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Quinolines as extremely potent and selective PDE5 inhibitors as potential agents for treatment of erectile dysfunction

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Abstract—In a continuing effort to discover novel chemotypes as potent and selective PDE5 inhibitors for the treatment of male erectile dysfunction (ED), we have found that 4-benzylaminoquinoline derivatives are very potent and selective PDE5 inhibitors. Some compounds in this series had PDE5 IC_{50}'s as low as 50 pM. While an electron withdrawing group at the C6-position of the quinoline substantially improved PDE5 potency, an ethyl group at the C8-position not only improved the PDE5 potency but also the isozyme selectivity. Substitutents at the C3-position can incorporate a variety of different groups. The synthesis and primary structure–activity relationship of this new series of potent PDE5 inhibitors are described.

Viagra® (sildenafil, **1a**, Fig. 1) has been shown to be an effective therapy for the treatment of erectile dysfunction (ED) in men.[1] Discovered serendipitously, sildenafil acts as an inhibitor of phosphodiesterase Type 5 (PDE5) in the *corpus cavernosum* of the penis, effectively elevating the levels of cGMP in that tissue. Increased levels of cGMP leads to decreased intracellular calcium 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.[2]

Sildenafil (**1a**), the prototypical (PDE5) inhibitor, has opened an entire field of drug discovery focused on diseases which affect one's quality-of-life, and the treatment of male erectile dysfunction (ED) is one of those areas. In spite of the efficacy of **1a** as a treatment for ED, there are notable drawbacks associated with its use. Clinically significant adverse effects such as nausea, headache, cutaneous flushing 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.[3,4] Thus, the identification of more potent and more selective PDE5 inhibitors is of substantial medicinal and commercial

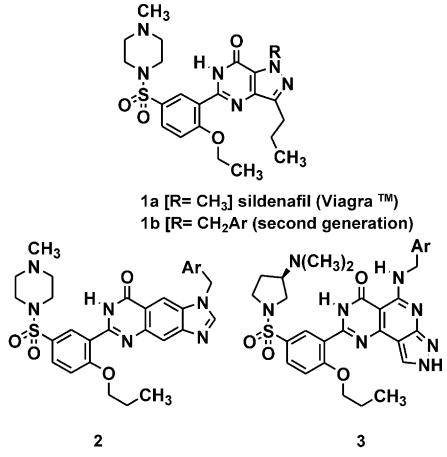

Figure 1.

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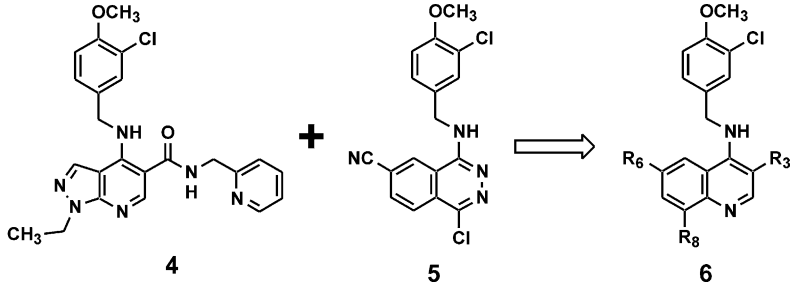
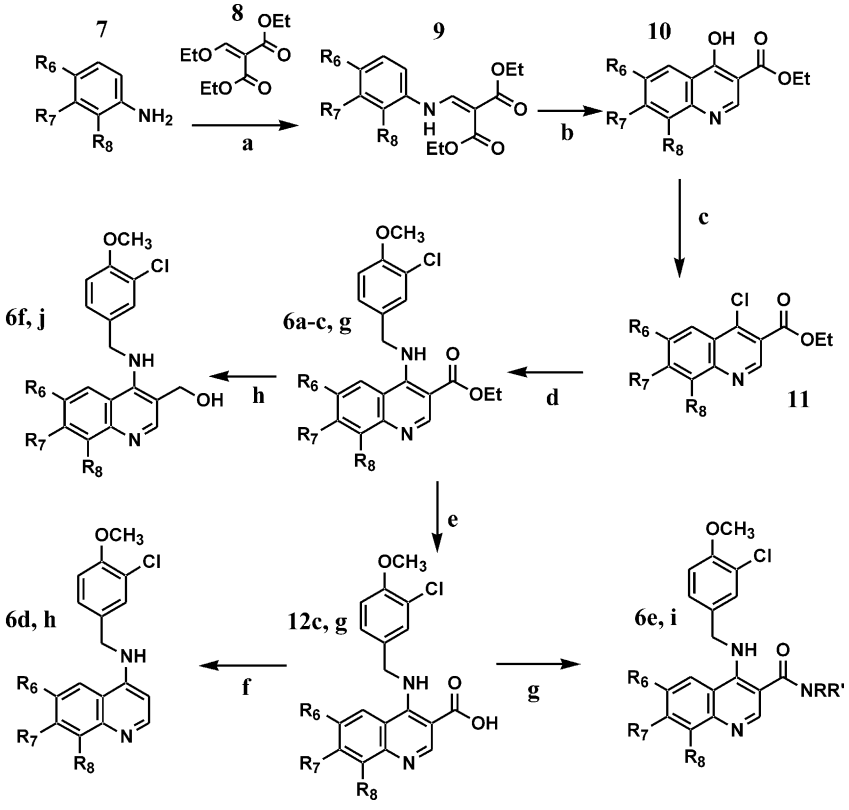
interest. Therefore, it is not surprising that significant effort has been expended towards the discovery of more isozyme selective PDE5 inhibitors.[5,6] In this communication, we detail our continued efforts in this area,[7–9] which have yielded a new series of picomolar potent and selective PDE5 inhibitors.

