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QUINOLINES AS POTENT 5-LIPOXYGENASE INHIBITORS: SYNTHESIS AND BIOLOGICAL PROFILE OF L-746,530

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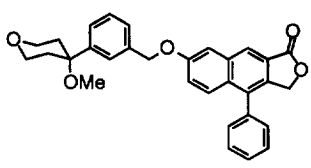
Abstract: Leukotriene biosynthesis inhibitors have potential as new therapeutic agents for asthma and inflammatory diseases. A series of novel substituted 2-cyanoquinolines have been synthesized and the structure activity relationships were evaluated with respect to their ability to inhibit the formation of leukotrienes via the 5-lipoxygenase enzyme. [1*S*,5*R*]-2-Cyano-4-(3-furyl)-7-{3-fluoro-5-[3-(3α-hydroxy-6,8-dioxabicyclo[3.2.1]-octanyl)]phenoxymethyl}quinoline (L-746,530) **3** represents a distinct class of inhibitors and possesses in vitro and in vivo potency comparable or superior to naphthalenic analog (L-739,010) **2**.

Introduction. Leukotrienes are important mediators derived from the biotransformation of arachidonic acid through the action of 5-lipoxygenase (5-LO).[1] Inhibition of leukotriene (LT) biosynthesis could give rise to new class of therapeutic agents for the treatment of asthma and other inflammatory disorders.[2] We have previously introduced new classes of indirect FLAP (5-lipoxygenase activating protein)[3] and direct 5-LO inhibitors such as the naphthalenic lignan lactone **1**.[4] In the latter series, in vivo and in vitro metabolism studies have shown that the lactone portion of the molecule was highly susceptible to metabolism.[5] The replacement of the lactone moiety of the lignan series by a cyano group gave potent and metabolically more stable naphthalenenitrile inhibitors[6] but created very lipophilic derivatives that are poorly absorbed. One successful strategy to improve the bioavailability of the series was achieved by replacing the phenyl ring by a pyridine and this modification provided the pyridinylsubstituted 2-cyanonaphthalene **2** (L-739,010) which underwent preclinical animal toxicity studies.[7]

Our continuing effort to find other potent and orally active inhibitors has led us to explore new series of compounds in which the naphthalene of **2** was replaced by other heterocycles. Thus, a series of analogs were prepared leading to the identification of derivative **3** (L-746,530), a 2-cyanoquinoline that presents an overall biological profile similar or better than the parent 2-cyanonaphthalene L-739,010 (**2**).



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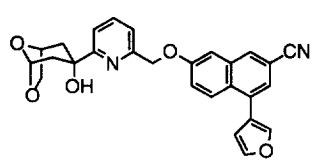
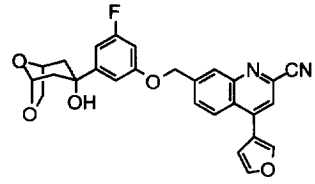


2 L-739,010

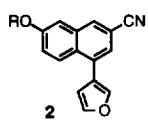
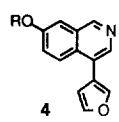
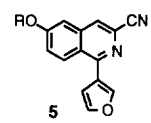
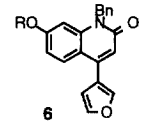
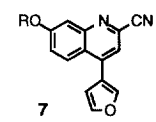


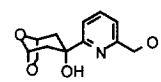
3 L-746,530

PII: S0960-894X(98)00201-7

Structure–Activity Relationship. In this paper, we report further investigation on the SAR with particular emphasis on modifications of the naphthalene portion of the molecule in order to improve the bioavailability of this series. From previous SAR studies in the 2-cyanonaphthalenes[6,7] and lignan lactones,[4] we learned that a polar carbonyl or a nitrile functional group was essential at the position 2 on the naphthalene for good in vitro potency. Heterocycles containing nitrogen could be formulated as salts, which could improve aqueous solubility and potentially oral absorption.[8] Therefore, we synthesized substituted isoquinolines **4** and **5**, quinolinone **6**, and quinoline **7** and linked them to the previously optimized dioxabicylooctanyl phenyl or pyridinyl moiety. All the compounds prepared were evaluated for their potency to inhibit the oxidation of arachidonic acid by recombinant human 5-LO (H5-LO),[9] the production of LTB_4 in human peripheral blood polymorphonuclear leukocytes (HPMN)[10] and the production of LTB_4 in human whole blood (HWB).[10]

Table 1. In vitro potency for isoquinolines **4** and **5**, quinolinone **6**, and quinoline **7** compared to cyanonaphthalene **2**.

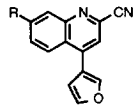
entry	 2	 4	 5	 6	 7
	IC_{50} (nM)				
H5-LO	20	1460*	1960*	102	36*
HPMN	1.6	10.3	18	5.8	4.0
HWB	42	90	47*	160*	103

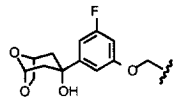
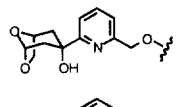
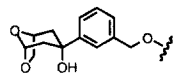
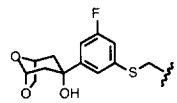
RO = 

*Each IC_{50} value corresponds to an average of at least two independent determinations, except those identified with an asterisk, which derived from a single titration.

