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Discovery of a substituted 8-arylquinoline series of PDE4 inhibitors: Structure–activity relationship, optimization, and identification of a highly potent, well tolerated, PDE4 inhibitor

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Abstract—The discovery and SAR of a new series of substituted 8-arylquinoline PDE4 inhibitors are herein described. This work has led to the identification of several compounds with excellent in vitro and in vivo profiles, including a good therapeutic window of emesis to efficacy in several animal models. Typical optimized compounds from this series are potent inhibitors of PDE4 ($IC_{50} < 1$ nM) and also of LPS-induced TNF-α release in human whole blood ($IC_{50} < 0.5$ μM). The same compounds are potent inhibitors of ovalbumin-induced bronchoconstriction in conscious guinea pigs ($EC_{50} < 0.1$ mg/kg ip) but require a dose of about 10 mg/kg po in the squirrel monkey to produce an emetic response. From this series of compounds, **23a** (L-454,560) was identified as an optimized compound.

Type 4 phosphodiesterases, encoded by 4 genes (A to D), are a family of cAMP-specific hydrolases responsible for the degradation of cAMP in many cell types.[1] Inhibition of this enzyme can significantly increase the intracellular c-AMP concentration, leading to various signaling events including the inhibition of various cytokines.[1c] For example, LPS-stimulated TNF-α release in human blood mononuclear cells can be blocked with PDE4 inhibitors.[2] Antigen-induced bronchospasm is another pharmacological event that can be attenuated using PDE4 inhibitors.[3] Because airway inflammation and bronchoconstriction are major hallmarks of asthma and COPD, PDE4 is a promising therapeutic target for these common and serious diseases. One of the major issues with the development of PDE4 inhibitors has been the side effect of emesis observed for several prototypical compounds.[4] However, it has become clear that some PDE4 inhibitors are less emetic than others, while possessing the same potency.[4,5] That is, some PDE4 inhibitors have a larger therapeutic window than others. For several years, efforts to improve the therapeutic window of PDE4 inhibitors have involved the identification of compounds that appeared to be more potent for inhibiting the enzyme activity and less potent on the high affinity rolipram-binding site of the enzyme.[1] More recently, however, it has been shown that the high affinity rolipram-binding site of the enzyme is simply the cofactor (e.g., Mg^{2+}) bound active site on the holoenzyme (active form of the enzyme). The conformational difference between the PDE4 apoenzyme and the holoenzyme is responsible for the differential binding of inhibitors.[5d,e] Other efforts have been directed toward the identification of isozyme-selective compounds.[1a] Finally, another approach which we have used was to identify a highly emetic and efficacious photoaffinity

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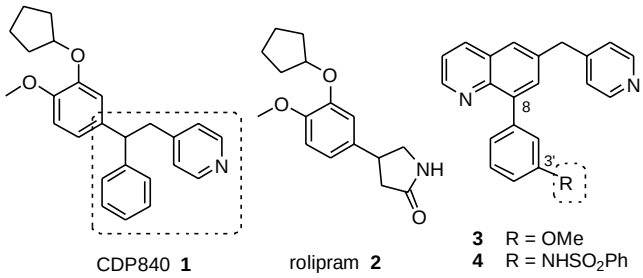


Figure 1.

probe aimed at identifying the molecular targets of emesis and efficacy for PDE4 inhibitors.[8]

Our medicinal chemistry objective was to identify a new structural class of PDE4 inhibitors with a lower potential to induce emesis at a dose well above that required for efficacy in animal models. Examples of compounds that meet these criteria are the clinical candidates ariflo,[5c] CDP-840 **1**,[5a,b] and roflumilast.[5g] These compounds are structural analogs of the prototypical compound rolipram **2**, which induces emesis at roughly the same dose that is required for efficacy.[4] In the process of our work toward identifying an emetic probe,[8] we discovered that introduction of a large substituent at the 3′-position of an 8-arylquinoline derivative led to compounds with an improved emetic threshold in the ferret, while maintaining similar potency. For example, **3**[6] and **4**[8,9] (Fig. 1 and Tables 1 and 3) have similar HWBA IC_{50}s (8.3 and 7.8 μM, respectively). The emetic threshold for **3** in the ferret is 1.0 mpk po (C_{max} = 0.2 μM), while **4** is non-emetic up to 10 mpk po (C_{max} = 2.0 μM).

