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3-(3-Aryloxyaryl)imidazo[1,2-*a*]pyridine sulfones as liver X receptor agonists

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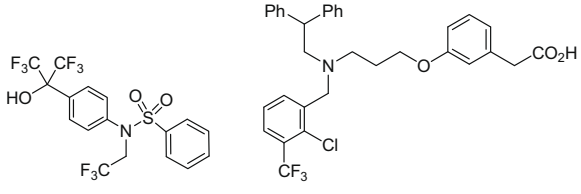
ABSTRACT

Replacement of a quinoline with an imidazo[1,2-*a*]pyridine in a series of liver X receptor (LXR) agonists incorporating a [3-(sulfonyl)aryloxyphenyl] side chain provided high affinity LXR ligands **7**. In functional assays of LXR activity, good agonist potency and efficacy were found for several analogs.

Liver X receptors (LXRs) are members of the nuclear receptor superfamily.[1] LXRs act as ligand activated transcription factors which increase the expression of several genes when turned on by agonists including oxysterols, the endogenous agonists. The activation requires the formation of an LXR-RXR (retinoid X receptor) heterodimer. Among the key genes activated by LXR-RXR heterodimers are those corresponding to the ATP-binding cassette proteins (ABCs), a group of lipid transporters partly responsible for controlling lipid homeostasis.[2] Increasing the expression of ABCs and in particular ABCA1, an important transporter in macrophages and other cells, may increase reverse cholesterol transport (RCT). Enhancing RCT could have the effect of slowing the development of atherosclerosis. However activation of undesired genes, especially sterol regulatory element-binding protein-1c (SREBP-1c) and fatty acid synthetase (FAS), also under the control of LXRs, may lead to increases in triglycerides (TGs) and to steatosis in the liver.[3] To minimize the potential for undesired effects, agonism of the LXRβ subtype (present in macrophages and independently able to upregulate ABCA1) rather than of the α-subtype (more prevalent in liver than LXRβ and the site of TG synthesis) has been the focus for several groups.[4]

As an alternative or addition to statin therapy, several companies have targeted LXR agonists for dislipidemia. These include T0901317 (**1**)[5] from Tularik and GW3965 (**2**)[6] from GlaxoSmithKline (Fig. 1). These compounds are high affinity LXR ligands with potent LXR agonism. An indazole-based LXR agonist, WAY-252623 (**3**),[7] has been shown to upregulate ABCA1 in whole blood of cynomolgus monkeys[8] and like wise in humans in a phase I clinical trial (Fig. 2).[9] A quinoline-based series also developed by Wyeth is exemplified by WAY-254011 (**4**).[10]



1 T0901317 (Tularik) **2** GW3965 (GSK)

Figure 1. LXR Agonists from Tularik and GlaxoSmithKline.

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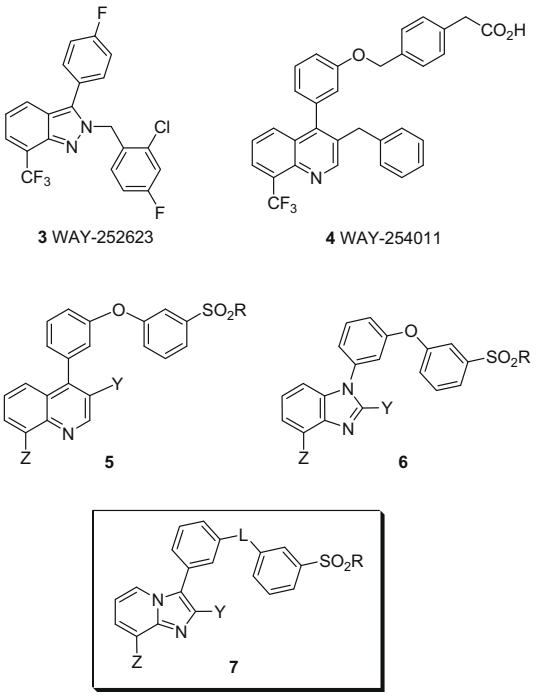


