Discovery of Phenyl Acetic Acid Substituted Quinolines as Novel Liver X Receptor Agonists for the Treatment of Atherosclerosis

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Abstract: A structure-based approach was used to optimize our new class of quinoline LXR modulators leading to phenyl acetic acid substituted quinolines **15** and **16**. Both compounds displayed good binding affinity for LXRβ and LXRα and were potent activators in LBD transactivation assays. The compounds also increased expression of ABCA1 and stimulated cholesterol efflux in THP-1 cells. Quinoline **16** showed good oral bioavailability and in vivo efficacy in a LDLr knockout mouse model for lesions.

Liver X receptors (LXRs: LXRα and LXRβ)[a] are members of the nuclear hormone receptor super family and are involved in the regulation of cholesterol and lipid metabolism.[1] They are ligand-activated transcription factors and bind to DNA as obligate heterodimers with retinoid X receptors (RXR). To date, several LXR agonists (Figure 1), such as a natural ligand 24-(*S*), 25-epoxycholesterol (**1**, EPC),[2] as well as two structurally distinct synthetic nonsteroidal ligands **2** (GW3965)[3] and **3** (TO901317),[4] have been shown to increase expression of the ATP binding cassette transport A1 (ABCA1) gene and raise HDL levels in mice. ABCA1 is required for efflux of cholesterol from cells to lipid-poor apoA-I protein and HDL particles.[5] Activation of LXRs also results in the inhibition of inflammatory gene expression.[6] Thus, LXR agonists have the potential to be beneficial therapeutic agents in the treatment of atherosclerosis.

An undesirable effect observed with these known LXR compounds was a significant increase in serum and liver triglyceride levels via the upregulation of SREBP-1c and other lipogenic genes in the liver. In this report, we describe our structure-based efforts in the optimization of novel substituted quinolines as liver X receptor agonists.

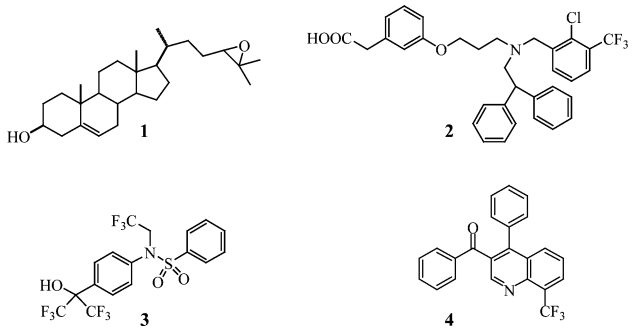

Figure 1. Known LXR agonists and the initial quinoline lead.

Our initial quinoline lead **4** arose from a preliminary SAR study of a screening hit identified using a CHO-cell based reporter assay employing a stably transfected hLXRβ reporter cell line (LAFβ).[7] Quinoline **4** showed a moderate LXRβ binding affinity (Table 1) with an IC_{50} of 107 nM.[8] Compound **4** also demonstrated the LAFβ activity with an EC_{50} value of 1.4 μM, however, it was a partial agonist (25% efficacy) when compared to reference standard **3**. To improve the potency of **4**, a structure-based design approach was undertaken. To date, several LXR X-ray crystal structures of the ligand binding domain (LBD) have been published, and our understanding at the molecular level of how LXR ligands exert their effects has been dramatically enhanced by elucidation of these crystal structures.[9,10]

The structures revealed a flexible ligand binding pocket, which allows ligands of different shapes and sizes to be accommodated by adjustment of rotational conformers of several residues within the binding pocket. Examination of the published X-ray structure of LXRβ/**2**[9] revealed several features, which seem important for the high affinity (LXRβ IC_{50} = 10 nM) observed for this ligand. In addition to the observed binding pocket being considerably larger than that of **3**, **2** took advantage of the cavities used by **3**, as well as formed additional interactions with the receptor. The key interaction of this ligand came from the terminal acid group, which made a well-ordered hydrogen bond network with the main-chain nitrogen of residue Leu330 and the Nϵ, NH atoms of Arg319, while the diphenylethyl and the chloro-trifluoromethyl benzyl groups took advantage of several hydrophobic groups that line this pocket.