These observations led us to create a new structural class by incorporating the structural features from CDP-840, which are different from those of rolipram, into the 3′-position of the 8-arylquinoline (dashed boxes in Fig. 1). The resulting hybrid compounds **5** and **6** (Fig. 2) were found to be potent PDE4 inhibitors (Table 1). Herein, we describe our medicinal chemistry efforts on the new structural class which led to compounds with higher potency and improved pharmacokinetics. The optimized compounds allowed us to show that the new structural class has a therapeutic window similar to that of other PDE4 inhibitors that are considered to have a low emetic potential.

The 8-bromoquinoline core **7** was prepared by condensing either a 4-isopropyl or a methyl-substituted-2-bromoaniline with glycerol (Scheme 1).[6] The 6-methyl-8-bromoquinoline **7a** was further functionalized on the methyl group by radical bromination followed by displacement with either cyanide or methanesulfinate to give **8a** and **b**. Methyl groups were then introduced by activation of the

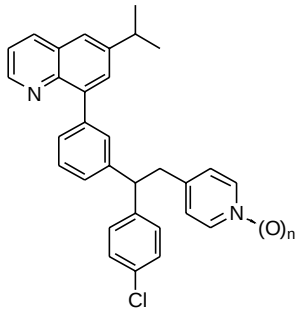
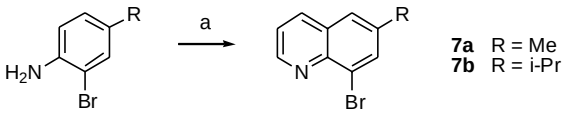


Figure 2. Hybrid molecule created by substitution of the arylquinoline with the substituent from the catechol that leads to a non-emetic catechol.

Table 1. Enzyme and human whole blood assay potency

Compound	IC_{50} (nM)[a]				
	PDE4A	PDE4B	PDE4C	PDE4D	HWBA
CDP 840 **1**	2.1 ± 0.8	1.4 ± 0.8	4.5 ± 3.3	2.1 ± 0.9	14 ± 8
L-869,298	0.4 ± 0.2	0.4 ± 0.2	1.0 ± 3.3	0.4 ± 0.1	0.09 ± 0.02
3	1.5 ± 0.4	2.3 ± 0.2	3.3 ± 3.0	2.5 ± 4.0	8.3 ± 1.0
4	5.6 ± 3.2	3.0 ± 1.0	11.9 ± 5.8	2.0 ± 1.0	7.8 ± 3.0
5	11.8 ± 6.9	6.4 ± 3.0	22 ± 23	38 ± 35	31 ± 25
6	52 ± 45	19 ± 17	68 ± 68	45 ± 32	11 ± 3
12	3.4 ± 1.5	1.8 ± 0.9	106 ± 153	4.4 ± 4.2	12 ± 6
15	0.5 ± 0.1	0.3 ± 0.1	5.7 ± 0.3	0.6 ± 0.1	1.2 ± 0.3
16	0.47 ± 0.01	0.3 ± 0.2	0.7 ± 0.1	0.19 ± 0.02	0.12 ± 0.06
17	0.2 ± 0.1	0.2 ± 0.1	0.4 ± 0.1	0.2 ± 0.1	0.12 ± 0.05
18	0.4 ± 0.1	0.3 ± 0.2	0.5 ± 0.2	0.5 ± 0.1	0.61 ± 0.27
19	0.16 ± 0.04	0.07 ± 0.01	1.2 ± 0.2	0.2 ± 0.1	0.26 ± 0.07
20	0.3 ± 0.1	0.3 ± 0.1	3.8 ± 0.7	0.5 ± 0.1	1.6 ± 0.7
21	0.3 ± 0.3	0.3 ± 0.4	2.9 ± 3.5	0.6 ± 0.9	0.14 ± 0.06
22a	0.8 ± 0.4	0.3 ± 0.1	6.8 ± 4.6	0.7 ± 0.3	0.07 ± 0.07
22b	1.0 ± 0.5	0.4 ± 0.1	11.4 ± 1.4	0.5 ± 0.1	0.21 ± 0.12
23a	1.4 ± 1.2	0.5 ± 0.3	9.1 ± 2.2	1.2 ± 0.6	0.16 ± 0.14
23b	4.8 ± 7.8	1.1 ± 1.4	14 ± 17	1.9 ± 1.7	0.20 ± 0.14
24	0.9 ± 0.3	0.5 ± 0.1	14 ± 7	2.3 ± 1.7	0.93 ± 0.42
25	1.7 ± 1.8	1.1 ± 1.1	11 ± 7	2.0 ± 1.0	0.21 ± 0.08

[a] Values are means of at least two experiments, ±standard error.

