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Quinoline-3-carboxamide containing sulfones as liver X receptor (LXR) agonists with binding selectivity for LXRβ and low blood–brain penetration

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ABSTRACT

A series of quinoline-3-carboxamide containing sulfones was prepared and found to have good binding affinity for LXRβ and moderate binding selectivity over LXRα. The 8-Cl quinoline analog **33** with a high TPSA score, displayed 34-fold binding selectivity for LXRβ over LXRα (LXRβ IC_{50} = 16 nM), good activity for inducing ABCA1 gene expression in a THP macrophage cell line, desired weak potency in the LXRα Gal4 functional assay, and low blood–brain barrier penetration in rat.

It is widely recognized that elevated levels of low density lipoprotein cholesterol (LDLc) and reduced levels of high density lipoprotein cholesterol (HDLc) represent major risk factors for cardiovascular disease.[1] Despite the wide use of effective lipid-lowering drugs, cardiovascular disease is still the leading cause of morbidity and mortality in the industrialized world. Liver X receptors (LXRα and LXRβ) are members of the nuclear hormone receptor superfamily and are involved in the regulation of cholesterol and lipid metabolism.[2,3] They are ligand-activated transcription factors and bind to DNA as obligate heterodimers with retinoid X receptors (RXR). Activation of LXRs induces the expression of several genes involved in lipid metabolism and reverse cholesterol transport including ATP binding cassette transporters A1 and G1 (which drive cellular cholesterol efflux), A5 and G8 (which promote hepatocyte-biliary and enterocyte excretion of cholesterol), adipocyte and macrophage-ApoE (which promote cholesterol efflux), and cholesterol ester transfer protein (CETP, which transfer cholesterol from HDL to non-HDL lipoproteins). The potential to prevent or even reverse atherosclerotic processes by increasing the expression of these genes makes LXR an attractive drug target for the treatment of cardiovascular diseases. A number of LXR agonists (Fig. 1), such as TO901317 (**1**),[4] GW3965 (**2**),[5] and WAY-254011 (**3**),[6] have been shown to significantly reduced lesion size in an atherosclerosis mouse model. However, these pan agonists also caused substantial liver and plasma triglyceride (TG) increases by the up-regulation of sterol regulatory element binding protein 1c (SREBP-1c) and fatty acid synthase (FAS) which limits the utility of these synthetic LXR agonists. Several strategies[2,3] have been proposed for improving the therapeutic window of LXR agonists including LXRβ subtype selective agonists, partial agonists, and gene or tissue specific agonists. The first hypothesis is based on the observation that LXRα is the predominant subtype expressed in the liver and that activation of LXRα may be responsible for the TG liability in vivo. Therefore, LXRβ selective LXR agonists may have less impact on TG synthesis, but may be effective in macrophage reverse cholesterol transport. A modest level of LXRβ binding selectivity in small molecules has been achieved. A series of cinnolines/quinolines was reported by Wyeth[7] and it was found that these LXRβ binding selective agonists displayed good activity for inducing ABCA1 gene expression and poor efficacy in the LXRα Gal4 functional assay. However, these cinnolines/quinolines exhibited poor drug-like properties.

WAY-252623 (**4**), the first LXR agonist clinical candidate which was also reported by Wyeth, possessed potent LXR binding affinity (LXRβ binding IC_{50} of 23 nM) with a modest ~7-fold binding selectivity for LXRβ.[8] Compound **4** had acceptable oral bioavailability of 63%, 28%, 35% in mice, rat, and monkey, respectively. It showed reduction of aortic arch lesion progression in LDLR −/− mice with much reduced triglyceride elevation over agonists **1** and **3**. A single ascending-dose (SAD) study of **4** in healthy humans was conducted and it was found that **4** dose-dependently increased LXR target gene expression (ABCA1 and ABCG1).[9] However, central nervous system (CNS)-related adverse events were observed at the two

