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Article

Hypervalent Iodine(III)-Promoted C3−H Regioselective Halogenation of 4-Quinolones under Mild Conditions

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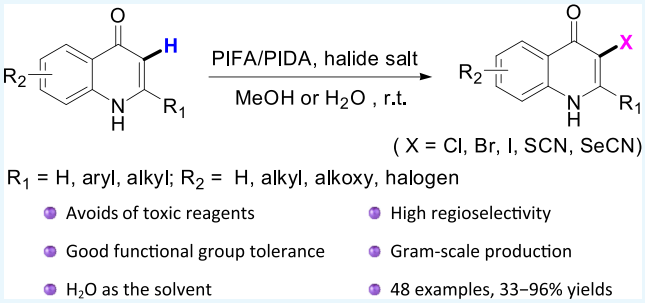
ABSTRACT: A simple and practical protocol for the C3−H regioselective halogenation of 4-quinolones by the action of potassium halide salt and PIFA/PIDA in good to excellent yields was developed. The current approach provides feasible access to the diversity of C3-halgenated 4-quinolones at room temperature with high regioselectivity and good functional group tolerance, from which bioactive compounds can be easily constructed. Moreover, the current method featured eco-friendly, operational convenience and is suitable for halogenation in a gram scale of 4-quinolones in water without sacrificing yields.



INTRODUCTION

The direct transformation of C(sp^2)−H bonds to C(sp^2)−X (X = heteroatom) bonds is desired for creating new and useful molecules, and halide groups are the most frequent functional groups in chemical transformations and cross-coupling to synthesize compounds with pharmaceutical and biological activities.[1] Particularly, the late-stage C(sp^2)−H functionalization offers an efficient way to facilitate the process of drug discovery and development.[2] Hypervalent iodine reagents are considered as environmentally benign synthetic tools due to their readily available property and unique reactivities similar to those of heavy metals.[3] Previous studies have demonstrated that the direct functionalizations of C−H bonds via hypervalent iodine reagents are powerful tools for C−C and C−heteroatom bond formation, such as halogination,[4] hydroxylation,[5] alkoxylation,[6] acetoxylation,[7] amination,[8] azidation[9] thiocyanation,[10] etc.

The structural motif of 4-quinolone is recognized as a central backbone in multiple pharmaceuticals and natural products in view of its broad range of bioactivities.[11] For instance, ciprofloxacin represents an important category of synthetic antibacterial agents and is widely used in the treatment of bacterial infections (Figure 1).[12] Meanwhile, many of bioactive 2-alkyl/aryl-substituted or 2,3-disubstituted 4-quinolone natural products have also been discovered over the years, including pseudanes III−IX,[13] graveoline,[14] waltherione C,[15] aurachin C/D,[16] and quinolactacin A2[17] (Figure 1). Furthermore, it has been reported that aryl substituents at the C2 position of 4-quinolones significantly enhance their antitumor and antimitotic activities, while variation of substituents located at the C3 position of 4-quinolones influences their cytotoxicities.[18] Thus, the biological activities of 4-quinolones depend on their substitution pattern and abundant molecular libraries of such types are crucial in providing candidate compounds for new drugs.

Due to distinctive pharmaceutical and biological activities of 4-quinolones, exploring efficient methods for the functionalization of 4-quinolones is a vital research topic, and especially, C3−H-functionalized 4-quinolones have attracted much attention.[19] In 2015, Ravi *et al.* described a method for arylation of 4-quinolones in the presence of a base by using arylhydrazine as a radical source under an air atmosphere.[20] In 2018, Xie and colleagues described the 3,4-difunctionalization of 2-phenyl-4-quinolones employing PhI($OAc)_2$ (PIDA) as the oxidant via a convenient cascade reaction under base conditions.[21] Recently, Kumar's group accomplished a regioselective C3, C5, and C8 arylation of 4-quinolones using a diaryliodonium salt and palladium catalyst at a temperature of 100 °C.[22] Besides the arylation of 4-quinolines, Ghosh and co-workers successively provided easily accesses to 3-aryl thioether/selenide and 3-thio/selenocyanide derivatives of 4-quinolones via direct C−H bond functionalization techniques and C−H bond activation approaches (Scheme 1a).[23] By using photochemical reactions, thiocyanation transformations of 2-aryl-4-quinolones were realized under ARS-TiO_2 photosensitizer and eosin Y catalytic conditions, respectively (Scheme 1a).[24] Furthermore, Chu's group disclosed an electrochemical method for trifluoromethylation of 4-quinolones via a free radical mechanism (Scheme 1b).[25]

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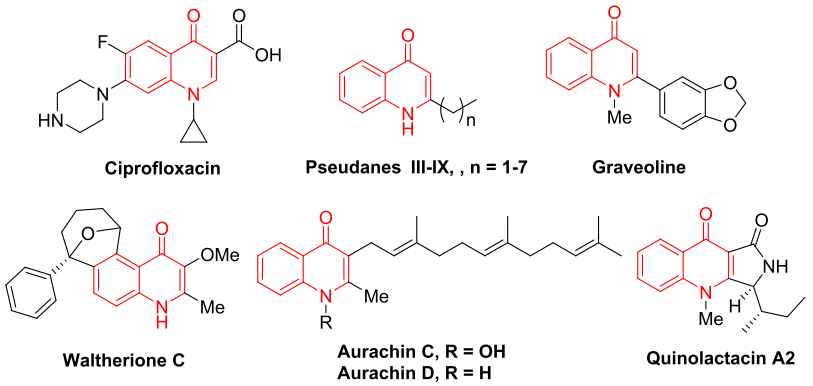
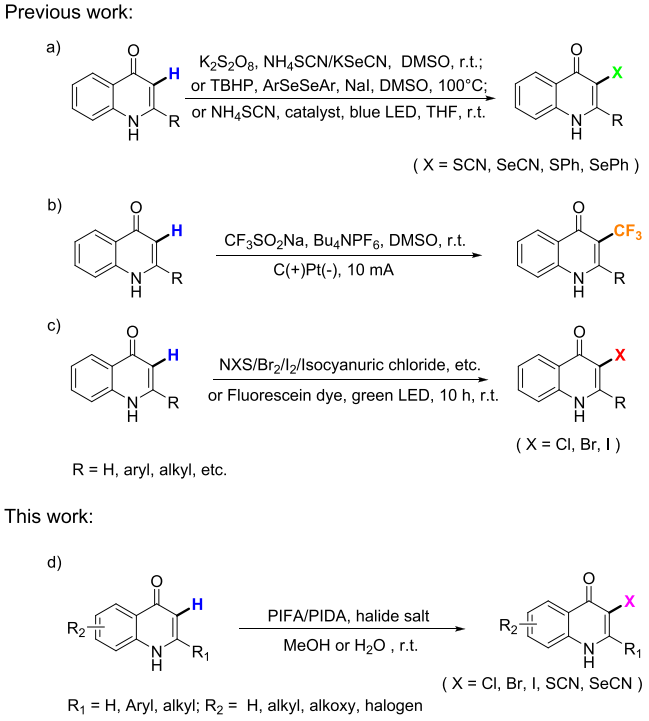


Figure 1. Representative active molecules containing 4-quinolone motifs.