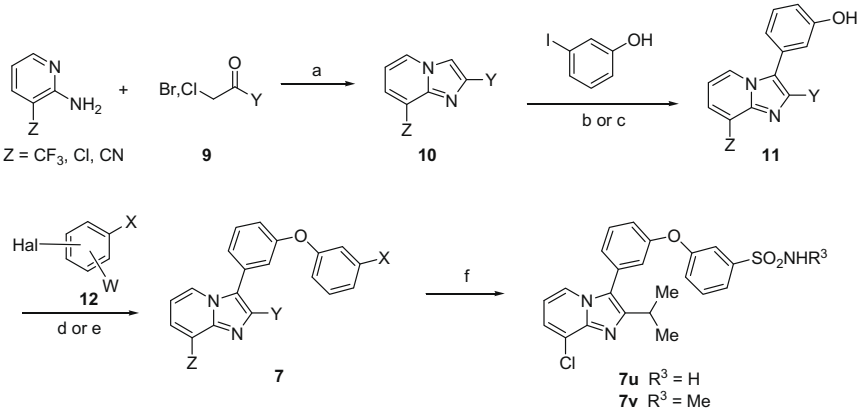
Figure 2. LXR Agonists from Wyeth.

The moderate peroxisome proliferator-activated receptor (PPAR) agonism of quinoline **4**, which activated all three subtypes of the receptor,[11] led us to target quinolines with a biarylether substituent and to identify non-carboxylic acid hydrogen bond acceptors,[12] leading to 4-[(3-sulfone-phenoxy)phenyl]quinolines **5**.[13] These compounds were essentially devoid of PPAR agonism. To further develop the SAR, we explored replacements for the quinoline such as benzimidazole which maintained a key sp^2 nitrogen and trifluoromethyl (Z = CF_3) on the core heterocycle (**6**).[14] As an extension of this approach, we describe here the synthesis and structure–activity relationships of a series of imidazo[1,2-*a*]pyridines **7**.

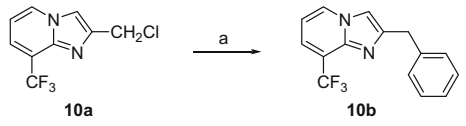
The first approach to targets **7** involved ether bond formation between a 3-(3-hydroxyphenyl)imidazo[1,2-*a*]pyridine core **11** and an arylhalide **12** (Scheme 1). The phenols were typically prepared by reaction of 2-aminopyridines **8** with α-haloketones **9** to give imidazo[1,2-*a*]pyridines **10**[15] in which substituents Y and Z were varied by appropriate choice of starting materials.[16] Since preparation of $PhCH_2C(O)CH_2Cl$ (**9**, Y = benzyl) was problematic, imidazo[1,2-*a*]pyridine **10b** (Y = CH_2Ph, Z = CF_3) was made from **10a** by standard Suzuki coupling with phenylboronic acid (Scheme 2).[17] Direct arylation of compounds **10** with 3-iodophenol using $Pd(OAc)_2$[18] or more conveniently with $Pd(OH)_2$ on carbon[19] gave phenols **11** in good yield. Introduction of the sulfone or sulfonamide side chains by reaction with arylhalide **12**[20] was accomplished either through copper-mediated coupling with aryliodides and arylbromides[21] or by aromatic substitution for arylfluorides and arylchlorides.[22] Incorporation of amines and azacycles on a methylene group at the 2-position required bromination of 2-methyl analog **7a** to give **7j** followed by displacement reactions to give **7k**–**7o** (Scheme 3). When sulfonamides were prepared, *para*-methoxybenzyl protection[23] was employed to provide **7s** and **7t** which were deprotected with trifluoroacetic acid to give primary and secondary sulfonamides **7u** and **7v**, respectively.

Alternative approaches to **7** were used to explore the structure–activity relationships, especially for various linkers between the aromatic rings of the side chain other than oxygen (Scheme 4). For example, synthesis of compounds with biaryl side chains in which the aromatic rings were connected by other linkers (L) including methylene (**7x**) and oxymethylene (**7y**) was accomplished by making arylbromides such as **14**[24] and **17** for use in the direct arylation. Ultimately, coupling a preformed biarylether (L = O) to a 3-*H*-imidazo[1,2-*a*]pyridine was even used to efficiently prepare biarylethers **7** (L = O). Compounds **7z** and **7aa** were made by alkylation with benzyl bromides **15**. Finally, two biarylsulfones were prepared by coupling of 4-bromo-1-iodobenzene to imidazo[1,2-*a*]pyridine **10c** (Y = 2-Pr, Z = CF_3) to give **18** followed by Suzuki coupling with methylsulfonylbenzeneboronic acids to provide **19a** and **19b** (Scheme 5).

