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1-(3-Aryloxyaryl)benzimidazole sulfones are liver X receptor agonists

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ABSTRACT

A series of 1-(3-aryloxyaryl)benzimidazoles incorporating a sulfone substituent (**6**) was prepared. High affinity LXR ligands were identified (LXRβ binding IC_{50} values <10 nM), some with excellent agonist potency and efficacy in a functional assay of LXR activity measuring ABCA1 mRNA increases in human macrophage THP1 cells. The compounds were typically stable in liver microsome preparations and had good oral exposure in mice.

Nuclear receptors are a superfamily of receptors which regulate gene expression. Among these gene transcription factors are the liver X receptors (LXRs) comprised of two subtypes: LXRα and LXRβ.[1] The highest level of LXRα is found in the liver but it is also found in intestine, lung, kidney, spleen, and macrophages while the LXRβ subtype is expressed in nearly all cell types. Both subtypes form heterodimers with retinoid X receptors (RXRs) and this dimerization is required for activity.[2] The heterodimer is activated by binding either an RXR agonist (e.g., 9-*cis*-retinoic acid) or an LXR agonist (e.g., endogenous oxysterols such as 24,25-epoxycholesterol).[3] Activation causes expression of genes coding for several ATP-binding cassette proteins (ABCs) which are responsible for lipid efflux from cells.[4] Among the more important ABCs are ABCA1, a key lipid transporter in macrophages, and ABCG5 which is localized on the intestinal wall and may reduce cholesterol absorption. Besides their function in lipid efflux, LXRs have an anti-inflammatory role so it has been proposed that LXR agonists may help prevent or reverse atherosclerosis through these two mechanisms.[3,5] These activities have made LXR agonists a pharmaceutical target.[6]

Several structurally diverse LXR agonist series have been reported. Among the earliest potent agonists for LXRα and LXRβ were Tularik's T0901317 (**1**)[7] and GlaxoSmithKline's GW3965 (**2**)[8] (Fig. 1). An indazole LXR agonist from Wyeth, LXR-623 (**3**),[9] advanced to the clinic but had CNS effects at higher doses in phase I.[10]

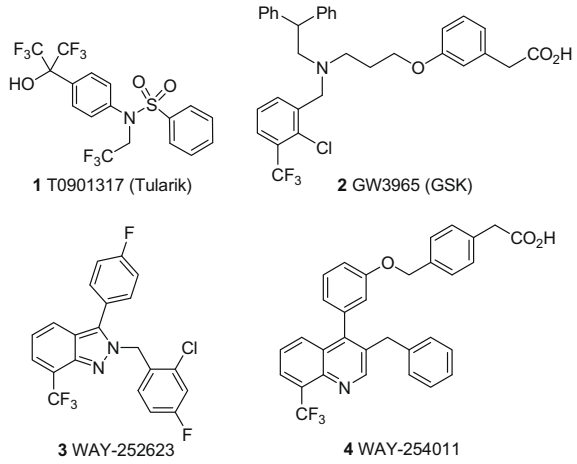

Figure 1. LXR agonists.

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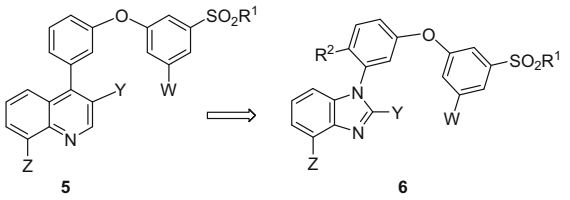
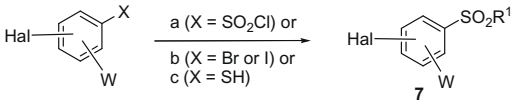


Figure 2. Modifications of 4-[3-(ArO)-Ph]quinolines **5** to 1-[3-(ArO)-Ph]benzimidazoles **6**.



