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Further modification on phenyl acetic acid based quinolines as liver X receptor modulators

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Abstract—A series of phenyl acetic acid based quinolines was prepared as LXR modulators. An SAR study in which the C-3 and C-8 positions of the quinoline core were varied led to the identification of two potent LXR agonists **23** and **27**. Both compounds displayed good binding affinity for LXRβ and LXRα, and increased expression of ABCA1 in THP-1 cells. These two compounds also had desirable pharmacokinetic profiles in mice and displayed in vivo efficacy in a 12-week Apo E knockout mouse lesion model.

1. Introduction

Coronary heart disease (CHD) is the leading cause of mortality in the western world, and accounting for nearly 50% of all deaths.[1] Major risk factors for the development of CHD are hypercholesterolemia and dyslipoproteinemia. Numerous studies have identified decreased high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL) cholesterol as major contributors to CHD. As a result, many current therapies for the treatment of CHD, including the statins, are aimed at lowering LDL or increasing HDL. Liver X receptors (LXRα and LXRβ) are members of the nuclear hormone receptor super-family and are involved in the regulation of cholesterol and lipid metabolism.[2,3] The α-subtype is expressed primarily in liver, while the β-subtype is ubiquitously expressed. They are ligand-activated transcription factors and bind to DNA as obligate heterodimers with retinoid X receptors (RXRs). Several LXR agonists (Fig. 1), such as a natural ligand 24(*S*), 25-epoxycholesterol (**1**, EPC)[4] as well as two structurally distinct synthetic non-steroidal ligands **2** (GW3965)[5] and **3** (TO901317),[6] have been shown to increase expression of several genes involved in lipid metabolism and reverse cholesterol transport including ABCA1, ABCG1, and ApoE. These compounds reduced or even reversed atherosclerotic processes in

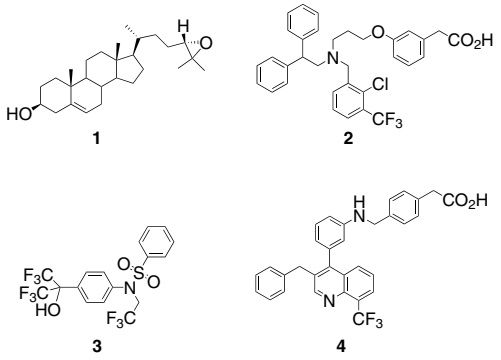

Figure 1. LXR agonists.

Keywords: Liver X receptor (LXR); LXR agonists; Quinoline; Phenyl acetic acid.
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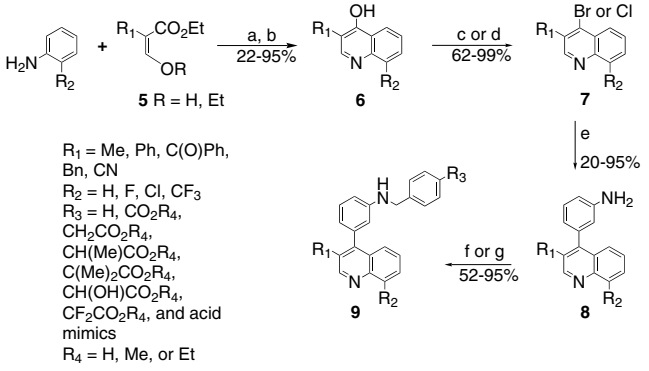
mouse models of atherosclerosis. Currently available synthetic LXR agonists, however, also activated triglyceride (TG) synthesis in the liver by the upregulation of SREBP-1c and FAS which limits the utility of these LXR synthetic agonists. Thus, there is a clear need for new LXR modulators which retain the antiatherosclerotic activity while avoiding the undesired lipogenic activity.

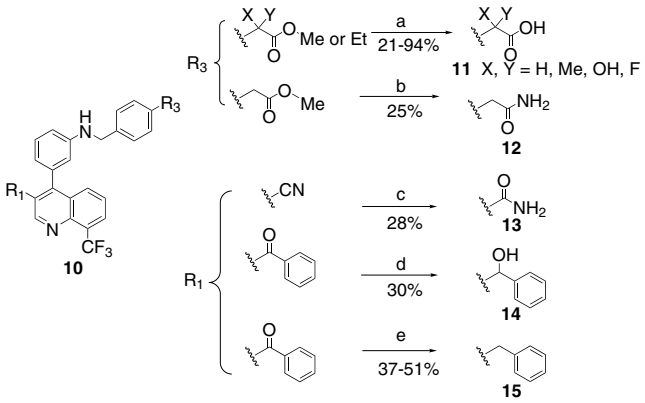
Recently, we reported the identification and optimization of phenyl acetic acid substituted quinolines as potent LXR agonists.[7] These quinolines displayed good binding affinity for LXRβ and LXRα, and were potent agonists in Gal4 transactivation assays. We also reported in vivo efficacy (inhibition of lesion progression) of quinoline **4** in LDLr knockout mouse. We present here additional phenyl acetic acid substituted quinoline analogs, varying the substituents on the quinoline core at the C-3 and C-8 positions. Some carboxylic acid replacements were also evaluated.

2. Synthetic chemistry

Our initial research efforts focused on variations of substituents at position 3 and 8 of the quinoline nucleus. The general approach for the syntheses of these kinds of molecules is depicted in Scheme 1. Condensation of acrylates **5** with various anilines followed by thermal cyclization provided 4-hydroxyquinoline **6**. Conversion of **6** to bromide or chloride **7** was accomplished readily with phosphorus oxybromide or phosphorus oxychloride, respectively. Reaction of **7** with 3-aminophenylboronic acid under Suzuki conditions provided **8**. Alkylation with benzyl bromides or reductive amination with benzaldehydes gave key intermediate **9**. Further functional transformations were carried out as illustrated in Scheme 2. Carboxylic acids **11** were obtained by hydrolysis of the corresponding esters. Conversion of the esters into amides **12** was easily achieved with ammonium hydroxide in methanol. A base catalyzed conversion of nitrile by hydrogen peroxide afforded amide **13**. Reduction of the quinoline C-3 carbonyl with sodium borohydride gave the corresponding alcohol **14**.



Scheme 1. Reagents: (a) Toluene; (b) Dowtherm; (c) $POBr_3$, DMF; (d) $POCl_3$, DMF; (e) 3-aminophenylboronic acid, K_3PO_4, $Pd(PPh_3)_4$, dioxane; (f) benzyl bromides, K_2CO_3; (g) benzaldehydes, $NaBH(OAc)_3$, DMF.



Scheme 2. Reagents: (a) LiOH, THF/MeOH/water; (b) NH_4OH, MeOH; (c) H_2O_2, NaOH, EtOH; (d) $NaBH_4$, MeOH; (e) N_2H_4, KOH, ethane-1,2-diol.

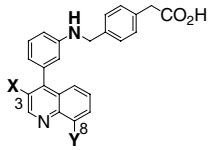
The C-3 benzyl analog **15** was obtained by hydrazine reduction of **10**.

3. Results and discussion

The LXR binding activity of the newly synthesized compounds was evaluated (Table 1) in binding assays using recombinant human LXRα or LXRβ ligand binding domains (LBD) with [^{3}H]T0901317 as a tracer. A CHO-cell based reporter assay employing a stably transfected hLXRβ reporter cell line (LAFβ) was next used to determine agonist potency and efficacy.[7] As seen earlier,[7] the removal of the C-3 carbonyl (**16** vs **4**) did not have a large effect on the binding affinity or on the agonist activity in the LAFβ assay (Table 1). Compared to **16**, similar binding affinities were observed for C-3 methyl analog **17** and C-3 phenyl analog **18**, which had binding hLXRβ IC_{50} values of 4.3 nM and 3.7 nM, respectively. Both compounds also showed good potency ($EC_{50} \leqslant 100$ nM) in the LAFβ assay. However, replacement of the C-3 carbonyl group with the more polar hydroxyl methyl group caused a 24-fold reduction in hLXRβ binding affinity (**19** vs **16**). Likewise, replacement of the C-3 carbonyl with the more polar nitrile group resulted in a 14-fold loss of hLXRβ binding affinity (**20** vs **16**). C-3 amide analog **21** was essentially inactive with an hLXRβ IC_{50} value of >10 μM. These results suggested that lipophilic groups are preferred for the C-3 substituents.

Several sterically small replacements for the C-8 trifluoromethyl substituent were also evaluated (Table 1). Compared to C-8 trifluoromethyl analog **16**, a small loss of binding activity was seen in the C-8 methyl analog **22**. Replacing the trifluoromethyl with a fluorine (**24**) resulted in reduced affinity in the binding assays (hLXRβ IC_{50} = 17 nM) and reduced potency in the LAFβ assay (EC_{50} = 700 nM). C-8 hydrogen analog **25** lost substantial potency but maintained its full agonist efficacy (110%) in LAFβ. Chlorine proved to be a good replacement for trifluoromethyl since the 8-chloro quinoline **26** had essentially the same binding affinity and LAFβ activity as the trifluoromethyl substituted quinoline **16**. Removal of the C-3 carbonyl had minimal effect on the agonist activity (**22** vs **23,** and **26** vs **27**).