Scheme 1. (a–d) Strategies for the Direct C3–H Functionalization of 4-Quinolones

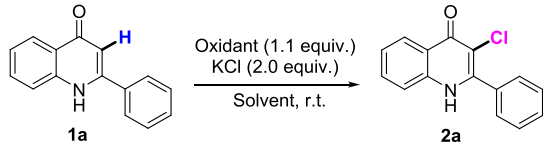


Hitherto, the direct halogenation methods of 4-quinolones have been reported mainly using *N*-halogen succinimide (NXS),[11d,26] Br_2,[27] I_2,[28] pyridinium tribromideor,[28] isocyanuric chloride,[11a] and other toxic halogenating sources under harsh reaction conditions (Scheme 1c), except for a photoredox-catalyzed halogenation of 4-quinolones reported by Ritu *et al.* very recently, which uses eosin Y or rose bengal as the halogen source and photosensitizer (Scheme 1c).[29] Although glorious achievements and remarkable progresses have been accomplished, the need to develop general and green protocols for the derivatization of 4-quinolones to meet the goal of sustainable chemistry remains. Herein, we wish to report a facile and highly effective method for regioselective halogenation of 4-quinolones at the C3 position, employing potassium halide salts as the halogen source and hypervalent iodine(III) reagent as the oxidant (Scheme 1d).

RESULTS AND DISCUSSION

Initially, 2-phenyl-4-quinolone (**1a**) was chosen as the model substrate to explore the synthetic conditions of 3-chloro-2-phenyl-4-quinolone (**2a**). Hypervalent iodine(III) as the oxidant reagent and KCl as the chlorine source were utilized. To our delight, the chlorination of **1a** was performed smoothly in the presence of PIFA/KCl or PIDA/KCl in MeOH at ambient temperature within 10 min, giving the only desired product **2a** in 86 and 79% yields, respectively (Table 1, entries 1 and 2). As for $PhICl_2$/KCl and PhIO/KCl reaction conditions, both of which could not completely convert **1a** to the desired product **2a** even up to 8 h, with significantly decreased isolated yields of 6% and even lower (Table 1, entries 3 and 4). Next, we turned our attention to other common oxidants. When *tert*-butyl hydroperoxide (TBHP),

Table 1. Optimization of the Chlorination Conditions[a]



entry	oxidant	solvent	time (h)	yield (%)[b]
1	PIFA	MeOH	0.2	86
2	PIDA	MeOH	0.2	79
3	PhIO	MeOH	8	6
4	$PhICl_2$	MeOH	8	trace
5	TBHP[c]	MeOH	8	n.d.
6	H_2O_2[d]	MeOH	8	n.d.
7	$K_2S_2O_8$	MeOH	8	n.d.
8	oxone[e]	MeOH	8	62
9	PIFA[f]	MeOH	0.2	78
10	PIFA[g]	MeOH	0.2	85
11	PIFA[h]	MeOH	0.2	81
12	PIFA	THF	0.2	76
13	PIFA	CH_3CN	8	37
14	PIFA	DCM	8	83
15	PIFA	HFIP	8	27
16	PIFA	H_2O	8	80

[a]Reaction conditions: 2-phenyl-4-quinolone **1a** (0.2 mmol, 1.0 equiv), chloride salt (0.4 mmol, 2.0 equiv), oxidant (0.22 mmol, 1.1 equiv), solvent (2.0 mL); reaction time 0.2 h means 12 min. [b]Isolated yields. [c]2.0 equiv of 70% aq. TBHP was used. [d]2.0 equiv of 30% aq. H_2O_2 was used. [e]Oxone was 2.0 equiv. [f]NaCl was the chlorine source. [g]$MgCl_2$ was the chlorine source. [h]$CuCl_2$ was the chlorine source. n.d. = not detected.

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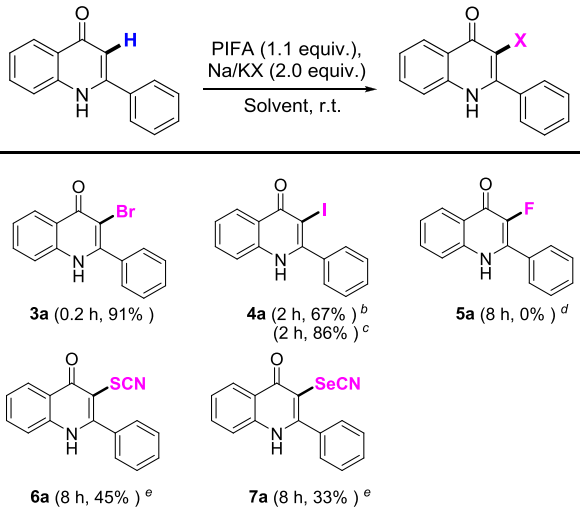
hydrogen peroxide (H_2O_2), or potassium persulfate ($K_2S_2O_8$) were used as the oxidants, no reaction was observed (Table 1, entries 5−7), except for oxone affording **2a** in a yield of 62% with an undefined byproduct (Table 1, entry 8). Further, NaCl, $MgCl_2$, and $CuCl_2$ were used instead of KCl to investigate other chloride salts and all of them provided comparable yield of **2a** to that of KCl (Table 1, entries 9−11), showing good tolerance to various sources of inorganic chloride. Finally, various solvents were tested in sequence and the chlorinated product **2a** was isolated in 27−83% yields when the reaction was performed in THF, CH_3CN, DCM, HFIP, and H_2O for 0.2−8 h (Table 1, entries 12−16). Of all the tested solvent, MeOH led to the best isolated yields. Interestingly, the chlorination reaction could take place in water without any organic solvent added (heterogeneous reaction) and gave an isolated yield in 80% (Table 1, entry 16). Thus, the current chemical transformation could be environmentally sustainable without toxic reagents used and generation as well as easy separation.

The optimal chlorination conditions used for **1a** were then chosen to investigate other halide and pseudo-halide salts. First, KBr was used for the bromination reactions and it proceeded successfully under the standard conditions, giving the corresponding product **3a** in 91% yields (Table 2, **3a**).

Table 2. Scope of Introduced Functional Groups[a]



[a]Reaction conditions: 2-phenyl-4-quinolone **1a** (0.2 mmol, 1.0 equiv), sodium or potassium salt (0.4 mmol, 2.0 equiv), PIFA (0.22 mmol, 1.1 equiv), MeOH (2.0 mL), isolated yields. [b]PIDA was used instead of PIFA. [c]PIDA (0.4 mmol, 2.0 equiv) was used instead of PIFA. [d]NaF was used as the fluorine source. [e]PIFA (0.6 mmol, 3.0 equiv), DMSO was used as the solvent.

However, this process was not compatible with KI. Next, PIDA instead of PIFA was used under the optimal halogenation conditions. Gratifyingly, the desired 3-iodo-2-phenyl-4-quinolone was isolated in a satisfactory yield of 67%, with 27% of the substrate remaining unreacted. When 2.0 equiv of PIDA was used, the substrate converted completely and the yield increased to 86% (Table 2, **4a**). While the attempt to obtain the fluorinated product failed despite PIFA or PIDA being used (Table 2, **5a**), it was probably because fluoride ion is highly electronegative and could not provide its electrons. Other regioselective functionalization of 2-phenyl-4-quinolone using KSCN, KSeCN, was applicable in a DMSO solvent under similar reaction conditions, resulting in modest isolated yields (Table 2, **6a** and **7a**). When the pseudo-halogenation reactions were carried out in MeOH or H_2O, no desired product was detected (SI, Table 1), manifesting that the solvent effect played an important role in pseudo-halogenation transformations. Furthermore, the attempt to achieve NaN_3, $NaNO_2$, and NaSPh by adopting 2-phenyl-4-quinolone under the developed procedure failed (results were not shown). Thus, we developed a method that was widely applicable to construct C−Cl, C−Br, C−I, C−SCN, and C−SeCN bonds at the C3 position of 4-quinolones with high regioselectivity, from which further derivatization of 4-quinolones could be easily achieved.[4e,11d,30]

