Structure−Activity Relationships for a Series of Quinoline-Based Compounds Active against Replicating and Nonreplicating *Mycobacterium tuberculosis*

Annamaria Lilienkampf,[†] Jialin Mao,[†,‡] Baojie Wan,[‡] Yuehong Wang,[‡] Scott G. Franzblau,*[,‡] and Alan P. Kozikowski*[,†]

Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois 60612, Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois 60612

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Tuberculosis (TB) remains as a global pandemic that is aggravated by a lack of health care, the spread of HIV, and the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains. New anti-TB drugs are urgently required to shorten the long 6−12 month treatment regimen and to battle drug-resistant *Mtb* strains. We have identified several potent quinoline-based anti-TB compounds, bearing an isoxazole containing side-chain. The most potent compounds, **7g** and **13**, exhibited submicromolar activity against the replicating bacteria (R-TB), with minimum inhibitory concentrations (MICs) of 0.77 and 0.95 μM, respectively. In general, these compounds also had micromolar activity against the nonreplicating persistent bacteria (NRP-TB) and did not show toxicity on Vero cells up to 128 μM concentration. Compounds **7g** and **13** were shown to retain their anti-TB activity against rifampin, isoniazid, and streptomycin resistant *Mtb* strains. The results suggest that quinoline−isoxazole-based anti-TB compounds are promising leads for new TB drug development.

Introduction

Tuberculosis (TB[a]), which is caused predominantly by *Mycobacterium tuberculosis* (*Mtb*), is a life-threatening chronic infection primarily affecting the lungs. The World Health Organization (WHO) has estimated that one-third of the world's population is infected with *Mtb*, resulting in an estimated 1.7 million deaths from TB in 2006.[1] *Mtb* has the remarkable ability to lie dormant for years as a latent infection, and approximately 5−10% of the latently infected individuals will eventually develop an active disease. In addition, TB is a frequent HIV coinfection and a major cause of death among people living with HIV/AIDS. Despite the severe global impact of TB, it has been a neglected disease and no new anti-TB drugs have been introduced for the last four decades.[2]

Current TB treatment takes 6−12 months and requires patients to take a combination of three or four drugs (isoniazid (INH), rifampin (RMP), pyrazinamide, and ethambutol or streptomycin (SM)), often leading to poor patient compliance. The long treatment is necessary due to the presence of a nonreplicating persistent *Mtb* phenotype (NRP-TB), which is the putative cause of disease relapse. All the current drugs target the replicating form of *Mtb* (R-TB), however, only RMP and pyrazinamide have shown activity against NRP-TB.[3] Furthermore, recent years have seen an alarming emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) tuberculosis strains. There is an urgent demand for new anti-TB drugs possessing novel modes of action, not only to shorten the long treatment regimen by targeting NRP-TB but also to battle resistant *Mtb* strains. In addition, the retrovirals commonly used in AIDS/HIV treatment are usually not compatible with the current TB treatment, particularly due to the CYP3A induction by RMP.[4]

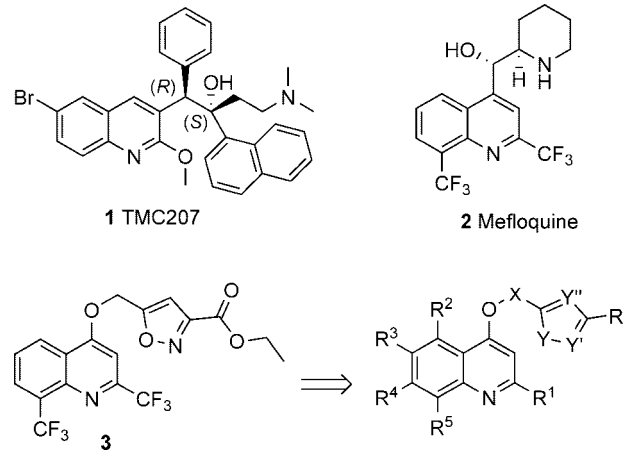

Figure 1. Examples of quinoline-based anti-TB agents and the outline of structural modifications on the lead compound.

Quinoline-based compounds are known to exhibit anti-TB properties.[5] Fluoroquinolones,[6] such as gatifloxcin and moxifloxacin, target DNA topoisomerase IV and DNA gyrase and can be used as anti-TB agents,[7] however, they often suffer from resistance.[8] Quinoline-based anti-TB compound **1** (TMC207),[9] bearing a bulky biaryl side chain at position C3, is a highly potent anti-TB agent and is currently in phase II clinical trials (Figure 1). We have previously reported the quinoline-based antimalarial drug mefloquine **2** (with a minimum inhibitory concentration (MIC) of 13 μM),[10] and its derivatives,[11] to show moderate activity against *Mtb*. The activity was significantly improved with compound **3**,[12] in which the quinoline core of

* To whom correspondence should be addressed. For A.P.K.: phone, +1-312-996-7577; fax, +1-312-996-7107; E-mail: kozikowa@uic.edu. For S.G.F.: phone, +1-312-355-1715; fax, +1-312-355-2693. E-mail: sgf@uic.edu.

† Drug Discovery Program, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago.

‡ Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago.

[a] Abbreviations: INH, isoniazid; LORA, low oxygen recovery assay; MABA, microplate Alamar Blue assay; MIC, minimum inhibitory concentration; MDR-TB, multidrug-resistant tuberculosis; *Mtb*, *Mycobacterium tuberculosis*; NRP-TB, nonreplicating persistent tuberculosis; PPA, polyphosphoric acid; R-TB, replicating tuberculosis; RMP, rifampin; SDR-TB, single drug resistant tuberculosis; SM, streptomycin; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

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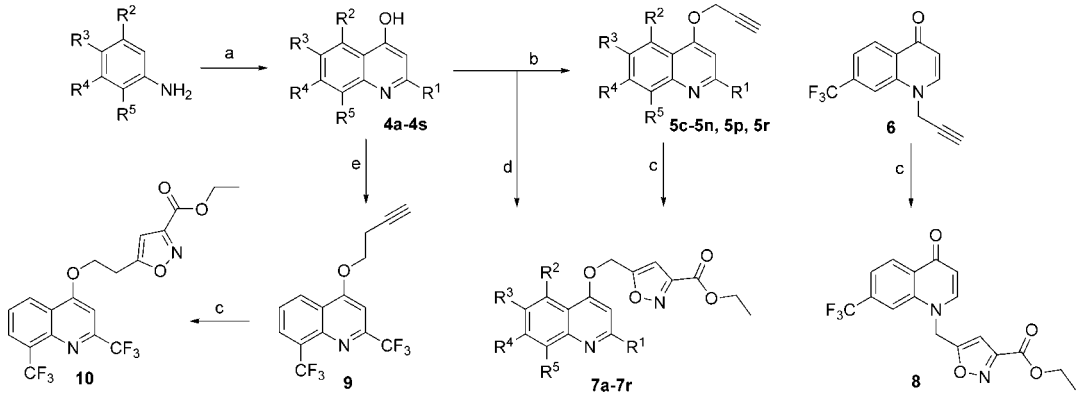
Scheme 1[a,b]



[a] Reagents and conditions: (a) PPA, ethyl 4,4,4-trifluoroacetoacetate, 150 °C, 12−48 h; (b) CH≡CCH$_2$Br, K_2CO_3, KI, acetone, reflux; (c) ethyl 2-chloro-2-(hydroxyimino)acetate, Et_3N, ether or THF; (d) 5-(bromomethyl)isoxazole-3-carboxylic acid ethyl ester,[14] K_2CO_3, acetone, reflux; (e) 3-butyn-1-ol, PPh_3, DEAD, THF. [b] For complete structures see Table 1. The substitution pattern in each intermediate corresponds to the substitution pattern in the final compound with the same letter.

mefloquine was linked to an isoxazole moiety via an oxymethylene linker (Figure 1). Compound **3** was shown to have activity against both R-TB and NRP-TB with an MIC of 0.9 and 12.2 μM, respectively. The ethyl ester moiety in **3** proved to be important for activity as the corresponding carboxylic acid was found to be inactive and various amides showed significantly reduced activity. However, it is possible that the ethyl ester acts as a prodrug for the corresponding carboxylic acid, which itself may be unable to penetrate through the thick *Mycobacterium* cell wall in the in vitro assay. No CYP3A4 inhibition was observed with **3**, which is a valuable feature in a possible coadministration regimen with HIV drugs.

In this paper, we describe the synthesis and biological activity of a series of anti-TB agents based on a quinoline core. Compound **3** was used as the lead compound, and for this study three modification sites were chosen: the quinoline core, the oxymethylene linker, and the isoxazole ring (Figure 1). Various substituents were introduced around the quinoline core in order to find the optimal substitution pattern as well as to study substituent effects. The side chain was kept at C4 position in all modifications, and the effect of the isoxazole moiety on the anti-TB activity was investigated by replacement with other heterocycles. All the synthesized compounds were first evaluated for their activity against R-TB. Selected compounds were also tested for their activity against NRP-TB and against single drug resistant *Mtb* strains (SDR-TB) as described herein.

