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Quinoline-Fused Lactones via Tandem Oxidation Cyclization: Metal-Free sp^3 C−H Functionalization

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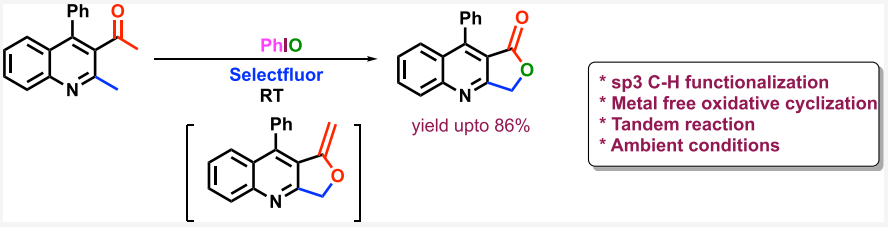

ABSTRACT: A unique lactonization of 2-methyl-3-acyl-4-phenylquinolines using PhIO as the oxidant and selectfluor as an additive is reported. The reaction occurs under ambient conditions through tandem oxidation and cyclization of sp^3 C−H bonds under metal-free conditions. The heterocycle-fused lactones are obtained in moderate to good yield.

INTRODUCTION

Aryl- and heteroaryl-fused lactones are useful scaffolds that display a range of biological properties.[1] Generally, the synthesis of these molecules is carried out in multiple steps using metal, ligand, or acid. Scheme 1A(i−viii) enlists some of the classical prefunctionalized starting materials that enable access to benzolactones. The methodologies involve (i) metal-mediated oxidative lactonization of benzene-1,2-dimethanol,[2] (ii) Tishchenko reaction of phthalaldehyde with actinide coordination complexes,[3] (iii) Zn/ligand-mediated lactonization of 2-formylbenzoates,[4] and (iv) lactonization of 2-(halomethyl)benzoic acid.[5] Alternatively, benzolactone formation has also been achieved via metal-catalyzed and directing group-assisted C−H activation/C−O bond formation in (v) *o*-toluic acid[6a,b] and aliphatic carboxylic acid,[6c] (vi) (*Z*)-2-(3-hydroxyprop-1-en-1-yl)benzoic acid,[7] (vii) γ-(2-methoxycarbonylphenyl)propargylic alcohol,[8] and (viii) benzyl alcohol and CO_2.[9] Pyridine-fused lactones (Scheme 1B) have been synthesized from pyridine-2,3-dimethanol or pyridine-3,4-dimethanol in the presence of metal and ligand (i),[10] while quinoline-fused lactones have been prepared from 2-aminobenzophenone in multiple steps using metal and/or acid at high temperature (ii).[11] In general, most of these methods suffer from limitations of prefunctionalized substrates, harsh reagents, multiple steps, high temperature, and toxicity. Therefore, seeking efficient, atom economical, and mild strategies for synthesizing heteroaryl-fused lactones is highly desirable. Direct sp^3 C−H functionalization has emerged as a powerful tool for construction of C−C, C−N, and C−O bonds.[12] Because of the inertness of the C(sp^3)−H bond, its late-stage functionalization is challenging, though attractive. Recent approaches for C(sp^3)−H functionalization describe the use of metal/oxidant via ionic pathway/free-radical process[13] or oxidative strategy using hypervalent iodine reagents.[14] As shown in (Scheme 1B(ii)), quinoline lactones serve as key synthetic intermediates for aza-podophyllotoxin derivatives. 1,4-Dihydroquinoline lactones (**I**), derived by reduction of 9-phenylfuro[3,4-*b*]quinolin-1(3*H*)-one, are known for their anti-leishmanial and anti-leukemic properties. Another biologically important molecule, 3-fluoromethylquinoline-2-carboxamide ([^{18}F]-AB5186) (**II**), known as a positron emission tomography imaging agent can be derived from 9-phenylfuro[3,4-*b*]quinolin-1(3*H*)-one.[15]

In view of the immense biological significance of heteroaryl-fused lactones and limited synthetic procedures, we delved into hypervalent iodine-assisted protocols to access them. In this work, we report an unprecedented synthesis of quinoline and quinoxaline lactones via oxidative cyclization of sp^3 C−H bonds using PhIO (iodosobenzene) and selectfluor under room temperature (RT) conditions (Scheme 1C).

RESULTS AND DISCUSSION

The study initiated with the reaction of 1-(2-methyl-6-nitro-4-phenylquinolin-3-yl)ethan-1-one (**1a**) using PhIO and selectfluor (1:1) at RT. After 24 h, a cyclic product, 7-nitro-9-phenylfuro[3,4-*b*]quinolin-1(3*H*)-one (**2a**) was isolated in 31% yield along with the formation of 7-nitro-5-phenyl-1*H*-pyrano[3,4-*b*]quinolin-4(3*H*)-one (**2a′**) in 17% yield (Table 1,

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Scheme 1. Synthetic Routes for Benzolactone and Heteroaryl-Fused Lactones

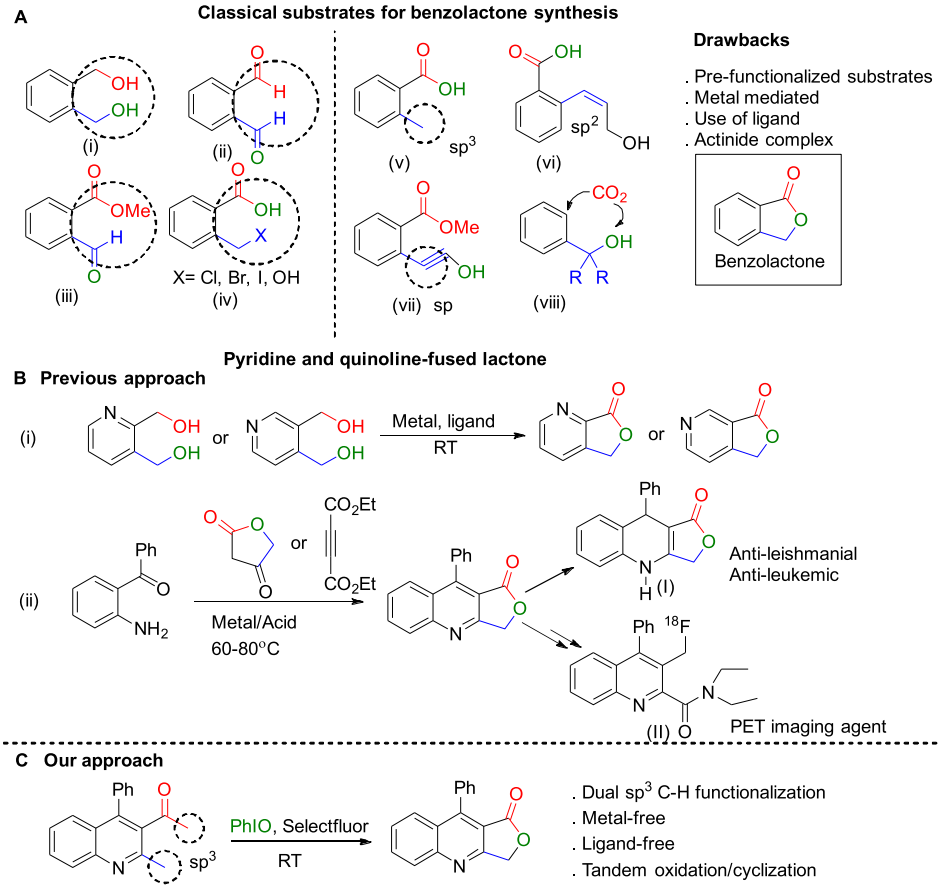
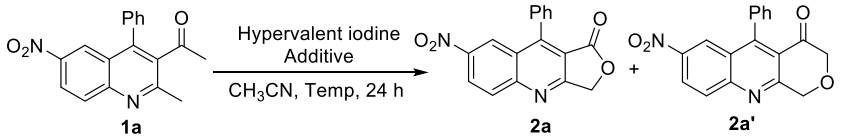


