Bioorganic & Medicinal Chemistry 17 (2009) 1663–1670

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Biarylether amide quinolines as liver X receptor agonists

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ARTICLE INFO

Article history:
Received 7 November 2008
Revised 19 December 2008
Accepted 22 December 2008
Available online 27 December 2008

Keywords:
Liver X receptor
LXR
Agonist
Quinoline
ABCA1

ABSTRACT

A series of 4-(amido-biarylether)-quinolines was prepared as potential LXR agonists. Appropriate substitution with amide groups provided high affinity LXR ligands, some with excellent potency and efficacy in functional assays of LXR activity. Novel amide **4g** had a binding IC_{50} = 1.9 nM for LXRβ and EC_{50} = 34 nM (96% efficacy relative to T0901317) in an ABCA1 gene expression assay in mouse J774 cells, demonstrating that 4-(biarylether)-quinolines with appropriate amide substitution are potent LXR agonists

1. Introduction

Nuclear hormone receptors comprise a superfamily of gene transcription factors that include estrogen receptors (ER), retinoid X receptors (RXRs), and liver X receptors (LXRs). Among these receptors, the LXRs are an increasingly important target since modulators of LXR function are potential therapeutic agents for the treatment of dyslipidemia.[1] There are two subtypes of LXR: LXRα and LXRβ. LXRα is principally expressed in the liver, kidney, intestine, lung, spleen, and macrophages, with the highest levels found in the liver. In contrast, LXRβ is found in nearly all tissues and was known as ubiquitous receptor (UR) prior to an understanding of its relationship to LXRα.[2] Both subtypes associate with RXR to form functionally active heterodimers. Binding of an RXR agonist (e.g., 9-*cis*-retinoic acid) to the RXR portion of the heterodimer or binding of an LXR agonist (e.g., oxysterols such as 24,25-epoxycholesterol) to the LXR portion activates the LXR response element (LXRE) (Fig. 1). This activation leads to increased transcription of mRNA encoding for various genes regulating lipids including ATP-binding cassette transporters (e.g., ABCA1, ABCG1, ABCG5),[3] and sterol regulatory element binding protein 1c (SREBP1c).[4] Of particular importance are ABCA1, which increases cholesterol efflux from macrophages, and SREBP1c, which is believed to be responsible for increases in triglyceride levels and ultimately hepatic steatosis. Selective activation of the ABCA1 over SREBP1c may have the desirable therapeutic profile of reducing lesion via reverse cholesterol transport (RCT) while having minimal effects on triglyceride production.[5] Recent studies have supported the idea that LXRβ-selective agonists would likely lead to an increase in cholesterol efflux from macrophages and other cell types, improving most dyslipidemia measures, while not increasing triglyceride levels.[6]

The potential of LXR agonists to treat dyslipidemia has led to the development of several high affinity LXR ligands with potent agonism for both subtypes.[7] Among the most studied are T0901317 (**1**) from Tularik[8] and GW3965 (**2**) from GlaxoSmithKline (Fig. 2).[9]

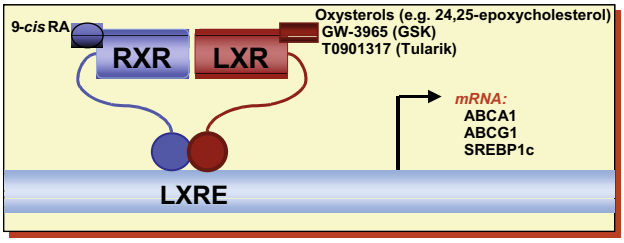

Figure 1. Either an LXR or RXR agonist at the RXR–LXR heterodimer activates the LXR response element (LXRE).

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doi:10.1016/j.bmc.2008.12.048

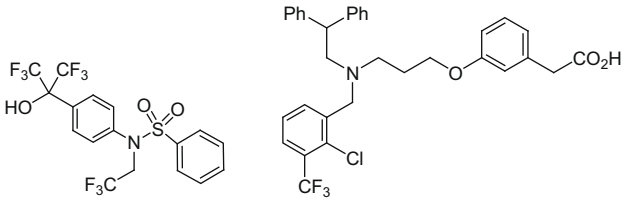


Figure 2. LXR agonists from Tularik and GlaxoSmithKline.

Wyeth has identified a series of quinolines incorporating an acid side chain.[10] The acid group interacts with the Arg-319 residue in the LXRβ receptor while the quinoline nitrogen forms a hydrogen bond with the His-435.[11] Typical of this quinoline-acid series is WAY-254011 (**3**), which reduced atherosclerotic lesion in an 8-week model using LDL-KO mice fed a high fat ('Western') diet.[12] Unfortunately, **3** increased plasma triglycerides levels relative to control in several rodent species including hamster, an effect consistent with its lack of selectivity for the LXRβ subtype.[10] Compound **3** also was a PPAR agonist, activating all three subtypes of the receptor. To further explore the SAR of the quinoline series, and to address the issue of PPAR agonism, several modifications of **3** were targeted (Fig. 3). To eliminate the benzylacetic acid group, which may be associated with the PPAR activity, the acetic acid was changed to a directly bonded amide (**4** X = $CONR_1R_2$) and the benzyl ether linkage replaced with an oxygen atom to form a biarylether. To reduce molecular weight, the 3-benzyl group was also replaced with a smaller and potentially more metabolically stable methyl group. We describe in this paper the synthesis and biological activity of compounds incorporating these modifications.

