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Photoredox halogenation of quinolones: the dual role of halo-fluorescein dyes†

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An efficient C-3 halogenation of quinolin-4-ones is reported with halogenated fluorescein dyes which serve both as a halogen source and photocatalyst. This reaction shows broad substrate scope and gives good to excellent yields of C-3 brominated/iodinated quinolones with eosin Y/rose bengal in green light under ambient conditions. The mechanistic investigations suggest a radical pathway involving the oxidative dehalogenation of the dye in the presence of air.

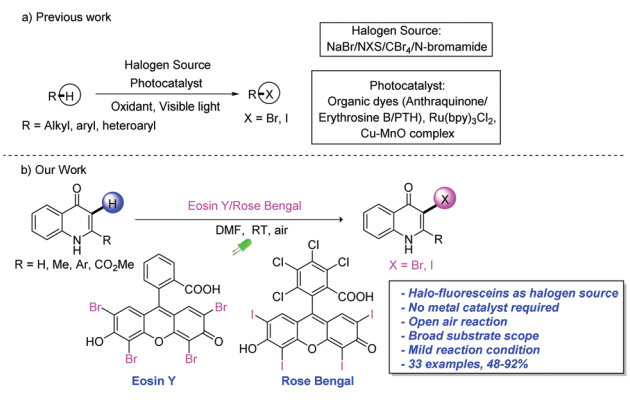
Introduction

Visible light photoredox catalysis has opened a new avenue for synthetic organic chemists to execute chemical reactions under mild and environmentally friendly conditions.[1] Recently, economically and ecologically benign fluorescein dyes such as eosin Y and rose bengal have been used as alternatives to transition-metal based photocatalysts in light mediated transformations involving single electron transfer (SET) and energy transfer pathways.[2] The use of halo-fluorescein dyes as photocatalysts has spanned a broad range of reactions including oxidation, reduction, cyclization, cross-coupling, addition and many more.[3] However, the use of these dyes as a halogen source in visible light has not been reported.

The introduction of the halogen atom into biologically active scaffolds is one of the most important transformations in organic synthesis.[4] Usually, halogenations with various halogenating reagents have been reported using metal/metal salt or oxidant/salt.[5] Though useful, most of these methods are associated with limitations such as the use of toxic metals, high temperature, harsh reaction conditions and side product formation. Therefore, the development of eco-friendly and transition metal free protocols for the halogenation of biologically active moieties is highly desirable. There are a few recent reports in which the halogenation of alkanes, arenes and heteroarenes has been carried out in visible light in the presence of an external oxidant, photocatalyst and halogenating reagent (Scheme 1a).[6]

Quinolin-4-ones possess a broad range of biological activities, such as anticancer, antimalarial, anti-HIV, antioxidant, and antibacterial activities, and they also act as xanthine oxidase inhibitors.[7,8] Recently, 3-halogenated quinolin-4-ones were used as building blocks for constructing biologically active molecules *via* cross-coupling[9,10] and C–N bond formation.[11] In the literature, C–3(H) halogenation of quinolin-4-ones has been reported *via* electrophilic addition of bromine and iodine with pyridinium tribromide/NBS/NIS or molecular bromine and iodine.[12] These reactions require an additional metal catalyst and base, a toxic halogenating source, and a dry solvent, and struggle with the lower reactivity of molecular bromine and iodine as halides.

Inspired by the recent report on the bromination of anilines[13] with eosin Y activated by selectfluor and as a continuation of our research towards exploring new synthetic strategies for the C-3 functionalization of quinolin-4-ones,[14] we investigated the bromination of quinolin-4-ones with eosin Y under visible light conditions (Scheme 1b). To the best of our knowledge, there is no report where halo-fluorescein dyes have been employed as halogenating reagents in visible light.



Scheme 1 Halogenation reactions in visible light.

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†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR and HRMS for all the synthesized compounds, and UV-Vis studies. See DOI: 10.1039/d1ob00538c

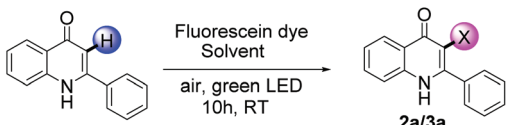
Results and discussion

We commenced our studies by the reaction of 2-phenyl quinolin-4-one (**1a**) with commercially available eosin Y/rose bengal in acetonitrile under air and a green LED. 50% of the C-3 brominated product (**2a**) and 42% of the C-3 iodinated product (**3a**) were isolated using eosin Y and rose bengal, respectively (Table 1, entry 1). Pleased with the result, screening of different solvents was carried out to improve the product yield (entries 2–8). DMF was found to be the best solvent, furnishing **2a** in 90% yield and **3a** in 85% yield (entry 3).