Table 1. Modification at the C-3 and C-8 positions[a,b]



Compound	X	Y	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	LAFβ EC_{50} (nM) (% ag)
4[7]	Ph–CH_2–	CF_3	1.9	7.6	33 (85%)
16	Ph–CO–	CF_3	2.4	7.0	29 (100%)
17	Me	CF_3	4.3	16	100 (89%)
18	Ph	CF_3	3.7	8.0	44 (101%)
19	Ph–CH(OH)–	CF_3	56.4	384	812 (68%)
20	–CN	CF_3	33.8	150	450 (89%)
21	–$CONH_2$	CF_3	>10,000	>10,000	
22	Ph–CO–	CH_3	5.5	18	61 (75%)
23	Ph–CH_2–	CH_3	5.0	21.0	90 (97%)
24	Ph–CO–	F	17.0	104	700 (142%)
25	Ph–CO–	H	154	650	1650 (110%)
26	Ph–CO–	Cl	2.7	9.0	39 (101%)
27	Ph–CH_2–	Cl	1.4	5.0	23 (107%)

[a] Results are given as means of two independent experiments. The standard deviations for these assays were typically ±30% of mean or less.
[b] % of efficacy is relative to **3**.

Compounds **23** and **27** were also tested in Gal4 functional transactivation assays (Table 2, for assay condition, see reference [7]). Both compounds showed greater potency in LXRβ vs hLXRα, however they were slightly more efficacious against LXRα. In addition, **23** and **27** up-regulated ABCA1 in THP-1 cells with an EC_{50} of 438 nM and 81 nM, respectively, and an efficacy of 139% and 162% relative to **3**, respectively.[8] On the other hand, in a liver cell line (Huh-7) **23** and **27** also increased expression of SREBP-1c with an EC_{50} value of 51 nM and 75 nM, and an efficacy of 114% and 137% relative to **3**, respectively, showing that these two compounds did not have the desired gene selectivity. Quinoline **23** and **27** had >140-fold receptor binding selectivity against a few closely related nuclear receptors (such as PXR and RXR, data not shown) but were shown to be PPAR agonists (particularly against PPARγ and PPARδ) in human Gal4-PPAR transactivation assays (Table 2). The PPAR activity for these two compounds may complicate the significance of the LXR agonist effect in vivo.

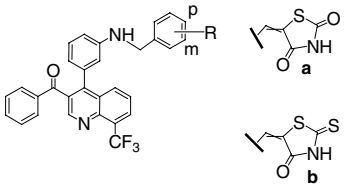
The contribution of the acetic acid to the LXR agonist activity was then investigated (Table 3). In general a greater variation in activity upon replacing the acetic acid group was observed in the LAFβ assay than in the binding assays. The *meta*-acetic acid isomer **28** and oxyacetic acid **29** had reduced activity in hLXRβ binding assay, while the acrylic acid analog **30** had very poor activity (hLXRβ binding IC_{50} >10 μM). We had earlier reported that truncation of the acetic acid to the benzoic acid reduced both binding affinity and functional potency.[7] This same effect was also seen in the benzylamine linker based quinoline series (**16** vs **31**). A few α-substituted acetic acid analog, with a mono-methyl (**32**), di-methyl (**33**), mono-hydroxy (**34**), and di-fluoro (**35**) group in the α-position, were synthesized and all showed potent affinity (binding IC_{50} <10 nM) in the hLXRβ binding assay. Although small alkyl groups at the α-position were tolerated in the LAFβ assay, introduction of a hydroxyl or di-fluoro group resulted in a dramatic reduction of LAFβ potency with EC_{50} of 4 μM for **34** and 2.4 μM for **35**, possibly due to decreased permeability resulting from decreased pKa relative to **16**. Likewise, the primary amide **36** and the ethanol analog **37** had potent hLXRβ binding affinity (hLXRβ IC_{50} = 1.4 nM for **36** and 5.4 nM for **37**), but compared to **16** both of them showed more than 10-fold reduction of LAFβ potency. Replacing the acid

Table 2. Gene expression activity and selectivity in Gal4 human transactivation assays (EC_{50} nM, % eff.)[9–11]

Compound	ABCA1[a]	SREBP1c[b]	Gal4 hLXRβ[c]	Gal4 hLXRα[c]	Gal4 PPARα[d]	Gal4 PPARγ[d]	Gal4 PPARδ[d]
23	438 (139%)	51.4 (114%)	267 (75%)	467 (101%)	1772 (7.5%)	1030 (46.6%)	1975 (46.7%)
27	81 (162%)	75 (137%)	54 (67%)	121 (89%)	2053 (12%)	506 (50.6%)	631 (40.8%)

[a] THP cell line. Results are given as means of two independent experiments. The standard deviations for these assays were typically ±50% of mean or less. % of efficacy is relative to **3**.
[b] Huh-7 cell line. Results are given as means of two independent experiments. The standard deviations for these assays were typically ±50% of mean or less. % of efficacy is relative to **3**.
[c] Transient transfection assays in Huh-7 cell line. Human LXR LBDs were fused to GAL4 DBD. The standard deviations for these assays were typically ±50% of mean or less. % efficacy is relative to **3**.
[d] Results are given as means of two independent experiments. % of efficacy is relative to references: PPARα: [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (WY-14643); PPARγ: 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl]methyl]-2,4-thiazolidinedione (Rosiglitazone); PPARδ: 3-chloro-4-[[3-[(3-phenyl-7-propyl-6-benzofuranyl)oxy]propyl]thio]-phenylacetic acid (L-796449).

Table 3. Acetic acid modifications[a,b]



Compound	R	LXRβ IC_{50} (nM)	LXRα IC_{50} (nM)	LAFβ EC_{50} (nM) (% ag)
16	*p*-CH_2CO_2H	2.4	7.0	29 (100%)
28	*m*-CH_2CO_2H	6.0	33.6	141 (88%)
29	*p*-OCH_2CO_2H	12.0	63.9	1271 (70%)
30	*p*-CH=$CHCO_2H$	>10,000	>10,000	
31	*p*-CO_2H	138	420	365 (34%)
32	*p*-$CH(Me)CO_2H$	2.6	15.2	58 (97%)
33	*p*-$C(Me)_2CO_2H$	3.8	17.2	78 (86%)
34	*p*-$CH(OH)CO_2H$	8.5	33.6	4003 (91%)
35	*p*-CF_2CO_2H	7.8	30.2	2395 (124%)
36	*p*-CH_2CONH_2	1.4	11.0	316 (85%)
37	*p*-CH_2CH_2OH	5.4	34	795 (102%)
38	H	45	241	770 (26%)
39	*p*-CH_2OH	12.8	90.5	2304 (105%)
40	*para*-**a**	276	456	369 (16%)
41	*para*-**b**	310	479	286 (12%)

[a] Results are given as the mean of two independent experiments. The standard deviations for these assays were typically ±30% of mean or less.
[b] % of efficacy is relative to **3**.

Table 4. C57 mouse pharmacokinetic parameters for **23** and **27**[a]

Compound	IV $t_{1/2}$ (h)	Cl (mL/min/kg)	V_{ss} (L/kg)	PO $t_{1/2}$ (h)	C_{max} (ng mL)	T_{max} (h)	AUC inf (h ng/mL)	%F
23	1.6	25	1.2	1.2	4191	0.25	3576	53
27	1.8	37	1.8	1.2	2505	0.25	2581	57

[a] 1 mg/kg IV, 10 mg/kg PO.

Table 5. In vivo activity dosed at 10 mg/kg/day for 12 weeks

Compound	Number of ApoE knockout mice	% of aortic arch lesion area	% of aortic arch lesion reduction	Difference of plasma triglyceride levels (mg/dL)[a]
Control	10	9.55 ± 0.45		
2	8	1.99 ± 0.54	79 ± 6	2.95
23	8	4.09 ± 1.25	57 ± 13	15.20
27	8	4.47 ± 0.53	53 ± 11	64.56

[a] Difference = mean of control-mean of sample.

functionality with hydrogen (**38**), methyl alcohol (**39**), and an acid mimic such as thiazolidine-2,4-dione (**40**) or rhodanine (**41**) all resulted in reduced agonist potency. The loss of agonist potency upon deletion of the acetic acid suggested that the acetic acid is necessary for LXR agonist activity.

To select compounds for in vivo efficacy studies, the pharmacokinetic (PK) profiles of **23** and **27** were evaluated in mice (Table 4). These two compounds were chosen because they were among the most potent in the in vitro assays and also they were stable against mouse and human liver microsomes. Following a single dose of 1 mg/kg iv and 10 mg/kg oral in mouse both compounds displayed moderate volume of distribution, moderate clearance, and good bioavailability (%F >50%). An atherosclerotic lesion study was conducted in a western diet (0.21% cholesterol)-fed ApoE knockout mouse model. Administration of quinoline **23** and **27** for 12 weeks at 10 mg/kg/day orally resulted in a significant reduction in lesion burden by 57% and 53%, respectively, compared to the control group (Table 5). In the same experiment, the literature standard **2** also significantly reduced the lesion burden by 79%. However, these two agonists (**23** and **27**) also caused a mean increase of plasma triglyceride levels.