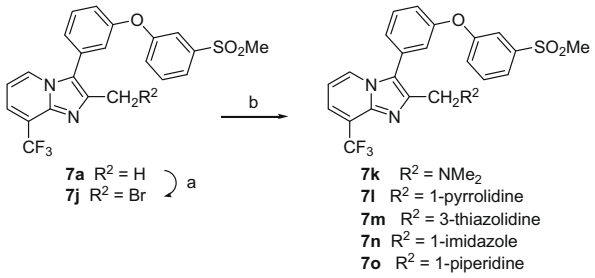
To determine the affinity of imidazo[1,2-*a*]pyridines for the two LXR subtypes, binding assays were run using recombinant human ligand binding domains (LBDs) of the respective LXRα and LXRβ subtypes, measuring displacement of [^{3}H]T0901317 from the LBD (Table 1).[25] Comparing the simpler analogs **5a**, **6a**, and **7a** from the quinoline, benzimidazole, and imidazo[1,2-*a*]pyridine series, respectively, there was a significant loss in affinity (almost 50-fold vs **5a** for LXRβ). The affinity did not improve with larger sulfones as the analogs **7b**–**7d** had similar affinity relative to **7a**. However, extensive exploration of the 2-substituent (Y) indicated it played an important role in LXR affinity in the series. While slightly larger groups like ethyl (**7e**), isopropyl (**7f**), and *t*-butyl (**7g**) and even larger phenyl (**7h**) had comparable affinity for LXRβ, enlarging to a benzyl group (**7i**) provided essentially the same affinity as seen with **5a**. While introduction of dimethylamine at the 2-position



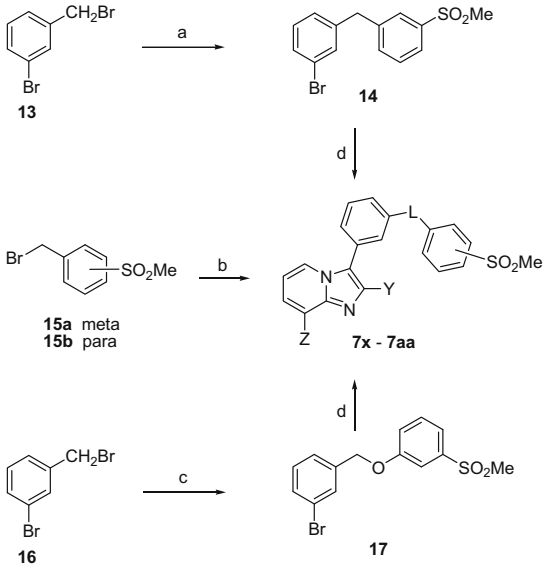
Scheme 1. Reagents and conditions: (a) EtOH, reflux, 16–24 h; (b) $Pd(OAc)_2$ (0.02 equiv), Ph_3P (0.04 equiv), Cs_2CO_3 (1.0 equiv), dioxane, reflux, 16–24 h; (c) 20% $Pd(OH)_2$ on carbon (0.1 equiv), KOAc (3.0 equiv), DMA, 145 °C, 16–24 h; d) **12** (Hal = Br, I,) (1.0–2.0 equiv), CuI (0.1 equiv), $Me_2NCH_2CO_2H$ hydrochloride (0.375 equiv), Cs_2CO_3 (3.0 equiv), dioxane, 100–110 °C, 16–24 h; (e) **12** (Hal = F, Cl) (1.0–2.0 equiv), K_2CO_3 (1.0–2.0 equiv), DMF, 120–150 °C, 16–24 h; (f) TFA, CH_2Cl_2, 20 °C, 18–24 h.



Scheme 2. Reagents and conditions: (a) $PhB(OH)_2$ (2.0 equiv), K_2CO_3 (3.0 equiv), $Pd(PPh_3)_4$ (0.03 equiv), dioxane, water, reflux, 1.5 h (51%).

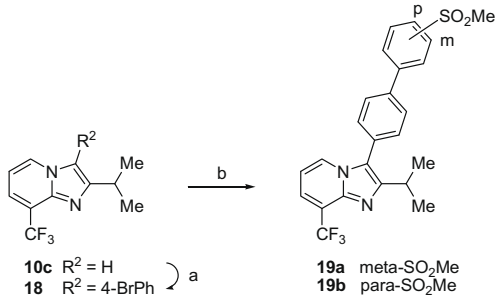


Scheme 3. Reagents and conditions: (a) *N*-bromosuccinimide (1.1 equiv), α,α-azobisisobutyronitrile (0.1 equiv), MeCN, reflux, 3 h (79%); (b) azacycle (3.0–5.0 equiv), DMSO or ethanol, rt, 1–24 h (37–68%).



