Substituted (Pyridylmethoxy)naphthalenes as Potent and Orally Active 5-Lipoxygenase Inhibitors: Synthesis, Biological Profile, and Pharmacokinetics of L-739,010

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Received January 21, 1997[⊗]

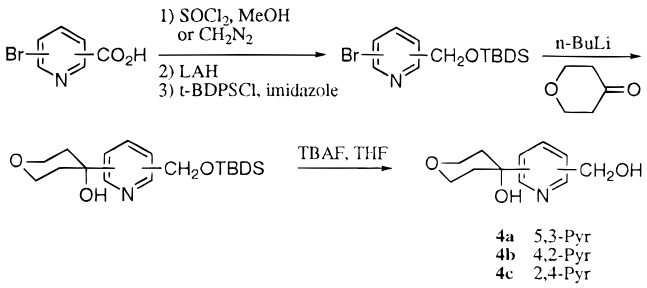
Dioxabicyclooctanyl naphthalenenitriles have been reported as a class of potent and nonredox 5-lipoxygenase (5-LO) inhibitors. These bicyclo derivatives were shown to be metabolically more stable than their tetrahydropyranyl counterparts but were not well orally absorbed. Replacement of the phenyl ring in the naphthalenenitrile **1** by a pyridine ring leads to the potent and orally absorbed inhibitor **3g** (L-739,010, 2-cyano-4-(3-furyl)-7-[[6-[3-(3-hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]-2-pyridyl]methoxy]naphthalene). Compound **3g** inhibits 5-HPETE production by human 5-LO and LTB_4 biosynthesis by human PMN leukocytes and human whole blood (IC_{50}s of 20, 1.6, and 42 nM, respectively). Derivative **3g** is orally active in the rat pleurisy model (inhibition of LTB_4, ED_{50} = 0.3 mg/kg) and in the anesthetized dog model (inhibition of *ex vivo* whole blood LTB_4 and urinary LTE_4, ED_{50} = 0.45 and 0.23 μg/kg/min, respectively, iv infusion). In addition, **3g** shows excellent functional activity against ovalbumin-induced dyspnea in rats (60% inhibition at 0.5 mg/kg, 4 h pretreatment) and Ascaris-induced bronchoconstriction in conscious sheep (50% and >85% inhibition in early and late phases, respectively at 2.5 μg/kg/min, iv infusion) and, more particularly in the conscious antigen sensitive squirrel monkey model (53% inhibition of the increase in R_L and 76% in the decrease of C_{dyn}, at 0.1 mg/kg, po). In rats and dogs, **3g** presents excellent pharmacokinetics (estimated half-lives of 5 and 16 h, respectively) and bioavailabilities (26% and 73% when dosed as its hydrochloride salt at doses of 20 and 10 mg/kg, respectively, in methocel suspension). Based on its overall biological profile, compound **3g** has been selected for preclinical animal toxicity studies.

Introduction

Leukotrienes are derived from the biotransformation of arachidonic acid through the action of 5-lipoxygenase (5-LO) and are postulated to be implicated in a variety of disorders.[1] Furthermore, it has been recently demonstrated that inhibitors of leukotriene (LT) biosynthesis[2] (by either 5-LO or 5-lipoxygenase-activating protein (FLAP)) or LTD_4 receptor antagonists[3] possess clinical efficacy in the treatment of asthma.

We have previously reported a novel class of selective and nonredox 5-lipoxygenase inhibitors, the naphthalenic lignan lactones.[4] These compounds were shown to be bioavailable and orally active when the open forms of the lactones were used as prodrugs. More recently we have described the structure−activity relationship (SAR) study performed on this series especially directed toward the improvement of the metabolic stability as well as the optimization of the *in vitro* potency.[5] From this SAR study a new class of highly potent and metabolically more stable inhibitors was identified, the dioxabicyclooctanyl naphthalenenitriles. One of the best representatives of this series is (1*S*,5*R*)-3-cyano-1-(3-furyl)-6-[[3-[3-(3-hydroxy-6,8-dioxabicyclo[3.2.1]-octanyl)]benzyl]oxy]naphthalene (**1**, L-708,780) which exhibits an excellent *in vitro* inhibitory profile. In addition, compound **1** was shown to be orally active in animal models of asthma and inflammation. However, the replacement of the lactone moiety of the lignan series by a cyano group to prevent the metabolism at this specific site resulted in very lipophilic derivatives that were generally shown to be poorly or not absorbed.

Scheme 1



In this paper, we describe the continuation of the SAR investigation with particular emphasis on modifications to improve the bioavailability of derivatives from this series. The strategy explored has involved the replacement of the middle phenyl ring by nitrogen-containing heterocycles. Thus, a series of compounds were prepared leading to the identification of the pyridine derivative **3g** (L-739,010) which presents an improved

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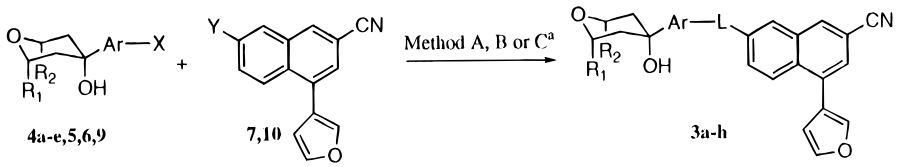
[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

S0022-2623(97)00046-0 CCC: $14.00

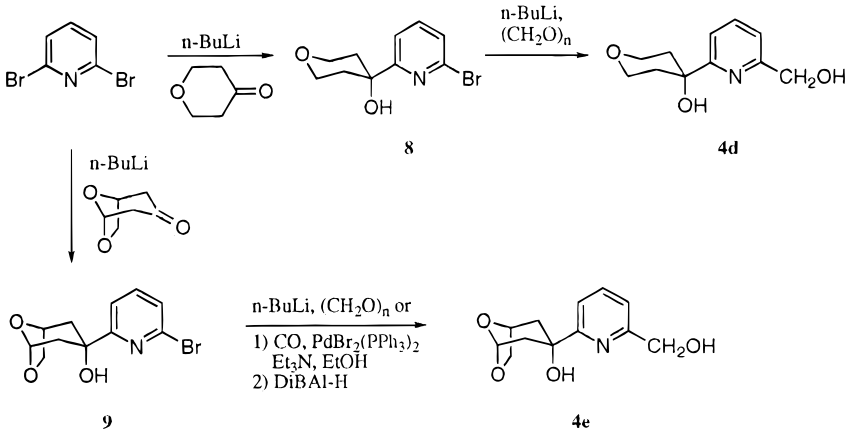
Table 1. Physical and Synthetic Data for Naphthalenes **3a**−**h**



compd			R_1	R_2	Ar	X	Y	L	method[a]	formula	anal.[b]	mp (°C)	yield (%)[c]
3a	**4a**	**7**	H	H	5,3-Pyr	CH_2OH	OH	CH_2O	A	$C_{26}H_{22}N_2O_4$	C,H,N	176−178	57
3b	**4b**	**7**	H	H	4,2-Pyr	CH_2OH	OH	CH_2O	A	$C_{26}H_{22}N_2O_4$	*d*	144	63
3c	**4c**	**7**	H	H	2,4-Pyr	CH_2OH	OH	CH_2O	A	$C_{26}H_{22}N_2O_4$	C,H,N	162−165	67
3d	**4d**	**7**	H	H	6,2-Pyr	CH_2OH	OH	CH_2O	A	$C_{26}H_{22}N_2O_4$	C,H,N	164−166	43
3e	**5**	**7**	H	H	7,2-Quin	CH_2Br	OH	CH_2O	B	$C_{30}H_{24}N_2O_4$	*d*	192−194	54
3f	**6**	**7**	H	H	2,4-Tz	CH_2Br	OH	CH_2O	B	$C_{24}H_{20}N_2O_4S$	C,H,N,S	157−159	51
3g	**4e**	**7**	O−CH_2		6,2-Pyr	CH_2OH	OH	CH_2O	A	$C_{27}H_{22}N_2O_5$	C,H,N	161−163	70
3h	**9**	**10**	O−CH_2		6,2-Pyr	Br	CH_2OH	OCH_2	C	$C_{27}H_{22}N_2O_5$	C,H,N	159−160	51

[a] Method A: PPh_3, TBADC, THF. Method B: Cs_2CO_3, DMF. Method C: NaOH, 18-crown-6, toluene. [b] Elemental analyses were within ±0.4% of the calculated values. [c] Isolated yield of the final step. [d] High-resolution mass spectrum was obtained for this compound.

