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Synthesis of 4-(3-biaryl)quinoline sulfones as potent liver X receptor agonists

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ABSTRACT

A series of 4-(3-biaryl)quinolines with sulfone substituents on the terminal aryl ring (**8**) was prepared as potential LXR agonists. High affinity LXRβ ligands with generally modest binding selectivity over LXRα and excellent agonist potency in LXR functional assays were identified. Many compounds had LXRβ binding IC_{50} values <10 nM while the most potent had EC_{50} values <1.0 nM in an ABCA1 mRNA induction assay in J774 mouse cells with efficacy comparable to T0901317. Sulfone **8a** was further evaluated in LDL (−/−) mice and shown to reduce atherosclerotic lesion progression.

A major cause of mortality in modern societies is atherosclerotic cardiovascular disease (CVD),[1] characterized by the accumulation of low density lipoprotein (LDL) particles in the arterial wall leading to the formation of cholesterol-laden foam cells and immune system activation.[2] Important therapeutics directed towards modification of the HMG-CoA reductase pathway (e.g., statins, Lipitor®) have been developed.[3] Although these therapies lower circulating levels of low density lipoprotein (LDL) cholesterol and successfully reduce the incidence of CVD,[4] myocardial infarction events and ischemic stroke are only reduced by one-third, and many individuals with 'normal' LDL levels suffer from atherosclerosis.

High density lipoprotein (HDL) bound cholesterol, sometimes called 'good cholesterol' seems to protect against cardiovascular diseases.[5] The HDL particle contributes to the transport of cholesterol from lipid-laden macrophages, (foam cells), present in the atherosclerotic arteries to the liver for secretion into the bile.[6] This pathway has been termed reverse cholesterol transport (RCT) and is considered as the classical protective function of HDL toward atherosclerosis. Therapeutic agents that promote RCT and affect the level of circulating HDL would potentially compliment the existing LDL-based therapies.

The liver X receptor (LXR) belongs to the nuclear hormone superfamily and is comprised of two subtypes: LXRα and LXRβ.[7] The LXRs in conjunction with retinoid X receptors (RXRs).[8] serve as intracellular oxysterol sensors and regulate expression of genes involved in lipid metabolism.[9] The LXR target genes include many of those known to be involved with the RCT pathway, specifically those regulating cellular cholesterol efflux, HDL metabolism, and biliary cholesterol excretion.[10]

We have examined LXR agonists to increase expression of cholesterol transporters including ATP-binding cassette proteins (ABCs), a family of lipid transporters responsible for regulating lipid homeostasis (Fig. 1).[11] Of particular importance is ABCA1, a transporter in macrophages and other cells which mediates cholesterol efflux from peripheral cells to the lipid-poor apo-lipoprotein acceptors.[12]

LXRα is expressed in intestine, lung, kidney, spleen, and macrophages, but especially in liver. In contrast, LXRβ is widely distributed in nearly all cell types. Both LXR subtypes (α and β) form heterodimers with RXRs and the resulting complex can be activated by binding of either an LXR agonist (e.g., endogenous oxysterols such as 24,25-epoxycholesterol) or an RXR agonist

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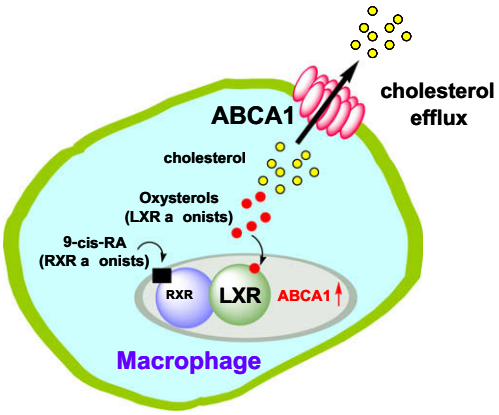


Figure 1. Oxidized cholesterol activates the LXR-RXR heterodimer, upregulating the ABCA1 transporter and increasing cholesterol efflux.

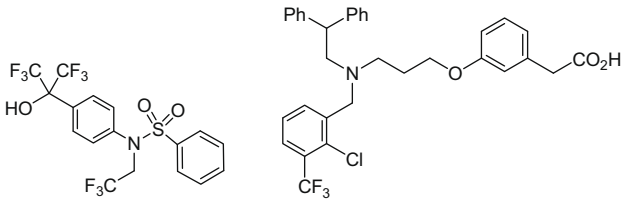


Figure 2. LXR agonists from Tularik and GlaxoSmithKline.

