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4-(3-Aryloxyaryl)quinoline alcohols are liver X receptor agonists

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ABSTRACT

A series of 4-(3-aryloxyaryl)quinolines with alcohol substituents on the terminal aryl ring was prepared as potential LXR agonists, in which an alcohol group replaced an amide in previously reported amide analogs. High affinity LXR ligands with excellent agonist potency and efficacy in a functional model of LXR activity were identified, demonstrating that alcohols can substitute for amides while retaining LXR activity. The most potent compound was **5b** which had an IC_{50} = 3.3 nM for LXRβ binding and EC_{50} = 12 nM (122% efficacy relative to T0901317) in an ABCA1 mRNA induction assay in J774 mouse cells.

1. Introduction

The leading cause of death in developed countries is cardiovascular disease.[1] One of the most successful drug therapies targeting cardiovascular disease has been to improve lipid profiles, in particular, to lower cholesterol and low density lipoproteins (LDL) levels and possibly increase high density lipoproteins (HDL) levels. Drug intervention based on this approach has focused on the HMG-CoA reductase pathway leading to the development of various statins including Lipitor® and Mevacor®.[2] More recently, other mechanisms for correcting dislipidemia have been examined. One such approach is to increase levels of cholesterol transporters including adenosine-binding cassette transporters (ABCs), a family of lipid transporters responsible for regulating lipid homeostasis (Fig. 1). Of particular importance is ABCA1, an important transporter in macrophages and other cells.[3]

Expression of ABCs is regulated by liver X receptors (LXRs), members of the nuclear hormone receptors superfamily of gene transcription factors.[4] Because of their role in cholesterol efflux, and their anti-inflammatory role, LXR agonists are an important therapeutic target for the treatment of dyslipidemia.[5] Of the two subtypes of LXR, LXRα and LXRβ, LXRβ is widely distributed in various cell types while LXRα is mainly expressed in kidney, intestine, lung, spleen, and macrophages, and especially in liver.[6] Both subtypes form obligate heterodimers with retinoid X receptors (RXRs). Binding of either an RXR agonist (e.g., 9-*cis*-retinoic acid) to the RXR portion of the heterodimer or of an LXR agonist (e.g., oxysterols such as 24,25-epoxycholesterol) to the LXR portion activates mRNA transcription encoding various genes including ABCs.[7] Nuclear receptors, including LXRs, may also play an important

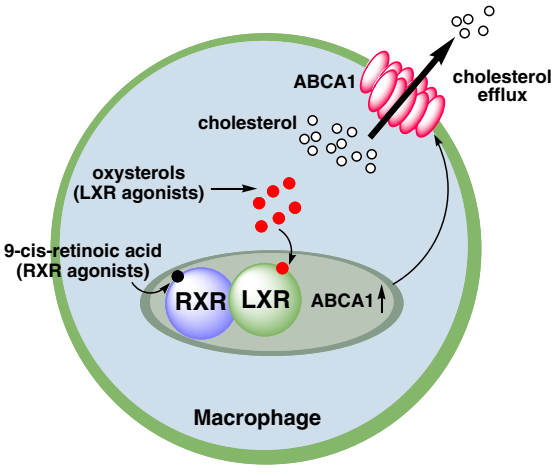

Figure 1. Oxidized cholesterol activates the LXR-RXR heterodimer, upregulating the ABCA1 transporter and increasing cholesterol efflux.

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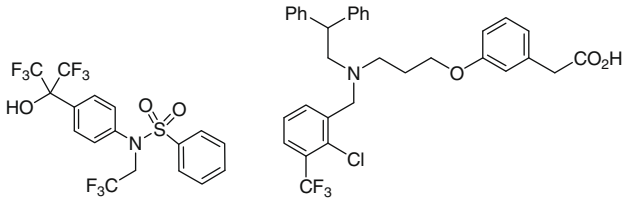


Figure 2. LXR agonists from Tularik and GlaxoSmithKline.

anti-inflammatory role which may help minimize the development of athlerosclerosis.[8]

Several pharmaceutical companies have been active in developing LXR agonists to treat dislipidemia. Several high affinity LXR ligands with potent agonism at both LXRβ and LXRα subtypes, notably Tularik's T0901317 (**1**)[9] and GlaxoSmithKline's GW3965 (**2**),[10] have been identified through these efforts (Fig. 2).

From an initial high throughput screening hit, researchers at Wyeth developed a series of 4-phenyl-quinolines with an additional acid side chain that interacts with the Arg 319 residue in the LXRβ subtype while the quinoline nitrogen interacts with the His435 (Fig. 3).[11] These quinolines-acids were generally high affinity LXR ligands with potent agonist activity. Based on X-ray analysis of co-crystals of LXRβ and WAY-254011 (**3**), it was determined that the carboxylic acid interacts with Arg 319 via a hydrogen bond.[12] Unfortunately, **3** also was a PPAR agonist, activating all three subtypes of the receptor. We embarked on an effort to identify compounds which maintained the 4-phenyl-quinoline core but with the benzylacetic acid moiety replaced with other potential hydrogen bond acceptors. Our first approach replaced the benzylacetic acid with a benzamide (**4**) which gave several high affinity LXR ligands with good agonist potency and reduced PPAR activation.[13] X-ray analysis of one analog (**4a** X = *meta*-C(O)–morpholine, Y = benzyl, Z = CF_3) cocrystallized in the ligand binding domain of LXRβ indicated strong hydrogen bond interactions with the oxygen of the amide as well as the quinoline nitrogen. Efforts to identify other potential acceptable hydrogen bond acceptors replacements led us to prepare and test quinolines incorporating biarylethers with alcohols in place of the amides (**5**).

