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Design, synthesis, and biological evaluation of 8-biarylquinolines: A novel class of PDE4 inhibitors

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Abstract—The structure–activity relationship of a novel series of 8-biarylquinolines acting as type 4 phosphodiesterase (PDE4) inhibitors is described herein. Prototypical compounds from this series are potent and non-selective inhibitors of the four distinct PDE4 (IC_{50} < 10 nM) isozymes (A–D). In a human whole blood in vitro assay, they inhibit (IC_{50} < 0.5 μM) the LPS-induced release of the cytokine TNF-α. Optimized inhibitors were evaluated in vivo for efficacy in an ovalbumin-induced bronchoconstriction model in conscious guinea pigs. Their propensity to produce an emetic response was evaluated by performing pharmacokinetic studies in squirrel monkeys. This work has led to the identification of several compounds with excellent in vitro and in vivo profiles, including a good therapeutic window of efficacy over emesis.

The phosphodiesterase (PDE) superfamily of cyclic nucleotide (cAMP and cGMP) hydrolyzing enzymes is composed of at least 11 members.[1] These enzymes are widely distributed in various cells, but the PDE4 subtypes are specifically found in inflammatory cells involved in the pathogenesis of diseases such as asthma, COPD, and rheumatoid arthritis.[2] Inhibition of PDE4 leads to an increase in intracellular cAMP which in turn inhibits the release of inflammatory mediators such as cytokines (TNF-α, IL-2, IL-12, LTB4, IFN-γ) as well as the recruitment and activation of inflammatory cells.[3] This observation can be replicated in vitro by measuring the ability of PDE4 inhibitors to block the LPS-stimulated TNF-α release in human whole blood thus allowing a direct measurement of their relative potency.[4] Intrinsic potency of inhibitors against the four PDE4 isozymes A, B, C, and D was assessed using PDE4-GST constructs, expressed in SF9 cells via the baculovirus expression system.[5]

Despite the pre-clinical and clinical evidence that PDE4 inhibitors represent a valuable therapeutic approach for the treatment of inflammatory-related respiratory diseases,[6] they are often associated with adverse effects such as nausea and emesis.[7] The work described in this paper aimed at identifying potent PDE4 inhibitors with an improved therapeutic index of efficacy over emesis in preclinical models. The in vivo efficacy of these inhibitors was assessed in an ovalbumin-induced bronchoconstriction model in conscious guinea pig,[8] while their propensity to produce an emetic response was evaluated by performing pharmacokinetic studies in squirrel monkeys.

Strategies to identify PDE4 inhibitors with a good therapeutic window of efficacy over emesis have been numerous. For examples, efforts have been made to identify isozyme-selective inhibitors,[9] to pinpoint the molecular target of emesis versus efficacy by using highly emetic photoaffinity probes[10] or finally to focus on peripherally restricted inhibitors.[11] Our approach

Keywords: Phosphodiesterases type 4; Inhibitors; Respiratory diseases; Emesis.
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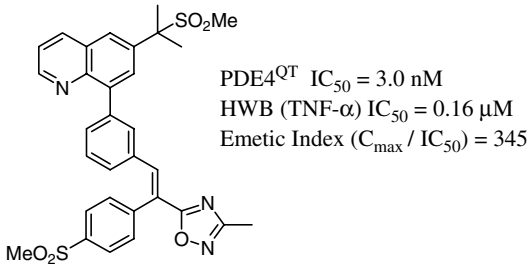
consisted in identifying a novel scaffold of PDE4 inhibitors by combining known pharmacophores in the public domain which display low incidence of emesis with highly potent ones. This strategy ultimately leads to discovery of L-454560 as our first development candidate.[12]

