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Biobased Spiroimides from Itaconic Acid and Formamides: Molecular Targets for a Novel Synthetic Application of Renewable Chemicals

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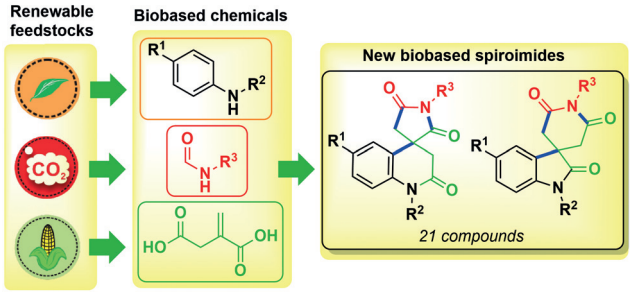

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Abstract Spiroimides exhibit a wide range of biological activities, such as anticonvulsant, antiarrhythmic, and antihyperglycemic activities. Herein, a novel synthetic application of renewable chemicals, itaconic acid and formamides, is described. Proper exploitation of the reactivity of itaconic acid and formamide allows for the development of an efficient synthetic approach for the production of several new biobased spiroimides, spiro[dihydroquinolin-2-one-succinimides] and spiro[indolin-2-one-glutarimides], in excellent overall yields (up to 98%).

Key words spiroimides, itaconic acid, formamides, renewable building blocks, photochemistry

Spiro compounds are a class of rigid scaffolds with unique structural features, which are often relevant for drug discovery.[1] In this context, spirosuccinimide and spiroglutarimide scaffolds are found in compounds of biological interest, such as anticonvulsant,[2] antiarrhythmic,[3] and antihyperglycemic[4] agents, sedatives,[5] and inhibitors of the enzyme aldose reductase[6,7] (Figure 1).

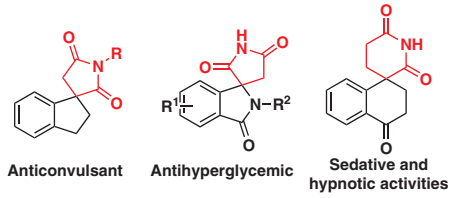
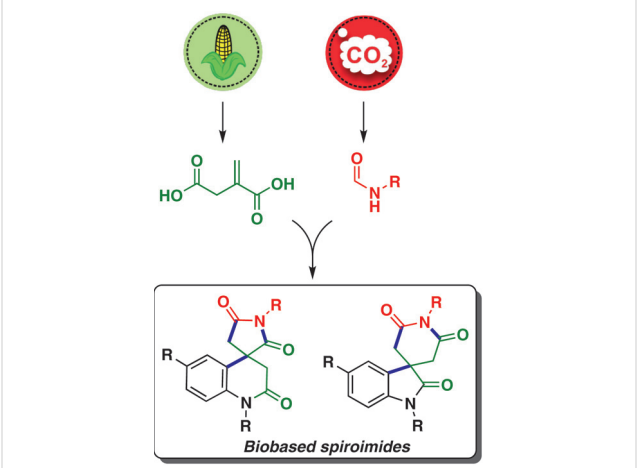


Figure 1 Selected examples of bioactive spiroimides

Despite these important biological activities of spiroimides, the development of general synthetic routes to obtain these compounds is quite scarce in the literature.[7,8] Most of the methods employ harsh conditions, such as high temperatures, long reaction times, and halogenated solvents, which are not attractive from a green chemistry perspective. Additionally, the lack of concern regarding the application of renewable compounds is apparent in those methodologies.

Considering the need for greener synthetic methodologies designed from renewable feedstocks,[9] we developed a novel synthetic pathway to obtain new biobased spiroimides, exploiting the reactivity of itaconic acid and formamide (Scheme 1).



Scheme 1 Biobased spiroimides as molecular targets for the synthetic application of renewable materials

Itaconic acid is a renewable chemical used in the synthesis of biobased polymers (polyesters and polyamides),[10,11] and can be produced from the fermentation of sugars or starch by *Aspergillus terreus*.[12] Moreover, formamide ($HCONH_2$) has been considered a key prebiotic precursor of relevant organic compounds.[13] There are studies

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dedicated to understanding its role in the origin of life on our planet.[14] In addition, formamide is ubiquitous in the universe and has been found in molecular clouds,[15] comets,[16] interstellar medium,[17] and also in protostellar cores.[13] Industrially, formamide is a well-known solvent. There are different synthetic routes for formamide, which include carbon monoxide (CO), carbon dioxide (CO_2), formic acid (HCO_2H), and methyl formate (HCO_2Me) as C1 starting materials.[18,19]

Our successful synthetic strategy to obtain new biobased spiroimides relies on the structural features of itaconic acid and formamide. Proper exploitation of both carboxyl groups of itaconic acid can result in two key intermediates, **1** and **2** (Scheme 2). Carbamoyl radical, which can be generated from formamide using Fenton's reaction,[20] can react with α,β-unsaturated esters **1** and amides **2** to produce 3,4-dihydroquinolin-2-one **3** and indolin-2-one **4** cores, respectively. Finally, succinimide and glutarimide frameworks can be generated via a cyclization reaction under basic conditions, yielding new biobased spiroimides **5** and **6**.

Initially, biobased amides **1a–j** were prepared through a selective ring-opening reaction of itaconic anhydride with *N*-alkylated aromatic amines, followed by an esterification reaction (Scheme 3). After three steps, compounds **1a–j** were obtained in high overall yields. It is worth mentioning that only one purification step by column chromatography was needed.

For the synthesis of methyl 3-(alkyl(aryl)carbamoyl)but-3-enoates **2a–d**, methyl 3-(chlorocarbonyl)but-3-enoate was prepared from itaconic acid methyl ester[21] and then reacted with *N*-alkylated aromatic amines (Scheme 4).

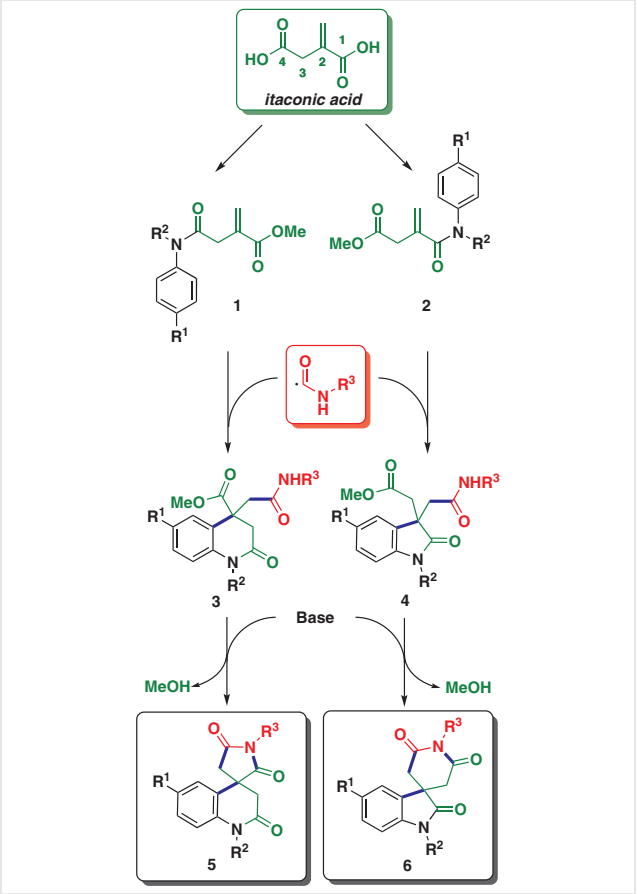
Having obtained the biobased amides **1a–j** and **2a–d**, the next step was the exploitation of their reactivity toward carbamoyl radicals. We employed Fenton's reaction (hydrogen peroxide, H_2SO_4, Fe^{2+})[20b] for a fast hydroxyl radical

Biographical Sketches

Milene M. Hornink was born in 1995 in Piracicaba, São Paulo, Brazil. She received her bachelor's degree in chemistry from the Federal Institute of Education, Science and Technology of São Paulo in 2017. Currently, she is working on her PhD research under the direction of Prof. Leandro H. Andrade. Her PhD research focuses on the development of catalytic methods employing haloperoxidases and on the exploitation of biomass-derived chemicals for the synthesis of nitrogen-containing spiro compounds.