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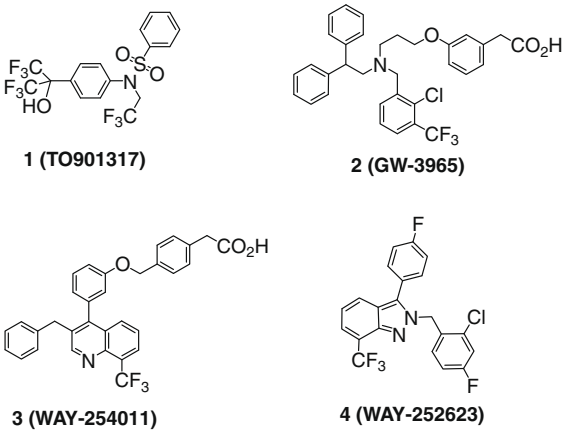
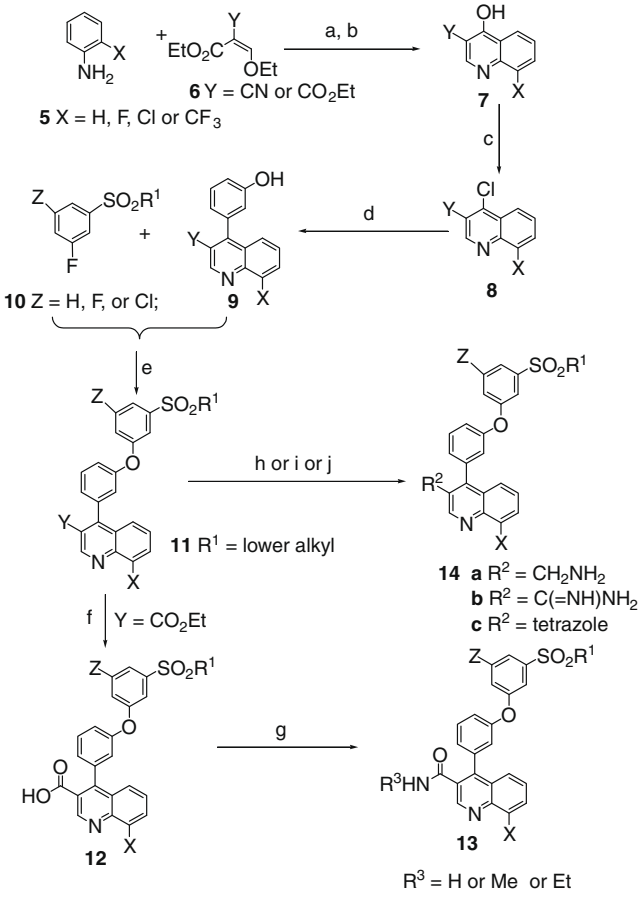


Figure 1. Reported LXR agonists.

top doses tested (150 mg and 300 mg). It is not clear whether the observed adverse effects were a result of an off-target effect of **4** or were related to LXR modulation in the brain. However, for a cardiovascular drug, a compound that does not penetrate the blood–brain barrier may offer benefits, particularly with regard to a CNS side effect profile. Analysis of CNS and non-CNS drugs revealed that the CNS drugs had lower polar surface areas (PSA) and higher calculated log *P*(*c* Log *P*) values.[10] Compound **4** has a low topological polar surface area (TPSA value of 17) and a high calculated log *P* value (*c* Log *P* = 7.5). It is widely accepted that compounds with high *c* Log *P* (>4.5) and low TPSA (<80) have much higher chances to penetrate the blood–brain barrier.[10] To avoid CNS-related side effects, we therefore focused our new efforts on LXRβ selective agonists with low *c* Log *P* (<4.5) and high TPSA (>90).