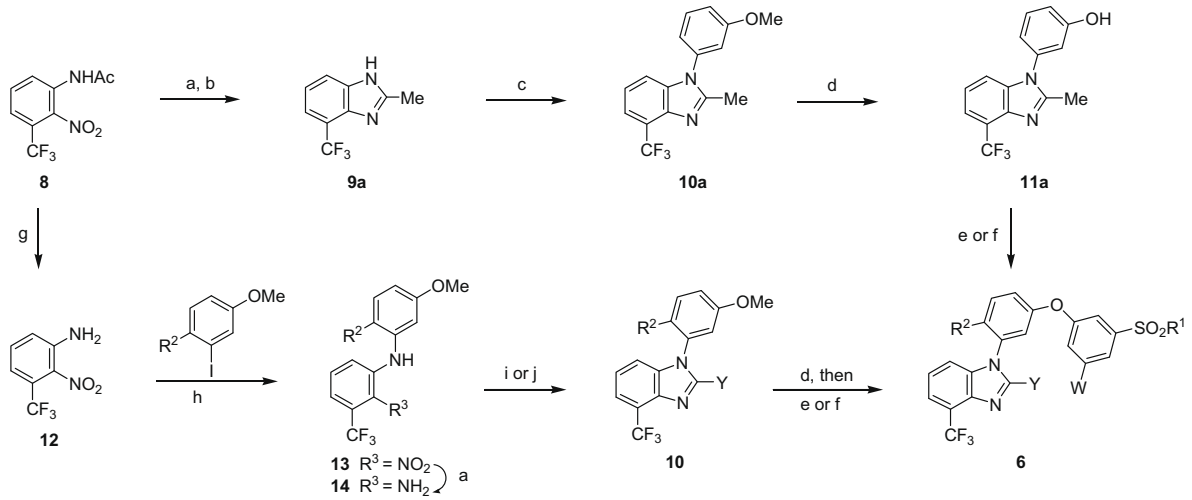
Scheme 1. Reagents and conditions: (a) Na_2SO_3 (1.87 equiv), $NaHCO_3$ (2 equiv), H_2O, 95–100 °C, 1 h, then tetrabutylammonium bromide (catalytic), R^1–Br or R^1–I (3–5 equiv), 35–90 °C; (b) $NaSO_2Me$ (1.2 equiv), CuI (0.1 equiv), L-proline (0.2 equiv), NaOH (0.2 equiv), DMSO, 95 °C, 18 h; (c) R^1–Br or R^1-I (1.3–1.5 equiv), K_2CO_3 (1.5–2 equiv), acetone, 60–70 °C, 2–3 h, then Oxone®, aq $NaHCO_3$, rt, 18–24 h.

Wyeth has also reported a quinoline series incorporating carboxylic acid side chains, typified by WAY-254011 (**4**).[11] Quinoline **4** was a high affinity LXRα and LXRβ ligand with potent LXR agonist activity. Unfortunately, **4** was a moderate PPAR agonist, activating all three subtypes of the receptor.[12] Modification of the benzylacetic acid group by incorporating other hydrogen bond acceptors and moving from a benzylic interaryl linker to an oxygen linker while retaining a 4-phenyl-quinoline core led to series of biarylether amides,[13] alcohols,[14] and sulfones[15] which gave high affinity LXR agonists. Sulfones **5** were especially potent in functional assays with good stability in liver microsomal incubations (Fig. 2). We turned to explorations of other replacements for the indazole and quinoline heterocycles in **3** and **5**, respectively, to understand the SAR of the series. Previous reports identified a histidine residue in the LXRβ protein that formed a key interaction with the N1 sp^2 nitrogen in both the indazole and quinoline. This suggested to us that a benzimidazole with a similarly positioned sp^2 nitrogen might be a good choice especially since, like indazole, it is a 5,6-fused bicyclic system. We describe here the synthesis and LXR activity of a series of benzimidazoles **6**.