Subsequently, the substrate scope of 4-quinolones was examined under the optimal conditions for chlorination and bromination reactions. Initially, we investigated the substrate scope with a variety of substituted 2-phenyl (R_1). As shown in Table 3, 2-aryl-4-quinolones reacted smoothly to produce 2-aryl-3-chloro/bromo-quinoline-4-ones in 58−96% yields (Table 3, entries **2a−2n**/**3a−3n**). Reactions of 2-aryl-4-quinolones bearing electron-donating groups on the 2-phenyl ring such as methyl, dimethyl, methoxy, and methylenedioxy with PIFA afforded 3-halogenated products **2a−2f**/**3a−3f** in yields of 79−96%. Also, reactions of 4-quinolones having electron-withdrawing groups on the 2-phenyl ring such as chloro, bromo, and trifluoromethyl with PIFA afforded **2g−2k**/**3g−3k** in yields of 63−92%. Therefore, the electron-withdrawing and electron-donating groups on the 2-phenyl ring were well tolerated, but the electron-withdrawing substituents led to relatively lower yields. In addition, the yields of substrates with multi-electron-withdrawing groups on the 2-phenyl ring (**1k**) were comparable with those of monosubstituted ones, with the corresponding products **2k**/**3k** in satisfactory yields of 73/89%. On the other hand, electron effects of the R_2 group also had no significant influence on the halogenation reactions and the desired products **2l−2n**/**3l−3n** were obtained in 58−84% yields. The substrates bearing electron-withdrawing groups (fluoro **1l** or bromo **1m**) located at the C6 position gave lower yields than the one bearing strong electron-donating groups (6,7-dimethoxy **1n**), and no dimerization product of **1n** was detected. Notably, the reactions were facile with 2-alkyl-substituted (**1o** and **1p**) and 2-hydrogen (**1q**) 4-quinolones, with the corresponding products **2o−2q**/**3o−3q** in 71−86% yields (Table 3). Especially, compound 2-heptyl-4-quinolone (**1o**), one of the important microbial secondary metabolites, and its analogues had been extensively studied as potential antimicrobial agents.[11b,31] Thus, this method might be valuable for efficient structure−activity relationship studies for new antibiotics. Furthermore, the X-ray analysis of the **2e** crystal unambiguously confirmed the regioselective C3 chlorination of 4-quinolones (Table 3, CCDC number: 2089951).

Next, we also explored the substrate scope of 4-quinolones for iodination reactions. Fortunately, the selected substrates were transferred to 3-iodo-4-quinolones under the optimal reaction conditions, and the satisfactory isolated yields are summarized in Table 4. The iodination reactions of 4-quinolones were tolerated with phenyl, alkyl, or hydrogen located at the C2 position. The substrates bearing electron-donating groups at the 2-phenyl afforded 89, 95, 90, and 96% yields, respectively (**4b**, **4c**, **4g**, and **4h**), which are higher than the electron-withdrawing ones located on the 2-phenyl group

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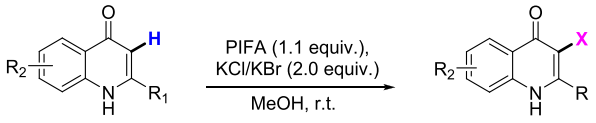
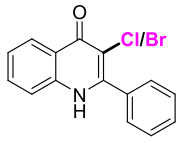
Table 3. Substrate Scope of 4-Quinolones for Chlorination and Bromination Reactions[a]

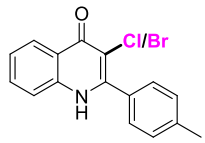


1 R_1 = H, alkyl, aryl; R_2 = H, F, Br, OMe

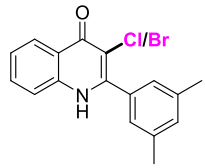
2/3 2, X = Cl; 3, X = Br



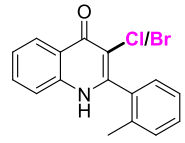
2a (0.2 h, 84%)
3a (0.2 h, 91%)



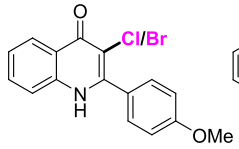
2b (0.2 h, 85%)
3b (0.2 h, 96%)



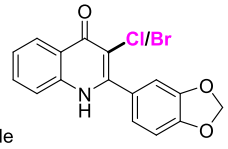
2c (0.2 h, 89%)
3c (0.2 h, 94%)



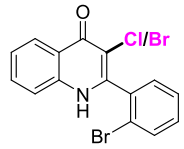
2d (0.2 h, 79%)
3d (0.2 h, 96%)



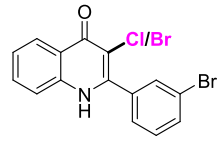
2e (0.2 h, 81%)
3e (0.2 h, 79%)



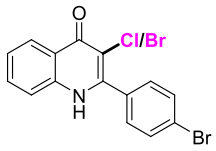
2f (0.2 h, 85%)
3f (0.2 h, 92%)



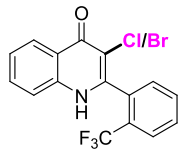
2g (0.2 h, 82%)
3g (0.2 h, 74%)



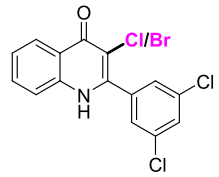
2h (0.2 h, 63%)
3h (0.2 h, 78%)



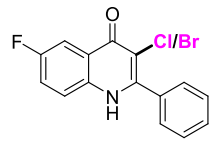
2i (0.2 h, 67%)
3i (0.2 h, 77%)



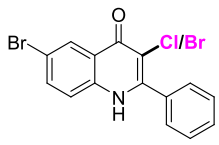
2j (0.2 h, 81%)
3j (0.2 h, 91%)



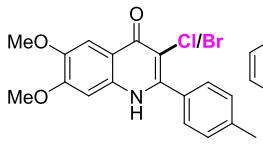
2k (0.2 h, 73%)
3k (0.2 h, 89%)



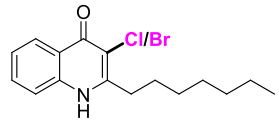
2l (2 h, 73%)
3l (2 h, 65%)



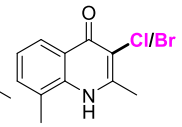
2m (2 h, 58%)
3m (2 h, 63%)



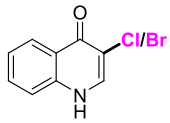
2n (0.2 h, 76%)
3n (0.2 h, 84%)



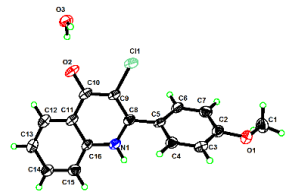
2o (0.2 h, 71%)
3o (0.2 h, 80%)



2p (0.2 h, 74%)
3p (0.2 h, 85%)



2q (0.2 h, 85%)
3q (0.2 h, 86%)



2e

[a]Reaction conditions: 4-quinolones (0.2 mmol, 1.0 equiv), KCl/KBr (0.4 mmol, 2.0 equiv), and PIFA (0.22 mmol, 1.1 equiv) in MeOH (2.0 mL) for 0.2−2 h at room temperature, isolated yields.

(**4d**−**4f** and **4i**). Meanwhile, the 4-quinolones with 2-hydrogen, 2-heptyl, and 2-methyl gave corresponding products **4j**, **4k**, and **4l** in 77−87% yields as the exclusive products. In addition, the nitrogen atom of 4-quinolones was not needed to be pre-protected for all of the halogenation reactions (Tables 3 and 4).