From Table 1, it should be noted that isoquinolines **4** and **5** and quinolinone **6** showed a marked decrease in potency in the H5-LO assay as compared to the reference compound L-739,010 (**2**). The 2-cyano quinoline **7** had the best overall in vitro profile. Since it has been demonstrated that the nature of the linkage between the aryl middle ring and the naphthalene group also influences the potency of H5-LO inhibitors,[4,7] it was pertinent to reexamine the linkage with this best quinoline replacement (Table 2). Substitution of the oxymethylene link by a methyleneoxy and changing the pyridine ring to a 3-fluorophenyl L-746,530 (**3**) resulted in total recovery of the original in vitro profile associated with naphthalenic analog L-739,010 (**2**). The replacement of the oxygen atom in the linker with a sulfur (Table 2, entry 9) was detrimental to the inhibition of the H5-LO enzyme in all three assays.

Table 2. In vitro potency for analogs bearing various links and aryl groups with the 7-substituted 2-cyano-4-(3-furyl)quinoline.



entry	R	IC_{50} (nM) H5-LO	HPMN	HWB
3		27	2.3	36
7		36*	4.0	103
8		>3000*	10*	287*
9		124	6.0	193*

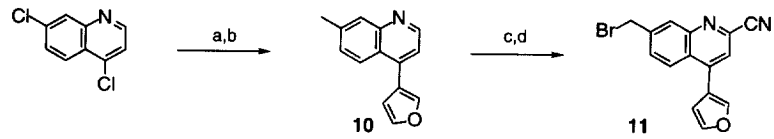
*Each IC_{50} value corresponds to an average of at least two independent determinations, except those identified with an asterisk, which derived from a single titration.

Bioavailability and in vivo Efficacy. Preliminary bioavailability studies performed on **3** as its mesylate salt demonstrated that this compound is very well absorbed when administered in 0.5% methocel suspension in rats at a dose of 100 mg/kg. We observed a bioavailability of 100% (0–24 h) and a maximum concentration ($C_{max.}$) of 16 μM between 4 and 6 h after dosing. The effect of **3** on the biosynthesis of leukotriene B_4 in vivo was evaluated in the rat pleural cavity using a carrageenan-induced model of inflammation.[10] In this model, L-746,530 (**3**) showed excellent activity with an $ED_{50} < 0.1$ mg/kg 6 h after oral dosing. For comparison, L-739,010 (**2**) and MK-0591 (FLAP inhibitor) gave ED_{50}s of 0.3 and 0.15 mg/kg, respectively, under the same conditions.

The potency of **3** as an inhibitor of urinary leukotriene E_4 production in dogs (an index of the systemic biosynthesis of peptidoleukotrienes) and of the ex vivo generation of leukotriene B_4 by whole blood stimulated with calcium ionophore A23187, was measured in anesthetized dogs.[11] In a dose dependent fashion, **3** was a very potent leukotriene biosynthesis inhibitor in vivo with an ED_{50} of 0.23 mg/kg/min for the inhibition of the baseline urinary LTE_4 excretion and with an ED_{50} of 0.26 mg/kg/min for the inhibition of ex vivo LTB_4 generation by the dog whole blood. For comparison, L-739,010 and MK-0591 (FLAP inhibitor) gave ED_{50}'s of 0.23 and 1.0 mg/kg/min (in vivo LTB_4 excretion), 0.45 and 0.51 mg/kg/min (ex vivo LTB_4 in dog whole blood), respectively, under the same conditions.

Chemistry. The quinoline backbone for compounds **3** and **9** was prepared starting from commercial 4,7-dichloroquinoline and the corresponding 3-furylboronic acid in a Suzuki type palladium catalyzed cross-coupling reaction to afford selectively the 4-(3-furyl)-7-chloro quinoline. The methyl group is introduced using a nickel catalyzed Grignard coupling[12] and the cyano group using TMSCN[13] on the N-oxide. The methyl group is oxidised to the bromomethyl precursor **11** using NBS in CCl_4 (Scheme 1).

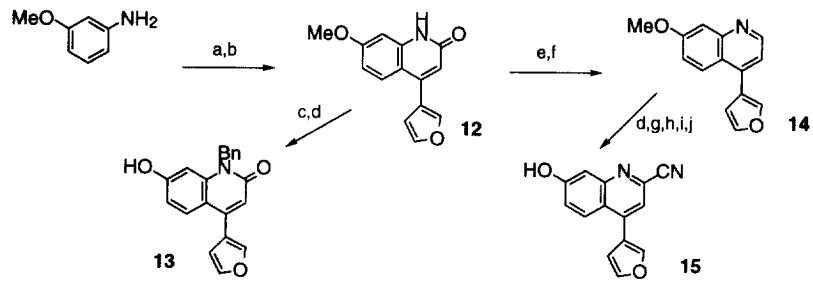
Scheme 1



Reagents: (a) 3-furylB(OH)$_2$,Na$_2$CO$_3$, PhH-EtOH, (Ph$_3$P)$_4$Pd (75%); (b) MeMgBr, Ni(DPPP)Cl$_2$, Et$_2$O (92%); (c) i. mCPBA ii. TMSCN, Me$_2$NCOCl, CHCl$_3$ (87%); (d) NBS, AIBN, CCl$_4$ (79%).