Chemistry

First, the effect of the quinoline core substitution on the antibacterial activity was explored (Table 1). The target compounds **7a**−**7r**, bearing various substituents on the core, were synthesized in two steps starting from suitably substituted 4-hydroxyquinolines (Scheme 1). The 4-hydroxyquinolines **4a**−**4s**, if not commercially available, were synthesized from the corresponding anilines in the PPA catalyzed condensation with ethyl 4,4,4-trifluoroacetoacetate.[13] Alkylation of **4c**−**4n** and **4p** with propargyl bromide, employing K_2CO_3 as a base, produced the acetylenic intermediates **5c**−**5n** and **5p** in good yields. With 7-(trifluoromethyl)-4-quinolinol (**4r**), the above Williamson reaction yielded both the *N*-alkylated and *O*-alkylated products **5r** and **6**. In the final step, the isoxazole moiety in compounds **7c**−**7n**, **7p**, **7r**, and **8** was introduced via dipolar cycloaddition of the nitrile oxide derived from ethyl 2-chloro-2-(hydroxyimino)acetate with the acetylene intermediates. Alternatively, the final compounds can be synthesized by alkylating the 4-hydroxyquinolines with 5-(bromomethyl)isoxazole-3-carboxylic acid ethyl ester,[14] as was done for compounds **7a**, **7b**, **7o**, and **7q**.

A similar synthetic route was used for compound **10**, bearing an oxyethylene linker, except the acteylenic intermediate **9** was synthesized via Mitsunobu coupling of 2,8-bis(trifluoromethyl)-4-quinolinol (**4s**) and 3-butyn-1-ol (Scheme 1). Compound **13**, with an aryl ether linker, was synthesized starting from 4-chloro-2-(trifluoromethyl)quinoline (**11**) (Scheme 2). The addition of 3-hydroxyphenylacetylene yielded the intermediate **12**, which in turn gave the final compound **13** in the cycloaddition reaction with the nitrile oxide generated from ethyl 2-chloro-2-(hydroxyimino)acetate.

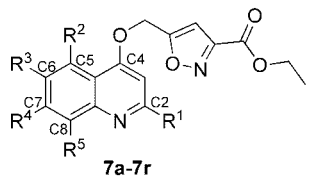
Finally, the effect of the isoxazole moiety was studied. The oxymethylene linker moiety, as well as the original quinoline core 2,8-bis(trifluoromethyl) substitution, were kept constant, allowing detailed derivation of structure–activity relationships (SARs) based on the variations in the anti-TB activity. The corresponding isoxazoline derivative **15** was synthesized from **4s** by employing the same methodology as for the isoxazole derivatives (Scheme 3). The reverse 3,5-substituted isoxazole regioisomer **19** was synthesized by alkylating **4s** with 3-(chloromethyl)isoxazole-5-carboxylic acid ethyl ester (**18**), which in turn was synthesized in two steps starting from chloroacetaldehyde (**16**) (Scheme 4).

The thiazole-2-carboxylic acid ethyl ester derivative **22** was synthesized via 4-(chloromethyl)-2-thiazolecarboxylic acid ethyl ester[15] (**21**), which was obtained from ethyl thiooxamate (**20**) in a cyclization reaction with 1,3-dichloroacetone (Scheme 5). Diethyl 2,6-pyridinedicarboxylate (**23**) was reduced with $NaBH_4$ to 6-(hydroxymethyl)-2-pyridinecarboxylic acid ethyl ester (**24**),[16] which was coupled with **4s** to give the pyridine derivative **25** (Scheme 6). The remaining isoxazole modified compounds (**26**−**35**) were synthesized in good yields by the above established Williamson ether synthesis protocol with **4s** and commercially available alkylhalides (Scheme 7, Table 2) followed by standard functional group interconversions.

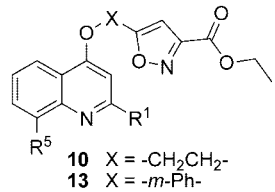
Results and Discussion

All the final compounds were first evaluated for their activity against the *Mtb* strain $H_{37}Rv$ in a microplate Alamar Blue assay (MABA).[17] The compounds showing good anti-TB activity in MABA were further evaluated for their potency against NRP-TB in a low oxygen recovery assay (LORA).[18]

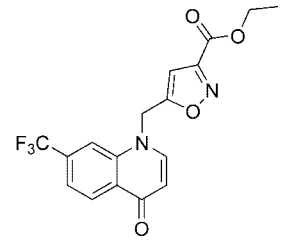
Table 1. Effect of Quinoline Core Substitution and the Linker Moiety on the Anti-TB Activity



7a-7r



10 X = -CH_2CH_2-
13 X = -*m*-Ph-

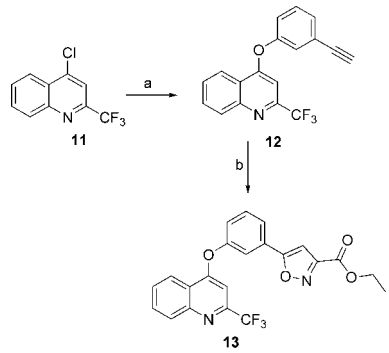


8

compd	R^1	R^2	R^3	R^4	R^5	MABA[a] MIC (μM)	LORA[a] MIC (μM)	Vero cells IC_{50} (μM)
7a	−H	−H	−H	−H	−H	25.1	13.2	>128
7b	−H	−H	−H	−H	$-CF_3$	10.6	56.6	>128
7c	$-CF_3$	−H	−H	−H	−H	3.2	25.1	>128
7d	$-CF_3$	−H	$-CF_3$	−H	−H	3.7	7.6	>128
7e	$-CF_3$	−H	−H	$-CF_3$	−H	1.3	nd[b]	>128
7f	$-CF_3$	$-CF_3$	−H	−H	−H	3.8	nd	>128
7g	$-CF_3$	$-CF_3$	−H	$-CF_3$	−H	0.77	10.0	>128
7h	$-CF_3$	−H	−H	−H	$-CH_3$	1.8	10.4	>128
7i	$-CF_3$	−H	−H	−H	$-OCF_3$	2.6	7.0	>128
7j	$-CF_3$	−H	−H	−H	−Cl	62.9	49.3	nd
7k	$-CF_3$	−H	−H	−H	−F	11.3	39.0	>128
7l	$-CF_3$	−Cl	−H	−Cl	−H	1.9	3.7	>128
7m	$-CF_3$	−F	−H	−H	−F	41.2	52.8	nd
7n	$-CF_3$	−H	−F	−H	−F	14.6	nd	nd
7o	$-CF_3$	−H	$-OCH_3$	−H	$-CF_3$	66.1	nd	>128
7p	$-CO_2Et$	−H	−H	−H	−H	7.9	15.7	>128
7q	−H	−H	−H	−Cl	−H	3.8	99.7	>128
7r	−H	−H	−H	$-CF_3$	−H	3.3	81.9	nd
8	−H	−H	−H	$-CF_3$	−H	>128	nd	nd
10	$-CF_3$	−H	−H	−H	$-CF_3$	3.4	9.9	>128
13	$-CF_3$	−H	−H	−H	−H	0.95	3.7	>128
3	$-CF_3$	−H	−H	−H	$-CF_3$	0.9−1.9	12.2	>128
RMP						0.1	1.9	127
INH						0.5	>128	>128

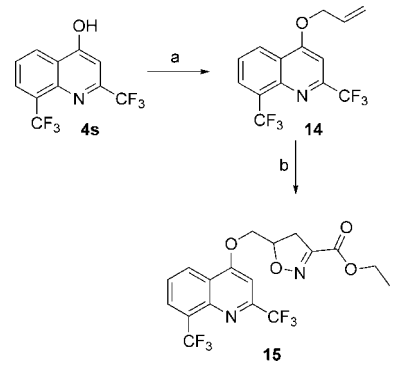
[a] *Mtb* $H_{37}Rv$. [b] nd: not determined.

Scheme 2[a]



[a] Reagents and conditions: (a) 3-hydroxyphenylacetylene, *t*-BuOK, THF, reflux; (b) ethyl 2-chloro-2-(hydroxyimino)acetate, Et_3N, THF.

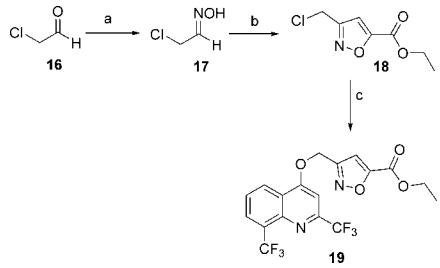
Scheme 3[a]



[a] Reagents and conditions: (a) CH_2═$CHCH_2Br$, K_2CO_3, KI, acetone, reflux; (b) ethyl 2-chloro-2-(hydroxyimino)acetate, Et_3N, ether.