(e.g., 9-cis-retinoic acid, 9-cis-RA) which activates mRNA transcription encoding various genes, including ABCs.[9] In addition to their role in lipid efflux, LXRs may also have an important anti-inflammatory role which may help minimize the development of athlerosclerosis.[13]

Several pharmaceutical companies have been active in developing LXR agonists. Among the most studied are Tularik's T0901317 (**1**)[14] and GlaxoSmithKline's GW3965 (**2**)[15] (Fig. 2) both of which are high affinity LXR ligands with potent agonism for both LXR subtypes.

Earlier Wyeth efforts identified potent LXR agonist LXR-623 (**3**),[16] which effectively treated dislipidemia in mice but showed unacceptable CNS effects at higher doses in a phase I clinical trial (Fig. 3).[17] An alternate series was found which replaced the indazole core with a substituted quinoline leading to WAY-254011 (**4**).[18] Typically quinoline benzyloxyacetic acids such as **4** had excellent affinity and were potent LXR agonists. Unfortunately, **4** possessed moderate PPAR agonism, activating all three subtypes of the receptor.[19]

Modification of the benzyloxyacetic acid by incorporating alternate hydrogen bond acceptors led to a series of biarylether amides[20] (**5**) and alcohols[21] (**6**) which gave high affinity LXR agonists with minimal or no PPAR activation (Fig. 4). Further changes in the hydrogen bond acceptor led to placement of sulfone groups on the terminal aryl ring providing a series of potent LXR agonists **7** which did not activate PPAR receptors.[22]

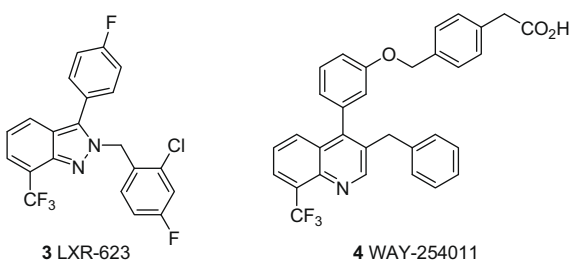
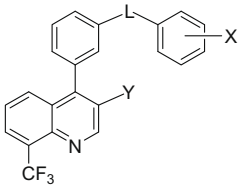


Figure 3. LXR agonists from Wyeth.



5 X = C(O)NR^{1}R^2, L = O
6 X = CR^{1}R^{2}OH, L = O
7 X = SO$_2$R^1, L = O
7a X = SO$_2$CH$_3$, Y = H, L = O
8 X = SO$_2$R^1, L = direct bond

Figure 4. Modifications of 4-[aryl-linked-Ph]quinolines.

Based on docking studies, replacing the oxygen linker in **7** (L = O) with a rigidifying direct bond as in **8** (L = bond) would provide an acceptable trajectory allowing the sulfone substituent to interact with key residues in the LXRβ ligand binding domain (LBD). An overlay of docked structure **8a** with an X-ray structure of **7a** co-crystallized with LXRβ illustrates the key interactions important for affinity[23] (Fig. 5). The His435 residue serves as a dual hydrogen bond donor with the quinoline nitrogen and the 7-trifluoro methyl group. In addition the critical hydrogen bond interaction between a sulfone oxygen and the backbone NH of Leu330 was also observed.

Sulfones **8** were synthesized starting with preparation of carbinol **9** by directed anion formation at low temperature followed by addition to 3-bromobenzaldehyde (Scheme 1). Oxidation of **9** afforded phenone **10**. Reaction with aqueous ammonia at elevated temperature and pressure provided aniline **11**. Friedlander cyclization[24] of **11** with an appropriately substituted aldehyde (YCH$_2$CHO) gave quinoline **12**. This high yielding sequence allowed introduction of diversity at the C-3 position of the quinoline core. Suzuki coupling[25] of bromide **12** with substituted phenylboronic acids provided target quinolines **8**.[26] Alternatively, **12** was converted into the corresponding borolane **13**[27] which was isolated as a white, room temperature stable solid. Coupling of **13** with to arylbromides or aryliodides gave an alternative approach to **8**.