Alice U. Lopes was born in 1998 in São Paulo, São Paulo, Brazil. Currently, she is an undergraduate student at the School of Pharmaceutical Sciences (University of São Paulo) in São Paulo. In 2018/2019, she spent one year in Prof. Andrade's lab working on the synthesis of spiro compounds from biobased chemicals.

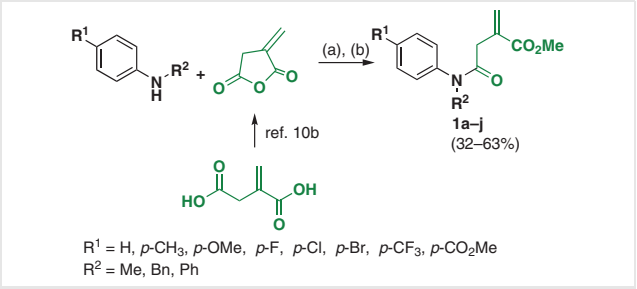
Leandro H. Andrade was born in Santo Antônio das Missões, Brazil. He received his M.S. degree in chemistry (1998) and his PhD degree in chemistry (2002) from the Federal University of Santa Maria (RS, Brazil), working under the direction of Professor A. L. Braga. In 2002, he was awarded a one-year postdoctoral fellowship to work with Professor J. V. Comasseto at São Paulo University. In 2005, he joined the Institute of Chemistry at São Paulo University as Professor of Chemistry. He served as the Chair of the Brazilian Chemical Society, Organic Chemistry Division (2011–2014). In 2013/2014, he spent a sabbatical year in the Department of Chemistry at the Massachusetts Institute of Technology, USA working with Professor Timothy F. Jamison. He is an Associate Editor of the journal Química Nova. His current research interests include sustainable synthesis, catalysis, and flow chemistry.



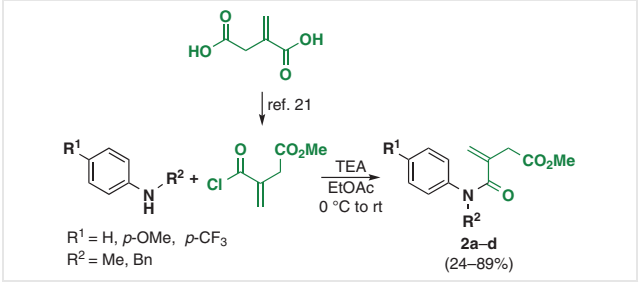
Scheme 2 Our synthetic strategy to obtain new biobased spiroimides

generation, a powerful oxidant[22] which produces carbamoyl radical in the presence of formamide. Our exploratory experiment under batch conditions, containing the biobased amide **1a**, successfully resulted in the full conversion of **1a** into dihydroquinolin-2-one **3a** after 2 hours at 65 °C (Scheme 5).

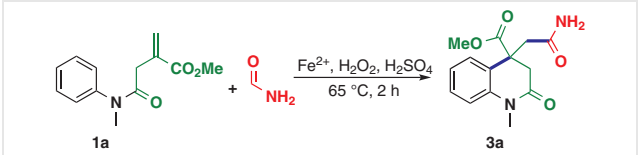
Although dihydroquinolin-2-one **3a** was successfully synthesized, we decided to use a photo-Fenton process for a faster generation of carbamoyl radical.[23] This methodology



Scheme 3 Synthesis of biobased amides **1a–j**. *Reagents and conditions*: (a) toluene, 70–80 °C, 1.5 h; (b) $SOCl_2$, MeOH, reflux, 2.5 h.



Scheme 4 Synthesis of methyl 3-(alkyl(aryl)carbamoyl)but-3-enoates **2a–d**



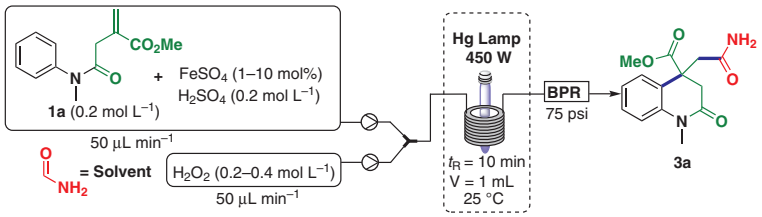
Scheme 5 Exploitation of carbamoyl radical generation under batch conditions for the synthesis of dihydroquinolin-2-ones

employs a photochemical flow reactor. Moreover, the incorporation of flow chemistry into our synthetic approach could offer some advantages, including safety, efficiency, and productivity.[24] Photochemical reactions performed under continuous flow conditions offer important advantages over batch conditions, especially regarding the issues associated with scale-up and efficient exposure of the whole reaction solution to irradiation.[24e,f]

The photochemical flow reactor utilized a UV lamp (medium-pressure, mercury vapor lamp, 450 W), a tube reactor (1 mL), and a syringe pump. The synthesis of dihydroquinolin-2-one **3a** under continuous flow conditions was evaluated at room temperature and with a short residence time (t_R). As shown in Table 1, the desired product, dihydroquinolin-2-one **3a**, was successfully obtained from biobased amide **1a** employing 10 minutes of residence time and different catalyst concentrations (10, 5, and 1 mol% Fe^{2+}). All reactions resulted in full conversion of amide **1a** (entries 1–4). Finally, as a control assay to verify the existence of a photochemical process, a reaction in the absence of UV light was carried out, and no product was observed (entry 5).

In comparison to batch conditions (Scheme 5; full conversion, 2 h, 65 °C), flow photochemistry enabled us to decrease the reaction time and temperature for the production of dihydroquinolin-2-one **3a** (Table 1; full conversion, 10 min, 25 °C). In addition to the above-mentioned advantages of flow chemistry, another key component in its performance relies on the fact that photochemistry applied to the Fenton reaction can increase the production of hydroxyl and carbamoyl radicals in a very short reaction time, consequently increasing the production of dihydroquinolin-2-one **3a**.

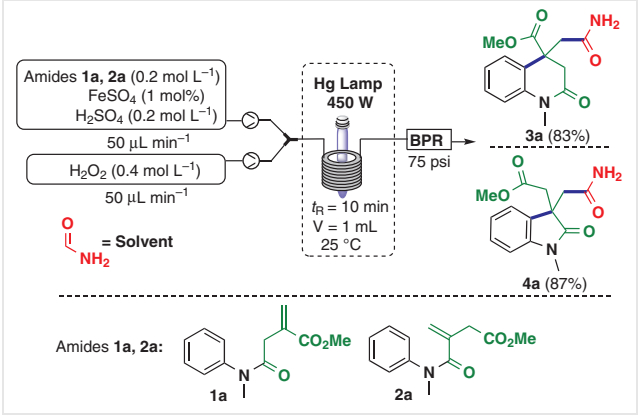
Table 1 Synthesis of Dihydroquinolin-2-one **3a** Using a Photochemical Flow Reactor[a]



Entry	$FeSO_4$ (mol%)	H_2O_2 (mol·L^{-1})	**3a** (%)[b]
1	10	0.2	>99
2	5	0.2	>99
3	1	0.2	>99
4	1	0.1	>99
5[c]	1	0.2	0

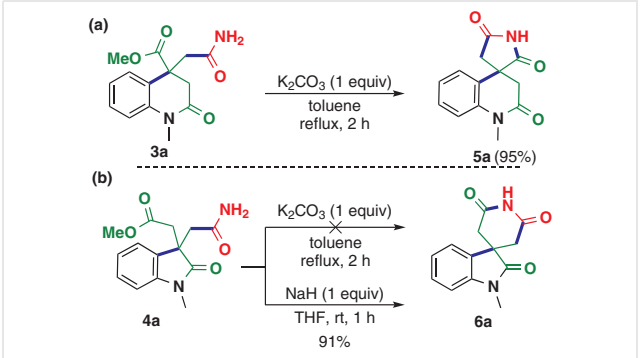
[a] Reaction conditions inside the reactor: **1a** (0.1 mol·L^{-1}), H_2SO_4 (0.1 mol·L^{-1}), $FeSO_4$ (1–10 mol%), H_2O_2 (0.1–0.2 mol·L^{-1}; 30% aqueous solution), formamide as solvent; residence time (t_R) = 10 min; 25 °C; back-pressure regulator (BPR) set to 75 psi.
[b] Conversion was determined by GC/MS analysis.
[c] Hg lamp off.