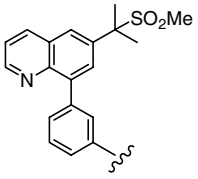
L-454560 was found to be intrinsically highly potent (Fig. 1) with good human whole blood (HWB) activity but more importantly displayed a low emetic index. Specifically, L-454560 triggered an emetic response in squirrel monkeys (SqM) at a plasma concentration of 3.8 μM while its IC_{50} in SqM whole blood is 11 nM (3800/11 = 45). Despite these data, two issues were identified and deemed significant enough to initiate a backup effort. First, L-454560 was found to be a competitive inhibitor of the cytochrome P450 2C9 (IC_{50} = 0.2 μM)[13] which could potentially lead to drug–drug interaction. Second, the olefin at the core of L-454560 was found to isomerize in human by the addition and elimination of glutathione. To address this problem a series of biaryl analogs were prepared (Table 1). The dimethyl sulfone 8-phenyl quinoline core was left unchanged as it was previously optimized for potency and metabolic stability. Their relative intrinsic potency is expressed as an average of the potency for all four isozymes A, B, C, and D ($PDE4^{QT}$). All PDE4 inhibitors described in this paper displayed little or no isozyme specificity.

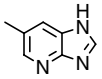


L-454560 (**1**)

Figure 1.

Table 1. Initial SAR on biaryl quinoline PDE4 inhibitors



Entry		IC_{50}[a] (μM)		
		$PDE4^{QT}$	TNF-α	CYP 2C9
2	–Ph-2-SO_2Me	0.0026	0.70	—
3	–Ph-3-SO_2Me	0.0010	0.31	0.58
4	–Ph-4-SO_2Me	0.0008	0.60	0.73
5	–Ph-4-CH_2SO_2Me	0.0011	0.12	1.6
6	3-Pyridinyl	0.0042	0.32	0.63
7	3-Pyridinyl *N*-oxide	0.030	0.58	36
8	4-Pyridinyl	0.0027	0.52	0.11
9	4-Pyridinyl *N*-oxide	0.022	1.1	—
10		0.0019	0.15	2.9

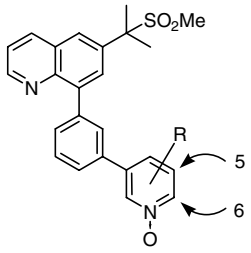
[a] IC_{50} determinations are averages of at least two experiments.

In general, mono-substituted phenyl group exhibited similar intrinsic potency ($PDE4^{QT}$) to L-454560 but their IC_{50} was shifted in presence of protein as exemplified by their relative whole blood activity (TNF-α). Moreover, they had limited effect on the affinity for CYP 2C9. The benzyl methyl sulfone **5** showed some improvement over L-454560 on the three parameters of interest. Introduction of heterocycles was tolerated with minimal loss in both intrinsic and whole blood potency as exemplified by entries **6** to **10**. The pyridine *N*-oxide **7** was not a competitive inhibitor of CYP 2C9 while the imidazolo-pyridine **10** was the overall best analog. These results suggested that reduction of CYP 2C9 affinity could be achieved by introducing polarity on the biaryl moiety and that the addition of appendage could modulate potency. A series of substituted pyridinyl *N*-oxides were prepared to validate this hypothesis. Pharmacokinetic data in rats were also generated for each analog, given that the imidazolo-pyridine **10** was not orally bioavailable in rats and the pyridine *N*-oxide **7** exhibited a short half-life.

Several permutations of the relative position of the pyridinyl *N*-oxide and the appendage were explored, but the 5 and 6 substituted 3-pyridinyl *N*-oxide scaffolds were optimum for potency (Table 2). Introduction of a methyl next to the *N*-oxide (entry **11**) led to modest gain in whole blood potency and bioavailability in rats. However, in rhesus monkey this analog was readily metabolized to the corresponding hydroxyl–methyl analog **12**. The latter was also observed in rats but to a lesser extent. Alcohol **12** has poor orally bioavailability in rats and the corresponding carboxylic acid **13** has low potency. To alleviate this metabolic instability, the tertiary alcohol **14** was prepared. This analog exhibited a good overall in vitro profile, an acceptable oral bioavailability across three species (rat, dog, and monkey) and therefore was further profiled (see Table 4) and assessed in our efficacy model. Introducing different functional groups such as urea, exemplified by **15**, improved significantly whole blood potency but was detrimental to oral bioavailability. The amide analog **16** was an acceptable compromise but with modest reduction for CYP 2C9 affinity. The reversed amide **17** suffered from lower bioavailability. Several 5-substituted 3-pyridinyl *N*-oxides were prepared but led to no improvement on the overall profile as compared to their 6-substituted counterparts. Surprisingly, in several cases, low oral bioavailability was observed as exemplified by the tertiary alcohol **16** and the amide **19**.

