Bioorganic & Medicinal Chemistry Letters 18 (2008) 5554–5558

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Optimization and structure–activity relationship of a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides: Identification of MK-0873, a potent and effective PDE4 inhibitor

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ARTICLE INFO

Article history:
Received 10 July 2008
Revised 1 September 2008
Accepted 3 September 2008
Available online 6 September 2008

Keywords:
PDE4
Type 4 phosphodiesterase
1,8-Naphthyridin-4-one-3-carboxamides
Asthma
COPD
MK-0873

ABSTRACT

A SAR study of a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides is described. Optimization of the series was based on in vitro potency against PDE4, inhibition of the LPS-induced production of TNF-α in human whole blood and minimizing affinity for the hERG potassium channel. From these studies, compounds **18** and **20** (MK-0873) were identified as optimized PDE4 inhibitors with good overall in vitro and in vivo profiles and selected as development candidates.

Cyclic nucleotide phosphodiesterases (PDEs) constitute a large family of enzymes responsible for the hydrolysis and consequent deactivation of the secondary messengers adenosine and guanosine 3′,5′-cyclic mono-phosphates (cAMP and cGMP, respectively).[1] In humans, there are many different PDE isoforms classified into 11 families according to their substrate specificity, sequence similarity and sensitivity to endogenous or exogenous regulators.[2] Encoded by 4 genes, the cAMP specific PDE4 isozymes (A, B, C and D) are abundant in many inflammatory, immune and airway smooth muscle cells.[3] Inhibition of this enzyme significantly increases the intracellular levels of cAMP resulting in the down-regulation of inflammatory cell activity in vitro and in vivo,[2c,4] and has been found to be anti-inflammatory and bronchodilatory in animal models.[5] The development of selective PDE4 inhibitors has recently attracted much interest for the treatment of various diseases including asthma and COPD and many compounds have been reported in clinical development.[6,7]

In previous communications, we described how we optimized the lead compound CDP-840 (**1**) with respect to PDE4 inhibitory potency, metabolism issues and pharmacokinetic properties while reducing the potential to induce emesis and to significantly prolong the QTc interval in vivo.[8] This work led to the identification of L-869,298 (**2**), a potent, selective and orally active PDE4 inhibitor (Fig. 1). More recently, we reported the discovery of a new structural class of highly potent and well tolerated PDE4 inhibitors based on substituted 8-arylquinoline as exemplified by compound **3**.[9]

As part of our medicinal chemistry program, one objective was to identify yet another structural class of potent PDE4 inhibitors with a decreased potential to induce emesis or to prolong the QTc interval at doses well above that required for efficacy in animal models. Having successfully modified an emetic PDE4 inhibitor into a more elaborate 8-arylquinoline derivative **3** with a much improved therapeutic index,[9] we thought we could apply our findings relative to potency and adverse effects to a different structural series. Our search then focused on identifying a bicyclic heterocyclic core to replace the quinoline moiety. At the time, a recent publication on 1,8-naphthyridin-4-ones derivatives as PDE4 inhibitors attracted our attention.[10] Examples such as the dichloropyridyl amide **4** were reported to have good in vitro potency so we sought to explore how our modifications that were successful in the quinoline series would apply to this new core template. Herein, we describe our medicinal chemistry efforts on the naphthyridinone class of PDE4 inhibitors. The optimized compounds show efficacy and a therapeutic window similar to that of other known inhibitors considered to have low potential for adverse events.

The general method used for the preparation of 1-aryl-1,8-naphthyridin-4-one-3-carboxylate is illustrated in Scheme 1. Reaction of 2-chloronicotinoyl chloride with the dianion of monoethyl

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doi:10.1016/j.bmcl.2008.09.009

