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Room-Temperature Synthesis of Isoindolone Spirosuccinimides: Merger of Visible-Light Photocatalysis and Cobalt-Catalyzed C−H Activation

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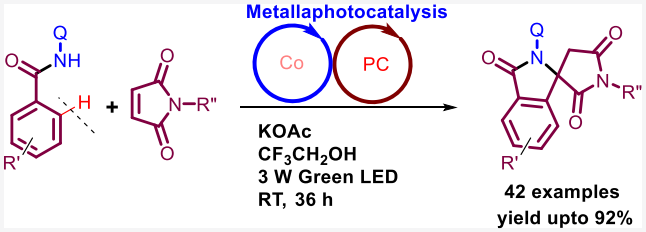
ABSTRACT: A room-temperature C−H bond functionalization of benzamides has been developed by merging a photocatalyst with a cobalt catalyst for the synthesis of isoindolone spirosuccinimides. The reaction proceeds in aerobic conditions and does not require any sacrificial external oxidants such as Ag(I) or Mn(III) salts. Visible light activates the photocatalyst, and it acts as an electron-transfer reagent and helps in the fundamental organometallic steps by modulating the oxidation state of the cobalt complex. This C−H bond functionalization and spirocyclization showed wide substrate scope and good functional group tolerance. A possible reaction mechanism was proposed from the experimental outcome, showing that C−H bond activation is irreversible and not the rate-determining step.



INTRODUCTION

The directing group-assisted transition-metal (TM)-catalyzed functionalization of unactivated C−H bonds is a research area that has received intensive investigation in recent years due to its atom economy and environmentally benign characteristics.[1] The majority of the C−H functionalization is carried out using precious 4d and 5d TM catalysts.[2] Unfortunately, these TM catalysts are rather toxic and cost-intensive. In addition, the presence of toxic metal contamination in the final product is highly undesirable in the synthesis of agrochemicals and pharmaceutical molecules. These factors motivate chemists to look for earth-abundant, economic, and less toxic 3d TM catalysts for C−H bond activation.[3] In this context, the cobalt catalyst played a central role and received significant attention by the chemists on C−H functionalization.[4]

N-containing heterocyclic compounds are a very important class of organic molecules in medicinal chemistry; around 59% of commercial drugs contain a nitrogen heterocycle.[5] Among them, isoindolone and succinimide moieties are present in several natural products and biologically active molecules.[6] Spirosuccinimide derivatives like ranirestat and minalrestat are used as aldose reductase inhibitors.[7] Synthesis of a spirocyclic succinimide compound is always a challenging task for the synthetic organic chemist starting with a maleimide as it prefers a Michael-type conjugate addition products.[8] In 2015, Miura and co-workers reported $Cu(OAc)_2/Cy_2NMe$-mediated C−H functionalization of benzamides with maleimide for the synthesis of spirosuccinimides using Duagulis auxiliary 8-aminoquinoline as a directing group.[9] However, super-stoichiometric (4 equiv) use of copper acetate is one of the limitations. The Zhang group reported a Cp*Co(III)/Ag(I) catalytic system for the spiroannulation of benzimidates with maleimides.[10] In 2017, Jeganmohan and co-workers reported the synthesis of isoindolone spirosuccinimides using cobalt(II) acetate as a catalyst; however, major drawback of this catalytic system is the excess use of sacrificial oxidants of Ag(I) salts. The role of the sacrificial oxidant is to reoxidize the *in situ* formed low-valent Co(I) to active high valent Co(II)/Co(III) species to continue the catalytic cycle.[11]

In principle, photocatalysts can do a similar job: the role of these catalysts is to adjust the oxidation state of the TM through synergistic catalysis.[12] In general, a photocatalyst on irradiation with light, upon excitation, either can take an electron or can give an electron to an organic or organometallic substrate *via* single electron transfer (SET).[13] Thus, it can effectively activate other TM catalysts, which are ineffective in the absence of a photocatalyst and light or can generate a reactive radical species under very mild conditions. In recent years, metallaphotocatalysis, the merger of TM catalysis and photocatalysis, has emerged as a new route for the development of C−H functionalization synthetic methodologies under mild conditions.[12,14] In this regard, pioneering work was carried out by Sanford and co-workers by merging the visible light photoredox catalyst $[Ru(bpy)_3]$ and palladium catalyst for C−C coupling reactions.[15] After this report, several works have

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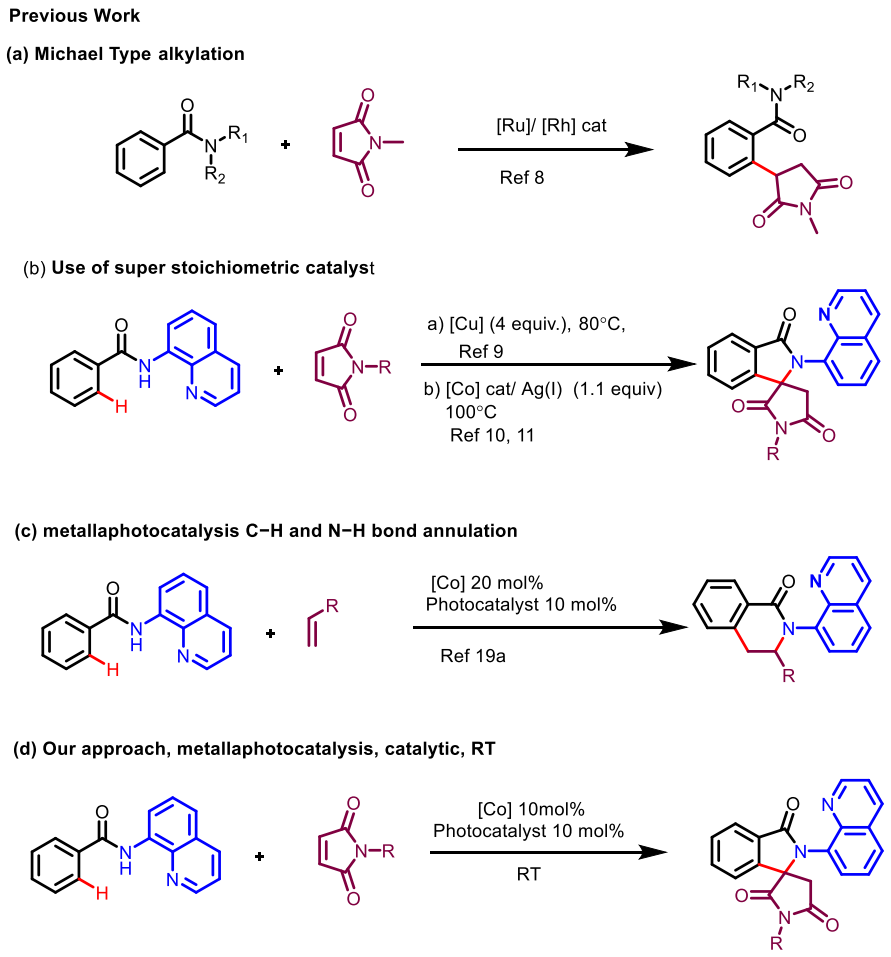
Scheme 1. Previous and Present Work on Spirocyclic Succinimide Synthesis and Metallaphotocatalysis on C−H and N−H Bond Annulation



been carried out by merging different photocatalysts with 3d, 4d, and 5d TMs.[16] Among these, 3d TMs like Cu, Co, and Ni are more preferable as they are economic and more earth-abundant to 4d/5d TMs. In 3d series metallophotocatalysis, nickel/photo redox,[17] copper/photo redox,[18] and cobalt/photoredox[19] catalytic systems have showcased several challenging direct C−C and C-heteroatom bond formation reactions under mild reaction conditions. Sundararaju and coworkers reported C−H and N−H bond annulation with alkene, any alkyne by merging cobalt catalyst with a suitable photocatalyst (Scheme 1c).[19a,b] Along the same lines, in our continuous effort to develop a sustainable catalytic system for the C−H functionalization reaction,[20] we herein report a readily available Co-catalyst, $Co(acac)_2$, in combination with a commonly available organic dye, Eosin-Y, as a photocatalyst provided isoindolone spirosuccinimides in good to excellent yields by oxidative cyclization of benzamides with maleimides *via* 8-aminoquinoline directed C−H activation at room temperature and without any sacrificial metal oxidant.

RESULTS AND DISCUSSION

We have begun our reaction optimization study by choosing *N*-(quinolin-8-yl)benzamide (**1a**) and *N*-methylmaleimide (**2a**) as model substrates. The initial optimization study was carried out using 0.25 mmol of **1a**, with 2 equiv of **2a**, by employing 10 mol % $Co(acac)_2$ as a catalyst, 3 equiv of KOAc as a base in 1.5 mL trifluoroethanol (TFE) (CF_3CH_2OH) solvent under irradiation with 3 W (3 W × 4) green light-emitting diode (LED) light at room temperature in the presence of a suitable photocatalyst (Table 1). To our delight, $Ru(bpy)_3(PF_6)_2$ (2 mol %) as a photocatalyst works very well and, our strategy of merger of the photocatalyst with the TM catalyst is found to be successful, we got the desired spirosuccnimide in 86% yield (entry 1, Table 1). Next, we have checked other common organic photocatalysts (10 mol %) for this reaction, and indeed, most of them are working very well (entries 2−6) and the economic Eosin-Y provides the best yield (entry 3, 91%).

In the control experiment, changing one parameter at a time reveals that the presence of KOAc, photocatalyst, oxygen, light, and cobalt catalyst all are mandatory for this reaction, and in the absence of one of them, reaction does not proceed (entries 7−11). When the reaction was carried out under an oxygen balloon, similar yield was observed (92%, entry 12). Next, we screen the solvent for this reaction: benzo trifluoride (BTF, entry 13) and hexafluoroisopropanol (HFIP, entry 14) were ineffective and acetonitrile, dichloroethane (DCE), and methanol provide the lower yield (entries 15−17).