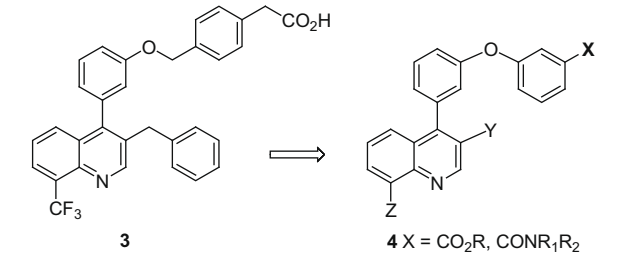
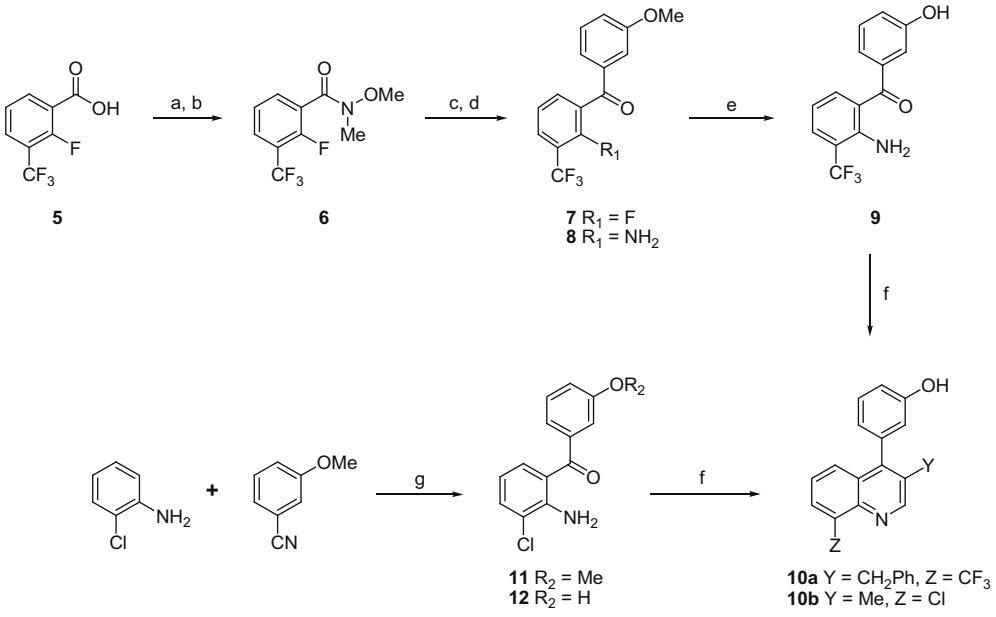


Figure 3. Targeted modifications of WAY-254011 (**3**).

2. Chemistry

Preparation of the biarylethers was accomplished in two parts: synthesis of the 4-(3-hydroxyphenyl)quinoline core structure followed by elaboration of the core into the functionalized biarylethers. Our approach to the core structure converted 2-fluoro-3-trifluoromethylbenzoic acid **5** into the Weinreb amide **6** via the acid chloride (Scheme 1). Addition of 3-methoxyphenylmagnesium bromide provided 2-fluorophenone **7**, which was converted to the 2-amino analog **8** using concentrated ammonium hydroxide under pressure. The methoxy group was efficiently removed using a pyridine hydrochloride melt at 200 °C to give **9**. Transformation of the 2-aminophenone into 8-trifluoromethyl-4-(3-hydroxyphenyl) quinoline (**10a**) using a Friedlander reaction[13] employed hydrocinnamaldehyde to afford the quinoline core.

An alternative shorter synthesis of the corresponding 8-chloroquinoline began with a Sugasawa reaction[14] between 2-chloroaniline and 3-methoxy-benzonitrile, which afforded the 2-aminophenone **11** directly. This reaction was generally accompanied by small amounts of the demethylated product **12**, with the amount of **12** relative **11** increasing as the temperature and reaction times were increased. We were able to combine the Sugasawa reaction and the desired deprotection in one pot by prolonged heating in chlorobenzene at reflux to directly give phenol **12**, albeit in modest yield. Phenol **12** was subjected to a Friedlander reaction using propionaldehyde diethylacetal to prepare 3-methylquinoline **10b**. While propionaldehyde could also be used in the Friedlander reaction, its low boiling point required the sequential addition of several equivalents and resulted in generally lower yields. Unfortunately, this shorter approach to quinolines was not useful for 8-tri-



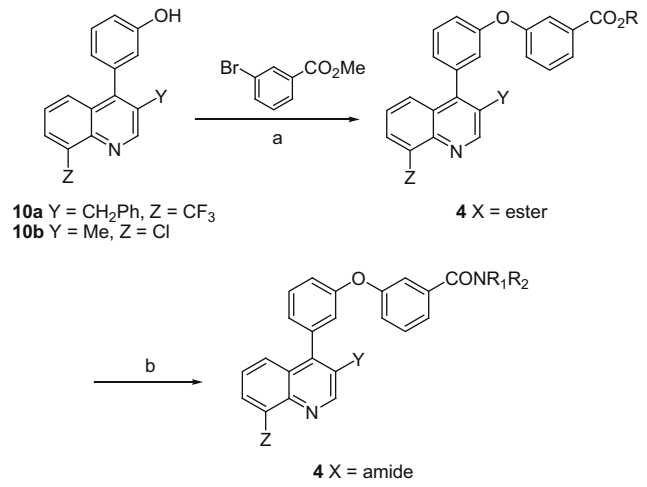
Scheme 1. Reagents and conditions: (a) $SOCl_2$, PhH; (b) HNMe(OMe)·HCl, pyridine, $CHCl_3$, rt (95% for two steps); (c) 3-MeOPhMgBr, THF, −78 to 0 °C (88%); (d) concd NH_4OH, sealed tube, 140 °C, 8–10 h (70%); (e) pyridine hydrochloride, 200 °C, 2 h (91%); (f) $PhCH_2CHO$ or $CH_3CH_2CH(OEt)_2$, cat. H_2SO_4, AcOH, 105 °C, 6–24 h (61–70%); (g) BCl_3 in xylenes, chlorobenzene, then 3-MeOPhCN, $AlCl_3$, reflux, overnight (37%).

fluoromethyl analogs because of the instability of the group to Sugasawa reaction conditions and workup.[15]

The second aromatic ring of the biaryl ether was incorporated next. Copper-mediated coupling of the 4-(3-hydroxyphenyl)quinoline cores with methyl 3-bromobenzoate[16] installed the biarylether side chain (Scheme 2). Copper acetate-mediated coupling with 3-(EtO_2C)PhB($OH)_2$[17] was also successful. Conversion of the esters into amides, generally using Weinreb's amidation procedure,[18] gave the final targets for testing.

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.[10] 4-(Biarylether)-quinolines incorporating a benzyl group at the 3-position of the quinoline were examined first. The ester intermediate **4a** had moderate affinity for LXRβ and was nearly fivefold selective over the LXRα subtype. 1-Propylamide **4b** had higher affinity and slightly improved binding selectivity, and was comparable to the 2-propyl analog **4c**. In general, the tertiary amides had higher affinity for both subtypes. For example, diethylamide **4d** had an LXRβ binding IC_{50} value of 2.8 nM. Tying up the amide substituents into a ring, whether a pyrrolidine (**4e**), piperidine (**4f**), or morpholine (**4g**), gave similar LXR affinity to the unconstrained tertiary analogs. To reduce the molecular weight we examined analogs in which the 3-benzyl group was replaced with a methyl and the 8-trifluoromethyl with a chlorine atom. Interestingly, these smaller analogs (**4i**–**4l**) still had good LXRβ affinity (binding $IC_{50} \leqslant 100$ nM). As before, the tertiary amides had generally higher LXR affinity compared to the secondary amides. The constrained analogs (**4n**–**4p**) had LXRβ binding IC_{50} values <10 nM. These results demonstrated that the smaller 8-chloro-3-methyl-quinoline core was a suitable replacement for the 8-trifluoromethyl-3-benzyl-quinoline core for LXR ligands incorporating the biarylether-amide motif.