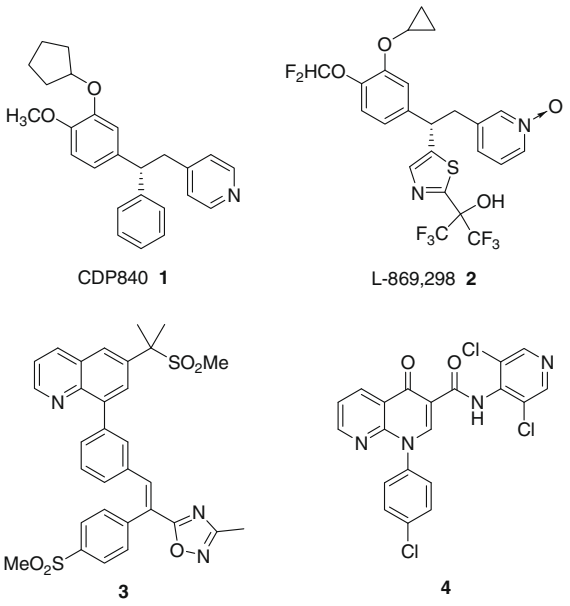
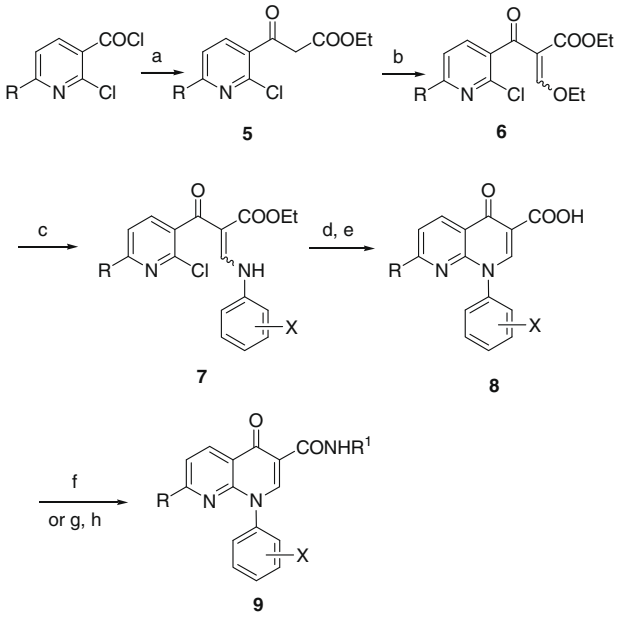
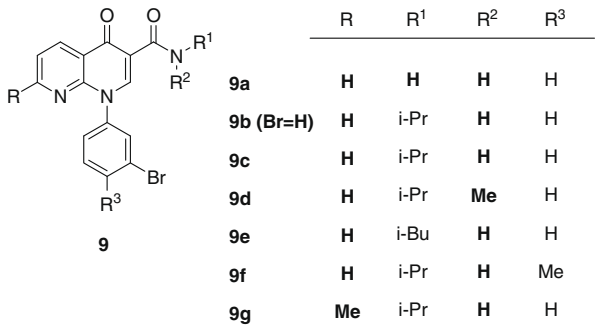


Figure 1. Recently reported PDE4 inhibitors.

malonate affords the β-ketoester **5**,[11] which is then treated with triethyl orthoformate and acetic anhydride at reflux to give the one-carbon homolog enol ether **6**.[12] Without purification, the ethoxy group is displaced with an aniline to give the corresponding enamino ketoester **7**. Cyclisation with sodium hydride in tetrahydrofuran yields the substituted ethyl 1-phenyl-1,8-naphthyridin-4-one-3-carboxylate which is subsequently hydrolyzed to the corresponding carboxylic acid **8**. Formation of amide **9** was accomplished using conventional coupling chemistry, usually via a mixed anhydride. In cases of deactivated or sterically congested amines, successful coupling required prior deprotonation of the amine with sodium hydride followed by reaction with the preformed acid chloride.

