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Nitrogen-bridged substituted 8-arylquinolines as potent PDE IV inhibitors

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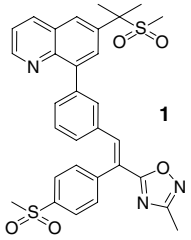
Abstract—Potent inhibitors of the human PDE IV enzyme are described. Substituted 8-arylquinoline analogs bearing nitrogen-linked side chain were identified as potent inhibitors based on the SAR described herein. The pharmacokinetic profile of the best analog and the in vivo efficacy in an ovalbumin-induced bronchoconstriction assay in conscious guinea pigs are reported.

Type 4 c-AMP specific phosphodiesterase (PDE IV) is an enzyme responsible for the hydrolysis of the 2nd messenger c-AMP in many cell types.[1] Inhibition of this enzyme can significantly increase the intracellular c-AMP concentration, leading to major alterations in cell biochemistry and function.[1c] For example, some inflammatory processes and antigen-induced bronchospasm can be attenuated using a PDE IV inhibitor.[2] Because inflammation and bronchoconstriction are major factors of respiratory diseases such as asthma and COPD (chronic obstructive pulmonary disease), the inhibition of PDE IV enzyme represents a promising therapeutic target. One of the major issues associated with the development of PDE IV inhibitors, however, has been their propensity to induce emesis. This observation has been reported on several prototypical compounds.[3,4]

We recently disclosed a new class of substituted 8-arylquinolines as potent and well-tolerated (emesis) PDE IV inhibitor[5] exemplified by compound **1**.



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In an effort to expand the SAR in this series of 8-arylquinolines, we explored the possibility of introducing heteroatoms to replace the photolytically unstable olefinic linker. Of all the potential replacements investigated, including ethers, thioethers, sulfones, and sulfonamides, the analogs bearing amine and amide linkers were found to be the most promising replacements for the double bond found in compound **1**.

Our initial SAR efforts focused on the evaluation of the amide tether. For that purpose, a series of compounds were prepared following the synthetic approach described in Scheme 1. Suzuki coupling of aryl bromide **2** and 3-carboxybenzeneboronic acid or 3-aminobenzeneboronic acid afforded the desired intermediates **3** and **4**, respectively. The latter was converted to the corresponding amide analogs (**5**–**10**) using HATU as the coupling reagent. The specific affinities of these derivatives for the four isoforms of the human PDE IV enzyme[6] were

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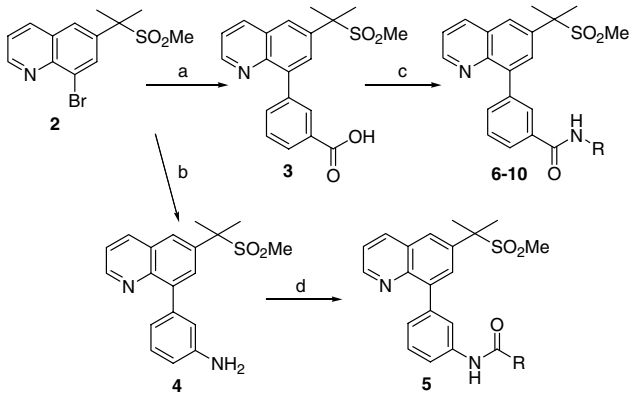


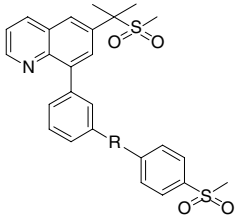
Scheme 1. Reagents and conditions: (a) 3-carboxybenzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, *n*-PrOH, 80 °C; (b) 3-aminobenzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, *n*-PrOH, 80 °C; (c) amine, HATU, Hünig's base, DMF; (d) carboxylic acid, HATU, Hünig's base, DMF.

measured. Their respective ability to block the release of TNF-α through inhibition of PDE IV in a LPS stimulated human whole blood assay (HWB) was also evaluated.[7] The results are summarized in Tables 1 and 2.

Both amide linkers (**5**,**6**) are equipotent in the enzyme assay but differ substantially (10-fold) in the human whole blood assay. Because the activity of amide **6** is less shifted in the presence of plasma proteins, it was selected as the linker of choice for further SAR. As exemplified by aryl amide **8** and primary amide **7**, substitution is required to obtain intrinsic potency on the PDE IV enzymes. Moreover, in order to achieve potency in the HWB assay, polar substituents in the para position are required (compounds **6**, **9**, and **10**).