With the optimized conditions established for carbamoyl radical generation (Table 1, entry 3), we carried out the continuous production of 3,4-dihydroquinolin-2-one **3a** and indolin-2-one **4a** using a photochemical flow reactor (Scheme 6). After 2 hours of production, formamide was removed by vacuum distillation, and 3,4-dihydroquinolin-2-one (**3a**) was isolated in high yield (83%). We also obtained indolin-2-one **4a** in excellent yield (87%).



Scheme 6 Production of dihydroquinolin-2-one **3a** and indolin-2-one **4a** using a photochemical flow reactor

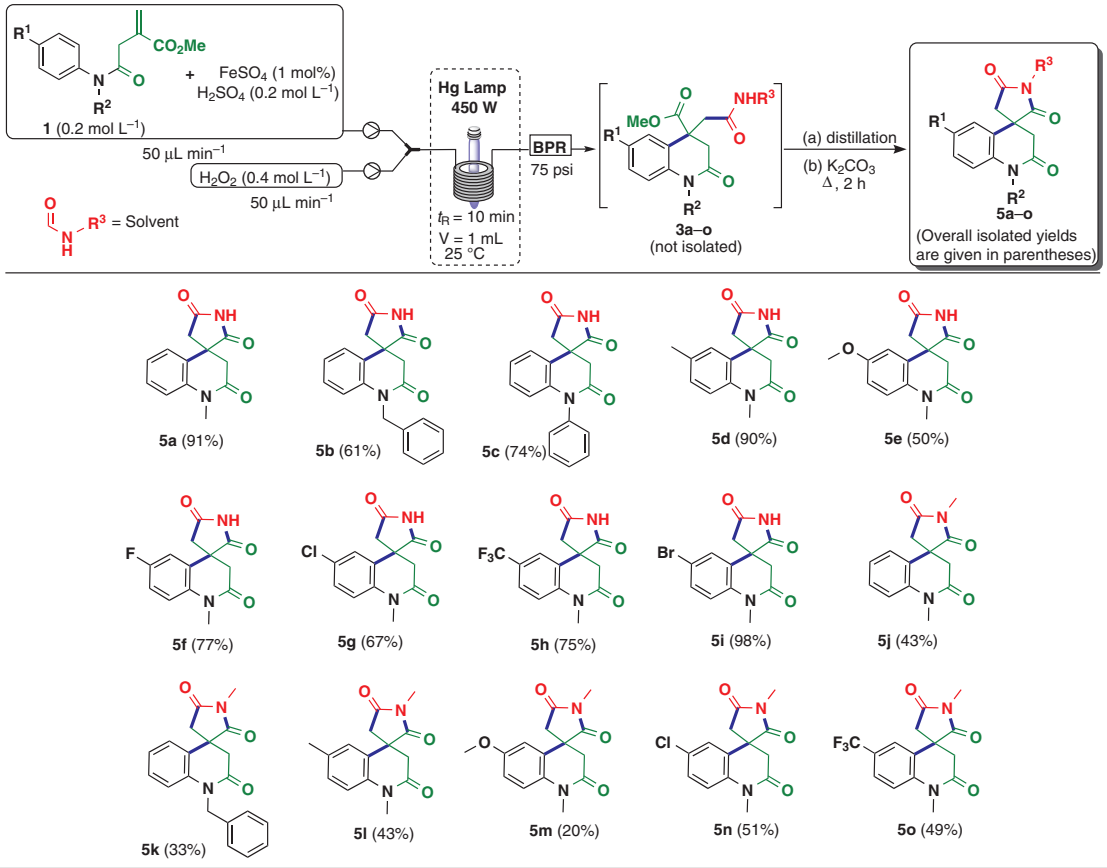
After the construction of 3,4-dihydroquinolin-2-one and indolin-2-one cores, succinimide and glutarimide frameworks were generated by a cyclization reaction under basic conditions. As depicted in Scheme 7, an inexpensive base, K_2CO_3, was employed in the imide formation. The conversion of dihydroquinolin-2-one **3a** into spiro[dihydroquinolin-2-one-succinimide] **5a** was excellent (Scheme 7a; 95% isolated yield, 2 h). The same protocol was applied to



Scheme 7 Base-promoted cyclization of intermediates **3a** and **4a**

3,3-disubstituted indolin-2-one **4a**, but spiro[indolin-2-one-glutarimide] **6a** could not be obtained. Therefore, a stronger base (sodium hydride) was employed, and spiroimide **6a** was obtained in excellent yield (91%) after 1 hour at room temperature (Scheme 7b).

A final setup for the production of biobased spiroimides was designed to avoid multiple steps, mainly aqueous workup and chromatographic purifications. The first step was the continuous production of dihydroquinolin-2-ones **3a–i** using a photochemical flow reactor. Then, formamide was recovered by vacuum distillation, and the crude material was treated with K_2CO_3 to produce spiro[dihydroquinolin-2-one-succinimides] **5a–i** (Scheme 8). Biobased amides **1** were fully converted into the corresponding 3,4-dihydroquinolin-2-ones **3a–i** using the photochemical flow reactor. A reaction time of 2 hours was chosen for the imide formation, and several spiro[dihydroquinolin-2-one-succinimides] **5** were produced in excellent overall yields (Scheme 8). It is noteworthy that the biobased amide **1** containing a



Scheme 8 Synthesis of spiro[dihydroquinolin-2-one-succinimides] **5a–o**

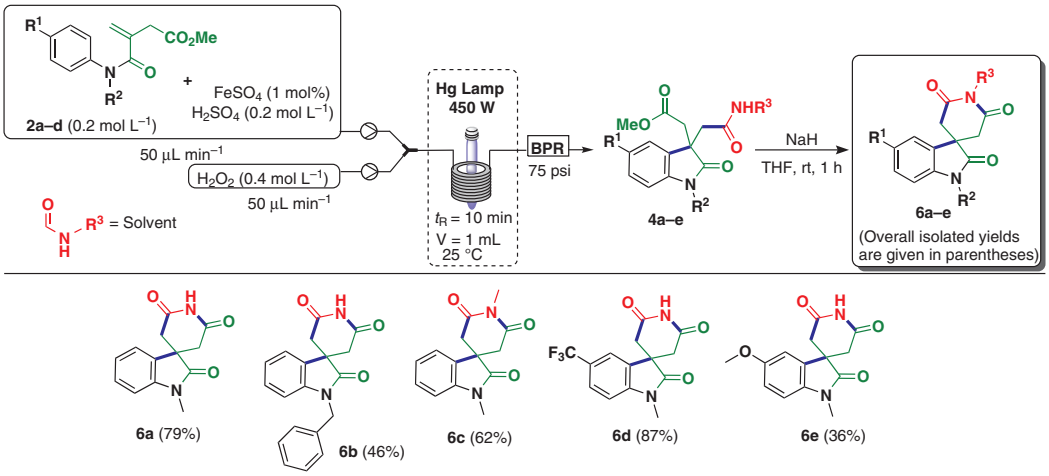
strong electron-donating group (methoxy) attached to the aromatic ring produced spiroimide **5e** in moderate overall yield. We assume that such an aromatic ring containing a strong electron-donating group is susceptible to degradation by the photo-Fenton process applied for fast carbamoyl generation.[25]

N-Methylformamide was also used to produce *N*-methylated spiroimides (Scheme 8). The carbamoyl radical generated from *N*-methylformamide was very efficient in producing 4,4-disubstituted dihydroquinolin-2-ones **3j–o** under continuous flow conditions. *N*-Methylformamide was recovered by vacuum distillation, and K_2CO_3 was added to the crude mixture to promote imide formation. Some *N*-methylated spirosuccinimides **5j–o** were obtained in good overall yields; however, some 4,4-disubstituted dihydroquinolin-2-ones were not fully transformed, resulting in moderate overall yields.