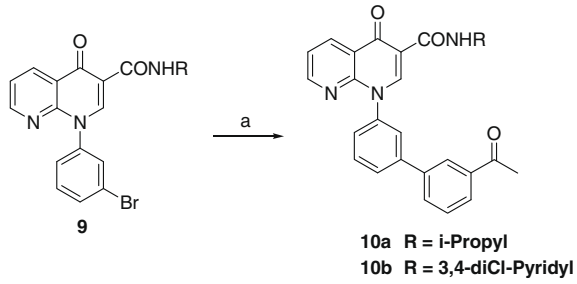


Scheme 1. Synthesis of 1,4-naphthyridin-4-one-3-carboxamide template. Reagents and conditions: (a) $CH_2(COOEt)COOH$, *n*-BuLi, THF, −70 °C to rt then HCl/H_2O; (b) $CH(OEt)_3$, Ac_2O, 130 °C; (c) (X)-$PhNH_2$, CH_2Cl_2, rt (d) NaH, THF; (e) NaOH, THF, EtOH, H_2O; (f) *i*-BuOCOCl, Et_3N, THF, 0 °C, then RNH_2, rt; (g) $SOCl_2$, THF, reflux; (h) R_1NH_2, NaH, DMF, rt for 30 min, then added to ArCOCl, rt.

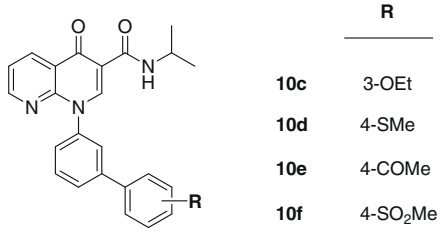


	R	R^1	R^2	R^3
9a	**H**	**H**	**H**	H
9b (Br=H)	**H**	i-Pr	**H**	H
9c	**H**	i-Pr	**H**	H
9d	**H**	i-Pr	**Me**	H
9e	**H**	i-Bu	**H**	H
9f	**H**	i-Pr	**H**	Me
9g	**Me**	i-Pr	**H**	H

Figure 2. List of 1-(3-bromo)phenyl-1,4-naphthyridin-4-one-3-carboxamides.



Scheme 2. Synthesis of compounds **10a** and **10b**. Reagents and conditions: (a) 3-$(CH_3CO)PhB(OH)_2$, 2M Na_2CO_3, Toluene, EtOH, $(Ph_3P)_2PdBr_2$ cat, reflux.



	R
10c	3-OEt
10d	4-SMe
10e	4-COMe
10f	4-SO_2Me

Figure 3. List of isopropyl 1-biphenyl-1,8-naphthyridin-4-one-3-carboxamide derivatives.

The 7-methyl derivative **9g** (Fig. 2) was prepared starting with 5-methyl-2-chloronicotinoyl chloride whereas **9d** was obtained by coupling of **8** (R = H and X = 3-Br) with *N*-isopropylmethylamine.

Biaryl derivatives such as **10a** and **10b** were prepared by coupling of the 3-acetyl phenylboronic acid derivative with the corresponding carboxamide of bromophenyl **9** (Scheme 2). Other biphenyl derivatives **10c**–**f** (Fig. 3) were prepared using similar Suzuki–Miyaura coupling reactions of **9**.

For a direct comparison with quinoline derivative **3**, we synthesized the corresponding naphthyridinone analog **13** (Table 1). The required aniline **12** was prepared starting from 3-nitrobenzaldehyde and the known oxadiazole **11** (Scheme 3).[9]

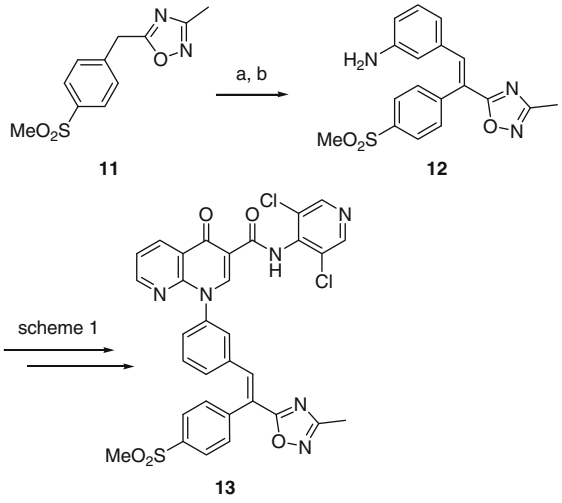
Replacement of the biphenyl moiety in **10** with a phenylpyridine was easily accomplished by Suzuki–Miyaura coupling of bromophenyl **9** with the appropriate pyridyl boronic acid (Scheme 4). Sonogashira coupling of **9** with various alkynes afforded the corresponding phenyl aryl alkynes.