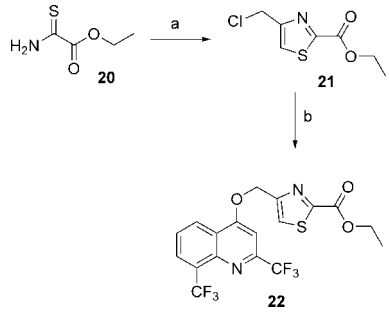
Several compounds were found to effectively inhibit the growth of replicating *Mtb* in MABA with low μM MICs (Table 1). The substitution pattern of the quinoline core was shown to significantly affect the potency and plausible SARs could be derived. In the first round of structural modifications, the trifluoromethyl groups were moved around the quinoline ring in order to obtain the optimal substitution pattern (**7b**−**7f**). The methylene ether linker was kept at the C4 position in all modifications. Removal of the trifluoromethyl substituents (compound **7a**) reduced the activity by 20-fold as compared to the lead **3**. The C2-CF_3 substituent seemed to contribute more to the anti-TB activity than the C8-CF_3 group (**7c** vs **7b**), although C7 monosubstituted compounds **7q** (MIC 3.8 μM) and **7r** (MIC 3.3 μM) also exhibited good activity. Comparable activity to that of **3** was obtained with C2, C7-disubstitution, **7e** having an MIC of 1.3 μM. C2,C5-disubstitution (**7f**, MIC 3.8 μM) also yielded good anti-TB activity. Introduction of different substituents at C8 was tolerated (**7h**−**7k**), trifluoromethyl and methyl groups yielding the best activity ($-CF_3 \geq -CH_3 > -OCF_3 > -F \gg -Cl$). The C2-$CF_3$ substituent could also be replaced with an ethyl ester, **7p** (MIC 7.9 μM) being slightly less active than **7c** (MIC 3.2 μM). Next, various trisubstitution patterns were explored and quinoline core C2,C5,C7-trisubstitution, as with compounds **7g** and **7l**, seemed to be preferred. In particular, 5-[[[2,5,7-tris(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic acid ethyl ester (**7g**) was the most potent anti-TB agent in the series, with an

Scheme 4[a]



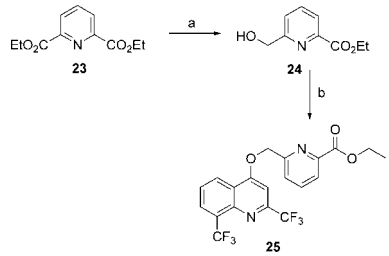
[a] Reagents and conditions: (a) $NH_2OH \cdot HCl$, NaOAc, H_2O, 1 h; (b) 10−15% NaOCl (aq), $CH{\equiv}CCO_2Et$, THF, overnight; (c) **4s**, K_2CO_3, KI, acetone, reflux.

Scheme 5[a]



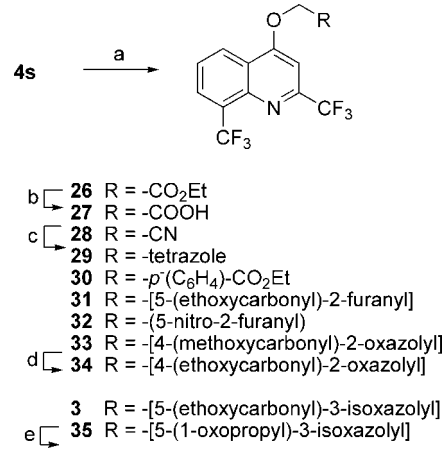
[a] Reagents and conditions: (a) 1,3-dichloroacetone, toluene, reflux; (b) **4s**, K_2CO_3, KI, acetone, reflux.

Scheme 6[a]



[a] Reagents and conditions: (a) $NaBH_4$, EtOH, 50 °C; (b) **4s**, DEAD, PPh_3, THF.

Scheme 7[a,b]



[a] Reagents and conditions: (a) $BrCH_2R$ or $ClCH_2R$, K_2CO_3, KI, acetone, reflux, 1−12 h; (b) LiOH, THF-MeOH-H_2O (8:1:1), 0 °C to rt; (c) NaN_3, NH_4Cl, DMF, 100 °C, 2 h; (d) KOH, abs. EtOH, reflux, overnight; (e) EtMgBr, ether, 0 °C to rt, 15 min. [b] For structures, see Table 2.

excellent MIC of 0.77 μM. Other trisubstitution patterns, namely C2, C5, and C8 (**7m**) or C2, C6, and C8 (**7n** and **7o**), were not as well tolerated and led to decreased activity.

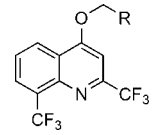
Elongation of the linker moiety at C4 by one methylene group decreased activity (**10**, MIC 3.4 μM) compared to **3**, whereas a more rigid arylether linker yielded excellent activity against the bacteria (**13**, MIC 0.95 μM). Introduction of the isoxazole side chain to the ring nitrogen, to give the quinol-4-one derivative **8**, led to a loss of the anti-TB activity. The isoxazole moiety proved to be essential for good anti-TB activity. All the attempts to modify this ring structure (**15**, **19**, **22**, **25**−**34**) led to reduced or a complete loss of potency (Table 2). Even subtle changes, i.e., other nitrogen and oxygen containing heterocycles, were not well tolerated, for example, regioisomer **19** being 3-fold and isoxazoline **15** being 20-fold less active. Comparison of the lead **3** with **19** (MIC 3.6 μM), with the thiazole **22** (MIC 16.5 μM), and the oxazole **34** (MIC > 128 μM) derivatives, suggests that the correct positioning of the nitrogen in the side chain ring may play a role in the activity. Compounds **26**−**28**, which lack a heterocycle on the side chain, as well as the methyl ester **33** did not show notable activity against *Mtb*. The importance of the ester moiety was again proven with compound **35**, in which the replacement of the ethyl ester with an ethyl ketone reduced the activity over 20-fold as compared to the lead compound.

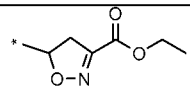
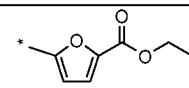
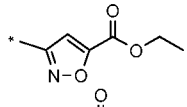
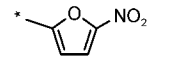
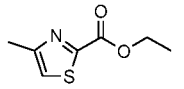
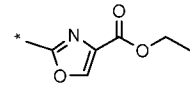
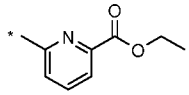
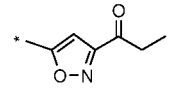
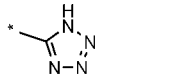
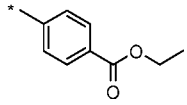
The compounds showing good anti-TB activity in MABA were also tested for potency against NRP-TB in LORA, which is a new luminescence-based high-throughput assay developed for evaluation of activity against the nonreplicating persistent phenotype in low oxygen conditions.[18] Significantly, although being somewhat weaker, these compounds seemed to retain their activity in LORA relatively well (Table 1). Compounds **7g** and **13** were active also against NRP-TB, with a LORA MIC of 10.0 and 3.7 μM, respectively, and also four other compounds (**7d**, **7i**, **7l**, and **10**) exhibited MICs of <10 μM. The SARs against NRP-TB seemed to be, to some extent, different compared to the SARs obtained against R-TB. In LORA, the dichloro derivative **7l** (LORA MIC 3.7 μM) exhibited better activity than **7g**. Trifluoromethyl substitution at C6 was favored, and compound **7d** (LORA MIC 7.6 μM) was only 2-fold less active in LORA. Surprisingly, monosubstitution at C7, which yielded good activity in MABA, was not tolerated and **7q** and **7r** were 25-fold less potent in LORA.

Vero cells were used for an in vitro cytotoxicity evaluation for the compounds exhibiting anti-TB activity. In general, these compounds did not show cytotoxicity (IC_{50} > 128 μM), confirming that the anti-TB activity does not arise from general toxicity of the compound class. The only compounds showing toxic effects were **35** and the furan derivatives **31** and **32**; however, these compounds did not show good potency and diverged structurally from the most active compounds. As for **32** (MIC 6.3 μM), 2-nitrofurans have been previously reported to have anti-TB activity,[19] but on the other hand, certain 2-nitrofurans are also known to demonstrate cytotoxicity.[20] Finally, the two most active compounds in the series, **13** and **7g**, were evaluated against three selected SDR-TB strains (Table 3). The compounds retained their activity against RMP, INH, and SM resistant strains, suggesting a different mode of action and indicating that this compound class also holds promise as lead compounds for treatment of drug resistant TB.