Table 1. Optimization Table[a]



s. no	hypervalent iodine	additive	solvent	yield[b] (%)
1	PhIO (1)	selectfluor (1)	CH_3CN	31, 17[c]
2	PhIO (1)	selectfluor (2)	CH_3CN	40, 13[c]
3	PhIO (2)	selectfluor (1)	CH_3CN	58, 7[c]
4	PhIO (3)	selectfluor (2)	CH_3CN	86
5	PhIO (3)	selectfluor (2)	CH_3CN	69[d], 56[e]
6	DPIB (3)	selectfluor (2)	CH_3CN	67
7	PIDA (3)	selectfluor (2)	CH_3CN	61
8	PIFA (3)	selectfluor (2)	CH_3CN	53
9	HTIB (3)	selectfluor (2)	CH_3CN	49
10	PhIO (3)	PTSA/BF_3·OEt/NFSI (2)	CH_3CN	51/53/8
11	PhIO (3)	selectfluor (2)	solvent[f,g,h]	0

[a]Reaction conditions: **1a** (1.0 equiv), hypervalent iodine, additive, solvent (3 mL) at RT for 24 h. [b]Yields of **2a**. [c]**2a′** are isolated yields. [d]50 °C. [e]80 °C. [f]DCE. [g]Dioxane. [h]THF.

entry 1). To improve the yield, optimization studies were carried out (Table 1, entries 2−4). On changing the stoichiometry of PhIO and selectfluor to 1:2 (Table 1, entry 2), the yield of **2a** increased slightly (40%) and **2a′** was formed in 13% yield (Table 1, entry 2). With a 2:1 stoichiometry, **2a** increased to 58% and **2a′** got reduced to 7% (Table 1, entry 3). Changing the ratio to 3:2 helped in driving the reaction to completion, and **2a** was isolated in 86% yield (Table 1, entry 4). Raising the temperature to 50 and 80 °C reduced the yield to 69 and 56%, respectively, because of the formation of unknown polar products (Table 1, entry 5). Use of other hypervalent iodine reagents such as dipivaloyloxyiodobenzene (DPIB), phenyliodine(III) diacetate (PIDA), [bis-(trifluoroacetoxy)iodo]benzene (PIFA), and hydroxy-(tosyloxy)iodobenzene (HTIB) did not help, and lower yields were obtained in all cases (Table 1, entries 6−9).

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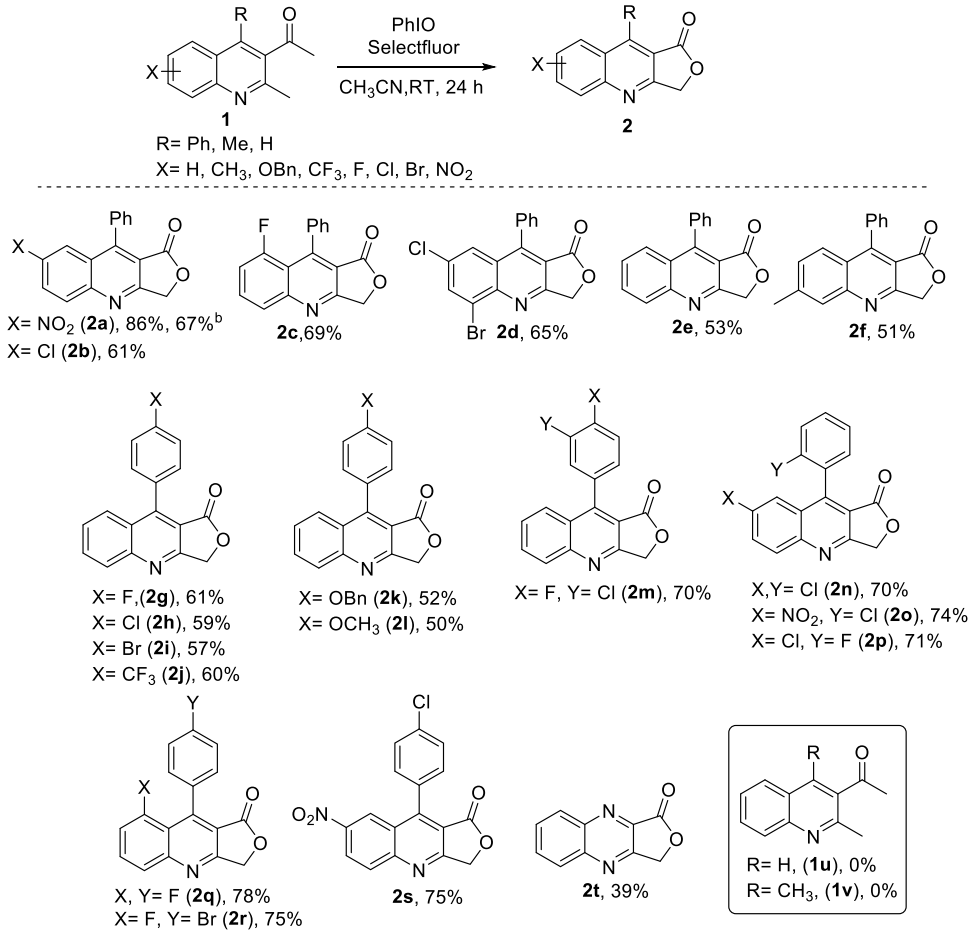
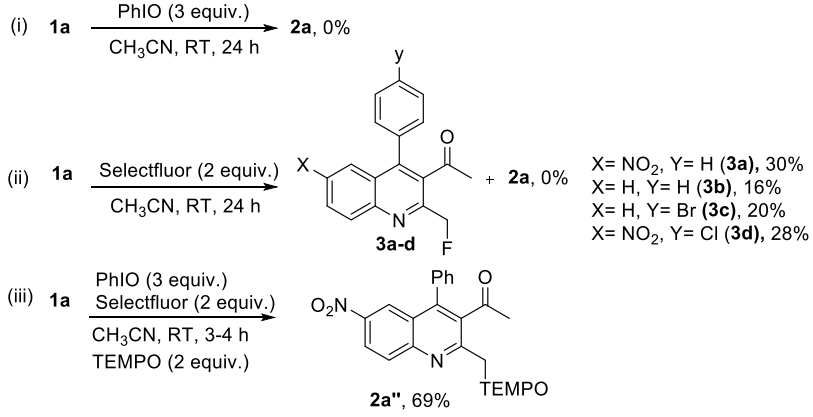
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (1.0 equiv), PhIO (3.0 equiv), selectfluor (2.0 equiv), CH_3CN, RT, 24 h. Yields are isolated yields. [b]Reaction carried on a gram scale with 1 g of **1a**.

