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2-Phenylquinazolin-4(3*H*)-one, a class of potent PDE5 inhibitors with high selectivity versus PDE6

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ABSTRACT

In our efforts to minimize the side effects associated with low selectivity against the other PDE isozymes, a novel class of 2-phenylquinazolin-4(3*H*)-one derivatives were designed and prepared as potent PDE5 inhibitors with high selectivity against PDE6. The syntheses and SAR studies of such molecules were reported.

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Male Erectile Dysfunction (MED) is a common public health problem affecting millions of men worldwide. Phosphodiesterase 5 (PDE5) inhibitors are very attractive therapeutic agents for treatment of MED.[1] Sildenafil (Viagra®, **2**, IC_{50} = 3 nM) is the first and most famous PDE5 inhibitor, however, there are still some side effects due to the low selectivity against other PDEs, mainly towards PDE6 which is distributed in the retina, and inhibition of it may cause visual disturbances, perception of bluish haze, and increased light sensitivity.[2] Due to its low selectivity over PDE6 (10-fold),[3] the hunt for both highly selective and more potent PDE5 inhibitors is of great medicinal and commercial interest. In recent years, numerous efforts have been made toward the discovery of selective PDE5 inhibitors,[4] several reviews were published to discuss the medicinal chemistry progresses in this field.[5–8] Structurally these PDE5 inhibitors can be mainly categorized as pyrazolopyrimidinones, β-carbolines, pyrroloquinolones, imidazoquinazolinones, pyrazolopyridines, pyrazolopyridopyridazines, pyrazolopyridopyrimidine, isoquinolinone, naphthyridine derivatives, xanthine analogs, and cyclic guanine derivatives.[8]

In this Letter, we disclosed the discovery of a new class of selective PDE5 inhibitors, phenylquinazolin-4(3*H*)-one derivatives, which exhibit good PDE5 inhibitory potency and high level selectivity over PDE6.

Among the PDE5 inhibitors reported, a class of flavonols isolated from *sophora flavescens* exhibited moderate activity, of which sophoflavescenol (**1**) is the most potent PDE5 inhibitor (IC_{50} = 13 nM).[9] Just as shown in Figure 1, by introducing the phenyl ring of molecule **1** (Part A) and combining with Part B of molecule **2** (sildenafil), a series of 2-phenylquinazolin-4(3*H*)-one derivatives (**11a–j**, **12a–j**) were designed and prepared. Among all these compounds, the chlorine derivate **11b** gave the most satisfactory result that it exhibited comparable PDE5 inhibitory activity (IC_{50} = 6 nM) with Sildenafil (IC_{50} = 3 nM) and a very excellent selectivity over PDE6 (more than 1667-fold), while sildenafil has only 10-fold selectivity over PDE6, which is the main reason for its side effect of visual disturbance.

The synthesis of **11a–d** were illustrated in Scheme 1. Commercially available compound **3** was converted into a library of 2-aminobenzamide **9a–c** according to the literature.[10–12] Coupled with 5-[(4-methyl-1-piperazinyl)sulfonyl]-2-ethoxybenzoyl chloride, **10a–c** were obtained in yields of 80–85%. Using *t*-BuOK as base, dehydrating cyclization of the amides in refluxing *t*-BuOH gave **11a–c** in good yields of 80–85%.[13] By the methods displayed in scheme 2, analogs **11f–j** were prepared from **11c** via Pd/P(*t*-Bu)$_3$ catalyzed Negishi cross-coupling reaction[14] and Stille cross-coupling reaction[15] with organozincs and alkenyltins respectively in yields of 65–90%. Through halogen exchange reactions with CuI at 110 °C, **11d** and **11e** were given from 11**c**.