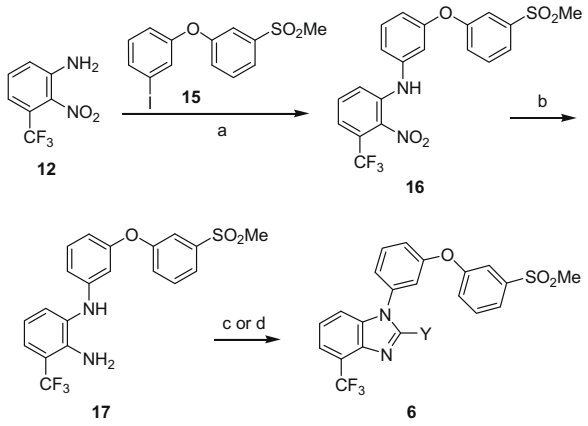
Preparation of biarylethers **6** generally relied on the synthesis of core phenols **11** which were either coupled with bromo- or iodoarylsulfones **7**, or reacted with fluoro- or chloroarylsulfones **7** in a displacement reaction. Noncommercial arylsulfones **7** were typically made by three methods (Scheme 1) to provide a diverse set of compounds. Partial reduction of an arylsulfonyl chloride with sodium bisulfite followed by alkylation in the same pot gave **7**.[16] Ma's copper iodide mediated coupling procedure[17] was also used to prepare methylsulfones directly from aryl iodide and bromides. Alkylation of thiophenols followed by oxidation, usually with Oxone®, also provided **7**.

1-(3-Hydroxyphenyl)-benzimidazoles **11** were synthesized by several complementary approaches. The first started with a literature nitration of *N*-acetyl-3-trifluoromethylaniline to afford a mixture of regioisomers, from which minor desired isomer **8** was isolated (Scheme 2).[18] Nitro reduction followed by heating with acetic acid gave benzimidazole **9a**.[19] Coupling[20] with iodoanisole provided **10a** which was demethylated to **11a**. An alternative approach to compounds **11** began with deacetylation of **8** to give nitroaniline **12** which was subjected to a coupling reaction with an iodoanisole to provide **13** which was in turn reduced to aniline **14**. Cyclization of **14** to **10** was accomplished using an acid chloride followed by treatment with phosphorous oxychloride. Alternatively, reaction of **14** with an orthoester under acidic conditions gave **10** directly.[21] Demethylation of **10** afforded **11** in which both the R^2 and Y groups could be varied. Two approaches were used to complete the targets from phenols **11** and halogenated arylsulfones **7**. Copper-mediated coupling of **11** to an aryl bromide or aryl iodide, using another Ma procedure,[22] afforded biarylethers **6**. Alternatively, biarylether formation could be accomplished by heating a fluoro or chlorophenylsulfone **7** in the presence of a base.

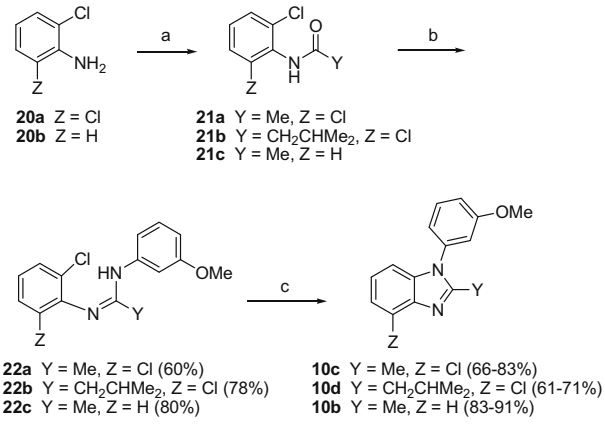
To efficiently explore the SAR around the 2-position of the benzimidazole, a modified route incorporating a biarylether–methylsulfone earlier in the sequence was developed (Scheme 3). 1-Iodo-3-[3-(methylsulfonyl)phenoxy]benzene (**15**)[23] was coupled to aniline **12** to afford **16**. The nitro group was reduced to give **17**. Benzimidazoles **6** were formed by treatment of **17** with an appropriate acid chloride. More simply, reaction of **17** with an orthoester in the presence of benzenesulfonic acid gave benzimid-