Having successfully replaced the olefinic moiety of compound **1**, we then evaluated the pharmacokinetic profile

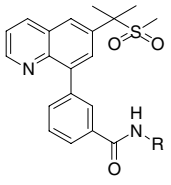
Table 1. Biological data for amide derivatives **5** and **6**



Compound	R	GST-PDE $IV^{QT}IC_{50}$[a] (nM)				HWB IC_{50}[b] (μM)
		A	B	C	D	
5		1.7	1.2	10.6	2.3	1 (±1)
6		3.5	0.5	26	2.8	0.14 (±0.06)

[a] Values are means of two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.

Table 2. Biological data for amide derivatives **7**–**10**



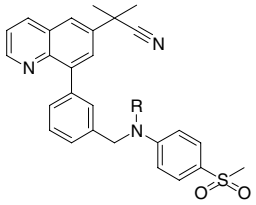
Compound	R	GST-PDE IV^{QT} IC_{50}[a] (nM)				HWB IC_{50}[b] (μM)
		A	B	C	D	
7	H	78	40	490	74	—
8	Ph	16	5.9	97	10	7 (±3)
9		3.1	0.9	17	3.0	0.2 (±0.1)
10		0.6	0.4	5.5	0.7	0.09 (±0.03)

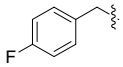
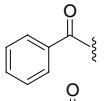
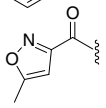
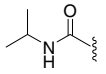
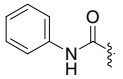
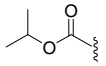
[a] Values are means of two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.

of these new compounds. We observed that most of these amides were poorly absorbed after oral dosing and were readily metabolized in rats to the inactive carboxylic acid **3**.

In an attempt to overcome this metabolic instability, a series of tertiary amines and amides (Table 3) were prepared. These analogs were synthesized via the Suzuki coupling of aryl bromide **2** or **2a** and 3-formylbenzeneboronic acid, followed by their reductive amination with 4-methylthioaniline to give amine **12**. This amine could then be converted into either an amide, urea or carbamate. Finally, oxidation using oxone produced the desired sulfones **14a**–**19a** (Table 3).

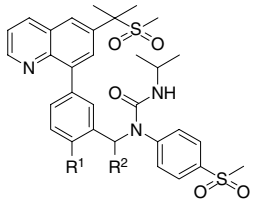
Table 3. Biological data for derivatives **14a**–**19a**



Compound	R	GST-PDE IV^{QT} IC_{50}[a] (nM)				HWB IC_{50}[b] (μM)
		A	B	C	D	
14a		1.0	0.1	9.5	0.5	1.8 (±0.6)
15a		0.2	0.1	1.0	0.3	0.08 (±0.03)
16a		0.3	0.1	0.9	0.1	0.03 (±0.005)
17a		0.1	0.1	1.7	0.1	0.14 (±0.14)
18a		0.1	0.03	0.05	0.1	0.04 (±0.04)
19a		0.3	0.3	4.2	0.3	0.08 (±0.03)

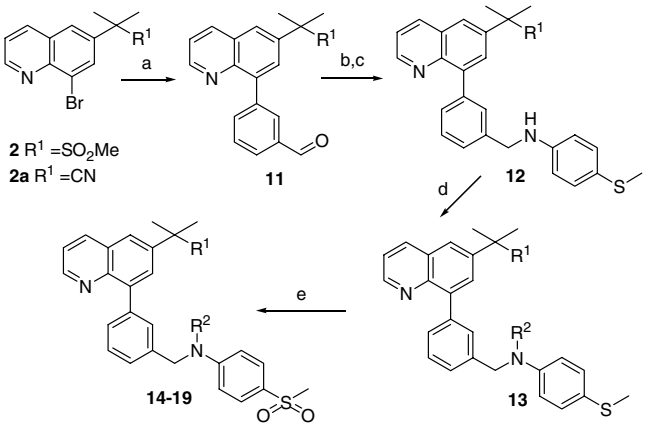
[a] Values are means of two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.

Table 4. Biological data for derivatives **20**–**23**



Compound	R^1	R^2	GST-PDE IV^{QT} IC_{50}[a] (nM)				HWB IC_{50}[b] (μM)
			A	B	C	D	
20	H	H	0.1	0.1	1.7	0.1	0.1 (±0.1)
21	Cl	H	15	4.4	70	10	4 (±1)
22	F	H	0.6	0.3	6.4	0.8	0.05 (±0.02)
23	H	Me	1.8	0.7	25	1.9	0.4 (±0.4)

[a] Values are means of two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.