In the previously described series, reduction of CYP 2C9 affinity was achieved by introducing the polar pyridine *N*-oxide moiety while the addition of appendage was shown to modulate potency. A parallel strategy in which the polar moiety was positioned on the appendage was also explored. Consequently, a series of analogs bearing a carboxylic acid group were prepared (Table 3). The benzoic and phenyl acetic acid derivatives **20** and **21** displayed high affinity for the PDE4 enzymes both intrinsi-

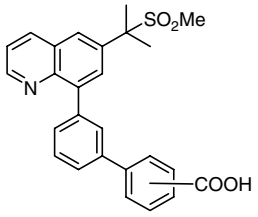
Table 2. SAR on substituted pyridinyl *N*-oxide



Entry	R	IC_{50}[a] (μM)			Rat PK
		$PDE4^{QT}$	TNF-α	CYP 2C9	F[b], $T_{1/2}$[c]
7		0.030	0.58	36	76, 1.2
11	6-Me	0.0099	0.48	26	83, 1.2
12	6-CH_2OH	0.012	0.56	—	10, 1.7
13	6-COOH	0.107	6.3	—	—
14	6-$C(CH_3)_2OH$	0.0068	0.48	15	100, 1.5
15	6-NHC(O)NH-iso-propyl	0.0015	0.08	1.5	11, 0.7
16	6-C(O)NH-Cyclopropyl	0.0017	0.4	4	100, 6.5
17	6-NHAc	0.0030	0.12		47, 0.2
18	5-$C(CH_3)_2OH$	0.039	0.82		0, <1
19	5-C(O)NH-Cyclopropyl	0.0087	0.85		0, <1

[a] IC_{50} determinations are averages of at least two experiments.
[b] Bioavailability (F) is expressed in percentage (%).
[c] Half-life ($t_{1/2}$) is expressed in hours.

Table 3. SAR on carboxylic acids



Entry		IC_{50}[a] (μM)			Rat PK
		$PDE4^{QT}$	TNF-α	CYP 2C9	F[b], $T_{1/2}$[c]
20	4-	0.0056	0.24		54, 2
21	4-CH_2–	0.0029	0.43		60, 0.3
22	2-CH_2CH_2–	0.0073	25		
23	3-CH_2CH_2–	0.0046	0.92	7.2	
24	4-CH_2CH_2–	0.0022	0.33	9.8	25, 1
25	4-$CH_2C(CH_3)_2$–	0.0015	1.8	1.6	
26	4-$C(CH_3)_2CH_2$–	0.0019	0.93	15	100, 2
27	4-$CH(CH_2)CH$– Enantiomer A	0.0008	1.4	1.7	100, 2
28	4-$CH(CH_2)CH$– Enantiomer B	0.0014	0.60	3.2	100, 2

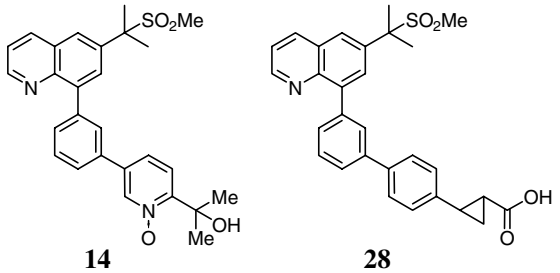
[a] IC_{50} determinations are averages of at least two experiments.
[b] Bioavailability (F) is expressed in percentage (%).
[c] Half-life ($t_{1/2}$) is expressed in hours.