Next, the stoichiometry of the dyes was optimized. It was found that a lower yield of products **2a** (85%) and **3a** (74%) was obtained with 25 mol% of the dye (entry 9). With 50 mol% of the dye, 100% conversion of the starting material was observed though some unreacted dye was recovered at the end of the reaction. To confirm if air was essential for the reaction, it was carried out under a nitrogen atmosphere. As expected, the desired products **2a** and **3a** did not form in the absence of air (entry 10). Replacing air with an O_2 balloon did not help much and the desired products **2a** and **3a** were obtained in 91% and 84% yields, respectively (entry 11). Furthermore, it was found that the presence of a small quantity of water in the reaction did not affect the product yield substantially (entry 12) but on increasing the amount of water (>15%), moderate to poor yields were obtained. Changing the source of light from a green to a blue LED did not bring about any change in the product yield (entry 13) but the time required by the reaction to undergo completion increased to 14 h. This might be due to the weak absorption of eosin Y in the blue light region (~452 nm). No product formation was seen in the dark (entry 14), confirming the role of light in mediating the reaction.

With the best conditions in hand, the reaction scope was investigated by varying the substituents on the 2-aryl ring of quinolin-4-one (Table 2). We presume that the presence of an electron donating group on the 2-aryl ring tends to increase the HOMO of the electron donor intermediate, thus giving higher product yields. In contrast, electron withdrawing groups do not improve the HOMO level resulting in relatively lower product yields. As expected, we found that the electron donating methyl and methoxy groups at the C-4 position of the 2-aryl ring afforded C-3 brominated products in 79% and 83% yields, respectively (**2b** and **2c**). With benzyloxy and phenyl groups, the desired products **2d** and **2e** were obtained in 62% and 65% yields, respectively. C-4 halogenated derivatives (bromo, chloro and fluoro) afforded the corresponding products in 85–93% yields (**2f–2h**). Notably, it was observed that with C-3 substitution on the 2-aryl ring, lower product yields (**2i–2l**) were obtained. This may be attributed to the low HOMO level of the electron donor reaction intermediate. The 2-phenyl ring of quinolone substituted with dimethoxy, ethoxymethoxy, bromomethoxy and trimethoxy substituents gave the desired products in 78–90% yields (**2m–2q**). Bromination of C2–H and C2–methyl substituted quinolones gave the desired products **2r** and **2s** in 81% and 75% yields, respectively. Furthermore, even the *N*-protected 1-ethylquinolin-4(1*H*)-one showed good compatibility and the brominated product **2t** was obtained in 86% yield. Next, we tested the substrate scope with 2-CO_2Me substituted quinolone derivatives (8-methyl, 5-methoxy, 5-chloro) and in all cases, the desired products (**2u–2x**) were formed in low yields. Again, the electron with-

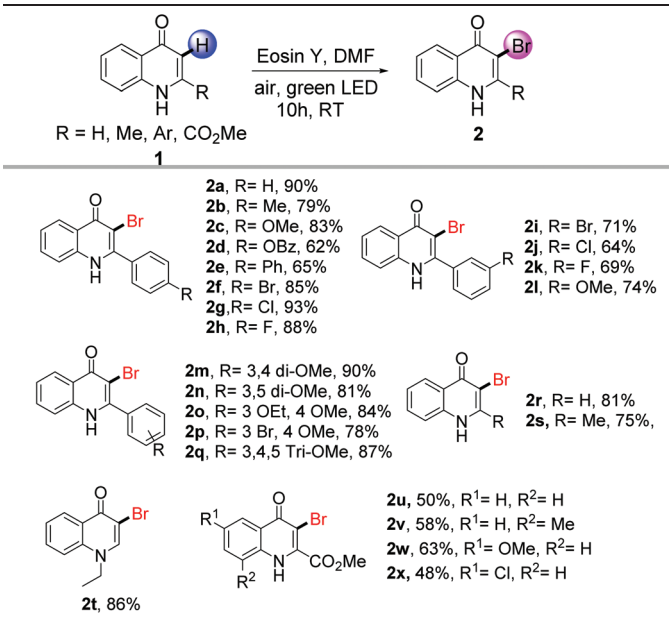
Table 1 Optimization of the reaction conditions[a]