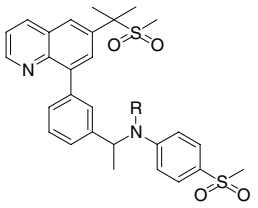


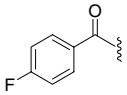
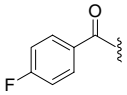
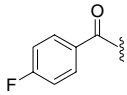
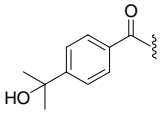
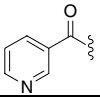
Scheme 2. Reagents and conditions: (a) 3-formylbenzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C; (b) 4-methylthioaniline, EtOH, reflux; (c) $NaBH_3CN$, EtOH; (d) acyl chloride, DMAP, Et_3N, CH_2Cl_2, or isocyanate, DBU, THF, or 4-fluorobenzyl bromide, NaH, DMF; (e) oxone, THF/MeOH/H_2O.

Tertiary amines as exemplified by **14a** exhibited good intrinsic potency but were found to be highly shifted in the HWB assay. Whole blood activity was regained by reintroducing the carbonyl group outside the tether (**14a** vs **15a**). Carbamate (**19a**) and ureas (**17a**, **18a**) were also found to exhibit acceptable whole blood potencies. Unfortunately, as it was the case for the previous amide series, these series of compounds were metabolically unstable. Indeed, oxidative cleavage occurred in vivo leading to carboxylic acid **3a** as the main circulating metabolite observed in rat plasma following oral dosing. For example, the concentration of acid **3a** present in the blood at T_{max} is 30 times higher than the parent drug for compound **15a** and 23 times higher for compound **17a**.

We then tried to circumvent this metabolic degradation through the introduction of electron-withdrawing substituents onto the phenyl ring adjacent to the site of metabolism (Table 4). The addition of a fluorine led to

Table 5. Biological data for derivatives **24**–**30**



Compound	R	GST-PDE IV^{QT} IC_{50}[a] (nM)				HWB IC_{50}[b] (μM)
		A	B	C	D	
24		10	4.2	41	6.7	2.0 (±0.8)
25		1.6	0.6	17	1.4	0.8 (±0.5)
26	 (racemic)	2.3	0.6	12	1.8	0.56 (±0.2)
27	 (enantiomer A)	15	5.8	51	7.0	1.4 (±0.4)
28	 (enantiomer B)	1.8	0.5	7.5	0.7	0.25 (±0.07)
29		1.5	0.4	5.9	0.5	0.27 (±0.08)
30		2.1	0.7	14	1.7	0.21 (±0.06)

[a] Values are means of two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.

the equipotent analog (**22**), while the introduction of the larger chlorine substituent (**21**) resulted in a dramatic loss in potency. Furthermore, these substitutions failed to block the oxidative cleavage of the molecule. However, the appendage of a methyl group directly onto the benzylic position (by using MeLi in THF at −78 °C instead of step (c) in Scheme 2) provided us with the desired metabolic stability with minimal loss in HWB potency.

Having resolved the metabolic stability issue with this type of tether, a series of amide derivatives were prepared (Table 5). As exemplified by the acetamide derivative **24**, smaller groups led to less potent compounds. By reintroducing bulkier groups, like 4-fluoro-benzoyl (i.e., derivative **26**), we were able to regain the desired potency on the enzyme as well as in the HWB assay.

The pharmacokinetic profile of compound **26** in rats and in squirrel monkey was established. It showed a half-life of 2 and 7 h, respectively, following iv administration, as well as good oral bioavailability when dosed in 60% PEG 200/water (67% with C_{max} = 2.7 μM and 98% with C_{max} = 0.9 μM, respectively). The in vivo efficacy of **26** was then evaluated in the ovalbumin-induced bronchoconstriction assay in conscious guinea pig.[8] Following this protocol, the amide **26** showed 74% inhibition at 30 μg/kg when administered interperitoneally (ip). In comparison, CDP-840[4a,b] a prototypical PDE IV inhibitor, which has shown efficacy in animal models as well as in human, exhibited a 55% inhibition when dosed ip at 1 mg/kg in this model.

The racemic mixture **26** was resolved[9] and the more potent enantiomer (**28**) exhibited a 2-fold improvement in intrinsic potency on PDE IV. Introduction of polar substituent (i.e., **29**) or heterocycle (i.e., **30**) also led to an increase in whole blood activity.

In conclusion, we have demonstrated that the introduction of nitrogen containing tethers to substituted 8-arylquinolines can lead to potent inhibitors of the PDE IV enzyme. Moreover, blocking the metabolic degradation of those compounds by introducing a substituent at the benzylic position gave us the desired pharmacokinetic profile in rats and in squirrel monkeys. Subsequently, a prototypical example of this series, compound **26** was found to be active in an ovalbumin-induced bronchoconstriction assay in conscious guinea pig and is currently been evaluated to determine its emetic threshold.

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9. Separation of the two enantiomers was performed by chiral HPLC (Chiralpak AD 5 × 50 cm, 20 μ, 60 ml/min, 40% hexanes/60% ethanol, rt = 55 and 79 min.).