually displaced previously developed options, such as intracavernosal or intraurethral injections of vasoactive substances or penile implants as mechanical aids.

In males, erection is triggered by the release of nitric oxide from non-adrenergic, non-cholinergic (NANC) neurons located in the corpus cavernosum of the penis, which takes place upon sexual stimulation. Nitric oxide initiates cGMP synthesis via activation of soluble guanylyl cyclase in the smooth muscle cells. cGMP mediates intracellular signal transduction, leading to a decrease in calcium concentration, followed by relaxation of smooth muscle in corpus cavernosum, increase of arterial flow to this tissue and engorgement of penis with blood. The mechanism of action of sildenafil stems from the inhibition of phosphodiesterase type 5 (PDE5), which is the major cGMP hydrolyzing enzyme in corpus cavernosum. As the breakdown of cGMP is slowed down, increased levels of this mediator lead to enhancement of erection.[1]

Despite its commercial success, sildenafil has shown clinically significant side effects,[2] some of which may be linked to insufficient selectivity versus other PDEs. Specifically, reported incidences of visual disturbances may be linked to inhibition of PDE6.

Several approaches to an improved PDE5 inhibitor were reported in the literature during the last several years,[3] with the most challenging aspect being achieving

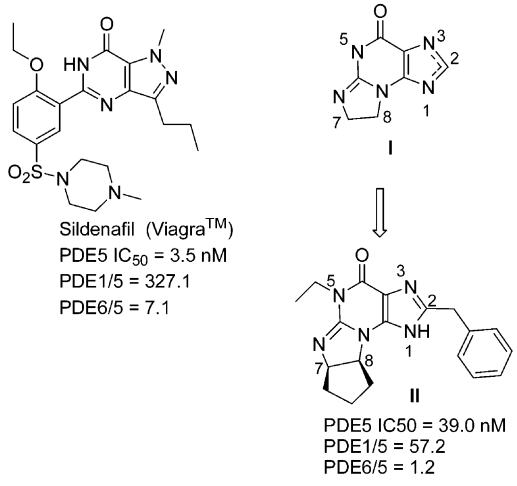


**Figure 1.** Structure **II** as initial lead.

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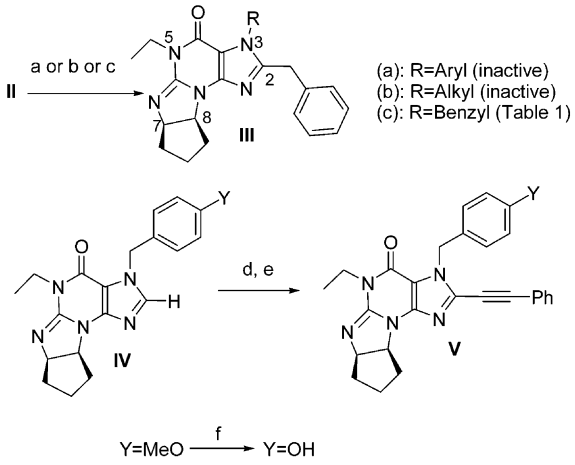
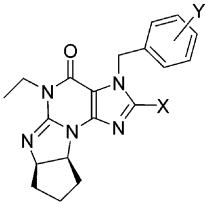
significant (e.g., several hundred-fold) selectivity over the closely related PDE6 isoform. In the light of this fact we wish to report our studies which culminated in the discovery of a novel, potent and selective series of PDE5 inhibitors.[4]

Cyclic guanines with framework of type **I** were discovered in these labs in the course of antihypertensive drug search, and were identified as dual inhibitors of PDE1 and PDE5. A representative of this class with N-5 ethyl substitution (**II**) was reported[5] to have modest levels of PDE5 inhibition, and was chosen as the lead molecule for the present study (Fig. 1).




**Scheme 1.** Synthesis of compounds of Table 1. (a) $ArB(OH)_2$, $Cu(OAc)_2$, Pyr, DCM, air; (b) Alk-I, DMF, $K_2CO_3$; (c) Br–$CH_2$–Ar, DMF, $K_2CO_3$; (d) LDA, THF, $I_2$; (e) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, TEA; (f) $BCl_3$, DCM.