Scheme 2



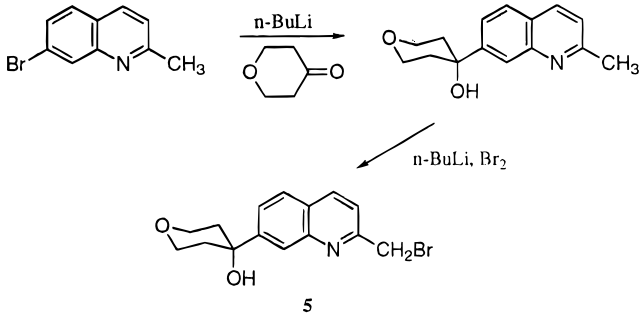
overall biological profile over **1**. The overall pharmacological profile obtained with compound **3g** will be presented.

Chemistry

The pyridine-containing final products **3a**−**d**,**g** were obtained via Mitsunobu-type condensations of pyridinemethanols **4a**−**e** with the cyanonaphthalene phenol **7**[5] (Table 1). The quinoline and thiazole derivatives **3e**,**f** resulted from alkylation of **7** with the appropriate bromides **5** and **6** using cesium carbonate in DMF. The reverse link analog **3h** was arrived at by coupling bicyclopyridine bromide **9** with the naphthalenemethanol derivative **10** in the presence of 18-crown-6 under basic conditions.

The required pyridinemethanols **4a**−**c** were derived from the appropriate bromopyridinecarboxylic acids (Scheme 1) via initial esterification, reduction to the primary alcohols, and protection as *tert*-butyldiphenylsilyl derivatives. After metalation with *n*-butyllithium, addition of tetrahydropyran-4-one and subsequent deprotection afforded the desired diols **4a**−**c**. Metalation of 2,6-dibromopyridine and condensation with tetrahydropyran-4-one or (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-3-one[5,6] (Scheme 2) led to the bromopyridines **8** and **9**. A further metalation with *n*-butyllithium with subsequent quenching by paraformaldehyde led to the pyridinemethanols **4d**,**e**. A more efficient preparation of **4e** was achieved by carbonylation of bromide **9** in ethanol in the presence of *trans*-bis(triphenylphosphine)palladium

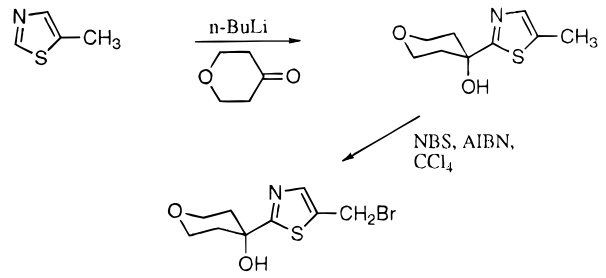
Scheme 3



bromide affording the corresponding ethyl ester which was efficiently reduced with diisobutylaluminum hydride to **4e**. Recently, an optimized approach to **4e**, involving initial condensation of the monolithiated derivative of 2,6-dibromopyridine with DMF, has been reported by Cai et al.[7]

The (bromomethyl)naphthalene **5** (Scheme 3) was obtained by initial metalation of 7-bromoquinaldine with *n*-butyllithium and quenching of the lithiated species with tetrahydropyran-4-one leading to the tetrahydropyranyl adduct. This material was in turn treated with *n*-butyllithium and the dianion reacted with bromine to yield the desired bromide **5.** For the preparation of the (bromomethyl)thiazole **6** (Scheme 4), 5-methylthiazole was metalated at the 2-position with subsequent quenching with tetrahydropyran-4-one, and the resulting intermediate was brominated using *N*-bromosuccinimide.

Scheme 4



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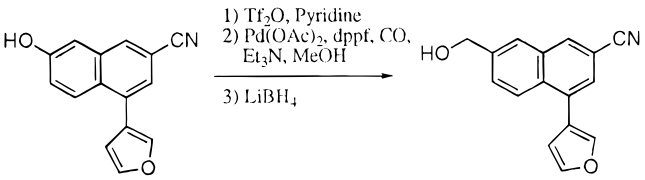
Scheme 5



7 **10**

The naphthalenemethanol intermediate **10** required for the synthesis of the reverse link analog **3h** was derived from the phenol **7** (Scheme 5) via initial derivatization to the corresponding triflate. Carbonylation in the presence of palladium acetate and 1,1′-bis(diphenylphosphine)ferrocene in methanolic solution led to the corresponding methyl ester which was conveniently reduced to the alcohol **10** by lithium borohydride in THF.

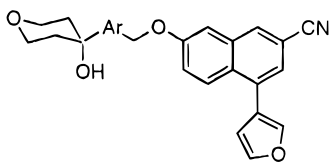
In Vitro Studies

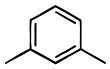
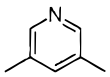
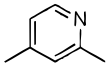
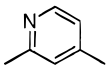
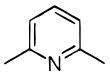
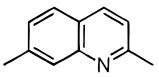
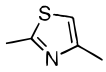
The compounds were evaluated for their potency to inhibit (a) oxidation of arachidonic acid by human recombinant 5-LO using a spectrophotometric assay monitoring 5-hydroperoxyeicosatetraenoic acid (5-H(P)-ETE) production,[8] (b) production of leukotriene B_4 in Ca^{2+}-ionophore-activated human polymorphonuclear (PMN) leukocytes,[9] and (c) production of LTB_4 in human whole blood activated with ionophore A23187.[9] The data are reported in Tables 2−4.

Heterocycle Insertion. A strategy considered to improve the bioavailability of derivatives in this series was to insert a nitrogen-containing heterocycle in the molecule. These heterocycles could be formulated as salts, thus improving aqueous solubility and consequently oral absorption.[10] We had learned from a previous SAR study[5] that attachment of such groups directly to the naphthalene ring results in significant loss of potency. Therefore, we investigated the replacement of the middle phenyl ring by various heterocycles. The compounds prepared are reported in Table 2.

All possible pyridine regioisomer analogs (**3a**−**d**) corresponding to the tetrahydropyranyl derivative **2**[5] were prepared, and the 2,6-disubstituted pyridine **3d** was found not only to be the most potent isomer but also to possess an overall *in vitro* profile 2−3-fold superior to **2**. Consequently plasma level studies with this compound were performed in rats. In contrast to the results observed with **2** where no drug was detected in plasma after oral administration, compound **3d** as its hydrochloride salt reached a plasma concentration of 2 μM 1 h after oral dosing at 20 mg/kg. In addition,