Entry	Fluorescein dye	Solvent	Yield[b] (2a/3a)
1	Eosin Y/rose bengal	CH_3CN	50/42
2	Eosin Y/rose bengal	DMSO	80/51
3	Eosin Y/rose bengal	DMF	90/85
4	Eosin Y/rose bengal	DMA	54/50
5	Eosin Y/rose bengal	Toluene	23/10
6	Eosin Y/rose bengal	DCM	11/25
7	Eosin Y/rose bengal	Methanol	53/22
8	Eosin Y/rose bengal	THF	50/62
9	Eosin Y[c,d]/rose bengal[c,d]	DMF	85/74, 91/86
10[e]	Eosin Y/rose bengal	DMF	NR/NR
11[f]	Eosin Y/rose bengal	DMF	91/84
12[g]	Eosin Y/rose bengal	DMF	87/74
13[h]	Eosin Y/rose bengal	DMF	88/76
14[i]	Eosin Y/rose bengal	DMF	NR/NR

[a] Reaction conditions: **1a** (0.5 mmol), eosin Y/rose bengal (35 mol%, 0.175 mmol), solvent (5 mL), a green LED, rt, 10 h, air. [b] Isolated yield. [c] 25 mol% dye. [d] 50 mol% dye. [e] Under N_2. [f] Under O_2 (balloon). [g] 10% H_2O added. [h] Blue LED, 14 h. [i] Reaction carried out in the dark.

Table 2 Substrate scope for bromination[a]



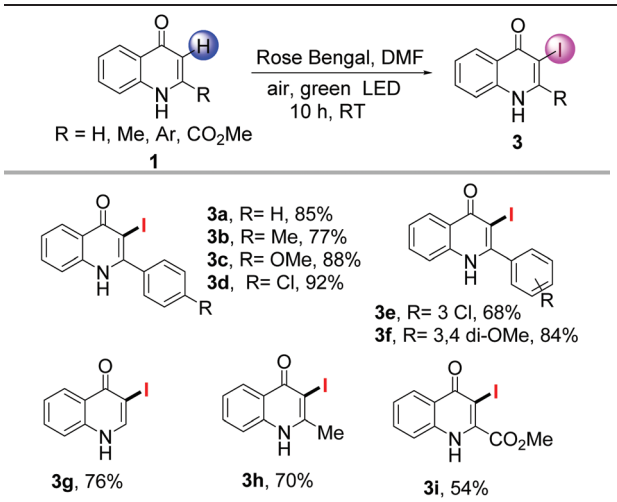
[a] Reaction conditions: **1** (0.5 mmol), eosin Y (0.175 mmol), DMF (5 mL), a green LED, rt, 10 h, air.

drawing nature of the 2-CO_2Me group decreases the HOMO level and hence the yield.

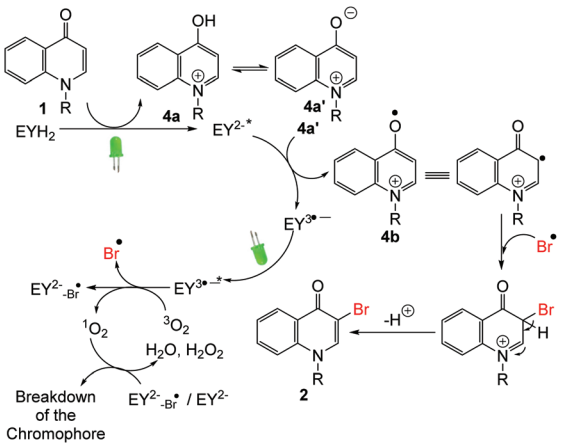
The substrate scope for iodination of various quinolin-4-ones was investigated with rose bengal (Table 3). The C-4 position of the 2-phenyl ring substituted with groups such as methyl, methoxy and chloro gave the desired iodinated products in 77%, 88% and 92% yields, respectively (**3b–3d**). However, 3-chloro and 3,4 dimethoxy groups on the 2-aryl ring gave the iodinated products in 68% and 84% yields, respectively (**3e** and **3f**). Furthermore, unsubstituted quinolone, and 2-Me and 2-COOMe substituted derivatives also yielded the iodinated products (**3g–3i**) in moderate yields.