With the optimization condition in hand, we next explore the substrate scope for the annulation reaction with substituted benzamides with *N*-methyl maleimide **2a** (Table 2). A variety of para-substituted benzamides with sensitive functional groups such as -methoxy, halides, −CHO, −CN, and $-NO_2$ are well compatible. Electron-releasing groups, like −Me and −OMe,

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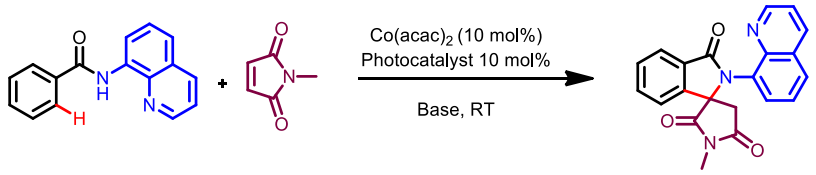
Table 1. Screening of Reaction Conditions[a]



entry	photocatalyst (mol %)	additive	Solvent	yield (%)[b]
1	$Ru(bpy)_3(PF_6)_2$ (2)	KOAc	CF_3CH_2OH	86
2	rhodamine B (10)	KOAc	CF_3CH_2OH	67
3	Eosin-Y (10)	KOAc	CF_3CH_2OH	91
4	rose bengal (10)	KOAc	CF_3CH_2OH	85
5	9-mesityl-10-methylacridinium perchlorate (10)	KOAc	CF_3CH_2OH	62
6	Na_2Eosin-Y (10)	KOAc	CF_3CH_2OH	89
7	Eosin-Y (10)		CF_3CH_2OH	trace
8		KOAc	CF_3CH_2OH	NR
9	Eosin-Y (10)	KOAc	CF_3CH_2OH	NR[c]
10	Eosin-Y (10)	KOAc	CF_3CH_2OH	NR[d]
11	Eosin-Y (10)	KOAc	CF_3CH_2OH	NR[e]
12	Eosin-Y (10)	KOAc	CF_3CH_2OH	92[f]
13	Eosin-Y (10)	KOAc	BTF	trace
14	Eosin-Y (10)	KOAc	HFIP	NR
15	Eosin-Y (10)	KOAc	CH_3CN	55
16	Eosin-Y (10)	KOAc	DCE	12
17	Eosin-Y (10)	KOAc	MeOH	19

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), $Co(acac)_2$ (10 mol %), photocatalyst (2−10 mol %), KOAc (3 equiv), 3 W (3 W × 4) green LED light, room temperature, open to air, 36 h, 1.5 mL solvent. [b]Isolated yield. [c]Under an argon atmosphere. [d]Without light. [e]In the absence of the Co-catalyst. [f]Under an oxygen atmosphere.

proceed well and gave the desired product in excellent yields (**3b**, 90%; **3c**, 86%). Halides (−F, −Cl, −Br, and −I)-substituted benzamides (**1d**−**1g**) provide the desired product in very good to excellent yields (entries **3d**−**3g**, 92, 90, 75, 77%, respectively). Electron-withdrawing $-CF_3$ (**3h**, 89%), −CN (**3i**, 76%), −CHO (**3j**, 69%), $-NO_2$ (**3k**, 55%)-substituted benzamides are also effective and provide the spiro annulated product in high yields. In general, the presence of the electron-withdrawing group in the arene provides a lower yield compared to electron-rich benzamides. Furthermore, the structure of compounds **3a**, **3h**, and **3j** were well characterized by X-ray crystallography.[21] Ortho-substituted benzamides −Me (**3l**, 70%), −OMe (**3m**, 61%), −F (**3n**, 81%, and $-NO_2$ (**3o**, 67%) provide the desired product in good yields.

Next, we check the reaction with meta-substituted substrates, that is, unsymmetrical benzamides, where two *ortho*-H is available for activation; to our delight, the reaction proceeds selectively on the less hindered side irrespective to the electronic nature of the substituent. The reaction with *meta*-Me, -Br, -CN-substituted benzamides with **2a** gave the desired product (**3p**, 65%; **3q**, 62%; and **3r**, 67%) in good yields. 3,4,5 tri-methoxy-substituted benzamides also proceed very well, and 68% (**3s**) of the desired product is obtained. Other N-substituted maleimides (Ph, **2b**, -*p*-tolyl, **2c**) also proceed well and gave the desired cyclized product in good yields (entry **3t**−**3u**). The cyclization reaction proceeds well with naphthalene-1-carboxamide and 2-thienyl amide and afford the desired product in 68% (**3v**) and 66% (**3w**), respectively. However, picolinamide (**1x**) and aryl sulfonamide (**1y**) derivatives were not compatible under the present optimized conditions.

Next, we further elaborate on the scope of these oxidative cyclization reactions with various functional groups substituting 8-amino quinoline derivatives as a directing group. The functional groups such as −Me, −OMe, −F, −Cl, −Br, −I, $-CF_3$, $-NO_2$, and −Ph group at different positions of the quinoline ring were explored, and the result is summarized in Table 3. Initially, C-6 substituted quinoline derivative with electron-donating substituent and halide (weak deactivating) substituted DG are tested, all of them proceed smoothly and gave the desired spiro-succinimide in very good to excellent yields (71−92%, Table 3, entries **5a**−**5e**). However, a strong electron-withdrawing trifluoromethyl ($-CF_3$) group at the C-6 position gave somewhat lower yield (41%, **5f**). For electron-donating methoxy group, weakly deactivating halide substituted at the C-5 position of quinoline derivatives works efficiently and gave the desired product in excellent yields (**5g**, −OMe, 91%; **5h**, −Cl, 88%; **5i**, −Br, 91%, and **5j**, −I, 89%), but as observed previously, strong electron-withdrawing substituents ($-CF_3$ and $-NO_2$) proceed in lower yields (**5k**, 54%; **5l**, 51%). Ester substituted (C5 position) also proceeds very well (**5m**, 85%). Iodo substituted at the C-3 position of quinoline also works very well, and the desired product is obtained in high yields (**5n**, 89%).

Additionally, compound **5h** and **5m** were characterized by X-ray crystallography.[21] 5,7 dichloro-substituted quinoline also proceeds well (**5o**, 65%). However, a *tert*-butyl group at the C2-position (**5p**) remains unreactive, might be due to the steric hindrance. Furthermore, to demonstrate the synthetic applicability, the reaction can be scaled up to a gram scale very easily without affecting the yield (Scheme 2a).

The halide-substituted isoindolone spirosuccinimides (**5n**) was efficiently coupled with phenylboronic acid under Suzuki coupling conditions (Scheme 2b),[22] thus late-stage function-

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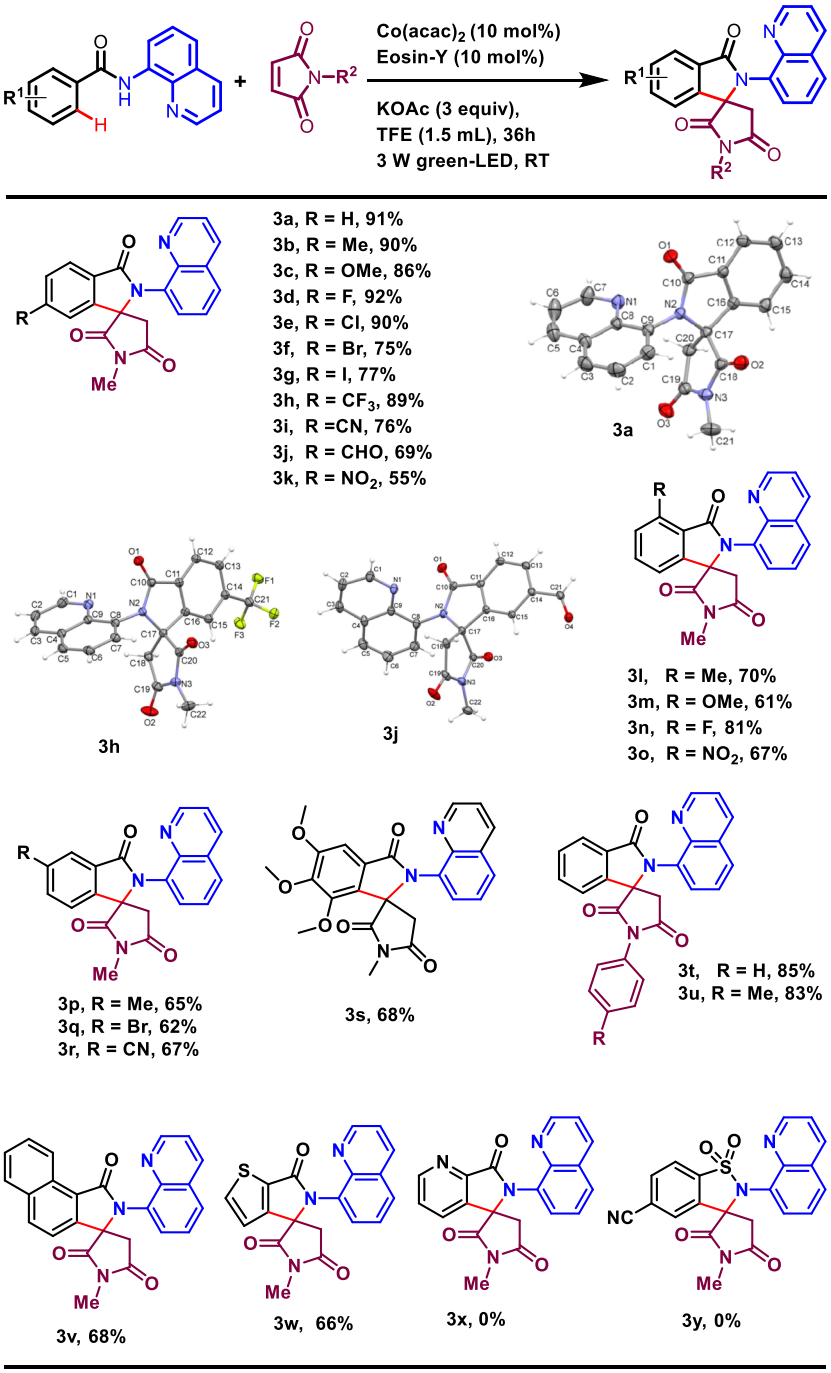
Table 2. Substrate Scope for Various Substituted Benzamides[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), $Co(acac)_2$ (10 mol %), Eosin-Y (10 mol %), KOAc (3 equiv), 3 W (3 W × 4) green LED light, room temperature, open to air, 36 h, 1.5 mL TFE.

alization to obtain an arylated product is possible. Finally, we have successfully removed the directing group,[9] and free NH-isoindolone spirosuccinimides were obtained in moderate yields (Scheme 2c). Next, we turned our attention to gain an insight into the reaction mechanism. First, we carried out the reaction in the presence of a radical scavenger like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxyl toluene (BHT) which significantly suppressed or completely inhibited the reaction (Scheme 3a) and indicated the involvement of the SET process during the catalytic cycle. Next, the H/D exchange experiment was checked (Scheme 3b), and no H/D exchange was observed in the recovered starting material as well as in the products. This study indicates the irreversibility of C−H bond activation. The parallel kinetic isotope effect (KIE) experiment was carried out next by the intermolecular competitive reaction of two isotopomeric substrates (**1a** and **1a-D$_2$**, Scheme 3c), and the k_H/k_D value was observed 1.04, which indicates that C−H bond activation is not the rate-determining step and it is irreversible. Finally, a five-membered organometallic Co(III) metallacycle was identified by high-resolution mass spectrometry (HRMS) (Scheme 3d), which further validate the involvement of

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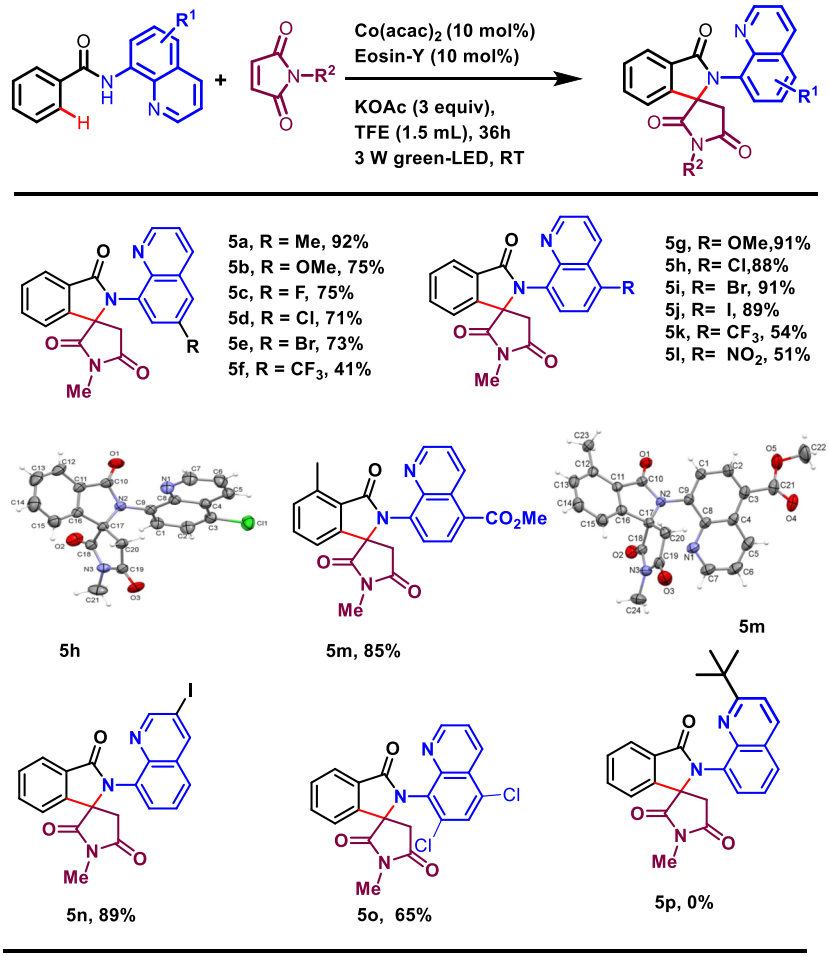
Table 3. Substrate Scope for Various Substituted 8-Amino Quinoline Derivatives as a Directing Group[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), $Co(acac)_2$ (10 mol %), Eosin-Y (10 mol %), KOAc (3 equiv), 3 W (3 W × 4) green LED light, room temperature, open to air, 36 h, 1.5 mL TFE.