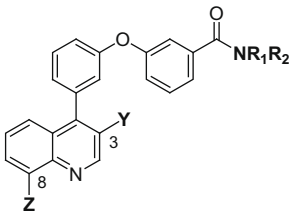


Scheme 2. Reagents and conditions: (a) CuO, K_2CO_3, pyridine, 110–120 °C (42–43%); (b) Me_3Al, HNR_1R_2, PhMe, 60–65 °C, 18–24 h (41–97%).

The compounds were also tested in Gal4β and Gal4α functional assays for LXR activity.[10] These LXR transactivation assays used Huh7 cells transfected with human LXR ligand binding domains fused to Gal4 DNA binding domains. The most potent analogs in both assays were the 3-benzylquinolines **4d–4g** incorporating tertiary amides, which had EC_{50} values <200 nM in the Gal4β assay and comparable efficacy compared to **1**. Comparison of the two morpholine amides **4g** and **4p** suggested some loss in potency and efficacy for the lower molecular weight compound. The compounds tended to be less potent in the Gal4α assays but with similar SAR to the Gal4β results.

In addition to the Gal4 assays, the functional activity of a selected group of compounds was characterized in a J774 mouse

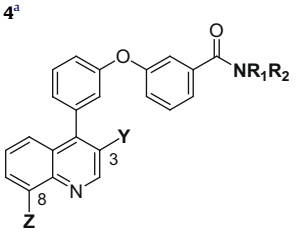
Table 1
Biarylether amide quinolines **4**[a]



Compound	Y	Z	NR_1R_2	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	Gal4 LXRβ EC_{50} (nM) (% ag)	Gal4 LXRα EC_{50} (nM) (% ag)
3	—	—	—	2.1	9.5	93 (63%)	238 (90%)
4a	CH_2Ph	CF_3	Methyl ester	53	231	nt	nt
4b	CH_2Ph	CF_3	NH(1-Pr)	8.5	91	1525 (107%)	2709 (43%)
4c	CH_2Ph	CF_3	NH(2-Pr)	10	74	nt	nt
4d	CH_2Ph	CF_3	NEt_2	2.8	12	144 (83%)	675 (73%)
4e	CH_2Ph	CF_3	Pyrrolidine	2.6	12	98 (89%)	435 (75%)
4f	CH_2Ph	CF_3	Piperidine	2.9	20	170 (85%)	477 (99%)
4g	CH_2Ph	CF_3	Morpholine	1.9	15	138 (80%)	345 (90%)
4h	Me	Cl	Methyl ester	230	1002	nt	nt
4i	Me	Cl	NHMe	9	125	800 (66%)	1306 (37%)
4j	Me	Cl	NHEt	20	272	1272 (55%)	2102 (28%)
4k	Me	Cl	NH(1-Pr)	25	280	1180 (45%)	1633 (8%)
4l	Me	Cl	NH(2-Pr)	100	357	nt	nt
4m	Me	Cl	NEt_2	12	108	nt	nt
4n	Me	Cl	Pyrrolidine	3	34	nt	nt
4o	Me	Cl	Piperidine	6	50	nt	nt
4p	Me	Cl	Morpholine	7	158	572 (46%)	1237 (33%)

[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 Gal4 assays were typically ±30% of the mean or less. % of efficacy is relative to **1**. nt = not tested.

Table 2
ABCA1 J774 activity for **4**[a]



Compound	Y	Z	NR_1R_2	ABCA1 EC_{50} (μM) (% ag)
3	—	—	—	0.041 (114%)
4b	CH_2Ph	CF_3	NH(1-Pr)	0.420 (155%)
4g	CH_2Ph	CF_3	Morpholine	0.034 (96%)
4k	Me	Cl	NH(1-Pr)	1.60 (281%)
4p	Me	Cl	Morpholine	0.070 (102%)

[a] Results are given as the mean of at least two independent experiments unless otherwise indicated. The standard deviations for the binding assays were typically ±50% of the mean or less. % of efficacy is relative to **1**.

macrophage cell line, testing for upregulation of ABCA1 mRNA (Table 2).[19] The ABCA1 protein is a transporter responsible for removing cholesterol from various cells including macrophages. When measuring mRNA induction relative to **3**, the secondary amides were relatively weak, with **4b** about an order of magnitude weaker than **3**. In contrast to these results the morpholine amides, which are tertiary, had good activity in the assay. This was true even for smaller ligands such as **4p**, in which a benzyl group was replaced with a methyl. While compound **4p** had about half the potency of **3**, it was still fully efficacious. However, compound **4g** was the most potent, with an EC_{50} value of 34 nM, potency comparable to **3**, and fully efficacious relative to the standard. Some minor differences in the potency of the compounds in the Gal4 assays relative to the ABCA1 assays may be attributed to the differences in species (human vs mouse), cell type (liver hepatocytes vs macrophages), and to the variations in the assay conditions.

To explore the nuclear hormone cross-reactivity of the biarylamides relative to **3**, PPAR functional activity in transiently transfected cell lines was examined. Lack of PPAR agonism was of particular interest as PPAR activation can be associated with several undesired effects. As indicated in Table 3, the biarylether amides did not have significant agonist activity for any of the PPARs examined, with the exception of **4b**, which had very weak agonism and poor efficacy for PPARγ. In contrast, **3** had weak partial agonism for all three PPAR subtypes.

4. X-ray crystal structure

The most potent compound for upregulating ABCA1 mRNA, **4g**, was cocrystallized with LXRβ protein to determine its interactions within the crystallized receptor. Unlike the functionally active heterodimer that forms in the presence of RXR, LXRβ by itself typically forms homodimers. Each subunit of the homodimer has very similar ligand–receptor interactions. With **4g**, key interactions within one subunit (Fig. 4) included interactions of the quinoline nitrogen with the His-435, and a strong hydrogen bond between the carbonyl oxygen of the amide with the backbone NH of the Leu-330. The 3-benzyl group on the quinoline is located in a hydrophobic pocket defined by three phenylalanines (Phe-329, Phe-340, and Phe-349), which is termed the 'Phe pocket'. Interestingly, many of the compounds with a 3-methyl group in place of the 3-benzyl group retained good affinity for the LXRs, though reduced filling of the 'Phe pocket' may account for the decrease in functional activity in both the Gal4 LXR and ABCA1 gene expression assays.