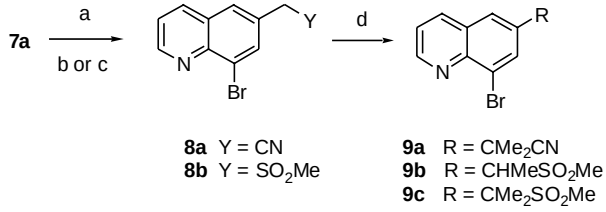


Scheme 1. Quinoline synthesis. Reagents and conditions: (a) glycerol, sodium 3-nitrobenzenesulfonate, iron(II) sulfate heptahydrate, methanesulfonic acid, 130 °C.

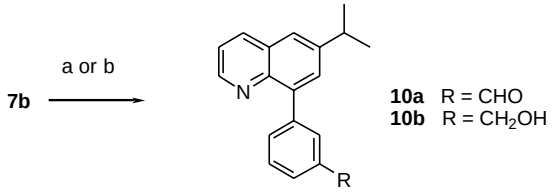
methylene with potassium *t*-butoxide followed by alkylation with iodomethane to give **9a**–**c** (Scheme 2). The 8-aryl substituent was introduced by the Pd-catalyzed cross-coupling of either a commercially available aryl boronic acid (Scheme 3), followed by further functionalization, or a boronate pinacol ester of a functionalized aryl (Scheme 10).

The saturated compounds **5** and **6** were prepared from aldehyde**10a** (Scheme 4). Addition of 4-chlorophenyl magnesium bromide was followed by conversion of the resulting alcohol to the corresponding benzyl chloride **11** using thionyl chloride. Coupling with ethyl pyridin-4-yl-acetate anion was followed by hydrolysis and decarboxylation to give the pyridine **5**. Oxidation of the pyridine with *m*CPBA afforded the pyridine-*N*-oxide **6**.

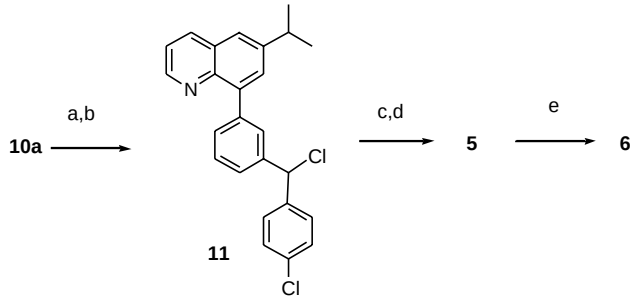
Compound **12** was prepared as in Scheme 5. Coupling of 3-bromobenzyl bromide with ethyl pyridin-4-yl acetate **13** anion was followed by conversion to the boronate pinacol ester **14**. Pd-catalyzed coupling of **14** with the 8-bromoquinoline **7b** followed by conversion of the ester to the tertiary alcohol with methylmagnesium bromide afforded compound **12**.



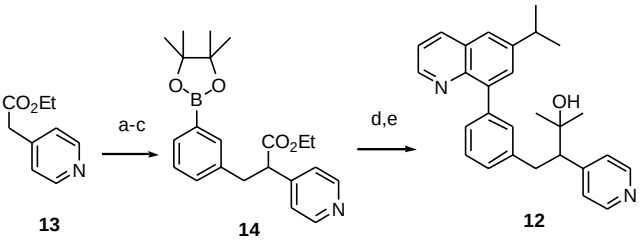
Scheme 2. Functionalization at the 6-position. Reagents and conditions: (a) NBS, AIBN, chlorobenzene, 70 °C; (b) KCN, DMF/water (2:1), 100 °C; (c) sodium methanesulfinate, DMF, 25 °C; (d) potassium *t*-butoxide, MeI, −78 to 25 °C.