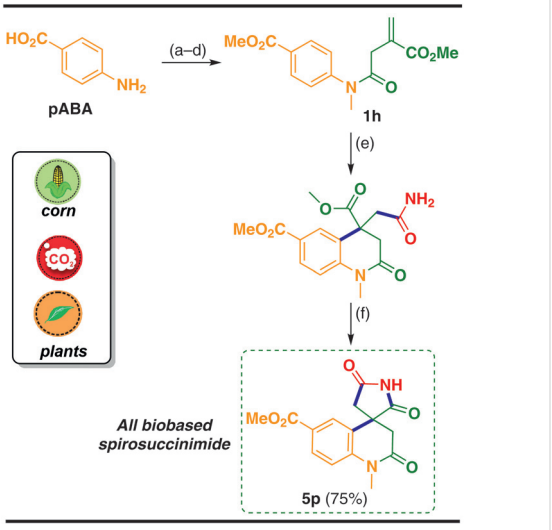
Next, we focused on spiro[indolin-2-one-glutarimides] **6a–e** with the biobased amides **2a–d** as key intermediates (Scheme 9). Carbamoyl radicals were generated from formamide and *N*-methylformamide in the presence of **2a–d** using the photochemical flow reactor. All reactions were carried out at 25 °C with t_R = 10 min, yielding 3,3-disubstituted indolin-2-ones **4**, which were purified by column chromatography prior to imide formation. Then, compounds **4a–e** were treated with sodium hydride at room temperature for 1 hour, affording spiro[indolin-2-one-glutarimides] **6a–e** in high overall yields.

As a proof of concept, we decided to synthesize one example of a spiroimide from renewable chemicals using all-biobased carbons (Scheme 10). We chose pABA (4-aminobenzoic acid), which is one of the few abundant anilines[26] found in nature. pABA is produced by plants and fungi and stored for the production of folate.[27] We applied pABA to produce amide **1h** in high yield (47%). The continuous generation of carbamoyl radicals in the presence of amide **1h** afforded the corresponding 4,4-disubstituted dihydroquinolin-2-one. Formamide was removed by distillation, and the crude material was treated with K_2CO_3 to give the imide. Finally, biobased spiro[dihydroquinolin-2-one-succinimide] **5p** was isolated in excellent overall yield (75%).

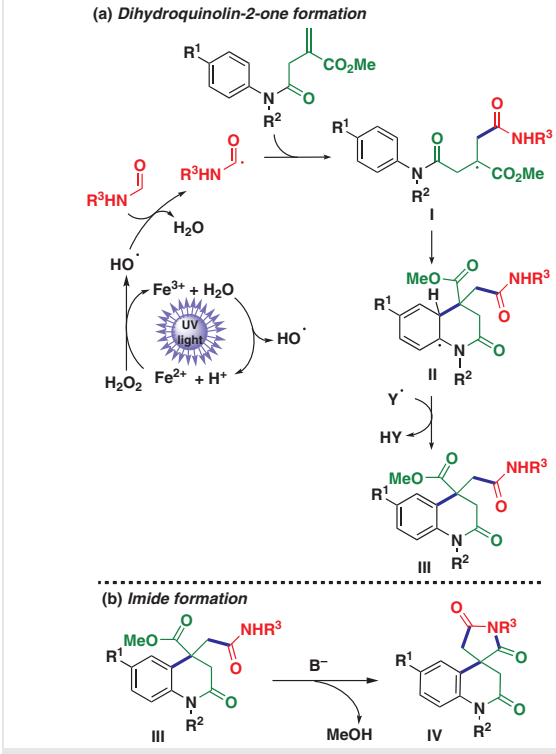
A plausible reaction mechanism for the formation of the 3,4-dihydroquinolin-2-one core is suggested in Scheme 11. Hydroxyl radical generation is driven by the photo-Fenton process. Once formed, hydroxyl radical can remove formyl hydrogen from formamide, producing carbamoyl radical. Then, carbamoyl radical can react with the C–C double



Scheme 9 Synthesis of spiro[indolin-2-one-glutarimides] **6a–e**



Scheme 10 Synthetic pathway for the production of spiroimide **5p** using all-biobased carbons. *Reagents and conditions*: (a) $SOCl_2$, MeOH, rt to reflux, 2 h; (b) NaOMe, HCOH, $NaBH_4$, MeOH, rt to reflux, 1.6 h; (c) itaconic anhydride, toluene, 70–80 °C, 1.5 h; (d) $SOCl_2$, MeOH, reflux, 2.5 h; (e) photochemical flow reactor: **1h** (0.2 mol·L^{-1}), H_2SO_4 (0.2 mol·L^{-1}), $FeSO_4$ (1 mol%), H_2O_2 (30% aqueous solution; 0.4 mol·L^{-1}), formamide as solvent, t_R = 10 min, 25 °C; (f) K_2CO_3 (1.0 equiv), reflux, Dean–Stark apparatus, 2 h.



Scheme 11 Proposed reaction mechanism for dihydroquinolin-2-one and imide formation

bond of the unsaturated amide, generating intermediate **I** that undergoes cyclization and rearomatization to produce the dihydroquinolin-2-one core. The reaction mechanism for indolin-2-one formation should follow a similar path. During imide formation, a cyclization reaction occurs due to the presence of a primary amide and an ester group under basic conditions, yielding spiroimides.

In summary, a novel synthetic application of renewable chemicals, itaconic acid and formamides, has been described for the production of biobased spiroimides. A photochemical flow reactor was used to generate carbamoyl radicals from formamides, which enabled the fast synthesis of dihydroquinolin-2-one and indolin-2-one cores. Finally, spiro[dihydroquinolin-2-one-succinimides] and spiro[indolin-2-one-glutarimides] were synthesized in excellent overall yields.

Formamides, itaconic acid, and itaconic anhydride were purchased from Sigma-Aldrich. Solvents were purified by standard procedures. Reactions were monitored using a GC/MS instrument (QP-2010 SE, Shimadzu) with low-resolution electron impact (EI, 70 eV) equipped with an Rtx-5MS capillary column (conditions: injector 260 °C, detector 110 °C, pressure 100 kPa, column temperature range 80 °C to 280 °C at 1 °C/min). Flash column chromatography was performed with silica gel (200–300 mesh). ^{1}H NMR spectra were recorded with 500 MHz and 300 MHz Bruker spectrometers. TMS was used as an internal standard ($CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.51 ppm; MeOD, δ 3.31 ppm). Coupling constants, *J*, are reported in hertz (Hz). Proton-decoupled ^{13}C NMR spectra were recorded with 500 MHz and 300 MHz Bruker spectrometers ($CDCl_3$, δ 77.0 ppm; DMSO-d_6, δ 40.0 ppm; MeOD, δ 47.6 ppm). High-resolution mass spectra were recorded with a Bruker Daltonics micrOTOF spectrometer using ESI-TOF techniques. Infrared spectra were recorded with an FTIR spectrometer (Nexus 670 Nicolet). Melting points were determined with a Büchi apparatus (B-545). *N*-Methylanilines, *N*-benzylanilines, and itaconic acid monoester were prepared according to the methods described previously (for more details, see the Supporting Information).