In this letter, only the intrinsic inhibitory potency of compounds on PDE4A is reported. As found for other structural series, these derivatives are essentially non-selective with respect to the inhibition of the PDE4 isozymes (less than a 5-fold difference in the IC_{50} values for inhibition of PDE4A compared to PDE4B, PDE4C and PDE4D; data not shown). The functional activity of these com-

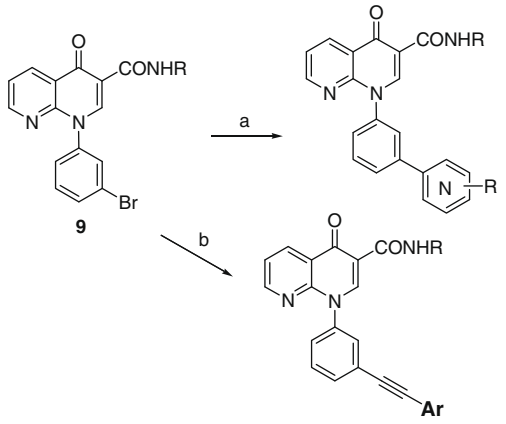
Table 1
Potency in enzyme and whole blood assays and affinity for the hERG potassium channel for compounds **3, 4, 9, 10 and 13**[a]

Compound	GST-PDE4A^{248} IC_{50}[b] (nM)	HWB IC_{50}[c] (μM)	hERG binding[d] IC_{50} (μM)
3	1.4 (±0.5)	0.16 (±0.02)	49.9
4	0.45 (±0.2)	0.18 (±0.07)	0.198 (±0.002)
13	0.06 (±0.02)	0.003 (±0.001)	0.68 (±0.08)
9[a]	141 (±9.5)	nd	>94.5
9b	15.3 (±0.6)	0.70 (±0.1)	71.5
9c	9.2 (±1.1)	0.70 (±0.1)	31.6 (±0.4)
9d	>1000	nd	nd
9e	3.54 (±0.1)	2.10 (±0.9)	31.8 (±1.7)
9f	66.5 (±9.1)	nd	nd
9g	>1000	nd	nd
10[a]	0.37 (±0.1)	0.47 (±0.08)	6.96 (±0.5)
10b	0.17 (±0.1)	0.005 (±0.001)	0.74 (±0.02)
10c	1.54 (±0.1)	0.84 (±0.2)	2.7
10d	0.75 (±0.3)	0.65 (±0.1)	0.96
10e	0.34 (±0.1)	0.075 (±0.1)	8.95 (±0.4)
10f	0.62 (±0.2)	0.069 (±0.01)	23.0 (±1)

[a] Values are single determinations or means of two or more experiments, ±standard error (nd, not determined).
[b] Assayed against the human PDE4A isoform using a construct representing the common region of spliced variants expressed as a GST-fusion protein in Sf9 cells.[15]
[c] Inhibition of LPS-induced TNF-α production in human whole blood.[4b]
[d] Displacement binding assay of [^{35}S]-radiolabeled MK-499 in membranes derived from HEK293 cells stably transfected with the hERG gene and expressing the I_{Kr} channel protein.[16]



Scheme 3. Synthesis of compound **10**. Reagents and conditions: (a) **11**, piperidine, 3-nitrobenzaldehyde; toluene, reflux; (b) $SnCl_2$, EtOH, reflux.



Scheme 4. Synthesis of pyridyl and acetylenic derivatives. Reagents and conditions: (a) pyridylboronic acid, 2M Na_2CO_3, $(Ph_3P)_2PdCl_2$ cat, EtOH, toluene, reflux; (b) HCCAr, Et_3N, CuI, $(Ph_3P)_2PdCl_2$ cat, DMF, heat.

pounds is measured by their ability to inhibit the LPS-induced production of TNF-α in human whole blood.[4b]

