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The Discovery of Novel, Potent and Selective PDE5 Inhibitors

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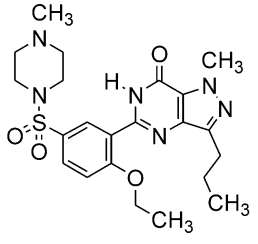
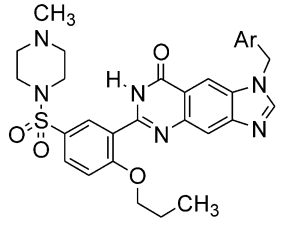
Abstract—The design and synthesis of a novel scaffold for potent and selective PDE5 inhibitors are described. Compound **3a** was more potent (PDE5 $IC_{50} = 0.31$ nM) and selective (>10,000-fold vs PDE1 and 160-fold selective vs PDE6) PDE5 inhibitor than sildenafil.

When a man is sexually stimulated, nitric oxide is released from non-cholinergic, non-adrenergic neurons in the penis. The nitric oxide released activates guanylyl cylase, which produces cGMP. Increased levels of cGMP lead to decreased intracellular calcium concentration in the cells of the *corpus cavernosum*, resulting in relaxation of the smooth muscle of the penis. This relaxation results in enhanced arterial blood flow into the penis, ultimately leading to an erection.[1] Since phosphodiesterase type 5 (PDE5) is the primary cGMP hydrolyzing enzymatic activity present in the *corpus cavernosum*, inhibition of PDE5 elevates levels of cGMP, thereby potentiating the signaling cascade that leads to an erection.[2]

Sildenafil (**1**, Viagra®, Fig. 1), the prototypical PDE5 inhibitor, has opened an entire field of drug discovery focused on quality-of-life issues. The treatment of male erectile dysfunction (ED) is one of those areas. It is not surprising that significant interest in the discovery of additional PDE5 inhibitors has emerged since the introduction of Viagra® as an efficacious orally active agent for the treatment of ED.[3,4] In spite of the efficacy of **1** as a treatment for ED, there are notable drawbacks associated with its use. Clinically significant adverse effects such as nausea, headache, cutaneous flushing, interactions with sources of NO and visual disturbances have been noted, and their incidence increases with the dose of the drug. Certain of these adverse events are thought to be due to nonspecific inhibition of other PDEs, specifically PDE1 and PDE6.[5,6] Thus, the identification of more potent and more selective PDE5 inhibitors is of substantial medicinal and commercial interest. This report communicates the design and



1 sildenafil (Viagra ™)



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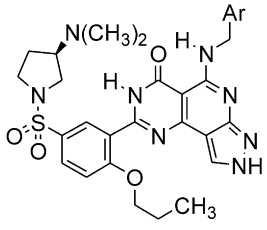

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Figure 1.