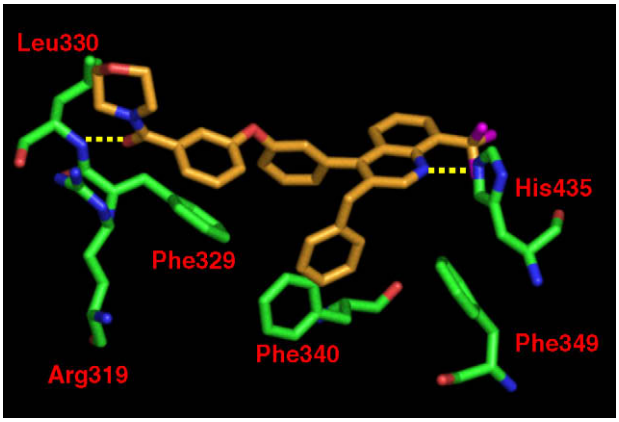


Figure 4. X-ray of LXRβ cocrystallized with **4g**.

5. Conclusion

In conclusion, a series of quinolines containing a biarylether amide group at the 4-position of the quinoline, was prepared. These were designed in part based on modifications of WAY-254011, a previously reported LXR agonist. Several compounds in the series had high affinity for the LXR receptors and exhibit potent agonism both in a transiently transfected cell line, and in a J774 mouse cell line examining ABCA1 gene regulation. Among the compounds tested, there was little or no PPAR agonist activity as measured in transiently transfected cell lines. The most potent compound for inducing ABCA1 gene expression was morpholine amide **4g**. This quinoline amide was cocrystallized with LXRβ and shown to have key hydrogen bonding interactions with His435 through the quinoline nitrogen and with Leu330 backbone amide nitrogen. While these compounds had little functional selectivity for LXRβ over LXRα, the results presented here demonstrate that 4-(biarylether)-quinolines with appropriately positioned amide substituents are potent LXR agonists with reduced or eliminated PPAR agonist activity.

Table 3
PPAR activity for **3** and biarylether amide quinolines **4**[a]

Compound	Y	Z	NR_1R_2	Gal4 PPARα EC_{50} (μM) (% ag)	Gal4 PPARδ EC_{50} (μM) (% ag)	Gal4 PPARγ EC_{50} (μM) (% ag)
3	—	—	—	1.31 (19%)	0.68 (47%)	0.63 (24%)
4b	CH_2Ph	CF_3	NH(1-Pr)	No ag eff	No ag eff	3.8 (7%)
4g	CH_2Ph	CF_3	Morpholine	No ag eff	No ag eff	No ag eff
4k	Me	Cl	NH(1-Pr)	No ag eff	No ag eff	No ag eff
4p	Me	Cl	Morpholine	No ag eff	No ag eff	No ag eff

[a] Results are for determinations in quadruplicate from a 12 concentration dose response curve, with the highest dose at 30 μM. The % efficacy is relative to the following references: PPARα, [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (WY-14643); PPARγ, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]2-2,4-thiazolidinone (Rosiglitazone); PPARδ, 3-chloro-4-[[3-[(3-phenyl-7-propyl-6-benzofuranyl)oxy]propyl]thio]-phenylacetic acid (L796449).

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 appearance, app. means apparent and br means broad.

6.1. 2-Fluoro-*N*-methoxy-*N*-methyl-3-trifluoromethylbenzamide (6)

To a stirred solution of **5** (15.0 g, 72 mmol) in benzene (150 mL) at rt was added drop-wise a solution of $SOCl_2$ (10.0 mL, 137 mmol) in CH_2Cl_2 (30 mL) over 30 min. The resulting solution was heated at reflux for 6 h, then cooled and concentrated in vacuo. The residue was concentrated three times from toluene (50 mL). The crude acid chloride was dissolved in $CHCl_3$ (250 mL) and N,O-dimethylhydroxylamine hydrochloride (10.0 g, 103 mmol) was added. The mixture was cooled to 0 °C, slowly treated with pyridine (16 mL), then stirred at 20 °C for 12 h. The reaction was concentrated in vacuo and the residue dissolved in 1:1 CH_2Cl_2/Et_2O (400 mL). The solution was washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 17.0 g (95%) of **6**. ^{1}H NMR (DMSO-d_6): δ 7.92–7.84 (2H, m), 7.51 (1H, app. t, J = 7.8 Hz), 3.66 (3H, br s), 3.32 (3H, br s); MS (ESI) m/z 252.0; HRMS: calcd for $C_{10}H_9F_4NO_2 + H^+$, 252.0642; found (ESI, $[M+H]^+$), 252.0651.

6.2. [2-Fluoro-3-(trifluoromethyl)phenyl](3-methoxyphenyl) methanone (7)

A stirred solution of **6** (17.0 g, 67.7 mmol) in THF (150 mL) at −78 °C was treated with 1.0 M 3-methoxyphenylmagnesium bromide in THF (97 mL, 97 mmol) over 1.5 h. After 1 h longer at −78 °C, the reaction was brought to 0 °C. After 2 h, the reaction was quenched by pouring into ice cold 1 M aqueous HCl. The product was extracted with ethyl acetate and the extracts washed with water, then brine, and then dried (Na_2SO_4). After concentration in vacuo, the crude product was purified by chromatography eluting with 90:10 methylene chloride/hexane to afford **7** as a colorless liquid (17.8 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.80 (1H, app. t, with additional fine coupling, J = 7.7 Hz), 7.72 (1H, app. t, with fine coupling, J = 7.7 Hz), 7.42–7.36 (3H, m), 7.31 (1H, app. d, with fine coupling, J = 7.5 Hz), 7.19 (1H, ddd, J = 1.1, 2.7, 8.1 Hz), 3.86 (3H, s); ^{19}F NMR ($CDCl_3$): δ −61.76 (s), −114.03 (m); MS (ES) m/z 299.1; HRMS: calcd for $C_{15}H_{10}F_4O_2 + H^+$, 299.0689; found (ESI, $[M+H]^+$), 299.0693.

6.3. [2-Amino-3-(trifluoromethyl)phenyl](3-methoxyphenyl) methanone (8)

A mixture of **7** (7.00 g, 23.5 mmol), DME (50 mL) and concentrated NH_4OH (150 mL) was heated in a steel bomb at 140 °C for 6 h. The vessel was cooled in ice, carefully opened, and the reaction mixture concentrated in vacuo. The residue was dissolved in ethyl acetate and the ethyl acetate layer washed with water, brine, and dried (Na_2SO_4). After concentrating in vacuo, the crude aniline was purified by chromatography with 98:2 methylene chloride/methanol to afford **8** as a colorless liquid (4.80 g, 70%). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.65–7.61 (2H, m), 7.39 (1H, app. t, J = 7.9 Hz), 7.15–7.09 (3H, m), 6.81 (2H, br s), 6.67 (1H, app. t, J = 7.8 Hz), 3.85 (3H, s); ^{19}F NMR ($CDCl_3$ + DMSO-d_6): δ −63.60 (s); MS (ESI) m/z 296; HRMS: calcd for $C_{15}H_{12}F_3NO_2 + H^+$, 296.0893; found (ESI, $[M+H]^+$), 296.0887.