Scheme 2. Reagents and conditions: (a) Fe (10 equiv), ethanol, aq HCl (catalytic), AcOH, 70 °C, 4 h; (b) AcOH, 100 °C, 4 h (96%); (c) 3-iodoanisole (2 equiv), CuI (0.2 equiv), *N*,*N*′-dimethyl-*trans*-1,2-cyclohexanediamine (0.4 equiv), Cs_2CO_3 (2.2 equiv), DMA, 130 °C, 20 h; (d) pyridine hydrochloride (ca. 20 equiv), 200 °C, 0.5–2 h; (e) **7** (Hal = F or Cl, 1.1–1.5 equiv), K_2CO_3 (2 equiv), DMF or DMA, 110–150 °C, 18–24 h; (f) **7** (Hal = Br or I, 1.5 equiv), CuI (0.2 equiv), $Me_2NCH_2CO_2H$ hydrochloride (0.3 equiv), Cs_2CO_3 (6 equiv), 1,4-dioxane, 100–110 °C, 16–24 h; (g) 2 M aq NaOH, MeOH, 60 °C, 1 h (100%); (h) $Pd_2(dba)_3$ (0.02 equiv), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (0.10 equiv), K_2CO_3 (1.2 equiv), ^{t}BuOH, 80–90 °C, 3 h (R^2 = H: 74%); (i) YCOCl (1–3 equiv), *i*-$PrNEt_2$ (1–3 equiv), THF, 20 °C, 16 h, then $POCl_3$ (1–3 equiv), then 60–65 °C, 2–20 h; (j) YC(*O*-alkyl)$_3$, $PhSO_3H$, THF, 50–60 °C.



Scheme 3. Reagents and conditions: (a) **15** (0.8 equiv), $Pd_2(dba)_3$ (0.005 equiv), K_2CO_3 (1.1 equiv), 2,4,6-triisopropylbiphenyl-dicyclohexylphosphine (0.025 equiv), ^tBuOH, 90 °C, 3 h, (80%); (b) Fe (10 equiv), AcOH, 2 N aq HCl, ethanol, 70 °C, 45 min (98%); (c) YCOCl (1–3 equiv), *i*-$PrNEt_2$, THF, 20 °C, 16 h, then $POCl_3$ (2–4 equiv), 60–65 °C. 2–20 h; (d) $YC(O\text{-alkyl})_3$ (excess), $PhSO_3H$ (catalytic), THF or $CHCl_3$, 50–60 °C, 20–60 min (Y = Me, 74%).



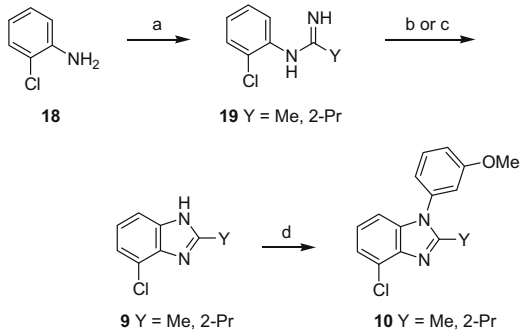
Scheme 5. Reagents and conditions: (a) YC(O)Cl (1.1 equiv), YCO_2H (as solvent), 100 °C; or YC(O)Cl (1.1 equiv), *p*TsOH hydrate, toluene, reflux, 2 h; (b) 2,6-lutidine (2.2 equiv, or 3.3 equiv for aniline hydrochlorides), $(CF_3SO_2)_2O$ (1.1 equiv), 0–20 °C, 30–45 min, then aniline, 20 °C, 3–18 h; (c) K_2CO_3 (1.6 equiv), NaO^tBu (1.6 equiv), $Pd(PPh_3)_4$ (0.01–0.15 equiv), toluene, xylenes or DMF, 110–130 °C, 18–32 h.

azole. Moving the diversity step to the end of the route allowed the Y group SAR to be examined quickly.