Scheme 3. Control Experiments for Mechanistic Investigation



On substituting selectfluor with N-fluorobenzenesulfonimide, the yield of **2a** dropped considerably (8%). With acid additives such as p-toluenesulfonic acid (PTSA) and $BF_3{\cdot}OEt_2$, **2a** was obtained in 51 and 53% yields, respectively (Table 1, entry 10). No reaction took place in dichloroethene (DCE), dioxane, and tetrahydrofuran (THF) (Table 1, entry 11), and acetonitrile was found to be the best solvent for the reaction.

With the optimized reaction conditions in hand, the generality of the reaction was examined. Quinoline derivatives with electron-withdrawing substituents such as NO_2, F, Cl, and Br at 5, 6, and 8 positions afforded the corresponding lactones in 61−86% yields (Scheme 2, entries **2a**−**2d**). However, unsubstituted and 7-methyl-substituted quinolines gave lower yield (Scheme 2, entries **2e** and **2f**), suggesting higher reactivity of methyl sp^3 C−H under the influence of electron-withdrawing groups. Next, the effect of substituents on 4-phenyl ring was examined. F, Cl, Br, and CF_3 groups at the para position showed good compatibility and afforded the

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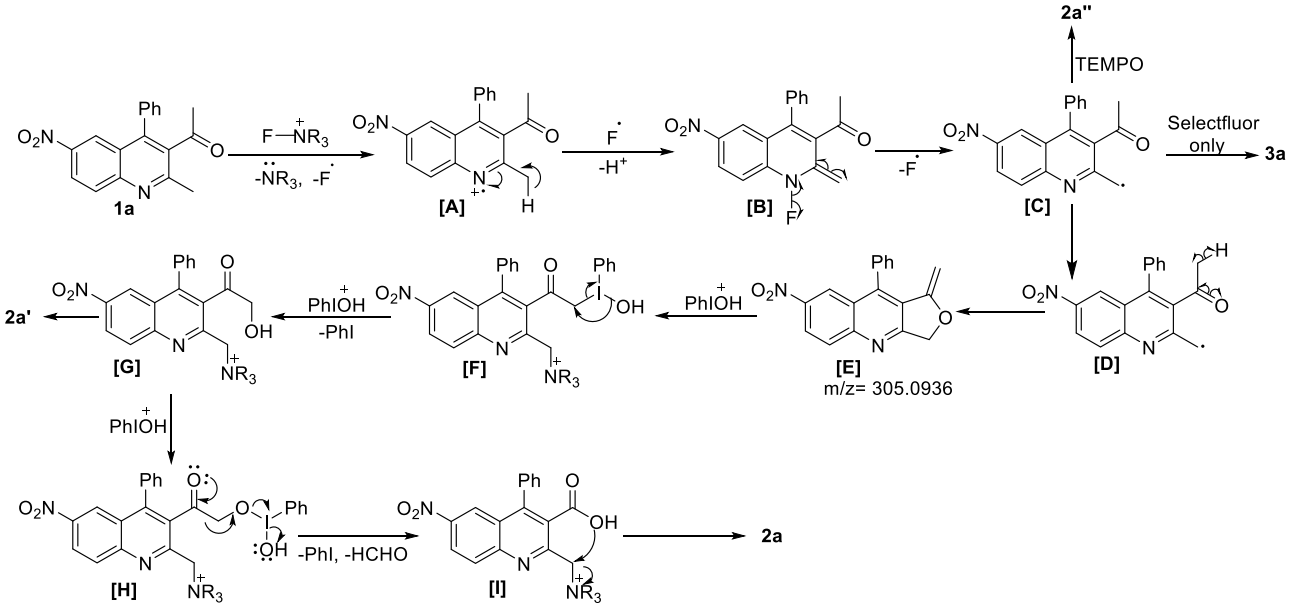
Scheme 4. Proposed Mechanism



corresponding products in moderate yields (Scheme 2, entries **2g−2j**). Lower yield was obtained with electron-donating *p*-methoxy and *p*-benzyloxy substituted derivatives as a substantial amount of starting material was left unreacted (Scheme 2, entries **2k−2l**). Next, disubstituted derivates with halo-/nitrosubstituents on both the phenyl rings were explored, and moderate-to-good product yields were obtained (Scheme 2, entries **2m−2s**). Interestingly, with 1-(3-methylquinoxalin-2-yl)ethanone, the desired lactone furo[3,4-*b*]-quinoxalin-1(3*H*)-one (**2t**) was obtained in 39% yield with considerable amount of unreacted **1t**.

Notably, it was found that the desired reaction did not take place with 1-(2-methylquinolin-3-yl)ethan-1-one (**1u**) and 1-(2,4-dimethylquinolin-3-yl)ethan-1-one (**1v**) (Scheme 2), and a mixture of polar products was formed in either case suggesting the importance of electron-withdrawing effect of 4-phenyl group in the reaction. The results indicated that the electron-withdrawing effect played a dominant role in activating the sp^3-C−H bond and enabling lactonization. Reaction was carried out on a gram scale, and **2a** was isolated in 67% yield (670 mg) under optimized reaction conditions (Scheme 2).

To gain insight into the reaction mechanism, some control experiments were carried out. The role of PhIO and selectfluor was studied by carrying out the reaction of **1a** in the presence of PhIO alone (Scheme 3(i)) and then in the presence of selectfluor alone (Scheme 3(ii)). In both the cases, **2a** was not formed. Interestingly, with selectfluor alone, fluorination of 2-methyl group took place, and 1-(2-(fluoromethyl)-6-nitro-4-phenylquinolin-3-yl)ethanone (**3a**) was obtained in 30% yield (Scheme 3(ii)). Few other substituted quinolines were also subjected to the reaction with selectfluor. However, small amounts of fluorinated products were obtained in all cases (Scheme 3(ii), **3a−3d**).[16] The involvement of methyl free radical in the reaction was ascertained by carrying out the reaction in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (2 equiv). It was found that the desired lactone **2a** did not form under these conditions, and a TEMPO adduct **2a″** was isolated in 69% yield (Scheme 3(iii)).