Due to the pseudo-halogenation of compound **1a** mediated by PIFA being less effective than that of $K_2S_2O_8$ reported by Das et al.,[23a] we only confirmed the feasibility of the C3−H pseudo-halogenation of 4-quinolones, and the substrate scope investigation was not carried out further.

In order to validate the protocol for commercial preparation of halogenation products, **1a** (1.5 g, 9.4 mmol) was carried out at a gram scale for bromination and iodination reactions in aqueous solution and the functionalized products **3a** and **4a** were produced with satisfactory isolated yields of 83 and 86%, respectively (Scheme 2). As for the chlorination reaction, **1e** (1.5 g, 6.8 mmol) was subjected to the standard reaction

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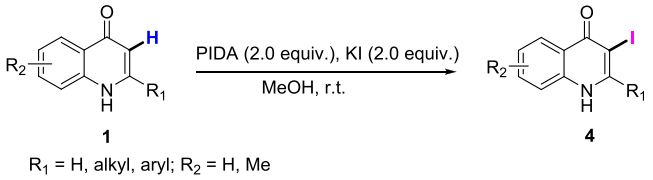
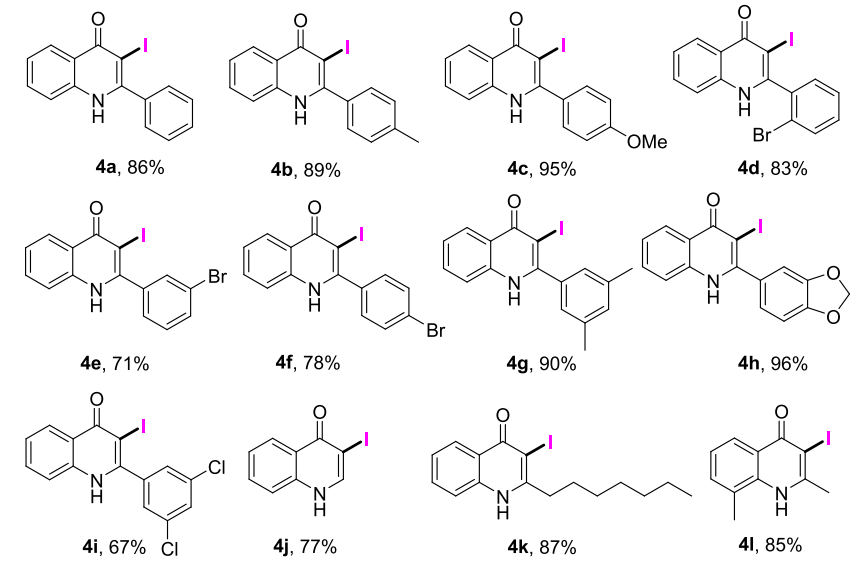
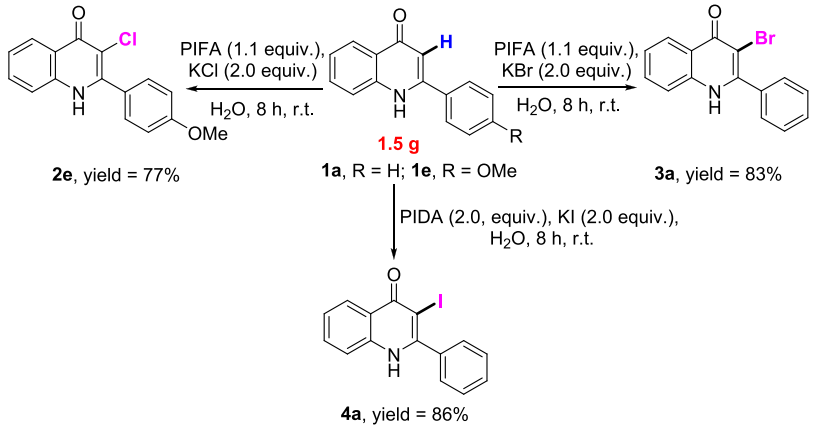
Table 4. Substrate Scope of 4-Quinolones for Iodination Reactions[a]





[a]Reaction conditions: 4-quinolones (0.2 mmol, 1.0 equiv), KI (0.4 mmol, 2.0 equiv), and PIDA (0.4 mmol, 2.0 equiv) in MeOH (2.0 mL) for 2 h at room temperature, isolated yields.

Scheme 2. Gram-Scale Preparation of 3-Halo-4-quinolones in Water



conditions using H_2O instead of MeOH, and the corresponding product **2e** was obtained in a yield of 77% (Scheme 2). Hence, all of the halogenation reactions could be easily amplified in water with comparable yields to the small amounts of reactions carried out in MeOH (Table 3, entries **2e** and **3a**; Table 4, entry **4a**). To the best of our knowledge, 3-halo-4-quinlones could be easily furnished via Suzuki−Miyaura cross coupling[30a,c] or functional group transformation reactions[18,26,30b] to elaborate the medicinal importance of 4-quinolones, implying the potential application value of this method.

Most reported mechanisms of the oxidative functionalization of 4-quinolones have been recognized via a radical pathway.[20,24b,25,29] To gain some mechanistic insights into these halogenation transformations, control experiments are designed and carried out. Under the standard reaction conditions, 3.0 equiv of free radical quenchers including TEMPO (2,2,6,6-tetra-methylpiperid-idine-*N*-oxyl), BHT (2,6-ditert-butyl-4-methylphenol), and 1,4-benzoquinone is added. The results indicate that the chlorination and bromination processes are nearly undisturbed, giving the terminal products **2a**/**3a** in a yield of about 80/90% within 0.2 h, respectively (Scheme 3a). As for iodination reactions, the isolation yield of **4a** decreases to 7, 11, and 41, respectively (Scheme 3a). In order to exclude the radical pathway of the iodination reaction, further control experiments are carried out using I_2 instead of KI, and **4a** is produced as the single product with a yield of 92%, while similar conversion cannot be

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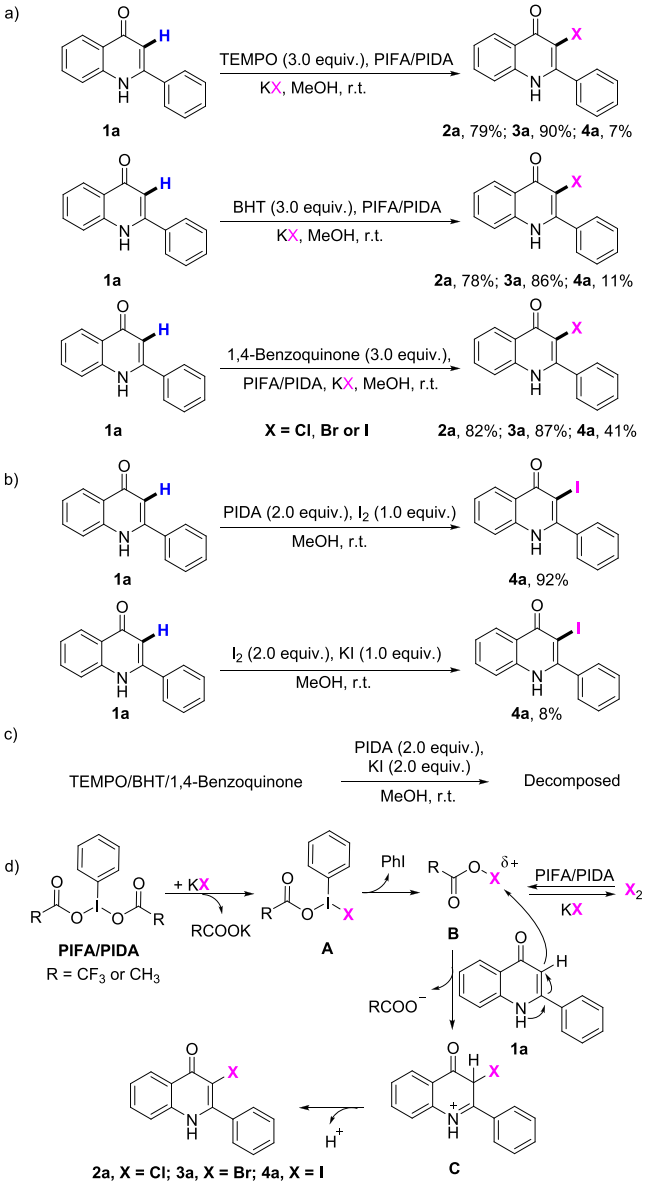
Scheme 3. (a−d) Controlled Experiments and Plausible Reaction Mechanism