Co(III) metallacycle in the reaction mechanism.[23] We have detected the presence of hydrogen peroxide in the reaction mixture using the KI/starch experiment, which confirms the formation of superoxide radical anion (ROS).[19a,b] Based on the experimental outcome and in accordance with the literature report,[11,19,23] a plausible reaction mechanism has been depicted in Scheme 4. Initially, Co(II) undergoes the ligand exchange, followed by the photocatalytic SET oxidation by Eosin-Y to obtain Co(III) complex (B). This Co(III) complex subsequently undergoes concerted metalation deprotonation to the cobaltacycle intermediate (C). Maleimide insertion takes place with the Co−C of intermediate C to afford intermediate D. *β*-hydride elimination followed by intramolecular insertion of amide N to the double bond leads to intermediate F. Finally, reductive elimination provides the desired spirocyclic product 3 along with the Co(I) species. This Co(I) is further oxidized by Eosin-Y in the presence of light and air to regenerate Co(II) species to continue the catalytic cycle (Scheme 4).

CONCLUSIONS

In conclusion, we have developed a convenient and efficient catalytic approach by merging a photocatalyst with a cobalt catalyst for the oxidative coupling of benzamides with maleimides to synthesize spirosuccinimides. The reaction was carried out under remarkably mild conditions at room temperature and without stoichiometric use of sacrificial oxidant. The reaction exhibits a vast substrate scope and excellent functional group tolerance such as aldehyde, ester, nitrile, and halides.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in an oven-dried glassware under standard reaction conditions. All chemicals were purchased from TCI Company and used without further purifications. ACN, DCE, and MeOH solvents were dried by the standard reported procedures and stored over activated molecular sieves. Purification of compounds carried out by flash chromatography (200−400 mesh silica gel) was used by gradient elution of ethyl acetate (EA) and the hexane mixture. $^1H/^{13}C$ NMR was recorded on a 600/151 MHz or 500/125 MHz NMR spectrometer in $CDCl_3$ unless otherwise mentioned using tetramethylsilane (TMS) as the reference in ppm. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet, and dd = doublet of a doublet. The coupling constant *J* was reported in hertz (Hz). Mass spectral data for the new compound were obtained using the electrospray ionization (ESI) time-of-flight mode on the mass spectrometer.

Experimental Procedure for Spirocyclization Reaction. *Representative Procedure.* To a mixture of *N*-(quinolin-8-yl)-benzamide **1a** (62 mg, 0.25 mmol, 1 equiv), *N*-methylmaleimide **2a** (55.5 mg, 0.5 mmol, 2 equiv), Eosin-Y (16 mg, 10 mol %), and

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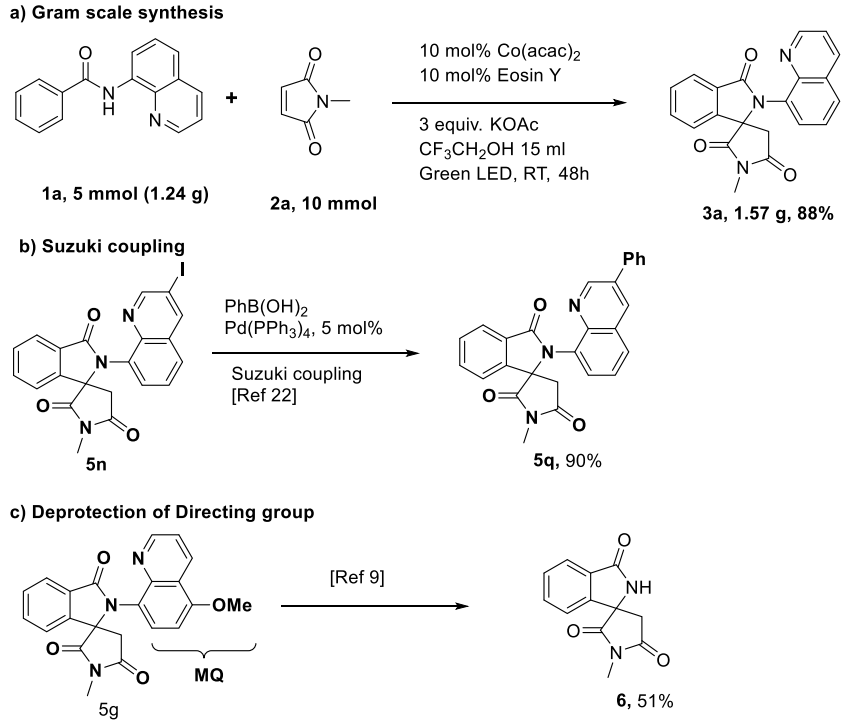
Scheme 2. Synthetic Applications



$Co(acac)_2$ (6 mg, 10 mol %) in 1.5 mL TFE was added potassium acetate (74 mg, 0.75 mmol, 3 equiv) under an air atmosphere. The reaction mixture was stirred at room temperature for 30 s; it looks like a clear red solution. Then, the reaction mixture was placed in a closed chamber and irradiated using a 3 W [3 W × 4, Murphy Base B22 3-Watt LED Globe Bulb (green): item part number, MLBL-ST-03GR-2] green LED light bulb at a distance of about 5 cm for 36 h. After completion of the reaction, the solvent was removed under reduced pressure. The crude mixture was extracted with water (15 mL)−EA (3 × 25 mL) and washed with brine solution (20 mL). The combined organic layer was dried over Na_2SO_4. The organic part was removed under reduced pressure, and the residue was obtained which was purified by flash chromatography using hexane/EA (50/50) as an eluent to isolate the desired spiro product **3a** (yield 81 mg, 91%, white solid). All other spiro products were prepared following this general procedure and purified by flash chromatography using hexane/EA (70/30 to 50/50) as an eluent.

Control Experiments Study for the Mechanism. *Control Experiment in the Presence of Radical Quencher.* To a mixture of *N*-(quinolin-8-yl)benzamide **1a** (62 mg, 0.25 mmol, 1 equiv), *N*-methylmaleimide **2a** (55.5 mg, 0.5 mmol, 2 equiv), potassium acetate (74 mg, 0.75 mmol, 3 equiv), photocatalyst Eosin-Y (16 mg, 10 mol %), and $Co(acac)_2$ (6 mg, 10 mol %) was added a radical inhibitor TEMPO or BHT. Solvent TFE (1.5 mL) was added over it under an air atmosphere. The reaction mixture was stirred at RT for 30 s. Then, the reaction mixture was placed in a closed chamber and irradiated using a 3 W [3 W × 4, Murphy Base B22 3-Watt LED Globe Bulb (green): item part number, MLBL-ST-03GR-2] green LED light bulb at a distance of about 5 cm. After 36 h, **3a** product was obtained as 25% (TEMPO, 1 equiv) and 11% (TEMPO, 2 equiv) which implied that the reaction was partially inhibited in the presence of TEMPO.

In the case of BHT (1 equiv), we monitored the reaction by TLC, no product (**3a**) was observed even after 36 h, and the experiment indicates that the reaction was completely inhibited by the radical quencher BHT.

H/D Exchange Experiments.

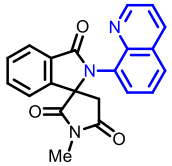
(A) An experiment was performed using **1a-D$_2$** (99% D) as a starting compound in the presence of *N*-methylmaleimide (**2a**) under standard reaction conditions for 5 h. After the reaction, the recovered starting material (**1a**, 79%) along with the isolated spiro product (**3a**, 18%) were checked in NMR, and it was found that no H/D exchange has been taken place in the starting material as well as in the product.

(B) A parallel reaction has also been carried out in the absence of *N*-methylmaleimide (**2a**) for 36 h. The recovered starting material (**1a**, 98%) was checked in NMR, and it was found that no H/D exchange has been taken place.

These experiments confirmed that the H/D interchange is irreversible.

KI/Starch Indicator Experiment.[19a,b] To a mixture of **1a** (62 mg, 0.25 mmol, 1 equiv), **2a** (55.5 mg, 0.5 mmol, 2 equiv), Eosin-Y (16 mg, 10 mol %), $Co(acac)_2$ (6 mg, 10 mol %), KI (1 equiv) in 1.5 mL TFE was added potassium acetate (74 mg, 0.75 mmol, 3 equiv) under an air atmosphere. Then, the reaction mixture was placed in a closed chamber and irradiated using a 3 W [3 W × 4, Murphy Base B22 3-Watt LED Globe Bulb (green): item part number, MLBL-ST-03GR-2] green LED light bulb source at a distance of about 5 cm for 36 h. To this reaction mixture, starch solution was added which led to a color change and formed a blue black solution. This result indicates the presence of superoxide anion in the reaction mixture.