cally and in whole blood along with being orally bioavailable in rats. To identify the preferred position of the acid residue, the three possible phenyl propionic acids were prepared. The *para*-substituted analog **24** clearly emerged as the most potent one but exhibited low oral bioavailability in rats. Rat liver microsome incubation of the latter along with careful analysis of the rat plasma samples following oral dosing revealed that the major metabolic degradation pathway involved a sequence of β-oxidation, elimination, and finally benzylic oxidation leading to the benzoic acid **20**.[14] This metabolic instability could easily be overcome by introducing methyl substituents at the benzylic position and therefore restoring oral bioavailability in rats. Moreover, the resulting *geminal*-dimethyl acid **26** showed low affinity for the CYP 2C9 enzyme but was highly

shifted in presence of protein as exemplified by the high ratio of whole blood over enzyme potency (0.93/0.0007 = 13,280). This shift was even more significant in the *geminal*-dimethyl analog **25**. An acceptable compromise was reached by linking the carboxylic acid moiety and the phenyl group through a *trans*-substituted cyclopropane ring. The resulting racemic mixture was resolved by chiral HPLC to afford the enantiomers **27** and **28**. Both were found to be orally bioavailable but enantiomer B (**28**) proved to be more potent in whole blood and moreover showed less affinity for the CYP 2C9 enzyme. Compound **28** was ultimately further profiled to determine its in vivo efficacy and emetic threshold (Table 4).

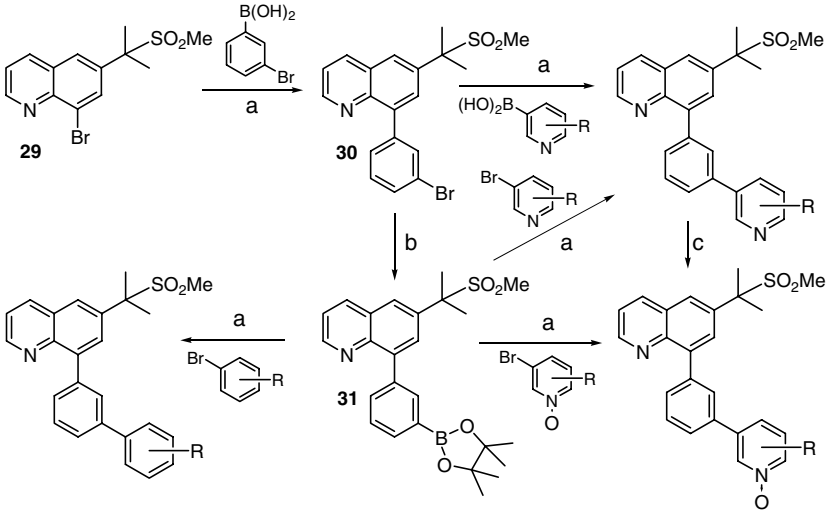
The compounds described herein were easily accessible in a four-step sequence (Scheme 1) starting from the previously published 8-bromo-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline (**29**).[12b] The latter was coupled via Suzuki coupling with commercially available 3-bromo phenylboronic acid in 50% yield. The resulting 8-(3-bromophenyl) quinoline **30** was converted to the corresponding pinacole boronate ester **31** in 62% yield using pinacolato diboron in a coupling reaction catalyzed by $PdCl_2(dppf)_2$. In most cases, the key intermediate **31** was coupled in conditions previously described with properly substituted aryl bromide (entry **2**–**5**, **20**–**28**) or 3-bromopyridine *N*-oxide (entry **12**–**19**). The pyridine derivatives **6** and **8** were prepared from the corresponding commercially available 3 or 4-pyridine boronic acid. Oxidation using *m*-CPBA led to analogs **7** and **9**. Analog **11** was prepared by coupling the boronic acid **43** (Scheme 2) with **30** followed by oxidation. The imidazolo-pyridine **10** was prepared by coupling the N-SEM protected 5 bromo imidazolo pyridine with the pinacole boronate 31. The series of compounds bearing an acid residue was obtained by saponification of the corresponding ester (NaOH 1 N/THF/MeOH at 50 °C for methyl and ethyl esters and TFA for *tert*-butyl esters).