As we began this SAR investigation of 1-phenyl-1,8-naphthyridin-4-ones, we sought to compare this core scaffold with the quinoline template we recently reported. As indicated in Table 1, the prototypical 1,8-naphthyridinone compound **4** is 3-fold more potent intrinsically than the substituted 8-arylquinoline compound **3** against PDE4A whereas both inhibitors have equivalent functional activity in human whole blood. However, compound **4** displays very high affinity for the voltage-gated potassium (K^+) channel encoded by the human ether-a-go-go related gene (hERG). This ion channel mediates the rapidly activating component of the delayed rectifier potassium current (I_{Kr}).[13] Blockade of hERG can lead to delayed repolarisation of the ventricle and hence an increase in the electrocardiographic QT interval. Longer QT is a known risk factor for a particular polymorphic ventricular arrhythmia known as Torsade de Pointe. Recent reports show that many drugs that exhibit prolongation of the QT_c interval do so by block of the hERG K^+ channel.[14] In exploring this new series, the affinity of compounds for this channel, as measured in a radioligand displacement binding assay, was taken as an indicator for their potential for causing QT_c interval prolongation. Our goal was then to identify structural modifications of **4** that maintained or improved the inhibitory potency against PDE4 while reducing its affinity for the hERG K^+ channel.

Hoping to find a synergistic effect on potency without significant affinity for the hERG K^+ channel, we initially prepared derivative **13** combining the aryl substituted vinyl moiety of **3** with the prototypical 1,8-naphthyridinone compound **4** (Table 1). Indeed, the intrinsic potency and the functional activity of this hybrid structure are significantly improved (8-fold and 60-fold, respectively). Unfortunately, this compound still retains unacceptable affinity for the potassium channel and clearly, we needed to identify structural features key to the desired activity and selectivity profile.

The first phase of our SAR investigation involved the evaluation of simple derivatives related to **4** in order to define the optimal substitution pattern. We began by examining variations of the 3-carboxamide group and its effect on the in vitro profile. Although not a particularly potent inhibitor of PDE4, the more polar primary amide **9a** is completely devoid of affinity for the hERG K^+ channel. The preference for a secondary carboxamide is obvious when one compares with substituted amides. The isopropyl derivative **9c** exhibits a 15-fold increase in potency against PDE4 relative to **9a** with only moderate affinity for the potassium channel. In contrast, tertiary amide **9d** is at least 100 times less potent as a PDE4 inhibitor and this may illustrate the requirement for the N–H bond or may result from a steric congestion caused by the methyl group. Addition of a methylene as in the isobutyl amide **9e** results in a compound 3 times more potent than **9c**. However, this increase in potency does not translate in terms of functional activity. In fact the isobutyl amide **9e** is actually 3 times less active than the isopropyl analog **9c** in the human whole blood assay with an IC_{50} of 2.1 μM. This exemplifies the potential for protein shift associated with cellular assays with certain compounds and when factored in, would predict a decrease of in vivo efficacy.

We also investigated the effect of adding substituents directly on the 1,8-naphthyridin-4-one core but quickly realized that such modifications were not tolerated. For example, introduction of a methyl at the 7-position as in **9g** resulted in complete loss of PDE4 activity.

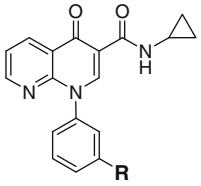
Analogous to other templates investigated such as the 8-arylquinolines, the presence of a lipophilic group on the phenyl in the *meta*-position is not only well tolerated but leads to a significant increase in potency (vide infra). On the other hand, the addition of another group at the *para*-position such as a 4-methyl group leads to 7-fold decrease of potency (**9f** vs **9c**).