Physical Properties and Characterization Data of the Synthesized Spiro Products. *1′-Methyl-2-(quinolin-8-yl)spiro-[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3a**).*[9]



White solid, mp 272−273 °C, hexane/EtOAc (50/50), 91% (81 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.85 (d, J = 4.7 Hz, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.68−7.66 (m, 1H), 7.65−7.60 (m, 2H), 7.46 (dd, J = 8.2, 4.3 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 3.38 (d, J = 18.9 Hz, 1H), 3.17 (d, J = 19.2 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ

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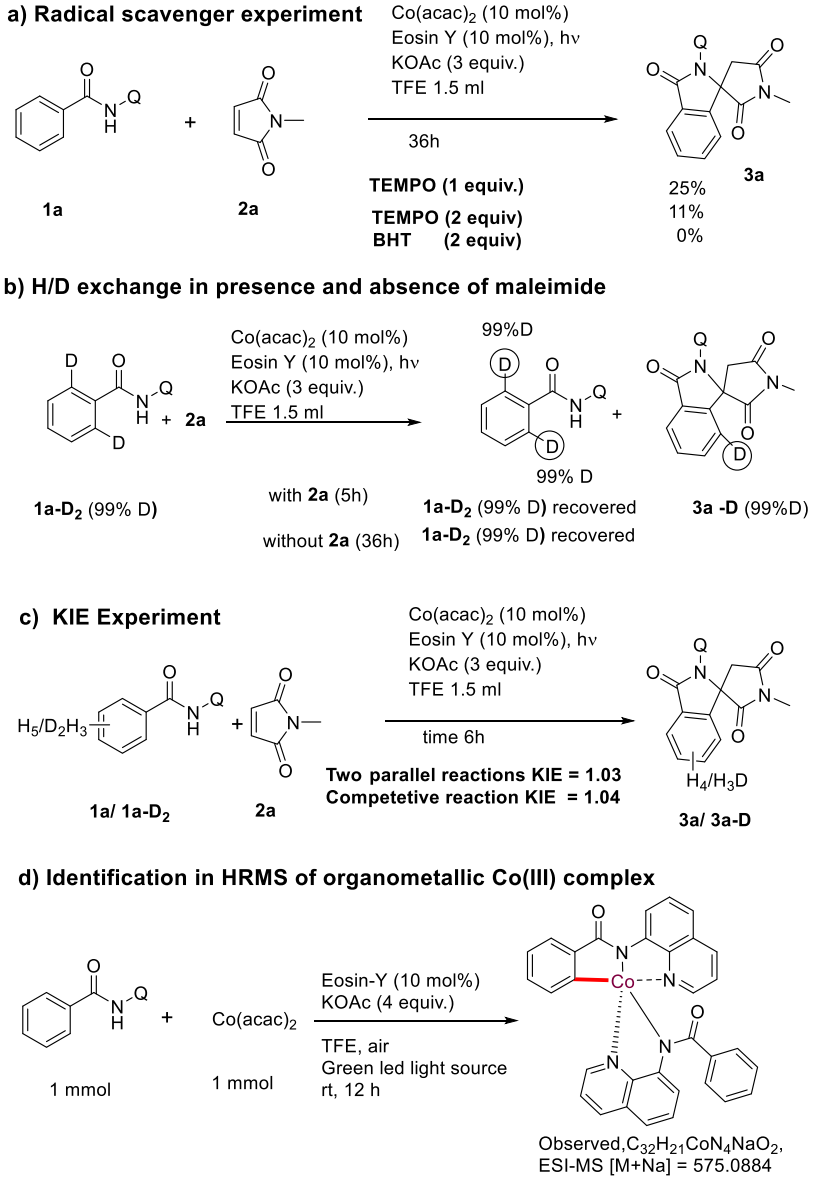
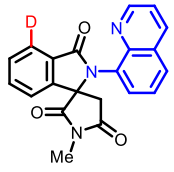
Scheme 3. Mechanistic Investigation



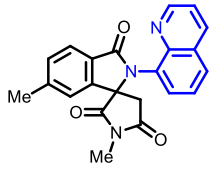
175.1, 174.0, 168.9, 151.2, 145.4, 144.7, 136.8, 133.2, 132.7, 131.7, 131.5, 130.1, 130.0, 129.8, 127.0, 125.3, 122.1, 120.3, 71.4, 37.8, 25.8. HRMS (ESI) *m/z*: calcd for $C_{21}H_{16}N_3O_3$ $[M + H]^+$, 358.1192; found, 358.1205.

*1′-Methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3a-D**).*



White solid, mp 270−272 °C, hexane/EtOAc (50/50), 91% (81 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.84 (d, J = 3.1 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.67−7.64 (m, 1H), 7.62−7.59 (m, 2H), 7.43 (dd, J = 8.2, 3.9 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 3.37 (d, J = 19.1 Hz, 1H), 3.17 (d, J = 19.0 Hz, 1H), 3.06 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.0, 173.9, 168.8, 151.2, 145.3, 144.6, 136.7, 133.1, 132.6, 131.6, 131.3, 129.9, 129.8, 129.7, 126.9, 124.9 (t, J = 20.6 Hz) 122.1, 120.3, 71.36, 37.67, 25.72. HRMS (ESI) *m/z*: calcd for $C_{21}H_{15}DN_3O_3$ $[M + H]^+$, 359.1254; found, 359.1241, and $C_{21}H_{14}DN_3O_3Na$ $[M + Na]^+$, 381.1074; found, 381.1074.

*1′,6-Dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3b**).*[11]



White solid, mp 274−275 °C, hexane/EtOAc (50/50), 90% (84 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.22 (dd, J = 8.3, 1.6 Hz, 1H), 7.94−7.88 (m, 2H), 7.83 (dd, J = 7.4, 1.2 Hz, 1H), 7.61−7.58 (m, 1H), 7.46−7.40 (m, 2H), 7.13 (s, 1H), 3.35 (d, J = 18.9 Hz, 1H), 3.14 (d, J = 19.0 Hz, 1H), 3.08 (s, 3H), 2.49 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.3, 174.1, 168.9, 151.1, 145.4, 145.1, 144.2, 136.7, 132.8, 131.7, 131.0, 129.8, 129.7, 128.8, 126.9,

https://dx.doi.org/10.1021/acs.joc.0c02120
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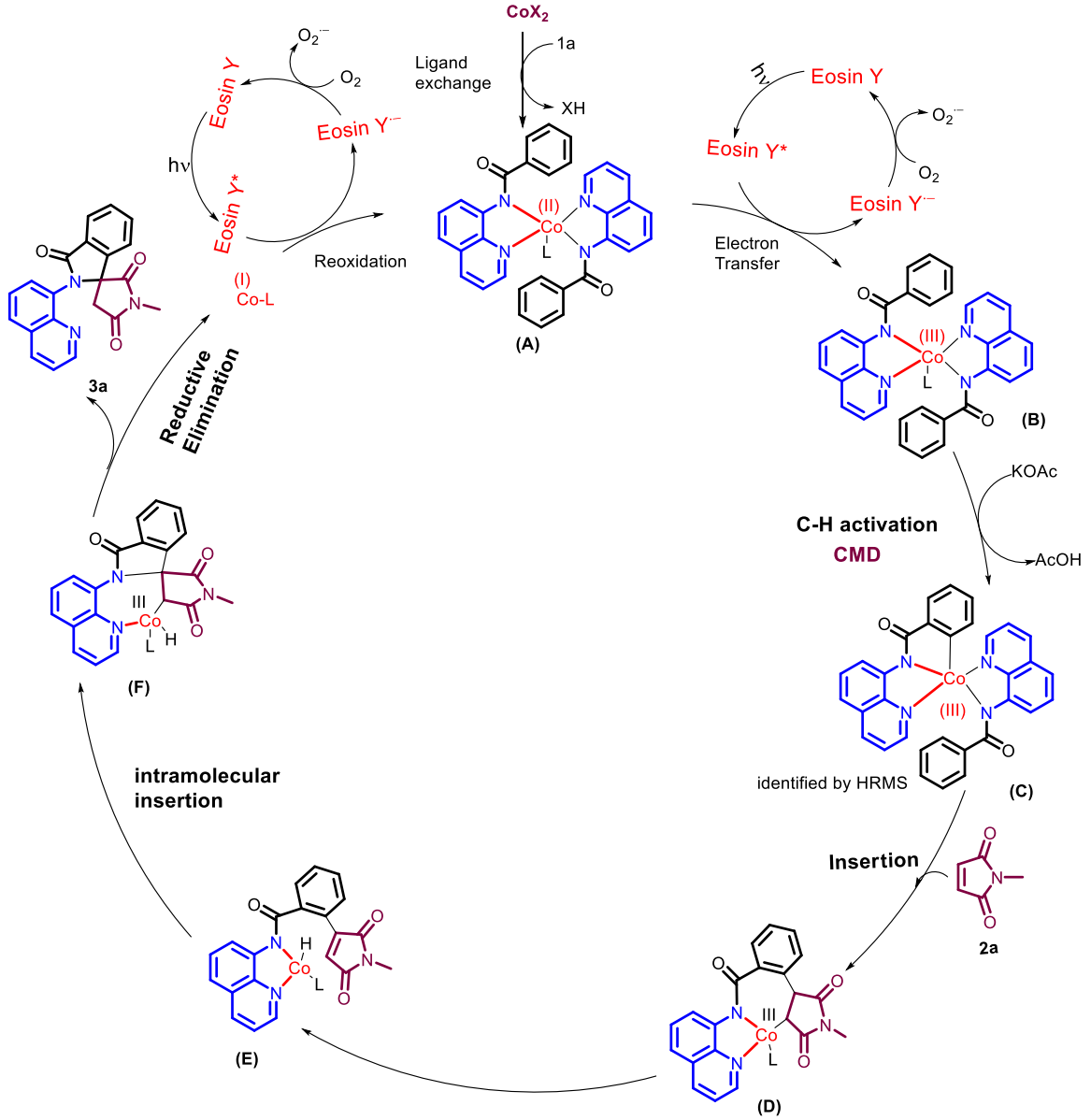
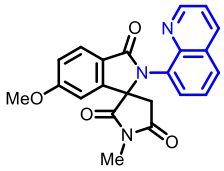
Scheme 4. Proposed Mechanism



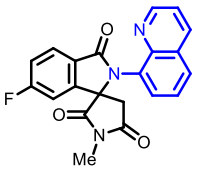
125.0, 122.0, 120.7, 71.2, 37.8, 25.7, 22.1. HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{18}N_3O_3$ $[M + H]^+$, 372.1348; found, 372.1348.

*6-Methoxy-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3c**).*



White solid, mp 251−252 °C, hexane/EtOAc (50/50), 86% (83 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dd, J = 4.2, 1.7 Hz, 1H), 8.23 (dd, J = 8.3, 1.7 Hz, 1H), 7.96−7.90 (m, 2H), 7.83 (dd, J = 7.4, 1.3 Hz, 1H), 7.62−7.59 (m, 1H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.12 (dd, J = 8.5, 2.1 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 3.90 (s, 3H), 3.37 (d, J = 19.0 Hz, 1H), 3.15 (d, J = 19.0 Hz, 1H), 3.07 (s, 3H).. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.2, 174.1, 168.7, 164.1, 151.1, 146.9, 145.5, 136.8, 132.9, 131.7, 129.8, 128.2, 126.9, 126.7, 123.9, 122.1, 116.0, 105.7, 71.1, 56.1, 37.9, 25.8. HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{18}N_3O_4$ $[M + H]^+$, 388.1297; found, 388.1293.

*6-Fluoro-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3d**).*



White solid, mp 248−250 °C, hexane/EtOAc (50/50), 92% (86 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dd, J = 4.2, 1.7 Hz, 1H), 8.23 (dd, J = 8.3, 1.6 Hz, 1H), 8.02 (dd, J = 8.4, 4.9 Hz, 1H), 7.93 (dd, J = 8.3, 1.2 Hz, 1H), 7.81 (dd, J = 7.4, 1.3 Hz, 1H), 7.63−7.57 (m, 1H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.33−7.29 (m, 1H), 7.05 (dd, J = 7.6, 2.1 Hz, 1H), 3.40 (d, J = 19.0 Hz, 1H), 3.15 (d, J = 19.0 Hz, 1H), 3.07 (s, 3H).. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 173.5, 167.7, 165.9 (d, C−F, $^1J_{C-F}$ = 253.7 Hz), 151.3, 146.8 (d, $^3J_{C-F}$ = 8.7 Hz), 145.3,

https://dx.doi.org/10.1021/acs.joc.0c02120
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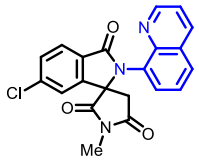
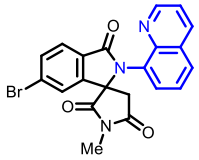
136.8, 132.4, 131.6, 130.1, 129.8, 127.6, 127.4 (d, $^{3}J_{C-F}$ = 8.7 Hz), 126.9, 122.2, 117.8 (d, $^{2}J_{C-F}$ = 22.5 Hz), 108.1 (d, $^{2}J_{C-F}$ = 25 Hz), 71.0, 37.6, 25.9. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{15}FN_3O_3$ $[M + H]^+$, 376.1097; found, 376.1096.