Our initial docking studies (QXP) of compound **4**, using the compound **2** ligand binding site, revealed a clear opportunity for optimizing this scaffold and prompted us to investigate further structural features necessary for improving its potency.[11] Figure 2 (the docked orientation of compound **4** overlayed with the X-ray structure of **2**) showed that the nitrogen atom of the quinoline ring was involved in a hydrogen bond interaction with the Nϵ of His435, while the 2-benzyl group lay oriented toward the region of hydrophobic residues Phe340, Phe349, and Phe271. Realizing that compound **4** did not occupy the pocket fully and was missing the crucial interaction with the Arg319 pocket, we decided to explore the 4-phenyl group of this ligand with additional substitution (for position definitions of 3, 4, 3′, 4′, m, and p, see Scheme 1, compound **9**). Subsequent docking analysis also suggested that the 3′ position rather than the 4′ from this ring would provide an open access to the pocket.

Our hypothesis that a carboxylic acid might be needed to facilitate binding to the Arg-319 residue of the LXRβ receptor

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[a] Abbreviations: ABCA1, ATP binding cassette transport A1; Apo, apolipoprotein; DBD, DNA-binding domain; HDL, high-density lipoprotein; LAF, L = LXRE, A = alkaline, and F = phosphates; LDL, low-density lipoprotein; LXR, liver X receptor; PPAR, peroxisomal proliferator-activated receptor; LXRE, LXR response elements; QXP, Quick eXPlore, a docking program; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element binding protein 1c.

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Table 1. LXR Activity of Quinolines of General Structure **9**[a]

compd	X	3′ or 4′	m or p	linker L	R	hLXRβ binding IC_{50} (nM)	hLXRα binding IC_{50} (nM)	LAFβ EC_{50} (nM/% eff.)
2						12	100	410 (30%)
3						10	10	16 (100%)
4						107	260	1400 (25%)
10	O	3′	p	OCH_2	CO_2H	67	130	186 (40%)
11	O	3′	p	OCH_2	CO_2Me	>1000	>1000	296 (17%)
12	O	3′	m	OCH_2	CO_2H	1033	1871	1500 (5%)
13	O	4′	p	OCH_2	CO_2H	2738	723	1500 (5%)
14	O	3′	p	OCH_2	CH_2CO_2H	5	16.5	143 (77%)
15	H,H	3′	p	OCH_2	CH_2CO_2H	2.1 ± 0.4 ($n = 14$)	9.5 ± 2.9 ($n = 14$)	71 ± 21 ($97 \pm 10\%$) ($n = 12$)
16	H,H	3′	p	$NHCH_2$	CH_2CO_2H	1.9 ± 0.6 ($n = 3$)	7.6 ± 0.8 ($n = 3$)	33 ± 2.4 ($85 \pm 13\%$) ($n = 3$)
17	H,H	3′	p	CH_2NH	CH_2CO_2H	7	47	not tested
18	H,H	3′	p	$N(Me)CH_2$	CH_2CO_2H	115	274	374 (60%)

[a] Results are given as the mean of two independent experiments unless otherwise indicated. The standard deviations for these assays were typically ±30% of mean or less. The % of efficacy is relative to **3**.