To understand the mechanistic pathway, control experiments, and EPR and UV-Vis studies were performed. A dose dependent quenching with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) showed a complementary decrease in the product yield. Furthermore, a quinolone–TEMPO adduct was also observed, confirming the generation of the quinolyl radical in light (Fig. S1, ESI†). The EPR spectroscopy of the reaction mixture at room temperature showed a signal with a g value of 2.00352 and a line width ΔH = 3.44G, validating the formation of radical species (Fig. S2, ESI†). Time dependent UV-Vis absorption spectra of the reaction mixture in DMF showed a decrease in the intensity of the main absorption band of eosin Y at 536 nm, and the appearance of a new peak at 463 nm. This pointed out towards the co-existence of different debrominated eosin Y species in the reaction mixture, generated through oxidative degradation (Fig. S3, ESI†). We hypothesized that the oxidative debromination and degradation of eosin Y proceeded *via* excitation of semi-reduced eosin Y ($EY^{3\bullet-}$) followed by energy transfer from excited semi-reduced eosin Y ($EY^{3\bullet-}*$) to $^3O_2$, resulting in a high energy $^1O_2$. To confirm this, $^1O_2$ trapping experiment with terpinene[15] was carried out. As expected, a peroxidized product of terpinene was obtained with no change in the yield of halogenated products, confirming the energy transfer hypothesis (Fig. S4, ESI†).

Table 3 Substrate scope for iodination[a]



[a] Reaction conditions: 1 (0.5 mmol), rose bengal (0.175 mmol), DMF (5 mL), a green LED, rt, 10 h, air.



Scheme 2 Plausible mechanism.

Based on the experimental evidence and previous literature,[14,15] we propose a radical-mediated reaction initiation followed by oxidative dehalogenation of the dye, as shown in Scheme 2. The reaction starts with proton abstraction by quinolone from the hydrogenated eosin Y (**EYH_2**) in the presence of green LED. EYH_2 gets excited to a higher energy state and increases the acidity of the –COOH and –OH protons of EYH_2, thus facilitating the proton transfer.[16] This results in the formation of the dianionic excited form of eosin Y (**EY^{2-}***) and positively charged hydroxy quinoline (**4a**). On reacting with other quinolone molecules or the basic solvent, **4a** forms the zwitterion (**4a′**) which is comparatively electron rich (Scheme S1, ESI†). Furthermore, an electron transfer from **4a′** to EY^{2-}* takes place, resulting in the formation of semi-reduced $EY^{3\bullet-}$ and the quinolyl radical cation (**4b**).[15d] Next, the $EY^{3\bullet-}$ gets excited in light to form the excited semi-reduced $EY^{3\bullet-}$* which then undergoes oxidative debromination by transferring its energy to $^3O_2$ and furnishes a free Br$^\bullet$ radical. The resultant high energy $^1O_2$ reacts with EY^{2-}–Br$^\bullet$/EY^{2-} and breaks the eosin Y chromophore.[15a] The generated Br$^\bullet$ radical reacts with the quinolyl radical cation (**4b**) and yields the desired brominated product **2** *via* deprotonation.

Conclusions

In conclusion, we demonstrate the commercially available halofluorescein dyes as highly practical and atom economical halogenating reagents for oxidative halogenation of quinolin-4-ones under metal-free conditions. The fluorescein dyes play the dual role of a halogen source and photocatalyst in visible light. The mechanistic investigations suggest the reaction to follow a radical pathway and reveal the crucial role of oxygen in the photodegradative halo-radical formation, thus enabling a highly efficient, mild and regioselective halogenation protocol.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H 400 MHz, ^{13}C 100 MHz) and 500 MHz spectrometer (^{1}H 500 MHz, ^{13}C 125 MHz) using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are in δ (ppm) relative to TMS. Coupling constants (J) are in Hz and splitting patterns are described as singlet (s), doublet (d), triplet (t) and multiplet (m). Melting points were determined on melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were recorded on a mass spectrometer using electrospray ionization-time-of-flight (ESI-TOF) reflectron experiments. Reactions were monitored on silica gel TLC plates. All glass apparatus was oven dried prior to use. Flash chromatography was performed over silica gel (100–200 Mesh). All chemicals and reagents were obtained from Aldrich (USA) and Alfa Aesar (England) and were used without further purification. All starting materials (1) are known compounds and were synthesized using reported procedures.[17–19]

General procedure for the synthesis of products 2a–2x and 3a–3i

A solution of 2-phenylquinolin-4(1*H*)-one **1a** (110 mg, 0.5 mmol) and eosin Y or rose bengal (0.175 mmol) was taken in DMF (5 mL) and stirred under a green LED for 10 h at RT. The reaction was diluted with water (60 mL) and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over sodium sulphate (anhydrous) and evaporated under reduced pressure to give the desired product **2a** and **3a** in 90% and 85% yields respectively after flash chromatography.