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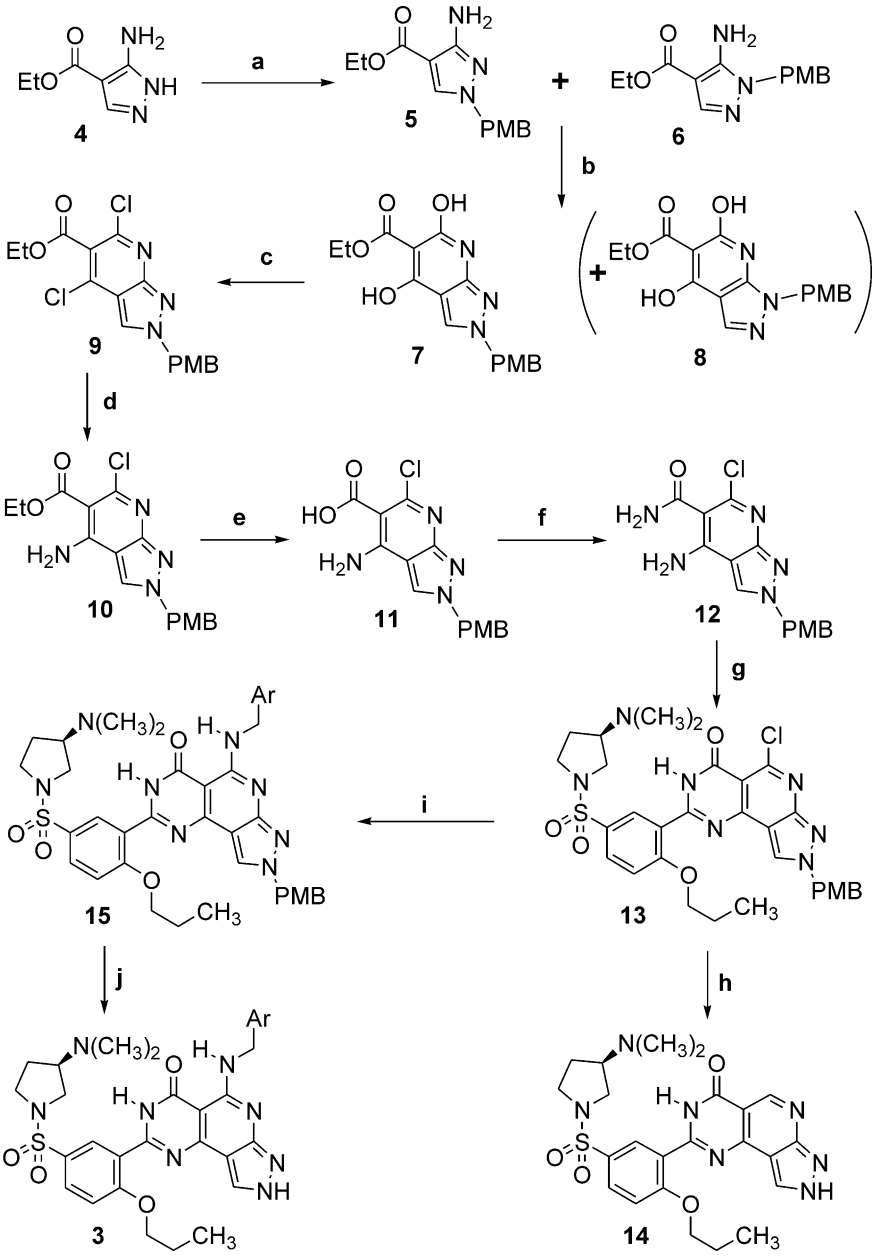
synthesis of a novel template (**3**), which leads to very potent and highly selective PDE5 inhibitors.

Rotella and co-workers[7] have described a series of N-3 substituted imidazoquinazolinones (**2**, Fig. 1) as potent and selective PDE5 inhibitors. In this series, significant improvement in PDE5 potency and PDE isozyme selectivity compared to sildenafil was achieved by the addition of a benzyl moiety at the N-3 position of the imidazole moiety of the imidazoquinazolinone template (**2**). In an attempt to further develop the SARs for this series, we designed a new template (**3**, Fig. 1) which incorporated another nitrogen into the middle ring, placed the key benzyl group in the middle ring, and changed the imidazole to pyrazole.

Commercially available 3-amino-4-carbethoxypyrazole (**4**) was treated with *p*-methoxybenzyl (PMB) chloride and sodium hydride in acetonitrile to give two regioisomers **5** and **6** (Scheme 1). The position of the *p*-methoxybenzyl group in each regiomer was determined based on NOE NMR studies on **5** and **6**. Since both isomers should ultimately give the same product after deprotection, they were carried on together to their respective pyrrazolopyridines (**7** and **8**) according to the method of Sanghvi.[8] However, only **7** appeared to be



Scheme 1. (a) PMBCl, NaH/CH_3CN, 24 h, 71%; (b) $CH_2(CO_2Et)_2$, NaOEt/HOEt, reflux, 20 h, 100%; (c) $POCl_3$, reflux, 3 h, 55%; (d) NH_3/HOEt, rt, 7 days, 60%; (e) LiOH/H_2O/THF/HOMe, 24 h, 78%; (f) (1) DCC/pentafluorophenol/DMF/EtOAc, 0 °C, overnight; (2) NH_3/THF, rt, overnight, 80%; (g) (1) 5[(3*R*)-(+)-(3-dimethylaminopyrrolidinyl)sulfonyl]-2-propoxybenzoyl chloride, KHMDS/THF, 3 h; (2) *t*BuOK/*t*BuOH, 80 °C, 1 h, 22% for two steps; (h) (1) Pd/C, H_2, 93%; (2) TFA, 60 °C, 1 h, 60%; (i) benzylamine, DIEA/*n*PrOH, reflux, 4 h, ~90%; (j) TFA, 60 °C, 1 h, ~80%.

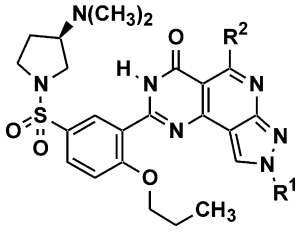
converted to its corresponding dichloro derivative (**9**) under reflux in phosphorus oxychloride, since no dichloro adduct from **8** was isolated or detected.