The SARs obtained from the series suggests a specific molecular target for these quinoline−isoxazole hybrid compounds. The quinoline-based anti-TB agent **1** has been shown to target the c subunit of ATP synthase,[21] and similarly it has been suggested that the target of mefloquine (**2**) in *Streptococcus pneumoniae* is an F_0F_1 bifunctional ATP synthase/ATPase.[22]

Table 2. Effect of the Side Chain Heterocycle on Anti-TB Activity[d]



	R[d]	MABA MIC (μM)	Vero cells IC_{50} (μM)		R	MABA MIC (μM)	Vero cells IC_{50} (μM)
15		22.2	> 128	**31**		> 128	118.5
19[b]		3.6	> 128	**32**		6.3	15.4
22		16.5	> 128	**34**		>128	nd
25		> 128	nd[c]	**35**		27.4	64.9
29		> 128	nd	**3**		0.9–1.9	> 128
30		> 128	> 128	RMP		0.1	127
				INH		0.5	> 128

[a] *Mtb* $H_{37}Rv$. [b] Contains 6−8% of the corresponding 3,4-regioisomer (3-[[[2,8-bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-4-isoxazolecarboxylic acid ethyl ester), which could not be separated by preparative HPLC. [c] Not determined. [d] * indicates the point of attachment.

However, since it was shown that the activity in this series depends heavily on the isoxazole moiety, it is debatable if these compounds could share the same target in *Mtb*. 3-Isoxazolecarboxylic acids are known to inhibit virulence factor *Mtb* protein tyrosine phosphatase (MptpB),[23] which is suggested to dephosphorylate human proteins involved in the interferon-γ signaling pathway[24] and thus preventing the initiation of defense mechanisms in host macrophages. Assuming that the 3-isoxazolecarboxylic acid ethyl ester is a prodrug for the corresponding acid, our compounds could be potential ligands for MptpB. On the other hand, it has been shown that MptpB is not essential for the survival and growth of the mycobacteria in vitro, ruling out MptpB as the primary target of our compounds.[24]

Conclusions

We have identified a class of quinoline−isoxazole hybrid compounds with good anti-TB activity against both the replicating and nonreplicating persistent forms of *Mtb*. Several compounds showed low micromolar MICs against R-TB in MABA. The most potent compounds in the series, **7g** and **13**, exhibited submicromolar activity, with MABA MICs of 0.77 and 0.95 μM, respectively. Compounds **7d**, **7g**,−**7i**, **7l**, **10**, and **13** also had good activity against NRP-TB (MICs $\leq$ 10 μM). Plausible SARs could be derived from the substitution pattern of the quinoline core, suggesting that C2,C8- or C2,C7-disubstitution and C2,C5,C7-trisubstition are preferred. Trifluomethyl substituents yielded the best activity against the bacteria, but also other groups were tolerated. The isoxazole moiety played a significant role in the activity, indicating that these compounds are likely to have a specific *Mtb* target. Replacement of the oxymethylene linker at the C4 position of the lead **3**, with a more rigid aryl ether linker, was successful and as such opens the possibility for more structural variations in this compound class. Notably, the two most potent compounds, **7g** and **13**, had similar activity against the RMP, INH, and SM resistant *Mtb* strains. In general, these compounds did not show toxicity on Vero cells at 128 μM concentration and therefore have excellent selectivity toward the bacteria. These results suggest quinoline−isoxazole based compounds to be promising lead structures for TB drug development, especially due to the notable activity against the NRP-TB phenotype, as well as against drug resistant *Mtb* strains. Clarifications of the metabolic pathways, in vivo efficacy studies, and target identification are currently under way in our laboratories.

Table 3. In Vitro Anti-TB Activity against Selected SDR Strains of *Mtb*

	MIC (μM)			
	$H_{37}Rv$	r-RMP[a]	r-INH[b]	r-SM[c]
7g	0.77	0.99	0.98	1.55
13	0.95	1.27	1.63	1.40
RMP	0.1	>32	0.06	0.05
INH	0.5	0.43	>128	0.45
SM	0.3	0.20	0.38	>32

[a] RMP resistant strain. [b] INH resistant strain. [c] SM resistant strain.

Experimental Section

Biology. The MICs were determined using *Mtb* $H_{37}Rv$ ATCC 27294 in MABA[17] and LORA[18] assays according to published procedures.

MABA. Briefly, the test compound MICs against R-TB were assessed by the MABA using RMP, INH, and **3** as positive controls. Compound stock solutions were prepared in DMSO at a concentration of 12.8 mM, and the final test concentrations ranged from 128 to 0.5 μM. Two-fold dilutions of compounds were prepared in Middlebrook 7H12 medium (7H9 broth containing 0.1% w/v casitone, 5.6 μg/mL palmitic acid, 5 mg/mL bovine serum albumin, 4 mg/mL catalase, filter-sterilized) in a volume of 100 μL in 96-well microplates (black viewplates). *Mtb* H_{37}RV (100 μL inoculum of 2×10^5 cfu/mL) was added, yielding a final testing volume of 200 μL. The plates were incubated at 37 °C. On the 7th day of incubation 12.5 μL of 20% Tween 80 and 20 μL of Alamar Blue (Trek Diagnostic, Westlake, OH) were added to the test plate. After incubation at 37 °C for 16−24 h, fluorescence of the wells was measured (ex 530, em 590 nm). The MICs ware defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacteria-only controls. Reported MICs are an average of two individual measurements.

LORA. Briefly, a low-oxygen adapted culture of recombinant H_{37}Rv (pFCA-luxAB), expressing a *Vibrio harveyii* luciferase gene with an acetamidase promoter, was grown in a BiostatQ fermentor. Cells were collected, washed in PBS, and stored at −80 °C. Then ca. 10^5 cfu/mL of thawed NRP cells were exposed to 2-fold serial dilutions of test compound in 7H12 medium in white 96-well plates, which were incubated 10 days anaerobically at 37 °C. Luminescence readings were obtained following a 28 h recovery in an aerobic environment (5% CO_2). The data were analyzed graphically, and the lowest concentration of test compound preventing metabolic recovery (90% reduction relative to untreated cultures) was determined as described previously.

Cytotoxicity Assay. Cytotoxicity was determined by exposing different concentrations of samples to Vero cells. Samples were dissolved at 12.8 mM in DMSO. Geometric 3-fold dilutions were performed in growth medium MEM (Gibco, Grand Island, NY) containing 10% fetal bovine serum (HyClone, Logan, UT), 25 mM *N*-(2-hydroxyethyl)-piperazine-*N*′-2-ethanesulfonic acid (HEPES, Gibco), 0.2% $NaHCO_3$ (Gibco), and 2 mM glutamine (Irvine Scientific, Santa Ana, CA). Final DMSO concentrations did not exceed 1% v/v. Drug dilutions were distributed in duplicate in 96-well tissue culture plates (Becton Dickinson Labware, Lincoln Park, NJ) at a volume of 50 μL per well. An equal volume containing either 5×10^5 log phase Vero cells (CCL-81; American Type Culture Collection, Rockville, MD) was added to each well and the cultures were incubated at 37 °C in an atmosphere containing 5% of CO_2. After 72 h, cell viability was measured using the CellTiter 96 aqueous nonradioactive cell proliferation assay (Promega Corp., Madison, WI) according to the manufacturer's instructions. Absorbance at 490 nm was read in a Victor^2 multilabel reader (PerkinElmer). The IC_{50}s were determined using a curve-fitting program.

Chemistry. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometer at 400 and 100 MHz or 300 and 75 MHz, respectively, with TMS as an internal standard. ^{19}F NMR spectra were recorded on Bruker spectrometer at 376 MHz with TFA as an external standard. HRMS experiments were performed on Q-TOF-2TM (Micromass). TLC was performed with Merck 60 F_{254} silica gel plates. Column chromatography was performed using CombiFlash Rf system with RediSep columns or alternatively using Merck silica gel (40−60 mesh). The purity of the target compounds was determined to be >95% by analytical HPLC.

General Procedures for the Synthesis of Compounds 7a−7r, 8, 10, and 13−14. Method A. Ethyl 2-chloro-2-(hydroxyimino)acetate (0.27 g, 1.8 mmol) and the acetylene intermediate **5c** (0.15 g, 0.6 mmol) were dissolved into anhydrous Et_2O (20 mL). Et_3N (0.25 mL, 1.8 mmol) in anhydrous Et_2O (10 mL) was added to the solution of **5c** via syringe pump over 6 h period and stirred overnight at room temperature. The reaction mixture was filtered, washed with Et_2O (2×15 mL), and the filtrate was evaporated in vacuo. The crude product was purified by flash chromatography using gradient elution from hexane to 50% EtOAc-hexane to give compound **7c** as a white powder in 73% yield.