Physical properties and characterization data of the synthesized compounds

3-Bromo-2-phenylquinolin-4(1*H*)-one (2a).[20] Isolated as a white solid, 90%, 135 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 6.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 5H), 7.43 (t, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 172.2, 150.4, 139.6, 135.5, 132.6, 130.4, 129.6, 128.9, 125.7, 124.4, 123.5, 119.0, 105.9.

3-Bromo-2-(*p*-tolyl)quinolin-4(1*H*)-one (2b). New, isolated as a white solid, 79%, 124 mg, mp 214–216 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.24 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 6.8 Hz, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.2, 150.4, 140.2, 139.5, 132.7, 132.6, 129.4, 129.4, 125.8, 124.5, 123.4, 118.9, 105.8, 21.4. HRMS (ESI, m/z) calcd for $C_{16}H_{13}BrNO$ [M + H]$^+$ 314.0175, found 314.0175.

3-Bromo-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (2c).[20] Isolated as a white solid, 83%, 137 mg. ^{1}H NMR (400 MHz, DMSO) δ 3.85 (s, 3H), 7.14 (d, J = 8.48 Hz, 2H), 7.39 (t, J = 6.48 Hz, 1H), 7.58 (d, J = 8.44 Hz, 2H), 7.66–7.72 (m, 2H), 8.15 (d, J = 8.0 Hz, 1H), 12.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 172.2, 160.9, 150.1, 139.4, 132.5, 131.1, 127.6, 125.7, 124.4, 123.3, 118.9, 114.2, 105.9, 55.9.

2-(4-(Benzyloxy)phenyl)-3-bromoquinolin-4(1*H*)-one (2d). New, isolated as a white solid, 62%, 126 mg, mp 268–270 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.24 (s, 1H), 8.22 (s, 1H), 7.79–7.69 (m, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.6 Hz, 3H), 7.41 (dd, J = 10.4, 14.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 5.29 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 172.3, 160.1, 150.3, 139.7, 137.2, 132.5, 131.2, 128.9, 128.4, 128.2, 127.9, 125.9, 124.4, 123.4, 119.0, 115.1, 106.1, 69.8. HRMS (ESI, m/z) calcd for $C_{22}H_{16}BrNO_2$ [M + Na]$^+$ 428.0257, found 428.0256.

2-([1,1′-Biphenyl]-4-yl)-3-bromoquinolin-4(1*H*)-one (2e). New, isolated as a white solid, 65%, 122 mg, mp 242–244 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 7.4 Hz, 2H), 7.72 (dd, J = 18.8, 8.1 Hz, 4H), 7.54 (t, J = 7.1 Hz, 2H), 7.49–7.39 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 172.3, 150.1, 142.2, 139.7, 139.5, 134.4, 132.6, 130.4, 130.2, 129.6, 128.5, 127.3, 127.1, 125.7, 124.6, 123.4, 119.0. HRMS (ESI, m/z) calcd for $C_{21}H_{14}BrNO$ [M + Na]$^+$ 398.0150, found 398.0150.

3-Bromo-2-(4-bromophenyl)quinolin-4(1*H*)-one (2f).[21] Isolated as a white solid, 85%, 160 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.75–7.68 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 149.2, 139.5, 134.6, 132.7, 131.9, 131.7, 125.7, 124.6, 124.0, 123.4, 119.0, 105.8.

3-Bromo-2-(4-chlorophenyl)quinolin-4(1*H*)-one (2g).[20] Isolated as a white solid, 93%, 154 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.68 (s, 5H), 7.43 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 149.2, 139.6, 135.3, 134.3, 132.6, 131.5, 128.9, 125.8, 124.6, 123.4, 119.0, 105.8.

3-Bromo-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2h).[20] Isolated as a white solid, 88%, 139 mg. ^{1}H NMR (500 MHz, DMSO) δ 12.38 (s, 1H), 8.17 (d, J = 6.0 Hz, 1H), 7.76–7.69 (m, 3H), 7.67 (d, J = 6.4 Hz, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.43 (dd, J = 5.6, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 172.2, 164.3, 162.3, 149.4, 139.4, 132.7, 132.1, 125.8, 124.6, 123.5, 119.0, 116.0, 115.8, 105.9.