4. Conclusion

In summary, modifications on previously reported compound **4** via SAR study produced two additional quinoline leads **23** and **27** with good potency and efficacy in vitro. The compounds also had good oral bioavail-

ability in mice and displayed *in vivo* efficacy in a 12-week Apo E knockout mouse lesion model. However, both compounds increased plasma triglyceride levels. The identification of novel LXR agonists without increasing the triglycerides is a great challenge in the pursuit of LXR modulators. It might be possible to develop LXR modulators free of TG liabilities through the development of LXRβ isoform selective agonist or tissue/gene selective agonist. To achieve this goal, we are continuing to investigate the SAR and biological properties of this new series of LXR agonists.

5. Experimental

General Solvents and chemicals were purchased from VWR and Aldrich Chemical Co. and were used without further purification. Anhydrous and deuterated solvents as well as fine chemicals were purchased from Aldrich Chemical Co. and used without further treatment. CHN analysis was performed by Robertson Microlit Labs (Madison, NJ). High-resolution mass spectra were recorded on a Waters LC-TOFMS instrument and were measured to within 5 ppm of the calculated values. ^{1}H NMR spectra were recorded on a Bruker DPX300 (300 MHz) instrument and delta values (δ) were measured in ppm using tetramethylsilane as an internal standard ($\delta = 0$ ppm). High-performance liquid chromatography (HPLC) was performed with an Agilent 1100F series instrument with auto sampler and a diode array detector (Xterra RP18, 3.5u, 150 × 4.6 mm column, 1.2 mL/min, 85/15-5/95 solvent A-solvent B for 10 min, hold 4 min, solvent A: ammonium formate buffer (pH 3.5), solvent B: ACN/MeOH 1:1). Appropriate safety practices were observed during all laboratory functions.

5.1. 3-Methyl-8-(trifluoromethyl)quinolin-4-ol (6a)

To ethyl propionate (65.0 mL, 566 mmol) in ethyl formate (150 ml) at 0 °C, under nitrogen atmosphere, was added sodium hydride (27.2 g, 680 mmol) in equal portions over 1.5 h. The resulting gray mixture was stirred at room temperature overnight, then quenched with 2 N aqueous HCl (dropwise at first, 600 mL total), and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was used without further purification.

2-(Trifluoromethyl)aniline (26.8 mL, 216 mmol) was added to a mixture of the crude material (60.96 g) in dichloromethane (250 mL) at room temperature. The mixture was stirred at room temperature overnight and concentrated in vacuo to yield a yellow oil. This oil was purified by silica gel chromatography (5:95 ethyl acetate–hexane) to afford ethyl 2-methyl-3-{[2-(trifluoromethyl)phenyl]amino}acrylate as a 3:1 *E*/*Z* mixture (33.76 g, 22% yield); MS (ESI) *m*/*z* 274.

The *E*/*Z* mixture of ethyl 2-methyl-3-{[2-(trifluoromethyl)phenyl]amino}acrylate (33.76 g, 123.6 mmol) and Dowtherm-A (200 ml) under a nitrogen atmosphere was heated at reflux for 1 h. The reaction vessel was equipped with a Dean-Stark adapter to remove the ethyl alcohol produced during the reaction. After cooling to ~100 °C, the reaction mixture was poured into hexane (600 mL) and allowed to stand overnight. A solid precipitated which was filtered off and dried to yield **6a** as an off-white solid (18.13 g, 65%); ^{1}H NMR (DMSO-d_6): δ 11.08 (s, 1H), 8.45 (d, $J = 8.0$ Hz, 1H), 8.04 (d, $J = 7.5$ Hz, 1H), 7.82 (s, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 2.01 (s, 3H); MS (ESI) *m*/*z* 228.

The following compounds (**6b–6e**) were prepared following essentially the same procedure as used for compound **6a**.

5.2. 4-Hydroxy-8-(trifluoromethyl)quinoline-3-carbonitrile (6b)

The title compound was prepared from 2-(trifluoromethyl)aniline and 2-cyano-3-ethoxy-acrylic acid ethyl ester as a white solid (11.0 g, 46%); ^{1}H NMR (DMSO-d_6): δ 12.10 (s, 1H), 9.37 (s, 1H), 8.64 (d, $J = 8.6$ Hz, 1H), 8.50 (d, $J = 9.5$ Hz, 1H), 8.04 (t, $J = 7.8$ Hz, 1H); MS (ESI) *m*/*z* 239; HRMS calcd for $C_{11}H_6F_3N_2O$[M+H]: 239.0427; found (ESI, $[M+H]^+$): 239.0424.

5.3. (4-Hydroxy-8-methylquinolin-3-yl)(phenyl)methanone (6c)

The title compound was prepared from 2-methylaniline and 2-benzoyl-3-ethoxy-acrylic acid ethyl ester as a white solid (1.88 g, 74%); ^{1}H NMR (DMSO-d_6): δ 11.60 (s, 1H), 8.20 (s, 1H), 8.12 (d, $J = 10.7$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.28 (t, $J = 7.8$ Hz, 1H), 2.58 (s, 3H); MS (ESI) *m*/*z* 264; HPLC purity = 98.3% at 7.2 min; HRMS calcd for $C_{18}H_{13}NO_2$ [M+H]: 264.1019; found (ESI, $[M+H]^+$): 264.1017; Anal. Calcd for $C_{17}H_{13}NO_2 \cdot H_2O$: C, 76.50; H, 5.06; N, 5.25. Found: C, 76.67; H, 4.77; N, 5.14.

5.4. (8-Fluoro-4-hydroxyquinolin-3-yl)(phenyl)methanone (6d)

The title compound was prepared from 2-fluoroaniline and 2-benzoyl-3-ethoxy-acrylic acid ethyl ester as a white solid (2.08 g, 98%); ^{1}H NMR (DMSO-d_6): δ 12.15 (s, 1H), 8.20 (d, $J = 6.3$ Hz, 1H), 8.07 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.60–7.25 (m, 4H), 6.98 (d, $J = 7.7$ Hz, 1H); MS (ES) *m*/*z* 266.1; HPLC purity 93.7%; HRMS calcd for $C_{16}H_9FNO_2$ [M−H]: 266.0623; found (ESI, $[M-H]^-$): 266.0626.

5.5. (4-Hydroxyquinolin-3-yl)(phenyl)methanone (6e)

The title compound was prepared from aniline and 2-benzoyl-3-ethoxy-acrylic acid ethyl ester as a white solid (0.93 g, 83%); ^{1}H NMR (DMSO-d_6): δ 12.12 (s, 1H), 8.28 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.6$ Hz, 2H), 7.60–7.30 (m, 6H), 6.98 (d, $J = 9.0$ Hz, 1H); MS (ES) *m*/*z* 248.1; HRMS calcd for $C_{16}H_{10}NO_2$ [M−H]: 248.0717; found (ESI, $[M-H]^-$): 248.0702.

5.6. 3-Phenyl-8-(trifluoromethyl)quinolin-4-ol (6f)

Step 1: 8-Trifluoromethyl-quinolin-4-ol (9.12 g, 42.8 mmol) was dissolved in acetic acid (300 mL). Bromine (2.20 mL

42.8 mmol) was dissolved in acetic acid (30 mL) and then added dropwise to the reaction mixture over 20 min. After 0.5 h, the solution was poured into 500 mL of 2 N aqueous NaOH and stirred. The resulting white precipitate was filtered off and dried in vacuo yielding 3-bromo-8-(trifluoromethyl)quinolin-4-ol as a white solid (10.3 g, 83%); mp 297–299 °C; ^{1}H NMR (DMSO-d_6): δ 11.67 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.26 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H); MS (ESI) m/z 292; MS (ESI) m/z 290; HRMS calcd for $C_{10}H_6BrNF_3O$ [M+H] 291.9585; found (ESI, $[M+H]^+$): 291.9585.

Step 2: A solution of 3-bromo-8-(trifluoromethyl)quinolin-4-ol (3.20 g, 10.95 mmol) and phenyl boronic acid (2.67 g, 21.9 mmol) in 2:1 toluene–methanol (120 mL) and saturated aqueous $NaHCO_3$ (40 mL) was treated with $Pd(PPh_3)_4$ (760 mg) and heated at reflux overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed sequentially with 2 N aqueous NaOH, water, and brine, then dried with magnesium sulfate. The extracts were concentrated and the residue was chromatographed with 1:4 ethyl acetate–hexanes to afford **6f** as a yellow solid (6.40 g, 59%); mp 272–275 °C; ^{1}H NMR (DMSO-d_6): δ 11.47 (s, 1H), 8.55 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 7.4 Hz, 1H), 7.98 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 7.4 Hz, 1H); MS (ESI) m/z 290; HRMS calcd for $C_{16}H_{11}NF_3O$ [M+H]: 290.0793; found (ESI, $[M+H]^+$), 290.0782.