completed using I_2 and KI reaction systems, with only 8% of the iodination product **4a** isolated and most starting substrate **1a** unreacted (Scheme 3b). These two control experiments indicate that $CH_3C(O)OI$ salt is presumably the active electrophilic species other than I_2.[4h] In addition, when control reactions are carried out without the addition of substrate **1a**, severe decomposition of TEMPO, BHT, and 1,4-benzoquinone is observed within 2 h (Scheme 3c). We speculate that the addition of these scavengers consumes the active $CH_3C(O)OI$ salt, leading to incomplete conversion of **1a** and the decreased yield of **4a**. It is because the chlorination and bromination reactions of **1a** are much quicker than its iodination reaction (0.2 h *vs* 2.0 h), and thus the scavengers used only slightly affected their productivity. On the basis of experimental results and the literature precedents,[4a,h] a plausible reaction procedure is depicted in Scheme 3d. Initially, PIFA reacted with KX via ligand exchange to give the plausible non-symmetrical hypervalent iodine intermediate **A**, which can evolve to produce the hypohalite salt **B**, the active electrophilic halogenation agent. Then, substrate **1a** attacks the halogen atom of **B** to produce the intermediate **C**. Finally, the loss of a proton and rearomatizing of intermediate **C** give the final halogenated product.

CONCLUSIONS

In summary, we have described a practical and green protocol for the C3 regioselective functionalization of 4-quinolones under mild conditions. The present study is an attractive alternative to previously described halogenation techniques. The straightforward transformation of the $C(sp^2)$−H bond to $C(sp^2)$−X (X = Cl, Br, I, SCN, and SeCN) bonds features high regioselectivity, broad reactivity, functional group compatibility, and eco-friendliness. Moreover, it is suitable for gram-scale production of the C3-halogenated 4-quinolones in water with good isolated yields. Compared with the previous reported methods, this is a representative example of hypervalent iodine(III) reagent-mediated regioselective functionalization of 4-quinolones, and a series of potential bioactive molecules containing 4-quinolone skeletons would be easily achieved by using of these valuable halogenated synthons.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial sources and used without treatment. Thin-layer chromatography (TLC) was performed on 60F254 silica gel and revealed with a UV lamp (λ_{max} = 254 nm). The products were purified by column chromatography on silica gel 200−300 mesh. ^1H and ^{13}C NMR spectra were recorded on 400 MHz (^1H 400 MHz, ^{13}C 100 MHz, and ^{19}F 376 MHz) and using DMSO-d_6 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 commercial apparatus (ESI Source, TOF). Single-crystal X-ray diffraction data were collected using a Bruker MicroTOF QII mass spectrometer. 4-Quinolone substrates were prepared according to the previous reports.

*General Procedure for the Synthesis of C3−H-Chlorinated or -Brominated 4-Quinolones (**2a−2q/3a−3q**).* A mixture of substrates **1a−1q** (0.2 mmol, 1.0 equiv) and KCl/KBr (0.4 mmol, 2.0 equiv) in MeOH (2.0 mL) was stirred at room temperature, and PIFA (0.22 mmol, 1.1 equiv) in MeOH (1.0 mL) was added into the reaction mixture dropwise. The mixture was stirred for about 0.2 or 2 h. Upon completion, the contents were concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 40:1 to afford the desired products.

*General Procedure for the Synthesis of C3−H-Iodinated 4-Quinolones (**4a−4l**).* A mixture of selected 4-quinolone (0.2 mmol, 1.0 equiv) and KI (0.4 mmol, 2.0 equiv) in MeOH (2.0 mL) was stirred at room temperature. PIDA (0.4 mmol, 2.0 equiv) was diluted in MeOH (1.0 mL) and added into the reaction mixture dropwise. The mixture was stirred for 2 h. After the reaction completion checked by TLC, saturated $Na_2S_2O_3$ (20 mL) was added and extracted with DCM three times (3 × 20 mL). Then, the organic layer was further washed with brine solution (40 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 40:1 to afford the desired product.

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Halogenation Transformations in H_2O. A mixture of substrate **1e**/**1a**/**1a** (1.5 g, 1.0 equiv) and KCl/KBr/KI (2.0 equiv) in H_2O (40.0 mL) was stirred at ambient temperature. Then, PIFA (1.1 equiv) or PIDA (2.0 equiv) was added as a solid to the corresponding reaction mixture and stirred for about 8.0 h. Upon completion, the precipitate was filtered and recrystallized with ethyl acetate to afford the pure products.

Preparation of Thio- and Selenocyanate Derivatives of 4-Quinolones. A mixture of **1a** (0.2 mmol, 1.0 equiv) and KSCN/KSeCN (0.4 mmol, 2.0 equiv) in DMSO (2.0 mL) was stirred at room temperature. PIFA (0.6 mmol, 3.0 equiv) was diluted in DMSO (1.0 mL) and added into the reaction mixture dropwise. The mixture was stirred for 8 h. After the reaction completion checked by TLC, the organic layer was diluted with dichloromethane and washed with brine solution (3 × 40 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using DCM/MeOH = 40:1 to afford the desired product.

Radical Trapping Experiments. To a solution of 2-phenyl-4-quinolone **1a** (0.2 mmol, 1.0 equiv), KCl/KBr/KI (0.4 mmol, 2.0 equiv), and TEMPO (0.6 mmol, 3.0 equiv) in MeOH (2.0 mL), PIFA (0.22 mmol, 1.1 equiv) or PIDA (0.4 mmol, 2.0 equiv) was added dropwise. The solution was stirred at room temperature for 0.2 or 2 h. Then, saturated $Na_2S_2O_3$ (20 mL) was added and extracted with DCM three times (3 × 20 mL). The organic layer was further washed with brine solution (40 mL), dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to give the crude product, which was purified by column chromatography on silica gel using DCM/MeOH = 40:1 to give the pure product as a white solid. Control experiments of 1,4-benzoquinone or BHT free radical quencher followed the procedure of TEMPO.

Characterization Data of Products. *3-Chloro-2-phenylquinolin-4(1H)-one (**2a**).* White solid, yield = (84%, 43 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.66−7.73 (m, 4H), 7.60−7.61 (m, 3H), 7.39−7.43 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.6, 148.3, 139.0, 133.4, 132.3, 130.2, 129.3, 128.6, 125.2, 124.1, 123.7, 118.8, 113.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}ClNO$ calcd for 256.0524; found, 256.0522.