Scheme 4. Reagents and conditions: (a) 3-$(MeSO_2)PhB(OH)_2$ (1 equiv), $Pd(PPh_3)_4$ (0.03 equiv), 1 M aqueous Na_2CO_3 (0.12 equiv), EtOH, PhMe, 80 °C, 18–24 h (8%); (b) **11a** (Y = 2-Pr, Z = CF_3, 0.83 equiv), Cs_2CO_3 (1.16 equiv), DMF, 40 °C, 20 h (96–99%); (c) 3-HO–$PhSO_2Me$, K_2CO_3, DMF, 80 °C, 24 h (82%); (d) **10b** (Y = Et, Z = CF_3), 20% $Pd(OH)_2$ on carbon (0.1 equiv), KOAc (3.0 equiv), DMA, 145 °C, 24 h (67–87%).

via a methylene linker gave much weaker affinity (**7k**), larger, more lipophilic azacycles (**7l**, **7m**) trended toward better binding. The much more weakly basic amine found in thiazolidine gave a compound with excellent affinity (**7n**, hLXRβ IC_{50} = 2.0 nM). However, imidazole in place of phenyl lost 30-fold in affinity (**7o**). Returning to a 2-isopropyl group and varying the Z-substituent, affinity decreased slightly in a chloro for trifluoromethyl exchange (**7f** vs **7p**) while cyano fared much worse (**7q**). The importance of the hydrogen bond accepting ability of the sulfone can be inferred from the dramatic reduction in affinity (over 50-fold) seen with the trifluoromethylsulfone **7r** compared to methylsulfone **7f**, suggesting the importance of more electron rich sulfone oxygens. The receptors were more tolerant of large lipophilic groups over primary sulfonamides as seen in a comparison of **7t**–**7u**. Interestingly, a secondary sulfonamide could also substitute for a sulfone



Scheme 5. Reagents and conditions: (a) 4-BrPhI, $Pd(OAc)_2$ (0.02 equiv), Ph_3P (0.04 equiv), Cs_2CO_3 (1.0 equiv), dioxane, reflux, 16–24 h; (b) $MeSO_2PhB(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (0.15 equiv), Na_2CO_3 (2.3 equiv), aqueous diglyme, 80 °C, 18–24 h.

as shown by **7v** which had similar binding affinity to **7p**, its closest analog. A methylene linker in place of oxygen lost sixfold in affinity (**7e** vs **7x**) while other linkers provided even weaker LXR ligands (**7y–7aa**). *para*-Biarylsulfones **19a** and **19b** had moderate and very weak LXR affinity, respectively.

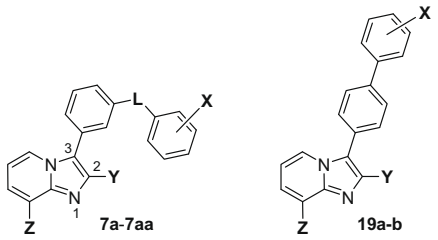
Binding selectivity for LXRβ over LXRα subtypes was only moderate, though **7e**, **7h**, and **7p** showed selectivity (LXRα IC_{50}/LXRβ IC_{50}) of greater than tenfold. However, the in vivo functional implications of this level of binding selectivity are unclear. Essentially none of compounds had PPAR agonism when tested in PPAR functional assays reported earlier.[12a]

LXR functional activity was first examined in Gal4 assays,[10] transient transactivation assays in Huh7 cells transfected with human LXR ligand binding domains (LBDs) fused to Gal4 DNA binding domains. The assays were performed for both LXRα and LXRβ LBDs. As in the binding affinity, the potency in the Gal4 assays for **7a** was weaker compared to the analogous benzimidazole **6a** and much weaker compared to quinoline **5a**. Efficacy was also reduced, especially compared to **7a**. Larger sulfone groups gave comparable or weaker potency (**7b**–**7d**) while more lipophilic Y groups had little impact until a benzyl group was used (**7i**). Compound **7i** was the most potent analog in this assay (Gal4β EC_{50} = 20 nM) and was essentially as efficacious as **1**. Saturated azacycles **7m** and particularly **7n** demonstrated good activity in the assay, with **7n** being nearly as potent and efficacious as **7i**. Both were more potent than **1**. Sulfonamides **7t** and **7v** were good agonists in the assay while the methylene (**7x**) and oxymethylene (**7z**) spacers were much weaker compared to the biarylether analogs. Rather modest functional selectivity for LXRβ over LXRα was seen for a few compounds particularly **7i** and **7m**, about sevenfold and fivefold selective, respectively. As noted above, none of the biarylethers tested had any PPAR activity.