As is shown in Table 1, besides the chlorine derivate **11b** mentioned above, the bromine and iodine derivates (**11c** and **11d**) also

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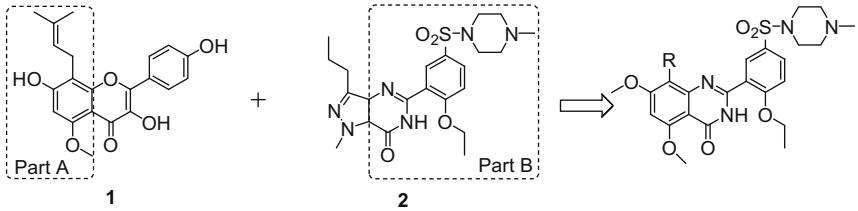
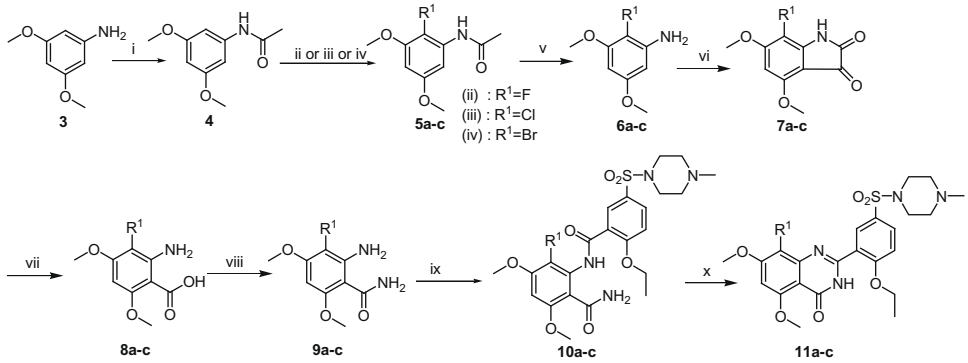
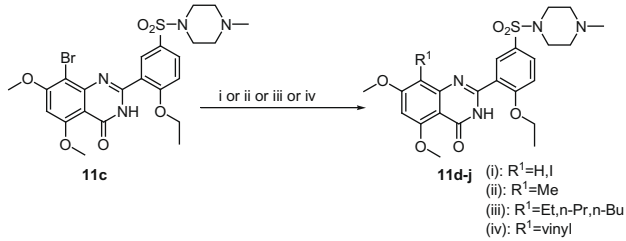


Figure 1. Sophoflavescenol **1** and sildenafil **2**.



Scheme 1. Reagents and conditions: (i) Ac_2O, Py, 0 °C–rt, 1 h; (ii) F-TEDA-BF_4, CH_3CN, 0 °C, 2 h; (iii) NCS, CH_2Cl_2, 0 °C–rt, 0.5 h; (iv) NBS, CH_2Cl_2, 0 °C–rt, 0.5 h; (v) HCl, CH_3OH, reflux, 4 h; (vi) oxalyl chloride, 1,3-dichloropropane, 85 °C, 8 h; (vii) 30% H_2O_2, NaOH, H_2O, rt, 3 h; (viii) EDCI, HOBt, THF, NH_3, 0 °C, 2 h; (ix) 5-[(4-methyl-1-piperazinyl)sulfonyl]-2-ethoxybenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C, 1 h; (x) *t*-BuOK, *t*-BuOH, reflux, 2 h.



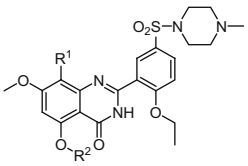
Scheme 2. Reagents and conditions: (i) CuI, NMP, 110 °C, 4 h; (ii) CH_3ZnCl, $[(t\text{-Bu})_3P]_2Pd$, NMP, 40 °C, 4 h; (iii) RZnI, $[(t\text{-Bu})_3P]_2Pd$, NMP, 40 °C, 4 h; (iv) $(n\text{-Bu})_3Sn\text{-}CH{=}CH_2$, $[(t\text{-Bu})_3P]_2Pd$, CsF, NMP, 50 °C, 4 h.

showed potent activity for 7 nM and 4 nM, respectively, and extraordinary selectivities towards PDE6 for 372-fold and 373-fold, respectively. We found that all these three halogen derivates could improve the PDE5 selectivity over PDE6, which was in agreement with the result reported in the earlier literature.[16] However, the introduction of a fluorine atom (**11a**) was detrimental, resulting in severe loss of activity (IC_{50} = 519 nm). The small size of fluorine atom may account for this phenomenon, since the hydrogen derivate (**11e**) showed poor inhibitory activity either (IC_{50} = 819 nM). Changing bromine group to various alkyl groups showed that PDE5 activity of analogs **11f–j** (R^1 = Me, Et, vinyl, *n*-Pr and *n*-Bu, respectively) were very similar and slightly lower than **11b**.