The preparation of the quinoline-3-carboxamide containing sulfones is depicted in Scheme 1. Condensation of aniline **5** with 2-(ethoxymethylene)malonate **6** followed by thermal cyclization provided the phenol **7**. Conversion of the phenol **7** to the chloride **8** was accomplished readily with phosphorus oxychloride. Reaction of **8** with 3-hydroxylphenylboronic acid under Suzuki conditions provided **9**. Arylation of **9** with fluorobenzene **10**[11] followed by aqueous basic hydrolysis of **11** (Y = CO_2Et) gave the carboxylic acids **12**. The resulting carboxylic acids were readily converted to C-3 carboxamide substituted biarylether **13** by reaction with carbonyldiimidazole in DMF followed by addition of amines. Reduction of ester in **11** (Y = CO_2Et) with lithium aluminum hydride followed by treatment with methylsulfonyl chloride and ammonium hydroxide gave the corresponding benzyl amine **14a**. The C-3 amidine analog **14b** was obtained by treatment of **11** (Y = CN) with ammonium chloride and trimethylaluminum. The C-3 tetrazole ring of **14c** was formed by cycloaddition of sodium azide with **11** (X = CN).

As stated previously phenyl acetic acid based analogs such as compound **3** had considerable PPAR activity that needed to be removed.[7] The phenyl acetic acid moiety was responsible for the PPAR activity. To find a polar group as a replacement for the phenyl acetic acid, a series of amides, alcohols, sulfonamides, and sulfones were screened by Wyeth.[12] The sulfone moiety was a superior polar group for potent quinoline LXR agonism (see **15** in Table 1). Compound **15** and analogs had no PPAR activity and lower *c* Log *P* (5.6 for **15**) relative to **4** (*c* Log *P* 7.8) or **3** (*c* Log *P* 7.7). In an effort to develop LXRβ-selective agonists with low brain penetration potential a series of 3-polar group substituted quinoline sulfones with low *c* Log *P* (<4.5) and high TPSA (>90) was prepared. The LXR binding affinity of the newly synthesized compounds was evaluated in radio ligand binding assays.[6] As a reference, TO-901317 (compound **1**) was tested in the binding assays and was found to

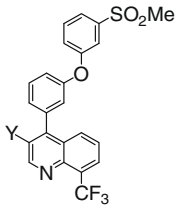


Scheme 1. Reagents and conditions: (a) toluene; (b) Dowtherm, total yield 70–90% for step (a) and (b); (c) $POCl_3$, 85–100%; (d) 3-OH-phenylboronic acid, K_3PO_4, $Pd(PPh_3)_4$; 50–85%; (e) K_2CO_3, DMF, 40–80%; (f) LiOH; (g) CDI/NH_4OH or NH_2Me or NH_2Et, total yield 55–79% for (f) and (g); (h) LAH; MsCl/NEt_3; NH_4OH; 21%; (i) $NH_2HCl/AlCl_3$, 25%; (j) NaN_3/NEt_3HCl, 84%.

be a potent LXR pan agonist. As can be seen in Table 1 the 3-primary carboxamide substituted quinoline sulfone **16** showed potent binding affinity (IC_{50} = 18 nM) for LXRβ, good subtype binding selectivity against LXRα (α/β 33-fold), lower *c* Log *P* (4.0) compared to **15** (*c* Log *P* = 5.6), and a high TPSA (99) value. Analogs incorporating a 3-methyl (**17**) or 3-ethyl (**18**) carboxamide resulted in >20-fold drop in the LXRβ binding affinity. While 3-ethyl ester **19** was a potent LXRβ binder with IC_{50} of 2 nM, poor binding selectivity was observed for this compound. The corresponding carboxylic acid **20** showed much reduced binding affinity (hLXRβ IC_{50} > 1 μM). Similarly, the 3-CN analog **21** showed potent binding affinity to LXRβ (IC_{50} = 2.2 nM), however, poor binding selectivity was observed (α/β = 6). A few 3-CN derivatives with high TPSA values (>80), such as, 3-tetrazole **22**, 3-methylamines **23**, and 3- amidine **24**, were prepared and all of them showed reduced LXRβ binding affinity and low binding selectivity against LXRα.