Attempts to extend the above approach to compounds **10** where Z is chlorine by coupling 3-iodoanisole to 3-chloro-2-nitroaniline gave complex mixtures. At least some of the by-products apparently arose from coupling of the aniline to another molecule of aniline via the nitro-activated chlorine, effectively competing with the iodoanisole. To overcome this issue, chloro analogs were made by converting aniline **18** into amidines **19**[24] which were readily cyclized to benzimidazoles **9** (Z = Cl) using iodosobenzene acetate[25] or sodium hypochlorite[26] (Scheme 4). Copper(II)-mediated coupling[27] of **9** with 3-methoxyphenylboronic acid afforded **10** which was converted to targets **6** as described above. However, the coupling step was capricious and often low yielding making this route suboptimal.

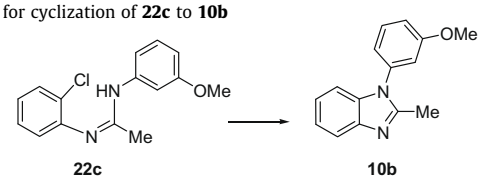
An alternative and more reliable approach to **10** was based on Brain and Brunton's[28] report of a Pd-catalyzed intramolecular coupling of an *N*-(2-bromophenyl)-*N*′-aryl-amidine to give 1-arylbenzimidazoles. The commercial availability of anilines **20** led us to try the coupling using chloro analogs (Scheme 5). Compounds **20** were converted to acetamides **21**.[29] Treatment of **21** with trifluoromethanesulfonic anhydride and 2,6-lutidine followed by an anisidine gave amidines **22**.[30] However, cyclization of **22** under the conditions of Brain and Brunton (PhMe, 80 °C, 5 to 10 mol % $Pd(PPh_3)_4$) gave low yields of **10**. At reflux, better yields were obtained (up to 83% using 8% catalyst). To improve the cyclization conditions, a small study using a simpler substrate (**22c**) was undertaken (Table 1). Using DMF as solvent at 80 °C and 5 mol % $Pd(PPh_3)_4$ gave a poor yield of **10b** but the yield improved dramatically at 130 °C.[31] Returning to a nonpolar solvent for ease of workup, xylenes at 130 °C also gave similar results. Reducing catalyst loadings down to 1 mol % provided comparable yields but no product formed in the absence of catalyst. Applying these conditions to more complex substrates **22** gave typically good yields, though somewhat higher catalyst loadings ($\geqslant$2 mol %) were often used. Demethylation and installation of the arylsulfones as before gave **6**. This synthetic route was very versatile since key positions R^1, R^2, W, Y and Z could be varied depending on the choice of reagents.

Binding affinities for sulfones **6** were determined using recombinant human ligand binding domains (LBDs) of the respective LXRα and LXRβ subtypes measuring displacement of [^{3}H]T0901317 from the LBD (Table 2).[32] Comparing quinoline **5a** to benzimidazole **6a**, there was a sevenfold loss in LXRβ affinity and a slightly larger decrease for LXRα. As in other series we have developed, similar LXR binding affinity was seen whether the Z group was trifluoromethyl or chlorine (compare **6a** to **6b**, **6d** to **6e**, **6f** to **6g**) but if Z was hydrogen, over a 35-fold drop in affinity was observed for both LXR subtypes (**6a** vs **6c**). Variations in the sulfone group from methyl (**6a**) to ethyl (**6d**), to isopropyl (**6f**) had little effect on affinity but longer chains such as *n*-propyl (**6h**) and 3-hydropropyl (**6i**) or larger and more electron withdraw-