The 7-hydroxy quinoline backbones for compound **6** and **7** were prepared from substituted β-ketoamides by way of the Knorr quinolone synthesis.[14] The ketoamide was produced by heating 3-anisidine and ethyl 3-furoyl acetate in the presence of pyridine. Treatment with hot phosphoric acid effected smooth conversion to quinolone **12** and then N-alkylation followed by demethylation gave **13**, the precursor for compound **6**. The same precursor **12** was dehydrated in two steps to the quinoline **14**, followed by insertion of the nitrile as described earlier, leading to the hydroxy quinoline precursor **15** (Scheme 2).

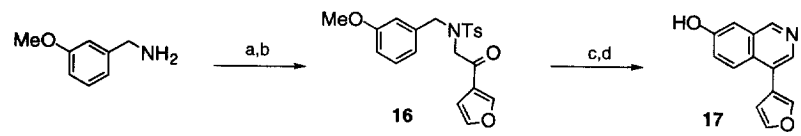
Scheme 2



Reagents: (a) EtO$_2$CCH$_2$CO-3-furyl, pyridine, xylene, reflux (45%); (b) H$_3$PO$_4$, 100 °C (90%); (c) NaH, BnBr, DMF (50%); (d) Pyr-HCl , 170 °C (79%); (e) LAH, THF, reflux; (f) CAN, CH$_2$CN-H$_2$O (38% 2 steps); (g) TBSCl, imidazole, DMF (91%); (h) mCPBA; (i) TMSCN, Me$_2$NCOCl, CHCl$_3$; (j) TBAF, THF (74% 3 steps).

The isoquinoline precursor for compound **4** can be prepared using a modified Pomeranz–Fritsh synthesis.[15] 3-Methoxy benzylamine is tosylated and then alkylated with chloroacetylfuran[16] to afford the amide **16** which is then treated with TFA to induce cyclisation, leading to the 2-isoquinoline **17** after demethylation (Scheme 3).

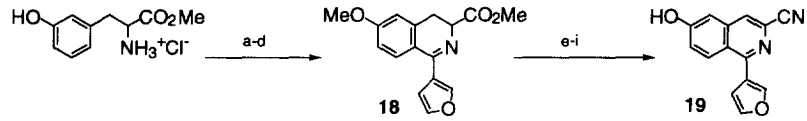
Scheme 3



Reagents: (a) TsCl, pyr, CH$_2$Cl$_2$ (66%); (b) Cs$_2$CO$_3$, ClCH$_2$CO-3-furyl, acetone (22%); (c) TFA (83%); (d) Pyr-HCl , 200 °C (67%).

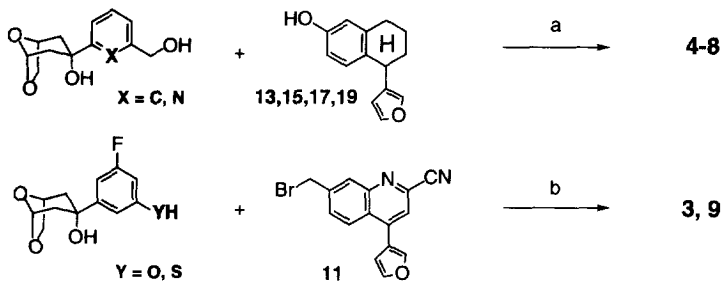
The isoquinoline **5** was prepared using the Bishler–Napieralski cyclisation[17] starting with *m*-tyrosine methyl ester which is converted to the dihydroisoquinoline **18** in 4 steps as outlined in Scheme 4. Aromatisation with DDQ followed by conversion of the ester to the nitrile provides the isoquinoline **19**.

Scheme 4



Reagents: (a) 3-furoyl chloride, TEA, DMAP; (b) NaOMe, MeOH (94% 2 steps); (c) K_2CO_3, MeI (96%); (d) P_2O_5, xylene, reflux (57%); (e) DDQ, PhH (82%); (f) Pyr-HCl, 200 °C; (g) HCl, MeOH (50% 2 steps); (h) NH_3, MeOH; (i) TFAA, pyr, dioxane (51% 2 steps).

Scheme 5



Reagents: (a) DBAD, Ph_3P, THF (80–87%). (b) Cs_2CO_3, acetone (69–76%).

The final products **3–9** were obtained via Mitsunobu type condensations of arylmethanols[18] with 7-hydroxyquinoline/isoquinoline or from alkylation of the bicyclooctanephenol/thiophenol[19] with the appropriate bromide using cesium carbonate in acetone (Scheme 5).

Conclusion. A series of novel heterocyclic 5-LO inhibitors were prepared to study structure–activity relationships. L-746,530 (**3**) reported herein showed a good oral bioavailability, an excellent overall biological profile and was considered as a candidate for preclinical animal toxicity studies.[20]

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