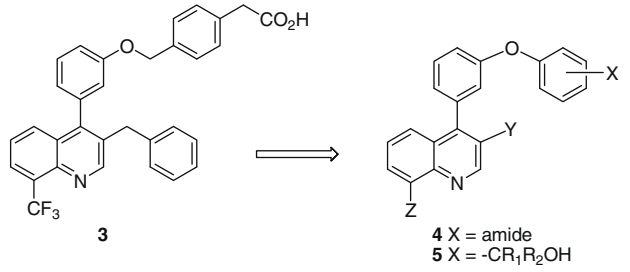


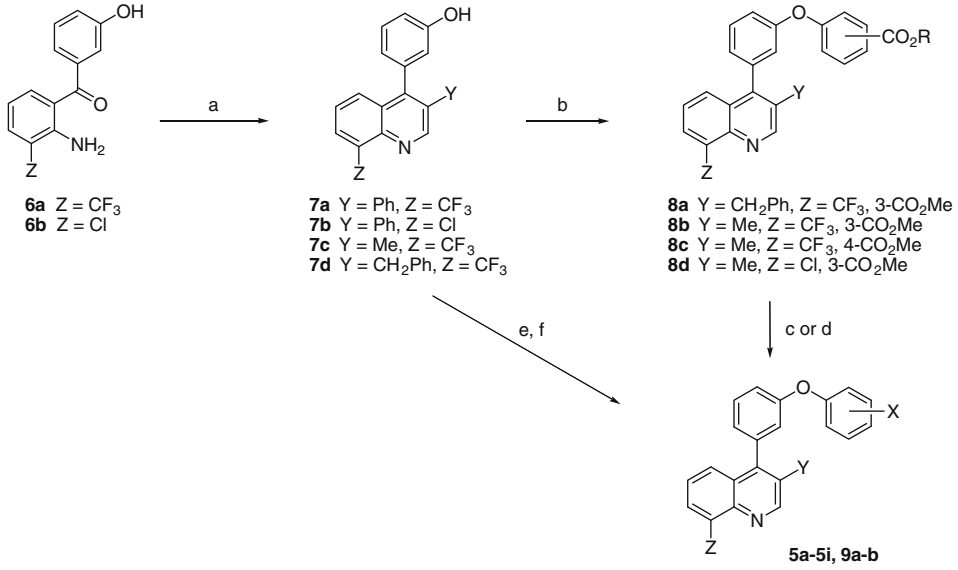
Figure 3. Modifications of WAY-254011 (**3**).

2. Chemistry

Preparation of targets **5** was accomplished in two parts: synthesis of the 4-(3-hydroxyphenyl)quinoline core structure followed by elaboration of the core into the functionalized biarylethers alcohols (Scheme 1).

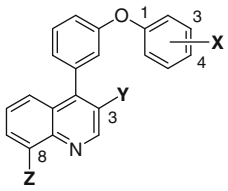
Syntheses of the 4-(3-hydroxyphenyl)quinolines began with the previously prepared 2-aminophenones **6a** and **6b**.[13] Phenones **6a** and **6b** were individually subjected to Friedlander reactions[14] with phenylacetaldehyde to afford 3-phenylquinolines **7a** and **7b**, respectively. This approach was analogous to the previously reported synthesis of **7d**.[13] Using propionaldehyde with **6a** gave 3-methylquinoline **7c**.

With the requisite 4-(3-hydroxyphenyl)quinoline cores in hand, installation of the aryl alcohol remained. Two approaches were used to complete the targets. Copper-mediated coupling of the phenol to an arylbromide afforded the biarylethers with a methyl ester either *meta* or *para* to the oxygen linker.[15] Subsequent reduction with lithium borohydride gave the primary alcohols while addition of excess methyl magnesium bromide afforded the tertiary alcohols. Alternatively, biarylether formation using *meta* or *para* $HOCH_2PhB(OH)_2$, again mediated by a copper salt, afforded the primary alcohols directly.[16] These reactions were often performed using a microwave reactor. We also prepared a phenol (**9b**) and its methoxy precursor (**9a**) to test the effect of removing the methylene spacer from the alcohol.



Scheme 1. Reagents and conditions: (a) $PhCH_2CHO$, $PhSO_3H$, toluene (Y = Ph) or $MeCH_2CHO$, cat. H_2SO_4, AcOH (Y = Me), heat, 3–24 h (63–79%); (b) $BrPhCO_2R$, CuI, $Me_2NCH_2CO_2H{\cdot}HCl$, Cs_2CO_3, dioxane, 105 °C (64–78%); (c) R_1MgX, THF (82–92%); (d) $LiBH_4$, THF (72–97%); (e) $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, microwave or heat (36–76%); (f) pyridine hydrochloride, 180–190 °C, 3 h (90%).

