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Quinazolines as potent and highly selective PDE5 inhibitors as potential therapeutics for male erectile dysfunction

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ABSTRACT

In an effort to minimize side effects associated with low selectivity against PDE isozymes, we have successfully identified a series of 6,7,8-substituted quinzaolines as potent inhibitors of PDE5 with high level of isozyme selectivity, especially against PDE6 and PDE11. PDE5 potency and isozyme selectivity of quinazolines were greatly improved with substitutions both at 6- and 8-position. The synthesis, structure–activity relationships and in vivo efficacy of this novel series of potent PDE5 inhibitors are described.

Male erectile dysfunction (MED) was a largely unmet medical need before the introduction of sildenafil (Viagra®) in 1998. As a potent inhibitors of phosphodiesterase 5 (PDE5) in the *corpus cavernosum* of the penis, it was originally studied for the treatment of angina before its effectiveness in treating MED was found in clinical trials serendipitously.[1] Increased levels of cGMP leads to decreased intracellular calcium in the cells of *corpus cavernosum*, resulting in vasorelaxation, inflow of arterial blood, and ultimately an erection.[2] As PDE5 is a member of phosphodiesterase family of enzymes metabolizing cGMP in penis, inhibition of PDE5 increases the cGMP concentration, enhancing the erection.[3]

The launch of Viagra® and vardenafil (Levitra®)[4] marked the new age in drug discovery by affecting one's quality-of-life, however, despite their success, side effects such as headache, nausea, flushing, and visual disturbances have been noted, which are associated with low selectivity against other PDE isozymes, most notably PDE1 and PDE6.[5] Although tadalafil (Cialis®) was shown to have a better PDE1 and PDE6 selectivity, it is not free from side effects such as headache, indigestion, and back pain.[6] The visual disturbances associated with use of PDE5 inhibitors can be linked to inhibition of PDE6, which controls function of rod and cone cells within the eye.[5] The function of PDE11 remains largely unknown,

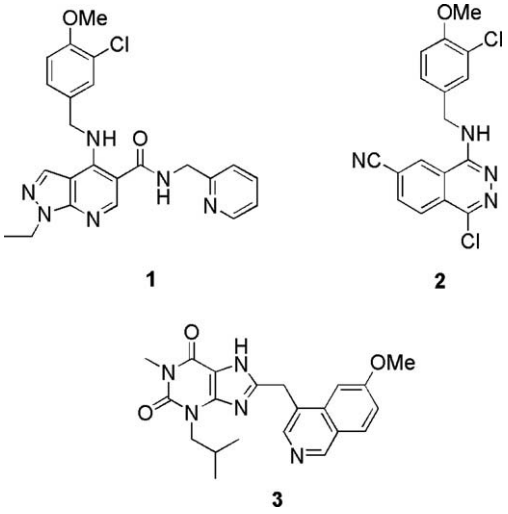

Figure 1. Some representative heterocyclic PDE5 inhibitors.

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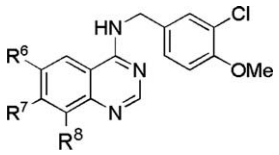
Table 1
PDE5 activity of quinazoline derivatives



Compound	R^6	R^7	R^8	PDE5[a]
6	No_2	Cl	H	0.008
8	No_2		H	0.57
9	No_2		H	0.071
10	No_2	OMe	H	0.032
12	No_2	OH		0.012
13	No_2	OMe		0.012
14	NH_2	OMe		1.1
Tadalafil				0.012
Sildenafil				0.01

[a] IC_{50} values are reported in μM (values are mean of >2 determinations).