Based on the experimental results, a reaction mechanism has been proposed as shown in Scheme 4. The reaction is believed to initiate via in situ generation of fluorine radical and radical cation intermediate [**A**] by the reaction of **1a** with selectfluor.[17a] [**A**] reacts with fluorine radical and forms intermediate [**B**], which subsequently loses the fluorine radical to generate a methylene radical intermediate [**C**] at the C-2 position. The formation of [**C**] is supported by the formation of **2a″** (TEMPO adduct) and **3a** (Scheme 3(ii)). [**C**] undergoes intramolecular cyclization by radical coupling with carbonyl oxygen and yields intermediate [**E**] (*m*/*z* 305.0936, Figure S1, Supporting Information) via [**D**]. [**E**] undergoes ring opening reaction with protonated PhIO, and the cationic site is attacked by the amine nucleophile derived from selectfluor[17b] to form [**F**]. It is noteworthy to mention that selectfluor plays a dual role. First, it activates the substrate (**1a**-[**A**]), and second the diazoniabicyclo[2.2.2]octane moeity acts as a nucleophile and facilitates the ring-opening step ([**E**]−[**F**]).[17c] Further, [**F**] undergoes reductive elimination of hypervalent iodine followed by hydroxide attack resulting in the formation of [**G**]. On reaction with protonated PhIO, [**G**] forms [**H**], while in it's absence, **2a′** is formed as a side product (Table 1). [**H**] undergoes reductive elimination of hypervalent iodine and loss of formaldehyde to give [**I**], which eventually yields **2a** after elimination of ammonia.

CONCLUSIONS

In conclusion, we report an unprecedented, metal-free sp^3 C−H functionalization of methyl group in 2-methyl-3-acyl-4-phenylquinolines. The reaction occurs under ambient conditions *via* oxidative cyclization using PhIO and selectfluor. The protocol offers metal- and ligand-free conditions, smooth scalability, and good functional group tolerance and provides quinoline-fused lactones in moderate to good yields.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F254 silica gel, precoated on aluminum plates, and revealed with a UV lamp (λ_{max} = 254 nm). The products were purified by

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column chromatography on silica gel 230−400 mesh. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz (^{1}H 300 MHz, ^{13}C 75 MHz), 400 MHz (^{1}H 400 MHz, ^{13}C 100 MHz, ^{19}F 376 MHz,) and 500 MHz spectrometers (^{1}H 500 MHz, ^{13}C 125 MHz) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at RT. Chemical shifts are in δ (ppm) relative to TMS. The coupling constants (J) are in Hz. High-resolution mass spectra (HRMS) were recorded on a mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflectron experiments.

*General Procedure for Synthesis of Compounds (**1a−1s**).* A mixture of 2-aminoaryl ketones (0.50 mmol, 1 equiv), β-ketoesters/ketones (1.0 mmol, 2 equiv), and 4-toluenesulfonic acid (0.10 mmol, 0.2 equiv) in EtOH (3 mL) was added into a Schlenk flask (25 mL), and the mixture was stirred at 80 °C using oil bath and stirred until the reaction was complete. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate-hexane.[18a] Isolated yields: **1a**[18c] (97%), **1b**[18c] (93%), **1c** (92)%, **1d** (89)%, **1e**[18a] (99%), **1f** (87%), **1g**[18c] (77%), **1h**[18a] (81%), **1i**[18c] (80%), **1j** (81%), **1k** (85%), **1l**[18c] (86%), **1m** (71%), **1n**[18a] (75%), **1o**[18a] (61%), **1p**[18a] (72%), **1q** (69%), **1r** (70%), **1s** (71%).

*General Procedure for Synthesis of Compound **1t**.* To a round-bottom flask containing water (15 mL), acetyl acetone (185 mg, 1 mmol) was added followed by *N*-bromo succinimide (393 mg, 1.2 mmol) and stirred for 20 min at 70 °C using oil bath. To this reaction mixture, 1,2-phenylene diamine (200 mg, 1.0 mmol) was added, and the contents were stirred until completion of the reaction as indicated by TLC.[18b] The reaction mixture was then cooled to RT and poured onto ice and extracted with ethyl acetate. The organic extract was washed successively with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate-hexane.

*General Procedure for Synthesis of Lactone-Fused Quinoline and Quinoxaline (**2a−2t**).* To a 25 mL round-bottom flask was added **1a** (60 mg, 1 equiv), PhIO (128 mg, 3 equiv), selectfluor (138 mg, 2 equiv), and CH_3CN (4 mL). The reaction mixture was stirred for 24 h at RT, and the reaction was monitored through TLC. After reaction completion, the contents were diluted with water, extracted with ethyl acetate, and concentrated at reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate-hexane.

*General Procedure for Synthesis of Fluorinated Compounds **3a−3d**.* To a 25 mL round-bottom flask was added **1a** (60 mg, 1 equiv), selectfluor (138 mg, 2 equiv), and CH_3CN (3 mL). The reaction mixture was stirred for 24 h at RT, and the reaction was monitored through TLC. After reaction completion, the contents were diluted with water, extracted with ethyl acetate, and concentrated at reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate-hexane.

*General Procedure for Preparation of TEMPO Adduct **2a″**.* To a 25 mL round-bottom flask was added **1a** (60 mg, 1 equiv), PhIO (128 mg, 3 equiv), selectfluor (138 mg, 2 equiv), TEMPO (61.1 mg, 2 equiv), and CH_3CN (3 mL). The reaction mixture was stirred for 24 h at RT, and the reaction was monitored through TLC. After reaction completion, the contents were diluted with water, extracted with ethyl acetate, and concentrated at reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate-hexane.

Physical Properties and Characterization Data of the Synthesized Compounds. *1-(5-Fluoro-2-methyl-4-phenylquinolin-3-yl)ethan-1-one (**1c**).* White solid, yield 92% (128.34 mg), hexane/EtOAc (92:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.48 Hz, 1H), 7.64−7.58 (m, 1H), 7.43−7.42 (m, 3H), 7.32−7.31 (m, 2H), 7.08−7.03 (m, 1H), 2.66 (s, 3H), 1.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 205.1, 158.6 (d, $^1J_{C-F}$ = 257.90 Hz), 154.1, 148.7, 141.0, 137.0 (d, $^4J_{C-F}$ = 3.54 Hz), 136.5, 129.7 (d, $^3J_{C-F}$ = 9.58 Hz), 129.0 (d, $^4J_{C-F}$ = 3.45 Hz), 128.4, 127.9, 125.2 (d, $^4J_{C-F}$ = 4.15 Hz), 115.3 (d, $^3J_{C-F}$ = 9.15 Hz), 111.8 (d, $^2J_{C-F}$ = 21.65 Hz), 31.8, 23.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{15}FNO^+$, 280.1132; found, 280.1080.

*1-(8-Bromo-6-chloro-2-methyl-4-phenylquinolin-3-yl)ethan-1-one (**1d**).* White solid, yield 89% (165.5 mg), hexane/EtOAc (92:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, J = 2.25 Hz, 1H), 7.54−7.53 (m, 4H), 7.32−7.30 (m, 2H), 2.73 (s, 3H), 1.99 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 204.7, 155.0, 143.5, 143.1, 136.2, 134.1, 133.9, 132.0, 129.9, 129.4, 129.0, 126.7, 125.6, 124.8, 31.7, 24.1; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}$ BrClNO$^+$, 373.9942; found, 373.9872.

