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Alkyl-bridged substituted 8-arylquinolines as highly potent PDE IV inhibitors

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ABSTRACT

Substituted 8-arylquinoline analogs bearing alkyl-linked side chain were identified as potent inhibitors of type 4 phophodiesterase. These compounds address the potential liabilities of the clinical candidate L-454560. The pharmacokinetic profile of the best analogs and the in vivo efficacy in an ovalbumin-induced bronchoconstriction assay in conscious guinea pigs are reported.

The 5′-cyclic nucleotide phosphodiesterases (PDEs) are a large family of bimetallic hydrolases responsible for the hydrolysis and consequent deactivation of cAMP and cGMP.[1] Of the eleven families, the cAMP-specific PDE4s (encoded by four genes) are particularly abundant in inflammatory cells, immune cells and in airway smooth muscle cells,[2] where inhibition of PDE4s blocks cell trafficking, cell proliferation, and modulates the production of inflammatory mediators and cytokines, including LTB4, TNF-α, IL-2, IFNγ, as well as reactive oxygen species.[3] In animal models, PDE4 inhibitors are generally anti-inflammatory and bronchodilatory. A number of them, including roflumilast, cilomilast and rolipram, were evaluated in humans and they have shown promising clinical efficacy for asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis and rheumatoid arthritis.[4] Among them, roflumilast has shown a significant improvement in FEV1 after 24 week treatment in COPD patients.[5]

Despite the promising clinical efficacy of PDE4 inhibitors, the major impediment for their further clinical development has been their mechanism-related adverse effects including nausea, emesis, and gastrointestinal adverse events.[6] In order to further improve the therapeutic window of efficacy over emesis and GI adverse events, several approaches have been attempted, including the designing of a highly emetic photoaffinity probe to elucidate the molecular targets of emesis versus efficacy,[7] selective targeting among the four PDE4 isoforms,[8] as well as restricting the compound tissue distribution.[9]

We previously disclosed a successful approach which led to the identification of our first clinical candidate L-454560 (**1**) (Fig. 1).[10] Although the compound was well tolerated, its inhibition of cytochrome P450 2C9 (IC_{50} of 0.2 μM) and potential liability of olefin-isomerisation prompted us to initiate a back-up program. Part of our efforts toward overcoming these two liabilities was recently published.[11] In extension of this work, we would like to report a series of alkyl-linked 8-arylquinolines as highly potent human PDE4 inhibitors.

Our initial SAR efforts focused on the evaluation of a series of ketones as previous studies suggested that a hydrogen bond acceptor could exhibit greater potency.[12] The relative intrinsic potency of these analogs is expressed as an average of the potency for three

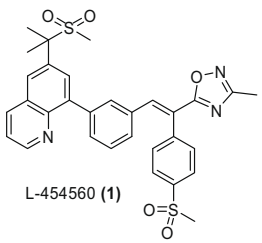

Figure 1. Clinical candidate L-454560.

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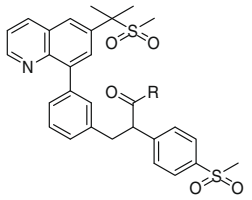
Table 1
Biological data for ketones **2–6**



Compd	R	PDE4-ABD^{QT} IC_{50}[a] (nM)	HWB IC_{50}[b] (μM)	CYP2C9 IC_{50}[a] (μM)
2	Me	1.7	0.3 (±0.1)	0.6
3	4-F-Ph	1.4	0.8 (±0.5)	0.2
4	3-Pyridinyl	0.9	0.3 (±0.1)	0.2
5	*t*-Bu	1.4	0.3 (±0.1)	0.7
6	Dimethylcarbinol	1.4	0.4 (±0.2)	3.6

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

human PDE4 isoforms (A, B, D).[13] The compounds described in this Letter displayed little or no isozyme specificity. Also, their cellular based functional efficacy at blocking the LPS-induced TNF-α release in human whole blood (HWB),[14] and their inhibition of the Cytochrome P450 2C9,[15] are summarized in Table 1.

Varying the substitution of the ketones from a methyl to a 4-fluorophenyl, 3-pyridinyl or a *tert*-butyl (compounds **2–5**) did not affect the activity in the enzyme assay nor in the whole blood assay. However, adding a tertiary alcohol, as exemplified by compound **6**, decreased the CYP 2C9 affinity. Furthermore, when we evaluated the pharmacokinetic profile of these new analogs (**2–6**), we found a significant amount of α-hydroxylated ketone metabolite circulating for all of them, except for compound **6**. That observation led us to postulate that the metabolite arises from oxidation of the enol form of the molecule which is prevented by the internal hydrogen bond present for the hydroxyketone **6**. Following that hypothesis, we replaced the ketone functionality by other hydrogen bond acceptor substituents described in Table 2.