6.4. [2-Amino-3-(trifluoromethyl)phenyl](3-hydroxyphenyl) methanone (9)

A stirred mixture of **8** (3.00 g, 10.0 mmol) and pyridine hydrochloride (40 g) was placed in a preheated bath at 190–200 °C. After 2 h, the reaction was cooled to near 20 °C and treated with aqueous 1 N HCl. The mixture was extracted with ethyl acetate and the combined extracts washed sequentially with water and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a semisolid material. This material was repeatedly stirred with portions of methylene chloride. The combined organic extracts were concentrated to provide crude product which could be further purified by chromatography eluting with 1:99 methanol/methylene chloride to give **9** as a yellow solid (2.60 g, 91%). Mp: 106–107 °C; ^{1}H NMR (DMSO-d_6): δ 9.82 (1H, s), 7.71 (1H, d, J = 7.7 Hz), 7.61 (1H, d, J = 7.9 Hz), 7.33 (1H, app. t, J = 7.9 Hz), 7.13 (2H, br s), 7.01 (3H, m), 6.71 (1H, app. t, J = 8.0 Hz); MS m/z 282; HRMS: calcd for $C_{14}H_{10}F_3NO_2 + H^+$, 282.0736; found (ESI, $[M+H]^+$), 282.0729.

6.5. 3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenol (10a)

A stirred mixture of **9** (3.00 g, 10.6 mmol) and 3-phenyl-propionaldehyde (2.11 g, 15.9 mmol) in glacial AcOH (20 mL) was treated with a 1:19 v:v mixture of concd H_2SO_4/glacial AcOH (1.5 mL) and then heated at 120 °C for 3 h. The reaction was cooled and then concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($NaSO_4$) and concentrated in vacuo. Purification of the oily residue by chromatography eluting with 2:98 methanol/CH_2Cl_2 gave **10a** as a light yellow solid from a foam (2.80 g, 70%). ^{1}H NMR (DMSO-d_6): δ 9.74 (1H, s), 8.98 (1H, s), 8.15 (1H, d, J = 6.9 Hz), 7.71–7.63 (2H, m), 7.37 (1H, app. t, J = 7.9 Hz), 7.24 (2H, app. t, J = 7.4 Hz), 7.17 (1H, app. t, J = 7.2 Hz), 7.03 (2H, d, J = 7.4 Hz), 6.94 (1H, dd, J = 1.8, 6.1 Hz), 6.71 (1H, d, J = 7.5 Hz), 6.69 (1H, s), 4.00 (2H, s); MS (ES) m/z 378.2; HRMS: calcd for $C_{23}H_{16}F_3NO + H^+$, 380.1257; found (ESI, $[M+H]^+$), 380.1257.

6.6. Methyl 3-{3-[3-benzyl-8-(trifluoromethyl)quinolin-4-yl] phenoxy}benzoate (4a)

A well-stirred mixture of **10a** (2.65 g, 7.00 mmol), methyl 3-bromobenzoate (3.01 g, 14.0 mmol), CuO (1.01 g, 12.6 mmol), and K_2CO_3 (1.93 g, 14.0 mmol) was heated in pyridine at 120 °C under nitrogen. After 48 h, the reaction was cooled, treated with water (100 mL), and extracted with diethyl ether (2 × 100 mL). The combined extracts were dried over $MgSO_4$, concentrated in vacuo with heat to remove solvents. The dark residue was purified by chromatography eluting with 20:80 ethyl acetate/hexanes to afford **4a** as a tacky glass ($R_f \sim 0.3$ in 20:80 ethyl acetate/hexanes) (1.53 g, 43%). ^{1}H NMR ($CDCl_3$): δ 8.99 (1H, s), 8.02 (1H, d, J = 7 Hz), 7.79 (1H, dt, J = 1.2, 7.8 Hz), 7.70 (2H, m), 7.49 (2H, app. t, J = 8.0 Hz), 7.40 (1H, app. t, J = 7.8 Hz), 7.23–7.13 (6H, m), 6.97 (2H, d, J = 7.5 Hz), 6.84 (1H, app. t, J = 1.0 Hz), 4.01 (2H, s), 3.88 (3H, s); MS (ESI) m/z 514; HRMS: calcd for $C_{31}H_{22}F_3NO_3 + H^+$, 514.1624; found (ESI, $[M+H]^+$), 514.1638.

6.7. 3-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-*N*-propylbenzamide (4b)

To a stirred mixture of 1-propylamine (59 mg, 1.00 mmol) in toluene (2 mL) at ambient temperature under nitrogen was added 2.0 M trimethylaluminum in toluene (0.50 mL, 1.00 mmol). After 0.75 h, a solution of **4a** (128 mg, 0.25 mmol) in toluene (7.0 mL) was added and the reaction heated at 65 °C for 16 h. The cooled

reaction was carefully treated with water (2 mL), then after 10 min with 2 M aqueous HCl (1 mL) resulting in gas evolution. The reactions were extracted with dichloromethane (5 mL, 2 mL) and the combined extracts were dried ($MgSO_4$). After concentrating in vacuo, the residues were chromatographed on silica gel using 25:75, then 50:50 ethyl acetate/hexane as eluent. Compound **4b** was isolated as a white solid-foam (121 mg, 89%). ^{1}H NMR (DMSO-d_6): δ 9.03 (1H, s), 8.49 (1H, t, J = 5.6 Hz), 8.16 (1H, d, J = 7.0 Hz), 7.73–7.57 (6H), 7.46 (1H, app. t, J = 7.9 Hz), 7.23–7.10 (5H), 7.00 (2H, d, J = 6.8 Hz), 6.93 (1H, m), 4.02 (2H, s), 3.20 (2H, q, J = 6.5 Hz), 1.51 (2H, m), 0.87 (3H, t, J = 7.4 Hz); MS (ESI) m/z 541; HRMS: calcd for $C_{33}H_{27}F_3N_2O_2 + H^+$, 541.2097; found (ESI, $[M+H]^+$), 541.2100.