Biobased Amides 1a–j; General Procedure[28,29]

Step 1: A solution of *N*-alkylaniline (5 mmol) in toluene (2 mL) was added to a stirred suspension of itaconic anhydride (0.68 g, 6 mmol) in toluene (5 mL) via a syringe pump at 70 °C (this addition was performed over 1 h). Then, the reaction mixture was stirred for 30 min at 80 °C. The solvent was removed under reduced pressure to yield the crude product, 4-(alkyl(aryl)amino)-2-methylene-4-oxobutanoic acid, which was used in the next step without further purification.

Step 2: Thionyl chloride (1.3 mL, 17.5 mmol) was added dropwise to MeOH (10 mL) at 0 °C, followed by addition of a solution of the 4-(alkyl(aryl)amino)-2-methylene-4-oxobutanoic acid in MeOH (10 mL). The mixture was stirred for 2.5 h under reflux. The volatiles were removed under reduced pressure. Sat. aq K_2CO_3 was added to the mixture to obtain pH 7, and the mixture was then extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc/hexanes, 1:1).

Methyl 4-(Methyl(phenyl)amino)-2-methylene-4-oxobutanoate (1a)

Yellow syrup; yield: 0.560 g (48%); R_f = 0.41 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (t, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.28–7.26 (m, 2 H), 6.23 (s, 1 H), 5.60 (s, 1 H), 3.74 (s, 3 H), 3.28 (s, 3 H), 3.10 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 166.9, 143.9, 135.1, 129.8, 127.9, 127.7, 127.4, 51.9, 37.7, 37.4.

MS (EI$^+$): *m*/*z* (%) = 233 (M^+, 3), 107 (100), 77 (29).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_3$: 234.1130; found: 234.1125.

Methyl 4-(Methyl(*p*-tolyl)amino)-2-methylene-4-oxobutanoate (1b)

Pale yellow solid; yield: 0.396 g (32%); R_f = 0.42 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.2 Hz, 2 H), 6.24 (s, 1 H), 5.59 (s, 1 H), 3.73 (s, 3 H), 3.25 (s, 3 H), 3.09 (s, 2 H), 2.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 167.0, 141.4, 137.9, 135.2, 130.4, 127.6, 127.1, 51.9, 37.7, 37.4, 21.1.

MS (EI$^+$): *m*/*z* (%) = 247 (M^+, 5), 121 (100), 91 (15).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_3$: 248.1287; found: 248.1283.

Methyl 4-((4-Methoxyphenyl)(methyl)amino)-2-methylene-4-oxobutanoate (1c)

White solid; yield: 0.434 g (33%); R_f = 0.34 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.24 (s, 1 H), 5.59 (s, 1 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.24 (s, 3 H), 3.08 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 167.0, 159.0, 136.7, 135.2, 128.4, 127.6, 114.9, 55.5, 51.9, 37.7, 35.5.

MS (EI$^+$): *m*/*z* (%) = 263 (M^+, 10), 137 (100), 122 (69).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_4$: 264.1236; found: 264.1238.

Methyl 4-((4-Fluorophenyl)(methyl)amino)-2-methylene-4-oxobutanoate (1d)

White solid; yield: 0.578 g (46%); R_f = 0.35 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H), 7.12 (t, $J_{H,F}$ = 8.4 Hz, 2 H), 6.26 (s, 1 H), 5.62 (s, 1 H), 3.74 (s, 3 H), 3.26 (s, 3 H), 3.07 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 166.9, 161.8 (d, $J_{C,F}$ = 246 Hz), 140.0 (d, $J_{C,F}$ = 1.3 Hz), 134.9, 129.2 (d, $J_{C,F}$ = 8.5 Hz), 127.8, 116.7 (d, $J_{C,F}$ = 23 Hz), 52.0, 37.7, 37.5.

MS (EI$^+$): *m*/*z* (%) = 251 (M^+, 3), 125 (100), 95 (23).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}FNO_3$: 252.1036; found: 252.1025.

Methyl 4-((4-Chlorophenyl)(methyl)amino)-2-methylene-4-oxobutanoate (1e)

White solid; yield: 0.709 g (53%); R_f = 0.36 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.5 Hz, 2 H), 7.23–7.20 (m, 2 H), 6.26 (s, 1 H), 5.62 (s, 1 H), 3.74 (s, 3 H), 3.26 (s, 3 H), 3.07 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 166.9, 142.5, 134.9, 133.8, 130.0, 128.8, 127.9, 52.0, 37.7, 37.4.

MS (EI$^+$): *m*/*z* (%) = 267 (M^+, 3), 141 (100), 99 (38).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}ClNO_3$: 268.0740; found: 268.0734.

Methyl 4-((4-Bromophenyl)(methyl)amino)-2-methylene-4-oxobutanoate (1f)

White solid; yield: 0.656 g (42%); R_f = 0.42 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.3 Hz, 2 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 6.26 (s, 1 H), 5.62 (s, 1 H), 3.74 (s, 3 H), 3.26 (s, 3 H), 3.08 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 166.9, 143.0, 134.9, 133.1, 129.9, 129.2, 128.0, 52.0, 37.7, 37.4.

MS (EI$^+$): *m*/*z* (%) = 313 (M^+, 5), 185 (80), 127 (100), 99 (56).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}BrNO_3$: 312.0235; found: 312.0235.

Methyl 4-(Methyl(4-(trifluoromethyl)phenyl)amino)-2-methylene-4-oxobutanoate (1g)

Yellowish solid; yield: 0.452 g (30%); R_f = 0.39 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 6.28 (s, 1 H), 5.64 (s, 1 H), 3.74 (s, 3 H), 3.31 (s, 3 H), 3.12 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 166.8, 147.1, 134.7, 128.1, 127.8, 127.0, 123.7 (q, *J* = 270 Hz), 116.7, 52.0, 37.8, 37.4.

MS (EI$^+$): *m*/*z* (%) = 301 (M^+, 2), 127 (100), 99 (47).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3NO_3$: 302.1004; found: 302.0999.

Methyl 4-(3-(Methoxycarbonyl)-*N*-methylbut-3-enamido)benzoate (1h)

Pale yellow solid; yield: 0.690 g (47%); R_f = 0.45 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 2 H), 7.36 (d, *J* = 8.5 Hz, 2 H), 6.27 (s, 1 H), 5.63 (s, 1 H), 3.94 (s, 3 H), 3.74 (s, 3 H), 3.31 (s, 3 H), 3.14 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 166.8, 166.2, 147.9, 134.8, 131.2, 129.5, 128.0, 127.2, 52.3, 52.0, 37.8, 37.4.

MS (EI$^+$): *m*/*z* (%) = 291 (M^+, 4), 165 (100), 127 (74).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}NO_5$: 292.1185; found: 292.1172.

Methyl 4-(Benzyl(phenyl)amino)-2-methylene-4-oxobutanoate (1i)

Colorless oil; yield: 0.974 g (63%); R_f = 0.64 (EtOAc/hexanes, 2:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 8 H), 7.05 (d, *J* = 6.9 Hz, 2 H), 6.27 (s, 1 H), 5.61 (s, 1 H), 4.89 (s, 2 H), 3.74 (s, 3 H), 3.09 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 166.9, 142.2, 137.4, 136.1, 129.6, 128.9, 128.5, 128.3, 128.1, 127.8, 127.4, 53.2, 51.2, 38.1.

MS (EI$^+$): *m*/*z* (%) = 309 (M^+, 3), 250 (14), 183 (21), 91 (100), 77 (23).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}NO_3$: 310.1443; found: 310.1435.