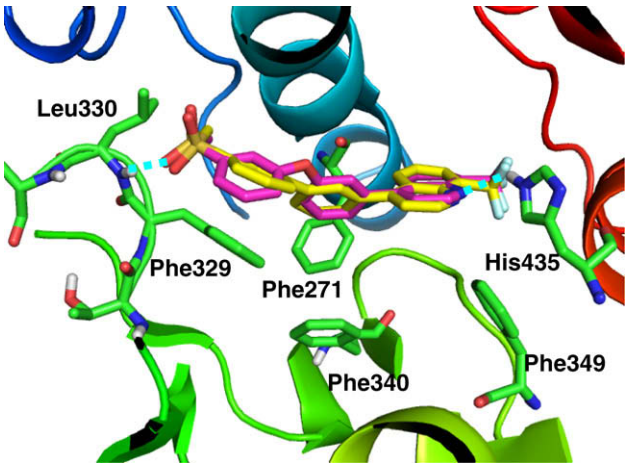
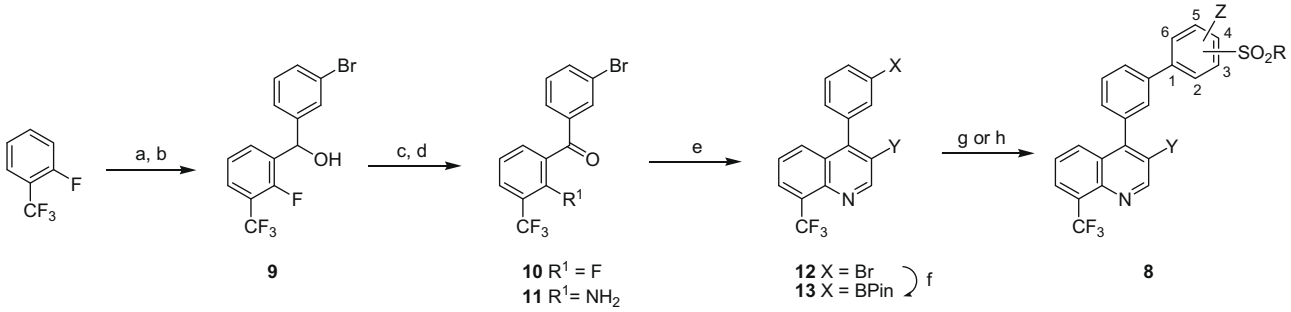


Figure 5. Docked structure of Compound **8a** (yellow) overlaid with X-ray structure of LXRβ and **7a** (magenta). Only important residues are shown for clarity. Hydrogen bonds are denoted by cyan dotted lines.

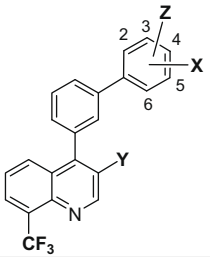


Scheme 1. Reagents and conditions: (a) *n*BuLi, THF, −78 to 0 °C, 6 h; (b) 3-bromobenzaldehyde, 0 °C, 2 h; (c) pyridinium chlorochromate, CH_2Cl_2; (d) DMSO, concd NH_4OH, sealed tube, 100 °C, 4–6 h; (e) YCH_2CHO, AcOH, H_2SO_4 (cat), 120 °C; (f) bis(pinacolato)diborane, $Pd(PPh_3)_4$, KOAc, toluene, 100 °C; (g) $ArB(OH)_2$, Cs_2CO_3, $Pd(PPh_3)_4$, DMF, 90 °C; (h) ArBr or ArI, Cs_2CO_3, $Pd(PPh_3)_4$, DMF, 90 °C.

Final targets **8** were tested to determine binding affinity for the two LXR subtypes (Table 1).[18] The binding assays used recombinant human ligand binding domains (LBDs) of the respective LXRα and LXRβ subtypes measuring displacement of [^{3}H]T0901317 from the LBD.[28] Typically, the *meta*-methylsulfones had excellent LXR affinity while the *para* analogs had an order of magnitude weaker affinity (compare **8a**, **8c**, and **8e** to **8b**, **8d**, and **8f**, respectively). Focusing on *meta*-sulfones, the effect of varying the 3-subsituent on the quinoline (Y) was investigated but little change in affinity was seen as Y changed from a large lipophilic benzyl group down to a hydrogen. (see **8a**, **8c**, **8e**, **8g**–**i**). Increasing the size of the alkylsulfone even from methylsulfone to ethylsulfone reduced affinity suggesting a steric limit to the LBD pocket (compare **8j** to **8a** and **8k** to **8c**). Finally, an additional substituent on the sulfone-bearing ring had little effect on affinity (**8l**–**q**) except for methoxy (**8m**), again suggesting steric issues. Subtype binding selectivity for LXRβ over LXRα was only moderate, though a few compounds showed binding selectivity (LXRα IC_{50}/LXRβ IC_{50}) of 10- to 20-fold.