**Table 1.** Discovery of Y = *p*-MeO and *p*-OH as optimized substituents at N-3 center



| Entry | X | Y | PDE5 $IC_{50}$, nM | PDE6/5 |
|---|---|---|---|---|
| **1** | –$CH_2$–Ph | H | 130.0 | 2.6 |
| **2** | –$CH_2$–Ph | *p*-Me | 40.0 | 1.5 |
| **3** | –$CH_2$–Ph | *m*-Me | 26%[a] | |
| **4** | –$CH_2$–Ph | *o*-Me | 18%[a] | |
| **5** | –$CH_2$–Ph | *p*-Cl | 160.0 | 1.6 |
| **6** | –$CH_2$–Ph | *p*-$NO_2$ | 8%[a] | |
| **7** | –$CH_2$–Ph | *p*-MeO | 20.0 | 1.1 |
| **8** | –$CH_2$–Ph | *p*-OH | 3.9 | 7.4 |
| **9** | –$CH_2$–Ph | *p*-$NH_2$ | 550.00 | 0.4 |
| **10** | –$CH_2$–Ph |  | 32%[a] | — |
| **11** | –$CH_2$–Ph | *m*-Cl | 26%[a] | — |
| **12** | –$CH_2$–Ph | *m*-Br | 33%[a] | — |
| **13** | –$CH_2$–Ph | *m*-MeO | 14%[a] | — |
| **14** | –$CH_2$–Ph | *p*-Me, *m*-Cl | 27%[a] | — |
| **15** | –$CH_2$–Ph | *p*-MeO, *m*-Cl | 58.0 | 6.7 |
| **16** | –$CH_2$–Ph | 3,4-methylenedioxy | 46.0 | 0.7 |
| **17** | –CC–Ph | H | 8.0 | 2.6 |
| **18** | –CC–Ph | *p*-Cl | 5.0 | 3.4 |
| **19** | –CC–Ph | *p*-MeO | 3.1 | 0.5 |
| **20** | –CC–Ph | *p*-OH | 0.3 | 10.3 |

[a] % Inhibition at 100 nM.

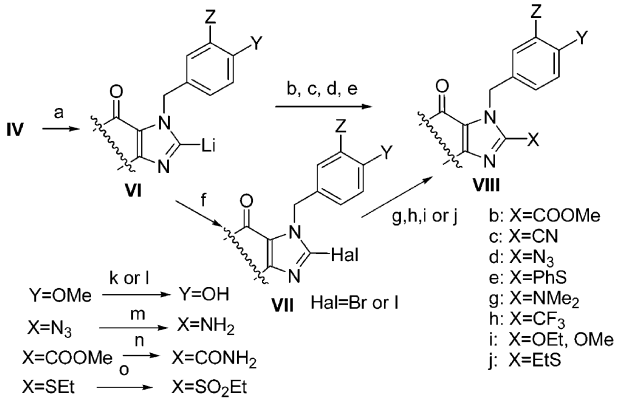
Molecule **II** allowed easy chemical modification at the N-3 atom by known N-arylation methodology[6] as well as by alkylation or benzylation in DMF in the presence of potassium carbonate (Scheme 1).[7] As the N-1 center represents a vinylogous amide, its reactivity is diminished so that a complete N-3 selectivity is achieved.

While simple alkyl- and aryl-substituted analogues of **II** lacked PDE5 activity, N-3 benzylation was tolerated. In order to systematize the investigation of benzyl substitution, a modified Topliss tree[8] approach was undertaken (Table 1).

Introduction of an electron-donating methyl group at the *para*-position of the phenyl ring (**2**) resulted in >3 fold improvement of PDE5 potency as compared to the unsubstituted case (**1**). *meta*- And *ortho*-substitution was not tolerated (**3**, **4**). Introduction of electron-withdrawing *para*-substituent (Cl, $NO_2$) resulted in diminishing (**5**) or loss (**6**) of PDE5 activity. As was expected, a substituent with stronger electron-donating properties, such as methoxy- and hydroxy-, allowed for further improvement in $IC_{50}$ as in **7** and **8**, the latter compound having potency and selectivity on a par with sildenafil. Despite the well-documented electron-donating properties of a *p*-amino group, it resulted in a drastic loss of activity (**9**). Di-substituted derivatives **14**–**16** as well as aryl substituted compound **10** were less active.