To enhance the LXRβ binding affinity and/or selectivity of **16**, a few small alkyl substituted sulfones (**25**–**29**) were prepared (Table 2). In general, these compounds had good binding affinity (hLXRβ IC_{50} < 60 nM) and good binding selectivity against LXRα (α/β > 20. Isopropyl sulfone **29** was the most selective compound in the C-8-trifluoromethyl quinoline series which had 57-fold binding selectivity over LXRα and good binding affinity (hLXRβ IC_{50} = 5 nM). While a fluorine at the meta position of the sulfone maintained LXRβ binding affinity and selectivity (**25** vs **16**), chlorine substitution at the same position resulted in decreased LXRβ binding affinity (**26** vs **16**).

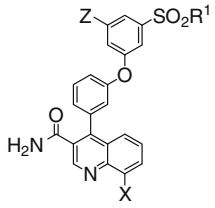
Table 1
Quinoline C3 modifications[a]



Compd	Y	*c* Log *P*	TPSA	hLXRβ $IC_{50,}$ (nM)	hLXRα $IC_{50,}$ (nM)	α/β
1		4.2	57	9	13	1
15[12d]	Me	5.6	56	1	2	2
16	$CONH_2$	4	99	18	600	33
17	CONHMe	4.3	85	367	>10,000	>4
18	CONHEt	4.9	85	730	6864	9
19	COOEt	5.9	82	2	6.6	3
20	COOH	4.6	93	1076	6348	6
21	CN	4.9	80	2.2	13.4	6
22	Tetrazole	4.3	111	5294	26,613	5
23	CH_2NH_2	4.0	82	77	445	6
24	$C(=NH)NH_2$	4.4	106	5133	29,850	6

[a] Results are given as the mean of at least two independent experiments. The standard deviations for these assays were typically ±30% of mean or less.

Table 2
SAR of C-8 and phenyl sulfone modifications[a,b]



Compd	R^1	X	Z	*c* Log *P*	hLXRβ $IC_{50,}$ (nM)	hLXRα $IC_{50,}$ (nM)	α/β
16	Me	CF_3	H	4	18	600	33
25	Me	CF_3	F	4.3	18	552	31
26	Me	CF_3	Cl	4.8	62	1772	29
27	Et	CF_3	H	4.5	11	453	41
28	Pr	CF_3	H	5.1	57	1365	24
29	*i*-Pr	CF_3	H	4.8	5	286	57
30	Me	Me	H	3.6	28	756	27
31	Me	F	H	3.3	590	12,700	22
32	Me	H	H	3.1	2850	>10,000	
33	Me	Cl	H	3.8	16	543	34

[a] Results are given as the mean of at least two independent experiments. The standard deviations for these assays were typically ±30% of mean or less.
[b] All compounds in Table 2 have the same TPSA value of 99.

Several less hydrophobic (lower *c* Log *P*) replacements (compounds **30**–**33**) for the C-8-trifluoromethyl substituent were then evaluated. Compared to C-8 trifluoromethyl analog **16** (*c* Log *P* 4.0), a small loss of binding activity was seen in the C-8 methyl analog **30** (*c* Log *P* 3.8). Replacing the trifluoromethyl with a fluorine (**31,** *c* Log *P* 3.3) or hydrogen (**32**, *c* Log *P* 3.1) resulted in much reduced affinity in the binding assays (hLXRβ IC_{50} >500 nM for **31** and **32**). Chlorine proved to be a good replacement for trifluoromethyl since the 8-chloro quinoline **33** had essentially the same LXRβ binding affinity and binding selectivity as **16**. Compared to **4**, 8-chloro quinoline **33** had much lower *c* Log *P* (7.8 for **4** vs 3.8 for **33**) and higher TPSA value (17 for **4** vs 99 for **33**), which may lead to lower blood–brain penetration and therefore may offer benefits over **4** in term of the CNS related side effects of **4**.