Methyl 4-(Diphenylamino)-2-methylene-4-oxobutanoate (1j)

Colorless solid; yield: 0.753 g (51%); R_f = 0.24 (EtOAc/hexanes, 3:7).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.17 (m, 10 H), 6.28 (s, 1 H), 5.66 (s, 1 H), 3.76 (s, 3 H), 3.27 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 166.9, 142.7, 140.6, 135.1, 128.9, 127.9, 126.4, 52.0, 39.1.

MS (EI$^+$): *m*/*z* (%) = 295 (M^+, 3), 169 (100), 127 (26).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}NO_3$: 296.1287; found: 296.1285.

Biobased Amides 2a–d; General Procedure

A solution of methyl 3-(chlorocarbonyl)but-3-enoate (0.975 g, 6 mmol) (for its preparation, see the Supporting Information) in EtOAc (20 mL) was added dropwise to a stirred solution of *N*-alkylaniline (5 mmol) and triethylamine (0.84 mL, 6 mmol) in anhydrous EtOAc (10 mL) at 0 °C. The mixture was stirred overnight at room temperature. Sat. aq $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc/hexanes, 1:1).

Methyl 3-(Methyl(phenyl)carbamoyl)but-3-enoate (2a)[30]

Yellow oil; yield: 1.038 g (89%); R_f = 0.51 (EtOAc/hexanes, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H), 5.27 (s, 1 H), 5.04 (s, 1 H), 3.71 (s, 3 H), 3.38 (s, 3 H), 3.30 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 169.6, 158.3, 137.7, 136.8, 127.9, 123.6, 114.4, 55.4, 51.9, 39.4.

MS (EI$^+$): *m*/*z* (%) = 233 (M^+, 3), 107 (100), 77 (29).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NO_3$: 234.1130; found: 234.1128.

Methyl 3-((4-Methoxyphenyl)(methyl)carbamoyl)but-3-enoate (2b)[31]

Yellow oil; yield: 0.684 g (52%); R_f = 0.28 (EtOAc/hexanes, 2:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 5.26 (s, 1 H), 5.06 (s, 1 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 3.34 (s, 3 H), 3.29 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 169.6, 158.3, 137.7, 136.7, 130.0, 127.9, 114.4, 55.4, 51.9, 39.4, 37.2.

MS (EI$^+$): *m*/*z* (%) = 263 (M^+, 19), 137 (100), 127 (74).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_4$: 264.1236; found: 264.1225.

Methyl 3-(Methyl(4-(trifluoromethyl)phenyl)carbamoyl)but-3-enoate (2c)

Yellow oil; yield: 0.648 g (43%); R_f = 0.46 (EtOAc/hexanes, 2:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 5.32 (s, 1 H), 5.00 (s, 1 H), 3.72 (s, 3 H), 3.42 (s, 3 H), 3.39 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 169.3, 148.2, 136.3, 128.6 (q, *J* = 32.6 Hz), 126.9, 126.3 (q, *J* = 3.70 Hz), 124.2, 123.8 (q, *J* = 270.3 Hz), 51.9, 39.2, 38.3.

MS (EI$^+$): *m*/*z* (%) = 301 (M^+, 2), 127 (100), 99 (54).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3NO_3$: 302.1004; found: 302.1004.

Methyl 3-(Benzyl(phenyl)carbamoyl)but-3-enoate (2d)

Yellow oil; yield: 0.371 g (24%); R_f = 0.44 (EtOAc/hexanes, 2:3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.17 (m, 10 H), 5.25 (s, 1 H), 5.06 (s, 1 H), 5.02 (s, 2 H), 3.69 (s, 3 H), 3.33 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 169.2, 143.5, 137.4, 136.8, 129.1, 128.4, 128.3, 127.7, 127.2, 127.1, 124.0, 53.8, 51.8, 39.6.

MS (EI$^+$): *m*/*z* (%) = 309 (M^+, 7), 250 (45), 127 (28), 91 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}NO_3$: 310.1443; found: 310.1473.

Spiro[dihydroquinolin-2-one-succinimides] 5a–p; General Procedure

Step 1: Carbamoyl radical generation using the photo-Fenton reaction under continuous flow conditions

Photochemical flow reactor assembly (also see the Supporting Information): A UV lamp (medium-pressure, mercury vapor lamp, 450 W, Ace Glass Inc., 7825-35) was inserted into a filter sleeve (Pyrex). Both were inserted into a quartz immersion well, which was placed in a water bath. A tube reactor (1 mL; high-purity perfluoroalkoxyalkane tubing, 1/16 in. o.d. × 0.030 in. × 7.25 ft) was wrapped around the quartz immersion well. The coil reactor was connected to syringes via

a Y-adapter. A photochemical reaction cabinet (46 × 64 × 44 cm, W × H × D) was built and can be maintained on a lab bench. A syringe pump (Harvard Apparatus PHD ULTRA) was used to infuse the solutions into the photochemical reactor. A back-pressure regulator (BPR, 75 psi) was connected to the end of the coil reactor, and the exiting stream was collected into a flask.

Two solutions containing the starting materials were prepared as follows. Solution 1: Biobased amide **1a–j** (0.2 mol·L^{-1}), $FeSO_4$·7 H_2O (1 mol%), and H_2SO_4 (0.2 mol·L^{-1}) were added to a volumetric flask, and formamide (or *N*-methylformamide) was added to fill the remaining volume of the flask. Nitrogen bubbling was employed for 5 min. Solution 2: Aq H_2O_2 (30 wt %, 0.4 mol·L^{-1}) was added to a volumetric flask, and formamide (or *N*-methylformamide) was added to fill the remaining volume of the flask. Nitrogen bubbling was employed for 5 min. These solutions were used to load two 8 mL stainless steel syringes that were attached to the syringe pump. For reactor equilibration, both solutions were infused at a flow rate of 50 µL/min for 0.5 h; the resulting collected mixture was discharged. After this stabilization, a sample of the reaction solution was collected every 5 min for analysis by GC/MS. This analysis was repeated three times. For extraction of the samples, sat. aq $NaHCO_3$ (0.5 mL) and $CHCl_3$ (1 mL) were added to the flask, and the organic layer was removed. The aqueous layer was washed with $CHCl_3$ (1 mL) in the same flask. The combined organic layers were dried over $MgSO_4$, filtered, and analyzed by TLC and GC/MS. The infusion of the solutions was maintained for an additional 45 min. The exiting stream was collected in a glass flask containing $NaHCO_3$ (0.038 g, 0.45 mmol) and Na_2SO_3 (0.113 g, 0.9 mmol). The resulting mixture was stirred for approximately 15 min for gas evolution. Then, 4 mL was transferred to a round-bottom flask for formamide removal by vacuum distillation to yield the crude product, 4,4-disubstituted dihydroquinolinone **3**.

Step 2: Imidation reaction

K_2CO_3 (55.3 mg, 0.4 mmol) and toluene (6 mL) were added to the crude 4,4-disubstituted dihydroquinolinone **3** (0.4 mmol). The resulting mixture was heated under reflux (Dean–Stark apparatus) for 2 h (**5a–i** and **5p**) or 5 h (**5j–o**). Toluene was removed under reduced pressure. Aq 2 M HCl (5 mL) was added and then the mixture was extracted with $CHCl_3$ (3 × 5 mL). The organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The spiro[dihydroquinolin-2-one-succinimides] were purified by silica gel column chromatography (**5a–i**: $CHCl_3$/MeOH, 95:5; **5j–o**: $CHCl_3$).