Table 2. *In Vitro* Potency of Naphthalenes **2** and **3a**−**f**



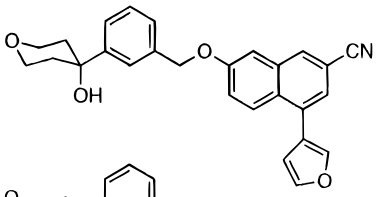
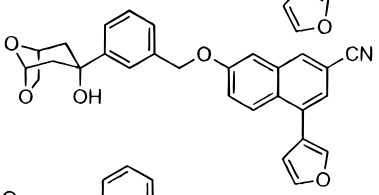
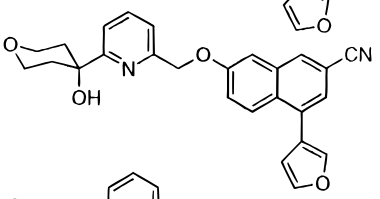
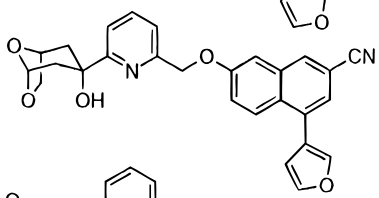
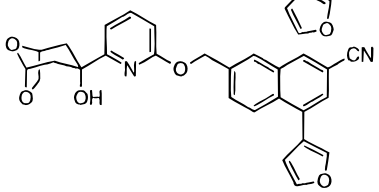
		IC_{50} (nM)[a]		
		H5-LO	HPMN	HWB
2		30	2	10
3a		100	10	100
3b		70	3.5	50
3c		350	5	250*
3d		15	0.6	30
3e		1000*	44*	-
3f		160	9	300

[a] Each IC_{50} value corresponds to an average of at least two independent determinations, except those identified with an asterisk, which are the result of a single titration.

a major metabolite with comparable plasma concentration (2.5 μM) to the parent compound was also observed. On the basis of metabolism studies performed in the previous series,[5] this metabolite is presumably the result of oxidative metabolism of the tetrahydropyran ring. Other heterocycles such as the quinoline **3e** and thiazole **3f** were found to be significantly less potent inhibitors.

2,6-Pyridine Optimization. (A) Tetrahydropyran Ring. To prevent the oxidative metabolism on the tetrahydropyran moiety, this ring was substituted by the metabolically more stable dioxabicyclooctanyl group.[5] As shown in Table 3, such substitution in the phenyl series (**1** versus **2**) led to an equipotent compound in the cellular HPMN assay but resulted in significant loss of potency in both enzymatic H5-LO and HWB assays (6−15-fold). However, in the pyridine series, the same substitution led to compound **3g** which was equipotent to the tetrahydropyranyl analog **3d** in all *in vitro* assays. Derivative **3g** as its hydrochloride salt was also well absorbed in rats reaching a plasma concentration of 3 μM 2 h after administration of a dose of 20 mg/kg. Furthermore, in contrast with the extensive metabolism observed with **3d**, no obvious circulating metabolite was detected (detection limit = 0.2 μM) after dosing **3g.** Thus, replacement of the middle phenyl ring in struc-

Table 3. *In Vitro* Potency and *in Vivo* Data of Naphthalenes **1**, **2**, and **3d**,**g**,**h**

		IC50 (nM)[a]			Rat Plasma Levels[b]	
		H5-LO	HPMN	HWB	Bioavailability[c] (%)	C_{max} (μM)
2		30	2	10	<5	1
1 (L-708,780)		190	3	150	10	2.5
3d		15	0.6	30	26	2[d]
3g (L-739,010)		20	1.6	42	26	5
3h		80	3.1	67	n d	n d

[a] Each IC_{50} value corresponds to an average of at least two independent determinations. [b] 20 mg/kg po in 0.5% methocel; 5 mg/kg iv in PEG-400/H_2O (3:1). [c] AUCpo/4 × AUCiv × 100. [d] A major metabolite was also observed at a concentration of 2.5 μM. nd, not determined.

Table 4. Comparison of *in Vitro* Potency of Zileuton, MK-0591, D-2138, and **3g**

	IC_{50} (nM)[a]		
	H5-LO	HPMN	HWB
Zileuton	3700	1100	2000
MK-0591	5000	3	500
D-2138	330	10	80
3g	20	1.6	42

[a] Each IC_{50} value is an average of at least two independent determinations.

tures **1** and **2** by the heterocycle pyridine led to increased oral absorption confirming the validity of our strategy.

(B) Methyleneoxy Link. Since it has been demonstrated that the nature of the linkage between the aryl and the naphthalene groups in the naphthalene series has a major effect on 5-LO inhibition,[4] it became pertinent to reexamine this modification in the newly optimized pyridine series. The oxymethylene derivative **3h** was found to be slightly less potent then the methyleneoxy analog **3g,** as previously observed for the naphthalene lactone series.

In summary compound **3g** (L-739,010) was found to possess the best *in vitro* biological profile with IC_{50}s of 1.6, 20, and 42 nM, respectively, in HPMN, H5-LO, and HWB assays. Derivative **3g** was also found to be more potent *in vitro* than MK-0591,[9] D-2138,[11] and Zileuton[12] (Table 4).

Further *in Vitro* Observations. Photoaffinity labeling of the active site of 5-lipoxygenase has been reported previously using the thiopyranoindole inhibitor L-708,714.[8] The labeling by this probe can be inhibited by arachidonic acid and several structurally unrelated 5-lipoxygenase inhibitors. Similarly, **3g** inhibited up to 80% of the labeling of 5-lipoxygenase by [^{125}I]L-708,-714 in a dose-dependent manner with an IC_{50} value of 34 nM (Figure 1), a value comparable to that observed for the inhibition of 5-lipoxygenase activity (IC_{50} = 20 nM). In this assay, the IC_{50} for compound D-2138 is 190 nM. This is in agreement with the lower potency of D-2138 as an inhibitor of enzymatic activity with IC_{50} of 330 nM (Table 4). These data are consistent with a nonredox mechanism of inhibition by **3g** involving competition with arachidonic acid for binding at the active site of the enzyme.

In Vivo Studies

Biochemical Efficacy. The inhibitory effect of **3g** on the biosynthesis of leukotriene B_4 *in vivo* was evaluated using the rat pleural cavity model following carrageenan-induced inflammation.[9] In this model, **3g** showed excellent activity with an ED_{50} of 0.3 mg/kg 6 h after oral dosing. For comparison, the ED_{50} for the FLAP inhibitor MK-0591 under the same conditions is 0.15 mg/kg.

The potency of **3g** on the inhibition of urinary leukotriene E_4 (an index of the systemic biosynthesis of peptidoleukotrienes) and of the *ex vivo* generation of

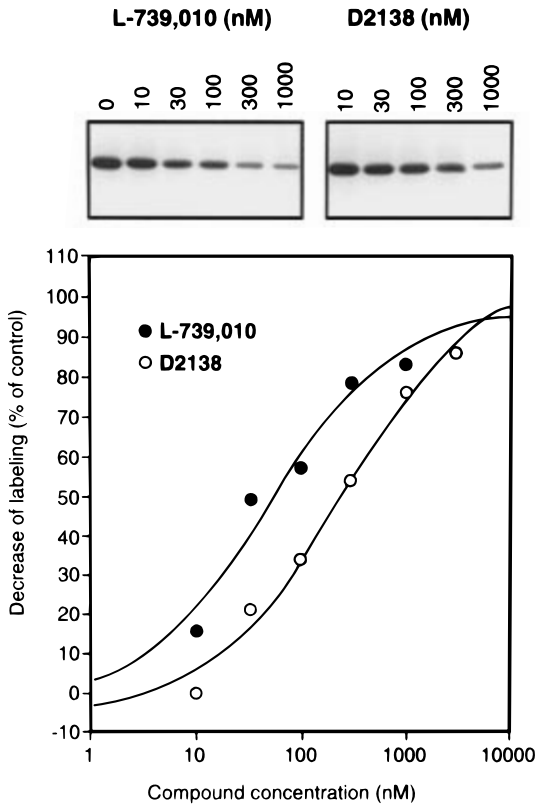


Figure 1. Inhibition of photoaffinity labeling of 5-LO by **3g**. Soluble extracts from baculovirus-infected insect cells (Sf9) overexpressing 5-LO were incubated with 10 nM [^{125}I]L-708,-714 and the indicated concentration of **3g** or D2138 prior to photolysis and electrophoresis as previously described.[8]

leukotriene B_4 by whole blood stimulated with calcium ionophore A23187 was measured in anesthetized dogs.[13] In a dose-dependent fashion, **3g** was demonstrated to be a very potent leukotriene biosynthesis inhibitor *in vivo* with an ED_{50} of 0.23 μg/kg/min for the inhibition of the base-line urinary LTE_4 excretion over 5−7 h after the commencement of the infusion and with an ED_{50} of 0.45 μg/kg/min for the inhibition of *ex vivo* LTB_4 generation by dog whole blood. For MK-0591, the ED_{50}s were 1.0 and 0.51 μg/kg/min, respectively.