Scheme 4. Reagents and conditions: (a) Me_3Al (1.5 equiv), toluene, 0–20 °C, 1–2 h, then Y–CN (2 equiv), 85–110 °C, 16–24 h (72–75%); (b) Y = 2-Pr: $PhI(OAc)_2$ (1 equiv), PhMe, reflux, 8–10 min, (54%); (c) aq 2 M HCl, MeOH, 5% aq NaOCl, 10 °C, then aq Na_2CO_3 (2 equiv), 75 °C (96%); (d) 3-$MeOPhB(OH)_2$ (1.67 equiv), $Cu(OAc)_2$ (1 equiv), pyridine (3 equiv), CH_2Cl_2, 4 Å mol sieves, 2–5 d (Y = 2-Pr: 51%).

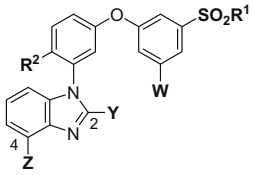
Table 1
Conditions for cyclization of **22c** to **10b**



Entry	Solvent	Temp[a] (°C)	$Pd(PPh_3)_4$ (mol %)	Yield of **10b**[b] (%)
1	DMF	80	5	16
2	DMF	130	5	88
3	Xylenes	130	5	91
4	Xylenes	130	3	88
5	Xylenes	130	2	83
6	Xylenes	130	1	87
7	DMF	130	0	0

[a] Reaction time was 24 h.
[b] Yield is of isolated product.

Table 2
Biarylether sulfone benzimidazoles **6**[a]



	R^1	R^2	W	Y	Z	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	IC_{50} α/β	ABCA1 mRNA EC_{50} in nM (% eff)	TG accum EC_{50} in nM (% eff)	Microsome stability $t_{1/2}$[b] (min) (m/r/h)
1	—	—	—	—	—	9	13	1	35 (100)	104 (100)	—
5a	Me	—	H	Me	CF_3	1.0	2.4	2	10 (82)	147 (69)	30/30/30
6a	Me	H	H	Me	CF_3	7.0	111	16	425 (126)	271 (37)	30/30/30
6b	Me	H	H	Me	Cl	7.3	100	14	270 (165)	124 (31)	30/30/30
6c	Me	H	H	Me	H	269	6400	17	nt[c]	nt	nt/15/nt
6d	Et	H	H	Me	CF_3	5.7	128	22	357 (109)	262 (42)	30/30/30
6e	Et	H	H	Me	Cl	5.1	99	19	753 (108)	220 (32)	28/28/30
6f	2-Pr	H	H	Me	CF_3	5.4	248	46	280 (108)	179 (34)	30/30/30
6g	2-Pr	H	H	Me	Cl	5.6	138	25	1310 (135)	134 (22)	22/25/30
6h	1-Pr	H	H	Me	CF_3	24	462	19	1330 (105)	273 (27)	23/14/28
6i						$(CH_2)_3OH$	H	H	Me	CF_3	13
436				1380	594	(35)	28/25/30				
	33			(108)							
6j	CF_3	H	H	Me	Cl	20	183	9	1300 (130)	122 (8)	30/30/29
6k	Me	H	F	Me	CF_3	13	315	24	1067 (117)	192 (33)	30/30/30
6l	Et	H	F	Me	CF_3	38	489	13	1270 (119)	168 (34)	30/30/30
6m	Me	H	H	H	CF_3	44	882	20	841 (84)	524 (35)	30/30/30
6n	Me	H	H	CF_3	CF_3	1.3	5.1	4	14 (94)	185 (49)	30/30/30
6o	Me	H	H	Et	CF_3	1.7	22	13	78 (90)	120 (42)	30/30/30
6p	Me	H	H	2-Pr	CF_3	1.0	16	16	137 (80)	212 (53)	30/30/30
6q	Me	H	H	*cyclo*-Pr	CF_3	4.2	93	22	439 (95)	907 (66)	30/30/23
6r	Me	H	H						CH_2CHMe_2	CF_3	0.8
3.2		10		(92)	76	(127)	3/24/30				
	4										
6s	Me	H	H	Ph	CF_3	1.1	4.7	4	333 (65)	2286 (94)	16/30/11
6t	Me	H	H	4-$FPhCH_2$	CF_3	1.2	2.6	2	nt	nt	8/30/23
6u	Me	H	H	2-Pr	Cl	1.5	26	17	156 (97)	617 (91)	9/7/30
6v	Me	Cl	H	H	CF_3	2.7	34	14	425 (104)	218 (45)	30/nt/30
6w	Et	Cl	H	H	CF_3	2.4	35	15	155 (122)	197 (35)	30/nt/30
6x	2-Pr	Cl	H	H	CF_3	4.0	45	11	240 (100)	205 (28)	27/nt/30
6y	Me	Cl	H	Me	Cl	3.7	14	4	154 (78)	50 (90)	26/nt/30
6z	Et	Cl	H	Me	Cl	3.5	12	3	245 (126)	184 (35)	20/22/30
6aa	2-Pr	Cl	H	Me	Cl	3.6	36	10	110 (99)	298 (43)	11/15/25
6bb	Me	Cl	F	Me	Cl	4.7	44	9	215 (110)	297 (57)	16/30/30
6cc	CF_3	Cl	H	Me	Cl	17	85	5	620 (117)	879 (38)	30/30/30