6.8. 3-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-*N*-isopropylbenzamide (4c)

Using essentially the same procedure as for **4b**, except using isopropylamine as the amine, **4c** was obtained as a white solid-foam (120 mg, 89%). ^{1}H NMR (DMSO-d_6): δ 9.03 (1H, s), 8.25 (1H, d, J = 7.7 Hz), 8.16 (1H, dd, J = 1.2, 7.0 Hz), 7.73–7.58 (5H), 7.46 (1H, app. t, J = 7.9 Hz), 7.23–7.15 (5H), 7.10 (1H, app. d with additional fine coupling, J = 7.6 Hz), 7.00 (2H, app. d, J = 6.9 Hz), 6.92 (1H, dd, J = 1.5, 2.2 Hz), 4.07 (1H, s), 4.03 (2H, m) 1.14 (6H, d, J = 6.5 Hz); MS (ESI) m/z 541; HRMS: calcd for $C_{33}H_{27}F_3N_2O_2 + H^+$, 541.2097; found (ESI, $[M+H]^+$), 541.2088.

6.9. 3-{3-[3-Benzyl-8-(trifluoromethyl)quinolin-4-yl]phenoxy}-*N*,*N*-diethylbenzamide (4d)

Using essentially the same procedure as for **4b**, except using diethylamine as the amine, **4d** was obtained as an oil (60 mg, 43%). ^{1}H NMR (DMSO-d_6): δ 9.04 (1H, s), 8.16 (1H, dd, J = 1.4, 7.0 Hz), 7.72–7.64 (2H), 7.60 (1H, app. t, J = 8.0 Hz), 7.44 (1H, app. t, J = 7.9 Hz), 7.31–7.09 (9H), 6.99–6.95 (3H), 4.03 (2H, m), 3.39 (2H, v. br s), 3.12 (2H, v. br s), 1.10 (3H, v. br s), 0.93 (3H, v. br s); MS (ESI) m/z 555; HRMS: calcd for $C_{34}H_{29}F_3N_2O_2 + H^+$, 555.2254; found (ESI, $[M+H]^+$), 555.2251.

6.10. 3-Benzyl-4-{3-[3-(pyrrolidin-1-ylcarbonyl)phenoxy]phenyl}-8-(trifluoromethyl)quinoline (4e)

Using essentially the same procedure as for **4b**, except using pyrrolidine as the amine and using 50:50 ethyl acetate/hexane, then ethyl acetate as eluent, **4e** was obtained as a white solid-foam (126 mg, 91%). ^{1}H NMR (DMSO-d_6): δ 9.04 (1H, s), 8.17 (1H, dd, J = 1.3, 7.2 Hz), 7.73–7.65 (2H), 7.60 (1H, app. t, J = 7.9 Hz), 7.44 (1H, app. t, J = 7.9 Hz), 7.26 (1H, app. t with additional fine coupling, J = 7.8 Hz), 7.24–7.11 (6H), 6.99 (2H, app. t, J = 6.8 Hz), 6.95 (1H, dd, J = 1.6, 2.2 Hz), 4.03 (2H, m), 3.42 (2H, t, J = 7.0 Hz), 3.28 (2H, t, J = 7.0 Hz), 1.82 (2H, m), 1.71 (2H, m); MS (ESI) m/z 553; HRMS: calcd for $C_{34}H_{27}F_3N_2O_2 + H^+$, 553.2097; found (ESI, $[M+H]^+$), 553.2108.

6.11. 3-Benzyl-4-{3-[3-(piperidin-1-ylcarbonyl)phenoxy]phenyl}-8-(trifluoromethyl)quinoline (4f)

Using essentially the same procedure as for **4b**, except using piperidine as the amine and using 50:50 ethyl acetate/hexane, then ethyl acetate as eluent, **4f** was obtained as a white solid-foam (121 mg, 85%). ^{1}H NMR (DMSO-d_6): δ 9.04 (1H, s), 8.17 (1H, dd, J = 1.3, 6.9 Hz), 7.73–7.65 (2H, m), 7.60 (1H, app. t, J = 7.9 Hz), 7.44 (1H, app. t, J = 8.0 Hz), 7.36–7.09 (7H), 7.01–6.96 (4H), 4.03 (2H, m), 3.32 (2H, v. br s), 3.18 (2H, v. br s), 1.52 (4H, v. br), 1.29 (2H, v. br s); MS (ESI) m/z 567; HRMS: calcd for $C_{35}H_{29}F_3N_2O_2 + H^+$, 567.2254; found (ESI, $[M+H]^+$), 567.2275.

6.12. 3-Benzyl-4-{3-[3-(morpholin-4-ylcarbonyl)phenoxy]phenyl}-8-(trifluoromethyl)quinoline (4g)

Using essentially the same procedure as for **4b**, except using morpholine as the amine and using 50:50 ethyl acetate/hexane, then ethyl acetate as eluent, **4g** was obtained as a white solid-foam (137 mg, 96%). ^{1}H NMR (DMSO-d_6): δ 9.04 (1H, s), 8.16 (1H, dd, J = 1.0, 7.0 Hz), 7.73–7.65 (2H), 7.60 (1H, app. t, J = 7.9 Hz), 7.44 (1H, app. t, J = 8.1 Hz), 7.24–7.09 (8H), 7.01–6.97 (3H), 4.03 (2H, m), 3.70–3.40 (8H, v. br peaks); MS (ESI) m/z 569; HRMS: calcd for $C_{34}H_{27}F_3N_2O_3 + H^+$, 569.2047; found (ESI, $[M+H]^+$), 569.2048.

6.13. (2-Amino-3-chlorophenyl)(3-hydroxyphenyl)methanone (12)

A stirred mixture of 1.0 M boron trichloride in dichloromethane (202 mL, 202 mmol,) and chlorobenzene (350 mL) was treated with 2-chloroaniline (32.7 mL, 311 mmol) in chlorobenzene (150 mL) over ca. 15 min. The mixture was stirred for 5 min, then 3-methoxybenzonitrile (19.0 mL, 155 mmol) and aluminum chloride (26.93 g, 202 mmol) were added. The reaction was heated at ca. 50 °C while removing the dichloromethane. The reaction was then heated at reflux overnight. The mixture was cooled and treated with ice, followed by 2 N aqueous HCl (500 mL). This mixture was then heated at 100 °C for 3 h, then cooled. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The resulting material was triturated with 10:90 diethylether/hexane to give **12** as a tan solid (14.25 g, 37%). Mp: 126–127 °C; ^{1}H NMR (DMSO-d_6): δ 9.80 (s, 1H), 7.56–7.53 (m, 1H), 7.34–7.29 (m, 2H), 7.00–6.97 (m, 5H), 6.60 (m, 1H); MS (ES) m/z 248.1. Anal. calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.23; H, 3.83; N, 5.57.