Respiratory Functional Models. Compound **3g** was evaluated against antigen-induced dyspnea in hyperreactive rats.[14] When **3g** was administered orally at 0.5 mg/kg 4 h before ovalbumin challenge, it produced a 60% ($p < 0.01$) inhibition of dyspnea. This result is comparable to the activity observed with MK-0591 (56% inhibition) under the same conditions.

The activity of **3g** on antigen-induced bronchoconstriction in allergic conscious squirrel monkeys[9] was determined. After a 4 h pretreatment with an oral dose of 0.1 mg/kg ($n = 5$) followed by a challenge with an aerosol of Ascaris antigen, **3g** produced a 53% inhibition of the increase in airway resistance (R_L) and a 76% inhibition of decrease in dynamic compliance (C_{dyn}). For comparison, MK-0591 shows only comparable activity at 1 mg/kg with inhibitions of 71% and 70% for R_L and C_{dyn}, respectively. Thus, **3g** is approximately 10 times more potent than MK-0591 in this model.

In the conscious allergic sheep model,[15] the administration of **3g** as a bolus dose of 0.2 mg/kg followed by a constant infusion of 2.5 μg/kg/min ($n = 4$) resulted in inhibition of both the early and late phase bronchoconstriction (50% and >85% respectively) induced by Ascaris antigen (Figure 2A). MK-0591 was also effective at this dose with >75% and >90% inhibition of both phases. However, both **3g** and MK-0591 showed no significant activity at a lower dose of 0.8 μg/kg/min. Urinary LTE_4 production was also measured throughout the experiment (Figure 2B), and **3g** was shown to reduce LTE_4 excretion by 94% (0−1.5 h) relative to a vehicle control.

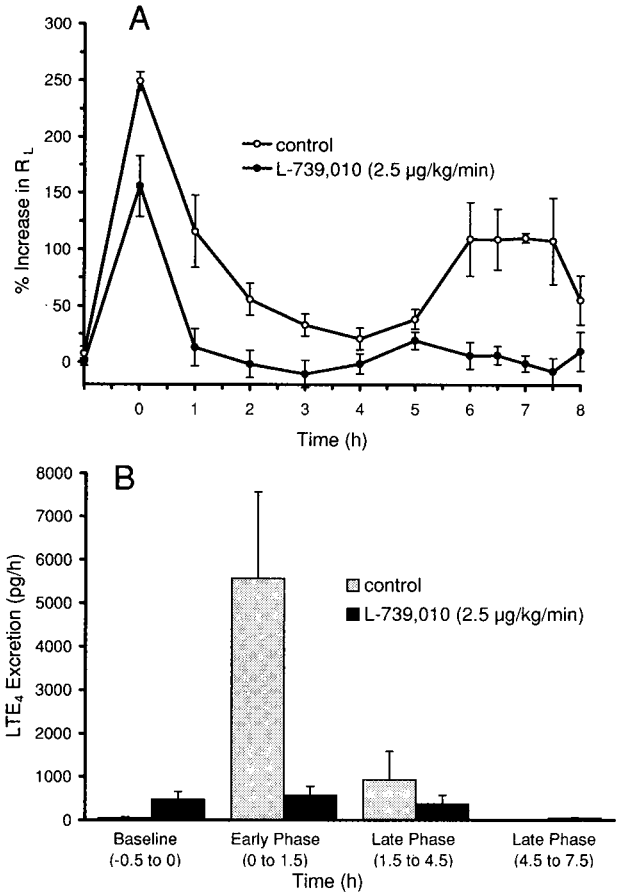


Figure 2. Intravenous infusion of **3g** at 2.5 μg/kg/min in allergic sheep: (A) effect on postantigen bronchoconstriction and (B) effect on postantigen urinary LTE_4 excretion.

Plasma Level Studies. Since the direct leukotriene inhibitor **3g** (L-739,010) possesses an overall biological profile at least comparable and in some assays or models superior to our clinical leukotriene biosynthesis inhibitor candidate MK-0591 (Table 5), further pharmacokinetic studies have been performed on this compound.

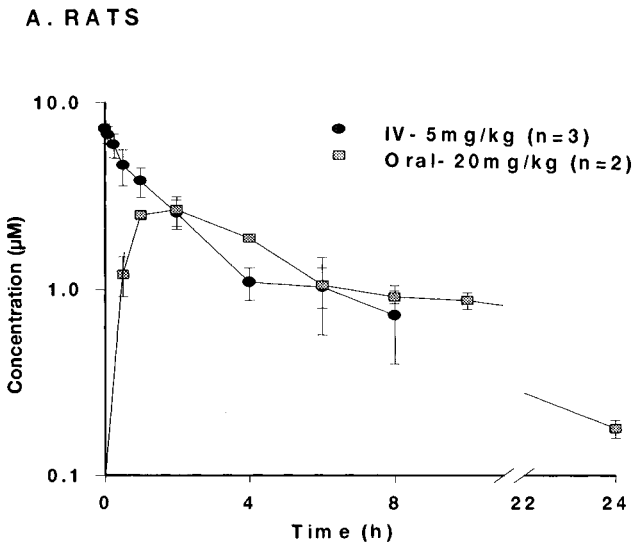
Initial bioavailability studies performed on **3g** (Table 3) as its hydrochloride salt have demonstrated that this compound is also well absorbed when administered in a 0.5% methocel suspension in rats at a dose of 20 mg/kg with a bioavailability of 26% (0−24 h) (Figure 3). In dogs, **3g** is also very well absorbed with a bioavailability of 73% (0−24 h) following oral administration of **3g** (HCl salt) at a 10 mg/kg dose. The half-lives determined from intravenous administration of **3g** (free base) in PEG-400/water (3:1) were 5 and 16 h in rats and dogs, respectively.

Conclusion

Replacement of the middle phenyl ring in the dioxabicyclooctanyl naphthalenenitrile **1** by the pyridine heterocycle leads to the identification of the optimized 5-LO inhibitor **3g** (L-739,010). Following oral admin-

Table 5. Comparison of *in Vivo* Potency of **3g** and MK-0591

	3g	MK-0591
LTB_4 inhibition in rat pleural cavity following carageenan-induced inflammation (ED_{50})	0.3 mg/kg	0.15 mg/kg
inhibition of *ex vivo* whole blood LTB_4	0.45 μg/kg/min	0.5 μg/kg/min
inhibition of urinary LTE_4 in dogs (ED_{50})	0.23 μg/kg/min	1.0 μg/kg/min
inhibition of ovalbumin-induced dyspnea in inbred hyperreactive rats at 0.5 mg/kg (% inhibition) (4 h pretreatment, po, in 1% methocel)	60%	56%
inhibition of Ascaris-induced bronchoconstriction in squirrel monkeys (% inhibition of R_L, C_{dyn}) (4 h pretreatment, po, in 1% methocel)	53%, 76% (at 0.1 mg/kg)	71%, 70% (at 1.0 mg/kg)
inhibition of Ascaris-induced bronchoconstriction in sheep at 2.5 μg/kg/min iv infusion (% inhibition in early and late phases)	50%, >85%	>75%, >90%