3-Bromo-2-(3-bromophenyl)quinolin-4(1*H*)-one (2i). New, isolated as a white solid, 71%, 133 mg, mp 250–252 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.88 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 6.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 148.8, 139.4, 137.5, 133.2, 132.7, 132.0, 131.1, 128.8, 125.7, 124.6, 123.4, 121.9, 119.0, 106.2. HRMS (ESI, m/z) calcd for $C_{15}H_9Br_2NNaO$ [M + Na]$^+$ 401.8923, found 401.8923.

3-Bromo-2-(3-chlorophenyl)quinolin-4(1*H*)-one (2j). New, isolated as a white solid, 64%, 106 mg, mp 265–267 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.36 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.81–7.71 (m, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 3.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 172.2, 148.8, 139.5, 137.3, 133.5, 132.7, 130.8, 130.3, 129.3,

128.5, 125.7, 124.6, 123.5, 119.0, 105. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_9BrClNNaO$ $[M + Na]^+$ 355.9448, found 355.9447.

3-Bromo-2-(3-fluorophenyl)quinolin-4(1*H*)-one (2k). New, isolated as a white solid, 69%, 109 mg, mp 260–262 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.39 (s, 1H), 8.18 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 6.0 Hz, 1H), 7.68 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.47 (dd, J = 19.2, 120.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 163.3, 160.9, 149.1, 139.5, 137.3, 132.7, 131.2, 131.1, 125.9, 125.7, 124.6, 123.4, 119.0, 117.4, 117.2, 116.8, 116.6, 106.2. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_9BrFNNaO$ $[M + Na]^+$ 339.9744, found 339.9744.

3-Bromo-2-(3-methoxyphenyl)quinolin-4(1*H*)-one (2l). New, isolated as a white solid, 74%, 122 mg, mp 238–240 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.32 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.75–7.67 (m, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.46–7.39 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.16 (dd, J = 8.0, 9.0 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 172.2, 159.4, 150.1, 139.4, 136.6, 132.5, 130.1, 125.7, 124.5, 123.4, 121.7, 119.0, 115.9, 115.1, 105.7, 55.8. HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{12}BrNNaO_2$ $[M + Na]^+$ 351.9944, found 351.9944.

3-Bromo-2-(3,4-dimethoxyphenyl)quinolin-4(1*H*)-one (2m). New, isolated as a white solid, 90%, 162 mg, mp 208–210 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 8.16 (d, J = 6.4 Hz, 1H), 7.70 (s, 2H), 7.41 (s, 1H), 7.26 (s, 1H), 7.18 (d, J = 9.4 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.2, 150.5, 150.2, 148.6, 139.4, 132.4, 127.6, 125.7, 124.4, 123.3, 122.4, 118.9, 113.3, 111.8, 105.9, 56.2, 56.2. HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{15}BrNO_3$ $[M + H]^+$ 360.0230, found 360.0230.

3-Bromo-2-(3,5-dimethoxyphenyl)quinolin-4(1*H*)-one (2n). New, isolated as a white solid, 81%, 145 mg, mp 228–230 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.70 (s, 2H), 7.41 (s, 1H), 6.78 (s, 2H), 6.72 (s, 1H), 3.82 (s, 6H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 160.8, 150.2, 139.4, 137.2, 132.7, 125.7, 124.6, 123.5, 119.0, 107.6, 105.7, 101.9, 56.0. HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{15}BrNO_3$ $[M + H]^+$ 360.0230, found 360.0230.

3-Bromo-2-(3-ethoxy-4-methoxyphenyl)quinolin-4(1*H*)-one (2o). New, isolated as a white solid, 84%, 157 mg, mp 190–192 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.19 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.70 (s, 2H), 7.48–7.35 (m, 1H), 7.25 (s, 1H), 7.16 (d, J = 3.6 Hz, 2H), 4.13 (q, J = 5.1 Hz, 2H), 3.83 (s, 3H), 1.38 (t, J = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.4, 150.2, 149.7, 148.8, 139.4, 132.5, 127.6, 125.7, 124.4, 123.3, 122.4, 118.9, 113.4, 112.7, 105.8, 64.2, 56.1, 15.5. HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{16}BrNNaO_3$ $[M + Na]^+$ 396.0206, found 396.0204.