Method B. 2,8-Bis(trifluoromethyl)-6-methoxy-4-quinolinol **4o** (0.03 g, 0.1 mmol) and anhydrous K_2CO_3 (1 g, 7.4 mmol) in anhydrous acetone (15 mL) were refluxed for 0.5 h. Ethyl 5-(bromomethyl)-3-isoxazolecarboxylate[14] (0.045 g, 0.2 mmol) was added slowly and the reaction mixture was refluxed overnight. After cooling to room temperature, the mixture was filtered and the filtrate was evaporated and dried in vacuo. The crude product was purified by column chromatography (EtOAc-hexane 1:4) to obtain **7o** as a white solid in 95% yield.

5-[[(4-Quinolinyl)oxy]methyl]isoxazole-3-carboxylic Acid Ethyl Ester (7a). Synthesized by method B using 4-hydroxyquinoline as a starting material. Yield 54% (white solid). ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, $J = 7.2$ Hz), 4.48 (2H, q, $J = 7.2$ Hz), 5.49 (2H, s), 6.88 (1H, d, $J = 8.0$ Hz), 6.91 (1H, s), 7.54 (1H, t, $J = 7.2$ Hz), 7.73 (1H, t, $J = 8.0$ Hz), 8.06 (1H, d, $J = 7.2$ Hz), 8.24 (1H, d, $J = 7.2$ Hz), 8.79 (1H, d, $J = 8.0$ Hz). HRMS (ESI) calculated for $C_{16}H_{14}N_2O_4$ $[M + H]^+$ 299.1032, found 299.1020.

5-[[[8-(Trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7b). Synthesized by method B using 8-(trifluoromethyl)-4-quinolinol as a starting material. Yield 56% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, $J = 7.2$ Hz), 4.46 (2H, q, $J = 7.2$ Hz), 5.52 (2H, s), 6.92 (1H, d, $J = 6.0$ Hz), 7.59 (1H, t, $J = 9.0$ Hz), 8.15 (1H, d, $J = 9.0$ Hz), 8.47 (1H, d, $J = 9.0$ Hz), 8.90 (1H, d, $J = 6.0$ Hz,). HRMS (ESI) calculated for $C_{17}H_{13}F_3N_2O_4$ $[M + H]^+$ 367.0906, found 367.0889.

5-[[[2-(Trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7c). Synthesized by method A by using **5c** as a starting material. Yield 63% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.51 (2H, s), 6.92 (1H, s), 7.13 (1H, s), 7.66 (1H, apparent t, $J = 7.8$ Hz), 7.84 (1H, apparent t, $J = 7.6$ Hz), 8.19 (1H, d, $J = 8.5$), 8.25 (1H, d, $J = 8.3$). HRMS (ESI) calculated for $C_{17}H_{13}F_3N_2O_4$ $[M + H]^+$ 367.0900, found 367.0904.

5-[[[2,6-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7d). Synthesized by method A by using **5d** as a starting material. Yield 70% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.56 (1H, s), 6.94 (1H, s), 7.24 (1H, s), 8.01 (1H, dd, $J = 1.3$ Hz $J = 8.8$ Hz), 8.30 (1H, d, $J = 8.8$ Hz), 8.54 (1H, s). HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_4$ $[M + H]^+$ 435.0774, found 435.0782.

5-[[[2,7-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7e). Synthesized by method A from compound **5e**/**5f** (mixture of regioisomers). The crude product was first purified by column chromatography to give **7e**/**7f** as an approximately 1:2 mixture of C5-CF_3 and C7-CF_3 regioisomers (yield 67%). The isomers were separated by preparative HPLC to give **7e** and **7f** as white powders. For **7e**: ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.49 (2H, q, $J = 7.1$ Hz), 5.55 (1H, s), 6.94 (1H, s), 7.25 (1H, s), 7.83 (1H, d, $J = 8.7$ Hz), 8.38 (1H, d, $J = 8.7$ Hz), 8.5 (1H, s). HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_4$ $[M + H]^+$ 435.0774, found 435.0771.

5-[[[2,5-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7f). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.54 (1H, s), 6.93 (1H, s), 7.30 (1H, s), 7.86 (1H, apparent t, $J = 8.0$ Hz), 8.14 (1H, d, $J = 7.4$ Hz), 8.39 (1H, d, $J = 8.5$ Hz). HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_4$ $[M + H]^+$ 435.0774, found 435.0787.

5-[[[2,5,7-Tris(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7g). Synthesized by method A by using **5g** as a starting material. Yield 42% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.57 (2H, s), 6.94 (1H, s), 7.41 (1H, s), 7.66 (1H, d, $J = 2.1$ Hz), 8.28 (1H, d, $J = 2.1$ Hz), 8.71 (1H, d, $J = 2.1$ Hz). HRMS (ESI) calculated for $C_{19}H_{11}F_9N_2O_4$ $[M + H]^+$ 503.0648, found 503.0662.

5-[[[8-Methyl-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7h). Synthesized by method A by using **5h** as a starting material. Yield 61% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 2.81 (3H, s) 4.47 (2H, q, $J = 7.1$ Hz), 5.48 (1H, s), 6.90 (1H, s), 7.11 (1H,

s), 7.53 (1H, apparent t, $J = 8.0$ Hz), 7.66 (1H, d, $J = 7.0$ Hz), 8.08 (1H, d, $J = 8.3$ Hz). HRMS (ESI) calculated for $C_{18}H_{15}F_3N_2O_4$ $[M + H]^+$ 381.1057, found 381.1061.

5-[[[8-(Trifluoromethoxy)-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7i). Synthesized by method A by using **5i** as a starting material. Yield 67% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.53 (1H, s), 6.93 (1H, s), 7.21 (1H, s), 7.34 (1H, m), 7.73 (1H, m), 8.19 (1H, dd, $J = 1.0$ Hz, $J = 1.0$ Hz). HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_5$ $[M + H]^+$ 451.0723, found 451.0728.

5-[[[8-Chloro-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7j). Synthesized by method A by using **5j** as a starting material. Yield 39% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.52 (1H, s), 6.92 (1H, s), 7.19 (1H, s), 7.56 (1H, apparent t, $J = 8.0$ Hz), 7.94 (1H, dd, $J = 1.0$ Hz, $J = 7.5$ Hz), 8.17 (1H, dd, $J = 1.0$ Hz, $J = 8.5$ Hz). HRMS (ESI) calculated for $C_{17}H_{12}ClF_3N_2O_4$ $[M + H]^+$ 401.0511, found 401.0513.

5-[[[8-Fluoro-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7k). Synthesized by method A by using **5k** as a starting material. Yield 65% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.53 (1H, s), 6.93 (1H, s), 7.20 (1H, s), 7.56 (2H, m), 8.03 (1H, m). HRMS (ESI) calculated for $C_{17}H_{12}F_4N_2O_4$ $[M + H]^+$ 385.0806, found 385.0792.

5-[[[5,7-Dichloro-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7l). Synthesized by method A by using **5l** as a starting material. Yield 48% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.48 (2H, s), 6.95 (1H, s), 7.15 (1H, s), 7.66 (1H, d, $J = 2.1$ Hz), 7.66 (1H, d, $J = 2.1$ Hz), 8.10 (1H, d, $J = 2.1$ Hz). HRMS (ESI) calculated for $C_{17}H_{11}Cl_2F_3N_2O_4$ $[M + H]^+$ 435.0121, found 435.0128.

5-[[[5,8-Difluoro-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7m). Synthesized by method A by using **5m** as a starting material. Yield 50% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 5.51 (2H, s), 6.95 (1H, s), 7.22 (1H, s), 7.26 (1H, m) 7.47 (1H, dt, $J = 9.0$ Hz, $J = 4.0$ Hz). HRMS (ESI) calculated for $C_{17}H_{11}Cl_2F_5N_2O_4$ $[M + H]^+$ 403.0712, found 403.0695.

5-[[[6,8-Difluoro-2-(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7n). Synthesized by method A by using **5n** as a starting material. Yield 51% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.49 (2H, q, $J = 7.1$ Hz), 5.52 (2H, s), 6.92 (1H, s), 7.22 (1H, s), 7.36 (1H, m) 7.65 (1H, m). HRMS (ESI) calculated for $C_{17}H_{11}Cl_2F_5N_2O_4$ $[M + H]^+$ 403.0712, found 403.0712.

5-[[[2,8-Bis(trifluoromethyl)-6-methoxy-4-quinolinyl]oxy]methyl]isoxazole-3-carboxylic Acid Ethyl Ester (7o). Synthesized by method B by using **4o** as a starting material. Yield 95% (white solid). ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, $J = 7.2$ Hz), 4.00 (3H, s), 4.48 (2H, q, $J = 7.2$ Hz), 7.84 (s, 1H), 7.60 (s, 1H), 7.20 (s, 1H), 6.92 (s, 1H), 5.53 (s, 2H). HRMS (ESI) calculated for $C_{19}H_{14}F_6N_2O_5$ $[M + H]^+$ 465.0885, found 465.0864.