Additional cell based assays tested for upregulation of ABCA1 mRNA in a THP1 human macrophage cell line[25] and for an increase in cellular triglyceride levels in a HepG2 (human liver) cell line (Table 2), with increases in ABCA1 mRNA and in TG levels using **1** taken as 100% efficacy. Ideally, good candidates for antiatherosclerotic agents would show an ABCA1 mRNA increase with no increase in TG accumulation. Most of imidazo[1,2-*a*]pyridines **7** were about 10-fold weaker at increasing ABCA1 levels compared to **5a**, with the exception of **7n** which was essentially equipotent. However, little selectivity for ABCA1 mRNA increases relative to TG accumulation was observed. About a fourfold selectivity in potency was found for **7n**, but this was less than seen for **5a**. Higher concentrations (3 μM and 10 μM) of both **7a** and **7b** led to decreases in TG levels, an effect possibly related to cell toxicity affecting TG synthesis.

In an assay testing for stability in mouse, rat and human microsomes, compounds with smaller sulfones and 2-substituents (**7a**, **7b**, **7e**) had good stability while larger 2-substituents

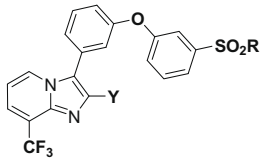
Table 1
Biarylether sulfone imidazo[1,2-*a*]pyridines **7**, **19**[a]



	L	X	Y	Z	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	Gal4β EC_{50} (μM) (% ag)	Gal4α EC_{50} (μM) (% ag)
1		—	—	—	9	13	0.170 (100%)	0.135 (100%)
5a	—	*m*-SO_2Me	Me	CF_3	1.0	2.4	0.031 (78%)	0.183 (75%)
6a	—	*m*-SO_2Me	Me	CF_3	7.0	128	0.162 (49%)	0.64 (42%)
7a	O	*m*-SO_2Me	Me	CF_3	49	799	0.84 (37%)	2.54 (25%)
7b	O	*m*-SO_2Et	Me	CF_3	30	561	0.68 (39%)	2.28 (26%)
7c	O	*m*-SO_2(*i*-Pr)	Me	CF_3	33	960	0.70 (25%)	4.1 (17%)
7d	O	*m*-$SO_2(CH_2)_3OH$	Me	CF_3	188	>1000	1.42 (17%)	6.0 (8%)
7e	O	*m*-SO_2Me	Et	CF_3	14	217	0.42 (62%)	1.22 (58%)
7f	O	*m*-SO_2Me	*i*-Pr	CF_3	3.5	137	0.95 (68%)	1.86 (44%)
7g	O	*m*-SO_2Me	*t*-Bu	CF_3	6.5	222	0.71 (71%)	2.18 (55%)
7h	O	*m*-SO_2Me	Ph	CF_3	7.2	91	0.57 (64%)	1.11 (54%)
7i	O	*m*-SO_2Me	CH_2Ph	CF_3	0.81	5.9	0.020 (88%)	0.144 (62%)
7j	O	*m*-SO_2Me	CH_2Br	CF_3	nt	nt	nt	nt
7k	O	*m*-SO_2Me	CH_2NMe_2	CF_3	>1000	>1000	nt	nt
7l	O	*m*-SO_2Me	CH_2-1-pyrrolidine	CF_3	279	>1000	nt	nt
7m	O	*m*-SO_2Me	CH_2-1-piperidine	CF_3	69	>1000	0.204 (56%)	0.92 (45%)
7n	O	*m*-SO_2Me	CH_2-3-thiazolidine	CF_3	2.0	9	0.032 (62%)	0.170 (64%)
7o	O	*m*-SO_2Me	CH_2-1-imidazole	CF_3	30	365	0.85 (81%)	1.7 (79%)
7p	O	*m*-SO_2Me	*i*-Pr	Cl	10	304	0.54 (50%)	1.66 (53%)
7q	O	*m*-SO_2Me	*i*-Pr	CN	43	>1000	1.68 (44%)	3.9 (20%)
7r	O	*m*-SO_2CF_3	*i*-Pr	CF_3	194	>1000	nt	nt
7s	O	*m*-$SO_2N(PMB)_2$	*i*-Pr	Cl	nt	nt	nt	nt
7t	O	*m*-SO_2NMe(PMB)	*i*-Pr	Cl	24	71	0.89 (48%)	0.93 (47%)
7u	O	*m*-SO_2NH_2	*i*-Pr	Cl	136	>1000	nt	nt
7v	O	*m*-SO_2NHMe	*i*-Pr	Cl	7.5	239	0.53 (61%)	1.61 (46%)
7w	O	*m*-CH_2SO_2Me	*i*-Pr	CF_3	187	>1000	nt	nt
7x	CH_2	*m*-SO_2Me	Et	CF_3	79	>1000	1.57 (48%)	3.2 (30%)
7y	CH_2O	*m*-SO_2Me	Et	CF_3	292	>1000	nt	nt
7z	OCH_2	*m*-SO_2Me	*i*-Pr	CF_3	89	>1000	3.24 (26%)	6.5 (9%)
7aa	OCH_2	*p*-SO_2Me	*i*-Pr	CF_3	>1000	>1000	nt	nt
19[a]	—	*m*-SO_2Me	*i*-Pr	CF_3	166	>1000	na	na
19b	—	*p*-SO_2Me	*i*-Pr	CF_3	>1000	>1000	na	na