5.7. 4-Bromo-3-methyl-8-(trifluoromethyl)quinoline (7a)

Phosphorus oxybromide (12.4 g, 43.3 mmol) was added to a mixture of **6a** (7.02 g, 30.9 mmol) in DMF (160 ml) at room temperature. The mixture was heated at 80 °C for 1 h and then allowed to cool to room temperature. The reaction mixture was poured into aqueous ethyl acetate and solid Na_2CO_3 was added until pH >8. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine and dried over $MgSO_4$. After concentrating in vacuo, the resulting material was purified by silica gel chromatography (5:95 ethyl acetate–hexanes) to afford **7a** as a white solid (7.89 g, 88%); ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 7.3 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 2.04 (s, 3H); MS (ESI) m/z 290.

The following compounds (**7b**–**7g**) were prepared following the procedure of compound **7a**.

5.8. 4-Bromo-3-phenyl-8-(trifluoromethyl)quinoline (7b)

The title compound was prepared from **6f** and $POBr_3$ (0.17 g, 86%); mp 75–77 °C; ^{1}H NMR (DMSO-d_6): δ 9.19 (s, 1H), 8.63(d, J = 8.4 Hz, 1H), 8.34 (d, J = 6.9 Hz, 1H), 7.96 (t, J = 8.1 Hz, 1H), 7.60–7.50 (m, 5H); HRMS calcd for $C_{16}H_{10}BrF_3N$ [M+H]: 351.9943; found (ESI, $[M+H]^+$): 351.9948; Anal. Calcd for $C_{16}H_9BrF_3N{\cdot}0.3H_2O$: C, 53.75; H, 2.71; N, 3.92. Found: C, 53.60; H, 2.64; N, 3.82.

5.9. 4-Chloro-8-(trifluoromethyl)quinoline-3-carbonitrile (7c)

The title compound was prepared from **6b** and $POCl_3$ as an off-white solid (6.70 g, 62%); ^{1}H NMR (DMSO-d_6): δ 9.19 (s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 7.1 Hz, 1H), 7.97 (t, J = 8.1 Hz, 1H); MS (ES) m/z 256.9; HRMS calcd for $C_{11}H_5ClF_3N_2$ [M+H]: 257.0088; found (ESI, $[M+H]^+$): 257.0095.

5.10. (4-Chloro-8-methylquinolin-3-yl)(phenyl)methanone (7d)

The title compound was prepared from **6c** and $POCl_3$ as an off-white solid (1.68 g, 99%); ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.0 Hz, 2H), 7.72 (d, J = 7.0 Hz, 1H), 7.70–7.60 (m, 2H), 7.50 (t, J = 7.8 Hz, 2H); MS (ESI) m/z 282; HPLC purity 97.6% at 10.8 min; Anal. Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.38; H, 3.93; N, 4.86.1

5.11. (4-Chloro-8-fluoroquinolin-3-yl)(phenyl)methanone (7e)

The title compound was prepared from **6d** and $POCl_3$ as an off-white solid (1.98 g, 92%); ^{1}H NMR ($CDCl_3$): δ 8.88 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.75–7.48 (m, 5H); MS (ESI) m/z 286; HPLC purity 97.1% at 9.7 min; HRMS calcd for $C_{16}H_{10}ClFNO$ [M+H]: 286.0429; found (ESI, $[M+H]^+$): 286.0421.

5.12. (4-Chloroquinolin-3-yl)(phenyl)methanone (7f)

The title compound was prepared from **6e** and $POCl_3$ as an off-white solid (2.18 g, 97%); ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.95–7.85 (m, 2H), 7.80–7.70 (m, 1H), 7.70–7.60 (m, 1H), 7.55–7.45 (m, 2H), 7.40–7.30 (m, 1H); HPLC purity 91.2% at 9.8 min; HRMS calcd for $C_{16}H_{10}ClNO$ [M+H]: 268.0524; found (ESI, $[M+H]^+$): 268.0518.

5.13. (4,8-Dichloroquinolin-3-yl)(phenyl)methanone (7g)

The title compound was prepared from 2-chloroaniline and 2-benzoyl-3-ethoxy-acrylic acid ethyl ester according to the procedure of **6a** followed by the procedure of **7a** with $POCl_3$ (0.97 g, 72%); ^{1}H NMR ($CDCl_3$): δ 8.95 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 9.6 Hz, 2H), 7.70–7.65 (m, 2H), 7.55–7.45 (m, 2H); MS (ESI) m/z 302; HRMS calcd for $C_{16}H_{10}Cl_2NO$ [M+H]: 302.0134; found (ESI, $[M+H]^+$): 302.0125.

5.14. {3-[3-Methyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amine (8a)

Compound **7a** (5.00 g, 17.2 mmol) was taken into toluene–ethanol–water (300 mL:75 mL:130 mL). Then 3-aminophenylboronic acid (5.34 g, 34.5 mmol) was added followed by Na_2CO_3 (5.48 g, 51.7 mmol) and $Pd(PPh_3)_4$ (1.99 g, 1.72 mmol). The reaction mixture was heated at 90 °C overnight. The solvent was removed

and the resulting material was purified via silica gel chromatography eluting with 20:80 ethyl acetate–hexane to afford 4.8 g (92%) of **8a** as a tan solid; ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.81 (dd, J = 8.2, 1.5 Hz, 1H), 6.61 (d, J = 7.4 Hz, 1H), 6.54 (br s, 1H), 3.80 (br s, 2H), 2.31(s, 3H); HPLC purity 99.4% at 9.6 min; HRMS calcd for $C_{17}H_{14}F_3N_2$ [M+H]: 303.1104; found (ESI, $[M+H]^+$): 303.1117.

The following compounds (**8b**, **8c**, **8e**–**8h**) were prepared following the procedure of compound **8a**.

5.15. {3-[3-Phenyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}-amine (8b)

The title compound was prepared from **7b** and 3-aminophenylboronic acid as a white solid (0.171 g, 69%); mp 163–165 °C; ^{1}H NMR (DMSO-d_6): δ 9.07 (s, 1H), 8.21 (d, J = 7.1 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.40–7.25 (m, 5H), 7.05 (t, J = 7.7 Hz, 1H), 6.60–6.55 (m, 1H), 6.45–6.40 (m, 1H), 6.37 (d, J = 8.3 Hz, 1H), 5.17 (s, 2H); MS (ES) m/z 365.1; HRMS calcd for $C_{22}H_{16}N_2F_3$ [M+H]: 365.1266; found (ESI, $[M+H]^+$): 365.1276.

5.16. 4-(3-Aminophenyl)-8-(trifluoromethyl)quinoline-3-carbonitrile (8c)

The title compound was prepared from **7c** and 3-aminophenylboronic acid as a white solid (0.35 g, 22%); ^{1}H NMR (DMSO-d_6): δ 9.37 (s, 1H), 8.40 (d, J = 6.9 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 6.84–6.80 (m, 1H), 6.69–6.65 (m, 1H), 6.64 (d, J = 7.4 Hz, 1H), 5.47 (s, 2H); MS (ES) m/z 314.0; HPLC purity 100% at 9.3 min; HRMS calcd for $C_{17}H_{11}F_3N_3$ [M+H]: 314.0900; found (ESI, $[M+H]^+$): 314.0905.

5.17. 4-(3-Aminophenyl)-8-(trifluoromethyl)quinoline-3-carboxamide (8d)

A mixture of **8c** (0.50 g, 1.6 mmol), NaOH (0.50 g, 12.5 mmol), and 30% aqueous H_2O_2 (5.0 mL) in ethanol (15 mL) was heated to 40 °C for 3 h. The reaction mixture was poured into water and the pH was adjusted to ~6 using dilute aqueous HCl. The aqueous solution was extracted with ethyl acetate and the residue from concentration was purified by reverse phase semi-preparative HPLC to afford **8d** as a white solid (0.15 g, 28%); ^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1H), 8.23 (d, J = 6.9 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.64 (br s, 1H), 7.56 (br s, 1H), 7.16 (t, J = 7.7 Hz, 1H), 6.70–6.68 (m, 1H), 6.56–6.53 (m, 1H), 6.51 (d, J = 7.6 Hz, 1H), 5.29 (s, 2H); MS (ESI) m/z 332; HPLC purity 100% at 7.3 min; HRMS calcd for $C_{17}H_{13}F_3N_3O$ [M+H]: 332.1005; found (ESI, $[M+H]^+$): 332.0994.

5.18. [4-(3-Aminophenyl)-8-methylquinolin-3-yl](phenyl) methanone (8e)

The title compound was prepared from **7d** and 3-aminophenyl-boronic acid as a white solid (1.12 g, 58%); ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.68–7.60 (m, 3H), 7.50–7.40 (m, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.03 (t, J = 8.7 Hz, 1H), 6.62 (d, J = 6.3 Hz, 1 H), 6.54–6.56 (m, 2H), 3.65 (br s, 2H), 2.90 (s, 3H); MS (ESI) m/z 339; HPLC purity 99.5% at 9.7 min; HRMS calcd for $C_{23}H_{19}N_2O$ [M+H]: 339.1492; found (ESI, $[M+H]^+$): 339.1487; Anal. Calcd for $C_{23}H_{18}N_2O{\cdot}H_2O$: C, 79.52; H, 5.51; N, 8.06. Found: C, 79.54; H, 5.46; N, 7.66.