Table 1
Biarylether alcohol quinolines **5**[a]



Compound	X	Y	Z	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	LAFβ EC_{50} (nM) (% agonism)
1	—	—	—	9	13	16 (100%)
3	—	—	—	2.1	9.5	71 (97%)
8a	3-CO_2Me	CH_2Ph	CF_3	53	231	895 (61%)
5a	3-CH_2OH	CH_2Ph	CF_3	11.7	75	1030 (94%)
5b	3-CMe_2OH	CH_2Ph	CF_3	3.3	5.2	31 (106%)
5c	3-CH_2OH	Ph	CF_3	14	47	210 (79%)
5d	4-CH_2OH	Ph	CF_3	10	107	646 (80%)
5e	4-CH_2OH	Ph	Cl	8.3	36	1010 (104%)
8b	3-CO_2Me	Me	CF_3	435	>1000	3400 (56%)
5f	3-CH_2OH	Me	CF_3	2.1	10.2	233 (69%)
8c	4-CO_2Me	Me	CF_3	>1000	>1000	nt
5g	4-CH_2OH	Me	CF_3	31	131	1370 (48%)
8d	3-CO_2Me	Me	Cl	231	1002	1810 (45%)
5h	3-CH_2OH	Me	Cl	12	59	938 (75%)
5i	3-CMe_2OH	Me	Cl	2.5	6.6	108 (84%)
9a	4-OMe	CH_2Ph	CF_3	287	494	612 (38%)
9b	4-OH	CH_2Ph	CF_3	28	115	406 (59%)

[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. The standard deviations for the LAF assays were typically ±30% of the mean or less. % of efficacy is relative to **1**. nt = not tested.

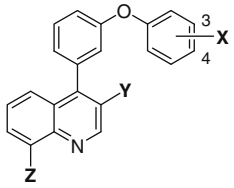
3. Biological assays

The final targets and their ester intermediates were tested to determine binding affinity for the two LXR subtypes (Table 1). The binding assays used recombinant human ligand binding domains (LBDs) of the respective LXRα and LXRβ subtypes and measured displacement of [^{3}H]T0901317 from the LBD.[11] 3-Benzylquinolines were examined first. The ester intermediate **8a** had good affinity for the LXRβ and was nearly fivefold selective over the LXRα subtype. The analogous alcohol **5a** had even higher affinity and slightly improved binding selectivity. The tertiary alcohol **5b** had an IC_{50} value of 3.3 nM at LXRβ but lost essentially all beta selectivity. To reduce the molecular weight, we examined the 3-phenyl primary alcohols, which had high LXRβ affinity whether *meta* (**5c**) or *para* (**5d**) substituted. Replacing the 8-trifluoromethyl group with a chlorine atom (**5e**) retained LXRβ affinity with some erosion in selectivity. To further reduce both clog *P* and molecular weight, we had prepared the 3-methyl quinolines. Both *meta* ester **8b** and *para* ester **8c** had poor affinity for LXR receptors. However, in alcohols **5**, this modification provided some of the highest affinity compounds including **5f** with an IC_{50} value of 2.1 nM at LXRβ receptors. Unlike the 3-phenyl analogs, the *meta*-alcohol was preferred over the *para*-alcohol **5g** by 15-fold. 8-Chloro-3-methyl-quinolines **5h** and **5i** incorporating the biarylether alcohol motif had comparable affinity to their higher clog *P* and molecular weight comparators **5a** and **5b**, respectively. Biarylether **9b** *para*-substituted with a hydroxyl group had good affinity for LXRs.

The compounds were also tested in a LAFβ functional assay.[17] The LAFβ assay determined the agonist potency of test compounds and their efficacy relative to **3** in CHO cells stably transfected with hLXRβ using secreted alkaline phosphatase as the reporter gene, driven by multiple response elements for LXRβ. The most potent in this assay was 3-benzylquinoline **5b**, which had an EC_{50} value of 37 nM and was as efficacious as the Tularik reference (**3**). However, two of the 3-methylquinolines, **5f** and **5i**, were also relatively potent with EC_{50} values below 250 nM and with similar efficacy to the reference compound.[18]

The functional activity of several compounds was further tested in a J774 mouse macrophage cell line, examining upregulation of mRNA from the transporter ABCA1 (Table 2).[19] The ABCA1 protein removes cholesterol from macrophages and other cells. The J774 cell line is reported to have a preponderance of the LXRβ subtype of the receptor.[20] Measuring the mRNA levels, tertiary alcohol **5b** was the most potent with an EC_{50} value of 12 nM, with another tertiary alcohol, **5i**, the second most potent at 37 nM. In contrast, **5c**, with a phenyl directly bonded at the 3-position of the quinoline, had very weak affinity. The primary alcohols at the *meta* position were generally weaker compared to their tertiary counterparts, for example: **5a** versus **5b**, and **5i** versus **5h**. Typically, the primary alcohols were weaker in the ABCA1 mRNA accumulation assay, especially **5c**, **5g**, and **5h**. When the 3-substituent on the quinoline was a phenyl, the *para*-substituted alcohols were slightly more potent compared to *meta*-analog **5c**. Some differences in potency in

Table 2
ABCA1 activity for **5**[a]



Compound	X	Y	Z	ABCA1 EC_{50} (nM) (% ag)
1	—	—	—	27 (100%)
3	—	—	—	41 (114%)
5a	3-CH_2OH	CH_2Ph	CF_3	111 (99%)
5b	3-CMe_2OH	CH_2Ph	CF_3	12 (122%)
5c	3-CH_2OH	Ph	CF_3	>1000 (61%)
5d	4-CH_2OH	Ph	CF_3	141 (44%)
5e	4-CH_2OH	Ph	Cl	168 (136%)
5f	3-CH_2OH	Me	CF_3	555 (112%)
5g	4-CH_2OH	Me	CF_3	>1000 (97%)
5h	3-CH_2OH	Me	Cl	>1000 (94%)
5i	3-CMe_2OH	Me	Cl	37 (147%)

[a] Results are the mean of at least two independent experiments. Standard deviations for the assays were typically ±30% of mean or less. % Efficacy is relative to **1**.