1′-Methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5a)

White solid; yield: 92.8 mg (91%); mp 201–204 °C; R_f = 0.35 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3129, 3063, 2943, 2911, 1767, 1705, 1643, 1593, 1577, 1138, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.78 (br s, 1 H), 7.39–7.35 (m, 1 H), 7.11–7.08 (m, 3 H), 3.41 (s, 3 H), 3.17 (d, *J* = 15.8 Hz, 1 H), 2.98 (d, *J* = 18.4 Hz, 1 H), 2.83 (d, *J* = 18.6 Hz, 1 H), 2.80 (d, *J* = 16.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 173.7, 166.5, 139.7, 129.5, 126.1, 124.8, 123.9, 116.0, 47.9, 43.1, 40.0, 29.7.

MS (EI$^+$): *m*/*z* (%) = 244 (M$^+$, 73), 173 (84), 144 (67), 130 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}N_2O_3$: 245.0926; found: 245.0930.

1′-Benzyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5b)

White solid; yield: 78.2 mg (61%); mp 263 °C (dec); R_f = 0.36 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3043, 2916, 2752, 1780, 1712, 1651, 1595, 1392, 759, 731 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.32–7.29 (m, 4 H), 7.22 (t, *J* = 6.5 Hz, 2 H), 7.16 (d, *J* = 6.8 Hz, 1 H), 7.08–7.05 (m, 2 H), 5.25 (m, 2 H), 3.19 (d, *J* = 15.9 Hz, 1 H), 3.06–3.00 (m, 2 H), 2.86 (d, *J* = 18.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.6, 176.5, 167.6, 139.3, 137.4, 129.3, 129.0, 127.4, 127.0 (2 C), 125.4, 123.0, 116.8, 47.5, 44.9, 42.9, 38.7.

MS (EI$^+$): *m*/*z* (%) = 320 (M$^+$, 10), 106 (20), 91 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}N_2O_3$: 321.1239; found: 321.1245.

1′-Phenyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5c)

Pale yellow solid; yield: 22.7 mg (74%); mp 231–234 °C; R_f = 0.39 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2935, 2910, 2841, 1770, 1708, 1681, 1595, 1356, 761, 713 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.76 (br s, 1 H), 7.55 (t, *J* = 7.4 Hz, 2 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.26 (d, *J* = 7.4 Hz, 2 H), 7.19–7.15 (m, 2 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 6.30 (d, *J* = 8.0 Hz, 1 H), 3.11–2.99 (m, 4 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.6, 176.7, 167.1, 141.7, 138.9, 130.2, 129.7, 129.1, 128.7, 126.6, 125.2, 123.7, 117.9, 49.1, 47.6, 42.5.

MS (EI$^+$): *m*/*z* (%) = 306 (M$^+$, 100), 234 (63), 206 (43).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}N_2O_3$: 307.1083; found: 307.1077.

1′,6′-Dimethyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5d)

Yellowish solid; yield: 93.0 mg (90%); mp 227–229 °C; R_f = 0.39 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3211, 2931, 2907, 1775, 1715, 1643, 1611, 1344, 1179, 812 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (br s, 1 H), 7.16 (d, *J* = 8.2 Hz, 1 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 6.88 (s, 1 H), 3.39 (s, 3 H), 3.16 (d, *J* = 15.8 Hz, 1 H), 2.97 (d, *J* = 18.4 Hz, 1 H), 2.81 (d, *J* = 18.4 Hz, 1 H), 2.77 (d, *J* = 15.8 Hz, 1 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6, 173.8, 166.4, 137.2, 133.7, 129.9, 126.0, 125.3, 115.9, 47.9, 43.2, 40.1, 29.7, 20.7.

MS (EI$^+$): *m*/*z* (%) = 258 (M$^+$, 98), 187 (95), 144 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_3$: 259.1083; found: 259.1085.

6′-Methoxy-1′-methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5e)

White solid; yield: 54.8 mg (50%); mp 216–218 °C; R_f = 0.33 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3210, 2932, 2913, 2883, 1778, 1717, 1649, 1581, 1503, 1036, 800 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (br s, 1 H), 7.01 (d, *J* = 8.9 Hz, 1 H), 6.88 (dd, *J* = 8.9, 2.8 Hz, 1 H), 6.64 (d, *J* = 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.28 (s, 3 H), 3.15 (d, *J* = 15.8 Hz, 1 H), 2.97 (d, *J* = 18.5 Hz, 1 H), 2.81 (d, *J* = 18.4 Hz, 1 H), 2.77 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 173.7, 166.1, 155.9, 133.2, 127.5, 116.9, 113.5, 111.5, 55.7, 48.0, 43.1, 40.1, 29.9.

MS (EI$^+$): *m*/*z* (%) = 274 (M^+, 100), 203 (48), 188 (52).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_4$: 275.1032; found: 275.1036.

6′-Fluoro-1′-methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5f)

White solid; yield: 80.8 mg (77%); mp 229–232 °C; R_f = 0.26 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3210, 3065, 2947, 2913, 2830, 1778, 1717, 1649, 1582, 1503, 1177, 1036, 799 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.25–7.23 (m, 1 H), 7.14 (td, *J* = 8.9, 2.8 Hz, 1 H), 6.94 (dd, *J* = 8.9, 2.8 Hz, 1 H), 3.38 (s, 3 H), 3.04 (d, *J* = 16.0 Hz, 1 H), 2.96 (d, *J* = 18.3 Hz, 1 H), 2.88 (d, *J* = 15.9 Hz, 1 H), 2.88 (d, *J* = 18.2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.1, 176.2, 166.7, 158.2 (d, $J_{C,F}$ = 239 Hz), 137.2 (d, $J_{C,F}$ = 2.1 Hz), 128.6 (d, $J_{C,F}$ = 6.7 Hz), 118.0 (d, $J_{C,F}$ = 8.0 Hz), 115.6 (d, $J_{C,F}$ = 22.1 Hz), 112.6 (d, $J_{C,F}$ = 24.3 Hz), 47.4, 42.3, 39.0, 29.9.

MS (EI$^+$): *m*/*z* (%) = 262 (M^+, 74), 191 (67), 148 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}FN_2O_3$: 263.0832; found: 263.0828.

6′-Chloro-1′-methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5g)

White solid; yield: 74.7 mg (67%); mp 266–269 °C; R_f = 0.35 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3224, 3074, 2931, 2912, 1774, 1724, 1645, 1591, 1415, 1176, 819 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.39 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.13 (d, *J* = 2.3 Hz, 1 H), 3.37 (s, 3 H), 3.05 (d, *J* = 16.0 Hz, 1 H), 2.96 (d, *J* = 18.2 Hz, 1 H), 2.88 (d, *J* = 16.1 Hz, 1 H), 2.88 (d, *J* = 18.2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.1, 176.2, 166.8, 139.7, 129.1, 128.7, 127.3, 125.1, 118.2, 47.4, 42.3, 38.9, 29.7.

MS (EI$^+$): *m*/*z* (%) = 278 (M^+, 58), 207 (64), 44 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}ClN_2O_3$: 279.0536; found: 279.0525.

6′-Bromo-1′-methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5h)

White solid; yield: 126.7 mg (75%); mp 240–243 °C; R_f = 0.43 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3180, 2939, 2914, 1774, 1712, 1658, 1614, 1330, 1280, 1187, 1114, 829 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.04 (br s, 1 H), 7.53 (d, *J* = 8.7 Hz, 1 H), 7.26 (s, 1 H), 7.16 (d, *J* = 8.8 Hz, 1 H), 3.36 (s, 3 H), 3.04 (d, *J* = 16.0 Hz, 1 H), 2.97 (d, *J* = 18.2 Hz, 1 H), 2.88 (d, *J* = 16.0 Hz, 1 H), 2.87 (d, *J* = 18.2 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.1, 176.2, 166.8, 140.1, 132.0, 129.1, 127.8, 118.5, 115.1, 47.4, 42.4, 38.9, 29.7.

MS (EI$^+$): *m*/*z* (%) = 324 (M^+, 100), 322 (98), 251 (84).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}BrN_2O_3$: 323.0031; found: 323.0018.