Rotella and co-workers[7] have described a series of N-3 substituted imidazoquinazolinones (**2**, Fig. 1) as potent and selective PDE5 inhibitors. We have also reported on a series of novel pyrazolopyridopyrimidines (**3**, Fig. 1) that provided PDE5 inhibitors which were more potent and selective than sildenafil.[8] More recently, Yu et al.[9] reported substituted pyrazolopyridines as potent and selective PDE5 inhibitors (**4**, Scheme 1). Use of an appropriately substituted benzylamino moiety placed in the 'northern' region of the scaffolds consistently conferred substantial improvement in both PDE5 potency and selectivity in all of these series. Follow-up work at Pfizer with sildenafil also apparently found a similar effect from a 'northern benzyl' group when attached to the heterocyclic scaffold of sildenafil (**1b**).[10]

As part of our continuing effort to discover novel chemotypes as potent and selective PDE5 inhibitors for the treatment of ED, we decided to explore combinations of key functional groups in recently discovered inhibitors. Combining the important features of the two potent PDE5 inhibitors **4** (BMS) and **5** (Eisai) led to the design of the quinoline derivatives (**6**, Scheme 1).[11] To test this combination hypothesis, quinoline **6a** was prepared in two steps from commercial available starting materials (Scheme 2). The hydroxyl group in compound **10a** ($R_6 = R_8 = H$, $R_7 = CF_3$) was converted to the corresponding chloride by reflux in $POCl_3$. The chloride was then displaced by 3-chloro-4-methoxybenzyl amine to



Scheme 1.



Scheme 2. (a) Toluene, reflux, 4 h (70–90%); (b) Ph_2O, reflux, 2 h (70–95%); (c) $POCl_3$, reflux, 24–48 h (70–100%); (d) 3-chloro-4-methoxybenzyl amine·HCl, DIEA/*n*-PrOH, reflux, 2 h (40–95%); (e) NaOH (1 N)/MeOH, rt, 1 h (>90%); (f) Ph_2O, 240 °C, 30 min, (75%); (g) 1. DCC/EtOAc, pentafluorophenol/DMF, rt, 18 h; 2. NHRR′/DMF, 18 h (>60%); (h) $LiAl(OtBu)_3H$/THF, reflux, overnight (50–90%). All compounds were characterized minimally by ^1H and ^{13}C NMR, LCMS, HPLC and HRMS.

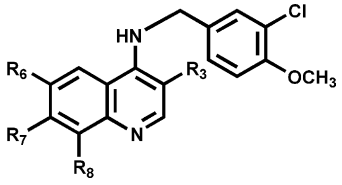
give **6a**. This benzylamine was consistently the best moiety in many of our PDE5 inhibitors.[7–9] Our combination hypothesis was supported as compound **6a** was a selective PDE5 inhibitor (PDE5 $IC_{50}=160$ nM, PDE6 $IC_{50}=20$ μM, $IC_{50}>50$ μM for PDE1-4).

The chemistry to provide analogues of **6a** is shown in Scheme 2, and their in vitro results are shown in Table 1. The appropriate anilines **7** were converted to **9** by refluxing in toluene with ethoxymethylenemalonate **8**. Cyclization of **9** in refluxing diphenylether afforded quinolines **10** in good yields. Reaction of **10** with $POCl_3$ afforded the chloroquinolines **11** often in quantitative yield. Reaction of quinolines **11** with 3-chloro-4-methoxybenzyl amine afforded the quinoline esters **6a–c** and **g**. Reduction of the ester in **6c** (R_6 = –CN, R_7 and R_8 = –H) and **6g** (R_6 = –CN, R_7 = –H, and R_8 = –Et) to the hydroxymethyl derivatives afforded **6f** and **j**, respectively (Table 1). Alternatively, hydrolysis of the ester in **6c** and **6g** afforded the carboxylic acids **12c** and **12g**. Decarboxylation of these acids at elevated temperatures afforded **6d** (R_6 = –CN, R_7 and R_8 = –H) and **6h** (R_6 = –CN, R_7 = –H, and R_8 = –Et), respectively. The acids **12c** and **12g** were also converted to amides via their pentafluorophenyl esters to afford quinoline amides **6e** (R_6 = –CN, R_7 and R_8 = –H) and **6i** (R_6 = –CN, R_7 = –H, and R_8 = –Et), respectively (Table 1).