4-[[5-(Ethoxycarbonyl)-2-isoxazole]methoxy]-2-quinolinecarboxylic Acid Ethyl Ester (7p). Synthesized by method A by using **5p** as a starting material. Yield 52% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 1.52 (3H, t, $J = 7.2$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 4.57 (2H, q, $J = 7.2$ Hz), 5.53 (2H, s), 6.91 (1H, s), 7.63 (2H, m), 7.80 (1H, m), 8.25 (2H, m). HRMS (ESI) calculated for $C_{19}H_{18}N_2O_6$ $[M + H]^+$ 371.1238, found 371.1225.

5-[[(7-Chloro-4-quinolinyl)oxy]methyl]isoxazole-3-carboxylic Acid Ethyl Ester (7q). Synthesized by method B using 7-chloro-4-quinolol as a starting material. Yield: 54% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, $J = 7.2$ Hz), 4.48 (2H, q, $J = 7.2$ Hz), 5.46 (2H, s), 6.82 (1H, d, $J = 4.8$ Hz), 6.89 (s, 1H), 7.51 (1H, d, $J = 6.4$ Hz), 8.08 (1H, s), 8.16 (1H, d, $J = 6.4$ Hz,), 8.80 (1H, d, $J = 4.8$ Hz). HRMS (ESI) calculated for $C_{16}H_{13}ClN_2O_4$ $[M + H]^+$ 333.0642; found 333.0626.

5-[[[7-(Trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (7r). Synthesized by method A by using **5r** as a starting material. Yield 56% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.47 (2H, q, $J = 7.1$ Hz), 5.48 (2H, s), 6.89 (1H, s), 6.92 (1H, d, $J = 5.2$ Hz), 7.72 (1H, dd, $J = 1.2$ Hz, $J = 8.7$ Hz), 8.33 (1H, d, $J = 8.7$ Hz), 8.37 (1H, s), 8.88 (1H, d, $J = 5.2$ Hz). HRMS (ESI) calculated for $C_{17}H_{13}F_3N_2O_4$ $[M + H]^+$ 367.0900, found 367.0900.

5-[[4-*oxo*-7-(Trifluoromethyl)-1(4*H*)-quinolinyl]methyl]-3-isoxazolecarboxylic Acid Ethyl Ester (8). Synthesized by following the method A by using **6** as a starting material. The product was purified by preparative HPLC to give **8a** as a white powder in 55% yield. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, $J = 7.1$ Hz), 4.33 (2H, q, $J = 7.1$ Hz), 5.93 (2H, s), 6.27 (1H, d, $J = 7.9$ Hz), 6.94 (1H, s), 7.71 (1H, d, $J = 8.3$ Hz), 8.16 (1H, s), 8.26 (1H, d, $J = 7.9$ Hz), 8.37 (1H, d, $J = 8.4$ Hz). HRMS (ESI) calculated for $C_{17}H_{13}F_3N_2O_4$ $[M + H]^+$ 367.0900, found 367.0897.

5-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]ethyl]-3-isoxazolecarboxylic Acid Ethyl Ester (10). Synthesized by method A by using **9** as a starting material. Yield 49% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, $J = 7.1$ Hz), 3.54 (3H, t, $J = 6.0$ Hz), 4.44 (2H, q, $J = 7.1$ Hz), 4.62 (2H, t, $J = 6.0$ Hz), 6.65 (1H, s), 7.13 (1H, s), 7.67 (1H, apparent t, $J = 7.9$ Hz), 8.15 (1H, d, $J = 7.1$ Hz), 8.37 (1H, d, $J = 8.3$ Hz). HRMS (ESI) calculated for $C_{19}H_{14}F_6N_2O_4$ $[M + H]^+$ 449.0931, found 449.0944.

5-[3-[[2-(Trifluoromethyl)-4-quinolinyl]oxy]phenyl]-3-isoxazolecarboxylic Acid Ethyl Ester (13). Synthesized by method A by using **12** as a starting material. Yield 45% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, t, $J = 7.1$ Hz), 4.48 (2H, q, $J = 7.1$ Hz), 6.88 (1H, s), 7.00 (1H, s), 7.34 (1H, dd, $J = 1.5$ Hz, $J = 8.2$ Hz), 7.64−7.75 (3H, m), 7.81 (1H, d, $J = 7.8$ Hz), 7.89 (1H, m), 8.24 (1H, d, $J = 8.5$ Hz), 8.43 (1H, d, $J = 8.4$ Hz). HRMS (ESI) calculated for $C_{22}H_{15}F_3N_2O_4$ $[M + H]^+$ 429.1057, found 429.1046.

5-[3-[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]phenyl]-4,5-dihydro-3-isoxazolecarboxylic Acid Ethyl Ester (15). Synthesized by method A by using **14** as a starting material. Yield 52% (white solid). ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, d, $J = 8.0$ Hz), 8.15 (1H, d, $J = 7.2$ Hz), 7.67 (1H, t, $J = 7.6$ Hz), 7.14 (1H, s), 5.36 (1H, s), 4.42 (4H, m), 3.52 (1H, dd, $J = 11.0$, $J = 17.6$ Hz), 3.37 (1H, dd, $J = 7.7$, $J = 17.6$ Hz,), 1.42 (3H, t, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 29.3, 46.8, 69.4, 80.3, 97.7 (q, $J = 2$ Hz), 122.3 (q, $J = 274$ Hz), 125.1, 126.5 (q, $J = 274$ Hz), 127.6, 128.2 (q, $J = 35$ Hz), 129.5 (q, $J = 6$ Hz), 132.4, 144.6, 151.5 (q, $J = 35$ Hz), 158.8, 160.3, 162.2. HRMS (ESI) calculated for $C_{18}H_{14}F_6N_2O_4$ $[M + H]^+$ 437.0936, found 437.0903.

2,5-Bis(trifluoromethyl)-4-(3-butyn-1-yloxy)quinoline (9). A solution of 2,8-bis(trifluoromethyl)-4-quinolinol **4s** (0.4 g, 1.4 mmol), butyn-1-ol (0.22 mL, 0.2 g, 2.8 mmol), and PPh_3 (0.7 g, 2.8 mmol) in anhydrous THF (15 mL) was cooled to 0 °C. DEAD (0.45 mL, 0.5 g, 2.8 mmol) was added dropwise and the solution was stirred for 30 min at room temperature. The solvent was evaporated and the resulting crude material was purified by flash chromatography using gradient elution from hexane to 50% hexane-EtOAc to give compound **9**. Yield 97% (pale-yellow powder). ^{1}H NMR ($CDCl_3$) δ 2.10 (1H, t, $J = 2.6$ Hz), 2.90 (2H, m), 4.41 (2H, t, $J = 6.6$ Hz), 7.12 (1H, s), 7.66 (1H, apparent t, $J = 7.6$ Hz), 8.14 (1H, d, $J = 7.1$ Hz), 8.49 (1H, d, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 19.5, 67.2, 71.0, 79.4, 97.8 (q, $J = 2$ Hz), 121.3 (q, $J = 276$ Hz), 122.4, 123.8 (q, $J = 274$ Hz), 126.4, 126.6, 128.5 (q, $J = 30$ Hz), 129.6 (q, $J = 5$ Hz), 144.8, 149.8 (q, $J = 35$ Hz), 162.8. MS-ESI $[M + H]^+$ 334.

4-(3-Ethynylphenoxy)-2-(trifluoromethyl)quinoline (12). To a solution of 3-hydroxyphenylacetylene (0.32 g, 2.7 mmol) in anhydrous THF (4 mL), 2.7 mL of 1 M *t*-BuOK (0.31 g, 2.7 mmol) in THF and 4-chloro-2-(trifluoromethyl)quinoline (0.6 g, 2.6 mmol) in anhydrous THF (5 mL) were added dropwise, respectively. The reaction mixture was heated to reflux for 48 h. After cooling to room temperature, cold H_2O (50 mL) was added and the solution was made acidic (pH ~ 4) with 5% HCl, followed by extraction with EtOAc (3 × 25 mL). The combined organic phases were washed with brine (20 mL) and dried with Na_2SO_4. After filtration,

the solvent was evaporated and the crude product was purified by flash chromatography using gradient elution from hexane to 8% EtOAc-hexane. Yield 37% (white powder). ^{1}H NMR ($CDCl_3$) δ 3.17 (1H, s), 6.84 (1H, s), 7.22 (1H, m), 7.35 (1H, m), 7.48 (2H, m), 7.71 (1H, m), 7.87 (1H, m), 8.22 (1H, d, J = 8.4 Hz), 8.40 (1H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 78.9, 82.2, 100.2 (q, J = 2 Hz), 121.3 (q, J = 276 Hz), 121.70, 121.75, 121.8, 124.6, 124.8, 128.2, 129.9, 129.9, 130.1, 130.6, 131.5, 148.8, 148.9 (q, J = 35 Hz), 153.6, 163.0.