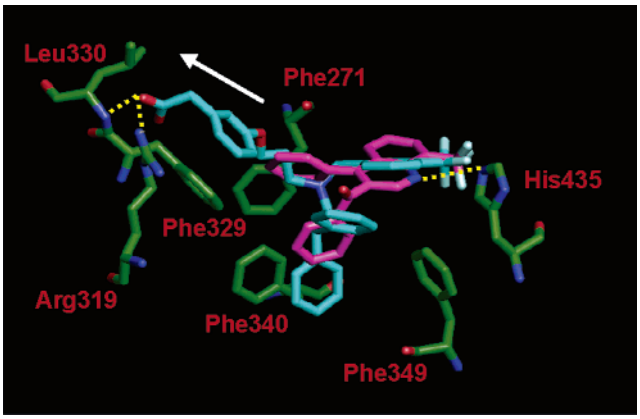
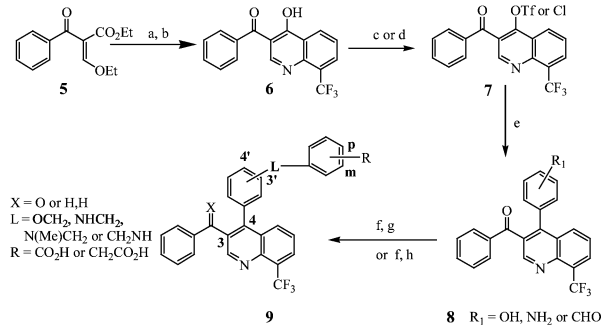


Figure 2. Docked orientation of compound **4** (magenta) overlayed with LXRβ complexed with ligand **2** (cyan). Only key residues are shown for clarity. The white arrow draws attention to the corresponding region for which there is an open access for substitution from the 3′-position of the 4-phenyl group.

Scheme 1[a]



[a] Reaction conditions: (a) 2-(trifluoromethyl)aniline, toluene, 82%; (b) Dowtherm, 56%; (c) *N*-phenylbis(trifluoromethane-sulfonamide), K_2CO_3, DMF, 65%; (d) $POCl_3$, DMF; (e) phenylboronic acids, K_3PO_4, $Pd(PPh_3)_4$, dioxane; (f) benzyl bromides, K_2CO_3 or benzylamines, $NaBH(OAc)_3$, DMF; (g) NaOH, THF/MeOH/H_2O; (h) N_2H_4, KOH, ethane-1,2-diol.

led to the design and synthesis of a few quinoline acids prepared according to Scheme 1. Condensation of ethyl 2-benzoyl-3-ethoxyacrylate (**5**) with 2-trifluoromethylaniline, followed by thermal cyclization, provided the phenol **6**. Conversion of the phenol **6** to the triflate or chloride **7** was accomplished readily with *N*-phenylbis(trifluoromethanesulfonimide) or phosphorus oxychloride. Reaction of **7** with phenylboronic acid under Suzuki conditions provided **8**. Alkylation of **8** with benzyl bromides or reductive amination of **8** with benzyl aldehydes, followed by aqueous basic hydrolysis, gave the carboxylic acids. The C-3 carbonyl was reduced via hydrazine reduction.

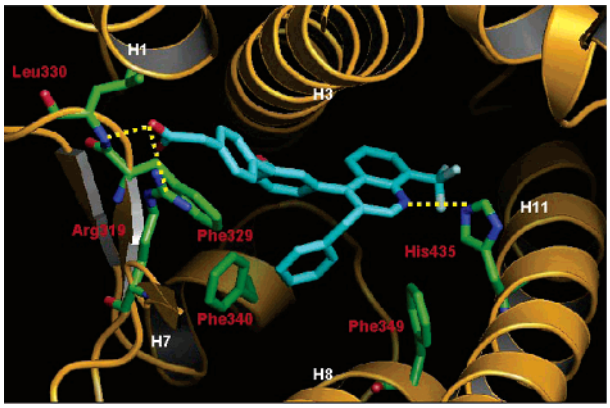


Figure 3. X-ray crystal structure of **15** bound to hLXRβ. Only key residues involved in ligand interaction are shown for clarity. Hydrogen bonds to key residues are shown as yellow dotted lines.