*6-Chloro-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3e**).*



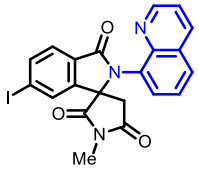
White solid, mp 260−262 °C, hexane/EtOAc (50/50), 90% (88 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.84 (d, *J* = 3.0 Hz, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.94 (dd, *J* = 15.0, 8.2 Hz, 2H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.61−7.59 (m, 2H), 7.45 (dd, *J* = 8.2, 3.9 Hz, 1H), 7.35 (s, 1H), 3.37 (d, *J* = 18.9 Hz, 1H), 3.16 (d, *J* = 18.9 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.4, 173.5, 167.7, 151.3, 146.1, 145.2, 139.4, 136.8, 132.2, 131.5, 130.6, 130.1, 129.9, 129.7, 126.9, 126.3, 122.2, 121.0, 70.97, 37.5, 25.9. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{15}ClN_3O_3$ $[M + H]^+$, 392.0802; found, 392.0802.

*6-Bromo-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3f**).*



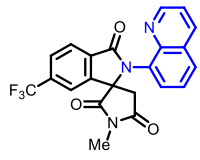
White solid, mp 261−262 °C, hexane/EtOAc (50/50), 75% (82 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.83−7.79 (m, 1H), 7.76 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.62−7.59 (m, 1H), 7.52−7.49 (m, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.37 (d, *J* = 19.1 Hz, 1H), 3.16 (d, *J* = 19.1 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 173.5, 167.8, 151.3, 146.2, 145.2, 136.8, 133.5, 132.3, 131.6, 130.4, 130.1, 129.8, 127.7, 126.9, 126.5, 123.9, 122.2, 71.0, 37.5, 25.9. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{14}KBrN_3O_3$ $[M + K]^+$, 473.9856; found, 473.9842.

*6-Iodo-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3g**).*



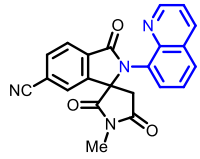
White solid, mp 289−290 °C, hexane/EtOAc (50/50), 77% (93 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, *J* = 4.1 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.95 (dd, *J* = 19.6, 8.1 Hz, 2H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.62−7.59 (m, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.36 (d, *J* = 19.1 Hz, 1H), 3.15 (d, *J* = 19.1 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 173.6, 168.1, 151.3, 146.2, 145.2, 139.4, 136.8, 132.2, 131.6, 131.0, 130.1, 129.8, 129.7, 126.9, 126.5, 122.2, 99.8, 70.8, 37.5, 25.9. HRMS (ESI) *m*/*z*: calcd for $C_{21}H_{15}IN_3O_3$ $[M + H]^+$, 484.0158; found, 484.0143.

*1′-Methyl-2-(quinolin-8-yl)-6-(trifluoromethyl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3h**).*



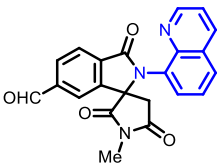
White solid, mp 246−248 °C, hexane/EtOAc (50/50), 89% (95 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, *J* = 1.1 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.92 (dd, *J* = 18.8, 8.0 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.66−7.58 (m, 2H), 7.45 (dd, *J* = 8.1, 4.0 Hz, 1H), 3.42 (d, *J* = 19.2 Hz, 1H), 3.21 (d, *J* = 19.1 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.3, 173.3, 167.3, 151.4, 145.1, 144.9, 136.8, 135.0 (q, C−F, $^{2}J_{C-F}$ = 32.5 Hz), 134.8, 132.0, 131.4, 130.0, 129.8, 127.4, 126.8, 125.8, 123.5 (q, C−F, $^{1}J_{C-F}$ = 271.2 Hz), 122.2, 71.3, 60.5, 37.3, 25.9. HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{15}F3N_3O_3$ $[M + H]^+$, 426.1066; found, 426.1062.

*1′-Methyl-2′,3,5′-trioxo-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-6-carbonitrile (**3i**).*



White solid, mp 290−291 °C, hexane/EtOAc (50/50), 76% (73 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.96 (dd, J = 8.3, 1.2 Hz, 1H), 7.92 (dd, J = 7.8, 1.2 Hz, 1H), 7.78 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.72 (s, 1H), 7.65−7.59 (m, 1H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.40 (d, *J* = 19.1 Hz, 1H), 3.18 (d, *J* = 19.1 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.9, 173.0, 166.8, 163.3, 151.4, 145.0, 136.8, 135.3, 134.0, 131.8, 131.3, 130.4, 129.7, 126.9, 126.0, 124.6, 122.3, 117.6, 116.5, 71.2, 37.2, 26.0. HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{15}N_4O_3$ $[M + H]^+$, 383.1144; found, 383.1131.

*1′-Methyl-2′,3,5′-trioxo-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-6-carbaldehyde (**3j**).*



White solid, mp 297−298 °C, hexane/EtOAc (50/50), 69% (67 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.86 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.65−7.61 (m, 1H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.42 (d, *J* = 19.1 Hz, 1H), 3.21 (d, *J* = 19.1 Hz, 1H), 3.10 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 191.1, 174.4, 173.4, 167.5, 151.4, 145.2, 145.2, 139.9, 136.9, 136.5, 132.8, 132.2, 131.5, 130.4, 129.8, 127.0, 126.0, 122.3, 120.4, 71.4, 37.4, 26.0. HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{16}N_3O_4$ $[M + H]^+$, 386.1141; found, 386.1120.

https://dx.doi.org/10.1021/acs.joc.0c02120
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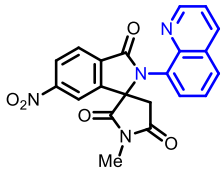
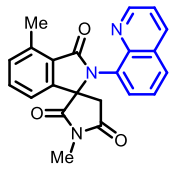
*1′-Methyl-6-nitro-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3k**).*



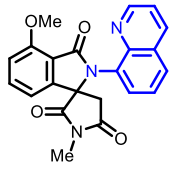
White solid, mp 175−177 °C, hexane/EtOAc (50/50), 55% (55 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.86 (d, J = 3.4 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.24 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.65−7.63 (m, 1H), 7.49 (dd, J = 8.3, 4.1 Hz, 1H), 3.46 (d, J = 19.3 Hz, 1H), 3.23 (d, J = 19.3 Hz, 1H), 3.11 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 173.9, 173.1, 166.5, 151.5, 151.1, 145.5, 145.1, 136.9, 136.8, 131.8, 131.4, 130.6, 129.9, 127.0, 126.4, 125.7, 122.4, 116.5, 71.4, 37.2, 26.1. HRMS (ESI) m/z: calcd for $C_{21}H_{15}N_4O_5$ [M + H]$^+$, 403.1042; found, 403.1021.

*1′,4-Dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3l**).*[9]



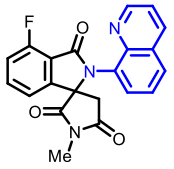
White solid, mp 204−205 °C, hexane/EtOAc (50/50), 70% (65 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.21 (dd, J = 8.3, 1.6 Hz, 1H), 7.91 (dd, J = 8.2, 1.1 Hz, 1H), 7.84 (dd, J = 7.4, 1.1 Hz, 1H), 7.61−7.58 (m, 1H), 7.51−7.48 (m, 1H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.34 (dd, J = 7.6, 0.4 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 3.39 (d, J = 19.0 Hz, 1H), 3.15 (d, J = 19.0 Hz, 1H), 3.05 (s, 3H), 2.78 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.3, 174.1, 169.6, 151.2, 145.5, 145.1, 139.3, 136.7, 132.8, 132.5, 132.0, 131.8, 129.8, 129.7, 128.2, 126.8, 122.0, 117.6, 70.7, 38.0, 25.7, 17.4. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_3$ [M + H]$^+$, 372.1348; found, 372.1349.

*4-Methoxy-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3m**).*[9]



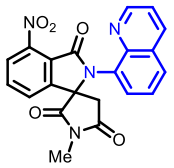
White solid, mp 148−150 °C, hexane/EtOAc (50/50), 61% (59 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.83 (d, J = 4.5 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.60−7.57 (m, 2H), 7.42 (dd, J = 8.3, 4.1 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 4.00 (s, 3H), 3.33 (d, J = 19.1 Hz, 1H), 3.13 (d, J = 18.9 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.1, 174.2, 167.5, 158.2, 151.0, 147.2, 145.4, 136.7, 134.9, 132.9, 131.7, 129.7, 129.6, 126.9, 121.9, 118.6, 112.4, 112.1, 70.7, 56.3, 38.0, 25.7. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_4$ [M + H]$^+$, 388.1297; found, 388.1294.

*4-Fluoro-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3n**).*



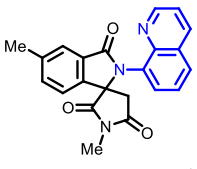
White solid, mp 280−282 °C, hexane/EtOAc (50/50), 81% (76 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (dd, J = 4.1, 1.7 Hz, 1H), 8.23 (dd, J = 8.3, 1.6 Hz, 1H), 7.93 (dd, J = 8.2, 1.2 Hz, 1H), 7.82 (dd, J = 7.4, 1.3 Hz, 1H), 7.66−7.59 (m, 2H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.26 (dd, J = 10.7, 6.5 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 3.40 (d, J = 19.0 Hz, 1H), 3.16 (d, J = 19.0 Hz, 1H), 3.06 (s, 3H). ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$): δ 174.6, 173.7, 165.4, 159.3 (d, C−F, $^1J_{C-F}$ = 262.5 Hz), 151.3, 147.1, 145.3, 136.8, 135.2 (d, C−F, $^3J_{C-F}$ = 7.5 Hz), 132.2, 131.8, 130.1, 129.8, 126.9, 122.2, 118.9 (d, C−F, $^2J_{C-F}$ = 13.1 Hz), 117.6 (d, C−F, $^2J_{C-F}$ = 19.0 Hz), 116.4, 71.1, 37.9, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{14}FNaN_3O_3$ [M + Na]$^+$, 398.0917; found, 398.0913.

*1′-Methyl-4-nitro-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3o**).*



Brown solid, mp 240−241 °C, hexane/EtOAc (50/50), 67% (67 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dd, J = 4.1, 1.5 Hz, 1H), 8.24 (dd, J = 8.3, 1.4 Hz, 1H), 7.95 (dd, J = 8.2, 0.9 Hz, 1H), 7.91 (dd, J = 8.0, 0.7 Hz, 1H), 7.84−7.77 (m, 2H), 7.64−7.56 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 3.50 (d, J = 19.1 Hz, 1H), 3.20 (d, J = 19.1 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$): δ 173.9, 173.3, 163.3, 151.4, 147.0, 146.8, 145.1, 136.9, 134.0, 131.8, 131.7, 130.5, 129.8, 126.9, 124.7, 124.4, 123.6, 122.3, 70.7, 37.5, 26.0. HRMS (ESI) m/z: calcd for $C_{21}H_{15}N_4O_5$ [M + H]$^+$, 403.1042; found, 403.1041.