Typical Procedure for the Synthesis of Compounds 19, 22, 26, 28, 30−33. 2,8-Bis(trifluoromethyl)-4-quinolinol **4s** (0.2 g, 0.7 mmol) and anhydrous K_2CO_3 (0.6 g, 4 mmol) were refluxed in anhydrous acetone (20 mL) for 15 min. Subsequently, KI (60 mg, 0.36 mmol) and methyl 2-(chloromethyl)-1,3-oxazole-4-carboxylate (0.15 g, 0.85 mmol) were added. The reaction mixture was refluxed for 2 h until disappearance of the starting material on TLC (EtOAc-hexane 1:4 as an eluent). The reaction mixture was cooled, filtered, and the filtrate was evaporated in vacuo. The residue was purified by flash chromatography using gradient elution from 5% EtOAc-hexane to 60% EtOAc-hexane to give **33** as a white powder in 97% yield.

3-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-5-isoxazolecarboxylic Acid Ethyl Ester (19). Compound **19** was synthesized by the typical procedure described above using **4s** and **18** as starting materials. According to ^{1}H NMR, the product **19** is an inseparable 15:1 mixture of 3,5 and 3,4 regioisomers. Yield 64% (white solid). For the major isomer **19**: ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7.1 Hz), 4.39 (2H, q, J = 7.1 Hz), 5.79 (2H, s), 7.58 (1H, s), 7.80 (1H, s), 7.88 (1H, apparent t, J = 7.9 Hz), 8.35 (1H, d, J = 7.2 Hz), 8.58 (1H, d, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6) δ 13.9, 62.2, 62.7, 99.6 (q, J = 2 Hz), 109.4, 121.0 (q, J = 275 Hz), 121.7, 123.7 (q, J = 273 Hz), 126.3 (q, J = 30 Hz), 127.1, 127.4, 130.2 (q, J = 5 Hz), 143.5, 148.5 (q, J = 35 Hz), 156.0, 160.5 (two overlapping resonances), 162.4. HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_4$ [M + H]$^+$ 435.0774, found 435.0781.

5-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-2-thiazolecarboxylic Acid Ethyl Ester (22). Compound **22** was synthesized by the typical procedure described above using **21** as the alkyhalide. Yield 58% (pale-yellow powder). ^{1}H NMR ($CDCl_3$) δ 1.47 (3H, t, J = 7.1 Hz), 4.53 (2H, q, J = 7.1 Hz), 5.60 (2H, s), 7.26 (1H, s), 7.66 (1H, apparent t, J = 8.0 Hz), 7.75 (1H, s), 8.15 (1H, d, J = 7.2 Hz), 8.49 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 63.0, 66.7, 98.1 (q, J = 2 Hz), 121.1 (q, J = 276 Hz), 122.2, 123.6 (q, J = 274 Hz), 123.7, 126.29, 126.33, 128.5 (q, J = 30 Hz), 129.5 (q, J = 5 Hz), 144.8, 145.3, 149.7 (q, J = 35 Hz), 152.3, 159.4, 159.6, 162.3. HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_3S$ [M + H]$^+$ 451.0546, found 451.0568.

2-[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]acetic Acid Ethyl Ester (26). Compound **26** was synthesized by the typical procedure described above using ethyl bromoacetate as the alkyhalide. Yield 90% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.1 Hz), 4.94 (2H, s), 7.00 (1H, s), 7.69 (1H, apparent t, J = 7.8 Hz), 8.16 (1H, d, J = 7.1 Hz), 8.55 (1H, d, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6) δ 14.0, 61.1, 65.9, 99.6 (q, J = 2 Hz), 121.1 (q, J = 276 Hz), 121.7, 123.7 (q, J = 273 Hz), 126.4 (q, J = 30 Hz), 126.8, 127.4, 130.3 (q, J = 5 Hz), 143.6, 148.5 (q, J = 34 Hz), 162.5, 167.5. HRMS (ESI) calculated for $C_{15}H_{11}F_6NO_3$ [M + H]$^+$ 368.0716, found 368.0712.

2-[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]acetonitrile (28). Was synthesized by the typical procedure described above using bromoacetonitrile as the alkyhalide. Yield 90% (pale-yellow powder). ^{1}H NMR ($CDCl_3$) δ 5.13 (2H, s), 7.31 (1H, s), 7.20 (1H, s), 7.75 (1H, apparent t, J = 7.6 Hz), 8.21 (1H, d, J = 7.2 Hz), 8.45 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 53.9, 97.9 (q, J = 2 Hz), 113.2, 121.0 (q, J = 276 Hz), 121.8, 123.6 (q, J = 273 Hz), 126.0, 127.7, 128.9 (q, J = 31 Hz), 130.2 (q, J = 5 Hz), 145.0, 149.6 (q, J = 34 Hz), 160.7. HRMS (ESI) calculated for $C_{13}H_6F_6N_2O$ [M + H]$^+$ 321.0457, found 321.0442.

5-[[[2,6-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-2-furancarboxylic Acid Ethyl Ester (31). Compound **31** was synthesized by the typical procedure described above using ethyl 5-(chloromethyl)-2-furancarboxylate as the alkyhalide. Yield 75% (white powder). ^{1}H NMR (CD_3OD) δ 1.36 (3H, t, J = 7.1 Hz), 4.35 (2H, q, J = 7.1 Hz), 5.55 (2H, s), 6.86 (1H, d, J = 3.4 Hz), 7.27 (1H, d, J = 3.4 Hz), 7.60 (1H, s), 7.76 (1H, apparent t, J = 7.7 Hz), 8.22 (1H, d, J = 7.3 Hz), 8.51 (1H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 61.4, 62.9, 97.8 (q, J = 2 Hz), 113.1, 118.4, 121.1 (q, J = 276 Hz), 122.2, 123.6 (q, J = 273 Hz), 126.3, 126.5, 128.4 (q, J = 30 Hz), 129.5 (q, J = 5 Hz), 144.7, 145.9, 149.6 (q, J = 35 Hz), 151.5, 158.4, 162.1. HRMS (ESI) calculated for $C_{19}H_{13}F_6NO_4$ [M + H]$^+$ 434.0822, found 434.0829.

4-[(5-Nitro)-2-furanylmethoxy]-2,8-bis(trifluoromethyl)quinoline (32). Was synthesized by the typical procedure described above using 2-(bromomethyl)-5-nitrofuran as the alkyhalide. Yield 71% (pale-yellow solid). ^{1} H NMR ($CDCl_3$) δ 5.40 (2H, s), 6.84 (1H, d, J = 3.7 Hz), 7.23 (1H, s), 7.37 (1H, d, J = 3.7 Hz), 7.68 (1H, apparent t, J = 7.9 Hz), 8.16 (1H, d, J = 7.3 Hz), 8.43 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 62.6, 97.7 (q, J = 2 Hz), 111.9, 114.0, 121.0 (q, J = 276 Hz), 121.9, 123.5 (q, J = 273 Hz), 126.2, 126.7, 128.5 (q, J = 30 Hz), 129.7 (q, J = 5 Hz), 144.7, 149.5 (q, J = 35 Hz), 150.6, 152.5 (broad s), 161.7. HRMS (ESI) calculated for $C_{16}H_8F_6N_2O_4$ [M + H]$^+$ 407.0467, found 407.0469.

4-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]benzoic Acid Ethyl Ester (30). Compound **30** was synthesized by the typical procedure described above using ethyl 4-(bromomethyl)-benzoate as the alkyhalide. Yield 86% (white powder). ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.1 Hz), 4.41 (2H, q, J = 7.1 Hz), 5.43 (2H, s), 7.21 (1H, s), 7.59 (2H, d, J = 8.0 Hz), 7.68 (1H, apparent t, J = 7.8 Hz), 8.15 (3H, m), 8.51 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 61.2, 70.5, 98.1 (q, J = 2 Hz), 121.1 (q, J = 276 Hz), 122.3, 123.6 (q, J = 274 Hz), 126.33, 126.35, 127.3, 128.4 (q, J = 30 Hz), 129.5 (q, J = 5 Hz), 130.2, 131.0, 139.4, 144.7, 149.7 (q, J = 35 Hz), 162.6, 166.1. HRMS (ESI) calculated for $C_{21}H_{15}F_6NO_3$ [M + H]$^+$ 444.1029, found 444.1036.

2-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-4-oxazolecarboxylic Acid Methyl Ester (33). Compound **33** was synthesized by the typical procedure described above using 2-(chloromethyl)-4-oxazolecarboxylic acid methyl ester as the alkyhalide. Yield 97% (white solid). ^{1}H NMR ($CDCl_3$) δ 3.96 (3H, s), 5.52 (2H, s), 7.30 (1H, s), 7.13 (1H, s), 7.68 (1H, apparent t, J = 7.9 Hz), 8.16 (1H, d, J = 7.3 Hz), 8.34 (1H, s), 8.47 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 52.5, 62.4, 97.9 (q, J = 2 Hz), 121.0 (q, J = 276 Hz), 122.0, 123.5 (q, J = 274 Hz), 124.9, 125.1, 128.5 (q, J = 30 Hz), 129.7 (q, J = 5 Hz), 134.1, 144.7, 145.3, 149.6 (q, J = 35 Hz), 158.3, 161.0, 161.7. HRMS (ESI) calculated for $C_{17}H_{10}F_6N_2O_4$ [M + H]$^+$ 421.0618, found 421.0618.