5.19. [4-(3-Aminophenyl)-8-fluoroquinolin-3-yl](phenyl)-methanone (8f)

The title compound was prepared from **7e** and 3-aminophenylboronic acid as a white solid (0.71 g, 59%); ^{1}H NMR ($CDCl_3$): δ 9.02 (s, 1H), 7.70–7.60 (m, 3H), 7.55–7.45 (m, 3H), 7.33 (t, J = 8.2 Hz, 2H), 7.06 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 6.59–6.57 (m, 2H), 3.70 (br s, 2H); HPLC purity 100% at 8.9 min; HRMS calcd for $C_{22}H_{16}FN_2O$ [M+H]: 343.12412; found (ESI, $[M+H]^+$): 343.1241.

5.20. [4-(3-Aminophenyl)quinolin-3-yl](phenyl)methanone (8g)

The title compound was prepared from **7f** and 3-aminophenylboronic acid as a white solid (0.49 g, 70%); ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.80 (t, J = 8.5 Hz, 1H), 7.75–7.25 (m, 6H), 7.04 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.60–6.55 (m, 2H), 3.70 (br s, 2H); HPLC purity 100% at 6.3 min.

5.21. [4-(3-Aminophenyl)-8-chloroquinolin-3-yl](phenyl) methanone (8h)

The title compound was prepared from **7g** and 3-aminophenylboronic acid as a white solid (0.93 g, 83%); ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.52–7.45(m, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.05 (t, J = 7.8 Hz, 1H), 6.65–6.55 (m, 3H), 1.63(br s, 2H); MS (ES) m/z 359.2; HRMS: calcd for $C_{22}H_{16}ClN_2O$ [M+H]: 359.0946; found (ESI, $[M+H]^+$): 359.0965.

5.22. Methyl {4-[({3-[3-methyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino) methyl]phenyl}acetate (9a)

Compound **8a** (0.10 g, 0.33 mmol) and (4-formyl-phenyl)-acetic acid methyl ester (0.117 g, 0.66 mmol) were mixed in acetonitrile (4.0 mL) and then treated with $NaBH(OAc)_3$ (0.28 g, 1.32 mmol) and acetic acid (0.5 mL). After stirring at 45 °C under a N_2 atmosphere for 1 h, the mixture was quenched with water and then extracted with ethyl acetate. The organic residue was purified by reverse phase semi-preparative HPLC to provide **9a** as a yellow oil (0.14 g, 91%); ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H), 7.98 (d, J = 6.5 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.50–7.25 (m, 6H), 6.76 (d, J = 8.2 Hz, 1H), 6.57 (d, J = 6.9 Hz, 1H), 6.45 (s, 1H), 4.34 (s, 2H), 3.70 (s, 3H), 3.63 (s, 2H), 2.27 (s, 3H); HPLC purity 99.1% at 11.2 min; HRMS calcd for $C_{27}H_{24}F_3N_2O_2$ [M+H]: 465.1784; found (ESI, $[M+H]^+$): 465.1797.

5.23. Methyl {4-[({3-[3-phenyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino) methyl] phenyl}acetate (9b)

To a solution of {3-[3-phenyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amine (0.163 g, 0.45 mmol) and potassium carbonate (0.068 g, 0.49 mmol) in DMF at 80 °C was added 4-bromomethylphenylacetic acid ethyl ester (0.204 g, 0.89 mmol) dropwise over 5 min. After an additional 4 h, the cooled reaction mixture was poured into 2 N aqueous HCl and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, and dried with magnesium sulfate. The extracts were concentrated and the residue was chromatographed with 1:9 ethyl acetate–hexanes to afford **9b** as a yellow syrup (0.127 g, 52%); ^{1}H NMR (DMSO-d_6): δ 9.05 (s, 1H), 8.19 (d, J = 7.1 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.30–7.15 (m, 8H), 7.05 (t, J = 7.0 Hz, 1H), 6.65–6.60 (m, 1H), 6.44 (s, 1H), 6.40–6.30 (m, 2H), 4.18 (d, J = 6.2 Hz, 2H), 3.65 (s, 2H), 3.59 (s, 3H); MS (ES) m/z 527.0; HRMS calcd for $C_{32}H_{26}F_3N_2O_2$ [M+H]: 527.1941; found (ESI, $[M+H]^+$): 527.1966.

5.24. Ethyl {4-[({3-[3-benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino) methyl]phenyl}(hydroxy)acetate (9c)

Step 1: A mixture of (4-cyano-phenyl)-oxo-acetic acid ethyl ester (0.41 g, 2.0 mmol) in 25 mL of 90% formic acid and a large excess of Raney nickel (50% slurry in water) was refluxed for 1 h. The solid was filtered off and the filtrate was concentrated. The crude material was purified by silica gel chromatography eluting with a 5:95–100:0 ethyl acetate–hexane gradient to give 0.35 g of (4-formyl-phenyl)-hydroxy-acetic acid ethyl ester as an oil. This material was used in the next step.

Step 2: Compound **9c** was prepared from [4-(3-aminophenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl- methanone[7] and (4-formyl-phenyl)-hydroxy-acetic acid ethyl ester according to the procedure of compound **9a** (0.21 g, 95%); ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.15 (d, J = 7.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.9 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.35–7.25 (m, 4H), 7.06 (t, J = 7.8 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.46 (s, 1H), 5.16 (d, J = 4.4 Hz, 1H), 4.2 5(q, J = 7.1 Hz, 2H), 3.48 (d, J = 7.0 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H); MS (ES) m/z 585.3.

5.25. Ethyl {4-[({3-[3-benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino) methyl]phenyl}(difluoro)acetate (9d)

Step 1: A mixture of (4-cyano-phenyl)-oxo-acetic acid ethyl ester (1.00 g, 4.9 mmol) in dichloromethane (20 mL) and (diethylamino)sulfur trifluoride (DAST) (1.0 g, 6.2 mmol) was stirred at room temperature for 3 h. The mixture was poured into iced water and extracted with ethyl acetate. The organics were dried over $MgSO_4$ and concentrated to give crude (4-cyano-phenyl)-difluoro-acetic acid ethyl ester, which was used for the next reaction.

Step 2: Difluoro-(4-formyl-phenyl)-acetic acid ethyl ester was prepared from (4-cyano-phenyl)-difluoro-acetic acid ethyl ester by Raney nickel reduction as described in step 1 of **9c**.

Step 3: Compound **9d** was prepared from [4-(3-aminophenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl- methanone[7] and difluoro-(4-formyl-phenyl)-acetic acid ethyl ester according to the procedure of **9a** as a gummy yellow solid (0.20 g, 81%); ^{1}H NMR (DMSO-d_6): δ 9.07 (s, 1H), 8.30 (d, J = 7.3 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.2 Hz, 1H), 7.60–7.50 (m, 5H), 7.41 (d, J = 8.1 Hz, 2H), 7.33 (t, J = 8.2 Hz, 3H), 6.98 (t, J = 7.6 Hz, 1H), 6.60–6.35 (m, 4H), 4.29 (q, J = 7.1 Hz, 2H), 4.22 (br s, 2H), 1.21 (t, J = 7.1 Hz, 3H); MS (ES) m/z 605.3.

5.26. {4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl}acetic acid (16)

Step 1: [4-(3-Aminophenyl)-8-(trifluoromethyl)quinolin-3-yl](phenyl)methanone[7] (0.39 g, 1.0 mmol) and (4-formyl-phenyl)-acetic acid methyl ester[12] (0.17 g, 0.96 mmol) were mixed in THF (15 mL) and then treated with $NaBH(OAc)_3$ (0.43 g, 2.0 mmol) and acetic acid (0.50 mL). After stirring at 40 °C under an N_2 atmosphere for 2 h, the mixture was quenched with water and then extracted with ethyl acetate. The organic residue was purified by silica gel chromatography eluting with a 5:95–50:50 ethyl acetate–hexane gradient to give methyl {4-[({3-[3-benzoyl-8-(trifluoromethyl)quinolin-4- yl]phenyl}amino)methyl]phenyl}acetate as an orange solid (0.30 g, 54%): ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 8.30 (d, J = 7.3 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.72 (t, J = 8.6 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.22–7.18 (m, 4H), 6.98 (t, J = 7.7 Hz, 1H), 6.49 (d, J = 6.8 Hz, 2H), 6.40 (d, J = 6.8 Hz, 2H), 4.12 (d, J = 6.0 Hz, 2H), 3.66 (s, 2H), 3.61 (s, 3H); MS (EI) m/z 555.3 $(M+H)^+$.

Step 2: To a stirred solution of methyl {4-[({3-[3-benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)methyl]-phenyl}acetate (0.06 g, 0.11 mmol) in THF–methanol–water (2:1:1, 10 mL) was added lithium hydroxide monohydrate (0.060 g, 1.40 mmol). The reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was made acidic (pH 6) with glacial acetic acid, and the solid was collected and dried over P_2O_5 to give **16** as an orange solid (0.05 g, 93%); ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 8.29 (d, J = 7.1 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.22–7.15 (m, 4H), 6.97 (t, J = 7.4 Hz, 1H), 6.55–6.35 (m, 4H), 4.12 (d, J = 5.8 Hz, 2H), 3.53 (s, 2H); MS (ESI) m/z 541; HPLC purity 94.3% at 10.6 min; HRMS calcd for $C_{32}H_{24}F_3N_2O_3$ [M+H]: 541.1734; found (ESI, $[M+H]^+$): 541.1720.