*1-(2,7-Dimethyl-4-phenylquinolin-3-yl)ethan-1-one (**1f**).* White solid, yield 87% (119.6 mg), hexane/EtOAc (93:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.51−7.49 (m, 4H), 7.35−7.33 (m, 2H), 7.283−7.280 (m, 1H), 2.67 (s, 3H), 2.55 (s, 3H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 205.9, 153.3, 147.7, 143.8, 140.6, 135.4, 134.1, 130.0, 128.8, 128.7, 128.6, 127.9, 125.8, 123.0, 32.0, 23.8, 21.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{18}NO^+$, 276.1383; found, 276.1392.

*1-(2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolin-3-yl)ethan-1-one (**1j**).* White solid, yield 81% (133.2 mg), hexane/EtOAc (92:8); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 8.30 Hz, 1H), 7.79 (d, J = 8.10 Hz, 2H), 7.76−7.73 (m, 1H), 7.51−7.46 (m, 4H), 2.71 (s, 3H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 205.1, 153.4, 147.5, 142.1, 139.0, 134.9, 130.5, 130.3, 129.1, 126.9, 125.7, 125.6 (2C), 124.5, 123.8 (q, $^1J_{C-F}$ = 270.62 Hz), 32.2, 23.8; HRMS (ESI-TOF) m/z: [M + H]$^+$; calcd for $C_{19}H_{15}F_3NO^+$, 330.1100; found, 330.1036.

*1-(4-(4-(Benzyloxy)phenyl)-2-methylquinolin-3-yl)ethan-1-one (**1k**).* White solid, yield 85% (155.9 mg), hexane/EtOAc (93:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.48 Hz, 1H), 7.70−7.67 (m, 2H), 7.47−7.44 (m, 2H), 7.42−7.38 (m, 3H), 7.35−7.33 (m, 1H), 7.29−7.26 (m, 2H), 7.12−7.10 (m, 2H) 5.12 (s, 2H), 2.69 (s, 3H), 2.00 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 205.9, 159.3, 153.3, 147.5, 143.7, 136.5, 134.9, 131.4, 130.0, 128.8, 128.6, 128.1, 127.5, 127.4, 126.4, 126.1, 125.3, 115.1, 70.1, 31.9, 23.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{22}NO_2^+$, 368.1645; found, 368.1647.

*1-(4-(3-Chloro-4-fluorophenyl)-2-methylquinolin-3-yl)ethan-1-one (**1m**).* White solid, yield 71% (111.1 mg), hexane/EtOAc (93:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.40 Hz, 1H), 7.77−7.74 (m, 1H), 7.55−7.54 (m, 1H), 7.51−7.48 (m, 1H), 7.46−7.45 (m, 1H), 7.33−7.30 (m, 1H), 7.28−7.25 (m, 1H), 2.71 (s, 3H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 205.0, 158.4 (d, $^1J_{C-F}$ = 250.48 Hz), 153.4, 147.5, 141.2, 135.0, 132.18, 132.12, 130.3, 130.0 (d, $^3J_{C-F}$ = 7.22 Hz), 129.1, 127.0, 125.5, 124.7, 121.7 (d, $^2J_{C-F}$ = 18.18 Hz), 117.1 (d, $^2J_{C-F}$ = 21.05 Hz), 32.2, 23.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}ClFNO^+$, 314.0742; found, 314.0680.

*1-(5-Fluoro-4-(4-fluorophenyl)-2-methylquinolin-3-yl)ethan-1-one (**1q**).* White solid, yield 69% (104.6 mg), hexane/EtOAc (92:8); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.45 Hz, 1H), 7.67−7.63 (m, 1H), 7.31−7.28 (m, 2H), 7.15−7.12 (m, 2H), 7.10−7.08 (m, 1H), 2.65 (s, 3H), 1.99 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 205.1, 162.8 (d, $^1J_{C-F}$ = 247.05 Hz), 158.6 (d, $^1J_{C-F}$ = 257.52 Hz), 154.1, 148.8, 140.0, 136.8, 132.9, 130.9 (d, $^4J_{C-F}$ = 3.60 Hz), 130.8 (d, $^4J_{C-F}$ = 3.55 Hz), 129.9 (d, $^3J_{C-F}$ = 9.57 Hz), 125.3 (d, $^4J_{C-F}$ = 4.37 Hz), 115.1 (d, $^2J_{C-F}$ = 26.60 Hz), 112.0 (d, $^2J_{C-F}$ = 21.71 Hz), 32.0, 23.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}F_2NO^+$, 298.1038; found, 298.1042.

*1-(4-(4-Bromophenyl)-5-fluoro-2-methylquinolin-3-yl)ethan-1-one (**1r**).* White solid, yield 70% (124.9 mg), hexane/EtOAc (93:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.50 Hz, 1H), 7.64−7.60 (m, 1H), 7.55 (d, J = 8.20 Hz, 2H), 7.18 (d, J = 8.10 Hz, 2H), 7.09−7.05 (m, 1H), 2.63 (s, 3H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 204.9, 158.5 (d, $^1J_{C-F}$ = 257.50 Hz), 154.1, 148.7, 139.6, 136.5, 135.9, 131.1, 130.6 (d, $^4J_{C-F}$ = 3.55 Hz), 129.9 (d, $^3J_{C-F}$ = 9.55 Hz), 125.3 (d, $^4J_{C-F}$ = 4.18 Hz), 122.9, 115.1 (d, $^3J_{C-F}$ = 9.13 Hz), 112.0 (d, $^2J_{C-F}$ = 21.71 Hz), 32.1, 23.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}BrFNO^+$, 358.0237; found, 358.0238.

*1-(4-(4-Chlorophenyl)-2-methyl-6-nitroquinolin-3-yl)ethan-1-one (**1s**).* White solid, yield 71% (120.7 mg), hexane/EtOAc (93:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51−8.48 (m, 2H), 8.20 (d, J = 9.05

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Hz, 1H), 7.57 (d, J = 8.35 Hz, 2H), 7.31 (d, J = 8.35 Hz, 2H), 2.73 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 204.2, 157.8, 149.5, 145.7, 144.1, 136.4, 136.3, 131.9, 131.2, 130.9, 129.6, 124.1, 123.7, 122.7, 31.9, 24.2; Anal. Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.45; H, 3.85; N, 8.22. Found: C, 61.61; H, 3.52; N, 7.62%.

7-Nitro-9-phenylfuro[3,4-b]quinolin-1(3H)-one (**2a**). White solid, yield 86% (51.5 mg), hexane/EtOAc (83:17); ^1H NMR (300 MHz, $CDCl_3$): δ 8.86 (d, J = 2.52 Hz, 1H), 8.64 (dd, J_1 = 9.21 Hz, J_2 = 2.40 Hz, 1H), 8.35 (d, J = 9.30 Hz, 1H), 7.68−7.64 (m, 3H), 7.50−7.47 (m, 2H), 5.51 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.1, 166.7, 153.6, 153.1, 146.1, 131.3, 130.5, 130.0, 129.9, 128.7, 126.3, 125.7, 124.9, 115.1, 69.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}N_2O_4^+$, 307.0713; found, 307.0714.