3-Bromo-2-(3-bromo-4-methoxyphenyl)quinolin-4(1*H*)-one (2p). New, isolated as a white solid, 78%, 158 mg, mp 238–240 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.29 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.42 (t, J = 7.0 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 172.2, 157.1, 148.7, 139.3, 133.8, 132.6, 130.8, 128.8, 125.8, 124.5, 123.3, 119.0, 112.7, 110.6, 106.0, 57.1. HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{11}Br_2NNaO_2$ $[M + Na]^+$ 431.9028, found 431.9029.

3-Bromo-2-(3,4,5-trimethoxyphenyl)quinolin-4(1*H*)-one (2q). New, isolated as a white solid, 87%, 169 mg, mp 254–256 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.27 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.83–7.59 (m, 2H), 7.41 (t, J = 8.5 Hz, 1H), 6.97 (s, 2H), 3.84 (s, 6H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, DMSO) δ 172.4, 153.5, 150.7, 139.3, 139.1, 132.5, 130.8, 125.7, 124.4, 123.3, 118.9, 107.3, 105.7, 60.6, 56.7. HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{16}BrNNaO_4$ $[M + Na]^+$ 412.0155, found 412.0154.

3-Bromoquinolin-4(1*H*)-one (2r).[22] Isolated as a white solid, 81% yield, 90 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.48 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 6.8 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 171.8, 140.6, 139.7, 132.3, 125.7, 124.7, 124.4, 119.0, 104.6.

3-Bromo-2-methylquinolin-4(1*H*)-one (2s).[23] Isolated as a white solid, 75% yield, 89 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.10 (d, J = 9.6 Hz, 1H), 7.68 (t, J = 6.8 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 6.8 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.5, 149.0, 139.2, 132.4, 126.1, 124.2, 123.3, 118.2, 106.4, 22.0.

3-Bromo-1-ethylquinolin-4(1*H*)-one (2t). New, isolated as a white solid, 86%, 108 mg, mp 198–200 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.65 (s, 1H), 8.4 (d, J = 8.4 Hz, 1H), 7.84–7.74 (m, 2H), 7.51–7.42 (m, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.3, 144.7, 139.1, 132.8, 126.7, 125.6, 124.6, 117.3, 104.3, 47.8, 14.9. HRMS (ESI, *m*/*z*) calcd for $C_{11}H_{10}BrNO$ $[M + Na]^+$ 273.9838, found 273.9837.

Methyl-3-bromo-4-oxo-1,4-dihydroquinoline-2-carboxylate (2u). New, isolated as a white solid, 50% yield, 70 mg, mp 220–222 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.76 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.79–7.70 (m, 2H), 7.45 (dd, J = 14.8, 8.0 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 162.6, 141.0, 139.0, 133.3, 125.7, 125.3, 123.8, 119.4, 103.6, 54.4. HRMS (ESI, *m*/*z*) calcd for $C_{11}H_8BrNO_3$ $[M + Na]^+$ 303.9580, found 303.9579.

Methyl-3-bromo-8-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylate (2v). New, isolated as a white solid, 55% yield, 81 mg, mp 130–132 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H), 8.05 (s, 1H), 7.60 (s, 1H), 7.36 (s, 1H), 3.99 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 162.6, 143.0, 137.9, 134.1, 127.7, 125.0, 124.1, 123.7, 102.6, 54.0, 17.8. HRMS (ESI, *m*/*z*) calcd for $C_{12}H_{10}BrNO_3$ $[M + Na]^+$ 317.9736, found 317.9736.

Methyl-3-bromo-6-methoxy-4-oxo-1,4-dihydroquinoline-2-carboxylate (2w). New, isolated as a white solid, 63% yield, 98 mg, mp 210–212 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.77 (s, 1H), 7.70 (d, J = 4.4 Hz, 1H), 7.51 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 4.00 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.1, 163.0, 141.0, 139.0, 133.3, 125.7, 125.3, 123.8, 119.4, 103.6, 54.4. HRMS (ESI, *m*/*z*) calcd for $C_{12}H_{10}BrNO_4$ $[M + Na]^+$ 333.9685, found 333.9685.

Methyl-3-bromo-6-chloro-4-oxo-1,4-dihydroquinoline-2-carboxylate (2x). New, isolated as a white solid, 48%, 75 mg, mp 218–220 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 8.08 (s, 1H), 7.86–7.72 (m, 2H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 171.2, 162.6, 141.1, 137.8, 133.4, 129.9, 124.6, 124.6, 122.0, 104.1, 54.3. HRMS (ESI, *m*/*z*) calcd for $C_{11}H_7BrClNNaO_3$ $[M + Na]^+$ 337.9190, found 337.9190.