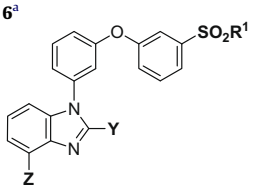
[a] Results are given as the mean of two independent experiments. The standard deviations for the binding assays were typically ±30% of the mean or less. % of efficacy is relative to **1**.
[b] m = mouse, r = rat, h = human; $t_{1/2}$ of 30 min means indicates a half-life of $\geqslant$30 min.
[c] nt = not tested.

ing groups (trifluoromethyl, **6j**) tended to reduce affinity. Fluorine substitution on the sulfone-bearing aryl ring (**6k**, **6l**, **6bb**) either reduced affinity or had little effect. Decreasing the size of the 2-substituent Y to hydrogen (**6m**) reduced affinity at least sixfold while improved affinity was found as Y was increased in size (**6n**–**6t**). However, even **6n** (Y = CF_3) gave improved affinity, indicating larger groups like phenyl (**6s**) and 4-fluorobenzyl (**6t**) disproportionately increased size relative to affinity increases. Introduction of a chloro group at R^2, which was proposed from docking studies to compensate for a small group (hydrogen) at the 2-position, did improve LXRβ affinity about 15-fold (compare **6m** to **6v**) but had less impact on binding for compounds where Y was methyl (**6b** vs **6y**).

Binding selectivity for LXRβ over LXRα subtypes was moderate to good (typically 10–25-fold) with one analog (**6f**) approaching 50-fold selectivity. Generally, the level of LXRβ binding selectivity was higher for the benzimidazoles **6** than for quinolines **5**. LXRβ agonist functional selectivity may have advantages in increasing cholesterol efflux without increases in triglyceride levels seen with nonselective LXR agonists[33] though others have suggested LXRα agonism is a better therapeutic target.[34] Finally, none of the compounds tested had any significant PPARα, PPARδ, or PPARγ agonism in transiently transfected cell lines previously described.[13]