*1′,5-Dimethyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3p**).*[9]



White solid, mp 238−240 °C, hexane/EtOAc (50/50), 65% (60 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.22 (dd, J = 8.3, 1.6 Hz, 1H), 7.91 (dd, J = 8.3, 1.3 Hz, 1H), 7.85−7.80 (m, 2H), 7.60 (dd, J = 8.1, 7.5 Hz, 1H), 7.49−7.40 (m, 2H), 7.23 (d, J = 7.8 Hz, 1H), 3.33 (d, J = 18.9 Hz, 1H), 3.13 (d, J = 18.9 Hz, 1H), 3.06 (s, 3H), 2.49 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.2, 174.1, 169.0, 151.1, 145.3, 142.0, 140.4, 136.7, 134.0, 132.8, 131.6, 131.5, 129.8, 129.7, 126.9, 125.4, 122.1, 120.0, 71.2, 37.7, 25.7, 21.5. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_3$ [M + H]$^+$, 372.1348; found, 372.1354.

https://dx.doi.org/10.1021/acs.joc.0c02120
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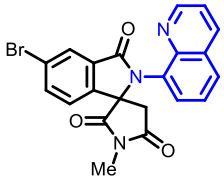
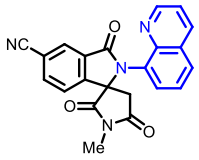
*5-Bromo-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3q**).*



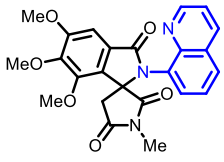
White solid, mp 182−183 °C, hexane/EtOAc (50/50), 62% (68 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.15 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.78 (dd, J = 16.4, 7.5 Hz, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.50−7.40 (m, 1H), 7.24 (d, J = 7.9 Hz, 1H), 3.35 (d, J = 19.0 Hz, 1H), 3.13 (d, J = 19.0 Hz, 1H), 3.05 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.5, 173.6, 167.3, 151.3, 145.2, 143.2, 136.8, 136.1, 133.5, 132.3, 131.5, 130.2, 129.8, 128.3, 126.9, 124.3, 122.2, 122.0, 71.2, 37.4, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{14}BrNaN_3O_3$ $[M + Na]^+$, 458.0116; found, 458.0091.

*1′-Methyl-2′,3,5′-trioxo-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-5-carbonitrile (**3r**).*



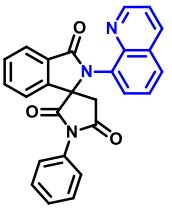
White solid, mp 208−210 °C, hexane/EtOAc (50/50), 67% (64 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.33−8.29 (m, 1H), 8.25 (dd, J = 8.3, 1.6 Hz, 1H), 7.96 (dd, J = 8.3, 1.2 Hz, 1H), 7.93 (dd, J = 7.9, 1.5 Hz, 1H), 7.79 (dd, J = 7.4, 1.3 Hz, 1H), 7.65−7.59 (m, 1H), 7.54−7.44 (m, 2H), 3.41 (d, J = 19.1 Hz, 1H), 3.17 (d, J = 19.1 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$): δ 173.9, 173.2, 166.6, 151.4, 148.3, 145.1, 136.9, 136.5, 132.8, 131.8, 131.5, 130.5, 129.8, 129.1, 126.9, 122.4, 121.7, 117.6, 114.5, 71.5, 37.3, 26.0. HRMS (ESI) m/z: calcd for $C_{22}H_{14}N_4O_3Na$ $[M + Na]^+$, 405.0964; found, 405.0961.

*5,6,7-Trimethoxy-1′-methyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3s**).*



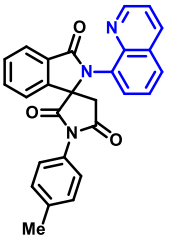
White solid, mp 188−189 °C, hexane/EtOAc (50/50), 68% (76 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (dd, J = 4.2, 1.7 Hz, 1H), 8.22 (dd, J = 8.3, 1.6 Hz, 1H), 7.92 (dd, J = 8.3, 1.3 Hz, 1H), 7.76 (dd, J = 7.3, 1.4 Hz, 1H), 7.61−7.58 (m, 1H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.29 (s, 1H), 3.96 (s, 3H), 3.92 (s, 6H), 3.21 (d, J = 18.6 Hz, 1H), 3.16 (d, J = 18.7 Hz, 1H), 3.05 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.6, 174.4, 168.5, 156.4, 151.3, 147.4, 145.6, 145.2, 136.7, 132.7, 131.7, 130.0, 129.8, 129.3, 127.0, 126.9, 122.1, 102.7, 69.8, 61.3, 60.9, 56.7, 36.6, 25.6. HRMS (ESI) m/z: calcd for $C_{24}H_{22}N_3O_6$ $[M + H]^+$, 448.1509; found, 448.1494.

*1′-Phenyl-2-(quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3t**).*



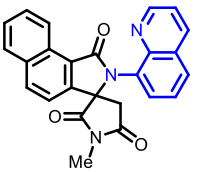
White solid, mp 235−236 °C, hexane/EtOAc (50/50), 85% (89 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.89−8.84 (m, 1H), 8.26 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 7.4 Hz, 1H), 7.97−7.94 (m, 2H), 7.73−7.70 (m, 1H), 7.67−7.63 (m, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.49−7.45 (m, 3H), 7.42−7.40 (m, 1H), 7.23 (d, J = 7.4 Hz, 2H), 3.54 (d, J = 18.5 Hz, 1H), 3.32 (d, J = 19.4 Hz, 1H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.0, 172.8, 168.9, 151.2, 145.2, 144.7, 136.8, 133.3, 132.7, 131.6, 131.6, 131.5, 130.2, 129.9, 129.8, 129.5, 129.2, 127.0, 126.2, 125.4, 122.2, 120.2, 71.3, 37.9. HRMS (ESI) m/z: calcd for $C_{26}H_{18}N_3O_3$ $[M + H]^+$, 420.1348; found, 420.1331.

*2-(Quinolin-8-yl)-1′-(p-tolyl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**3u**).*



White solid, mp 230−232 °C, hexane/EtOAc (50/50), 83% (90 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dd, J = 3.9, 1.2 Hz, 1H), 8.23 (dd, J = 8.2, 1.1 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.97−7.89 (m, 2H), 7.70−7.67 (m, 1H), 7.62 (dd, J = 15.8, 7.8 Hz, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.51 (d, J = 18.9 Hz, 1H), 3.30 (d, J = 18.9 Hz, 1H), 2.36 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.1, 172.9, 168.9, 151.2, 145.2, 144.7, 139.3, 136.8, 133.3, 132.6, 131.6, 131.4, 130.1, 130.0, 129.9, 129.7, 128.9, 126.9, 126.0, 125.3, 122.1, 120.2, 71.3, 37.8, 21.3. HRMS (ESI) m/z: calcd for $C_{27}H_{20}N_3O_3$ $[M + H]^+$, 434.1505; found, 434.1501.

*1′-Methyl-2-(quinolin-8-yl)spiro[benzo[e]isoindole-3,3′-pyrrolidine]-1,2′,5′(2H)-trione (**3v**).*[9]



White solid, mp 236−238 °C, hexane/EtOAc (50/50), 68% (69 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.25 (d, J = 8.4 Hz, 1H), 8.84 (dd, J = 4.2, 1.7 Hz, 1H), 8.23 (dd, J = 8.3, 1.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.98−7.92 (m, 2H), 7.90 (dd, J = 7.4, 1.3 Hz, 1H), 7.74−7.69 (m, 1H), 7.63 (dd, J = 8.1, 7.4 Hz, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 3.47 (d, J = 19.1 Hz, 1H), 3.25 (d, J = 19.1 Hz, 1H), 3.10 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.0, 174.1, 169.9, 151.2, 145.5, 144.4, 136.8, 134.5, 134.0, 132.9, 131.8, 129.9, 129.8, 129.6, 128.9, 128.4, 127.6, 127.0, 125.8, 124.5,

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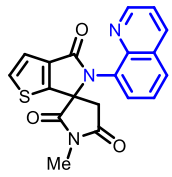
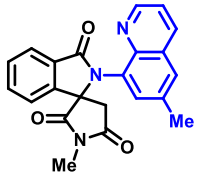
122.1, 116.8, 71.1, 37.3, 25.9. HRMS (ESI) m/z: calcd for $C_{25}H_{18}N_3O_3$ $[M + H]^+$, 408.1348; found, 408.1342.

*1-Methyl-5′-(quinolin-8-yl)spiro[pyrrolidine-3,6′-thieno[2,3-c]-pyrrole]-2,4′,5(5′H)-trione (**3w**).*



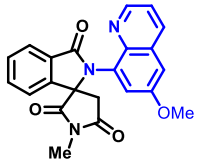
White solid, mp 223−225 °C, hexane/EtOAc (50/50), 66% (60 mg). 1H NMR (500 MHz, $CDCl_3$): δ 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.23 (dd, J = 8.3, 1.7 Hz, 1H), 7.93 (dd, J = 8.2, 1.3 Hz, 1H), 7.83 (dd, J = 7.4, 1.3 Hz, 1H), 7.80 (d, J = 4.9 Hz, 1H), 7.64−7.57 (m, 1H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.00 (d, J = 4.9 Hz, 1H), 3.40 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 19.0 Hz, 1H), 3.04 (s, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.0, 173.6, 164.4, 153.5, 151.3, 145.5, 137.2, 136.8, 136.2, 132.8, 131.9, 130.0, 129.8, 126.9, 122.2, 118.6, 70.3, 36.9, 25.8. HRMS (ESI) m/z: calcd for $C_{19}H_{13}N_3O_3SNa$ $[M + Na]^+$, 386.0575; found, 386.0584.

*1′-Methyl-2-(6-methylquinolin-8-yl)spiro[isoindoline-1,3′-pyrro-lidine]-2′,3,5′-trione (**5a**).*



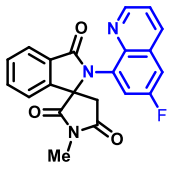
White solid, mp 238−240 °C, hexane/EtOAc (50/50), 92% (85 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 8.75 (dd, J = 4.1, 1.5 Hz, 1H), 8.10 (dd, J = 8.3, 1.5 Hz, 1H), 8.01 (d, J = 7.3 Hz, 1H), 7.70−7.65 (s, 2H), 7.65−7.56 (m, 2H), 7.40−7.31 (m, 2H), 3.35 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.07 (s, 3H), 2.52 (s, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, CDCl3): δ 175.0, 173.9, 168.8, 150.2, 144.6, 143.6, 137.0, 136.0, 133.5, 133.1, 132.1, 131.3, 129.9, 129.6, 128.8, 125.0, 122.0, 120.2, 71.3, 37.6, 25.7, 21.5. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_3$ $[M + H]^+$, 372.1348; found, 372.1348.

*2-(6-Methoxyquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyr-rolidine]-2′,3,5′-trione (**5b**).*



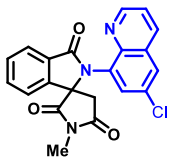
White solid, mp 241−242 °C, hexane/EtOAc (50/50), 75% (73 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 8.66 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 8.3, 1.5 Hz, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.68−7.58 (m, 2H), 7.53 (d, J = 2.8 Hz, 1H), 7.39−7.31 (m, 2H) 7.16 (d, J = 2.7 Hz, 1H), 3.91 (s, 3H), 3.33 (d, J = 18.9 Hz, 1H), 3.15 (d, J = 18.9 Hz, 1H), 3.09 (s, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.9, 174.0, 168.7, 157.6, 148.5, 144.7, 141.1, 135.5, 133.7, 133.2, 131.3, 130.5, 130.0, 125.2, 124.2, 122.3, 120.3, 107.4, 71.3, 55.9, 37.6, 25.8. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_4$ $[M + H]^+$, 388.1297; found, 388.1284.

