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# Discovery of potent, selective, and orally bioavailable PDE5 inhibitor: Methyl-4-(3-chloro-4-methoxybenzylamino)-8-(2-hydroxyethyl)-7-methoxyquinazolin-6-ylmethylcarbamate (CKD 533)

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ABSTRACT

In a continuing effort to discover novel PDE5 inhibitors, we have successfully found quinazolines with 4-benzylamino substitution as potent and selective PDE5 inhibitors. Initial lead compound (**1**) was found to be easily metabolized when incubated with human liver microsomes mainly through C6 amide hydrolysis. Blocking of this metabolic hot spot led to discovery of **10** (CKD533) which is highly potent, selective and orally efficacious in conscious rabbit model for erectile dysfunction and now is undergoing preclinical toxicology study.



Male erectile dysfunction (MED), now assumed to affect >500 million in the world, was a largely unmet medical need before the introduction of sildenafil (Viagra®) in 1998. Although it was discovered serendipitously,[1] the launch of Viagra marked the new age in drug discovery by affecting one's quality-of-life. 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] PDE5 inhibition blocks cGMP degradation, thus increases the cGMP concentration, enhancing the erection.[3] To date, 11 families (PDE1–PDE11) of phosphodiesterase were identified, and PDE5 is abundant in smooth muscle, lung and platelets.[4]

Although successful commercially, sildenafil use is associated with many adverse effects such as headache, nausea, flushing, and visual disturbances, which are the result of low PDE1 and PDE6 (PDE6 is the sole cGMP PDE in rod and cone cells within the eye) selectivity,[5] and similar side effects (indigestion, back pain, etc.) were seen with vardenafil (Levitra®)[6] and Tadalafil (Cialis®).[7]

The physiological significance of PDE11 is not clearly understood, but several lines of evidence suggested the PDE11 inhibition might have negative effect in male reproduction and muscle tissue, since PDE11 is predominantly present in muscle, prostate and testes.[8] Since tadalafil cross reacts with PDE11 at sub μM range (merely 10-fold selectivity ratio relative to PDE5), there is a growing concern over PDE11 selectivity. So, it is highly desirable to maintain high PDE11 selectivity when developing PDE5 inhibitors. Thus, there have been numerous efforts toward the discovery of more isozyme selective PDE5 inhibitors,[9] which is of great medicinal and commercial interest, although with limited success.

In this Letter, we detail our continuing efforts in PDE5 inhibitor, which have yielded a very potent inhibitor with $IC_{50}$ value of picomolar range and highly selective against other PDE isozymes as well as orally efficacious.

Previously, we reported the discovery of 6,7,8-substituted quinazolines as potent and selective PDE5 inhibitors with in vivo efficacy.[10] Optimization of PDE5 activity, isozyme selectivity and physicochemical properties led us to identification of **1** (Fig. 1) as a potent and selective PDE5 inhibitor (PDE5 $IC_{50}$ = 1 nM, selectivity ratio for PDE6 >470, and PDE11 >8600). Compound **1** demonstrated excellent efficacy in conscious rabbit model when dosed

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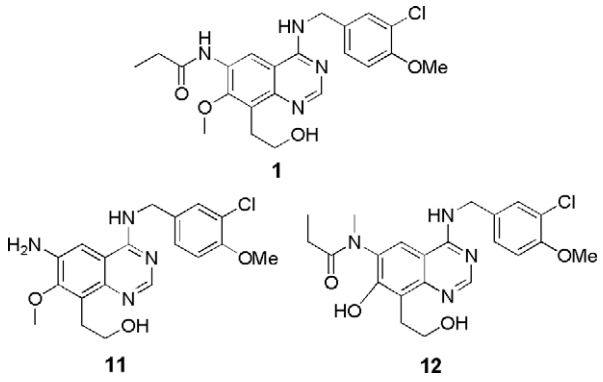
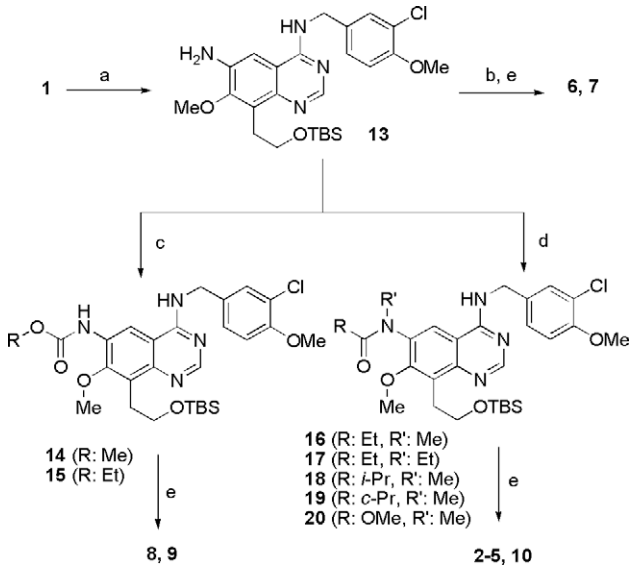