Scheme 3. 8-Aryl coupling. Reagents and conditions: (a) (3-formylphenyl)boronic acid, $Pd(Ph_3P)_4$, Na_2CO_3 (aq, 2 N), DMF, 80 °C; (b) 3-(hydroxymethyl)phenylboronic acid, $Pd(Ph_3P)_4$, $NaHCO_3$ (aq, 2 N), DME, 80 °C.



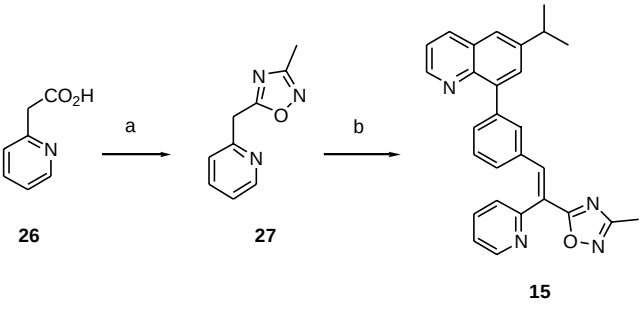
Scheme 4. Synthesis of hybrid compounds **5**–**6**. Reagents and conditions: (a) 4-chlorophenyl magnesium bromide, THF/DCM, 0 °C; (b) $SOCl_2$, DIEA, benzene; (c) ethyl pyridin-4-yl-acetate, HMPA, THF, NaHMDS; (d) NaOH; (e) *m*CPBA, DCM.



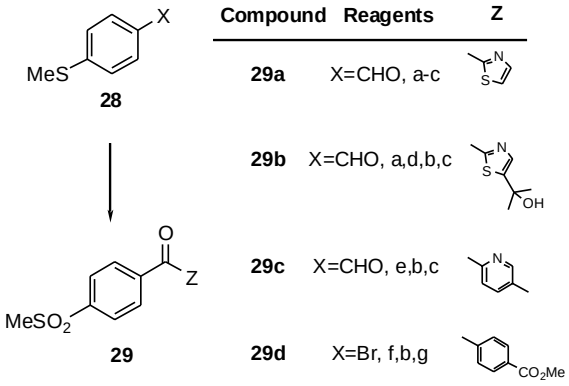
Scheme 5. Synthesis of compound **12**. Reagents and conditions: (a) HMPA, THF, NaHMDS; (b) 3-bromobenzyl bromide; (c) pinacol diborane, $Pd(dppf)Cl_2$, KOAc, DMF, 80 °C; (d) **7b**, Na_2CO_3 (aq, 2N), $Pd(dppf)Cl_2$, DMF, 80 °C; (e) MeMgBr, THF.

The unsaturated compounds (**15**–**25**) were prepared as described in Schemes 6, 8, and 10.

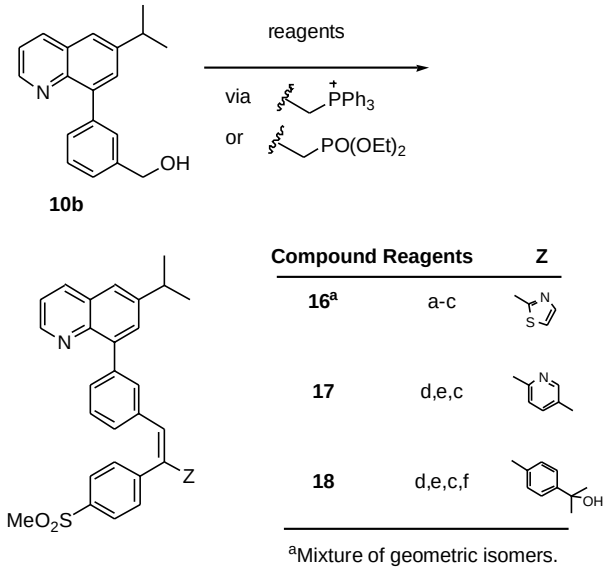
Compound **15** was prepared by converting pyridin-2-yl acetic acid **26** to the methyl oxadiazole **27** followed by a Knoevenagal condensation with the aldehyde **10a** (Scheme 6). Compounds **16**–**18** were prepared by elaboration of the required bis-aryl ketones **29** from **28** (Scheme 7), which were then condensed with the appropriate benzyl phosphorous reagent (Scheme 8). In the case of compound **18**, the tertiary alcohol was introduced by adding methylmagnesium bromide to the ester in the last step. Compounds **19**–**25** were prepared by elaboration of the functionalized boronate esters **30** (Scheme 9) followed by Pd-catalyzed coupling with the respective 8-bromoquinoline **7b** or **9** (Scheme 10).