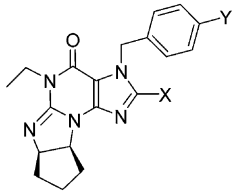
In line with the previous observations,[9] installation of an alkynyl substituent at C-2 provided excellent PDE5 inhibitors **17**–**20**. A combination of the optimized *p*-hydroxybenzyl substituent at N-3 with a phenylacetylene at C-2 resulted in a sub-nanomolar inhibitor (**20**).

Despite these promising results, we were concerned that conjugation of the acetylene in **17**–**20** with the electron-




**Scheme 2.** Synthesis of compounds of Tables 2 and 3. (a) LDA; (b) ClCOOMe; (c) TsCN; (d) $TsN_3$; (e) PhSSPh; (f) $BrF_2C$–$CF_2Br$ or $I_2$; (g) Hal = Br: $Me_2NH$, THF, 100 °C, sealed tube; (h) Hal = I: '$CuCF_3$' (lit.[10]), DMF, HMPA; (i) Hal = I: RONa; (j) Hal = Br: EtSNa; (k) $BCl_3$, DCM; (l) $AlCl_3$, EtSH:DCM = 1:1; (m) $PPh_3$, THF, $H_2O$; (n) $NH_3$, MeOH; (o) $NaBO_3$, AcOH, 50 °C.

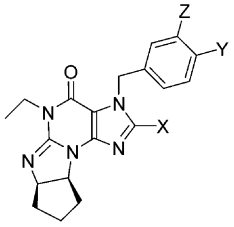
**Table 2.** Optimization of substituent X at C-2 site



| Entry | X | Y | PDE5 $IC_{50}$ (nM) | PDE6/5 |
|---|---|---|---|---|
| **21** | $SO_2Et$ | MeO | 31%[a] | — |
| **22** | $NMe_2$ | MeO | 27%[a] | — |
| **23** | H | MeO | 55.0 | 0.6 |
| **24** | $CF_3$ | MeO | 48.0 | 1.7 |
| **25** | OEt | MeO | 18.0 | 1.4 |
| **26** | SEt | MeO | 13.0 | 1.0 |
| **27** | COOMe | MeO | 6.8 | 0.8 |
| **28** | CN | MeO | 6.3 | 1.2 |
| **29** | $CONH_2$ | MeO | 4.0 | 3 |
| **30** | $NH_2$ | OH | 22.0 | 13 |
| **31** | $CF_3$ | OH | 7.0 | 23 |
| **32** | $CONH_2$ | OH | 2.1 | 28 |
| **33** | SEt | OH | 1.8 | 25 |
| **34** | OEt | OH | 0.9 | 21 |
| **35** | $N_3$ | OH | 0.61 | 67 |

[a] The value represents % inhibition at 100 nM of inhibitor.

**Table 3.** Effect of substituent Z



| Entry | X | Y | Z | PDE5 $IC_{50}$ (nM) | PDE6/5 |
|---|---|---|---|---|---|
| **36** | H | MeO | Br | 6.5 | 6 |
| **37** | H | MeO | Cl | 8.3 | 4 |
| **38** | H | OH | Br | 6.3 | 24 |
| **39** | $CONH_2$ | MeO | Br | 1.5 | 9.3 |
| **40** | $CONH_2$ | OH | Br | 0.9 | 50 |
| **41** | $CONH_2$ | OH | Cl | 1.1 | 82 |
| **42** | CONHMe | MeO | Cl | 2.3 | 6.5 |
| **43** | CONHMe | OH | Cl | 1.3 | 32 |
| **44** | OEt | MeO | Br | 5.4 | 11 |
| **45** | OEt | MeO | Cl | 6.5 | 8 |
| **46** | OEt | OH | Cl | 2.1 | 57 |
| **47** | OMe | MeO | Br | 2.8 | 32 |
| **48** | OMe | MeO | Cl | 5.0 | 10 |
| **49** | OMe | OH | Br | 1.6 | 194 |
| **50** | OMe | OH | Cl | 2.0 | 100 |

withdrawing moiety would set the former for Michael reaction with biological nucleophiles. Based on a hypothesis that the both electron-withdrawing π-system and sterically unencumbered nature of acetylene is important for PDE5 binding, we prepared a series of surrogates **21**–**35**, all bearing a *p*-methoxy- or *p*-hydroxybenzyl group on N-3 and either electron-negative or heteroatomic substituent X at C-2 (Table 2, Scheme 2).