*3-Chloro-2-(p-tolyl)quinolin-4(1H)-one (**2b**).* White solid, yield = (85%, 43 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.21 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.69 (m, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.39−7.40 (m, 3H), 2.41(s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 148.3, 140.0, 139.0, 132.1, 130.5, 129.1, 129.0, 125.2, 123.9, 123. 6, 118.7, 113.2, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{13}ClNO$ calcd for 270.0686; found, 270.0671.

*3-Chloro-2-(3,5-dimethylphenyl)quinolin-4(1H)-one (**2c**).* White solid, yield = (89%, 51 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.70 (s, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.25 (s, 2H), 7.20 (s,1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 148.5, 138.9, 137.8, 133.3, 132.1, 131.4, 126.7, 125.2, 123.9, 123.6, 118.6, 113.2, 20.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{17}H_{16}ClNO$ calcd for 284.0842; found, 284.0826.

*3-Chloro-2-(o-tolyl)quinolin-4(1H)-one (**2d**).* White solid, yield = (79%, 43 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.69−7.70 (m, 2H), 7.37−7.48 (m, 5H), 2.19 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 148.4, 139.1, 135.8, 133.4, 132.3, 130.4, 130.1, 129.0, 126.2, 125.3, 124.1, 123.9, 118.8, 114.1, 19.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{13}ClNO$ calcd for 270.0686; found, 270.0679.

*3-Chloro-2-(4-methoxyphenyl)quinolin-4(1H)-one (**2e**).* White solid, yield = (81%, 40 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 2.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.37−7.41 (m, 1H), 7.15 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 160.7, 148.1, 139.0, 132.1, 130.9, 125.5, 125.2, 123.9, 123.6, 118.7, 113.9, 113.3, 55.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{13}ClNO_2$ calcd for 286.0635; found, 286.0640.

*2-(Benzo[d][1,3]dioxol-5-yl)-3-chloroquinolin-4(1H)-one (**2f**).* White solid, yield = (85%, 49 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.19 (bs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.69 (m, 2H), 7.39−7.40 (m, 1H), 7.26 (m, 1H), 7.12−7.18 (m, 2H), 6.15 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.6, 148.8, 147.9, 147.3, 138.9, 132.2, 126.9, 125.2, 124.0, 123.7, 123.6, 118.7, 113.3, 109.8, 108.4, 101.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{11}ClNO_3$ calcd for 300.0428; found, 300.04128.

*2-(2-Bromophenyl)-3-chloroquinolin-4(1H)-one (**2g**).* White solid, yield = (82%, 55 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.70 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.82−8.84 (m, 1H), 7.69−7.71 (m, 2H), 7.59−7.61 (m, 2H), 7.52−7.53 (m,1H), 7.42−7.43 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 147.4, 139.0, 134.5, 132.8, 132.5, 132.0, 131.0, 128.2, 125.2, 124.3, 123.9, 122.0, 118.8, 114.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrClNO$ calcd for 333.9634; found, 333.9623.

*2-(3-Bromophenyl)-3-chloroquinolin-4(1H)-one (**2h**).* White solid, yield = (63%, 42 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.80−7.82 (m, 1H), 7.65−7.74 (m, 3H), 7.54−7.58 (m, 1H), 7.40−7.44 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.4, 146.7, 138.9, 135.4, 133.0, 132.3, 130.7, 128.6, 125.2, 124.1, 123.7, 121.6, 118.7, 113.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrClNO$ calcd for 333.9634; found, 333.9632.

*2-(4-Bromophenyl)-3-chloroquinolin-4(1H)-one (**2i**).* White solid, yield = (67%, 45 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.32 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.62−7.78 (m, 4H), 7.40 (t, J = 6.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 147.2, 139.0, 132.5, 132.3, 131.6, 131.5, 125.2, 124.1, 123.8, 123.7, 118.7, 113.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrClNO$ calcd for 333.9634; found, 333.9626.

*3-Chloro-2-(2-(trifluoromethyl)phenyl)quinolin-4(1H)-one (**2j**).* White solid, yield = (81%, 53 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.55 (bs, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.62−7.75 (m, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H); ^{19}F NMR (376 MHz, DMSO-d_6): δ −73.6 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.1, 146.0, 138.7, 133.1, 132.5, 131.3, 130.9, 127.3, 127.0, 126.7, 126.6, 125.3, 125.1, 124.2, 123.9, 122.3, 118.5, 114.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{10}ClF_3NO$ calcd for 324.0403; found, 324.0397.

*3-Chloro-2-(3,5-dichlorophenyl)quinolin-4(1H)-one (**2k**).* White solid, yield = (73%, 47 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.48 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.86−7.87 (m, 1H), 7.80 (m, 2H), 7.67−7.74 (m, 2H), 7.40−7.44 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.4, 145.5, 139.0, 136.3, 134.3, 132.4, 129.8, 128.3, 125.2, 124.3,

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123.8, 118.8, 113.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_9Cl_3NO$ calcd for 323.9750; found, 323.9753.

3-Chloro-6-fluoro-2-phenylquinolin-4(1H)-one (**2l**). White solid, yield = (73%, 40 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.44 (bs, 1H), 7.74−7.82 (m, 2H), 7.60−7.68 (m, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): δ −116.8 (s, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.8 (d, J_{CF} = 2.8 Hz), 158.2 (d, J_{CF} = 243.4 Hz), 148.4, 135.8, 133.2, 130.3, 129.2, 128.6, 124.8 (d, J_{CF} = 7.0 Hz), 121.7 (d, J_{CF} = 8.2 Hz), 121.3 (d, J_{CF} = 26.3 Hz), 112.9, 109.2 (d, J_{CF} = 22.6 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_{10}ClFNO_2$ calcd for 274.0435; found, 274.0417.

6-Bromo-3-chloro-2-phenylquinolin-4(1H)-one (**2m**). White solid, yield = (58%, 39 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.49 (bs, 1H), 7.73−7.81 (m, 2H), 7.58−7.66 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.2, 171.1, 160.0, 157.6, 150.1, 135.9, 135.0, 130.2, 129.2, 128.6, 124.2, 124.1, 121.7, 121.6, 121.4, 121.2, 109.5, 109.2, 105.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_{10}BrClNO$ calcd for 333.9634; found, 333.9622.

3-Chloro-6,7-dimethoxy-2-(p-tolyl)quinolin-4(1H)-one (**2n**). White solid, yield = (66%, 44 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.04 (bs, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.6, 153.3, 148.3, 147.3, 139.7, 134.8, 132.4, 129.1, 129.0, 117.2, 104.7, 104.4, 99.4, 55.8, 55.7, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{18}H_{18}ClNO_3$ calcd for 330.0897; found, 330.0883.

3-Chloro-2-heptylquinolin-4(1H)-one (**2o**).[31] White solid, yield = (71%, 39 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.03 (bs, 1H), 8.09 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.67 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.0, 150.8, 138.1, 138.6, 132.0, 125.2, 123.6, 123.5, 118.1, 113.4, 32.2, 31.2, 28.8, 28.4, 27.7, 22.1, 14.0.

3-Chloro-2,8-dimethylquinolin-4(1H)-one (**2p**). White solid, yield = (74%, 31 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 10.79 (bs, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 2.62 (s, 3H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.9, 147.7, 137.3, 132.9, 126.4, 123.8, 123.4, 123.2, 114.4, 18.7, 17.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{11}H_{11}ClNO$ calcd for 208.0529; found, 208.0522.