Scheme 6. Synthesis of compound **15**. Reagents and conditions: (a) EDCI, acetamide oxime, DME, 50 °C; (b) **10a**, piperidine, toluene, reflux.



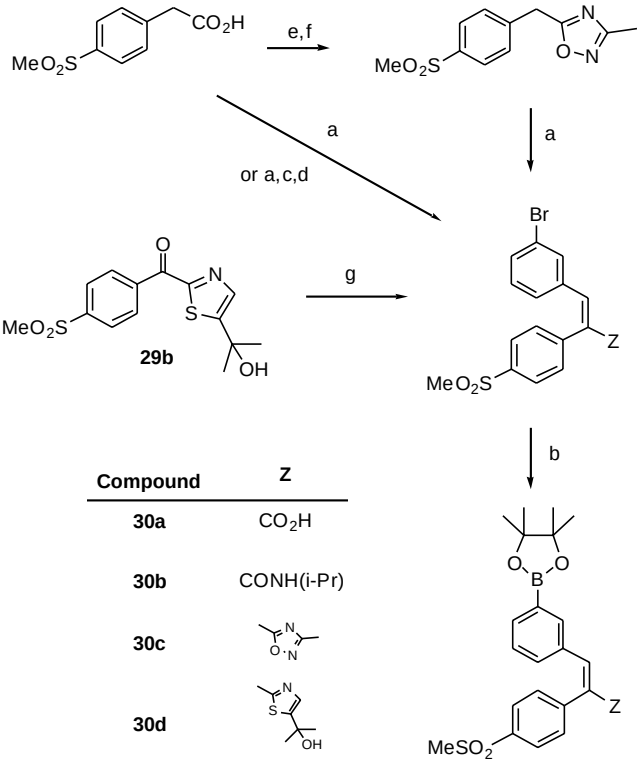
Scheme 7. Synthesis of ketones **29**. Reagents and conditions: (a) *n*-BuLi, thiazole, THF, −78 °C; (b) MnO_2, ethyl acetate, 25 °C-reflux; (c) Oxone, THF/MeOH/H_2O 2:1:1, 25 °C; (d) *n*-BuLi, acetone, THF, 25 °C; (e) *n*-BuLi, 2-bromo-5-methylpyridine, THF, −78 to 25 °C; (f) *n*-BuLi, 4-carboxymethylbenzaldehyde, THF, −78 to 25 °C; (g) *m*CPBA, $CHCl_3$, 25 °C.



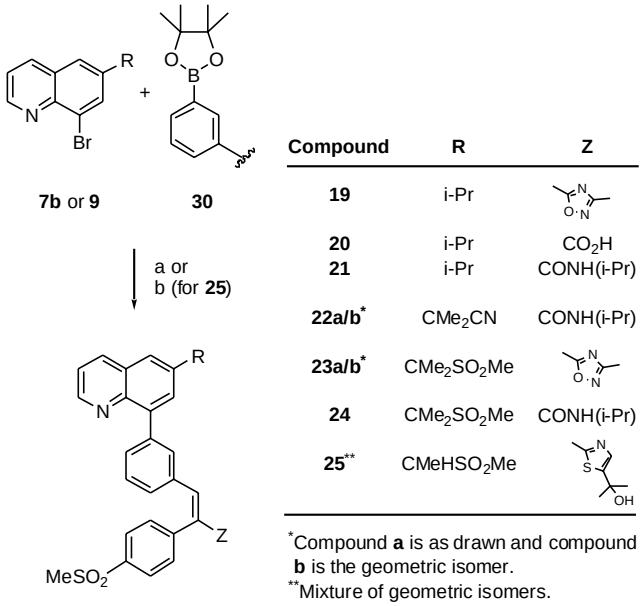
Scheme 8. Synthesis of compounds **16**–**18**. Reagents and conditions: (a) AcOH, 48% HBr, 100 °C; (b) Ph_3P, MeCN, 60 °C; (c)**29**, *t*-BuOK, THF, −78 to 25 °C; (d) MsCl, TEA, DCM, −78 °C; (e) diethylphosphite, potassium *t*-butoxide, THF, −78 to 25 °C; (f) MeMgCl, THF, 25 °C.