SPECIES	BIOAVAILABILITY(%)	HALF-LIFE(h)
Rats	25.9 ± 0.05	5.0 ± 3.0
Dogs	72.6 ± 1.4	16.2 ± 5.4

Figure 3. Mean plasma levels after intravenous administration of **3g** (free base) in PEG-400/water (3:1) and after oral administration of **3g** (HCl salt) in 0.5% methocel suspension in rats (A) and dogs (B) with dosing volumes of 10 and 5 mL/kg, respectively.

istration of **3g** in rats, no circulating metabolites were detected. Compound **3g** also shows excellent oral activity in inhibiting (1) LTB_4 production from carageenan-induced inflammation in rat pleural cavity and (2) urinary LTE_4 excretion and *ex vivo* generation of LTB_4 by whole blood in anesthetised dogs. In functional models, **3g** is orally potent to inhibit (1) ovalbumin-induced dyspnea in rats, (2) Ascaris-induced bronchoconstriction in sheep, and (3) more particularly, Ascaris-induced bronchoconstriction in squirrel monkeys, where **3g** is significantly more potent than MK-0591. In addition, **3g** presents excellent pharmacokinetics after intravenous administration and is orally well absorbed as its hydrochloride salt in both rats and dogs. Consequently **3g** has been selected for preclinical toxicity studies.[16]

Experimental Section

Biology. Activity of Human 5-Lipoxygenase (H5-LO). The activity of 5-LO was measured using a spectrophotometric assay and soluble extracts from Sf9 insect cells overexpressing human 5-LO as described by Falgueyret et al.[8]

Generation of LTB_4 in Human Peripheral Blood Polymorphonuclear Leukocytes (HPMN) and Human Whole Blood (HWB). The generation of LTB_4 in human peripheral blood polymorphonuclear leukocytes and human whole blood was measured as previously described by Brideau et al.[9]

Leukotriene Biosynthesis in Rat Pleural Cavity. LTB_4 levels in rat pleural exudates following interpleural injection of carrageenan followed 16−20 h later by ionophore A23187 were determined as previously described.[9]

Measurement of Urinary LTE_4 and *ex Vivo* Generation of LTE_4 in Anesthetized Dogs. The measurements of urinary LTE_4 and the *ex vivo* generation of LTB_4 by whole blood stimulated with calcium ionophore A23187 in anesthetized dogs were carried out as described by Tagari et al.[13]

Antigen-Induced Dyspnea in Hyperreactive Rat. The inhibition of ovalbumin-induced dyspnea in hyperreactive rats was assayed as previously described by Piechuta et al.[14]

Antigen-Induced Bronchoconstriction in Squirrel Monkeys. Naturally sensitized male squirrel monkeys were challenged with an aerosol of Ascaris antigen. Changes in pulmonary mechanics (airway resistance, R_L, and dynamic compliance, C_{Dyn}) were monitored in conscious animals using airflow measurements from a face mask and measurements of pleural pressure as previously described.[9]

Antigen-Induced Airway Responses in Allergic Sheep. Measurement of bronchoconstriction in conscious allergic sheep exposed to Ascaris antigen was performed according to Abraham et al.[15]

Measurement of Plasma Levels and Bioavailability. For po measurements, male Sprague−Dawley rats (2−4) were starved overnight and then dosed orally with the study compound as a suspension in 0.5% or 1% aqueous methocel. Blood was taken from the jugular vein prior to dosing and then 0.5, 1, 2, 4, 6, 8, 10, and 24 h after dosing. For iv studies, compounds were dissolved in PEG-400/water (3:1) and injected intravenously in the jugular vein at a dose of 5 mg/kg at a dose volume of 0.1 mL/100 g of body weight. Blood was taken from the jugular vein at 0, 5, 15, and 30 min and 1, 2, 4, 6, 8, and 24 h after dosing. The blood was centrifuged and plasma collected. To 100 μL of each plasma sample was added an equal volume of acetonitrile to precipitate protein. After centrifugation an aliquot of the supernatant was subjected to reverse-phase HPLC analysis. The parent compound was quantitated from the area of the pertinent peak relative to standardization curves obtained by spiking rat plasma with

varying concentrations of the compound. The bioavailability is calculated using the following equation: $(AUC_{po} \times dose_{iv})/(AUC_{iv} \times dose_{po}) \times 100$.

Chemistry. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 300 spectrometer, and proton chemical shifts are reported relative to tetramethylsilane as internal standard. Melting points were obtained on either a Buchi 510 or an Electrothermal 9100 apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN, Oneida Research Services, Whitesboro, NY, or Guelph Chemical Laboratories Ltd., Guelph, Ontario. Where reported only by symbols the results were within 0.4% of theoretical values. High-resolution mass spectra were recorded at the Biomedical Mass Spectrometry Unit, McGill University, Montreal, Quebec.

Preparation of Alcohols. 3-[4-(4-Hydroxytetrahydropyranyl)]-5-pyridylmethanol (4a). Step 1: 5-Bromo-3-pyridylmethanol. To a solution of methyl 5-bromonicotinate (14.5 g, 67.1 mmol) in THF (400 mL) under N_2 atmosphere was added in portions over 15 min LAH (2.85 g, 75 mmol). The slightly warm mixture was stirred at room temperature for 1 h; then the reaction was quenched carefully with saturated aqueous NH_4Cl (80 mL). After stirring for a further hour, the organic supernatant was decanted, and the insoluble aluminum salts were extracted (3×) with EtOAc (100 mL) with decantation. The combined organic fractions were dried over $MgSO_4$ and evaporated. The yellow oil obtained (12.3 g) was used as such in the next step: ^{1}H NMR ($CDCl_3$) δ 1.8 (br s, OH), 4.74 (s, 2H), 7.90 (dd, 1H), 8.49 (dd, 1H), 8.59 (dd, 1H).

Step 2: 5-Bromo-3-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]pyridine. To a solution of alcohol from step 1 (29 g, 154 mmol) and *tert*-butyldiphenylchlorosilane (47.5 g, 173 mmol) in CH_2Cl_2 (500 mL) was added imidazole (15.8 g, 232 mmol). After stirring at room temperature for 1 h, the mixture was filtered, and the filtrate material was chromatographed on silica gel eluting with a 1:7 mixture of EtOAc and hexane to afford the product (67 g, quantitative) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 4.72 (s, 2H), 7.33−7.48 (m, 6H), 7.62−7.75 (m, 4H), 7.80 (dd, 1H), 8.45 (dd, 1H), 8.57 (dd, 1H).

Step 3: 3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-[4-(4-hydroxytetrahydropyranyl)]pyridine. To a solution of silyl derivative from step 2 (1.28 g, 3 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi in hexanes (1.12 M, 3 mL, 3.36 mmol). The mixture was stirred in the cold for 10 min, and a solution of tetrahydropyran-4-one (360 mg, 3.6 mmol) in THF (1 mL) was added slowly. After 1.25 h at −78 °C the reaction was quenched with saturated aqueous NH_4Cl and the mixture allowed to warm up to room temperature. After dilution with EtOAc (200 mL) the organic phase was washed (4×) with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc to yield the desired product (784 mg, 58%) as a colorless oil which solidified: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.69 (d, 2H), 2.07−2.25 (m, 2H), 3.80−4.02 (m, 4H), 4.80 (s, 2H), 7.33−7.50 (m, 6H), 7.60−7.75 (m, 5H), 8.49 (dd, 1H), 8.68 (dd, 1H).

Step 4: 5-[4-(4-Hydroxytetrahydropyranyl)]-3-pyridylmethanol (4a). To a solution of THP derivative from step 3 (20.35 g, 45.5 mmol) in THF (350 mL) was added TBAF (1 M) in THF (52 mL). After 1 h at room temperature the mixture was evaporated and the residue chromatographed on silica gel eluting with a 1:4 mixture of EtOH and EtOAc to afford the product (6.74 g, 71%) as a white solid: mp 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.74 (d, 2H), 2.10−2.32 (m, 2H), 3.83−4.03 (m, 4H), 4.78 (s, 2H), 7.86 (dd, 1H), 8.50 (dd, 1H), 8.68 (dd, 1H).