2-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-4-oxazolecarboxylic Acid Ethyl Ester (34). Compound **33** (80 mg, 0.19 mmol) and KOH (8 mg, 0.14 mmol) were refluxed overnight in abs EtOH (20 mL). The solvent was evaporated in vacuo and the residue was dissolved into EtOAc (30 mL), washed with 1 M HCl (15 mL) and brine (15 mL), and dried with Na_2SO_4. After filtration the solvent was evaporated and the crude product was purified by flash chromatography using gradient eluation from 5% EtOAc-hexane to 90% EtOAc-hexane. Yield 81% (white solid). ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.1 Hz), 4.43 (2H, q, J = 7.1 Hz), 5.51 (2H, s), 7.31 (1H, s), 7.68 (1H, apparent t, J = 7.9 Hz), 8.16 (1H, d, J = 7.3 Hz), 8.34 (1H, s), 8.47 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 61.7, 62.4, 97.9 (q, J = 2 Hz), 121.0 (q, J = 276 Hz), 122.0, 123.5 (q, J = 274 Hz), 126.3, 126.6, 128.5 (q, J = 30 Hz), 129.7 (q, J = 5 Hz), 134.4, 144.8, 145.2, 149.6 (q, J = 35 Hz), 158.2, 160.6, 161.8. HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_4$ [M + H]$^+$ 435.0774, found 435.0783.

6-[[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-2-pyridinecarboxylic Acid Ethyl Ester (25). A solution of 6-(hydroxymethyl)-2-pyridinecarboxylic acid ethyl ester (**24**)[14] (0.3 g, 1 mmol), 2,8-bis(trifluoromethyl)quinolin-4-ol (**4s**) (0.2 g, 0.7 mmol), and PPh_3 (0.4 g, 1 mmol) in anhydrous THF (15 mL) was cooled to 0 °C. DEAD (0.25 g, 1.4 mmol, 0.22 mL) was added dropwise, and the reaction mixture was stirred for 45 min at room temperature. The solvent was evaporated in vacuo, and the residue was purified by column chromatography using CH_2Cl_2 as an eluent

to give compound **25** as a white powder in 81% yield. ^{1}H NMR ($CDCl_3$) δ 1.47 (3H, t, $J = 7.1$ Hz), 4.53 (2H, q, $J = 7.1$ Hz), 5.63 (2H, s), 7.28 (1H, s), 7.70 (1H, apparent t, $J = 7.9$ Hz), 7.78 (1H, d, $J = 7.8$ Hz), 7.96 (1H, apparent t, $J = 7.8$ Hz), 8.16 (2H, m), 8.55 (1H, d, $J = 8.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 61.3, 71.5, 98.5 (q, $J = 2$ Hz), 121.1 (q, $J = 276$ Hz), 122.2, 123.6 (q, $J = 274$ Hz), 124.5, 124.8, 126.2, 126.4, 128.5 (q, $J = 31$ Hz), 129.5 (q, $J = 5$ Hz), 144.7, 148.3, 149.8 (q, $J = 35$ Hz), 155.3, 162.3, 164.8. HRMS (ESI) calculated for $C_{20}H_{14}F_6N_2O_3$ $[M + H]^+$ 445.0981, found 445.0997.

2-[[2,8-Bis(trifluoromethyl)-4-quinolinyl]oxy]acetic Acid (27). The ester **26** (200 mg, 0.54 mmol) was dissolved into THF-MeOH-H_2O (3:1:1, 6 mL) and cooled to 0 °C. LiOH (50 mg, 2.0 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. After completion, the reaction was quenched with H_2O (50 mL), acidified with 6 M HCl (pH $\sim$ 3), extracted with EtOAc (2×30 mL), washed with brine (20 mL), and dried with Na_2SO_4. After filtration, the solvent was evaporated to give **27** in 98% yield as a white powder (HPLC purity 99.5%). ^{1}H NMR (CD_3OD) δ 5.14 (2H, s), 7.33 (1H, s), 7.78 (1H, apparent t, $J = 7.9$ Hz), 8.23 (1H, d, $J = 7.2$ Hz), 8.64 (1H, d, $J = 8.4$ Hz), $-OH$ exchanged. ^{13}C NMR (DMSO-d_6) δ 65.8, 99.4 (q, $J = 2$ Hz), 121.1 (q, $J = 276$ Hz), 121.8, 123.7 (q, $J = 273$ Hz), 126.4 (q, $J = 30$ Hz), 126.9, 127.2, 130.2 (q, $J = 5$ Hz), 143.7, 148.5 (q, $J = 34$ Hz), 162.7, 168.9. HRMS (ESI) for $C_{13}H_7F_6NO_3$ $[M + H]^+$ 340.0403, found 340.0387.

2,8-Bis(trifluoromethyl)-4-(2*H*-tetrazol-5-ylmethoxy)-quinoline (29). A mixture of nitrile **28** (100 mg, 0.31 mmol), NaN_3 (71 mg, 1.1 mmol), and NH_4Cl (58 mg, 1.1 mmol) in anhydrous DMF (6 mL) was heated to 80 °C for 3 h. The cooled reaction mixture was quenched with H_2O (10 mL) and made acidic (pH $\sim$ 3) with 5% HCl, resulting in a formation of a white precipitate. EtOAc (20 mL) was added, and the mixture was stirred until the precipitate was dissolved. Organic layer was separated, and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (20 mL) and dried with Na_2SO_4. After filtration, the solvent was evaporated and the crude product was purified by preparative HPLC to give compound **29** in 50% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ 6.02 (2H, s), 7.86 (1H, s), 7.90 (1H, apparent t, $J = 8.0$ Hz), 8.35 (1H, d, $J = 7.2$ Hz), 8.66 (1H, d, $J = 8.4$ Hz). ^{13}C NMR (DMSO-d_6) δ 61.4, 99.8 (q, $J = 2$ Hz), 121.1 (q, $J = 276$ Hz), 121.6, 123.7 (q, $J = 273$ Hz), 126.3 (q, $J = 30$ Hz), 127.2, 127.3, 130.3 (q, $J = 5$ Hz), 143.6, 148.6 (q, $J = 34$ Hz), 153.0 (broad s), 162.3. HRMS (ESI) calculated for $C_{13}H_7F_6N_5O$ $[M + H]^+$ 364.0628, found 364.0629.

[5-[[[2,6-Bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-3-isoxazolyl]-1-propanone (35). Compound **3** (100 mg, 0.23 mmol) in anhydrous Et_2O (15 mL) was cooled to 0 °C followed by dropwise addition of 3 M EtMgBr in Et_2O (0.09 mL, 0.28 mmol, 37 mg). The reaction mixture was allowed to reach room temperature and stirred for 15 min. The reaction was quenched with sat. NH_4Cl (20 mL), and Et_2O (20 mL) was added. The organic phase was separated, washed with brine (20 mL) and water (20 mL), and dried with Na_2SO_4. After filtration, the solvent was evaporated. Purification by flash chromatography, using gradient eluation from hexane to 80% EtOAc-hexane, afforded compound **35** as a white powder in 75% yield. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, $J = 7.3$ Hz), 3.13 (2H, q, $J = 7.3$ Hz), 5.52 (2H, s), 7.88 (1H, s), 7.23 (1H, s), 7.70 (1H, apparent t, $J = 7.8$ Hz), 8.18 (1H, d, $J = 7.1$ Hz), 8.46 (1H, d, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 7.4, 33.4, 61.4, 97.7 (q, $J = 2$ Hz), 103.2, 121.0 (q, $J = 276$ Hz), 121.9, 123.5 (q, $J = 274$ Hz), 126.1, 126.8, 128.7 (q, $J = 30$ Hz), 129.7 (q, $J = 5$ Hz), 144.8, 149.6 (q, $J = 35$ Hz), 161.7, 161.8, 166.7, 194.5. HRMS (ESI) calculated for $C_{18}H_{12}F_6N_2O_3$ $[M + H]^+$ 419.0830, found 419.0832.

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Supporting Information Available: HPLC purity determinations, ^{13}C NMR or ^{19}F NMR data for the target compounds **7a**−**7r**, **8**, **10**, and **13**, synthesis of the noncommercial 4-hydroxyquinolines and intermediates **5c**−**5f**, **5h**−**5n**, **5p**−**5r**, **6**, **14**, and **18**, HPLC chromatograms for key target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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