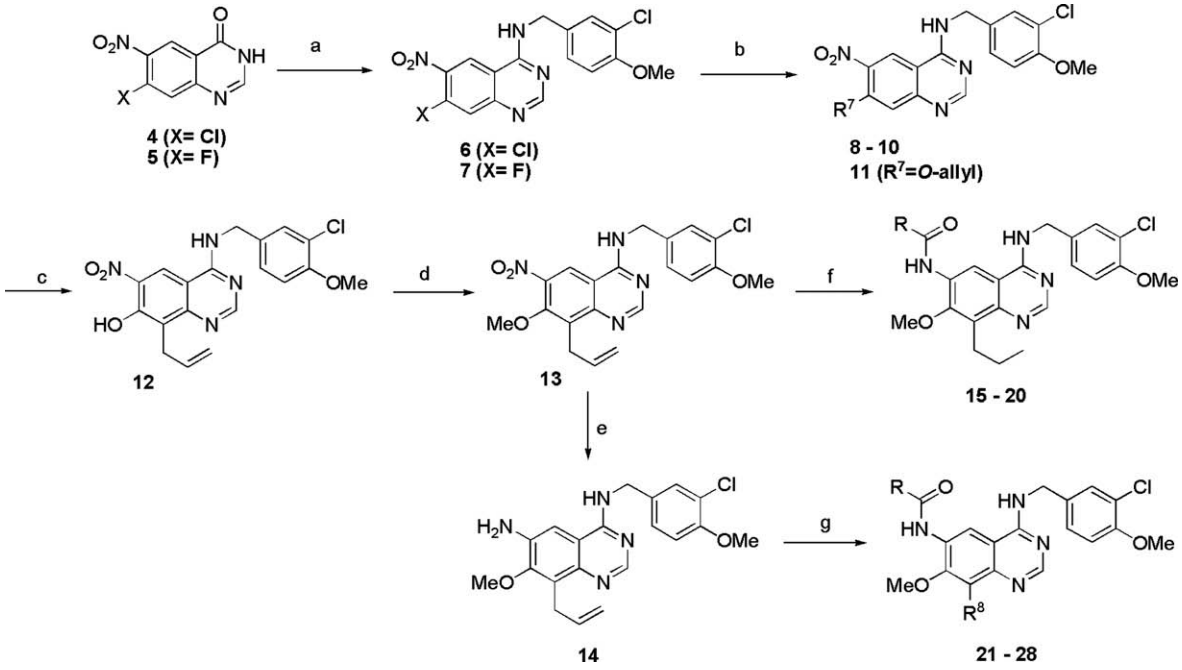
but potential role in male reproduction was recently suggested from several lines of evidences.[7] Since tadalafil cross reacts with PDE11 at sub μM range, there is a growing concern over PDE11 selectivity. Therefore, the identification of highly selective, especially against PDE1, PDE6 and PDE11 as well as more potent PDE5 inhibitors is of great medicinal and commercial interest. Thus, there have been numerous efforts toward the discovery of more isozyme selective PDE5 inhibitors[8] and some representative examples (**1**[9], **2**[10], and **3**[11]) are shown in Figure 1.

In this communication, we disclose the discovery of novel, 6,7,8-substituted quinazoline-based PDE5 inhibitors which exhibit good potency and high levels of selectivity over other PDE isoforms especially PDE6 and PDE11 as well as potent in vivo efficacy in inducing penile erection in conscious rabbit model.

Screening of focused in-house library yielded a 4-(3-chloro-4-methoxy)benzylamino substituted quinazoline hit (**6**) for PDE5, which is equipotent to tadalafil (Table 1). Initially, there was a concern about this quinazoline scaffold because of its prevalence in protein kinase inhibitors, most of which showed potent anticancer activity.[12] However, it was found that 4-aniline or 4-phenol substitution is required to possess anticancer activity, whereas our PDE5 inhibitors contain 4-benzylamino group, which is devoid of cytotoxicity. Quinazoline with simple substitution at 6-, 7-, or 8-position was described[13] as potent inhibitors of several PDEs', but no selectivity data against PDE6 and PDE11 had been reported let alone the in vivo efficacy for erectile dysfunction.

The quinazolines in this study were obtained in a straightforward manner and their synthesis is shown in Scheme 1. The C-4 carbonyl group of **4** or **5**[13] was chlorinated ($SOCl_2$), followed by reaction with 3-chloro-4-methoxybenzyl amine to give **6** or **7** in good yield. With appropriate amines or sodium methoxide, compound **6** (or **7**) was converted to **8**, **9** and **10** (see Table 1 for substitution pattern), while reaction with allyl alcohol gave intermediate **11**. Allyl group was incorporated at C8 by Claisen rearrangement (xylene, 150 °C in sealed tube) of **12** and C7 hydroxyl group was capped with methyl to give **13** for further modification. Selective reduction of C6 ($SnCl_2$, EtOH) afforded **14,** which was used for further allyl group modification (vide infra).

The effect of modification with simple R6, R7, and R8 is shown in Table 1. Tadalafil was used as a positive reference together with sildenafil.[14] By varying the amine substituent at C4 of the quinazoline, we identified 3-chloro-4-methoxybenzylamine as the optimal amine for PDE5 inhibitory potency, which was also observed in several heterocyclic PDE5 inhibitors.[15] Introduction of longer ethylenediamine group (**8**) at C7 resulted in a dramatic loss of activity, while shorter dimethylamino linker (**9**) was also detri-



Scheme 1. Reagents and conditions: (a) 1—DMF (cat), $SOCl_2$, 2—3-chloro-4-methoxybenzylamine, Et_3N, isopropyl alcohol; (b) amine, DIPEA, DMF or NaOMe, MeOH or allyl alcohol, NaH, DMF; (c) xylene, 150 °C, sealed tube; (d) CH_3I, K_2CO_3, acetone, reflux; (e) $SnCl_2$, EtOH, reflux; (f) 1—H_2, PtO_2, MeOH; 2—amide formation; (g) 1—amide formation, 2—OsO_4/$NaIO_4$, then reductive amination ($NaCNBH_3$, AcOH) or $NaBH_4$, MeOH, 0 °C.