6.14. 3-(8-Chloro-3-methylquinolin-4-yl)phenol (10b)

A stirred mixture of **12** (2.47 g, 10.0 mmol) and propionaldehyde diethylacetal (4.90 mL, 30.0 mmol) in glacial acetic acid (20 mL) was treated with concd H_2SO_4 (6 pipette drops) and then heated at 105–110 °C for 18 h. The reaction was cooled and poured carefully onto $NaHCO_3$ (28 g) in water (100 mL) in a large beaker. After further dilution with water (150 mL), the neutralized mixture was extracted with ethyl acetate (2 × 100 mL) and the extracts dried with $MgSO_4$. Concentration in vacuo afforded a brown oil-solid which was triturated with 20:80 ethyl acetate/hexanes to give a tan to slightly yellow solid, **10b** (1.64 g, 61%). Mp: 241–243 °C; ^{1}H NMR (DMSO-d_6): δ 9.70 (1H, br s), 8.93 (1H, s), 7.84 (1H, dd, J = 1.3, 7.4 Hz), 7.43 (1H, dd, J = 7.5, 8.4 Hz), 7.34 (2H, m), 6.88 (1H, br d, J = 8.4 Hz), 6.66 (1H, br d, J = 7.8 Hz), 6.62 (1H, m), 2.21 (3H, s); MS (ESI) m/z 269.9; HRMS: calcd for $C_{16}H_{12}ClNO + H^+$, 270.0680; found (ESI, $[M+H]^+$), 270.0683.

6.15. Methyl 3-[3-(8-chloro-3-methylquinolin-4-yl)phenoxy]benzoate (4h)

A well-stirred mixture of **10b** (1.35 g, 5.00 mmol), methyl 3-bromobenzoate (2.15 g, 10.0 mmol), CuO (0.72 g, 9.0 mmol), and K_2CO_3 (1.38 g, 10.0 mmol) was heated in pyridine at 110 °C under nitrogen. After 3 d, the reaction was cooled, treated with water (100 mL), and extracted twice with CH_2Cl_2 (100 mL each). The combined extracts were dried over $MgSO_4$, concentrated in vacuo with heat to remove solvents. The residue was purified by chromatography eluting with 25:75 ethyl acetate/hexanes to afford a solid which was triturated with a small volume of 20:80 ethyl acetate/hexane to afford **4h** as an off-white solid (0.86 g, 43%, $R_f \sim 0.4$ in

25:75 ethyl acetate/hexanes). Mp: 150–152 °C. ^{1}H NMR ($CDCl_3$): δ 8.96 (1H, s), 7.80–7.73 (3H, m), 7.53 (1H, app. t, J = 7.9 Hz), 7.45–7.41 (2H, m), 7.35 (1H, app. t, J = 7.8 Hz), 7.28 (1H, dd, J = 2.5, 8.0 Hz), 7.14 (1H, dd, J = 2.4, 8.2 Hz), 7.02 (1H, d, J = 7.5 Hz), 6.92 (1H, app. t, J = 1.9 Hz), 3.91 (3H, s), 2.32 (3H, s); MS (ES) m/z 404.2; HRMS: calcd for $C_{24}H_{18}ClNO_3 + H^+$, 404.1048; found (ESI, $[M+H]^+$), 404.1063.

6.16. 3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]-*N*-methylbenzamide (4i)

In essentially the same manner as described for **4j**, except using freshly dried methylamine hydrochloride as the amine, **4i** was obtained as a white solid (82 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 8.96 (1H, s), 7.77 (1H, dd, J = 1.3, 7.3 Hz), 7.54–7.50 (2H), 7.45–7.34 (4H), 7.22 (1H, m), 7.14 (1H, ddd, J = 1.0, 2.6, 8.3 Hz), 7.02 (1H, ddd, J = 1.0, 1.4, 7.5 Hz), 6.92 (1H, app. m), 6.06 (1H, v. br s), 3.02 (3H, d, J = 4.9 Hz), 2.32 (3H, s). MS (ES) m/z 403.2; HRMS: calcd for $C_{24}H_{19}ClN_2O_2 + H^+$, 403.1208; found (ESI, $[M+H]^+$), 403.1203.

6.17. 3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]-*N*-ethylbenzamide (4j)

To a stirred suspension of ethylamine hydrochloride (41 mg, 0.50 mmol) in toluene (2 mL) at ambient temperature under nitrogen was added 2.0 M trimethylaluminum in toluene (0.25 mL, 0.50 mmol). After 0.5 h, **4h** (101 mg, 0.25 mmol) was added and the reaction heated at 60–65 °C for 16 h. The cooled reaction was carefully treated with water (2 mL), then 2 M aqueous HCl (1 mL) 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 50:50, then 75:25 ethyl acetate/hexane as eluent. Compound **4j** was isolated as a glass (101 mg, 97%, $R_f \sim 0.3$ in 50:50 ethyl acetate/hexane). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 8.51 (1H, br t, J = 5.5 Hz), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.65–7.61 (2H), 7.58 (1H, app. t, J = 2.0 Hz), 7.48 (1H, dd, J = 7.5, 8.4 Hz), 7.41 (1H, dd, J = 1.3, 8.5 Hz), 7.27 (1H, ddd, J = 1.0, 2.6, 8.1 Hz), 7.20 (1H, ddd, J = 0.9, 2.5, 8.5 Hz), 7.13 (1H, ddd, J = 1.0, 1.4, 8.0 Hz), 7.01 (1H, dd, J = 1.6, 2.3 Hz), 3.27 (2H, m), 2.28 (3H, s), 1.11 (3H, t, J = 7.2 Hz); MS (ES) m/z 417.2; HRMS: calcd for $C_{25}H_{21}ClN_2O_2 + H^+$, 417.1364; found (ESI, $[M+H]^+$), 417.1357.