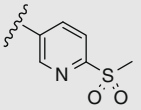
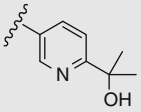
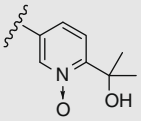
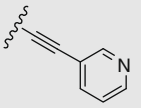
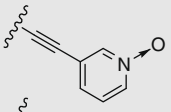
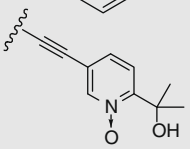
Having identified the optimal substitution pattern of the parent bicyclic template, we decided to continue our SAR and further explore the *meta*-position by preparing a number of substituted biphenyl analogs. These modifications invariably led to increased inhibitory potency against PDE4 (**10a**–**f**). For example, the biphenyl methyl ketone **10a** is intrinsically 40 times more potent than the simple phenyl analog **9b**. However, once again this improvement does not translate in the functional assay (HWB IC_{50} 0.47 vs 0.7 μM) and is accompanied by an increased affinity (10-fold) for the hERG K^+ channel. A more dramatic effect on the PDE4 potency and functional activity of these derivatives is observed when one combines lipophilic substituents on the phenyl with the non-polar carboxamide moiety found in **4**. The dichloropyridyl amide **10b** is two orders of magnitude more active than the isopropyl amide **10a** in human whole blood with an IC_{50} of 5 nM. Unfortunately, as observed with **13** (vide infra), this compound also has increased affinity in the hERG binding assay. In fact, this is a general trend observed within this series of 1,8-naphthyridin-4-one derivatives where more lipophilic compounds tend to have an increased affinity for the potassium channel (cf. **10c** and **10d**). Moving the acetyl group from the 3- to the 4-position resulted in a derivative equally potent against PDE4 but with 6-fold increased activity in human whole blood (**10a** vs **10e**). Changing this methyl ketone for a methyl sulfone (**10f**) maintained very good functional activity (IC_{50} = 69 nM) while significantly reducing the compounds' affinity for the hERG K^+ channel.

Encouraged by this result, we wished to further increase the polarity of the biaryl moiety by introducing substituted heterocycles such as pyridines. An added benefit to this modification would be the possibility of salt formation in order to increase the solubility of the compounds. For the next phase of our SAR, we elected to slightly modify the parent scaffold and replace the 3-isopropyl carboxamide with a cyclopropyl analog for increased metabolic stability. The rationale for this change was the observation that the isopropyl amide suffered from oxidative metabolism (α-hydroxylation) and hydrolysis to the primary amide in vitro and in vivo in rats, resulting in poor pharmacokinetics. This metabolic pathway was greatly reduced with the cyclopropylamide moiety and significantly improved the half-life of the compounds.

Incorporation of a phenyl-pyridine motif resulted in compounds with low affinity for the potassium channel; the 3-pyridyl isomer **15** being 4-fold more potent in the functional assay than the 4-pyridyl analog **14** (Table 2). Addition of a variety of substituents such as a methyl sulfone (**16)** maintained the activity and selectivity profile. A significant improvement was noticed with the dimethyl carbinol derivative **17** as this PDE4 inhibitor has an IC_{50} of 66 nM in human whole blood and exhibits low affinity for the hERG K^+ channel (IC_{50} = 37 μM). Unfortunately, this compound suffered from a very short half-life ($T_{1/2}$ < 30 min) when dosed in rats. When we prepared its corresponding pyridine *N*-oxide **18**, we were pleased to find that this analog is only 2-fold less potent than the parent pyridine. In fact, **18** is the major metabolite of **17** observed in vivo and this pyridine *N*-oxide has a better pharmacokinetic profile with good exposure and longer half-lives (vide infra). In addition, **18** has even less affinity for the hERG K^+ channel than the parent pyridine **17**. Further expanding the scope of this SAR, we also introduced an acetylenic spacer in the biaryl moiety to give alkyne pyridine derivatives (cf. **19**–**21**). This modification maintained good inhibitory potency in the human whole blood assay (cf. **15** vs **19** and **18** vs **21**). Again, the pyridine *N*-oxide is equipotent to the parent pyridine but exhibits less affinity for the potassium channel (**19** vs **20**).

Table 2
Potency and binding affinity to the hERG potassium channel for pyridine derivatives **14–21**



Compound	R	HWB IC_{50} (μM)	hERG binding IC_{50} (μM)
14		0.67 ± 0.16	18.6 ± 2.1
15		0.16 ± 0.06	34.0 ± 4.0
16		0.14 ± 0.04	13.6 ± 2.1
17		0.066 ± 0.01	36.6 ± 7.8
18		0.12 ± 0.02	50.1 ± 1.8
19		0.16 ± 0.02	16.7 ± 2.8
20		0.18 ± 0.03	65.7 ± 17
21		0.30 ± 0.08	89.4 ± 5.6

Based on these results and on preliminary pharmacokinetic data, we selected pyridine *N*-oxides **18** and **20** for further evaluation. Their comparative in vitro profiles along with that of previous candidate **3** are listed in Table 3. All three compounds have similar intrinsic potency against PDE4 and good functional activity in human and squirrel monkey whole blood.