Our first attempt to utilize an acid group as an Arg319 acceptor (compound **10**) showed an improvement in potency with hLXRβ binding IC_{50} value of 67 nM and LAFβ efficacy of 40%. The corresponding methyl ester **11** was much less active (hLXRβ binding IC_{50} value of more than 1 μM), which provided evidence of the necessity of the negatively charged carboxylic acid interaction with the Arg319 residue. However, because the Arg319 residue does show some flexibility in the different X-ray structures (**2** versus **3** X-ray[10]), we decided to probe further the optimal orientation of this acid group in that pocket. The *meta*-carboxylic acid isomer of **10**, namely **12**, was a much weaker LXRβ agonist with hLXRβ binding IC_{50} value of 1 μM. A dramatic difference in activity was also observed with **13**, its 4′-substituted isomer, which had an IC_{50} value of greater than 2 μM. All these observations suggested that *para*-substituted carboxylic acid, which was attached to the 3′ position of the 4-phenylquinoline, might orient the acid group toward the Arg319 residue. Another large increase in potency was observed with the addition of a methylene spacer between the carboxylic acid and the adjacent phenyl ring to provide **14**, which had hLXRβ binding IC_{50} value of 5 nM. The cellular potency of **14** (LAFβ EC_{50} of 143 nM and 77% efficacy) was also improved through conversion of benzoic acid to phenyl acetic acid.

The in vitro stability of **14** was then determined in pooled liver microsomes prepared from male C57 mice and mixed-gender humans. Compound **14** was moderately metabolized in rodent liver microsomes (data not shown), but was rapidly metabolized in human liver microsomes ($t_{1/2}$ = 3.5 min). Metabolite ID analysis of **14** indicated that the carbonyl attached to the C_3-quinoline was rapidly reduced to a hydroxyl moiety. To eliminate this metabolically labile C=O, a C_3-benzyl

Table 2. Gene Expression Activity of **15** and **16** and Selectivity in Gal4 Human Transactivation Assays[a]

compd	ABCA1[b]	SREBP1c[b]	Gal4 hLXRβ[b]	Gal4 hLXRα[b]	Gal4 PPARα[c]	Gal4 PPARγ[c]	Gal4 PPARδ[c]
15	55 (172%)	45 (106%)	90 (63%)	240 (90%)	1312 ± 225 (19 ± 5%) (n = 8)	680 ± 230 (47 ± 11%) (n = 9)	627 ± 365 (24 ± 5%) (n = 8)
16	33 (151%)	15 (73%)	87 (70%)	160 (82%)	1300 (71%)	320 (20%)	1320 (37%)

[a] EC_{50} in nM, % eff.[13−15] [b] Results are given as the mean of two independent experiments. The standard deviations for these assays were typically ±50% of mean or less. The % of efficacy is relative to **3**. [c] Results are given as the mean of two independent experiments unless otherwise indicated. The % of efficacy is relative to references: PPARα, [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (WY-14643); PPARγ, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione (Rosiglitazone); PPARδ, 3-chloro-4-[[3-[(3-phenyl-7-propyl-6-benzofuranyl)oxy]propyl]thio]-phenylacetic acid (L-796449).

substituted quinoline, compound **15**, was prepared. The removal of the C═O greatly improved the stability of **15** in human liver microsomes, giving an in vitro $t_{1/2}$ of 107 min. Quinoline **15** maintained its potency in the binding assays as well as the cellular assays. It showed a binding affinity of 2.1 nM against hLXRβ, an EC_{50} of 71 nM with 97% efficacy in LAFβ, and an EC_{50} of 90 nM with 63% efficacy in Gal4-DBD-hLXRβ LBD transactivation assay.[12a] It also had potent affinity to LXRα (binding IC_{50} = 9.5 nM) and was nearly a full agonist in the Gal4-DBD-hLXRα LBD transactivation assay (EC_{50} = 240 nM, 90% efficacy). In addition, **15** increased expression of ABCA1 in THP-1 cells with an EC_{50} of 55 nM and an efficacy of 172% relative to **3**.[12b] It further stimulated cholesterol efflux in a concentration-dependent manner in THP-1 macrophages preincubated with acetylated LDL and [1,2-^{3}H]cholesterol. An estimated EC_{50} value of 20 nM was observed for **15** in these lipid-laden cells resembling atherosclerotic foam cells.[12b] However, in the Huh7 liver cell line, **15** increased expression of SREBP-1c with an EC_{50} value of 45 nM and an efficacy of 106% relative to **3**, showing that this compound did not have the desired gene selectivity.