Table 4. Best overall 8-biarylquinolines

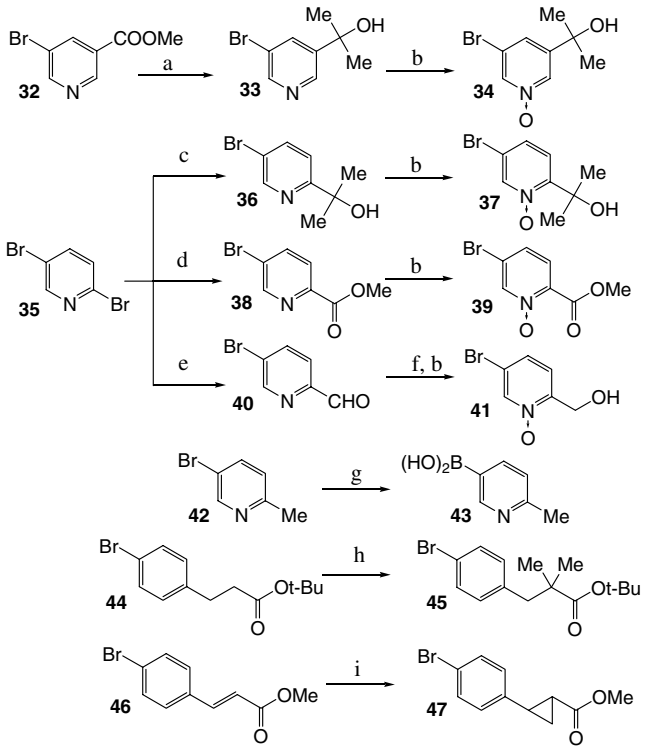


Entry	SqM C_{max}[a] (μM) @ dose (mpk)	SqM WB IC_{50} (μM)	Ratio C_{max}/IC_{50}[b]	Guinea pig % @ μg/kg[c]
1	3.8 @ 10	0.011	345	53 ± 11 @ 30 (n = 4)
14	41 @ 3	0.070	585	69 ± 11 @ 100 (n = 4)
28	65 @ 10	0.034	1911	62 ± 15 @ 30 (n = 8)

[a] Squirrel monkey plasma concentration at which emesis was observed in at least two animals.
[b] Ratio of SqM plasma concentration at which emesis was observed over SqM whole blood IC_{50}.
[c] % of inhibition of ovalbumin-induced bronchoconstriction following intra-peritoneal injection.



Scheme 1. Reagents and conditions: (a) $Pd(OAc)_2/PPh_3$ (1/3), Na_2CO_3, *n*-propanol, 80 °C; (b) Pd $Cl_2(dppf)_2$, KOAc, pinacolato diboron, DMF, 70 °C; (c) *m*-CPBA, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) MeMgBr, Et_2O, −30 °C; (b) *m*-CPBA, CH_2Cl_2, rt; (c) i—*n*-BuLi, Tol, −78 °C; ii—acetone, rt; (d) i—*n*-BuLi, Tol, −78 °C; ii—CO_2, rt; iii—CH_2N_2; (e) i—*n*-BuLi, Tol, −78 °C; ii—DMF, rt; (f) $NaBH_4$, MeOH, rt; (g) i—*n*-BuLi, THF, −78 °C; ii—B(*O*-isopropyl)$_3$, −78 °C–rt; iii—HCl; (h) i—*n*-BuLi, cyclohexyl-isopropylamine, THF, −78 °C; ii—add **44**, −78 °C; iii—MeI, −78 °C–rt. Repeat three step sequence twice; (i) $Pd(OAc)_2$, THF, rt then add CH_2N_2 portionwise until completion.