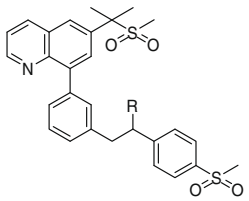
By introducing polar functionalities such as an alcohol (compounds **7–9**), sulfone **10** or phosphonate **11**, we were able to gain potency in the HWB assay while decreasing the inhibitory activity for CYP 2C9. For example, the decreased CYP 2C9 activity observed for compound **10** translated to a 36-fold improvement in the therapeutic index over L-454560. Unfortunately, the overall pharmacokinetic profile in rats for these inhibitors showed no improvement over the ketone derivatives discussed in Table 1. We then decided to block the benzylic position by introducing a fluorine atom. The pharmacokinetic profiles of these newly prepared fluoro analogs were then systematically evaluated (Table 3). Alcohol **12** showed a significant improvement over the non-fluorinated analog **9**, decreasing its clearance from 50 ml/min/kg to 17 ml/min/kg. Furthermore, the introduction of the benzylic fluorine atom improved the bioavailability from 21% to 84%.

Having solved the pharmacokinetic issue in rats, maintained the potency over PDE 4 and kept the affinity for CYP 2C9 low (Table 3), we decided to concentrate our efforts on finding more potent analogs. Introducing a methylsulfonyl group, exemplified by compound **13**, did not translate into a significantly more potent analog, while incorporating a phosphonyl group led to a compound with very high clearance (entry **14**). Increasing the lipophilicity as in the biscyclopropyl **15** gave a compound with improved HWB potency. The same modification could also be applied in the sulfone series and led to the potent derivative **16**. In fact, once being resolved by chiral HPLC,[16] compounds such as **18** and **20** were found to be over 10 times more potent than L-454560 (**1**) in the HWB (IC_{50} = 0.2 μM).

Compounds **18** and **20** were then further profiled (Table 4). The observed increase in HWB potency did translated similarly in our in vivo model.[17] Compared to L-454560 (**1**), which showed a 53% inhibition of ovalbumin-induced bronchoconstriction in conscious guinea pigs at 0.03 mg/kg, compounds **18** an **20** showed 85% and 73% inhibition when dosed interperitoneally (ip) at 0.01 mg/kg, respectively. Evaluation of their propensity to cause emesis was then established by dosing in squirrel monkeys (SqM). For the bis-cyclopropane analog **18**, emesis was observed at a plasma concentration of 0.2 μM or 100-fold over its IC_{50} in the SqM whole blood assay (Table 4). The therapeutic window of potency versus emesis was even greater for compound **20** where emesis was displayed at a concentration of 1.9 μM. This 1900-fold window compared favorably over the 380-fold therapeutic index observed for L-454560 (**1**).

All the compounds described[18] in this Letter were prepared from the previously disclosed 8-bromo-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline (**21**)[10b] following the synthetic approach described in Scheme 1. Suzuki coupling of arylbromide **21** with 3-

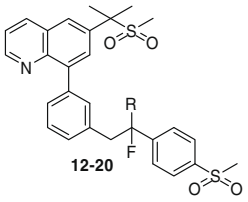
Table 2
Biological data for derivatives **7–11**



Compd	R	PDE4-ABD^{QT} IC_{50}[a] (nM)	HWB IC_{50}[b] (μM)	CYP2C9 IC_{50}[a] (μM)	Rat PK[c] F[d], Cl[e]
7	CH_2OH	1.5	0.21 (±0.04)	3.6	9, 51
8	*t*-Butylcarbinol	0.3	0.09 (±0.06)	1.5	—
9	Dimethylcarbinol	0.7	0.10 (±0.09)	6.4	21, 50
10	SO_2Me	0.9	0.19 (±0.09)	6.9	1, 76
11	$PO(OMe)_2$	1.3	0.03 (±0.02)	11.4	3, 48

[a] Values are means of at least two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.
[c] Dosed as 60% PEG 200/water solution.
[d] Bioavailability (F) expressed in percentage.
[e] Clearance is expressed in ml/min/kg and calculated using the following formula: Cl = (Dose IV)(1E6)/(Total AUC IV)(Mol. weight).