7-Chloro-9-phenylfuro[3,4-b]quinolin-1(3H)-one (**2b**).[11e] White solid, yield 61% (36.6 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.95 Hz, 1H), 7.86 (d, J = 2.25 Hz, 1H), 7.83 (dd, J_1 = 8.95 Hz, J_2 = 2.35 Hz, 1H), 7.60−7.59 (m, 3H), 7.44−7.42 (m, 2H), 5.44 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.4, 163.8, 150.5, 149.6, 133.6, 133.4, 130.9, 130.9, 129.8, 129.7, 128.4, 127.8, 126.6, 114.2, 69.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{10}ClNNaO_2^+$, 318.0292; found, 318.0303.

8-Fluoro-9-phenylfuro[3,4-b]quinolin-1(3H)-one (**2c**). White solid, yield 69% (41.3 mg), hexane/EtOAc (91:9); ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.50 Hz, 1H), 7.88−7.83 (m, 1H), 7.53−7.52 (m, 3H), 7.39−7.38 (m, 2H), 7.27−7.28 (m, 1H), 5.43 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.0, 164.1, 160.07 (d, $^1J_{C-F}$ = 260.37 Hz), 152.2, 149.7, 134.0 (d, $^4J_{C-F}$ = 4.56 Hz), 132.7 (d, $^3J_{C-F}$ = 9.67 Hz), 128.9, 127.9 (d, $^4J_{C-F}$ = 3.38 Hz), 127.6, 125.7 (d, $^4J_{C-F}$ = 4.55 Hz), 117.8 (d, $^3J_{C-F}$ = 9.27 Hz), 115.0, 112.9 (d, $^2J_{C-F}$ = 21.67 Hz), 69.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{10}FNNaO_2^+$, 302.0587; found, 302.0594.

5-Bromo-7-chloro-9-phenylfuro[3,4-b]quinolin-1(3H)-one (**2d**). White solid, yield 65% (39 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, J = 2.25 Hz, 1H), 7.83 (d, J = 2.25 Hz, 1H), 7.61 (d, J = 1.85 Hz, 2H), 7.60 (d, J = 2.35 Hz, 1H), 7.42 (d, J = 1.85 Hz, 1H), 7.41−7.40 (m, 1H), 5.52 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.8, 164.5, 151.2, 146.9, 136.4, 133.2, 130.6, 130.0, 129.6, 128.8, 128.5, 126.4, 125.7, 115.0, 69.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{10}BrClNO_2^+$, 373.9577; found, 373.9588.

9-Phenylfuro[3,4-b]quinolin-1(3H)-one (**2e**)[11]. White solid, yield 53% (31.7 mg), hexane/EtOAc (93:7); ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.24 Hz, 1H), 7.93−7.89 (m, 2H), 7.61−7.57 (m, 4H), 7.47−7.45 (m, 2H), 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.8, 163.6, 151.4, 151.3, 132.5, 131.6, 129.8, 129.5, 129.3, 128.2, 128.0, 127.4, 127.0, 113.5, 69.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{11}NNaO_2^+$, 284.0681; found, 284.0680.

6-Methyl-9-phenylfuro[3,4-b]quinolin-1(3H)-one (**2f**). White solid, yield 51% (30.6 mg), hexane/EtOAc (93:7); ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.79 (d, J = 8.68 Hz, 1H), 7.59−7.56 (m, 3H), 7.45−7.44 (m, 2H), 7.42−7.40 (m, 1H) 5.43 (s, 2H), 2.62 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.1, 163.8, 151.6, 151.2, 143.7, 131.8, 129.8, 129.7, 129.4, 128.3, 128.2, 127.7, 125.1, 112.7, 69.8, 22.0 HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_2^+$, 276.1019; found, 276.1011.

9-(4-fluorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2g**).[11e] White solid, yield 61% (36.6 mg), hexane/EtOAc (92:8); ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.40 Hz, 1H), 7.94−7.89 (m, 2H), 7.63−7.59 (m, 1H), 7.48−7.44 (m, 2H), 7.30−7.29 (m, 2H), 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.8, 163.5 (d, $^1J_{C-F}$ = 248.26 Hz), 163.6, 151.3, 150.3, 132.6, 131.8 (d, $^3J_{C-F}$ = 8.45 Hz), 129.5, 127.64 (d, $^2J_{C-F}$ = 20.37 Hz) (2C), 127.01, 115.55 (d, $^2J_{C-F}$ = 21.76 Hz) (2C), 113.57, 69.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2^+$, 280.0768; found, 280.0770.

9-(4-Chlorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2h**). White solid, yield 59% (35.4 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 8.45 Hz, 1H), 7.93−7.87 (m, 2H), 7.62−7.59 (m, 2H), 7.56 (d, J = 8.45 Hz, 1H), 7.40 (d, J = 8.40 Hz, 2H), 5.45 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.8, 163.5, 151.3, 150.0, 135.9, 132.7, 131.2, 129.9, 129.5, 128.6, 127.7, 127.6, 126.7, 113.4, 69.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{10}ClNNaO_2^+$, 318.0292; found, 318.0275.

9-(4-Bromophenyl)furo[3,4-b]quinolin-1(3H)-one (**2i**). White solid, yield 57% (34.2 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, J = 8.52 Hz, 1H), 7.94−7.87 (m, 2H), 7.73−7.71 (d, J = 6.4 Hz, 2H), 7.63−7.59 (d, J = 6.2 Hz, 1H), 7.36−7.33 (m, 2H), 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.8, 163.5, 151.3, 149.9, 132.7, 131.6, 131.4, 130.4, 129.5, 127.6 (2C), 126.7, 124.1, 113.4, 69.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}BrNO_2^+$, 339.9967; found, 339.9961.

9-(4-(Trifluoromethyl)phenyl)furo[3,4-b]quinolin-1(3H)-one (**2j**). White solid, yield 60% (36.0 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, J = 8.45 Hz, 1H), 7.95−7.91 (m, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.05 Hz, 1H), 7.59 (d, J = 7.95 Hz, 2H), 5.47 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.7, 163.4, 151.3, 149.4, 135.3, 132.8, 131.5 (d, $^2J_{C-F}$ = 32.5 Hz), 130.2, 129.6, 127.9, 127.4, 126.5, 125.3 (d, $^4J_{C-F}$ = 3.76 Hz), 123.94 (d, $^1J_{C-F}$ = 270.62 Hz), 113.5, 69.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{10}F_3NNaO_2^+$, 352.0555; found, 352.0548.