The higher affinity compounds were tested in a Gal4β functional assay for LXR activity.[18] These LXR transactivation assays used Huh7 cells transfected with human LXR ligand binding domains fused to Gal4 DNA binding domains. The positional preference for *meta*-sulfone substitution over *para* in the functional assay was apparent comparing **8e** to **8f**, with a 33-fold greater potency favoring the *meta* over the *para* isomer. Another SAR point explored was the importance of the quinoline 3-substituent (Y). Benzyl and larger alkyl groups typically gave comparable activity but a methyl or hydrogen at this position had modestly weaker potency (e.g., **8a** and **8c**). Varying the alkyl group on the sulfone also slightly reduced potency (compare **8c** with **8k** and **8a** with **8j**) in this assay. The potency was maintained and tracked with the binding data for additional substituents (Z) on the phenylsulfone ring

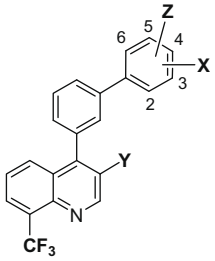
Table 1
Biarylsulfone quinolines **8**[a]



Compd	X	Y	Z	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	Gal4β EC_{50} (nM) (% agonism)	Microsomal stability $t_{1/2}$ (r, min)
1	—	—	—	9	13	170 (100 %)	>30 (r, h)
8a	3-SO_2Me	H	H	4.4	68	525 (73%)	>30 (r, h)
8b	4-SO_2Me	H	H	>1000	>1000	nt	>30 (r, h)
8c	3-SO_2Me	Me	H	1.8	9.0	284 (94 %)	>30 (r)
8d	4-SO_2Me	Me	H	355	>1000	nt	>30 (r, h)
8e	3-SO_2Me	CH_2Ph	H	1.5	7.0	100 (112%)	16 (r)
8f	4-SO_2Me	CH_2Ph	H	109	372	3300 (44%)	7 (r), 27 (h)
8g	3-SO_2Me	Et	H	2.4	4.8	76 (93%)	>30 (r, h)
8h	3-SO_2Me	Pr	H	3.8	7.6	106 (98%)	>30 (r, h)
8i	3-SO_2Me	*i*Pr	H	4.1	8.2	91 (97%)	>30 (r, h)
8j	3-SO_2Et	H	H	33	362	1080 (30%)	>30 (r, h)
8k	3-SO_2Et	Me	H	5.2	73	580 (67%)	>30 (r, h)
8l	3-SO_2Me	Me	4-Me	3.2	12	175 (110%)	27 (r), >30 (h)
8m	3-SO_2Me	Me	4-OMe	629	>1000	nt	>30 (h)
8n	3-SO_2Me	Me	4-F	1.7	10	161 (80%)	19 (r), >30 (h)
8o	3-SO_2Me	Me	4,6-di F	3.3	10	195 (81%)	>30 (r, h)
8p	3-SO_2Me	H	4-F	2.6	32	512 (76%)	12 (r), >30 (h)
8q	3-SO_2Me	H	4,6-di F	4.9	25	565 (76%)	>30 (r, h)

[a] Results are given as the mean of two independent experiments. The standard deviations for the binding and Gal4β assays were typically ±30% of the mean or less. % of efficacy is relative to **1**. nt = not tested. r = rat liver microsomes, h = human liver microsomes.