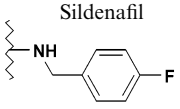
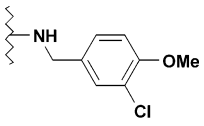
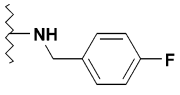
Regiospecific displacement of the chlorine *para* to the pyridine nitrogen with ammonia afforded **10**. The regioselectivity of this reaction was confirmed via X-ray crystallographic studies on another crystalline derivative of **9**.[9] The ester in **10** was converted to its corresponding primary amide (**12**) via hydrolysis to acid **11** followed by amide formation. The third ring of the heterocyclic scaffold was generated by acylation of the amino group with 5-[(3*R*)-(+)-(3-dimethylaminopyrrolidinyl)sulfonyl]-2-propoxybenzoyl chloride,[7] followed by base-mediated cyclization to give pyrazolopyridopyrimidine (**13**). (3*R*)-Dimethylaminopyrrolidine was chosen because it gave Rotella and co-workers some of their most potent PDE5 inhibitors. Removal of the chlorine atom *ortho* to the pyridine nitrogen in **13** via catalytic hydrogenation, followed by deprotection, afforded template **14**. Alternatively, displacement of the chlorine *ortho* to the pyridine nitrogen with benzylamines afforded **15**, and subsequent deprotection yielded pyrazolopyridopyrimidines (**3**)[10] with the desired benzyl substitution pattern.

The in vitro activity of **3**, **14**, and selected intermediates is summarized in Table 1. The pyrazolopyridopyrimidine scaffold clearly is a useful template for the preparation of potent PDE5 inhibitors. Even the least substituted analogue in the series (**14**) was similar to sildenafil in terms of potency and selectivity. Interestingly, intermediates containing the *p*-methoxybenzyl protecting group (**13** and **15a**) were potent PDE5 inhibitors (PDE5 IC_{50}'s = 13 and 1.7 nM, respectively), suggesting that there was an unexplored region of space where the PMB moiety may be interacting with the enzyme. While **13** offered no PDE isozyme selectivity advantages versus sildenafil, the *p*-fluorobenzyl substitution in **15a** clearly improved PDE1 selectivity ($>10^4$-fold) when compared with sildenafil (140-fold). However, the selectivity of **15a** versus PDE6 was only slightly better than that of sildenafil.

Derivatives **3a** and **3b** were prepared to complement the SAR seen with the imidazoquinazolinone series of PDE5 inhibitors.[7] Namely, incorporation of an appropriately substituted benzyl group at R^2 (Table 1) was expected to lead to more potent and selective analogues. Following the SAR seen by Rotella and co-workers,[7] the PDE5 activity and selectivity for **3a** and **3b** was substantially improved over the parent derivative (**14**). The *p*-fluorobenzyl derivative (**3a**) was approximately 6-fold more potent (PDE5 $IC_{50} = 0.31$ nM) than sildenafil, whereas the *p*-methoxy-*m*-chlorobenzyl analogue (PDE5 $IC_{50} = 0.90$ nM) was only slightly more potent than sildenafil. However, the PDE isozyme selectivity profiles of **3a** and **3b** were clearly superior to that of sildenafil. Whereas sildenafil is only 140-fold selective versus PDE1, both **3a** and **3b** were approximately 10,000-fold selective versus PDE1. The selectivity of **3a** and **3b** versus PDE6 is especially noteworthy since the vision disturbances associated with sildenafil use are believed to be a result of its modest selectivity (8-fold) versus PDE6. The approximate 200-fold selectivity

Table 1. PDE5 inhibition and isozyme selectivities[a]



Compd	R^1	R^2	IC_{50} PDE5 (nM)	IC_{50} Ratio 1/5	IC_{50} Ratio 2/5	IC_{50} Ratio 3/5	IC_{50} Ratio 4/5	IC_{50} Ratio 6/5
1		Sildenafil	1.6±0.5	140	$>10^4$	3500	2600	8
3a	–H		0.31±0.14	$>10^5$	$>10^5$	$>10^5$	$>10^4$	160
3b	–H		0.90±0.29	10^4	$>10^4$	$>10^4$	$>10^4$	180
13	–PMB	—Cl	13±1.4	130	1200	1100	310	17
14	–H	—H	2.1±1.2	400	2000	$>10^4$	3200	22
15a	–PMB		1.7±1.0	$>10^4$	$>10^4$	$>10^4$	2500	15

[a]Assays performed as described in ref 7; enzyme sources: PDE1: bovine heart; PDE2: rat kidney; PDE3: human platelet; PDE4: rat kidney; PDE5: human platelet; PDE6: bovine retina; all IC_{50} determinations are averages based on three or more determinations.

versus PDE6 for **3a** and **3b** represents a major advance in the discovery of selective PDE5 inhibitors. To our knowledge, compound **3a** represents one of the most potent and selective PDE5 inhibitors disclosed to date. Should **3a** be used in the treatment of ED, one would expect a significantly reduced side-effect profile when compared to sildenafil.