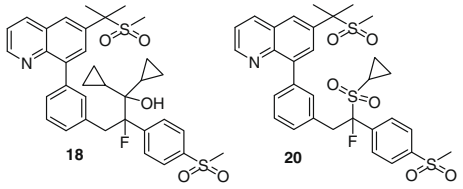
Table 3
Biological data for derivatives **12–20**



Compd	R	PDE4-ABD^{QT} IC_{50}[a] (nM)	HWB IC_{50}[b] (μM)	CYP2C9 IC_{50}[a] (μM)	Rat PK[c] F[d], Cl[e]
1	—	1.0	0.2 (±0.1)	0.2	100, 7
12	Dimethylcarbinol	0.8	0.2 (±0.2)	4.6	84, 17
13	SO_2Me	0.6	0.1 (±0.1)	4.5	53, 9
14	$PO(OMe)_2$	0.4	0.1 (±0.09)	—	51,177
15	(*c*-Pr)$_2$carbinol	0.4	0.04 (±0.02)	2.8	99, 8
16	SO_2(*c*-Pr)	0.2	0.08 (±0.07)	3.8	—
17	(*c*-Pr)$_2$carbinol Enantio A	0.4	0.02 (±0.05)	2.1	69, 11
18	(*c*-Pr)$_2$carbinol Enantio B	0.2	0.006 (±0.003)	3.8	99, 38
19	SO_2(*c*-Pr) Enantio A	0.2	0.09 (±0.06)	3.7	36, 9
20	SO_2(*c*-Pr) Enantio B	0.2	0.015 (±0.002)	3.9	99, 3

[a] Values are means of at least two experiments.
[b] Values are means of three experiments, standard deviation is given in parentheses.
[c] Dosed as 60% PEG 200/water solution.
[d] Bioavailability (F) expressed in percentage.
[e] Clearance is expressed in ml/min/kg and calculated using the following formula: Cl = (Dose IV)(1E6)/(Total AUC IV)(Mol. weight).

Table 4
In vivo data for derivatives **18** and **20**



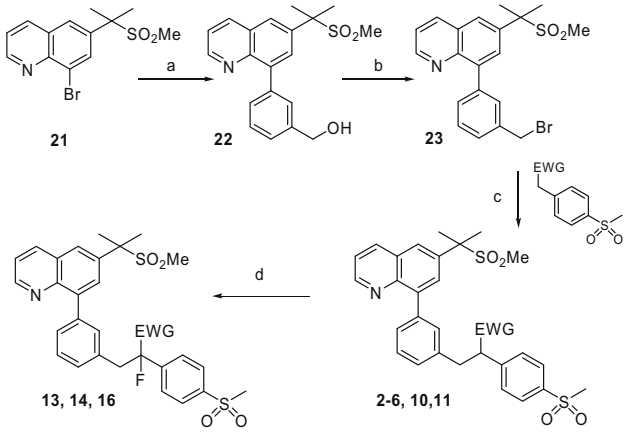
Compd	SqM WB IC_{50}[a] (μM)	SqM PK[b] C_{max} (μM) @ dose (mpk)	Ratio[c] C_{max}/IC_{50}	Guinea pig[d] % @ μg/kg
1	0.01	3.8 @ 10	380	53 @ 30
18	0.001	0.1 @ 0.4	100	85 @ 10
20	0.001	1.9 @ 2	1900	73 @ 10

[a] Values are means of two experiments.
[b] Squirrel monkey plasma concentration at which emesis was observed in at least two animals when dose as a 60% PEG200/water solution.
[c] Ratio of SqM plasma concentration at which emesis was observed over SqM whole blood IC_{50}.
[d] Percentage of inhibition of ovalbumin-induced bronchoconstriction following ip injection.