*2-(6-Fluoroquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrroli-dine]-2′,3,5′-trione (**5c**).*



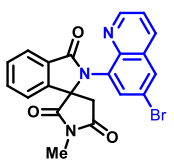
White solid, mp 271−272 °C, hexane/EtOAc (50/50), 75% (70 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 8.79 (dd, J = 4.1, 1.6 Hz, 1H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 8.07−8.01 (m, 1H), 7.73 (dd, J = 9.0, 2.8 Hz, 1H), 7.70−7.67 (m, 1H), 7.65−7.62 (m, 1H), 7.56 (dd, J = 8.2, 2.8 Hz, 1H), 7.47 (dd, J = 8.3, 4.2 Hz, 1H), 7.37−7.33 (m, 1H), 3.29 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.13 (d, J = 6.2 Hz, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.8, 173.8, 168.8, 160.8 (d, C−F, $^1J_{C-F}$ = 247 Hz), 150.2, 144.7, 142.4, 136.2, 134.8 (d, C−F, $^3J_{C-F}$ = 11.2 Hz), 133.5, 131.0, 130.2, 130.0 (d, C−F, $^3J_{C-F}$ = 10 Hz), 125.4, 122.9, 122.0 (d, C−F, $^2J_{C-F}$ = 26.2 Hz), 120.3, 112.8 (d, C−F, $^2J_{C-F}$ = 21.2 Hz), 71.3, 37.8, 25.9. HRMS (ESI) m/z: calcd for $C_{21}H_{14}FN_3O_3K$ $[M + K]^+$, 414.0656; found, 414.0691.

*2-(6-Chloroquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrro-lidine]-2′,3,5′-trione (**5d**).*



White solid, mp 278−280 °C, hexane/EtOAc (50/50), 71% (70 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 8.84−8.75 (m, 1H), 8.14 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.69−7.62 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 3.27 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 19.0 Hz, 1H), 3.12 (s, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.8, 173.7, 168.8, 151.2, 144.7, 143.7, 135.9, 134.1, 133.4, 132.4, 130.9, 130.1, 130.0, 128.5, 125.3, 123.0, 120.3, 71.3, 37.7, 25.9. HRMS (ESI) m/z: calcd for $C_{21}H_{14}ClN_3O_3Na$ $[M + Na]^+$, 414.0621; found, 414.0615.

*2-(6-Bromoquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrro-lidine]-2′,3,5′-trione (**5e**).*



White solid, mp 269−270 °C, hexane/EtOAc (50/50), 73% (79 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.14 (dd, J = 8.4, 1.4 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.71−7.59 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 3.26 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.12 (s, 3H).·$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.7, 173.7, 168.8, 151.3, 144.6, 144.0, 135.8, 134.8, 134.1, 133.4, 131.8, 130.9, 130.5, 130.1, 125.3, 122.9, 120.3, 120.1, 71.3, 37.7, 25.9. HRMS (ESI) m/z: calcd for $C_{21}H_{15}BrN_3O_3$ $[M + H]^+$, 436.0297; found, 436.0292.

https://dx.doi.org/10.1021/acs.joc.0c02120
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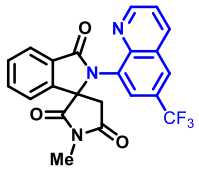
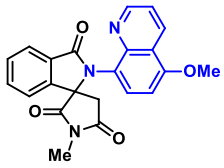
*1′-Methyl-2-(6-(trifluoromethyl)quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5f**).*



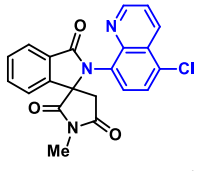
White solid, mp 206−208 °C, hexane/EtOAc (50/50), 41% (44 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96−8.91 (m, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.23 (s, 1H), 8.03−8.02 (m, 2H), 7.70−7.62 (m, 2H), 7.55 (dd, J = 8.3, 4.2 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 3.22 (d, J = 18.9 Hz, 1H), 3.17 (d, J = 18.9 Hz, 1H), 3.09 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.8, 173.6, 168.7, 153.1, 146.2, 144.6, 137.7, 134.2, 133.5, 130.9, 130.2, 128.9 (q, C−F, $^2J_{C-F}$ = 33 Hz), 128.8, 127.5, 127.1, 125.2, 123.8 (q, C−F, $^1J_{C-F}$ = 271.1 Hz), 123.2, 120.4, 71.2, 37.7, 25.8. HRMS (ESI) m/z: calcd for $C_{22}H_{15}F_3N_3O_3$ $[M + H]^+$, 426.1066; found, 426.1070.

*2-(5-Methoxyquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5g**).*



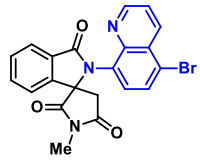
White solid, mp 260−262 °C, hexane/EtOAc (50/50), 90% (88 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.84 (d, J = 5.1 Hz, 1H), 8.62 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.66−7.60 (m, 2H), 7.42 (dd, J = 8.6, 4.1 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.04 (s, 3H), 3.46 (d, J = 18.8 Hz, 1H), 3.17 (d, J = 19.3 Hz, 1H), 3.05 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.2, 174.2, 169.1, 156.5, 151.5, 146.1, 144.6, 133.0, 132.3, 131.7, 131.6, 130.0, 125.2, 124.6, 122.0, 121.2, 120.3, 104.4, 71.5, 56.1, 37.8, 25.7. HRMS (ESI) m/z: calcd for $C_{22}H_{18}N_3O_4$ $[M + H]^+$, 388.1297; found, 388.1295.

*2-(5-Chloroquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5h**).*



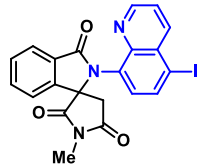
White solid, mp 266−268 °C, hexane/EtOAc (50/50), 88% (86 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.89 (dd, J = 4.1, 1.4 Hz, 1H), 8.63 (dd, J = 8.6, 1.4 Hz, 1H), 8.02 (d, J = 7.3 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.67−7.60 (m, 2H), 7.56 (dd, J = 8.6, 4.2 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 3.32 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.07 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 173.7, 168.8, 151.7, 145.9, 144.6, 133.8, 133.3, 131.9, 131.6, 131.1, 130.1, 127.7, 127.0, 125.2, 122.8, 120.3, 71.3, 37.7, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{15}ClN_3O_3$ $[M + H]^+$, 392.0802; found, 392.0805.

*2-(5-Bromoquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5i**).*



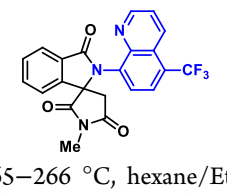
White solid, mp 258−260 °C, hexane/EtOAc (50/50), 91% (99 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (d, J = 3.8 Hz, 1H), 8.59 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.68−7.61 (m, 2H), 7.56 (dd, J = 8.6, 4.1 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 3.31 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 173.7, 168.8, 151.7, 146.0, 144.6, 136.4, 133.3, 132.6, 132.0, 131.1, 130.7, 130.1, 129.1, 125.2, 123.9, 123.2, 120.3, 71.3, 37.7, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{15}BrN_3O_3$ $[M + H]^+$, 436.0297; found, 436.0307.

*2-(5-Iodoquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5j**).*



White solid, mp 254−256 °C, hexane/EtOAc (50/50), 89% (108 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (dd, J = 4.1, 1.5 Hz, 1H), 8.44 (dd, J = 8.6, 1.5 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.68−7.61 (m, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 8.6, 4.2 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H), 3.30 (d, J = 18.9 Hz, 1H), 3.15 (d, J = 18.9 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 173.7, 168.8, 151.8, 145.7, 144.7, 141.3, 138.0, 133.7, 133.3, 132.5, 131.6, 131.1, 130.1, 125.2, 123.8, 120.3, 100.7, 71.3, 37.7, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{15}IN_3O_3$ $[M + H]^+$: 484.0158; found, 484.0157.

*1′-Methyl-2-(5-(trifluoromethyl)quinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5k**).*



White solid, mp 265−266 °C, hexane/EtOAc (50/50), 54% (58 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (d, J = 3.0 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H), 8.02 (dd, J = 16.0, 7.6 Hz, 2H), 7.95 (d, J = 7.8 Hz, 1H), 7.70−7.63 (m, 2H), 7.60 (dd, J = 8.7, 4.1 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 3.24 (d, J = 18.9 Hz, 1H), 3.16 (d, J = 18.9 Hz, 1H), 3.12 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.8, 173.6, 168.9, 151.4, 145.2, 144.8, 137.2, 133.5, 133.4, 130.9, 130.2, 129.9, 127.6 (q, C−F. $^2J_{C-F}$ = 31.2 Hz), 126.0, 125.6, 125.5 125.3, 123.2, 120.2 (q, C−F, $^1J_{C-F}$ = 272.5 Hz), 71.3, 37.8, 25.9. HRMS (ESI): m/z: calcd for $C_{22}H_{15}F_3N_3O_3$ $[M + H]^+$, 426.1066; found, 426.1069.

https://dx.doi.org/10.1021/acs.joc.0c02120
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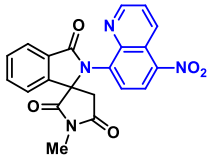
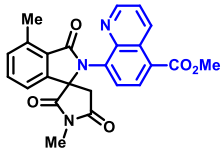
*1′-Methyl-2-(5-nitroquinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5l**).*



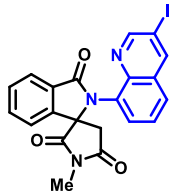
White solid, mp 236−238 °C, hexane/EtOAc (50/50), 51% (51 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.05 (dd, J = 8.9, 1.5 Hz, 1H), 8.91 (dd, J = 4.1, 1.5 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.05 (dd, J = 7.8, 4.7 Hz, 2H), 7.73−7.63 (m, 3H), 7.37 (d, J = 7.5 Hz, 1H), 3.17 (s, 2H), 3.16 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.6, 173.3, 168.9, 151.5, 145.4, 144.8, 144.7, 139.2, 133.8, 132.9, 130.5, 130.3, 129.4, 125.4, 124.9, 124.7, 122.6, 120.2, 71.3, 37.9, 26.0. HRMS (ESI) m/z: calcd for $C_{21}H_{15}N_4O_5$ $[M + H]^+$, 403.1042; found, 403.1034.

*Methyl 8-(1′,4-dimethyl-2′,3,5′-trioxospiro[isoindoline-1,3′-pyrrolidin]-2-yl)quinoline-5-carboxylate (**5m**).*



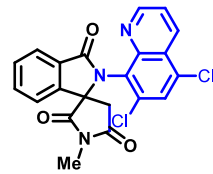
White solid, mp 202−204 °C, hexane/EtOAc (50/50), 85% (91 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.40 (d, J = 8.8 Hz, 1H), 8.86 (d, J = 3.9 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.59−7.47 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 4.03 (s, 3H), 3.25 (d, J = 18.8 Hz, 1H), 3.12 (d, J = 19.1 Hz, 1H), 3.10 (s, 3H) 2.79 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.2, 173.9, 169.6, 166.4, 150.8, 145.4, 145.0, 139.6, 137.7, 135.2, 132.9, 132.2, 130.9, 129.9, 128.5, 127.9, 127.9, 123.2, 117.6, 70.6, 52.7, 38.1, 25.8, 17.5. HRMS (ESI) m/z: calcd for $C_{24}H_{20}N_3O_5$ $[M + H]^+$, 430.1403; found, 430.1419.