In summary, we have identified a novel pyrazolopyridopyrimidine template that provided PDE5 inhibitors which are more potent and selective than sildenafil. Use of an appropriately substituted benzylamino moiety placed at the R^2 region of the scaffold (Table 1) conferred substantial improvement in both PDE5 potency and selectivity in this series. One could hypothesize that a similar substitution on the sildenafil molecule could improve the selectivity of sildenafil (especially vs PDE1 and PDE6). In fact, a recent patent application exemplifies that type of sildenafil derivative.[11] The improved selectivity found in **3a** may translate into an improved PDE-related side-effect profile in vivo, based on experience to date with sildenafil. We are continuing to optimize the activity of this series of molecules and will report the results in due course.

References and Notes

1. Andersson, K.-E.; Wagner, G. *Physiol. Rev*. **1995**, *75*, 191.
2. Gibson, A. *Eur. J. Pharmacol*. **2001**, *411*, 1.
3. (a) Martel, A. M.; Graul, A.; Rabasseda, X.; Castañer, R. *Drugs Future* **1997**, *22*, 138. (b) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1819. (c) Boolell, M.; Allen, M. J.; Ballard, S. A.; Gepi-Attee, S.; Muirhead, G. J.; Naylor, A. M.; Osterloh, I. H.; Gingell, C. *Int. J. Urol. Res*. **1996**, *8*, 47.
4. (a) Eardley, I. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1803. (b) Garcia-Reboll, L.; Mulhall, J. P.; Goldstein, I. *Drugs Aging* **1997**, *11*, 140. (c) Truss, M. C.; Stief, C. G. *Drugs Today* **1998**, *34*, 805.
5. Beavo, J. A. *Physiol. Rev*. **1995**, *75*, 725.
6. *Scrip*, October 9, 1997.
7. Rotella, D. P.; Sun, Z.; Zhu, Y.; Krupinski, J.; Pongrac, R.; Seliger, L.; Normandin, D.; Macor, J. E. *J. Med. Chem*. **2000**, *43*, 1257.
8. Sanghvi, Y. S.; Larson, S. B.; Robins, R. K.; Revankar, G. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2943.
9. Bi, Y.; Stoy, P.; Macor, J. Unpublished results.
10. The structures of all compounds were confirmed by NMR and LC–MS. Compound **3a**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, $J=2.4$ Hz, 1H), 8.30 (s, 1H), 8.05 (dd, $J=8.8$, 2.4 Hz, 1H), 7.46 (dd, $J=8.7$, 5.4 Hz, 2H), 7.40 (d, $J=8.8$ Hz, 1H), 7.08 (t, $J=8.7$ Hz, 2H), 4.78 (s, 2H), 4.27 (t, $J=6.3$ Hz, 2H), 3.88 (m, 1H), 3.62–3.52 (m, 3H), 3.24 (dd, $J=18.0$, 8.1 Hz, 1H), 2.89 (s, 6H), 2.38 (m, 1H), 2.17 (m, 1H), 1.95 (m, 2H), 1.10 (t, $J=7.4$ Hz, 3H). MS (MH^+) 621.35. **3b**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, $J=2.5$ Hz, 1H), 8.19 (s, 1H), 8.07 (dd, $J=9.1$, 2.6 Hz, 1H), 7.45 (d, $J=2.0$ Hz, 1H), 7.43 (d, $J=9.1$ Hz, 1H), 7.34 (dd, $J=8.5$, 2.0 Hz, 1H), 7.00 (d, $J=8.6$ Hz, 1H), 4.72 (s, 2H), 4.26 (t, $J=6.6$ Hz, 2H), 3.87 (s, 3H), 3.66–3.57 (m, 3H), 3.46 (m, 1H), 3.22 (dd, $J=18.2$, 8.1 Hz, 1H), 2.89 (s, 6H), 2.39 (m, 1H), 2.16 (m, 1H), 1.94 (m, 2H), 1.09 (t, $J=7.3$ Hz 3H). MS (MH^+) 667.32 (100%), 669.30 (42%).
11. Bunnage, M. E.; Mathias, J. P.; Street, S. D. A.; Wood, A. WO 9849166, 1998; *Chem. Abstr*. **1998**, *129*, 330741.