3-Chloroquinolin-4(1H)-one (**2q**). White solid, yield = (85%, 37 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.36 (bs, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.3, 139.2, 138.1, 132.0, 125.2, 124.8, 124.0, 118.7, 114.2. HRMS (ESI-TOF) m/z: $[M + K]^+$ C_9H_6ClNOK calcd for 217.9775; found, 217.9766.

3-Bromo-2-phenylquinolin-4(1H)-one (**3a**).[3] White solid, yield = (91%, 54 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.35 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.67−7.71 (m, 2H), 7.58−7.64 (m, 5H), 7.39−7.43 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.9, 150.0, 139.1, 135.1, 132.3, 130.1, 129.2, 128.6, 125.4, 124.2, 123.1, 118.7, 105.5.

3-Bromo-2-(p-tolyl)quinolin-4(1H)-one (**3b**).[29] White solid, yield = (96%, 60 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.66−7.70 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.38−7.40 (m, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 150.0, 139.8, 139.1, 132.3, 132.2, 129.0, 129.0, 125.4, 124.1, 123.0, 118.6, 105.4, 21.1.

3-Bromo-2-(3,5-dimethylphenyl)quinolin-4(1H)-one (**3c**). White solid, yield = (90%, 59 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.66−7.70 (m, 2H), 7.38−7.42 (m, 1H), 7.22 (s, 3H), 2.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 150.2, 139.1, 137.8, 135.0, 132.2, 131.3, 126.6, 125.4, 124.1, 123.0, 118.6, 105.3, 20.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{17}H_{15}BrNO$ calcd for 328.0337; found, 328.0320.

3-Bromo-2-(o-tolyl)quinolin-4(1H)-one (**3d**). White solid, yield = (96%, 60 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.38 (bs, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.69−7.74 (m, 1H), 7.62−7.64 (t, J = 8.4 Hz, 1H), 7.38−7.50 (m, 5H), 2.19 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.7, 150.0, 139.1, 135.5, 135.1, 132.3, 130.3, 130.0, 128.7, 126.2, 125.4, 124.2, 123.2, 118.6, 106.2, 18.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{16}H_{13}BrNO$ calcd for 314.0181; found, 314.0173.

3-Bromo-2-(4-methoxyphenyl)quinolin-4(1H)-one (**3e**).[29] White solid, yield = (79%, 52 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.21 (bs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.57−7.60 (m, 2H), 7.38−7.42 (m, 1H), 7.12−7.14 (m, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 160.5, 149.8, 139.1, 132.2, 130.8, 127.3, 125.4, 124.0, 123.0, 118.6, 113.8, 105.6, 55.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{16}H_{13}BrNO_2$ calcd for 330.0130; found, 330.0122.

2-(Benzo[d][1,3]dioxol-5-yl)-3-bromoquinolin-4(1H)-one (**3f**). White solid, yield = (92%, 63 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.66−7.70 (m, 2H), 7.39 (t, J = 6.8 Hz, 1H), 7.23 (s, 1H), 7.12 (s, 2H), 6.15 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 149.5, 148.6, 147.1, 139.0, 132.2, 128.6, 125.3, 124.1, 123.5, 123.0, 118.6, 109.8, 108.3, 105.6, 101.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{16}H_{11}BrNO_3$ calcd for 343.9922; found, 343.9904.

3-Bromo-2-(2-bromophenyl)quinolin-4(1H)-one (**3g**). White solid, yield = (74%, 56 mg). ^1H NMR (300 MHz, DMSO-d_6): δ 12.52 (bs, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.58−7.63 (m, 3H), 7.50−7.55 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 148.9, 139.1, 136.2, 132.7, 132.4, 131.9, 130.9, 128.2, 125.4, 124.3, 123.3, 121.8, 118.6, 106.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_{10}Br_2NO$ calcd for 377.9129; found, 377.9121.

3-Bromo-2-(3-bromophenyl)quinolin-4(1H)-one (**3h**). White solid, yield = (78%, 59 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.37 (bs, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.79−7.80 (m, 1H), 7.71−7.72 (m, 1H), 7.65−7.67 (m, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.42 (s, J = 6.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 148.5, 139.1, 137.2, 132.9, 132.4, 131.6, 130.7, 128.5, 125.4, 124.3, 123.1, 121.6, 118.7, 105.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_{10}Br_2NO$ calcd for 377.9129; found, 377.9119.

3-Bromo-2-(4-bromophenyl)quinolin-4(1H)-one (**3i**). White solid, yield = (77%, 58 mg). ^1H NMR (400 MHz, DMSO-d_6): δ 12.36 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.72−7.75 (m, 1H), 7.64−7.67 (m, 1H), 7.59−7.61 (m, 2H), 7.40−7.44 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.8, 148.9, 139.1134.2, 132.4, 131.5, 131.4, 125.4, 124.3, 123.6, 123.1, 118.7, 105.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_{10}Br_2NO$ calcd for 377.9129; found, 377.9125.

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3-Bromo-2-(2-(trifluoromethyl)phenyl)quinolin-4(1H)-one (**3j**). White solid, yield = (91%, 69 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (bs, 1H), 8.18 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.90 (t, J = 7.2 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.69−7.76 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H); ^{19}F NMR (376 MHz, DMSO-d_6): δ −58.5 (s, 3F); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.5, 147.7, 138.9, 133.1, 133.0, 132.5, 131.3, 130.8, 127.0, 126.7, 126.7, 126.6, 125.4, 125.1, 124.4, 123.2, 122.3, 118.5, 106.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{16}H_{10}BrF_3NO$ calcd for 367.9898; found, 367.9888.

3-Bromo-2-(3,5-dichlorophenyl)quinolin-4(1H)-one (**3k**). White solid, yield = (89%, 58 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.56 (bs, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.80 (s, 2H), 7.68−7.77 (m, 2H), 7.42 (t, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.7, 147.2, 139.1, 138.0, 134.1, 132.4, 129.6, 128.2, 125.3, 124.4, 123.2, 118.7, 105.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_9BrCl_2NO$ calcd for 367.9245; found, 367.9237.

3-Bromo-6-fluoro-2-phenylquinolin-4(1H)-one (**3l**). White solid, yield = (65%, 41 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.49 (bs, 1H), 7.73−7.81 (m, 2H), 7.58−7.66 (m, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): δ −116.7 (s, 1F); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2 (d, J_{CF} = 2.6 Hz), 158.8 (d, J_{CF} = 242.4 Hz), 150.1, 135.9, 135.0, 130.2, 129.2, 128.6, 124.2 (d, J_{CF} = 7.2 Hz), 121.6 (d, J_{CF} = 8.4 Hz), 121.3 (d, J_{CF} = 25.8 Hz), 109.3 (d, J_{CF} = 22.7 Hz), 105.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrFNO$ calcd for 317.9930; found, 317.9918.

6-Bromo-3-bromo-2-phenylquinolin-4(1H)-one (**3m**). White solid, yield = (63%, 48 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (bs, 1H), 8.24 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.61−7.66 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 170.3, 148.6, 137.8, 135.0, 133.1, 130.3, 129.2, 128.6, 127.2, 125.0, 121.3, 116.6, 113.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}Br_2NO$ calcd for 377.9129; found, 377.9121.

3-Bromo-6,7-dimethoxy-2-(p-tolyl)quinolin-4(1H)-one (**3n**). White solid, yield = (84%, 63 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 7.48−7.50 (m, 3H), 7.37 (d, J = 7.6 Hz, 2H), 7.16 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 170.4, 153.3, 148.4, 147.3, 139.7, 134.9, 132.3, 129.1, 128.9, 117.1, 104.6, 104.3, 99.4, 55.8, 55.7, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{18}H_{17}BrNO_3$ calcd for 374.0392; found, 374.0383.