The compounds were evaluated for their inhibitory potency on the PDE4A, B, C, and D enzymes,[1c,5d] and also on LPS-induced TNF-α formation in human whole blood (Table 1).[2] For comparison, the data for CDP-840 and L-869,298[5j] are included.

Structure–activity relationship (SAR) studies on the hybrid compounds led to the conclusion that the 4-chlorophenyl moiety of **5** or **6** was not necessary for activity and small polar groups, such as a hydroxyalkyl, α to the pyridine, lead to improved potency (Fig. 3). This is illustrated by comparing compounds **12** and **5** in Table 1 (3.4 and 11.8 nM, respectively, on PDE4A).



Scheme 9. Synthesis of boronate esters **30**. Reagents and conditions: (a) 3-bromobenzaldehyde, piperidine, toluene, reflux; (b) diboron pinacol ester, Pd(dppf)Cl_2, KOAc, DMF, 80 °C; (c) $SOCl_2$, TEA, toluene, 25 °C; (d) *i*-$PrNH_2$, 0 °C; (e) CDI, 25 °C; (f) acetamide oxime, 25–120 °C; (g) 3-bromobenzyltriphenyl-phosphonium bromide, THF/DMF(2:1), LiHMDS, 0 °C.



Scheme 10. Synthesis of compounds **19**–**25**. Reagents and conditions: (a) Pd(dppf)Cl_2, Na_2CO_3 (2 M, aq), DMF 80 °C; (b) $Pd(OAc)_2$, Ph_3P, Na_2CO_3 (2 M, aq), *n*-propanol, 80 °C.

The first prototypical representative in this new class, compound **12** (Table 1), has a similar PDE4 inhibitory potency, both on the purified enzyme and in the

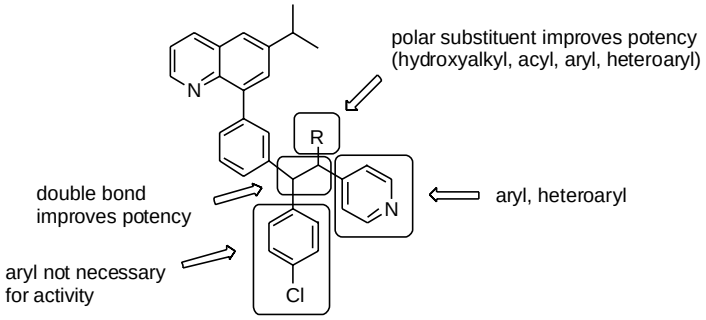


Figure 3. Structure–activity relationship of the new hybrid series.

Table 2. Pharmacokinetics of compounds in rats at 20 mg/kg po

Compound	C_{max} (μM)	T_{max} (h)	F (%)
19	0.5	0.5	11
22a	4.1	6	80
23a	5.1	6	100

Dosed po in 60% PEG/water using a dose volume of 10 mL/kg.

human whole blood assay, to that of CDP-840. The emetic threshold of **12** in the ferret is similar to that of CDP-840 (Table 3). This compound also possesses good bioavailability in the ferret (C_{max} = 2.9 μM at 10 mpk po).

Further SAR studies in the series led to the discovery of several modifications that either improve or maintain the potency. These include introduction of an unsaturated link, replacement of the pyridine with a substituted aryl or another heterocycle, and replacement of the link substituent with an acyl, aryl, or heteroaryl (Fig. 3). With the combination of all the best substituents, the potency was improved by 20- to 100-fold from the lead compounds **5** and **6** on both the purified enzyme and in the human whole blood assay (see compounds **15**–**21** in Table 1).

However, these first compounds, which were optimized for in vitro potency, were found to be metabolically unstable in vivo leading to modest oral bioavailabity. For example, compound **19** (Table 2) is extensively metabolized to give two major metabolites, which have plasma concentrations 15- to 30-fold greater than the parent compound. LCMS analysis indicated that the metabolites contain 1 and 2 hydroxyl groups on the isopropyl group. In order to prevent or reduce the metabolism, we prepared several isopropyl analogs. The best modifications were those with a nitrile or a methyl sulfone (compounds **22**–**25**). These have a similar potency to the corresponding isopropyl compounds (Table 1) but have superior pharmacokinetics in the rat with very low levels of circulating metabolites. Examples are compounds **22a** and **23a** in Table 2.