Compounds **6** were further tested for increases in ABCA1 mRNA in a THP1 (human macrophage) cell line[32] and for changes in cellular triglyceride (TG) levels in an HepG2 (human liver) cell line (Table 2).[12] Increases in the ABCA1 levels should correlate to lipid efflux from macrophages, a desired effect in the treatment of atherosclerosis while increases in cellular TG concentrations could relate to the undesired accumulation of lipids, especially in the liver, leading to steatosis. Efficacy in both assays was measured relative to **1** with the maximum increase in mRNA and in TG levels taken as 100% efficacy. Comparing quinoline **5a** to benzimidazole **6a**, the latter had an EC_{50} over 40-fold weaker in the ABCA1 assay. Despite the high binding affinity and though they typically had efficacies comparable to **1**, most of the benzimidazoles **6** had EC_{50} values >100 nM in the assay. The exceptions (**6n**, **6o**, and **6r**) had Y groups that were slightly larger than methyl, though much larger Y groups (**6s**, Y = Ph) reduced activity. Efficacies for the benzimidazoles in the triglyceride accumulation assay were generally lower than for **1**, but only **6n** and **6r** showed significantly higher potency in

Table 3
Mouse PK for compounds **6**[a]



	R^1	Y	Z	AUC_{0-last} ng h/mL	$t_{1/2}$ (h)
6a	Me	Me	CF_3	12,917	13.5
6b	Me	Me	Cl	1499	1.7
6d	Et	Me	CF_3	2944	4.7
6e	Et	Me	Cl	1776	3.6
6f	2-Pr	Me	CF_3	1291	0.9
6m	Me	H	CF_3	12,148	7.9
6n	Me	CF_3	CF_3	14,338	nc[b]
6o	Me	Et	CF_3	1781	2.7

[a] C57 mouse dosing: 10 mg/kg po (gavage) in 0.5% methylcellulose/2% Tween in water.
[b] Not calculated—a longer study time was needed to determine $t_{1/2}$.

the ABCA1 assay compared to the TG accumulation assay. The relevance of this level of selectivity is not clear given the different cell types and potentially differing cell penetration by the drugs.

In an assay testing for in vitro metabolic stability in mouse, rat and human microsomes, most of the compounds had good stability as measured by the half-life. Typically, as noted above, compounds with larger alkyl groups and benzyl substitution at Y appeared more susceptible to microsomal metabolism (**6r**–**6t**). 4-Chloro benzimidazoles were occasionally slightly less stable compared to their trifluoromethyl analogs. Since the majority of the compounds were stable in vitro, several compounds were tested to determine systemic exposure and half-life ($t_{1/2}$) following a 10 mg/kg oral (gavage) dose in mice (Table 3). Compounds where the Z-substituent was trifluoromethyl had higher exposure and longer half-life compared to their chlorine analogs (compare **6a** to **6b**, **6d** to **6e**) while when the Y-substituent was ethyl (**6o**), the pharmacokinetic (PK) parameters were less favorable compared to when Y was hydrogen (**6m**), methyl (**6a**) or trifluoromethyl (**6n**). The compound with the shortest half-life (**6f**) had an isopropyl group for R^1 which might be more readily metabolized.

Replacement of a 8-trifluormethylquinoline core with a 4-trifluoromethylbenzimidazole core while retaining a sulfone-substituted biarylether fragment gave a series of high affinity LXR ligands **6**. Several routes were developed to allow efficient exploration of the SAR. Many of the compounds showed modest to good selectivity for LXRβ over LXRα binding. A functional assay using a human macrophage cell line (THP1) showed increases in mRNA for ABCA1, a key protein involved in lipid transport. In this assay, the potency and efficacy were often comparable to **1**, with a few compounds having even higher potency. Unfortunately, a second functional assay measuring increases in TG levels in a human hepatic cell line (HepG2) indicated the most potent compounds for increasing desired ABCA1 mRNA levels also increased intracellular TG levels. Stability in mouse and human liver microsomes was high for the majority of analogs **6**. 1-(3-Aryloxyaryl)benzimidazoles with a meta-sulfone group on the distal phenyl ring are high affinity LXR ligands, often with excellent agonist potency for upregulating ABCA1 mRNA and excellent microsomal stability.

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