The substituted phenyl and pyridinyl building blocks were commercially available or prepared according to the procedures described in Scheme 2. The *N*-oxide **34** was prepared in two steps by first converting methyl 5-bromonicotinate to the corresponding tertiary alcohol **33** by addition of an excess of MeMgBr followed by oxidation using *m*-CPBA. The analogous *N*-oxide **37** was prepared in two steps. Selective lithium halogen exchange at position 2 of 2,5-dibromopyridine using *n*-BuLi at −78 °C in toluene, followed by addition of acetone, led to the tertiary alcohol **36** which was oxidized to the corresponding *N*-oxide **37** as described before. Similarly, the ester **38** and the aldehyde **40** were prepared by quenching the 2-lithio pyridine, respectively, with CO_2 (followed by CH_2N_2) and DMF. The latter was reduced to the hydroxyl methyl by the action of $NaBH_4$ in methanol, prior to the oxidation step to afford **41**. When applicable, an aryl bromide or a bromopyridine was converted to the corresponding boronic acid by treatment with *n*-BuLi at −78 °C followed by the addition of tri-isopropylboronate and subsequent hydrolysis to the boronic acid (i.e., **43**) using HCl 1 N. The *geminal*-dimethyl *tert*-butylester **45** was synthesized by deprotonation using the sterically hindered base cyclohexyl isopropylamine/*n*-BuLi followed by addition of iodomethane. The reaction had to be run twice to give the desired dimethylated analog **46**. Attempts to use a large excess of base and MeI to generate in one step the desired material only lead to a mixture of mono- and disubstituted analogs. The *trans*-cyclopropyl ester **47** was prepared from the analogous cinnamate **46** using a catalytic amount of $Pd(OAc)_2$ to activate the olefin followed by the addition of diazomethane in excess.

All other building blocks were easily prepared in one step by amide bond formation from commercially available acids. The intermediate urea leading to **16** was prepared from 5-bromo 2-aminopyridine and *iso*-propyl isocyanate.

To establish the full potential of the optimized 8-biarylquinoline as novel therapeutic agent for the treatment of inflammatory-related respiratory diseases, the pyridine *N*-oxide **14** and the cyclopropane carboxylic acid **28** were evaluated in the conscious guinea pig (GP) model. Their relative susceptibility to produce an emetic response was estimated by performing pharmacokinetic studies in squirrel monkeys (Table 4). In general, whole blood IC_{50}'s in squirrel monkeys (SqM) are significantly lower than in human whole blood as exemplified in Table 4. Following oral dosing of the *N*-oxide **14** in squirrel monkeys at 3 mpk, an emetic response was observed shortly after dosing (15 min) at an average plasma concentration of 41 μM or 585-fold over its IC_{50} in SqM whole blood. The *N*-oxide **14** was also able to reverse by 53% the ovalbumin-induced bronchoconstriction in guinea pigs following a 100 μg/kg intra-peritoneal administration (ip). The cyclopropane carboxylic acid **28** proved to be a superior PDE4 inhibitor in regard to its therapeutic index. Not only did it show a greater ratio of plasma concentration at which emesis was observed over the whole blood IC_{50} in SqM. (65/0.034 = 1911) but it was also found to be more efficacious in our GP model resulting in 62% inhibition of ovalbumin-induced bronchoconstriction at a dose of 30 μg/kg ip.

In conclusion, we were able to identify two compounds in distinct series that addressed the liabilities associated with L-454560 (**1**). Both **14** and **28** were found to be less emetic in squirrel monkeys than **1** and the acid **28** exhibited superior efficacy in the guinea pig model of bronchoconstriction.

Acknowledgments

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14. A manuscript describing in detail this metabolism driven degradation of unsubstituted phenyl propionic acid derivatives will be submitted shortly.