9-(4-(Benzyloxy)phenyl)furo[3,4-b]quinolin-1(3H)-one (**2k**). White solid, yield 52% (31.2 mg), hexane/EtOAc (93:7); ^1H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, J = 7.40 Hz, 1H), 8.00 (d, J = 7.20 Hz, 1H), 7.91−7.89 (m, 1H), 7.61−7.57 (m, 1H), 7.51−7.49 (m, 2H), 7.44−7.43 (m, 4H), 7.38−7.35 (m, 1H) 7.19−7.17 (m, 2H), 5.44 (s, 2H), 5.17 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.1, 163.7, 160.0, 151.5, 151.3, 136.6, 132.4, 131.7, 129.3, 128.7, 128.6, 128.19, 128.17, 127.6, 127.2, 123.8, 114.6, 113.3, 70.2, 69.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{17}NNaO_3^+$, 390.1106; found, 390.1081.

9-(4-Methoxyphenyl)furo[3,4-b]quinolin-1(3H)-one (**2l**). White solid, yield 50% (30.0 mg), hexane/EtOAc (91:9); ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, J = 8.40 Hz, 1H), 8.00 (d, J = 8.15 Hz, 1H), 7.90−7.87 (m, 1H), 7.58 (t, J = 7.25 Hz, 1H), 7.43 (d, J = 8.65 Hz, 2H), 7.10 (d, J = 8.65 Hz, 2H), 5.43 (s, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.2, 163.7, 160.7, 151.6, 151.3, 132.5, 131.6, 129.3, 128.2, 127.29, 127.24, 123.4, 113.7, 113.3, 69.4, 55.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_3^+$, 292.0968; found, 292.0975.

9-(3-Chloro-4-fluorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2m**). White solid, yield 70% (70.0/42 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, J = 8.50 Hz, 1H), 7.95−7.91 (m, 1H), 7.87 (d, J = 8.60 Hz, 1H), 7.66−7.62 (m, 1H), 7.51 (d, J = 6.80 Hz, 1H), 7.36 (d, J = 6.80 Hz, 2H), 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.7, 163.5, 158.8 (d, $^1J_{C-F}$ = 250.8 Hz), 151.3, 148.5, 132.8, 132.0, 129.9 (d, $^3J_{C-F}$ = 7.5 Hz), 129.6, 128.5 (d, $^4J_{C-F}$ = 4.2 Hz), 127.9, 127.3, 126.6, 121.4 (d, $^2J_{C-F}$ = 17.10 Hz), 116.7 (d, $^2J_{C-F}$ = 21.50 Hz), 113.6, 69.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{10}ClFNO_2^+$, 314.0378; found, 314.0370.

7-Chloro-9-(2-chlorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2n**). White solid, yield 70% (42.0 mg), hexane/EtOAc (92:8); ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 9.05 Hz, 1H), 7.83 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 7.63−7.61 (m, 2H), 7.55 (td, J_1 = 7.60 Hz, J_2 = 1.70 Hz, 1H), 7.48 (td, J_1 = 7.45 Hz, J_2 = 1.30 Hz, 1H), 7.28 (dd, J_1 = 7.60 Hz, J_2 = 1.75 Hz, 1H), 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.0, 163.6, 149.7, 146.9, 133.9, 133.6, 132.9, 131.1, 131.0, 130.6, 130.5, 130.0, 127.5, 126.9, 126.0, 115.3, 69.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_9Cl_2NNaO_2^+$, 351.9902; found, 351.9903.

9-(2-Chlorophenyl)-7-nitrofuro[3,4-b]quinolin-1(3H)-one (**2o**). White solid, yield 74% (74.0/44.3 mg), hexane/EtOAc (90:10); ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 1H), 7.83 (dd, J_1 = 9.05 Hz, J_2 = 2.40 Hz, 1H), 7.64−7.61 (m, 2H), 7.57−7.53 (m, 1H), 7.50−7.47 (m, 1H), 7.29 (dd, J_1 = 7.55 Hz, J_2 = 1.65 Hz, 1H), 5.48 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.0, 163.6, 149.7, 146.9, 133.9, 133.6, 132.9, 131.1, 131.0, 130.6, 130.5, 130.0, 127.4, 126.9, 126.0, 115.3, 69.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{10}ClN_2O_4^+$, 341.0323; found, 341.0328.

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7-Chloro-9-(2-fluorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2p**). White solid, yield 71% (42.6 mg), hexane/EtOAc (93:7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 1H), 7.85 (dd, J_1 = 9.05 Hz, J_2 = 2.35 Hz, 1H), 7.79 (s, 1H), 7.63−7.59 (m, 1H), 7.39−7.36 (m, 2H), 7.34−7.31 (m, 1H), 5.47 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.0, 163.5, 159.60 (d, $^1J_{C-F}$ = 247.50 Hz), 149.7, 143.8, 133.9, 133.5, 132.07 (d, $^3J_{C-F}$ = 8.15 Hz), 131.24 (d, $^4J_{C-F}$ = 2.47 Hz), 131.0, 127.6, 126.0, 124.27 (d, $^4J_{C-F}$ = 3.60 Hz), 118.98 (d, $^2J_{C-F}$ = 15.9 Hz), 116.19 (, $^2J_{C-F}$ = 21.2 Hz), 115.3, 69.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{10}ClFNO_2^+$, 314.0378; found, 314.0370.

8-Fluoro-9-(4-fluorophenyl)furo[3,4-b]quinolin-1(3H)-one (**2q**). White solid, yield 78% (46.8 mg), hexane/EtOAc (92:8); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05−8.03 (m, 1H), 7.87−7.83 (m, 1H), 7.37−7.34 (m, 2H), 7.26−7.23 (m, 1H), 7.22−7.20 (m, 1H), 7.19−7.17 (m, 1H), 5.42 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.1, 164.0, 163.6 (d, $^1J_{C-F}$ = 246.81 Hz), 159.9 (d, $^1J_{C-F}$ = 261.03 Hz), 152.3, 148.7, 132.8 (d, $^3J_{C-F}$ = 9.81 Hz), 130.0 (d, $^4J_{C-F}$ = 3.6 Hz), 129.9 (d, $^4J_{C-F}$ = 3.53 Hz), 125.8 (d, $^4J_{C-F}$ = 4.35 Hz), 114.9 (2C) (d, $^1J_{C-F}$ = 28.7 Hz), 113.0 (2C) (d, $^1J_{C-F}$ = 21.7 Hz), 69.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_9F_2NNaO_2^+$, 320.0493; found, 320.0476.

9-(4-Bromophenyl)-8-fluorofuro[3,4-b]quinolin-1(3H)-one (**2r**). White solid, yield 75% (45 mg), hexane/EtOAc (92:8); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 8.55 Hz, 1H), 7.89−7.84 (m, 1H), 7.65−7.63 (m, 2H), 7.27−7.26 (m, 1H), 7.25−7.23 (s, 2H), 5.44 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.0, 164.5, 159.6 (d, $^1J_{C-F}$ = 277.65 Hz), 152.3, 148.3, 132.9, 132.88, 132.81, 131.0, 129.6 (d, $^4J_{C-F}$ = 3.53 Hz), 125.9 (d, $^4J_{C-F}$ = 4.31 Hz), 123.4, 115.6, 113.1 (d, $^4J_{C-F}$ = 4.31 Hz), 69.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_9BrFNNaO_2^+$, 379.9692; found, 379.9693.