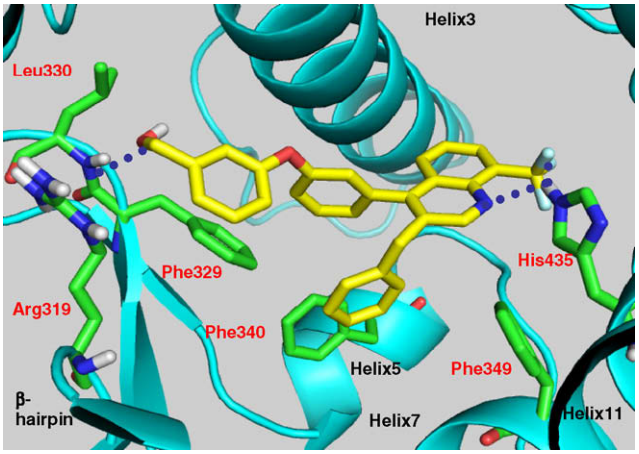


Figure 4. A docked orientation of **5a** (yellow) using the previously disclosed X-ray structure of hLXRβ/**4a** complex. Only key residues and helices are shown for simplicity. Hydrogen bonds to key residues are shown by dotted lines.

the LAFβ assay compared to the ABCA1 assay may be attributable to differences in cell type, species, and compound penetration into the cells. Nearly all the compounds were essentially as efficacious as **1** and the best compounds demonstrated comparable potency to **3**. These results indicate that with optimal substitutions, the 4-(3-aryloxyaryl)quinoline alcohols were high affinity LXR ligands, with good potency in the ABCA1 induction assay in J774 macrophage cells, showing that an alcohol group could take the place of an amide while maintaining activity. Furthermore, none of the five most potent compounds in the ABCA1 assay (**5a**, **5b**, **5d**, **5e**, **5i**) had any PPARα, PPARδ, or PPARγ agonist activity in functional assays using transiently transfected cell lines described earlier.[13]

4. Molecular modeling studies

Docking studies[21] were carried out on compound **5a** to understand the ligand binding mode within the LXRβ cavity and shed further light on residues which are important for ligand recognition. Figure 4 shows the top scoring pose of **5a** from docking.

The ligand binding mode was similar to that of the previously disclosed X-ray structure of hLXRβ/**4a** (**4a** X = *meta*-C(O)-$N(CH_2CH_2)_2O$, Y = CH_2Ph, Z = CF_3). Ligand recognition was achieved by hydrogen bond interaction between the quinoline nitrogen atom and His435 residue. Additionally, the 7-trifluoromethyl group was in close proximity to His435 residue, that is, d(N–F) = 3.0 Å to make favorable electrostatic interaction with this residue. The N2-benzyl group was enclosed in a hydrophobic pocket surrounded by three Phe residues (329, 340, and 349), while the benzyloxy linker was able to extend the alcohol group towards the β-hairpin loop region and make hydrogen bond interaction with the backbone NH group of Leu330. It is interesting to note that in the X-ray structure of **4a**, a similar hydrogen bond interaction was seen from the carbonyl group of the amide to the NH backbone of Leu330 residue. In fact, the distance between the quinoline nitrogen atom and alcohol oxygen atom in **5a**, that is, 12.8 Å is almost identical to the distance of 12.7 Å observed between the nitrogen atom of the quinoline ring and the carbonyl oxygen atom in the X-ray structure of **4a**.

5. Conclusion

To further explore the SAR in a series of quinolines containing a biarylether, compounds were synthesized in which an alcohol replaced an amide as the hydrogen bond acceptor. Several of the alcohols prepared had high affinity for both LXRα and LXRβ subtypes and were potent agonists in a J774 mouse cell line examining ABCA1 gene regulation, based on increases in ABCA1 mRNA levels. The most potent compound for inducing ABCA1 gene expression was tertiary alcohol **5b**, with an EC_{50} = 12 nM and fully efficacious relative to the test ligand, T0901317 (**1**). The affinity and activity of the alcohols was generally similar to the comparable amides, with similar trends in SAR. For example, the molecular weight and *c*log *P* could be reduced by changing the 3-substituent on the quinoline from a benzyl to a methyl with little loss in ABCG1 mRNA induction. While these compounds had at best modest binding selectivity for LXRβ over LXRα, we have demonstrated that 4-(3-aryloxyaryl)quinolines with appropriately positioned alcohol substituents, especially tertiary alcohols, are high affinity LXR ligands with good agonist potency.

6. Experimental

General experimental: Solvents and chemicals were purchased from EM Sciences, VWR, Oakwood, and Aldrich Chemical Co. and used without further purification. High-resolution mass spectra were obtained on a Waters LC-TOFMS instrument and were measured to within 5 ppm of calculated values. ^{1}H NMR spectra were taken on a Bruker DPX300 (300 MHz) or Varian (400 MHz) instruments. NMR data are given as delta values (δ) ppm using tetramethylsilane as an internal standard (δ = 0 ppm). For the NMR data peak descriptions, app means apparent, fc indicates additional fine coupling (<1 Hz), and br means broad.