3-Bromo-2-heptylquinolin-4(1H)-one (**3o**).[31] White solid, yield = (80%, 52 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 8.08 (dd, J_1 = 7.2 Hz, J_2 = 1.0 Hz, 1H), 7.67 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 2.86 (t, J_1 = 8.0 Hz, 2H), 1.66−1.70 (m, 2H), 1.22−1.36 (m, 8H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.4, 152.2, 138.1, 138.8, 132.0, 125.4, 123.8, 122.8, 118.1, 105.7, 34.7, 31.2, 28.8, 28.4, 27.8, 22.2, 14.1.

3-Bromo-2,8-dimethylquinolin-4(1H)-one (**3p**). White solid, yield = (85%, 43 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (bs, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.3, 149.1, 137.5, 132.9, 126.4, 123.5, 123.4, 123.1, 106.8, 21.5, 17.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{11}H_{11}BrNO$ calcd for 252.0024; found, 252.0016.

3-Bromoquinolin-4(1H)-one (**3q**).[29] White solid, yield = (86%, 43 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (bs, 1H), 8.48 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.69 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz,1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 171.5, 140.3, 139.4, 132.0, 125.3, 124.3, 124.1, 118.7, 104.2.

3-Iodo-2-phenylquinolin-4(1H)-one (**4a**).[29] White solid, yield = (86%, 53 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.31 (bs, 1H), 8.15 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.65−7.73 (m, 2H), 7.55−7.60 (m, 5H), 7.41 (dt, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.7, 153.2, 139.4, 138.0, 132.3, 130.0, 128.5, 125.6, 124.3, 121.0, 118.4, 86.0.

3-Iodo-2-(p-tolyl)quinolin-4(1H)-one (**4b**).[29] White solid, yield = (89%, 64 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.64−7.72 (m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.37−7.42 (m, 3H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 153.2, 139.6, 139.3, 135.2, 132.2, 129.0, 128.9, 125.6, 124.2, 120.9, 118.4, 86.0, 21.0.

3-Iodo-2-(4-methoxyphenyl)quinolin-4(1H)-one (**4c**).[29] White solid, yield = (95%, 72 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (bs, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.65−7.72 (m, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 0.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.7, 160.4, 153.0, 139.4, 132.2, 130.7, 130.2, 125.6, 124.2, 120.9, 118.4, 113.7, 86.3, 55.5.

2-(2-Bromophenyl)-3-iodoquinolin-4(1H)-one (**4d**). White solid, yield = (83%, 71 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.48 (bs, 1H), 8.16 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.84 (d, J_1 = 8.0 Hz, 1H), 7.70−7.74 (m, 1H), 7.49−7.63 (m, 4H), 7.41−7.44 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 152.2, 139.0, 132.7, 132.4, 131.7, 130.9, 128.1, 125.6, 124.4, 121.8, 121.2, 118.4, 87.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrINO$ calcd for 425.8991; found, 425.8994.

2-(3-Bromophenyl)-3-iodoquinolin-4(1H)-one (**4e**). White solid, yield = (71%, 60 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (bs, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.77−7.81 (m, 1H), 7.69−7.73 (m, 2H), 7.64−7.66 (m, 1H), 7.52−7.60 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 151.5, 139.9, 139.3, 132.7, 132.3, 131.6, 130.6, 128.5, 125.6, 124.4, 121.4, 121.0, 118.4, 86.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrINO$ calcd for 425.8991; found, 425.8986.

2-(4-Bromophenyl)-3-iodoquinolin-4(1H)-one (**4f**). White solid, yield = (78%, 66 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (bs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 7.2 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 152.1, 139.4, 137.0, 132.3, 131.4, 131.3, 125.6, 124.3, 123.4, 121.0, 118.4, 85.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{15}H_{10}BrINO$ calcd for 425.8991; found, 425.8998.

2-(3,5-Dimethylphenyl)-3-iodoquinolin-4(1H)-one (**4g**). White solid, yield = (90%, 68 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (bs, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.65−7.72 (m, 2H), 7.37−7.41 (m, 1H), 7.20 (s, 1H), 7.16 (s, 2H), 2.37 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.7, 153.4, 139.3, 137.9, 137.7, 132.2, 131.2, 126.6, 125.6, 124.3, 121.0, 118.4, 85.8, 21.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ $C_{17}H_{15}INO$ calcd for 376.0198; found, 376.0191.

2-(Benzo[d][1,3]dioxol-5-yl)-3-iodoquinolin-4(1H)-one (**4h**). Light yellow solid, yield = (96%, 75 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.66−7.70 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.05 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.7,

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152.7, 148.4, 147.0, 139.3, 132.2, 131.6, 125.5, 124.2, 123.4, 120.9, 118.4, 109.8, 108.3, 101.7, 86.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{16}H_{11}INO_3$ calcd for 391.9789; found, 391.9779.

*2-(3,5-Dichlorophenyl)-3-iodoquinolin-4(1H)-one (**4i**).* White solid, yield = (67%, 56 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.41 (bs, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.85 (t, J = 1.6 Hz, 1H), 7.71−7.75 (m, 3H), 7.62 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 150.3, 140.9, 139.3, 134.1, 132.4, 129.5, 128.1, 125.6, 124.5, 121.1, 118.4, 86.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{15}H_9Cl_2INO$ calcd for 415.9106; found, 415.9107.

*3-Iodoquinolin-4(1H)-one (**4j**).*[29] White solid, yield = (77%, 42 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.68 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.1, 144.7, 139.5, 132.0, 125.5, 124.2, 122.5, 118.5, 80.7.

*2-Heptyl-3-iodoquinolin-4(1H)-one (**4k**).* White solid, yield = (87%, 64 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (bs, 1H), 8.08 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.67 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.57 (d, J_2 = 8.0 Hz, 1H), 7.34 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 2.91 (t, J = 8.0 Hz, 2H), 1.64−1.70 (m, 2H), 1.22−1.41 (M, 8H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.2, 154.6, 139.1, 132.0, 125.6, 123.9, 120.7, 117.8, 85.9, 31.2, 28.8, 28.4, 28.0, 22.1, 14.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{16}H_{21}INO$ calcd for 370.0668; found, 370.0671.

*3-Iodo-2,8-dimethylquinolin-4(1H)-one (**4l**).* White solid, yield = (85%, 51 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (bs, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 6.8 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 3.33 (s, 3H), A2.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.2, 151.7, 137.7, 132.9, 126.1, 123.6, 123.6, 121.0, 87.2, 26.4, 17.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ $C_{11}H_{11}INO$ calcd for 299.9885; found, 299.9870.

*2-Phenyl-3-thiocyanatoquinolin-4(1H)-one (**6a**).*[23a] Light yellow solid, yield = (45%, 25 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.63 (bs, 1H), 8.20 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.78 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.63−7.72 (m, 6H), 7.51 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.6, 156.0, 139.3, 133.7, 133.1, 130.6, 129.0, 128.7, 125.4, 125.2, 123.8, 119.1, 111.9, 101.3.

*2-Phenyl-3-selenocyanatoquinolin-4(1H)-one (**7a**).*[23a] Light yellow solid, yield = (33%, 22 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (bs, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.60−7.79 (m, 7H), 7.45−7.49 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 173.8, 155.8, 139.5, 135.3, 132.9, 130.3, 129.1, 128.5, 125.6, 124.9, 123.4, 118.9, 104.7, 104.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05455.

Crystallographic data of this work (CIF)

Preparation procedures of the substrates **1a**−**3q**; thiocyanidation conditions screened of **1a**; and copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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