9-(4-Chlorophenyl)-7-nitrofuro[3,4-b]quinolin-1(3H)-one (**2s**). White solid, yield 75% (45 mg), hexane/EtOAc (90:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, J = 2.55 Hz, 1H), 8.66 (dd, J_1 = 9.25 Hz, J_2 = 2.55 Hz, 1H), 8.37 (d, J = 9.25 Hz, 1H), 7.63 (d, J = 7.90, 2H), 7.44 (d, J = 8.35, 2H), 5.51 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.1, 166.6, 153.1, 152.2, 146.3, 137.1, 131.5, 131.3, 129.2, 128.3, 126.1, 125.8, 124.4, 115.2, 69.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{10}ClN_2O_4^+$, 341.0323; found, 341.0324.

Furo[3,4-b]quinoxalin-1(3H)-one (**2t**). White solid, yield 39% (23.4 mg), hexane/EtOAc (92:8); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (dd, J_1 = 8.45 Hz, J_2 = 1.7 Hz, 1H), 8.24 (dd, J_1 = 8.42 Hz, J_2 = 1.45 Hz, 1H), 8.04−8.00 (m, 1H), 7.98−7.95 (m, 1H), 5.61 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.3, 156.5, 144.2 (2C), 138.4, 133.6, 131.5, 131.3, 129.3, 69.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{10}H_7N_2O_2^+$, 187.0502; found, 187.0491.

7-Nitro-5-phenyl-1H-pyrano[3,4-b]quinolin-4(3H)-one (**2a′**). White solid, hexane/EtOAc (85:15), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (dd, J_1 = 9.20 Hz, J_2 = 2.44 Hz, 1H), 8.51 (d, J = 2.44 Hz, 1H), 8.23 (d, J = 9.20 Hz, 1H), 7.60−7.58 (m, 3H), 7.25−7.23 (m, 2H), 5.16 (s, 2H), 4.41 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.7, 162.6, 153.5, 150.6, 146.0, 134.5, 130.8, 129.1, 128.7, 128.2, 127.0, 125.4, 125.0, 122.1, 74.3, 71.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{13}N_2O_4^+$, 321.0869; found, 321.0880.

1-(2-(Fluoromethyl)-6-nitro-4-phenylquinolin-3-yl)ethan-1-one (**3a**). White solid, yield 30% (19.05 mg), hexane/EtOAc (94:6); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 2.44 Hz, 1H), 8.53 (dd, J_1 = 9.16 Hz, J_2 = 2.52 Hz, 1H), 8.28 (d, J = 9.20 Hz, 1H), 7.62−7.60 (m, 3H), 7.38−7.36 (m, 2H), 5.74 (d, $^1J_{H-F}$ = 46.44 Hz, 2H), 1.99 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 203.7, 155.6 (d, $^2J_{C-F}$ = 18.6 Hz), 148.9, 146.8, 146.4, 134.9, 133.2, 131.6, 130.1, 129.8, 129.4, 125.6, 123.9, 123.1, 84.7 (d, $^1J_{C-F}$ = 168.41 Hz), 31.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}FN_2O_3^+$, 325.0982; found, 325.0990.

1-(2-(Fluoromethyl)-4-phenylquinolin-3-yl)ethan-1-one (**3b**). White solid, yield 16% (10.2 mg), hexane/EtOAc (95:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.35 Hz, 1H), 7.79−7.76 (m, 1H), 7.69−7.68 (d, J = 8.35 Hz, 1H), 7.54−7.51 (m, 4H), 7.38−7.36 (m, 2H), 5.72 (d, $^1J_{H-F}$ = 46.70 Hz, 2H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 204.9, 151.65 (d, $^2J_{C-F}$ = 18.43 Hz), 146.9, 145.0, 134.8, 133.6, 130.5, 129.9 (2C), 129.6, 129.1, 128.8, 127.8, 126.2, 85.06 (d, $^1J_{C-F}$ = 166.55 Hz), 31.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{15}FNO^+$, 280.1132; found: 280.1125.

1-(4-(4-Bromophenyl)-2-(fluoromethyl)quinolin-3-yl)ethan-1-one (**3c**). White solid, yield 20% (12.6 mg), hexane/EtOAc (95:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.45 Hz, 1H), 7.80−7.77 (m, 1H), 7.69 (d, J = 3.3 Hz, 2H), 7.63 (dd, J_1 = 7.63 Hz, J_2 = 1.45 Hz, 1H), 7.56−7.53 (m, 1H), 7.26−7.25 (m, 2H), 5.72 (d, $^1J_{H-F}$ = 46.65 Hz, 2H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 204.5, 151.6 (d, $^2J_{C-F}$ = 18.65 Hz), 146.9, 143.5, 133.6, 132.1 (2C), 131.5, 130.6 (2C), 129.7, 128.0, 125.9, 125.8, 123.7, 85.0 (d, $^1J_{C-F}$ = 166.8 Hz), 32.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.5; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}BrFNO^+$, 358.0237; found, 358.0247.

1-(4-(4-Chlorophenyl)-2-(fluoromethyl)-6-nitroquinolin-3-yl)-ethan-1-one (**3d**). White solid, yield 28% (17.6 mg), hexane/EtOAc (95:5); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56−8.53 (m, 1H), 8.52 (d, J = 2.28 Hz, 1H), 8.29 (d, J = 9.04 Hz, 1H), 7.61−7.59 (m, 2H), 7.33−7.32 (m, 2H), 5.73 (d, $^1J_{H-F}$ = 46.44 Hz, 2H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 202.2, 154.58 (d, $^2J_{C-F}$ = 18.88 Hz), 147.8, 145.5, 144.3, 135.5, 134.0, 130.7, 130.5, 130.1, 128.7, 124.3, 123.0, 121.6, 83.64 (d, $^1J_{C-F}$ = 168.53 Hz), 30.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{13}ClFN_2O_3^+$, 359.0593; found, 359.0600.

1-(6-Chloro-4-phenyl-2-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-methyl)quinolin-3-yl)ethan-1-one (**2a″**). White solid, yield 69% (62.37 mg), hexane/EtOAc (98:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, J = 2.40 Hz, 1H), 8.47 (d, J = 2.45 Hz, 1H), 8.26 (d, J = 9.20 Hz, 1H), 7.60−7.58 (m, 3H), 7.39−7.38 (m, 2H), 5.23 (s, 2H), 2.05 (s, 3H), 1.53−1.51 (m, 3H), 1.48−1.46 (m, 3H), 1.22 (s, 6H), 1.05 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 203.3, 157.4, 149.2, 146.0 (2C), 135.6, 133.7, 131.6, 129.9, 129.8, 129.2, 125.3, 123.3, 123.0, 80.3, 60.1, 39.9, 32.8, 32.1, 20.6, 17.0; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{32}N_3O_4^+$, 462.2387; found, 462.2309.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02238.

Copies of ^{1}H NMR, ^{13}C NMR, and HRMS for all synthesized compounds and mechanistic investigation (PDF)

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Notes

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