6.18. 3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]-*N*-propylbenzamide (4k)

To a stirred mixture of 1-propylamine (59 mg, 1.00 mmol) in toluene (2.0 mL) at ambient temperature under nitrogen was added 2.0 M trimethylaluminum in toluene (0.50 mL, 1.00 mmol). After 45 min, a solution of **4h** (82 mg, 0.20 mmol) in toluene (7.0 mL) was added and the reaction heated at 65 °C for 16 h. The cooled reaction was carefully treated with water (2 mL), then after 10 min with 2 M aqueous HCl (1 mL) resulting in gas evolution. The reactions were extracted with dichloromethane (5 mL, 2 mL) and the combined extracts were dried ($MgSO_4$). After concentrating in vacuo, the residues were chromatographed on silica gel using 50:50, then ethyl acetate as eluent. Compound **4k** was isolated as a white solid-foam (78 mg, 91%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 8.49 (1H, br t, J = 5.7 Hz), 7.90 (1H, dd, J = 1.3, 7.3 Hz), 7.65–7.61 (2H), 7.58 (1H, app. t, J = 1.9 Hz), 7.49 (1H, dt, J = 1.4, 8.0 Hz), 7.41 (1H, dd, J = 1.3, 8.5 Hz), 7.27 (1H, ddd, J = 1.0, 2.5, 8.1 Hz), 7.20 (1H, ddd, J = 0.9, 2.5, 8.3 Hz), 7.13 (1H, ddd, J = 1.0, 2.5, 8.1 Hz), 7.01 (1H, dd, J = 1.6, 2.2 Hz), 3.20 (2H, q, J = 6.3 Hz), 2.28 (3H, s), 1.50 (2H, m), 0.89 (3H, t, J = 7.4 Hz), MS (ESI) m/z 431; HRMS: calcd for $C_{26}H_{23}ClN_2O_2 + H^+$, 431.1521; found (ESI, $[M+H]^+$), 431.1519.

6.19. 3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]-*N*-isopropylbenzamide (4l)

Using essentially the same procedure as for **4k**, except using isopropylamine as the amine, **4l** was obtained as a white solid-foam (82 mg, 95%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 8.26 (1H, d, J = 7.8 Hz), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.66–7.63 (2H), 7.60 (1H, m), 7.49 (1H, dt, J = 2.2, 7.4 Hz), 7.41 (1H, dd, J = 1.3, 8.4 Hz), 7.26 (1H, ddd, J = 1.0, 2.6, 8.1 Hz), 7.18 (1H, ddd, J = 0.9, 2.6, 8.3 Hz), 7.12 (1H, app. dt, J = 1.2, 7.6 Hz), 7.00 (1H, dd, J = 1.7, 2.4 Hz), 4.09 (1H, m), 2.28 (3H, s), 1.15 (6H, d, J = 6.5 Hz). MS (ESI) m/z 431; HRMS: calcd for $C_{26}H_{23}ClN_2O_2 + H^+$, 431.1521; found (ESI, $[M+H]^+$), 431.1501.

6.20. 3-[3-(8-Chloro-3-methylquinolin-4-yl)phenoxy]-*N*,*N*-diethylbenzamide (4m)

Using essentially the same procedure as for **4k**, except using diethylamine as the amine, **4m** was obtained as an oil (42 mg, 47%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 7.90 (1H, dd, J = 1.2, 7.4 Hz), 7.63 (1H, app. t, J = 7.8 Hz), 7.51–7.45 (2H), 7.39 (1H, dd, J = 1.2, 8.5 Hz), 7.22 (1H, m), 7.17 (1H, m), 7.13 (1H, d, J = 7.7 Hz), 7.10 (1H, d, J = 7.5 Hz), 3.39 (2H, v. br s), 3.14 (2H, v. br s), 2.26 (3H, s), 1.11 (3H, v. br s), 0.95 (3H, v. br s); MS (ESI) m/z 445; HRMS: calcd for $C_{27}H_{25}ClN_2O_2 + H^+$, 445.1677; found (ESI, $[M+H]^+$), 445.1694.

6.21. 8-Chloro-3-methyl-4-{3-[3-(pyrrolidin-1-ylcarbonyl) phenoxy]phenyl}quinoline (4n)

Using essentially the same procedure as for **4k**, except using pyrrolidine as the amine and using ethyl acetate as the eluent, **4n** was obtained as a white solid-foam (79 mg, 89%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.63 (1H, app. t, J = 7.9 Hz), 7.51–7.44 (2H), 7.40 (1H, dd, J = 1.3, 8.4 Hz), 7.26 (1H, dt, J = 1.1, 7.7 Hz), 7.22–7.18 (2H), 7.13 (1H, app. dt, J = 1.2, 7.5 Hz), 7.02 (1H, m), 3.43 (2H, t, J = 6.9 Hz), 3.30 (2H, app. t, J = 6.5 Hz), 2.27 (3H, s), 1.83 (2H, m), 1.73 (2H, m); MS (ESI) m/z 443; HRMS: calcd for $C_{27}H_{23}ClN_2O_2 + H^+$, 443.1521; found (ESI, $[M+H]^+$), 443.1523.

6.22. 8-Chloro-3-methyl-4-{3-[3-(piperidin-1-ylcarbonyl) phenoxy]phenyl}quinoline (4o)

Using essentially the same procedure as for **4k**, except using piperidine as the amine and using ethyl acetate as the eluent, **4o** was obtained as a white solid-foam (87 mg, 91%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 7.90 (1H, dd, J = 1.3, 7.5 Hz), 7.65 (1H, app. t, J = 7.9 Hz), 7.51–7.45 (2H), 7.40 (1H, dd, J = 1.3, 8.6 Hz), 7.22 (1H, ddd, J = 0.9, 2.6, 8.3 Hz), 7.17 (1H, ddd, J = 1.9, 2.5, 7.8 Hz), 7.12 (1H, app. t, J = 8.4 Hz), 7.03 (1H, m), 3.54 (2H, v. br s), 3.21 (2H, v. br s), 1.60–1.45 (2H, v. br), 1.32 (2H, v. br s); MS (ESI) m/z 457; HRMS: calcd for $C_{28}H_{25}ClN_2O_2 + H^+$, 457.1677; found (ESI, $[M+H]^+$), 457.1673.

6.23. 8-Chloro-3-methyl-4-{3-[3-(morpholin-4-ylcarbonyl) phenoxy]phenyl}quinoline (4p)

Using essentially the same procedure as for **4k**, except using morpholine as the amine and using ethyl acetate as the eluent, **4p** was obtained as a white solid-foam (87 mg, 95%). ^{1}H NMR (DMSO-d_6): δ 8.99 (1H, s), 7.90 (1H, dd, J = 1.3, 7.4 Hz), 7.63 (1H, app. t, J = 7.9 Hz), 7.52–7.46 (2H), 7.40 (1H, dd, J = 1.3, 8.4 Hz), 7.24–7.10 (5H), 7.04 (1H, m), 3.70–3.40 (8H, v. br peaks), 2.27 (3H, s); MS (ESI) m/z 459; HRMS: calcd for $C_{27}H_{23}ClN_2O_3 + H^+$, 459.1470; found (ESI, $[M+H]^+$), 459.1472.

Acknowledgments

We thank Anita Halpern, Dawn Savio, Ronald Magolda, and Magid Abou-Gharbia for project support.

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