Moving the trifluoromethyl group from C7 to C6 on the quinoline scaffold led to compound **6b**, and this modification resulted in a slight improvement in PDE5 inhibition (Table 1). This SAR observation was analogous to that described by Watanabe et al. in the development of **5**.[12] Led by this SAR, we next explored the cyano analogue of **6b**. Introduction of the C6 cyano group in the quinoline scaffold provided **6c** and further improved PDE5 inhibitory activity by about 20-fold (PDE5 $IC_{50}=4.0$ nM) with excellent PDE isozyme selectivities against PDEs 1–4 (Table 1). Because our hypothesis to merge the structures of PDE5 inhibitors **4** and **5** led to a new scaffold for potent and selective PDE5 inhibition, we sought to further capitalize on this SAR overlap and incorporate the *N*-ethyl group in the pyrazolopyridines **4**. This line of reasoning afforded quinoline **6g** which was almost 10-fold more potent than its des-ethyl analogue **6c**. Compounds **6c** and **6g** provided ideal scaffolds for additional structure activity development. We explored modifications of the ester at C3 of the quinoline moiety in an attempt to improve isozyme selectivity and PDE5 potency.

We were delighted to observe that the C-3 position was quite tolerant to varied substitution. Ester (**6c** and **g**), hydrogen (**6d** and **h**), amide (**6e** and **i**) and alcohol (**6f** and **j**) moieties all maintained excellent PDE5 potency and PDE 1-4 selectivity with moderate-to-good PDE6 selectivity (Table 1). In all cases, incorporation of a C8 ethyl group into our quinoline template to mimic the ethyl group in **4** resulted in a moderate (up to 10-fold), but significant increase in PDE5 potency compared to the C8 unsubstituted quinoline analogue. This modification also led to compounds with improved PDE5 potency and isozyme selectivities. Of special note is the C3-hydroxymethyl analogue (**6j**, Table 1). We believe that compound **6j** represents the most potent and selective PDE5 inhibitor seen to date (PDE5 $IC_{50}=50$ pM). Compound **6j** is not only more than 30-fold more potent than sildenafil, it is significantly more selective against other PDE isozymes than sildenafil, especially against PDE6. This would suggest that **6j** would represent a drug that would be devoid of any clinical side effects which result from inhibition of PDEs 1–4 or PDE6.

Table 1. PDE5 potency and selectivity ratios for other PDEs[a,b,c]



Compd	R_3	R_6	R_7	R_8	PDE5 IC_{50} (nM)	Ratio (PDE X/PDE5) 1	2	3	4	6
Sildenafil	—	—	—	—	1.6±0.5	140	$>10^4$	3500	2600	8
6a	COOEt	H	CF_3	H	160±80	>310	>310	>310	>310	125
6b	COOEt	CF_3	H	H	73±41	>680	>680	>510	247	75
6c	COOEt	CN	H	H	4.0±2.1	$>10^4$	$>10^4$	$>10^4$	3800	15
6d	H	CN	H	H	1.4±0.9	6400	$>10^4$	2900	3500	29
6e	$CONHCH_2$2-Py	CN	H	H	1.3±0.7	$>10^4$	$>10^4$	$>10^4$	3100	64
6f	CH_2OH	CN	H	H	0.48±0.04	$>10^4$	8600	$>10^4$	$>10^4$	23
6g	COOEt	CN	H	Et	0.60±0.19	$>10^4$	$>10^4$	$>10^4$	$>10^4$	110
6h	H	CN	H	Et	0.40±0.06	$>10^4$	$>10^4$	$>10^4$	2200	40
6i	$CONHCH_2$2-Py	CN	H	Et	0.55±0.43	$>10^4$	$>10^4$	$>10^4$	4500	82
6j	CH_2OH	CN	H	Et	0.05±0.04	$>10^5$	$>10^4$	$>10^5$	$>10^4$	7800

[a] Enzyme sources: PDE1: bovine heart; PDE2: rat kidney; PDE3: human platelet; PDE4: rat kidney; PDE5: human platelet; PDE6: bovine retina. Enzyme assays performed as described in references 7a and 7b.
[b] All IC_{50} determinations are averages based on ≥3 determinations and shown as ±SD.
[c] Py = pyridyl.

In summary, we have found that the 4-benzylaminoquinoline scaffold provided very potent and selective PDE5 inhibitors. Starting from **6a** (PDE5 $IC_{50} = 160$ nM), we utilized insight derived from other similar series to develop a series of potent and selective quinoline PDE5 inhibitors. In this series, C6-cyano and C8-ethyl provided the most potent compounds. Substitution at C3 of the quinoline scaffold could be varied while still maintaining potent PDE5 inhibition. Our SAR efforts resulted in the discovery of **6j**, which contained a C3-hydroxymethyl group. Compound **6j** is the most potent and selective PDE5 inhibitor identified to date, being 30-fold more potent than sildenafil and significantly more selective than sildenafil against other PDE isozymes. We continue to profile this series of PDE5 inhibitors and will report additional SAR and pharmacology in due course.

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