4-[4-(4-Hydroxytetrahydropyranyl)]-2-pyridylmethanol (4b). Step 1: Methyl 4-Bromopicolinate. A suspension of 4-bromopicolinic acid[17] (1 g) in EtOAc (25 mL) was esterified with excess ethereal diazomethane. After chromatography (1:1 EtOAc/hexane) the ester was obtained (785 mg) as a solid.

Step 2: 4-Bromo-2-pyridylmethanol. The ester from step 1 was reduced with LAH as described above to afford the alcohol in 71% yield as a yellow-brown oil: ^{1}H NMR ($CDCl_3$) δ 3.55 (br s, OH), 4.75 (s, 2H), 7.38 (m, 1H), 7.50 (br s, 1H), 8.39 (d, 1H).

Step 3: 2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-bromopyridine. Silylation as described above afforded the TBDPS derivative in 93% yield: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 4.85 (s, 2H), 7.30−7.48 (m, 7H), 7.64−7.73 (m. 4H), 7.82 (br s, 1H), 8.27 (d, 1H).

Step 4: 2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-[4-(4-hydroxytetrahydropyranyl)]pyridine. The product from step 3 was condensed with tetrahydropyran-4-one as described above to afford the hydroxy THP derivative in 20% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 2H), 2.05 (s, 1H, OH), 2.09−2.21 (m, 2H), 3.85−4.00 (m, 4H), 4.91 (s, 2H), 7.23 (m, 1H), 7.30−7.47 (m, 6H), 7.62−7.70 (m, 4H), 7.73 (br s, 1H), 8.48 (d, 1H).

Step 5: 4-[4-(4-Hydroxytetrahydropyranyl)]-2-pyridylmethanol (4b). The desilylation was done as described above to afford the product in 71% yield as a white solid: ^{1}H NMR (acetone-d_6) δ 1.61 (d, 2H), 2.00−2.12 (m, 2H), 3.69−3.93 (m, 4H), 4.34 (s, 1H, OH), 4,50 (t, 1H, OH), 4.69 (br s, 2H), 7.35 (m, 1H), 7.61 (br s 1H), 8.44 (d, 1H).

2-[4-(4-Hydroxytetrahydropyranyl)]-4-pyridylmethanol (4c). The same sequence of steps as in the preparation of **4b**, starting with 2-bromoisonicotinic acid,[18] afforded **4c** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 2H), 2.09−2.20 (m, 2H), 2.25 (br s, OH), 3.85−4.07 (m, 4H), 4.80 (s, 2H), 5.25 (br s, OH), 7.22 (d, 1H), 7.40 (s, 1H), 8.50 (d, 1H).

2-[4-(4-Hydroxytetrahydropyranyl)]-6-pyridylmethanol (4d). Step 1: 2-Bromo-6-[4-(4-hydroxytetrahydropyranyl)]pyridine (8). A solution of 2,6-dibromopyridine (15 g, 63.3 mmol) in Et_2O (225 mL) was cooled to −78 °C. To the resulting suspension was added *n*-BuLi (2.0 M) in hexanes (28.5 mL, 57 mmol), and a yellow solution resulted. After the mixture stirred for 15 min, a solution of tetrahydropyran-4-one (6.98 g, 69.8 mmol) in Et_2O (15 mL) was added, and a white solid precipitated out of solution. After a further 15 min, the reaction was quenched with saturated aqueous NH_4Cl and the mixture allowed to warm up to room temperature. Partition of the mixture between EtOAc and H_2O and evaporation of the organic phase afforded a white solid which was triturated with Et_2O and filtered to yield **8** (11.43 g, 78%) as a white solid: mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 2H), 2.04−2.19 (m, 2H), 3.84−4.03 (m, 4H), 4.20 (br s, OH), 7.35 (d, 1H), 7.42 (d, 1H), 7.60 (t, 1H).

Step 2: 2-[4-(4-Hydroxytetrahydropyranyl)]-6-pyridylmethanol (4d). To *n*-BuLi (2.0 M) in hexanes (65 mL, 130 mmol) cooled to −78 °C was added a solution of bromide from step 1 (16 g, 62 mmol) in THF (350 mL), keeping the temperature below −60 °C. The resulting dark yellow solution was stirred for a further 10 min. Solid paraformaldehyde (5 g, 166 mmol) was added, the mixture was stirred for 15 min, and more paraformaldehyde was added (5 g). After a further 15 min of stirring at −78 °C, the mixture was warmed to 0 °C and the reaction quenched with saturated aqueous NH_4Cl. Partition between EtOAc and H_2O and chromatography of the organic material on silica gel eluting with a 1:1 mixture of EtOAc and hexane afforded **4d** (3.8 g, 29%) as a thick yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 2H), 2.09−2.25 (m, 2H), 3.04 (t, 1H, OH), 3.75−4.05 (m, 4H), 4.62 (s, 1H, OH), 4.80 (d, 2H), 7.24 (d, 1H), 7.33 (d, 1H), 7.78 (t, 1H).

6-[3-(3-Hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]-2-pyridylmethanol (4e). Method 1, Step 1: 2-Bromo-6-[3-(3-hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]pyridine (9). The procedure described above for the preparation of **8** was applied using (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octan-3-one[5,6] as starting material to yield **9** in 46% yield as a white solid: mp 161−163 °C; ^{1}H NMR ($CDCl_3$) δ 1.81−1.98 (m, 2H), 2,43 (d, 1H), 2.66 (m, 1H), 3.70 (m, 1H), 4.41 (s, 1H, OH), 4.50 (d, 1H), 4.70 (m, 1H), 5.77 (s, 1H), 7.35 (dd, 1H), 7.51−7.62 (m, 2H).

Step 2: 6-[3-(3-Hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]-2-pyridylmethanol (4e). The procedure of step 2 in the preparation of **4d** was followed using the product from step 1 as starting material to afford **4e** in 20% yield as a white solid: mp 163−164 °C; ^{1}H NMR ($CDCl_3$) δ 1.86−1.99 (m, 2H), 2.44 (d, 1H), 2.68 (m, 1H), 3.57 (t, 1H, OH), 3.82 (m, 1H), 4.54 (d, 2H), 4.65 (s, 1H, OH), 4.70−4.77 (m, 2H), 5.78 (s, 1H), 7.14 (d, 1H), 7.53 (d, 1H), 7.72 (t, 1H).

Method 2, Step 1: Ethyl 6-[3-(3-Hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]-2-pyridinecarboxylate. A mixture of **9** (5.0 g, 17.5 mmol), *trans*-bis(triphenylphosphine)palladium bromide (500 mg, 0.63 mmol), triethylamine (4.9 mL, 35 mmol), and EtOH (50 mL) was placed under an atmosphere of carbon monoxide using a balloon and heated at 75 °C for 2 days. The solvent was evaporated, and the residue was chromatographed on silica gel eluting with a mixture of EtOAc and hexane (2:1) to yield the ester (4.23 g, 87%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H), 1.89−2.03 (m, 2H), 2.39 (d, 1H), 2.63 (m, 1H), 3.83 (m, 1H), 4.44 (q, 2H), 4.59 (d, 1H), 4.72 (m, 1H), 5.23 (s, 1H, OH), 5.78 (s, 1H), 7.72 (d, 1H), 7.86 (t, 1H), 8.00 (d, 1H).

Step 2: 6-[3-(3-Hydroxy-6,8-dioxabicyclo[3.2.1]octanyl)]-2-pyridylmethanol (4e). To a solution of ester from step 1 (8.6 g, 30.8 mmol) in THF (150 mL) at 0 °C was added diisobutylaluminum hydride (1.5 M) in toluene (68 mL, 102 mmol). The resulting red mixture was stirred in the cold for 1 h, and then the reaction was quenched with saturated aqueous NH_4Cl resulting in a slurry which was diluted with EtOAc (150 mL) and filtered. The organic portion of the filtrate was retained. The solids were suspended in EtOAc (200 mL), and 5 N aqueous NaOH was added in portions until the solids became a paste. The organic layer was decanted, washed (4×) with brine, dried, and filtered. The filtrate was combined with the first organic filtrate, and the solution was dried and evaporated to an oil which solidified. The solid was triturated with Et_2O and filtered to afford **4e** (5.42 g, 74%).