5.27. {4-[({3-[3-Methyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl}acetic acid (17)

The title compound was prepared from **9a** following the procedure of step 2 for compound **16** (0.119 g, 85%); ^{1}H NMR (DMSO-d_6): δ 8.96 (s, 1H), 8.08 (d, J = 7.2 Hz,

1H), 7.66 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.30–7.15 (m, 5H), 6.73 (d, J = 8.2 Hz, 1H), 6.50–6.38 (m, 4H), 4.23 (d, J = 5.6 Hz, 2H), 3.42 (s, 2H), 2.20 (s, 3H); HPLC purity 97.8% at 10.6 min.; HRMS calcd for $C_{26}H_{22}F_3N_2O_2$ [M+H]: 451.1628; found (ESI, $[M+H]^+$): 451.1609.

5.28. {4-[({3-[3-Phenyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl}acetic acid (18)

The title compound was prepared from **9b** following the procedure of step 2 for compound **16** as a tan tacky solid (0.021 g, 31%); mp 71–73 °C; ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1H), 9.05 (s, 1H), 8.19 (d, J = 7.1 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.30–7.15 (m, 8H), 7.05 (t, J = 7.6 Hz, 1H), 6.61 (dd, J = 8.2, 1.5 Hz, 1H), 6.45 (s, 1H), 6.40–6.30 (m, 3H), 4.17 (d, J = 6.1 Hz, 2H), 3.53 (s, 2H); MS (ESI) m/z 513; HPLC purity 90.2% at 11.0 min; HRMS calcd for $C_{31}H_{24}F_3N_2O_2$ [M+H]: 513.1784; found (ESI, $[M+H]^+$): 513.1795.

5.29. {4-[({3-[3-[Hydroxy(phenyl)methyl]-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)methyl]phenyl}acetic acid (19)

Step 1: Phenyl[4-(3-aminophenyl)-8-(trifluoromethyl)-quinolin-3-yl]methanone[7] (0.39 g, 1.0 mmol) was dissolved in MeOH (20 mL), cooled to 0 °C, and treated with $NaBH_4$ (0.060 g, 1.5 mmol). The ice bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The MeOH was removed and water was added to the resulting material, and the mixture was extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and concentrated in vacuo. The crude product was used for the next step.

Step 2: Compound **19** was prepared according to the procedure of step 2 of **16** as a ~1:1 mixture of rotomers, isolated as an off-white solid, (0.15 g, 28%); MS (ES) m/z 541.2; HRMS calcd for $C_{32}H_{26}F_3N_2O_3$ [M+H]: 543.1890; found (ESI, $[M+H]^+$): 543.1870.

5.30. {4-[({3-[3-Cyano-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl}acetic acid (20)

The title compound was prepared from **8c** and (4-formyl-phenyl)-acetic acid methyl ester[12] following the procedure of compound **16** as a yellow solid (0.015 g, 21%); ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1H), 9.36 (s, 1H), 8.37 (d, J = 7.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.35–7.27 (m, 3H), 7.22 (d, J = 8.2 Hz, 2H), 6.84 (dd, J = 8.5, 1.6 Hz, 1H), 6.75–6.60 (m, 3H), 4.29 (d, J = 5.9 Hz, 2H), 3.55 (s, 2H); MS (ES) m/z 459.9; HPLC purity 100% at 10.2 min; HRMS calcd for $C_{26}H_{19}F_3N_3O_2$ [M+H]: 462.1424; found (ESI, $[M+H]^+$): 462.1408.

5.31. {4-[({3-[3-(Aminocarbonyl)-8-(trifluoromethyl)quinolin-4-yl]phenyl}-amino)methyl]phenyl}acetic acid (21)

The title compound was prepared from **8d** and (4-formyl-phenyl)-acetic acid methyl ester[12] following the procedure of compound **16** as a pale yellow solid (0.034 g, 59%); ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1H), 9.02 (s, 1H), 8.20 (d, J = 6.6 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.70–7.60 (m, 2H), 7.54 (br s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.25–7.15 (m, 3H), 6.73 (dd, J = 8.2, 1.6 Hz, 1H), 6.60 (s, 1H), 6.55 (d, J = 7.5 Hz, 1H), 6.47 (t, J = 5.8 Hz, 1H), 4.25 (d, J = 4.2 Hz, 2H), 3.54 (s, 2H); MS (ESI) m/z 480; HPLC purity 100% at 8.9 min; HRMS calcd for $C_{26}H_{21}F_3N_3O_3$ [M+H]: 480.1530; found (ESI, $[M+H]^+$): 480.1516.

5.32. [4-({[3-(3-Benzoyl-8-methylquinolin-4-yl)phenyl]-amino}methyl)phenyl]acetic acid (22)

[4-({[3-(3-Benzoyl-8-methylquinolin-4-yl)phenyl]amino}-methyl)phenyl] acetic acid methyl ester was prepared from **8e** and (4-formyl-phenyl)-acetic acid methyl ester[12] according to the procedure of step 1 of compound **16**. Basic hydrolysis of the methyl ester following the procedure of step 2 of compound **16** gave **22** as a yellow solid (0.2 g, 82%); ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1H), 8.92(s, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.60–7.45 (m, 5H), 7.40–7.30 (m, 2H), 7.22–7.15 (m, 4H), 6.94 (t, J = 7.6 Hz, 1H), 6.46–6.44 (m, 2H), 6.36–6.30 (m, 2H), 4.12 (d, J = 5.8 Hz, 2H), 3.54 (s, 2H), 2.80 (s, 3H); MS (ESI) m/z 487; HPLC purity 100% at 10.5 min; HRMS calcd for $C_{32}H_{27}N_2O_3$ [M+H]: 487.2016; found (ESI, $[M+H]^+$): 487.2029; Anal. Calcd for $C_{32}H_{26}N_2O_3 \cdot 0.3H_2O$: C, 78.12; H, 5.45; N, 5.69. Found: C, 77.90; H, 5.22; N, 5.56.

5.33. [4-({[3-(3-Benzyl-8-methylquinolin-4-yl)phenyl]amino}-methyl)phenyl]acetic acid (23)

A solution of [4-({[3-(3-benzoyl-8-methylquinolin-4-yl)-phenyl]amino}methyl)phenyl] acetic acid methyl ester (0.50 g, 1.00 mmol), hydrazine (0.50 mL), and KOH (0.20 g, 3.6 mmol) in ethyleneglycol (8.0 ml) was heated to 160 °C. After 3 h, the reaction mixture was cooled, poured into water mixture and acidified with acetic acid. The solution was extracted with ethyl acetate, concentrated, and the residue was purified by reverse phase semi-preparative HPLC to give **23** as a pale brown solid (0.035 g, 37%); ^{1}H NMR (DMSO-d_6): δ 12.27 (br s, 1H), 8.73 (s, 1H), 7.54 (d, J = 6.7 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.30–7.10 (m, 9H), 6.98 (d, J = 6.9 Hz, 2H), 6.72 (dd, J = 8.2, 1.5 Hz, 1H), 6.45–6.35 (m, 3H), 4.19 (d, J = 5.7 Hz, 2H), 3.52 (s, 2H), 2.71 (s, 3H); MS (ES) m/z 473.3; HPLC purity 100% at 11.1 min; HRMS calcd for $C_{32}H_{29}N_2O_2$ [M+H]: 473.2224; found (ESI, $[M+H]^+$): 473.2224.

5.34. [4-({[3-(3-Benzoyl-8-fluoroquinolin-4-yl)phenyl]amino}-methyl)phenyl]acetic acid (24)

The title compound was prepared from **8f** and 3-(4-formyl-phenyl)-acetic acid methyl ester[12] according to the procedure of compound **16** as a yellow solid (0.029 g, 40%); ^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.50–7.40 (m, 3H), 7.34–7.24 (m, 5H), 7.05 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.51–6.49 (m, 3H), 4.20 (s, 2H), 3.67 (s, 2H); HPLC purity 99.5% at 9.9 min;

HRMS calcd for $C_{31}H_{24}FN_2O_3$ [M+H]: 491.1766; found (ESI, $[M+H]^+$): 491.1758.

5.35. [4-({[3-(3-Benzoylquinolin-4-yl)phenyl]amino}methyl)-phenyl]acetic acid (25)

The title compound was prepared from **8g** and 3-(4-formyl-phenyl)-acetic acid methyl ester[12] according to the procedure of compound **16** as a yellow solid (0.016 g, 33%); ^{1}H NMR ($CDCl_3$): δ 8.96 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.79 (t, J = 6.9 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.32–7.20 (m, 5H), 7.05 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 7.4 Hz, 1H), 6.50–6.45 (m, 3H), 4.20 (s, 2H), 3.68 (s, 2H); MS (ES) m/z 471.1; HPLC purity 100% at 9.9 min; HRMS calcd for $C_{31}H_{25}N_2O_3$ [M+H]: 473.1860; found (ESI, $[M+H]^+$): 473.1867.