6.1. (3-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)methanol (5a)

A stirred mixture of **8a** (128 mg, 0.25 mmol) in dry THF (2.5 mL) was treated with $LiBH_4$ (55 mg, 2.50 mmol) and heated at 40 °C for 6 h. The reaction was treated carefully with 2 M hydrochloric acid (ca. 1 mL), diluted with water (10 mL), and stirred 15 min. The solution was extracted with dichloromethane (2 × 15 mL) and the combined extracts dried ($MgSO_4$) and concentrated in vacuo to an oil, which was purified by chromatography eluting with 50:50 ethyl acetate/hexanes to afford **5a** as a slightly colored viscous oil (115 mg, 94%). ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, s), 8.02 (1H, d, *J* = 6.7 Hz), 7.70 (1H, d, *J* = 6.5 Hz), 7.50–7.45 (2H, m), 7.31 (1H, app t, *J* = 7.9 Hz), 7.23–7.09 (6H), 6.99–6.92 (4H, m), 6.84 (1H, m), 4.66 (2H, s), 4.00 (2H, s); MS (ES) *m/z* 486.2; HRMS: calcd for $C_{30}H_{22}F_3NO_2$+H$^+$, 486.1675; found (ESI, [M+H]$^+$), 486.1691. HPLC purity: 100%.

6.2. 2-(3-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)propan-2-ol (5b)

A stirred solution of **8a** (128 mg, 0.25 mmol) in dry THF (2.5 mL) at 0 °C under nitrogen was treated with 3.0 M MeMgBr in THF (0.50 mL, 1.50 mmol). The reaction was allowed to warm to ambient temperature over 2 h, treated with 2 M aqueous HCl (3 mL) followed by brine (5 mL) and extracted with ethyl acetate (2 × 15 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and the resulting oil was chromatographed on silica gel using 50:50 ethyl acetate/hexane as eluent to afford **5b** as a tan solid (105 mg, 82%). Mp <80 °C. ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, s), 8.02 (1H, d, *J* = 7.3 Hz), 7.70 (1H, d, *J* = 8.4 Hz), 7.49–7.44 (2H), 7.31–7.13 (7H), 6.98 (2H, d, *J* = 7.7 Hz), 6.93 (1H, dd, *J* = 0.9, 7.4 Hz), 6.89 (1H, br d, *J* = 7.9 Hz), 6.85 (1H, s), 4.00 (2H, s), 1.59 (1H, br s), 1.55 (6H, s); MS (ES) *m/z* 514.2; HRMS: calcd for

$C_{32}H_{26}F_3NO_2$+H^+, 514.1988; found (ESI, $[M+H]^+$), 514.1963. HPLC purity: 95.1%.

6.3. (3-{3-[3-Phenyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)methanol (5c)

Compound **7a** (0.074 g, 0.21 mmol), 3-(hydroxymethyl)phenylboronic acid (0.068 g, 0.44 mmol), copper acetate (0.033 g, 0.21 mmol), and powdered 4 Å molecular sieves were stirred at ambient temperature in dichloromethane (26 mL) for 10 min. Triethylamine (0.10 mL, 0.61 mmol) was added. After 24 h, the reaction was filtered and the crude reaction solution was loaded directly on a silica gel column. Chromatography eluting with 5:95–50:50 ethyl acetate/hexane gradient gave **5c** as a tan solid (66 mg, 67%). ^{1}H NMR (DMSO-d_6): δ 9.10 (1H, s), 8.24 (1H, d, J = 6.8 Hz), 7.92 (1H, d, J = 7.5 Hz), 7.75 (1H, app t, J = 7.8 Hz), 7.46 (1H, app t, J = 7.9 Hz), 7.39–7.32 (4H), 7.28–7.26 (2H), 7.24 (1H, d, J = 7.8 Hz), 7.11–7.02 (3H), 6.88–6.86 (2H, 6.55 (1H, m), 5.21 (1H, t, J = 5.7 Hz), 4.46 (2H, d, J = 5.6 Hz); MS (ESI) *m/z* 472; HRMS: calcd for $C_{29}H_{20}F_3NO_2$+H^+, 472.1519; found (ESI-FT/MS, $[M+H]^+$), 472.1517.

6.4. (4-{3-[3-Phenyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)methanol (5d)

Compound **5d** was prepared in essentially the same manner as **5c** above except employing 4-(hydroxymethyl)phenylboronic acid to provide a white solid (42 mg, 44%). ^{1}H NMR (DMSO-d_6): δ 9.10 (1H, s), 8.24 (1H, d, J = 7.0 Hz), 7.92 (1H, d, J = 7.5 Hz), 7.75 (1H, app t, J = 8.1 Hz), 7.48 (1H, app t, J = 7.9 Hz), 7.39–7.35 (4H), 7.28–7.23 (3H), 7.14 (1H, m), 7.05 (1H, d with fc, J = 7.4 Hz), 6.80 (1H, app t, J = 2.0 Hz), 6.69 (2H, app d, J = 8.6 Hz), 5.13 (1H, t, J = 5.7 Hz), 4.44 (2H, d, J = 5.6 Hz); MS (ESI) *m/z* 472; HRMS: calcd for $C_{29}H_{20}F_3NO_2$+H^+, 472.1519; found (ESI-FT/MS, $[M+H]^+$), 472.1513. HPLC purity: 100%.