**Figure 1.** Structures of **1** and metabolites (**11**, **12**).

orally. However, disappointingly it was later found to be highly unstable with just 3% of parent compound left when incubated in human liver microsomes (HLM).[11] This was in sharp contrast to the results from rat and rabbit liver microsomes where 96% and 85% of **1** remained, respectively. A LC/MS analysis of incubation mixture with human liver microsomes (1.25 mg/ml) revealed that **1** was rapidly converted to **11** (ca. 90% of all metabolites determined from peak areas), indicating amide hydrolysis was a major culprit of instability (Fig. 1). Interestingly, negligible amount of **11** was detected from incubation mixtures with rat and rabbit liver microsomes, and this may be attributed to different type and/or content of proteases across species.[12a] It was clear that more stable compound might be obtained if the rapid amide hydrolysis at C6 in **1** were blocked. To this end, several analogs that have a variation at C6 position of **1** were prepared according to Scheme 1.

We utilized the already synthesized compound **1**[10] to facilitate synthesis, that is, compound **1** was hydrolyzed under acidic condition followed by TBS protection to provide common intermediate **13**. Compounds **6** and **7** were prepared by reaction of appropriate sulfonyl chloride or sufamoyl chloride followed by acidic desilylation. Alternatively, secondary carbamate was installed by reaction of methyl- and ethyl chloroformate to provide **8** and **9**. The suitable

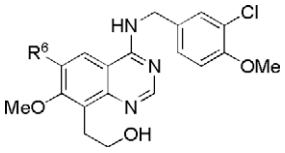


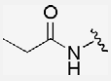
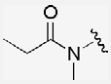
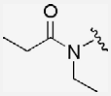
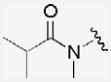
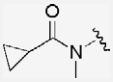
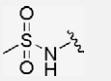
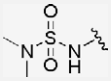
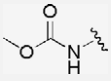
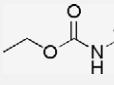
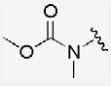

**Scheme 1.** Reagents and conditions: (a) (i) 2 M HCl, MeOH, reflux, 15 h; (ii) imidazole, TBSCl, DCM, rt, 2 h; (b) MsCl (for **6**) or dimethyl sulfamoyl chloride (for **7**), pyridine, DCM, 0 °C to rt; (c) $ClCO_2Me$ or $ClCO_2Et$, pyridine, DCM, rt, 2 h; (d) (i) amide formation or $ClCO_2Me$, rt, 2 h; (ii) MeI or EtI, NaH, THF, rt, 6 h; (e) 1 M HCl, 1,4-dioxane, rt, 1 h.

amides prepared from **13** were further manipulated to provide tertiary amides (NaH, MeI or EtI, THF), which afforded compounds **2**–**5** after desilylation. Finally, N-methylation of **14** followed by desilylation afforded tertiary carbamate **10**.[13] In the case of **10**, another efficient procedure was developed in which up to 1 Kg of **10** was synthesized for preliminary toxicology study, and its synthesis will be reported elsewhere.

Initially, it was assumed that incorporation of tertiary amide would render **1** more resistant toward hydrolysis by various amidases in HLM. As shown in Table 1, *N*-methyl analog (**2**) had com-

**Table 1**
PDE5 activity and isozyme selectivity of 4-(3-chloro-4-methoxy)-benzylamino-7-methoxy-8-hydroxyethyl quinazoline derivatives



| Compound | $R^6$ | PDE5[a] | PDE6[a] | PDE11[a] |
|---|---|---|---|---|
| **1** |  | 0.001 | 0.46 | 10.5 |
| **2** |  | 0.001 | 0.32 | 5.2 |
| **3** |  | 0.001 | ND | ND |
| **4** |  | 0.003 | 1.1 | ND |
| **5** |  | 0.001 | 0.34 | ND |
| **6** |  | 0.011 | ND | ND |
| **7** |  | 0.012 | 7.95 | ND |
| **8** |  | 0.003 | 0.71 | 5.7 |
| **9** |  | 0.017 | 0.6 | 5.0 |
| **10** |  | 0.0006 | 0.14 | 12.0 |
| Tadalafil | | 0.012 | 3.0 | 0.29 |
| Sildenafil | | 0.01 | 0.14 | 3.0 |

ND = not determined.
[a] Enzyme sources: see Ref. 18. $IC_{50}$ values are reported in μM (values are mean of >2 determinations).