Preparation of Halides. 2-(Bromomethyl)-7-[4-(4-hydroxytetrahydropyranyl)]quinoline (5). Step 1: 7-[4-(4-Hydroxytetrahydropyranyl)]-2-methylquinoline. To a solution of 7-bromoquinaldine (444 mg, 2 mmol) in THF (10 mL) at −70 °C was added *n*-BuLi (1.1 M) in hexanes (2 mL, 2.2 mmol). The resulting purple solution was stirred for 10 min, and a solution of tetrahydropyran-4-one (250 mg, 2.5 mmol) in THF (1.5 mL) was added slowly resulting in a green solution which was stirred in the cold for a further 20 min; then the reaction was quenched with saturated aqueous NH_4Cl and the mixture allowed to warm up. The mixture was partitioned between EtOAc and H_2O, and the organic fraction was evaporated to an oily residue which solidified. Trituration with Et_2O afforded the desired THP product (126 mg, 26%) as a white crystalline solid: mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 1H, OH), 1.82 (d, 2H), 2.30 (m, 2H), 2.76 (s, 3H), 3.87−4.06 (m, 4H), 7.27 (dd, 1H), 7.68 (dd, 1H), 7.80 (dd, 1H), 8.03 (d, 1H), 8.11 (s, 1H).

Step 2: 2-(Bromomethyl)-7-[4-(4-hydroxytetrahydropyranyl)]quinoline (5). To a solution of THP quinaldine from step 1 (121 mg, 0.5 mmol) in THF (2 mL) at −70 °C was added *n*-BuLi (1.1 M) in hexanes (1 mL, 1.1 mmol). The resulting dark red solution was stirred for a further 10 min, and then it was added via cannula to a −70 °C solution of bromine (120 mg, 0.75 mmol) in THF (2 mL). A yellow solution resulted which was stirred in the cold for 30 min and the reaction quenched with saturated aqueous NH_4Cl. Partition of the mixture between EtOAc and H_2O and evaporation of the organic phase led to a mixture which was chromatographed on silica gel eluting with EtOAc to yield **5** (33 mg, 22%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 2H), 1.97 (s, 1H, OH), 2.30 (m, 2H), 3.86−4.05 (m, 4H), 4.71 (s, 2H), 7.58 (d, 1H), 7.75 (dd,1H), 7.84 (d, 1H), 8.15 (s, 1H), 8.17 (d, 1H).

4-(Bromomethyl)-2-[4-(4-hydroxytetrahydropyranyl)]-thiazole (6). Step 1: 2-[4-(4-Hydroxytetrahydropyranyl)]-4-methylthiazole. The procedure of step 1 in the preparation of **5** was applied using 4-methylthiazole as starting material and yielded after chromatography on silica gel eluting with a 1:1 mixture of EtOAc and hexane the desired THP product in 52% yield as a light yellow solid: mp 98−100 °C; $_1$H NMR ($CDCl_3$) δ 1.80 (m, 2H), 2.15−2.31 (m, 2H), 2.42 (s, 3H), 3.14 (s, 1H, OH), 3.81−3.98 (m, 4H), 6.83 (s, 1H).

Step 2: 4-(Bromomethyl)-2-[4-(4-hydroxytetrahydropyranyl)]thiazole (6). A mixture of THP product from step 1 (995 mg, 5 mmol), NBS (979 mg, 5.5 mmol), and AIBN (50 mg) in CCl_4 (10 mL) was refluxed for 30 min. The cooled mixture was diluted with Et_2O and filtered, and the filtrate material was chromatographed on silica gel eluting with a 1:1 mixture of EtOAc and hexane to afford **6** (175 mg, 13%) as an oil which solidified: ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 2H), 2.16−2.35 (m, 2H), 2.94 (s, 1H, OH), 3.82−3.96 (m, 4H), 4.55 (s, 2H), 7.25 (s, 1H).

Preparation of 2-Cyano-4-(3-furyl)-7-(hydroxymethyl)-naphthalene (10). Step 1: 2-Cyano-4-(3-furyl)-7-[[(trifluoromethyl)sulfonyl]oxy]naphthalene. To a suspension of phenol **7**[5] (9.4 g, 40 mmol) in CH_2Cl_2 (100 mL) was added pyridine (4.85 mL, 60 mmol). After the mixture cooled to 0 °C, trifluoromethanesulfonic anhydride (13.54 g, 48 mmol) was added slowly, and the mixture was stirred in the cold for 2 h. After dilution with CH_2Cl_2 (200 mL) the mixture was washed (2×) with H_2O, dried, and evaporated, and the residue was chromatographed on silica gel eluting with hexane/EtOAc (1:5) to afford the triflate (14 g) as a yellow oil.

Step 2: Methyl 2-Cyano-4-(3-furyl)-7-naphthoate. Carbon monoxide gas was bubbled for a few minutes into a mixture of triflate from step 1 (4.5 g, 12.26 mmol), palladium acetate (275 mg, 1.22 mmol), 1,1′-bis(diphenylphosphino)-ferrocene (1.36 g, 2.5 mmol), and triethylamine (2.72 g, 26.9 mmol) in MeOH (40 mL) and DMSO (70 mL). A balloon filled with carbon monoxide was placed over the flask, and the mixture was stirred at 60 °C for 3 h. After dilution with H_2O, the mixture was extracted (3×) with EtOAc, and the combined extracts were washed (4×) with H_2O, dried, and evaporated. The residue was stirred with a small volume of Et_2O and filtered to yield the methyl ester (3.32 g, 97%) as a light brown solid, used as such in the next step.

Step 3: 2-Cyano-4-(3-furyl)-7-(hydroxymethyl)naphthalene (10). To a solution of ester from step 2 (840 mg, 3.03 mmol) in THF (25 mL) at room temperature was added in portions $LiBH_4$ (330 mg, 15 mmol). The mixture was stirred at room temperature for 24 h, the reation quenched with saturated aqueous NH_4Cl, and the mixture extracted with EtOAc. The organic fraction was washed (3×) with H_2O, dried, and evaporated, and the crude product was chromatographed on silica gel eluting with hexane/EtOAc (1:1) leading to the desired alcohol **10** (440 mg, 58%) as a white solid: mp 131−134 °C.

Preparation of Final Products: 2-Cyano-4-(3-furyl)-7-[[5-[4-(4-hydroxytetrahydropyranyl)]-3-pyridyl]-methoxy]naphthalene (3a). To a mixture of pyridine alcohol **4a** (157 mg, 0.75 mmol), cyanophenol **7** (176 mg, 0.75 mmol), and triphenylphosphine (236 mg, 0.9 mmol) in THF (8 mL) was added di-*tert*-butyl azodicarboxylate (207 mg, 0.9 mmol). The mixture was stirred at room temperature for 2 h, evaporated to dryness, and chromatographed on silica gel. Elution with EtOAc afforded **3a** as a yellow oil. Trituration with hexane led to a yellow solid which was filtered, affording pure **3a** (183 mg, 57%) as a cream-colored solid: ^{1}H NMR ($CDCl_3$) δ 1.65−1.82 (m, 3H), 2.14−2.33 (m, 2H), 3.85−4.02 (m, 4H), 5.25 (s, 2H), 6.68 (s, 1H), 7.28−7.42 (m, 2H), 7.50 (d, 1H), 7.62 (m, 1H), 7.68 (s, 1H), 7.99 (m, 1H), 8.05−8.17 (m, 2H), 8.67 (m, 1H), 8.78 (d, 1H).