The emetic threshold of several of these compounds was evaluated in the squirrel monkey and found to be similar to that of CDP-840 **1**, even though the in vitro potency (human and squirrel monkey whole blood assays) is 20- to 200-fold greater (Tables 1 and 3). This improvement in tolerability is illustrated by the ratio of emesis threshold plasma concentration/squirrel monkey whole blood IC_{50}. The ratio is 9 for CDP-840 **1** while the hybrid

Table 3. In vivo comparative profiles of selected compounds with **CDP-840** and **L-869,298**

Compound	Guinea pig[a] (%) (mg/kg)	Sheep early(%)/late(%)[b]	Emesis C_{max}[c] (μM) (dose mg/kg, responders)	Squirrel monkey whole blood IC_{50}(μM)[d]	Ratio[e] Emesis Cmax/IC_{50}
CDP-840 **1**	54 (1)	39/88	2.5 (30, 2/6)[f], 4 (10, 1/4)[g]	0.60	9
L-869,298	62 (0.01)	68/92	1.6 (0.5, 2/4)[g]	0.005	320
3	70 (0.3)	ND	0.2 (1.0, 2/2)[f]	ND	ND
4	46 (1)	ND	>2.0 (10, 0/2)[f]	ND	ND
12	47 (1)	ND	2.9 (10, 1/2)[f], 11.9 (10, 1/2)[g]	0.45	26
22a	75 (0.03)	ND	1.9 (10, 2/4)[g]	0.015	127
23a	53 (0.03)	73/95	3.8 (10, 3/6)[g]	0.011	345
24	59 (0.1)	ND	>2.5 (3, 1/2)[g]	ND	ND

[a] Mean percent inhibition of ovalbumin-induced bronchoconstriction in conscious guinea pigs dosed ip 30 min prior to challenge (n = 4–8). See Ref. 3b. Dose (mg/kg) shown in brackets.

[b] Mean percent inhibition of early/late-phase antigen induced bronchoconstriction in Ascaris sensitive sheep (n = 2–4) dosed iv with 0.5 mg/(kg day) of test compound for 4 days and challenged 2 h post dose on day 4. See Ref. 3c. ND = not determined.

[c] See Ref. 7. In a rising dose (dose ranging study), the average maximal plasma concentration (C_{max}) is achieved after the first po dose in which emesis is observed in at least one animal in the dosing group ($n \geqslant 2$). Dose (mg/kg) and number of responders exhibiting emesis are shown in parentheses.

[d] Inhibition of LPS-induced TNFα production in squirrel monkey whole blood. This assay was performed according to Ref. 2 using squirrel monkey whole blood and employing a 4 h incubation after LPS stimulation rather than 24 h. IC_{50} represents the mean ± EM ($n \geqslant 3$).

[e] Ratio of the C_{max} plasma concentration to the IC_{50} for inhibition of LPS-induced TNFα production in squirrel monkey whole blood.

[f] Ferret.

[g] Squirrel monkey.

compounds have ratios of 26–345 (Table 3). The compounds are also well absorbed with good pharmacokinetics in the squirrel monkey. In a guinea pig functional model (ovalbumin induced bronchoconstriction), these compounds are also 10- to 100-fold more potent than CDP-840 **1** (Table 3).

In summary, a new structural class of highly potent PDE4 inhibitors has been discovered with a therapeutic window between emesis and efficacy larger than that of CDP-840 **1**. All of these compounds are non-selective for the PDE4A, B, C, and D subtypes. The compound **23a** (L-454,560:[10] PDE4A IC_{50} = 1.4 nM, human whole blood IC_{50} = 0.16 μM) was selected as a candidate for further development. Compound **23a** was well tolerated in the squirrel monkey with an emesis window of 345-fold. It was also effective in the guinea pig ovalbumin-induced bronchoconstriction model (53% at 0.03 mg/kg ip) and in the sheep ascaris-induced bronchoconstriction model (73%/95%, early/late, 0.5 mg/kg, iv). L-869,298,[5j] the most optimized analog of CDP-840, also has a biological profile similar to that of **23a**.

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