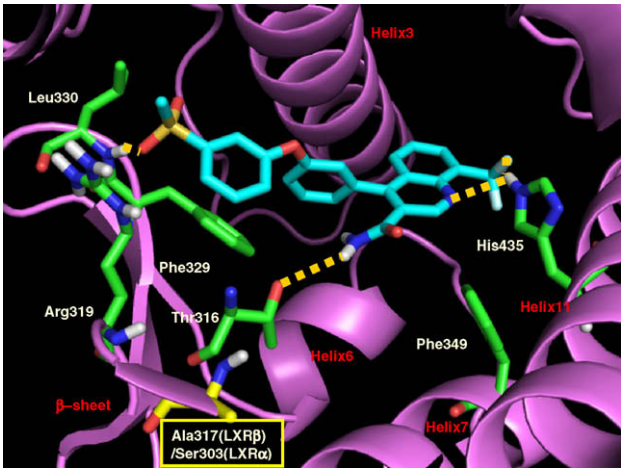


Figure 2. Docked structure of **16** bound to hLXRβ. Hydrogen bonds are shown by yellow dotted lines. Residue adjacent to Thr_{316} , that is, Ala_{317} is highlighted in yellow and is different between LXRα/LXRβ, that is, Ala_{317}(LXRβ)/Ser_{303}(LXRα).

In order to understand the modest LXRβ selectivity (α/β 33-fold) of **16**, we docked this ligand into a previously solved in-house X-ray structure of compound **3**.[6] The best scoring pose[13] of **16** from the docking studies is shown in Figure 2. The N1 atom of the quinoline ring made a hydrogen bond interaction with the Nε atom of His_{435} residue. In addition the 8-CF_3 group was in close proximity, that is, *d*(N–F) = 3.1 Å to make favorable electrostatic interactions with this residue and provide additional binding affinity. The benzyloxy group further extended towards the β-hairpin loop and placed the sulfone group in position to make hydrogen bond interaction with the backbone NH of Leu_{330}. The C-3 carboxamide group was twisted slightly out of the plane with respect to the quinoline ring and the amino group made a weak hydrogen bond interaction, that is, *d*(N–O) = 3.2 Å with the Thr_{316} residue within the helix-5 region. Since all residues in close proximity (<5 Å) of the ligand-binding pocket of LXRα and LXRβ are identical it is possible that the modest selectivity of **16** comes from perturbations of residues within the 2nd shell which are different between these two recep-

Table 3
Functional assays[a,b]

Compd	hLXRβ IC_{50} (nM)	α/β	LXRβ Gal4 EC_{50} (μM, % eff)	LXRα Gal4 EC_{50} (μM, % eff)	ABCA1 (THP1) EC_{50} (μM, % eff)	TG (HepG2) EC_{50} (μM, % eff)
1[8]	9	1	0.17 (100%)	0.14 (100%)	0.044 (100%)	0.137 (100%)
4[8]	24	7	3.67 (73%)	6.66 (53%)	0.54 (100%)	1.0 (38%)
16	18	33	1.6 (85%)	4.5 (22%)	0.11 (104%)	0.37 (47%)
33	16	34	0.63 (72%)	3.0 (57%)	0.44 (107%)	1.25 (68%)

[a] Results are given as the mean of two to three independent experiments. The standard deviations for functional assays were typically ±50% of mean or less. The % of efficacy is relative to reference compound **1**.
[b] LXR transactivation assay used Huh7 cells transfected with human LXR LBD fused to Gal4 DBD; ABCA1 gene regulation by LXR ligands was measured in THP1 (human) cells; LXR-mediated TG accumulation was measured in HepG2 cells.