6.5. {4-[3-(8-Chloro-3-phenylquinolin-4-yl)phenoxy]phenyl}-methanol (5e)

Compound **5e** was prepared in the same manner as **5d** above except using **7b** as the phenol reactant giving a colorless, tacky solid (17 mg, 36%). ^{1}H NMR (DMSO-d_6): δ 9.06 (1H, s), 8.01 (1H, dd, J = 2.8, 5.8 Hz), 7.62–7.57 (2H), 7.47 (1H, app t, J = 7.9 Hz), 7.39–7.32 (3H), 7.25–7.22 (3H), 7.12 (1H, finely coupled d, J = 7.5 Hz), 7.05 (2H, m), 6.77 (1H, m), 6.69 (2H, d with fc, J = 8.6 Hz), 5.13 (1H, t, J = 5.7 Hz), 4.44 (2H, d, J = 5.7 Hz); MS (ES) *m/z* 438.2; HRMS: calcd for $C_{28}H_{20}ClNO_2$+H^+, 438.1255; found (ESI, $[M+H]^+$), 438.1239. HPLC purity: 90%.

6.6. 3-{3-[3-Methyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)methanol (5f)

A stirred mixture of **8b** (502 mg, 1.125 mmol) in dry THF (20 mL) was added $LiBH_4$ (62 mg, 2.81 mmol). After 24 h, the reaction was treated with additional $LiBH_4$ (125 mg, 5.63 mmol) and stirred 6 d. The reaction was carefully treated with 2 M hydrochloric acid (ca. 15 mL), diluted with water (10 mL), and stirred 3 d. The solution was extracted with dichloromethane (2 × 20 mL) and the combined extracts dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by chromatography eluting with 35:65 ethyl acetate/hexanes to afford **5f** as a colorless viscous oil (446 mg, 97%). ^{1}H NMR ($CDCl_3$): δ 8.99 (1H, s), 8.00 (1H, d, J = 7.1 Hz), 7.71 (1H, d, J = 8.5 Hz), 7.53–7.45 (2H, m), 7.35 (1H, app t, J = 7.8 Hz), 7.16–7.11 (2H, m), 6.99 (2H, m), 6.91 (1H, br s), 4.69 (2H, s), 2.31 (3H, s), 1.65 (1H, v br s); MS (ESI) *m/z* 410; HRMS: calcd for $C_{24}H_{18}F_3NO_2$+H^+, 410.1362; found (ESI, $[M+H]^+$), 410.1362. HPLC purity: 100%.

6.7. (4-{3-[3-Methyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenyl)methanol (5g)

Compound **8c** (529 mg, 1.21 mmol) stirred in dry THF (20 mL) at 20 °C under nitrogen was treated with $LiBH_4$ (66 mg, 3.0 mmol). After 1 d, additional $LiBH_4$ (130 mg, 6.1 mmol) was added and stirring continued for 5 d. The reaction was treated carefully with 2 M hydrochloric acid (~10 mL), diluted with water (10 mL), and stirred 3 d. The solution was extracted with dichloromethane (2 × 20 mL) and the combined extracts dried ($MgSO_4$) and concentrated in vacuo to an oil which slowly solidified. Purification by chromatography eluting with 35:65 ethyl acetate/hexanes afforded **5g** as a white solid (355 mg, 72%). ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, s), 8.00 (1H, d, J = 7.1 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.53–7.44 (2H), 7.36 (2H, d, J = 8.7 Hz), 7.13 (1H, m), 7.08 (2H, d, J = 8.7 Hz), 6.97 (1H, ddd, J = 1.0, 2.5, 7.7 Hz), 6.89 (1H, m), 4.67 (2H, s), 2.31 (3H, s); MS (ESI) *m/z* 410; HRMS: calcd for $C_{24}H_{18}F_3NO_2$+H^+, 410.1362; found (ESI, $[M+H]^+$), 410.1342. HPLC purity: 97.9%.

6.8. {3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]phenyl}-methanol (5h)

To a stirred solution of **8d** (101 mg, 0.25 mmol) in dry THF (2.5 mL) was added $LiBH_4$ (55 mg, 2.5 mmol). After heating at 40 °C for 4 h, the reaction was cooled, carefully treated with 2 M aqueous hydrochloric acid (ca. 1 mL), and diluted with water (5 mL). The solution was extracted with dichloromethane (2 × 5 mL) and the combined extracts dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography eluting with 50:50 ethyl acetate/hexanes to afford **5h** as a tacky gum (87 mg, 92%). ^{1}H NMR (DMSO-d_6): δ 8.98 (1H, s), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.60 (1H, dd, J = 7.4, 8.4 Hz), 7.50 (1H, dd, J = 7.5, 8.4 Hz), 7.40 (1H, dd, J = 1.3, 8.4 Hz), 7.35 (1H, app t, J = 7.9 Hz), 7.16 (1H, ddd, J = 1.1, 2.6, 8.3 Hz), 7.11–7.07 (3H, m), 6.98–6.96 (2H, m), 5.23 (1H, t, J = 5.8 Hz), 4.49 (2H, d, J = 5.7 Hz), 2.27 (3H, s); MS (ES) *m/z* 376.1; HRMS: calcd for $C_{23}H_{18}ClNO_2$+H^+, 376.1099; found (ESI, $[M+H]^+$), 376.1090. HPLC purity: 99.3%.