An X-ray structure of the LBD domain of hLXRβ complexed with **15** (Figure 3, resolution 2.15 Å)[16] was subsequently solved, and as predicted, the acid group did form a network of well-ordered hydrogen bond interactions with the NH backbone of Leu330 and Arg319. The quinoline nitrogen was involved in a hydrogen bond interaction with His435, while the 3-benzyl group protruded into the hydrophobic pocket formed by residues Phe340, Phe349, and Phe271. The overall folding of this structure is similar to those previously reported[9,10] and will not be described in detail here.

Further modifications on the linker region were undertaken, and the benzylamine based quinoline **16** was found to have the same LXR activity in the LXR binding and Gal4 transactivation assays (LXRβ binding IC_{50} value of 1.9 nM, EC_{50} of 87 nM with 70% efficacy in Gal4-DBD-hLXRβ assay) as **15**. X-ray structure of the LBD domain of LXRβ complexed with **16** showed the bound conformation of this ligand is identical to that of **15**, and the acid group makes similar hydrogen bond interactions with the NH backbone of Leu330 and Arg319 residues (the X-ray structure of **16** is not shown). However, **16** showed a 2-fold increase in LAFβ with an EC_{50} value of 33 nM. Quinoline **16** increased expression of ABCA1 in THP-1 cells as well with an EC_{50} of 33 nM and an efficacy of 151% relative to **3**, which is slightly more potent than **15**. It also stimulated cholesterol efflux with an EC_{50} value of 37 nM. However, in the liver cell line, **16** increased expression of SREBP-1c with an EC_{50} value of 15 nM and an efficacy of 73% relative to **3**, again demonstrating a lack of desired gene selectivity. Compared to **16**, the reversed benzylamine analogue **17** displayed a 3-fold reduction in binding affinity with LXRβ IC_{50} value of 7 nM. The *N*-methylated derivative **18**, however, showed much weaker LXR activities in both binding and LAF cells, with LXRβ IC_{50} value of 115 nM and LAFβ EC_{50} value of 374 nM.

Quinoline **15** and **16** were selective against a few closely related nuclear receptors (data not shown). However, in human Gal4-PPAR transactivation assays, both compounds were shown to be PPAR active (Table 2), with an EC_{50} value of 0.3 μM or higher.

After oral dosing at 10 mg/kg in male C57 mice, the bioavailability of **16** was 67%, with a C_{max} of 3.74 μg/mL, $AUC_{(0\rightarrow\infty)}$ of 4.44 μg hr/mL, terminal $t_{1/2}$ of 1.3 h and a T_{max} of 0.5 h. An accelerated atherosclerotic lesion study[17] was conducted in high fat/high cholesterol (1.25%)-fed LDLr knockout mice and administration of quinoline **16** for 8 weeks at 10 mg/kg/day orally resulted in a significant reduction in lesion burden by 45 ± 22% (n = 8) compared to the control group. In the same experiment, the literature standard **2** also significantly reduced the lesion burden by 27 ± 7% (n = 8). The details of these studies will be reported in due course.

In summary, quinoline **16** has been identified using structure-based design as a potent LXR agonist that upregulates ABCA1 binding cassette transporter in macrophage cells. The compound also has good oral bioavailability in mice and displayed in vivo efficacy in LDLr knockout mice for lesions. We are continuing to investigate the SAR and biological properties of this new series of LXR agonists.

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Supporting Information Available: Experimental details, ^{1}H NMR, MS, and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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