*2-(3-Iodoquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5n**).*



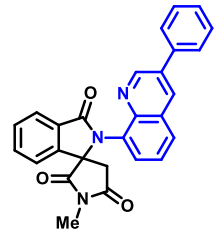
White solid, mp 252−253 °C, hexane/EtOAc (50/50), 89% (108 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (d, J = 1.9 Hz, 1H), 8.62 (d, J = 1.9 Hz, 1H), 8.03 (d, J = 7.3 Hz, 1H), 7.85−7.81 (m, 2H), 7.71−7.59 (m, 3H), 7.35 (d, J = 7.5 Hz, 1H), 3.27 (d, J = 18.9 Hz, 1H), 3.15 (d, J = 18.9 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.9, 173.7, 168.8, 156.5, 144.6, 144.3, 143.6, 133.3, 133.0, 132.2, 131.3, 131.2, 130.1, 128.9, 128.0, 125.3, 120.3, 91.3, 71.3, 37.8, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{15}IN_3O_3$ $[M + H]^+$, 484.0158; found, 484.0135.

*2-(5,7-Dichloroquinolin-8-yl)-1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5o**).*



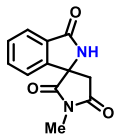
White solid, mp 286−288 °C, hexane/EtOAc (50/50), 65% (69 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (dd, J = 4.1, 1.4 Hz, 1H), 8.58 (dd, J = 8.5, 1.4 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.74−7.71 (m, 1H), 7.67−7.64 (m, 1H), 7.54 (dd, J = 8.5, 4.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 3.29 (d, J = 19.1 Hz, 1H), 3.14 (d, J = 19.1 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 174.2, 173.8, 169.7, 152.6, 146.6, 145.3, 138.2, 134.1, 133.9, 133.6, 130.8, 130.3, 130.1, 128.6, 126.6, 125.3, 122.8, 120.9, 70.3, 37.6, 25.8. HRMS (ESI) m/z: calcd for $C_{21}H_{14}N_3O_3Cl_2$ $[M + H]^+$, 426.0412; found, 426.0411.

*1′-Methyl-2-(3-phenylquinolin-8-yl)spiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**5q**).*



White solid, mp 199−200 °C, hexane/EtOAc (50/50), 90% (98 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.04 (dd, J = 6.7, 0.7 Hz, 1H), 7.98 (dd, J = 8.3, 1.3 Hz, 1H), 7.82 (dd, J = 7.4, 1.3 Hz, 1H), 7.68−7.64 (m, 3H), 7.64−7.61 (m, 2H), 7.53−7.50 (m, 2H), 7.46−7.41 (m, 1H), 7.36 (d, J = 7.4 Hz, 1H), 3.41 (d, J = 19.0 Hz, 1H), 3.19 (d, J = 19.0 Hz, 1H), 3.08 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 175.1, 173.9, 168.9, 150.8, 144.6, 144.3, 137.4, 135.0, 133.8, 133.2, 132.6, 131.4, 130.1, 130.0, 129.6, 129.4, 128.5, 127.6, 127.3, 125.2, 120.3, 71.4, 37.7, 25.8. HRMS (ESI) m/z: calcd for $C_{27}H_{20}N_3O_3$ $[M + H]^+$, 434.1505; found, 434.1488.

*1′-Methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**6**).*[9]



MQ Directing group was removed by reported procedure[9] in 0.125 mmol scale to afforded 1′-methylspiro[isoindoline-1,3′-pyrrolidine]-2′,3,5′-trione (**6**) as a white solid (15 mg, 51%). White solid, mp 198−200 °C, hexane/EtOAc (50/50). ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.77 (s, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.71−7.63 (m, 2H), 7.58 (t, J = 7.2 Hz, 1H), 3.34 (d, J = 18.3 Hz, 1H), 3.13 (d, J = 18.3 Hz, 1H), 2.99 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 176.1, 174.7, 169.5, 145.9, 133.2, 132.2, 130.0, 123.6, 122.8, 64.5, 25.86. HRMS (ESI) m/z: calcd for $C_{12}H_{11}N_2O_3$ $[M + H]^+$, 231.0770; found, 231.0761.

Spectral Characterization Data of Starting Materials. *Preparation of Carboxamides.* All amides were synthesized from the acid chlorides (compounds starting material **1a**, **1b**, **1c**, **1e**, **1h**, **1i**,

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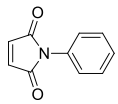
1l, **1n**, **1o**, **1p**, **1v**, **1w**, **1x**, **1y**, **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4n**) and from the carboxylic acid (compounds starting material **1d**, **1f**, **1g**, **1j**, **1k**, **1m**, **1q**, **1r**, **1s**), according to our previous reported method,[20a] and C-5 halogenated compounds of starting material (**4h**, **4i**, **4j**) and[24] C-5 carboxylated compounds of starting material **4m** were synthesized, according to our previous reported method.[20a]

General Procedure for the Synthesis of *N*-Arylmaleimide Derivatives. *N*-Aryl maleimides **2t** and **2u** were prepared using the modified reported procedure.[25]

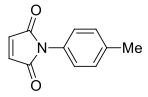
Representative Procedure. Maleic anhydride (2.0 equiv) in 4.5 mL acetic acid was added with stirring until maleic anhydride dissolved fully at RT. Later, aniline (3 mmol, 1.0 equiv) was added dropwise. The reaction mixture was heated for 6−8 h at 125 °C. After completion of the reaction, the reaction mixture was then allowed to cool to room temperature and the whole reaction mixture was transferred to a 500 mL beaker. Saturated sodium bicarbonate aqueous solution was added to the beaker containing the reaction mixture until bubbles stop. The aqueous mixture was extracted with EA (3 × 50 mL). The organic layer was further washed with 1(N) HCl (2 × 50 mL) and brine solution (30 mL), respectively. The excess solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using EA/hexane (10/90) to obtain highly pure *N*-arylmaleimide (crystalline yellow solid) in good yields.

*1-Phenyl-1H-pyrrole-2,5-dione (**2t**).*[25]



Yellow solid, hexane/EtOAc (90/10), 90% (467 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.45 (m, 2H), 7.40−7.33 (m, 3H), 6.85 (s, 2H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.7, 134.3, 131.3, 129.3, 128.1, 126.2.

*1-(p-Tolyl)-1H-pyrrole-2,5-dione (**2u**).*[25]



Yellow solid, hexane/EtOAc (90/10), 91% (511 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, J = 8.1 Hz, 2H), 7.22−7.19 (m, 2H), 6.83 (s, 2H), 2.38 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.8, 138.2, 134.3, 129.9, 128.6, 126.2, 21.3.

General Procedure for the Synthesis of Deuterated Amide. Deuterated carboxamide **1a-D$_2$**,[26] starting material **4k**,[27] **4l**[28] and **4o**[29] was prepared using the reported method.

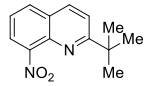
*Procedure for the Synthesis of N-(2-(tert-Butyl)quinolin-8-yl)benzamide (**4p**).* The compound **4p** was synthesized in a three-step process

Step-1. Synthesis of 2-(*tert*-butyl)-8-nitroquinoline (**7p**):[30] A mixture of 8-nitroquinoline (435 mg, 2.5 mmol), pivalic acid (2.5 equiv), $AgNO_3$ (20 mol %), ammonium persulphate (2 equiv), and CF_3COOH (1 equiv) in 50 mL water and chlorobenzene (1:1) was refluxed for 12 h. The mixture was neutralized by Na_2CO_3 solution and extracted with water−EA (three times). Finally, the organic part was washed with a brine solution, and the organic layer was dried over Na_2SO_4. The residue was purified by flash column chromatography using hexane/EA (95/5) as an eluent to isolate the title compound 2-(*tert*-butyl)-8-nitroquinoline (yield 460 mg, 80%, 2 mmol, yellow solid).

Step-2. 2-(*tert*-butyl)quinolin-8-amine (**6p**): Compound was prepared in 2 mmol scales by the reported procedure[20a] and directly used in the next step without further purification.

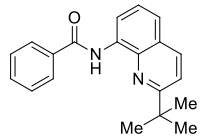
Step-3. *N*-(2-(*tert*-butyl)quinolin-8-yl)benzamide: (**4p**) Compound was prepared using the reported procedure[20a]

*2-(tert-Butyl)-8-nitroquinoline (**7p**).*[30]



Yellow liquid, hexane/EtOAc (95/5), 80% (460 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.8 Hz, 1H), 7.96−7.92 (m, 2H), 7.64 (d, J = 8.7 Hz, 1H), 7.53−7.47 (m, 1H), 1.43 (s, 9H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 172.0, 148.5, 138.5, 135.9, 131.3, 127.4, 124.4, 123.0, 120.1, 38.8, 29.9.

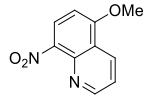
*N-(2-(tert-Butyl)quinolin-8-yl)benzamide (**4p**).*



White solid, hexane/EtOAc (90/10), 96% (525 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.00 (s, 1H), 8.90 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 6.9 Hz, 2H), 8.08 (d, J = 8.9 Hz, 1H), 7.59−7.49 (m, 5H), 7.47 (d, J = 8.1 Hz, 1H), 1.50 (s, 9H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.5, 165.0, 137.3, 136.6, 135.3, 134.4, 131.9, 128.9, 127.2, 126.7, 126.1, 121.3, 119.0, 116.3, 38.3, 30.2. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_2ONa$ [M + Na]$^+$, 327.1473; found, 327.1460.

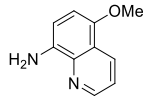
Synthesis of *N*-(5-Methoxyquinolin-8-yl)benzamide (4g). *N*-(5-methoxyquinolin-8-yl)benzamide (**4g**) was prepared using the reported procedure.[31]

*5-Methoxy-8-nitroquinoline (**7g**).*[32]



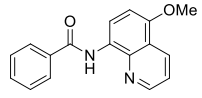
Yellow solid, hexane/EtOAc (95/5), 70% (1.4 g). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.10 (dd, J = 4.5, 2.0 Hz, 1H), 8.65 (d, J = 7.2 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 8.2, 4.4 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.11 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.9, 153.0, 141.2, 131.5, 127.1, 121.8, 121.1, 102.5, 56.61.

*5-Methoxyquinolin-8-amine (**6g**).*[32]



Yellow solid, hexane/EtOAc (95/5), 85% (296 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (d, J = 5.1 Hz, 1H), 8.51 (d, J = 7.7 Hz, 1H), 7.38 (dd, J = 8.2, 4.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.62 (s, 2H), 3.93 (s, 3H).·^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 148.2, 147.2, 139.3, 137.5, 131.0, 121.3, 120.6, 109.9, 105.5, 56.06.

*N-(5-Methoxyquinolin-8-yl)benzamide (**4g**).*[31]



Yellow solid, hexane/EtOAc (85/15), 93% (336 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (s, 1H), 8.91−8.80 (m, 2H), 8.61 (ddd, J = 8.4, 1.6, 0.8 Hz, 1H), 8.08−8.02 (m, 2H), 7.59−7.51 (m, 3H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 4.02 (s, 3H).·^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165.3, 150.6, 148.9, 139.7, 135.5, 131.7, 131.5, 128.9, 128.2, 127.3, 120.9, 120.7, 116.9, 104.6, 56.0.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02120.

^{1}H and ^{13}C spectra, H/D exchange experiments, KIE experimental data, identification in HRMS of organometallic Co(III) complex, and the crystallographic data (PDF).

Accession Codes

CCDC 2019963−2019967 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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