6.9. 2-{3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]phenyl}-propan-2-ol (5i)

A stirred mixture of **8d** (101 mg, 0.25 mmol) in dry THF (2.5 mL) at 0 °C under nitrogen was treated with 3.0 M MeMgBr in THF (0.50 mL, 1.50 mmol). The reaction was allowed to warm to ambient temperature after 30 min, then treated with 2 M hydrochloric acid (1 mL) and additional water, and extracted with dichloromethane (2 × 5 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and the resulting oil was chromatographed on silica gel using 1:1 ethyl acetate/hexanes as eluent to afford **5i** as a white solid (93 mg, 92%). Mp: 163–165 °C; ^{1}H NMR (DMSO-d_6): δ 8.98 (1H, s), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.61 (1H, app t, J = 8.0 Hz), 7.49 (1H, dd, J = 7.5, 8.4 Hz), 7.40 (1H, dd, J = 1.3, 8.6 Hz), 7.32 (1H, app t, J = 8.4 Hz), 7.23–7.20 (2H, m), 7.16 (1H, br d, J = 8.3 Hz), 7.09 (1H, br d, J = 7.9 Hz), 6.94–6.91 (2H, m), 5.05 (1H, s), 2.27 (3H, s), 1.39 (6H, s); MS (ES) *m/z* 404.2; HRMS: calcd for $C_{25}H_{22}ClNO_2$+H^+, 404.1412; found (ESI, $[M+H]^+$), 404.1414. HPLC purity: 100%.

6.10. 3-[3-Phenyl-8-(trifluoromethyl)quinolin-4-yl]phenol (7a)

A stirred mixture of **6a** (200 mg, 0.71 mmol) and phenylacetaldehyde (285 mg, 2.13 mmol, Aldrich 90% tech grade) in toluene (3.0 mL) was treated with benzenesulfonic acid (337 mg, 2.13 mmol) and heated at reflux under nitrogen overnight. The reaction was cooled, concentrated under a nitrogen stream, treated with saturated aqueous $NaHCO_3$ and the aqueous layer extracted

several times with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography using a 0:100–20:80 ethyl acetate/hexanes gradient to afford **7b** as a tan solid from a foam (205 mg, 79%). ^{1}H NMR (DMSO-d_6): δ 9.57 (1H, s), 9.09 (1H, s), 8.22 (1H, d, J = 7.1 Hz), 7.87 (1H, d, J = 8.3 Hz), 7.72 (1H, app t, J = 7.9 Hz), 7.34–7.26 (5H), 7.21 (1H, app t, J = 7.9 Hz), 6.78 (1H, dd, J = 1.6, 7.8 Hz), 6.68 (1H, d, J = 7.6 Hz), 6.62 (1H, m); MS (ES) m/z 366.1; HRMS: calcd for $C_{22}H_{14}F_3NO+H^+$, 366.1100; found (ESI, $[M+H]^+$), 366.1108.

6.11. 3-(8-Chloro-3-phenylquinolin-4-yl)phenol (7b)

A stirred mixture of **6b** (991 mg, 4.00 mmol) and phenylacetaldehyde (624 mg, 5.20 mmol, Aldrich 90% tech grade) in toluene (20 mL) was treated with benzenesulfonic acid (362 mg) and heated at 115 °C under nitrogen for 20 h. The reaction was cooled, treated with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography using a 0:100–30:70 ethyl acetate/hexanes gradient to afford **7b** as an off-white solid (912 mg, 69%). ^{1}H NMR (DMSO-d_6): δ 9.55 (1H, s), 9.05 (1H, s), 8.00 (1H, m), 7.59–7.54 (2H), 7.34–7.26 (5H), 7.20 (1H, app t, J = 7.9 Hz), 6.78 (1H, d with fc, J = 8.8 Hz), 6.66 (1H, app dt, J = 1.3, 7.6 Hz), 6.60 (1H, m); MS (ES) m/z 332.1; HRMS: calcd for $C_{21}H_{14}ClNO+H^+$, 332.0837; found (ESI, $[M+H]^+$), 332.0836. HPLC purity: 100%.

6.12. 3-[3-Methyl-8-(trifluoromethyl)quinolin-4-yl]phenol (7c)

A stirred mixture of **6a** (1.00 g, 3.56 mmol) and propionaldehyde (0.77 mL, 16.7 mmol) in glacial acetic acid (20 mL) was treated with concd H_2SO_4 (ca. 0.2 mL) and then heated at 115–120 °C for 6 h, adding additional propionaldehyde (0.5 mL) at intervals. The reaction was cooled, diluted with water, and extracted several times with ethyl acetate. The combined extracts were washed with twice with water and once with saturated aqueous $NaHCO_3$. The extracts were dried with $MgSO_4$ and concentrated in vacuo. Chromatography eluting with 20:80 ethyl acetate/hexanes afforded **7c** as a yellow solid (0.681 g, 63%). ^{1}H NMR (DMSO-d_6): δ 9.75 (1H, s), 9.01 (1H, s), 8.12 (1H, d, J = 7.0 Hz), 7.71 (1H, d, J = 7.7 Hz), 7.63 (1H, app t, J = 7.3 Hz), 7.39 (1H, app t, J = 7.8 Hz), 6.94 (1H, d with fc, J = 8.2 Hz), 6.72 (1H, d, J = 7.5 Hz), 6.69 (1H, m), 2.27 (3H, s); MS (ESI) m/z 304; HRMS: calcd for $C_{17}H_{12}F_3NO+H^+$, 304.0944; found (ESI, $[M+H]^+$), 304.0938. HPLC purity: 95%.