Dimethylamino and alkylsulfone groups at C-2 were not tolerated probably because of their size. SAR of other C-2 substituents followed the trend: $H < CF_3 <$ alkoxy ~ thioakyl ~ akoxycarbonyl ~ cyano ~ carboxamide.

Transformation of the N-3 substituent from *p*-methoxy to *p*-hydroxybenzyl resulted in a 2–20-fold increase in potency, with the effect most pronounced for C-2 alkoxy substituent. No useful PDE6 selectivity yet was observed, with the highest value of 67-fold for azide **35**, which could not be pursued as a drug due to potential toxicity.

In the next round of SAR development, we kept the optimized alkoxy and carboxamido substituents at C-2, *p*-methoxy or *p*-hydroxybenzyl at N3, and introduced an additional substituent Z = Cl or Br at the phenyl ring (Table 3).

For all the C-2 substituents studied, a single-digit nanomolar PDE5 potency was achieved. As before, free phenols (Y=OH) were superior in both the potency and selectivity. For C-2 carboxamides, Z= Cl was preferred over Z= Br (**41** versus **40**). For C-2 alkoxides, however, the highest selectivity of 194-fold was achieved for Z= Br (**49**).

We were interested in determining if the developed SAR would be maintained in a series with a modified C8–C7 region. Structure **IX** is a direct analogue of **II** featuring a benzyl substituent at C-7, which resulted in an improved PDE1 selectivity (Fig. 2). Gratifyingly, combination of the two SARs allowed us to further improve the profile of inhibitors (Table 4). Compounds **52**–**59** displayed 116–600-fold selectivity over PDE6 and ~400 to several thousand-fold selectivity over PDE1-4.

Subsequently, we became aware that other heterocyclic systems with similarly substituted benzyl groups were also developed as PDE5 inhibitors.[11] The notion suggests that this moiety is an important enzyme recognition element.

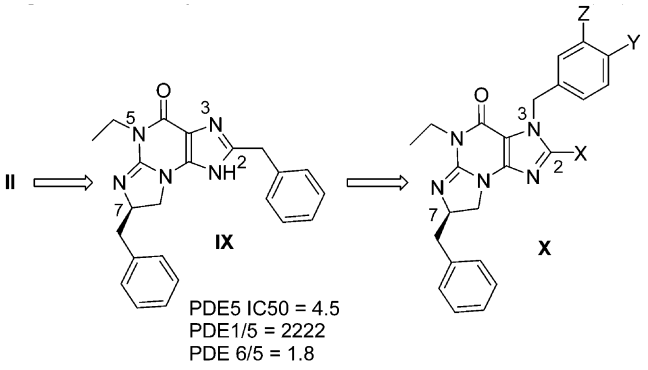
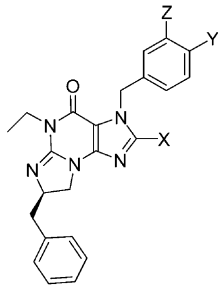



**Figure 2.** Overlap of structure **X** on determined SAR.

**Table 4.** Combination of structure IX with previously established SAR




| Entry | X | Y | Z | PDE5 $IC_{50}$ (nM) | PDE1/5 | PDE2/5 | PDE3/5 | PDE4/5 | PDE6/5 |
|---|---|---|---|---|---|---|---|---|---|
| **51** | $CONH_2$ | MeO | Cl | 2.8 | — | — | — | — | 61 |
| **52** | $CONH_2$ | OH | Cl | 3.0 | 2600 | 3333 | 3333 | 1733 | 600 |
| **53** | OBn | OH | Cl | 2.1 | 4762 | 4762 | 4762 | 2168 | 162 |
| **54** | OMe | MeO | CN | 11.0 | 536 | 909 | 909 | 464 | 445 |
| **55** | OMe | MeO | Br | 2.2 | 4091 | 4545 | 4545 | 418 | 173 |
| **56** | OMe | MeO | Cl | 1.6 | 4375 | 6250 | 6250 | 394 | 206 |
| **57** | OMe | OH | CN | 43.0 | — | — | — | — | 116 |
| **58** | OMe | OH | Br | 1.3 | 7692 | 7692 | 7692 | 3769 | 562 |
| **59** | OMe | OH | Cl | 1.9 | 5263 | 5263 | 5263 | 3105 | 416 |

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