3-Iodo-2-phenylquinolin-4(1*H*)-one (3a).[20] Isolated as a white solid, 85%, 147 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.75–7.64 (m, 2H), 7.58 (s, 5H), 7.41 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 174.0, 153.5, 139.7, 138.3, 132.6, 130.3, 129.4, 128.8, 125.9, 124.6, 121.3, 118.8, 86.3.

3-Iodo-2-(*p*-tolyl)quinolin-4(1*H*)-one (3b). New, isolated as a white solid, 77% yield, 139 mg, mp 224–226 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.14 (s, 1H), 7.68 (s, 2H), 7.45 (s, 2H), 7.38 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 173.9, 154.1, 140.2, 139.8, 135.9, 132.3, 129.3, 129.2, 125.9, 124.4, 121.5, 119.2, 86.3, 21.4. HRMS (ESI, m/z) calcd for $C_{16}H_{12}INNaO$ $[M + Na]^+$ 383.9856, found 383.9856.

3-Iodo-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (3c).[20] Isolated as a white solid, 88%, 144 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.21 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.74–7.62 (m, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 174.0, 160.7, 153.3, 139.8, 132.5, 131.1, 130.7, 125.9, 124.5, 121.2, 118.7, 114.1, 86.6, 55.9.

2-(4-Chlorophenyl)-3-iodoquinolin-4(1*H*)-one (3d).[20] Isolated as a white solid, 92% yield, 175 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.36 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 6.8 Hz, 1H), 7.64 (d, J = 11.2 Hz, 5H), 7.41 (t, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 174.1, 152.5, 140.1, 137.2, 135.0, 132.8, 131.5, 128.9, 126.1, 125.1, 121.7, 118.8, 86.4.

2-(3-Chlorophenyl)-3-iodoquinolin-4(1*H*)-one (3e). New, isolated as a white solid, 68%, 129 mg, mp 230–232 °C. ^{1}H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.77–7.71 (m, 1H), 7.69 (s, 1H), 7.67–7.65 (m, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 174.0, 152.0, 140.0, 139.7, 133.3, 132.7, 130.9, 130.2, 129.2, 128.4, 125.9, 124.8, 121.3, 118.8, 86.4. HRMS (ESI, m/z) calcd for $C_{15}H_9ClINNaO$ $[M + Na]^+$ 403.9310, found 403.9310.

2-(3,4-Dimethoxyphenyl)-3-iodoquinolin-4(1*H*)-one (3f). New, isolated as a white solid, 84%, 171 mg, mp 170–172 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.21 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.77–7.60 (m, 2H), 7.39–7.37 (m, 1H), 7.20 (s, 1H), 7.14 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 174.0, 153.2, 150.4, 148.6, 139.7, 132.5, 130.6, 125.9, 124.5, 122.3, 121.2, 118.7, 113.4, 111.7, 86.5, 56.2, 56.1. HRMS (ESI, m/z) calcd for $C_{17}H_{14}INNaO_3$ $[M + Na]^+$ 429.9911, found 429.9920.

3-Iodoquinolin-4(1*H*)-one (3g).[22] Isolated as a white solid, 76%, 103 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 8.51 (d, J = 6.4 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 14.0, 8.4 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 173.6, 145.1, 139.9, 132.4, 125.9, 124.6, 122.9, 118.8, 81.0.

3-Iodo-2-methylquinolin-4(1*H*)-one (3h).[24] Isolated as a white solid, 70%, 71 mg. ^{1}H NMR (400 MHz, DMSO) δ 12.18 (s, 1H), 8.08 (dd, J = 8.0, 8.0 Hz, 1H), 7.68–7.65 (m, J = 8.4, 7.1, 1.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.41–7.30 (m, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 173.3, 151.8, 139.3, 132.4, 125.9, 124.3, 121.0, 118.1, 86.5, 26.6.

Methyl-3-iodo-4-oxo-1,4-dihydroquinoline-2-carboxylate (3i). New, isolated as a white solid, 54%, 89 mg, mp 182–184 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.71 (s, 1H), 8.12 (d, J = 7.2 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 174.0, 163.6, 144.4, 139.3, 133.4, 126.0, 125.4, 121.8, 119.1, 82.0, 54.1. HRMS (ESI, m/z) calcd for $C_{11}H_8INNaO_3$ $[M + Na]^+$ 351.9441, found 351.9441.

Conflicts of interest

There are no conflicts to declare.

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