Table 4
Pharmacokinetic properties of **4** and **33** in long Evans rat[a,b]

Compd	C_{max} (ng/mL, plasma)	$AUC_{0\text{-inf}}$ (h*ng/mL, plasma)	C_{max} (ng/mL, brain)	$AUC_{0\text{-inf}}$ (h*ng/mL, brain)	B/P ratio
4	2853	13,057	3526	15,312	1.2
33	1269	5417	107	457	0.08

[a] Dose: oral gavage 30 mg/kg for **4** and 10 mg/kg for **33**.
[b] Formulation: Methocel 0.5%:Tween 80 2%.

tors. Indeed if one looks at the residue adjacent to the Thr_{316} residue, Ala_{317} in LXRβ is mutated to Ser_{303} in LXRα. We believe the C-3 carboxamide group of **16** may confer LXRβ binding selectivity due to the ability of the carboxamide group to make interaction with Thr_{316} residue. This conclusion is supported by our SAR studies which showed that methylation of one of the carboxamide hydrogens, that is, **17**, resulted in loss of potency and selectivity. Further docking studies on **17** showed that due to steric interactions with the C-4 phenyl group, the carboxamide group was forced to flip in a different orientation and thereby lost its hydrogen bonding ability with the Thr_{316} residue.

Binding selective LXR agonists **16** and **33** were tested in the Gal4 transactivation assays (Table 3, for assay conditions see reference 6). Like compound **4**, these two binding selective compounds were weak agonists for LXRα, but showed better efficacy and potency for LXRβ. In contrast, literature compound **1** is a potent agonist for both LXRα and LXRβ in the Gal4 assays. An LXR agonist having lower activity against LXRα may have less liability with respect to triglyceride synthesis. As expected, the compounds in this new series (without the acetic acid moiety) had no cross activity against PPARα, γ, and δ receptors (data not shown) as measured in transiently transfected cell lines. Furthermore, when profiled in THP1 macrophages, compound **16** and **33** showed good efficacy (>100%) for stimulating an endogenous LXR target gene ABCA1. Compound **33** also stimulated [^{3}H] cholesterol efflux in THP-1 foam cells and was as nearly potent (EC_{50} = 10 nM, 71% agonism) as **1** (EC_{50} = 3 nM, 100% agonism) or **3** (EC_{50} = 6 nM, 88% agonism). On the other hand, compound **33** showed reduced potency and efficacy in stimulating TG synthesis in HepG2 cells relative to **1**.

Given that **33** had desirable physicochemical properties[14] for low CNS penetration a rodent pharmacokinetic study was performed (Table 4) and it was confirmed that **33** had good exposure in plasma but a poor brain $AUC_{0\text{-inf}}$/plasma $AUC_{0\text{-inf}}$ (B/P) ratio of 0.08. In contrast, compound **4** had good exposure in brain and high brain penetration with a B/P ratio of 1.2. Thus, **33** may not produce the CNS related side effects which were observed for **4**. As stated above, compound **33** had good LXRβ binding selectivity, reduced potency and efficacy against LXRα relative to **1** in the Gal4 assay, and reduced potency and efficacy in stimulating TG synthesis relative to **1** in HegG2 cells. However, the amount of potency and efficacy reduction in the HepG2 cells was not deemed sufficient to see a favorable TG profile in vivo, therefore, the compound was not pursued further.

In summary, a series of novel quinoline 3-carboxamide containing sulfones, with relatively low *c* Log *P* (<4.5) and high TPSA scores (>90) was found to show potent LXRβ agonism and indeed this design led to compounds that showed reduced blood–brain penetration. This work has produced >30-fold LXRβ binding selective agonists. Some efficacy and potency selectivity in the Gal4 transactivation assays between LXRβ and LXRα was obtained; however, low separation between ABCA1 up-regulation in macrophage versus TG accumulation in HepG2 cells was observed for the series.

Acknowledgments

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14. A set of blood brain barrier (BBB) rules by Lobell et al. suggested that CNS penetrable compounds should have the following: N + O < 6; TPSA < 60–70; MW < 450; Log *D* = 1–3; *c* Log *P*-(N+O) > 0. Compound **33** with the following properties: N + O = 6; TPSA 99; MW = 452; Log D = 3.0−4.25 @ pH 2 ∼ 9; *c* Log *P*-(N + O) = −2.2 may suggest that the compound should have low brain penetration potential. For the BBB rule details see: Ref. 10b.