Table 2
Gene regulation and TG accumulation for **8**[a]



Compd	X	Y	Z	ABCA1[b] EC_{50} (nM) (% agonism)	SREBP-1c[d] EC_{50} (nM) (% agonism)	TG accum[e] EC_{50} (nM) (% agonism)
1	—	—	—	35 (100%)	36 (100%)	107 (100%)
8a	3-SO_2Me	H	H	77 (94%)	440 (93%)	77 (94%)
8c	3-SO_2Me	Me	H	23 (124%)	52 (118%)	23 (124%)
8f	4-SO_2Me	CH_2Ph	H	571 (101%)	571 (101%)	571 (101%)
8g	3-SO_2Me	Et	H	0.7 (121%)	8.0 (121%)	0.7 (121%)
8h	3-SO_2Me	Pr	H	0.4 (107%)	8.0 (129%)	0.4 (107%)
8i	3-SO_2Me	*i*Pr	H	0.5 (110%)	6.0 (117%)	0.5 (110%)
8j	3-SO_2Et	H	H	156 (80%)	521 (74%)	156 (80%)
8k	3-SO_2Et	Me	H	190 (69%)	250 (108%)	190 (69%)
8p	3-SO_2Me	H	4-F	140 (103%)[c]	nt	41 (43%)
8q	3-SO_2Me	H	4,6-di F	11 (111%)	132 (81%)[f]	133 (43%)

[a] Results are given as the mean of two independent experiments. % efficacy is relative to **1**. nt = not tested. r = rat, h = human.
[b] J774 cell line.
[c] THP-1 cells.
[d] Huh7 cells.
[e] HepG2 cells

(cf. **8a** to **8p**, and **8q**, and **8c** to **8l**–**o**). The biaryl-sulfones typically showed no agonism when tested in Gal4-PPAR transactivation assays reported earlier.[20]

Most compounds were further tested for efficacy for upregulating ABCA1 mRNA in a J774 mouse macrophage cell line (Table 2).[28] Efficacy was measured relative to **1** with the maximum increase in mRNA using **1** taken as 100% efficacy. Overall, the same SAR trends in the Gal4β assay were seen here. For example, larger alkyl substituents Y on the quinoline core such as ethyl, propyl, and isopropyl gave very potent, fully efficacious compounds (**8g**–**i**). With smaller groups such as hydrogen and methyl, the potency dropped off (**8a**, **8c**) although the efficacy was maintained. Larger alkylsulfones reduced both affinity and potency (**8a** to **8j** and **8c** to **8k**). Additional phenyl sulfone ring substituents maintained activity and typically showed an increase in mRNA levels (**8p** and **8q**). Out of this series, **8a**, **8c**, and **8g**–**i** were the most potent and were all essentially as efficacious as **1**. Unfortunately compound **8a** also increased expression of SREBP-1c in Huh7 cells with an EC_{50} value of 440 nM and an efficacy of 93% relative to **1**, demonstrating a lack of desired gene selectivity.

Compound **8a** and several analogs were examined in a functional assay which measured changes in TG levels in a human hepatic cell line (HepG2). It was found that the most potent compounds for up regulating ABCA1 mRNA also increased intracellular TG levels. The increase in TG concentrations may relate to undesired accumulation of lipids, particularly in the liver.

In an assay testing for stability in rat and human microsomes,[29] the majority of compounds were stable in both rat and human microsomes. Typically, larger alkyl groups and benzyl substitution at C3 of the quinoline core provides less stable compounds. The pharmacokinetics of **8a** was characterized by a very long terminal $t_{1/2}$ of 13.9 h and excellent bioavailability (~100%) following 10 mg/kg po (gavage) dosing in 0.5% methylcellulose/2% Tween in water in male C57 mice, with a C_{max} of 106 ng/mL, $AUC_{0-\infty}$ of 3009 ng h/mL, and a T_{max} of 1.0 h.[30]

In an accelerated atherosclerotic lesion study[31] **8a** showed a statistically significant and dose dependent decrease in lesion progression (33%, 59% and 60% at 3, 10 and 30 mg/kg/day, respectively) but with an undesired increase in triglyceride levels.

In summary, a series of 4-(biaryl)quinolines **8** was prepared in which a bond replaced an oxygen atom in an earlier biarylether series **7**. An efficient, convergent synthesis allowed variation at key positions on the molecules furthering SAR studies. A *meta*-sulfone on the terminal aryl ring gave particularly high affinity LXR ligands, typically with excellent agonist potency for upregulating the ABCA1 transporter in macrophage cells. Among these compounds, **8a** had 15-fold binding selectivity for LXRβ over the LXRα subtype and excellent oral bioavailability in mice. While **8a** displayed in vivo efficacy in LDLr knockout mice for lesions, the undesired SREBP-1c agonism as well as the TG accumulation, both in a cellular assay and in vivo, hindered further development of this series.

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