A similar procedure was used to prepare the following compounds (**3b**−**d**,**g**).

2-Cyano-4-(3-furyl)-7-[[4-[4-(4-hydroxytetrahydropyranyl)]-2-pyridyl]methoxy]naphthalene (3b): from **4b** and **7** (63% yield), yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.64 (br d, 2H), 1.71 (s, OH), 2.04−2.22 (m, 2H), 3.89−3.93 (m, 4H), 5.35 (s, 2H), 6.68 (s, 1H), 7.30 (d, 1H), 7.37−7.41 (m, 1H), 7.43 (d, 1H), 7.47 (s, 1H), 7.60 (m, 1H), 7.68 (d, 1H), 8.05 (s, 1H), 8.11 (d, 1H), 8.63 (d, 1H); HRMS ($C_{26}H_{22}N_2O_4 + H^+$) calcd 427.16578, found 427.16569.

2-Cyano-4-(3-furyl)-7-[[2-[4-(4-hydroxytetrahydropyranyl)]-4-pyridyl]methoxy]naphthalene (3c): from **4c** and **7** (67% yield), yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.55−1.62 (m, 2H), 2.04−2.22 (m, 2H), 3.88−4.05 (m, 4H), 5.14 (s, OH), 5.27 (s, 2H), 6.68 (s, 1H), 7.25 (d, 1H), 7.32 (d, 1H), 7.40 (dd, 1H), 7.44−7.57 (m, 2H), 7.62 (m, 1H), 7.69 (s, 1H), 8.06 (s, 1H), 8.14 (d, 1H), 8.57 (d, 1H).

2-Cyano-4-(3-furyl)-7-[[6-[4-(4-hydroxytetrahydropyranyl)]-2-pyridyl]methoxy]naphthalene (3d): from **4d** and **7** (43% yield), light yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.55−1.62 (br d, 2H), 2.05−2.22 (m, 2H), 3.93−4.03 (m, 4H), 5.17 (s, OH), 5.36 (s, 2H), 6.67 (s, 1H), 7.28 (d, 1H), 7.35 (d, 1H), 7.40 (dd,

1H), 7.47−7.51 (m, 2H), 7.61 (s, 1H), 7.68 (s, 1H), 7.79 (t, 1H), 8.05 (s, 1H), 8.11 (d, 1H).

2-Cyano-4-(3-furyl)-7-[[6-[3-(3-hydroxy-6,8-dioxabicyclo-[3.2.1]octanyl)]-2-pyridyl]methoxy]naphthalene (3g, L-739,010): from **4e** and **7** (70% yield), light yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.89−2.05 (br d, 2H), 2.40 (d, 1H), 2.65 (dd, 1H), 3.86 (t, 1H), 4.59 (d, 1H), 4.73 (t, 1H), 5.08 (s, 1H), 5.34 (s, 2H), 5.80 (s, OH), 6.67 (s, 1H), 7.30 (d, 1H), 7.39 (dd, 1H), 7.42−7.46 (m, 2H), 7.50 (d, 1H), 7.60 (t, 1H), 7.67 (s, 1H), 7.77 (t, 1H), 8.05 (s, 1H), 8.09 (d, 1H).

2-Cyano-4-(3-furyl)-7-[[7-[4-(4-hydroxytetrahydropyranyl)]-2-quinolinyl]methoxy]naphthalene (3e). A mixture of bromide **5** (30 mg, 0.093 mmol), **7** (26 mg, 0.11 mmol), and Cs_2CO_3 (65 mg, 0.2 mmol) in DMF (2 mL) was stirred at room temperature for 20 h. The mixture was diluted with H_2O and extracted (2×) with EtOAc, and the extracts were washed (3×) with H_2O, dried, and evaporated. Chromatography on silica gel eluting with EtOAc led to **3e** (24 mg, 54%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.77 (s, OH), 1.83 (br d, 2H), 2.29−2.40 (m, 2H), 3.96−4.02 (m, 4H), 5.53 (s, 2H), 6.67 (s, 1H), 7.31 (d, 1H), 7.42−7.46 (m, 2H), 7.59 (m, 1H), 7.66−7.70 (m, 2H), 7.85 (dd, 1H), 7.87 (d, 1H), 8.02 (s, 1H), 8.10 (d, 1H), 8.19−8.21 (m, 1H); HRMS ($C_{30}H_{24}N_2O_4 + H^+$) calcd 477.18143, found 477.18147.

2-Cyano-4-(3-furyl)-7-[[2-[4-(4-hydroxytetrahydropyranyl)]-4-thiazolyl]methoxy]naphthalene (3f). The preceding procedure was used starting with **7** and halide **6** to afford **3f** in 51% yield as a cream-colored solid; ^{1}H NMR ($CDCl_3$) δ 1.85 (br d, 2H), 2.28−2.37 (m, 2H), 2.91 (s, OH), 3.91−3.94 (m, 4H), 5.32 (s, 2H), 6.68 (s, 1H), 7.32−7.40 (m, 3H), 7.47 (s, 1H), 7.61 (s, 1H), 7.68 (s, 1H), 8.07−8.12 (m, 2H).

2-Cyano-4-(3-furyl)-7-[[[6-[3-(3-hydroxy-6,8-dioxabicyclo-[3.2.1]octanyl)]-2-pyridyl]oxy]methyl]naphthalene (3h). A mixture of bicyclobromopyridine **9** (99 mg, 0.35 mmol), benzyl alcohol **10** (135 mg, 0.54 mmol), powdered NaOH (70 mg, 1.5 mmol), and 18-crown-6 (4.4 mg, 0.017 mmol) in toluene (7 mL) was refluxed with azeotropic removal of H_2O for 2 h. The mixture was poured into saturated aqueous NH_4Cl and extracted (3×) with EtOAc; the extracts were washed with brine, dried, and evaporated. Because the final product **3h** and starting material **10** coeluted on silica gel, the crude mixture was dissolved in DMF (4 mL), triethylamine (0.028 mL, 0.2 mmol) and *tert*-butyldimethylchlorosilane (30 mg, 0.2 mmol) were added, and the mixture was stirred at room temperature for 4 h. After the reaction quenched with saturated aqueous NH_4Cl, the mixture was extracted (3×) with EtOAc. These extracts were washed with brine, dried, and evaporated, and the residue was chromatographed on silica gel eluting with hexane/EtOAc (1:1) to afford the product **3h** (80 mg, 51%); ^{1}H NMR (acetone-d_6) δ 1.75 (m, 2H), 2.40 (m, 1H), 2.55 (m, 1H), 3.65 (m, 1H), 4.35 (s, 1H), 4.48 (m, 1H), 4.60 (m, 1H), 5.60 (br s, 3H), 6.70 (d, 1H), 6.85 (br s, 1H), 7.30 (d, 1H), 7.68 (m, 2H), 7.85 (m, 2H), 7.95 (s, 1H), 8.22 (m, 2H), 8.42 (s, 1H).

Preparation of the Hydrochloride Salt of 3g. To a solution of **3g** (6.245 g) in dry EtOAc (450 mL) was added slowly a dilute solution of HCl in EtOAc with care to avoid excess of the HCl. When no more precipitation occurred on further addition, the white microgranular solid was filtered under nitrogen atmosphere and washed with dry EtOAc. The hydrochloride salt was obtained (6.27 g, 93%) as a stable, white solid: mp 155 °C dec. Anal. C, H, N, Cl. HPLC analysis on reverse phase column indicated >99.5% purity with only traces (0.15%) of an impurity resulting from opening of the bicyclooctanyl ring.

Acknowledgment. We warmly acknowledge the contributions of Dr. W. M. Abraham, Mount Sinai Medical Center, University of Miami School of Medecine, for the sheep study and the personnel of Merck Frosst Laboratory Animal Resources for their technical support.

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JM970046B