Through demethylating the C-5 methoxy group of compounds **11a–j** regioselectively (Scheme 3), compounds **12a–j** were synthesized. Compared with **11a–j**, the data exhibited that both the inhibitory activity and selectivity did not change much.

From the compounds synthesized above, some SAR we can obtain: the proper size of C-8 substitutions (R^1) can be crucial for the PDE5 inhibitory activity, the chlorine, bromine and iodine derivates (**11b**, **11c** and **11d**) showed good activity , with PDE5 inhibitory activity of 6nM, 7nM and 4nM, respectively, while R^1 was changed into larger substituent groups like *n*-propyl (11i,

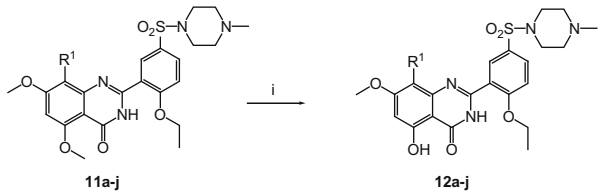
Table 1
Structures and activity of compounds for **11a–j** and **12a–j**



Compd	R^1	R^2	PDE5 IC_{50} (nM)	PDE6 IC_{50} (nM)	Radio (PDE6/PDE5)
11a	F	Me	519	—*	—
11b	Cl	Me	6	>10,000	>1667
11c	Br	Me	7	2616	372
11d	I	Me	4	1491	373
11e	H	Me	819	—	—
11f	Me	Me	61	—	—
11g	Et	Me	31	—	—
11h	Vinyl	Me	20	1014	51
11i	*n*-Pr	Me	45	—	—
11j	*n*-Bu	Me	61	—	—
12a	F	H	367	—	—
12b	Cl	H	29	—	—
12c	Br	H	6	3856	648
12d	I	H	6	440	74
12e	H	H	720	—	—
12f	Me	H	46	—	—
12g	Et	H	87	—	—
12h	Vinyl	H	31	—	—
12i	*n*-Pr	H	53	—	—
12j	*n*-Bu	H	70	—	—
Sildenafil			3	30	10

Assays carried out as described in Supplementary data. Enzyme sources: PDE5: rabbit platelets; PDE6: bovine retina. The IC_{50} values were determined from the logarithmic concentration–inhibition curve (at least five points). The value is given as the mean of at least two duplicate experiments.

* Compound with low PDE5 inhibitory activity (IC_{50} > 20 nM) were not tested for their PDE6 inhibitory activity.



Scheme 3. Reagents and conditions: (i) BBr_3, CH_2Cl_2, −10 °C, 4 h.

Table 2
In vivo results for **11b** and sildenafil

Compd	ICP/BP[a]
Vehicle	30.04 ± 8.26
Sildenafil	55.89 ± 5.59[b]
11b	50.44 ± 5.36[b]

Comparison of the erectile function in male rats treated with **11b** and Sildenafil ($n = 5$). Assays carried out as described in Ref. [17].
[a] ICP: intracavernous pressure. BP: arterial blood pressure.
[b] $p < 0.05$ versus vehicle.

45 nM) and *n*-butyl (**11j**, 61 nM) or smaller ones such as fluorine (**11a**, 519 nM) and hydrogen (**11e**, 819 nM), both were detrimental. The steric factor and hydrophobic interaction with the biological target may play an important role in the inhibitory mechanism.

Furthermore, compound **11b** was evaluated in vivo efficacy in the rat model of erection (Table 2). Electrically stimulated rats with 30 mg/kg po. dosing were utilized to measure the effects of administered compounds on the ICP/BP ratio. And electric stimulation was performed at 2 Hz, for 60 s with a pulse duration of 0.5 ms and 3 V using a stimulator.[17] Data in Table 2 indicated that **11b** demonstrated the same level of efficacy in comparison with sildenafil in rat erection model in vivo.

In conclusion, 2-phenylquinazolin-4(3*H*)-one derivative is a novel class of potent PDE5 inhibitors with high selectivity versus PDE6. Particularly, compound **11b** exhibited more than 100-fold selectivity versus PDE6 than sildenafil. Moreover, **11b** also showed comparable efficacy with sildenafil in rat erection model in vivo and it may lead a promising development towards to a novel class of PDE5 inhibitors. Based on the SAR we've received in this report, more analogs will be prepared to optimize the PDE5 inhibitory activity and selectivity further.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.125.

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