5.36. [4-({[3-(3-Benzoyl-8-chloroquinolin-4-yl)phenyl]amino}-methyl)phenyl]acetic acid (26)

The title compound was prepared from **8h** and (4-formyl-phenyl)-acetic acid methyl ester[12] according to the procedure of compound **16** as a yellow solid (0.18 g, 85%); H NMR (DMSO-d_6): δ 12.28 (s, 1H), 9.03 (s, 1H), 8.06 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.60–7.53 (m, 4H), 7.36 (t, J = 7.8 Hz, 2H), 7.21–7.15 (m, 4H), 6.96 (t, J = 8.1 Hz, 1H), 6.50–6.45 (m, 2H), 6.37 (d, J = 7.4 Hz, 2H), 4.12 (s, 2H), 3.54 (s, 2H); MS (ESI) m/z 507; HPLC purity 100% at 11.1 min; HRMS calcd for $C_{31}H_{24}ClN_2O_3$[M+H]: 507.1470; found (ESI, $[M+H]^+$): 507.1497.

5.37. [4-({[3-(3-Benzyl-8-chloroquinolin-4-yl)phenyl]amino}-methyl)phenyl]acetic acid (27)

The title compound was prepared from [4-({[3-(3-benzoyl-8-chloroquinolin-4-yl)phenyl]amino}methyl)phenyl]-acetic acid methyl ester following the procedure of compound **23** as a pale yellow solid (0.15 g, 51%); ^{1}H NMR ($CDCl_3$): δ 8.95 (s, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.35–7.22 (m, 6H), 7.20–7.10 (m, 3H), 6.96 (d, J = 6.9 Hz, 2H), 6.72 (dd, J = 8.2, 1.4 Hz, 1H), 6.53 (d, J = 7.4 Hz, 1H), 6.34 (s, 1H), 4.24 (d, J = 4.4 Hz, 1H), 4.20 (d, J = 4.4 Hz, 1H), 3.98 (d, J = 5.5 Hz, 1H), 3.93 (d, J = 5.5 Hz, 1H), 3.65 (s, 2 H); MS (ESI) m/z 493; HPLC purity 100% at 11.1 min; HRMS calcd for $C_{31}H_{24}ClN_2O_2$ [M−H]: 491.1532; found (ESI, $[M-H]^-$): 491.1519.

5.38. {3-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl} acetic acid (28)

The title compound was prepared from [4-(3-aminophenyl)-8-(trifluoromethyl)quinolin-3-yl](phenyl)methanone[7] and (3-formyl-phenoxy)-acetic acid according to the procedure of step 1 of **16** as a pale brown solid (0.079 g, 94%); ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.14 (d, J = 7.3 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.54 (t, J = 7.9 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.35–7.15 (m, 6H), 7.06 (t, J = 7.8 Hz, 1H), 6.57 (d, J = 7.1 Hz, 1H), 6.53 (dd, J = 8.3, 1.6 Hz, 1H), 6.47 (s, 1H), 4.20 (s, 2H), 3.65 (s, 2H); MS (ESI) m/z 541; HPLC purity 98.5 % at 10.4 min; HRMS calcd for $C_{32}H_{24}F_3N_2O_3$ [M+H]: 541.1734; found (ESI, $[M+H]^+$): 541.1732.

5.39. {4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenoxy} acetic acid (29)

The title compound was prepared from [4-(3-aminophenyl)-8-(trifluoromethyl)quinolin-3-yl](phenyl)methanone[7] and (4-formyl-phenoxy)-acetic acid according to the procedure of step 1 of **16** as a pale brown solid (0.095 g, 65%); ^{1}H NMR (DMSO-d_6): δ 12.97 (s, 1H), 9.08 (s, 1H), 8.30 (d, J = 7.1 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.42–7.30 (m, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.97 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 8.2 Hz, 2H), 6.55–6.30 (m, 4H), 4.65 (s, 2H), 4.06 (s, 2H); MS (ESI) m/z 557; HPLC purity 100% at 10.0 min; HRMS calcd for $C_{32}H_{24}F_3N_2O_4$ [M+H]: 557.1683; found (ESI, $[M+H]^+$): 557.1681.

5.40. (2*E*)-3-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)-methyl]phenyl}acrylic acid (30)

The title compound was prepared from [4-(3-aminophenyl)-8-(trifluoromethyl)quinolin-3-yl](phenyl)methanone[7] and 3-(4-formyl-phenyl)-acrylic acid according to the procedure of step 1 of **16** as a yellow solid (0.060 g, 41%); ^{1}H NMR (DMSO-d_6): δ 12.35 (br s, 1H), 9.07 (s, 1H), 8.29 (d, J = 6.9 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.68–7.52 (m, 6H), 7.37 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 7.8 Hz, 1H), 6.55–6.45 (m, 4H), 6.41 (d, J = 7.6 Hz, 1H), 4.19 (br s, 2H); MS (ESI) m/z 553; HPLC purity 100% at 10.7 min; HRMS calcd for $C_{33}H_{24}F_3N_2O_3$ [M+H]: 553.1734; found (ESI, $[M+H]^+$): 553.1728.

5.41. 4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-benzoic acid (31)

The title compound was prepared from [4-(3-aminophenyl)-8-(trifluoromethyl)quinolin-3-yl](phenyl)methanone[7] and 4-formyl-benzoic acid methyl ester according to the procedure of compound **16** as a yellow solid (0.125 g, 63%); ^{1}H NMR (DMSO-d_6): δ 9.07 (s, 1H), 8.29 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.40–7.30 (m, 4H), 6.98 (t, J = 7.8 Hz, 1H), 6.55–6.46 (m, 3H), 6.41 (d, J = 7.4 Hz, 1H), 4.23 (t, J = 5.2 Hz, 2H); MS (ESI) m/z 527; HPLC purity 100% at 10.8 min, HRMS calcd for $C_{31}H_{22}F_3N_2O_3$ [M+H]: 527.1577; found (ESI, $[M+H]^+$): 527.1581. Anal. Calcd for $C_{31}H_{21}F_3N_2O_3 \cdot 0.75H_2O$: C, 68.94; H, 4.20; N, 5.19. Found: C, 68.93; H, 3.81; N, 5.17.

5.42. 2-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)-methyl]phenyl}propanoic acid (32)

The title compound was prepared from [4-(3-aminophenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 2-(4-formyl-phenyl)-propionic acid methyl ester[12] according to the procedure of compound **16** as

a yellow solid (0.10 g, 65%); ^{1}H NMR (DMSO-d_6): δ 12.35 (br s, 1H), 9.08 (s, 1H), 8.30 (d, J = 7.1 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.71 (t, J = 7.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.30–7.15 (m, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.52–6.46 (m, 2H), 6.38 (d, J = 7.5 Hz, 2H), 4.11 (d, J = 5.8 Hz, 2H), 3.64 (q, J = 7.0 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H); MS (ESI) m/z 555; HPLC purity 96.1% at 10.9 min; HRMS calcd for $C_{33}H_{26}F_3N_2O_3$ [M+H]: 555.1890; found (ESI, [M+H]$^+$): 555.1895.

5.43. 2-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl}-2-methylpropanoic acid (33)

The title compound was prepared from [4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 2-(4-formyl-phenyl)-2-methyl-propionic acid methyl ester[13] according to the procedure of compound **16** as an orange solid (0.16 g, 56%); ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H), 8.13 (d, J = 7.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.32–7.22 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 7.04 (t, J = 7.8 Hz, 1H), 6.56 (d, J = 7.4 Hz, 1H), 6.50 (dd, J = 8.3, 1.7 Hz, 1H), 6.44 (s, 1H), 4.20–4.10 (m, 2H), 1.58 (s, 6H); MS m/z 569; HPLC purity 100% at 11.1 min; HRMS calcd for $C_{34}H_{28}F_3N_2O_3$ [M+H]: 569.2047; found (ESI, [M+H]$^+$): 569.2047.

5.44. {4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)-methyl]phenyl} (hydroxy)acetic acid (34)

The title compound was prepared from **9c** according to the procedure of step 2 of **16** as a yellow solid (0.16 g, 76%); ^{1}H NMR (DMSO-d_6): δ 9.07 (s, 1H), 8.28 (d, J = 7.3 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.72 (td, J = 7.8, 2.1 Hz, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.40–7.30 (m, 4H), 7.19 (d, J = 8.1 Hz, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.50–6.46 (m, 2H), 6.42–6.37 (m, 2H), 4.93 (s, 1H), 4.12 (d, J = 5.7 Hz, 2H); MS (ES) m/z 555.2; HPLC purity 100% at 9.9 min; HRMS calcd for $C_{32}H_{24}F_3N_2O_4$ [M+H]: 557.1683; found (ESI, [M+H]$^+$): 557.1665.