While these three compounds are neither inhibitors nor inducers of the ubiquitous cytochrome P450 3A4 enzyme, we found that **18** and **20** are much less potent at inhibiting the 2C9 isozymes than **3**. Both derivatives **18** and **20** are very well absorbed in rats and dogs resulting in excellent bioavailability (87–100%). Their half-lives of 1.5–2 h are slightly shorter compared to **3**. In squirrel monkey, the pharmacokinetic profiles are nearly identical for all three compounds.

The emetic thresholds of these compounds were evaluated in squirrel monkey by measuring the peak plasma concentration following an oral dose causing emesis. Similar to **3**, we found **18** and

Table 3
In vitro and in vivo profiles of **3, 18 and 20**

	3	18	20
GST-PDE4A^{248} (IC_{50}, nM)	1.4	6.2	6.7
Whole blood TNF-α (IC_{50}, nM)			
Human	161	123	178
Squirrel monkey	11	7	23
hERG binding (IC_{50}, μM)	50	50	66
CYP450 2C9 inhibition (IC_{50}, μM)	⩽1.0	59	41
Pharmacokinetics[a]—$T_{1/2}$ (F)			
Rat	4 h (95%)	1.5 h (87%)	2 h (98%)
Dog	5 h (55%)	2 h (100%)	2 h (100%)
Squirrel monkey	4 h (33%)	4 h (33%)	5 h (38%)
Emesis[b] C_{max} (μM)	3.0	3.7	5.1
Dose (mg/kg)	10	2	2
Ratio (C_{max}/IC_{50})	270	530	220
Guinea pig[c] (% inhibition)	53	69	65
Sheep[d] (%inhibition)	92	84	84

[a] Half-life ($T_{1/2}$) and bioavailability (F) determined following po and iv administration of test compound.
[b] In a dose ranging study (rising dose po), the maximal drug plasma level measured after the first episode of emesis in at least one animal ($n > 2$). See Ref. 17.
[c] Mean % inhibition of the ovalbumin-induced bronchoconstriction in conscious guinea pigs dosed 0.03 mg/kg ip 30 min prior to challenge ($n > 5$). See Ref. 5d.
[d] Mean % inhibition of the late-phase Ascaris-induced bronchoconstriction in sheep dosed iv with 0.5 mg/(kg day) for 4 days and challenged 2 h post dose on day 4. See Ref. 18.

20 to have a low potential for causing emesis at therapeutic doses as estimated by the high ratio of the emetic threshold C_{max} over the IC_{50} for inhibition of TNF-α in squirrel monkey whole blood (Table 3).

Finally, we evaluated the in vivo efficacy of these 1,8-naphthyridinone derivatives in two models of asthma. Intraperitoneal administration of either **18** or **20** produced potent and dose-dependent inhibition of the ovalbumin-induced bronchoconstriction in sensitized guinea pigs. Similarly, both compounds protected against the late-phase bronchoconstrictor response to antigen challenge in Ascaris-sensitive sheep following intravenous administration. Based on these overall profiles, **18** and **20** were selected for further evaluation and considered as potential candidates for development. Ultimately, compound **20** was chosen for clinical development and identified as MK-0873. Results from phase I studies are reported elsewhere.[19]

In summary, we have identified a series of 1-phenyl-1,8-naphthyridin-4-one-3-carboxamides as potent PDE4 inhibitors. A number of these compounds display reduced affinity for the hERG K^+ channel and have low potential to prolong the QTc interval. Two of these derivatives, **18** and **20,** have good pharmacokinetic profiles and were found to have low potential for causing emesis at therapeutic doses. This work led to the identification of MK-0873 for clinical development as a potential new therapeutic agent for chronic obstructive pulmonary disease and asthma.

References and notes

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