[a] Results are given as the mean of two independent experiments. The standard deviations for binding assays were typically ±30% of mean or less. The standard deviations for the Gal4 assays were typically ±30% of the mean or less. % of efficacy is relative to **1**. nt = not tested na = inactive. PMB = 4-MeOPhCH_2.

Table 2
Cell-based assays, solubility and microsomal stability



	R	Y	ABCA1 THP1 EC_{50}[a] (μM) (% eff)	Hepatocyte TG accum assay EC_{50}[a] (μM) (% eff)	Solubility (μg/mL)	Microsomal stability, $t_{1/2}$ m, r, h, (min)	C_{max}[c] (ng/mL)/$AUC_{0\text{-last}}$ (ng h/mL)	t_{max}[c] (h)/ $t_{1/2}$ (h)
1	—	—	0.044 (100%)	0.137 (100%)	—	30, 30, 30	—	—
5a	Me	Me	0.010 (82%)	0.147 (69%)	<1	30, 30, 30	457/1690	2/nd
6a	Me	Me	0.42 (126%)	0.270 (37%)	214	30, 30, 30	614/8938	2/13.5
7a	Me	Me	0.125 (99%)	0.072 (8%)[b]	>100	30, 30, 30	1136/4667	0.25/4.5
7b	Et	Me	0.130 (100%)	nd[b]	68	30, 30, 21	1421/7792	1.0/6.1
7e	Me	Et	0.243 (65%)	0.227 (38%)	228	20, 30, 30	—	—
7i	Me	CH_2Ph	0.12 (105%)	0.065 (81%)	3	2, 7, 19	—	—
7m	Me	CH_2-1-piperidine	0.044 (100%)	0.128 (26%)	73	2, 5, 3	—	—
7n	Me	CH_2-3-thiazolidine	0.010 (98%)	0.042 (36%)	1	3, 23, 6	—	—

[a] Results are given as the mean of at least two independent experiments. The EC_{50} values for the assays were typically ±50% of mean or less (variability for **7i** was higher). % efficacy is relative to **1**.
[b] TG levels decreased at higher concentrations. nd = not determined.
[c] C57 mouse PK dosing: 10 mg/kg po (gavage) in 0.5% methylcellulose/2% Tween in water, except **5a** dosed at 2.5 mg/kg po (gavage).

(**7i**, **7m**, **7n**) significantly reduced the half-life (Table 2). Solubility followed the same trends, increasing for smaller, less lipophilic compounds. In mice dosed orally (gavage) with several compounds, two imidazo[1,2-*a*]pyridines, **7a** and **7b**, gave comparable or slightly better C_{max} and exposure compared to representative examples from earlier series.

Compounds **7** in which an imidazo[1,2-*a*]pyridine replaced a quinoline or benzimidazole found in earlier biarylether sulfones led to a new series of LXR agonists. Efficient routes to synthesize **7** were developed, highlighted by a direct arylation reaction of imidazo[1,2-*a*]pyridines **10** with an arylbromide or aryliodide. A lipophilic 2-substituent was important for both good affinity and functional activity in Gal4 and ABCA1 mRNA gene expression assays. Little selectivity for desired increases in ABCA1 lipid transporter relative to undesired TG accumulation was found.

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