6.13. Methyl 3-{3-[3-methyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}benzoate (8b)

A vigorously stirred mixture of **7c** (606 mg, 2.00 mmol), methyl 3-bromobenzoate (860 mg, 4.00 mmol), CuO (288 mg, 3.60 mmol), and K_2CO_3 (552 mg, 4.00 mmol) in dry pyridine (5.0 mL) was heated under nitrogen at 120 °C for 65 h. The cooled reaction was diluted with water (15 mL) and extracted with ether (2 × 20 mL). The dried ($MgSO_4$) extracts were concentrated to a very dark oil which was chromatographed on silica gel using 25:75 ethyl acetate/hexanes as eluent to give compound **8b** as a tacky foam (0.56 g, 64%). ^{1}H NMR ($CDCl_3$): δ 8.99 (1H, s), 8.01 (1H, d, J = 7.3 Hz), 7.80 (1H, d, J = 7.8 Hz), 7.75–7.71 (2H, m), 7.54 (1H, app t, J = 7.9 Hz), 7.50–7.42 (2H), 7.30 (1H, br d, J = 8.0 Hz), 7.16 (1H, br d, J = 8.3 Hz), 7.03 (1H, br d, J = 7.7 Hz), 6.92 (1H, br s), 3.91 (3H, s), 2.33 (3H, s); MS (ESI) m/z 438; HRMS: calcd for $C_{25}H_{18}F_3NO_3+H^+$, 438.1312; found (ESI, $[M+H]^+$), 438.1339. HPLC purity: 98.6%.

6.14. Methyl 4-{3-[3-methyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}benzoate (8c)

Compound **8c** was prepared in essentially the same manner as **8b** except using methyl 4-bromobenzoate to provide a white solid (78%). ^{1}H NMR ($CDCl_3$): δ 9.01 (1H, s), 8.07–8.01 (3H), 7.70 (1H, d, J = 8.4 Hz), 7.58 (1H, app t, J = 7.9 Hz), 7.49 (1H, app t, J = 7.8 Hz), 7.21 (1H, m), 7.11–7.07 (2H, m), 6.98 (1H, m), 3.91 (3H, s), 2.33 (3H, s); MS (ESI) m/z 438; HRMS: calcd for $C_{25}H_{18}F_3NO_3+H^+$, 438.1312; found (ESI, $[M+H]^+$), 438.1331. HPLC purity: 98.5%.

6.15. 3-Benzyl-4-[3-(4-methoxyphenoxy)phenyl]-8-(trifluoromethyl)quinoline (9a)

A mixture 4-methoxyphenylboronic acid (76 mg, 0.50 mmol), $Cu(OAc)_2$ (45 mg, 0.25 mmol), and powdered 4 Å molecular sieves (100 mg) was treated with **7d**[13] (95 mg, 0.25 mmol) in dichloromethane (2.5 mL). Triethylamine (0.10 mL, 0.75 mmol) was added and the reaction stirred at 20 °C for 3 d. The reaction was filtered through Celite, treated with water (5 mL), and extracted with dichloromethane (2 × 10 mL). The combined extracts were concentrated in vacuo. Chromatography afforded compound **9a** as a colorless oil (89 mg, 76%). ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, s), 8.01 (1H, d, J = 7.2 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.48–7.41 (3H), 7.23–7.17 (3H), 7.07 (1H, m), 6.98–6.95 (3H), 6.89–6.84 (3H), 6.75 (1H, s with fc), 3.99 (2H, s), 3.78 (3H, s); MS (ES) m/z 485.9; HRMS: calcd for $C_{30}H_{22}F_3NO+H^+$, 486.1675; found (ESI, $[M+H]^+$), 486.1706. HPLC purity: 98.5%.

6.16. 4-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-phenol (9b)

A stirred mixture of **9a** (0.22 g, 0.45 mmol) and pyridine hydrochloride (3.0 g) was heated to 180–190 °C for 3 h, then cooled, treated with ethyl acetate, and the organic layer washed with 1 M aqueous hydrochloric acid and then brine. Organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography eluting with a 10:90–50:50 ethyl acetate/hexanes gradient to afford **9b** as an off-white solid (190 mg, 90%). Mp 55–60 °C; ^{1}H NMR ($CDCl_3$): δ 8.98 (1H, s), 8.01 (1H, d, J = 7.3 Hz), 7.68 (1H, d, J = 8.4 Hz), 7.48–7.41 (2H), 7.23–7.15 (3H), 7.07 (1H, d with fc, J = 8.4 Hz), 6.97 (2H, d, J = 8.1 Hz), 6.94–6.88 (3H), 6.80–6.75 (3H), 4.69 (1H, s), 3.99 (3H, s); MS (ES) m/z 469.9; HRMS: calcd for $C_{29}H_{20}F_3NO_2+H^+$, 472.1519; found (ESI, $[M+H]^+$), 472.1530. HPLC purity: 100%.

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