5.45. {4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl} (difluoro)acetic acid (35)

The title compound was prepared from **9d** according to the procedure of step 2 of **16** as a pale yellow solid (0.11 g, 52%); ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H), 8.29 (d, J = 7.1 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.58 (d, J = 7.0 Hz, 2H), 7.57–7.52 (m, 4H), 7.39 (d, J = 8.2 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 6.98 (t, J = 7.8 Hz, 1H), 6.51–6.47 (m, 2H), 6.40 (d, J = 7.4 Hz, 1H), 4.23 (br s, 2H); MS (ES) m/z 575.2; HPLC purity 100% at 9.6 min; HRMS: calcd for $C_{32}H_{22}F_5N_2O_3$ [M+H]: 577.1545; found (ESI, [M+H]$^+$): 577.1524.

5.46. 2-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]-phenyl}amino)methyl]-phenyl} acetamide (36)

A mixture of methyl {4-[({3-[3-benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)methyl]phenyl}acetate[7] (0.060 g, 0.110 mmol) in concentrated ammonium hydroxide (25 mL) and methanol (5.0 mL) was stirred at room temperature for 2 d. Removal of solvent under reduced pressure gave crude product that was purified by reverse phase semi-preparative HPLC to give **36** (0.015 g, 25%) as a pale yellow solid; ^{1}H NMR ($CDCl_3$): δ 9.06 (s, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.60–7.51 (m, 3H), 7.47 (t, J = 7.4 Hz, 1H), 7.35–7.25 (m, 6H), 7.05 (t, J = 7.7 Hz, 1H), 6.57 (d, J = 7.5 Hz, 1H), 6.52 (dd, J = 7.4, 1.4 Hz, 1H), 6.43 (s, 1H), 5.60 (br s, 1H), 5.35 (br s, 1H), 4.21 (d, J = 9.5 Hz, 1H), 4.17 (d, J = 9.5 Hz, 1H), 3.61 (s, 2H); MS (ESI) m/z 540; HPLC purity 100% at 10.2 min; HRMS calcd for $C_{32}H_{25}F_3N_3O_2$ [M+H]: 540.1893; found (ESI, [M+H]$^+$): 540.1881.

5.47. [4-(3-{[4-(2-Hydroxyethyl)benzyl]amino}phenyl)-8-(trifluoromethyl) quinolin-3-yl](phenyl)methanone (37)

The title compound was prepared from [4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 4-(2-hydroxyethyl)-phenyl-carbaldehyde[14] according to the procedure of compound **9a** (0.044 g, 32%); ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.15 (d, J = 6.9 Hz, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.32–7.20 (m, 4H), 7.04 (t, J = 7.8 Hz, 1H), 6.56 (d, J = 6.5 Hz, 1H), 6.52 (dd, J = 8.2, 1.6 Hz, 1H), 6.44 (s, 1H), 4.17 (d, J = 4.3 Hz, 1H), 4.14 (d, J = 4.3 Hz, 1H), 3.89 (t, J = 6.3 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H); MS (ESI) m/z 527; HPLC purity 96.0% at 10.8 min; HRMS calcd for $C_{32}H_{26}F_3N_2O_2$ [M+H]: 527.1941; found (ESI, [M+H]$^+$): 527.1954.

5.48. [4-[3-(Benzylamino)phenyl]-8-(trifluoromethyl)quinolin-3-yl](phenyl)-methanone (38)

The title compound was prepared from [4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and benzaldehyde according to the procedure of compound **9a** as a yellow solid (0.056 g, 46%); ^{1}H NMR (DMSO-d_6): δ 9.08 (s, 1H), 8.30 (d, J = 7.0 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 8.3 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.40–7.37 (m, 5H), 7.24 (d, J = 7.3 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.52–6.45 (m, 2H), 6.43–6.39 (m, 2H), 4.16 (br s, 2H); MS (ESI) m/z 483; HPLC purity 100% at 11.4 min; HRMS: calcd for $C_{30}H_{22}F_3N_2O$ [M+H]: 483.1679; found (ESI, [M+H]$^+$): 483.1664.

5.49. [4-(3-{[4-(Hydroxymethyl)benzyl]amino}phenyl)-8-(trifluoromethyl)-quinolin-3-yl](phenyl)methanone (39)

The title compound was prepared from 4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 4-hydroxymethylbenzaldehyde according to the procedure of compound **9a** (0.014 g, 41%); ^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H), 8.15(d, J = 7.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 6.8 Hz, 1H), 7.35–7.25 (m, 7H), 7.06 (t, J = 8.0 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 6.52 (dd, J = 7.4, 1.5 Hz, 1H), 6.46 (s, 1H), 4.70 (s, 2H), 4.21 (s, 2H), 1.70 (br s, 1H); MS (ES) m/z

513.2; HPLC purity 100% at 10.6 min; HRMS calcd for $C_{31}H_{24}F_3N_2O_2$ [M+H]: 513.1784; found (ESI, $[M+H]^+$): 513.1772.

5.50. (5*Z*)-5-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl} amino)methyl] benzylidene}-1,3-thiazolidine-2,4-dione (40)

The title compound was prepared from [4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzaldehyde according to the procedure of compound **9a** as a yellow solid (0.063 g, 52%); ^{1}H NMR (DMSO-d_6): δ 12.60 (br s, 1H), 9.07 (s, 1H), 8.29 (d, J = 7.2 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.60–7.50 (m, 4H), 7.40–7.30 (m 4H), 6.98 (t, J = 7.8 Hz, 1H), 6.53 (t, J = 5.9 Hz, 1H), 6.50–6.40 (m, 2H), 6.41 (d, J = 7.5 Hz, 1H), 4.30–4.15 (m, 2H); MS (ES) *m*/*z* 607.8; HPLC purity 98.4% at 11.4 min; HRRMS calcd for $C_{34}H_{23}F_3N_3O_3S$ [M+H]: 610.1407; found (ESI, $[M+H]^+$): 610.1407.

5.51. 5-{4-[({3-[3-Benzoyl-8-(trifluoromethyl)quinolin-4-yl]phenyl}amino)methyl] benzylidene}-2-thioxo-1,3-thiazolidin-4-one (41)

The title compound was prepared from [4-(3-amino-phenyl)-8-trifluoromethyl-quinolin-3-yl]-phenyl-methanone[7] and 4-(4-oxo-2-thioxo-thiazolidin-5-ylidenemethyl)-benzaldehyde according to the procedure of compound **9a** as an orange solid (0.10 g, 63%); ^{1}H NMR (DMSO-d_6): δ 13.81 (br s, 1H), 9.07 (s, 1H), 8.29 (d, J = 6.8 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.68 (t, J = 8.1 Hz, 1H), 7.65–7.50 (m, 6H), 7.40–7.30 (m 4H), 6.98 (t, J = 7.8 Hz, 1H), 6.54 (t, J = 6.0 Hz, 1H), 6.50–6.40 (m, 2H), 6.41 (d, J = 7.7 Hz, 1H), 4.29–4.17 (m, 2H); MS (ES) *m*/*z* 623.8; HPLC purity 94.9% at 11.9 min; HRMS calcd for $C_{34}H_{23}F_3N_3O_2S_2$ [M+H]: 626.1178; found (ESI, $[M+H]^+$): 626.1185.

5.52. ApoE knockout in vivo study

5.52.1. Animals. Four-week-old male ApoE knockout mice on a C57BL/6 background were obtained from Taconic (Germantown, NY). Mice were randomized by body weight and group housed 3 per cage in plastic cages with ad libitum access to water and diet (Purina Rodent Chow 5001). Animals were allowed to acclimate for one week under standard conditions with a 12:12-h light/dark cycle (lights on at 0600 h) and with temperature controlled at 22 ± 2 °C. All experimental procedures were performed according to protocols approved by the Wyeth Institutional Animal Care and Use Committee (Collegeville, PA). Animals were divided into four groups (n = 8–10 per group) and were fed western diet (AIN-76A) #1810100 (Test Diet, Richmond, IN) ad libitum with or without compounds. The western diet was supplemented with either GW3965, 23 or 27 in order to deliver a dose of 10 mg/kg/day per animal during normal chow consumption (4 g chow/day for a 20 g mouse). Following 12 weeks of treatment, animals were anesthetized with isoflurane and a blood sample was collected. The aortas were perfused with 0.9% saline followed by 10% neutral buffered formalin. The aortas were carefully excised down to the diaphragm and placed in a vial containing 10% neutral buffered formalin until time of analysis.

5.52.2. Quantification of atherosclerotic lesions. Quantitative analysis of atherosclerotic lesion was performed in the thoracic aorta by an observer blinded to the experimental protocol. Images of the aorta used for the analysis were processed using Adobe Photoshop 6.0 and Scion Imaging software (Scion Image Beta 4.02). The thoracic aorta was collected and adventitial tissue was carefully removed. The aorta was then opened longitudinally, pinned out on a black wax surface, and stained for lipid deposition with Oil Red-O. Images of the open luminal surface of the aorta were captured using a dissecting microscope (Nikon SMZ 800) equipped with a digital video camera (Nikon DXM 1200). Oil Red-O stained atherosclerotic plaque area was quantified and expressed as a percentage of total luminal surface area of the aorta.

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