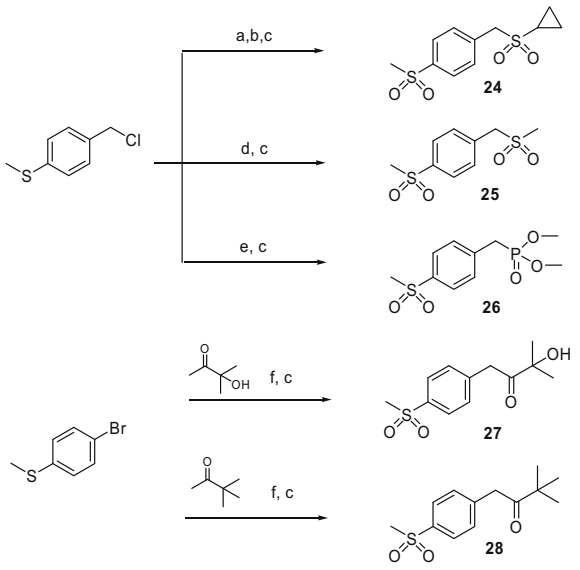
(hydroxymethyl)benzeneboronic acid afforded the desired biaryl scaffold **22**. The latter was converted to a common intermediate **23** by treatment with HBr 48% in acetic acid. Prior to being transformed into their fluorinated analogs (**13**, **14**, and **16**) by treatment with sodium *tert*-butoxide and $FN(SO_2Ph)_2$ in THF, the benzyl bromide **23** was converted into derivatives (**2–6**, **10**, and **11**) by alkylation with the proper benzylic groups (**24–28**) whose syntheses are described in Scheme 2.

Displacement of 4-methylthiobenzyl chloride either with sulfur followed by cyclopropyl magnesium bromide, sodium methanesulfinate or trimethyl phosphite under Arbuzov conditions led to the corresponding thioether which were all oxidized to the sulfone (**24–26**) using oxone as reagent. Alternatively, compounds **27** and **28** were prepared by a palladium mediated coupling of 4-methylthiobromobenzene with an appropriate methylketone followed by oxone oxidation.

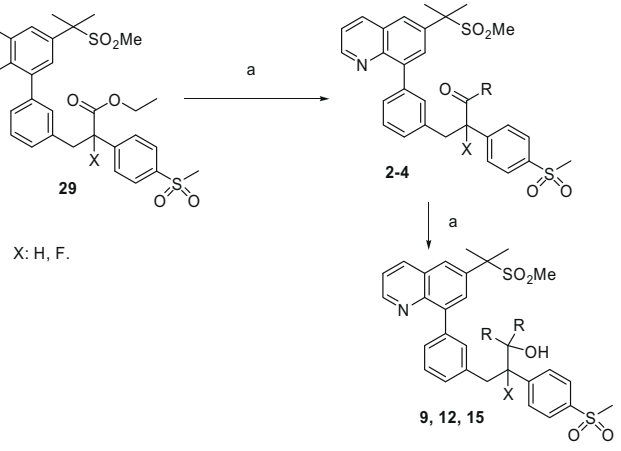
The alkylation of benzyl bromide **23** described earlier could also be performed with ethyl 4-methylthiophenylacetate to afford the substituted phenylacetate **29**. The latter was then either converted



Scheme 1. Reagents and conditions: (a) 3-(hydroxymethyl)benzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3 (2 M in H_2O), *n*-PrOH, 80 °C (b) HBr 48%, AcOH (c) *t*-BuOK, THF/DMF (1:1). (d) *t*-BuOK, $FN(SO_2Ph)_2$, THF/DMF (1:1).



Scheme 2. Reagents and conditions: (a) S_8, NaOH, TBAI, PEG400/benzene, 80 °C (b) *c*-PrMgCl, THF (c) oxone, THF/MeOH/H_2O (2:1:1) (d) $MeSO_2Na$, DMF. (e) $P(OMe)_3$, 140 °C (f) $Pd_2(dba)_3$, Xantphos, *t*-BuONa, THF, 65 °C.



Scheme 3. Reagents: (a) RMgCl, THF.

into the fluorinated analogs using conditions described earlier and/or the corresponding ketone (**2**–**4**) and alcohol (**9**, **12**, and **15**) by treatment with an appropriate Grignard reagent (Scheme 3).

In conclusion, we have identified two potent and selective PDE4 inhibitors, compounds **18** and **20**, which have improved potency and metabolic profile across the species in comparison to the clinical candidate L-454560 **1**. In addition, these inhibitors are devoid of the metabolically unstable olefin and have little affinity against CYP 2C9. Finally, their excellent pharmacokinetic properties resulted in compounds with improved in vivo functional efficacy as measured in our guinea pig model of bronchoconstriction.

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16. Separation of the two enantiomers **17** and **18** was performed by chiral HPLC (Chiralpak AD 5 × 50 cm, 20μ, 70 ml/min, 60% hexanes, 20% *iso*-propanol, 20% ethanol, (rt = 30 and 43 min.). Separation of the two enantiomers **19** and **20** was performed by chiral HPLC (Chiralpak AD 5 × 50 cm, 20μ, 55 ml/min, 30% hexanes, 30% *iso*-propanol, 30% ethanol, 10% methanol (rt = 63 and 81 min.).
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