1′-Methyl-6′-(trifluoromethyl)-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5i)

White solid; yield: 93.7 mg (98%); mp 254–256 °C; R_f = 0.32 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3344, 3332, 2943, 2908, 1776, 1695, 1637, 1589, 1379, 1138, 817 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.70 (d, *J* = 8.4 Hz, 1 H), 7.41–7.39 (m, 2 H), 3.42 (s, 3 H), 3.10 (d, *J* = 16.0 Hz, 1 H), 3.00 (d, *J* = 18.2 Hz, 1 H), 2.95 (d, *J* = 17.0 Hz, 1 H), 2.91 (d, *J* = 18.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 180.1, 176.2, 167.2, 144.1, 128.0, 126.7 (m), 124.5 (q, *J* = 290 Hz), 123.6, 122.2 (m), 117.0, 47.4, 42.3, 38.9, 29.8.

MS (EI$^+$): *m*/*z* (%) = 312 (M^+, 72), 241 (100), 198 (90).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_2O_3$: 313.0800; found: 313.0805.

1,1′-Dimethyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5j)

Due to low solubility of biobased amide **1j**, it was necessary to decrease its concentration (**1j**, 0.025 mol·L^{-1}).

White solid; yield: 44.4 mg (43%); mp 170–173 °C; R_f = 0.60 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2951, 2916, 2848, 1780, 1693, 1666, 1597, 1365, 1286, 1053, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.09–7.06 (m, 2 H), 6.94 (dd, *J* = 7.6, 1.1 Hz, 1 H), 3.42 (s, 3 H), 3.18 (d, *J* = 15.8 Hz, 1 H), 3.14 (s, 3 H), 2.91 (d, *J* = 18.2 Hz, 1 H), 2.80 (d, *J* = 18.2 Hz, 1 H), 2.71 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7, 174.1, 166.5, 139.6, 129.4, 126.5, 124.7, 123.8, 115.9, 46.6, 42.2, 40.2, 29.7, 25.5.

MS (EI$^+$): *m*/*z* (%) = 258 (M^+, 93), 173 (87), 130 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_3$: 259.1083; found: 259.1076.

1′-Benzyl-1-methyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5k)

White solid; yield: 44.1 mg (33%); mp 146–148 °C; R_f = 0.68 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2953, 2912, 2845, 1772, 1697, 1664, 1600, 1373, 1282, 777, 715 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.31–7.30 (m, 4 H), 7.24–7.19 (m, 2 H), 7.08–7.03 (m , 3 H), 5.28 (d, *J* = 16.4 Hz, 1 H), 5.23 (d, *J* = 16.4 Hz, 1 H), 3.19 (d, *J* = 15.9 Hz, 1 H), 3.04 (s, 3 H), 3.01 (d, *J* = 18.1 Hz, 1 H), 3.00 (d, *J* = 15.8 Hz, 1 H), 2.90 (d, *J* = 18.0 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 179.1, 175.0, 168.2, 138.8, 136.6, 128.8, 128.4, 126.9 (2 C), 126.4, 124.7, 123.6, 116.8, 46.2, 45.3, 41.2, 38.9, 24.1.

MS (EI$^+$): *m*/*z* (%) = 334 (M^+, 11), 306 (20), 91 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_2O_3$: 335.1396; found: 335.1397.

1,1′,6′-Trimethyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5l)

White solid; yield: 46.8 mg (43%); mp 195–197 °C; R_f = 0.68 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2938, 2911, 2830, 1778, 1715, 1649, 1580, 1177, 1036, 797 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.2 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.71 (s, 1 H), 3.39 (s, 3 H), 3.15 (d, *J* = 15.8 Hz, 1 H), 3.14 (s, 3 H), 2.93 (d, *J* = 18.2 Hz, 1 H), 2.78 (d, *J* = 18.2 Hz, 1 H), 2.68 (d, *J* = 15.8 Hz, 1 H), 2.29 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8, 174.2, 166.4, 137.4, 133.5, 129.8, 126.4, 125.3, 115.8, 46.6, 42.3, 40.3, 29.7, 25.5, 20.7.

MS (EI$^+$): *m*/*z* (%) = 272 (M^+, 79), 187 (84), 144 (100).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_2O_3$: 273.1239; found: 273.1241.

6′-Methoxy-1,1′-dimethyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5m)

Light brown powder; yield: 23.0 mg (20%); mp 180–182 °C; R_f = 0.45 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2930, 2918, 1778, 1679, 1665, 1595, 1364, 1288, 812, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8.9 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 1 H), 6.48 (s, 1 H), 3.77 (s, 3 H), 3.39 (s, 3 H), 3.15 (d, *J* = 15.2 Hz, 1 H), 3.13 (s, 3 H), 2.92 (d, *J* = 18.2 Hz, 1 H), 2.78 (d, *J* = 18.3 Hz, 1 H), 2.68 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5, 174.1, 166.1, 155.8, 133.3, 127.9, 116.8, 113.2, 111.7, 55.7, 46.7, 42.1, 40.2, 29.8, 25.5.

MS (EI$^+$): *m*/*z* (%) = 288 (M^+, 100), 203 (40), 160 (39).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_2O_4$: 289.1188; found: 289.1193.

6′-Chloro-1,1′-dimethyl-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5n)

White solid; yield: 59.7 mg (51%); mp 232–235 °C; R_f = 0.64 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2930, 2918, 1778, 1679, 1665, 1595, 1364, 1288, 812, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 8.7, 2.0 Hz, 1 H), 7.01 (d, *J* = 8.8 Hz, 1 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 3.39 (s, 3 H), 3.16 (d, *J* = 15.8 Hz, 1 H), 3.15 (s, 3 H), 2.93 (d, *J* = 18.3 Hz, 1 H), 2.78 (d, *J* = 18.4 Hz, 1 H), 2.71 (d, *J* = 15.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0, 176.1, 166.1, 138.5, 129.3, 129.0, 128.0, 125.0, 117.1, 46.5, 41.9, 40.0, 29.8, 25.6.

MS (EI$^+$): *m*/*z* (%) = 294/292 (M^+, 31/92), 207 (100), 164 (69).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}ClN_2O_3$: 293.0693; found: 293.0690.

1,1′-Dimethyl-6′-(trifluoromethyl)-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-2,2′,5(3′*H*)-trione (5o)

White solid; yield: 64.0 mg (49%); mp 182–184 °C; R_f = 0.61 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2938, 2911, 2830, 1778, 1715, 1649, 1582, 1177, 1036, 799, 671 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.6 Hz, 1 H), 7.18–7.17 (m, 2 H), 3.44 (s, 3 H), 3.17 (d, *J* = 16.0 Hz, 1 H), 3.16 (s, 3 H), 2.95 (d, *J* = 18.2 Hz, 1 H), 2.82 (d, *J* = 18.3 Hz, 1 H), 2.76 (d, *J* = 15.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 173.5, 166.3, 142.9, 126.9, 126.7 (q, *J* = 3.6 Hz), 125.8 (q, *J* = 33.1 Hz), 123.6 (q, *J* = 270 Hz), 122.0 (q, *J* = 3.6 Hz), 116.0, 46.4, 41.8, 40.1, 29.9, 25.7.

MS (EI$^+$): *m*/*z* (%) = 326 (M^+, 81), 241 (100), 198 (87).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}F_3N_2O_3$: 327.0956; found: 327.0961.

Methyl 1′-Methyl-2,2′,5-trioxo-2′,3′-dihydro-1′*H*-spiro[pyrrolidine-3,4′-quinoline]-6′-carboxylate (5p)

White powder; yield: 90.7 mg (75%); mp 219–220 °C; R_f = 0.29 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3022, 2945, 2905, 1773, 1707, 1657, 1599, 1252, 772, 642 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.64 (br s, 1 H), 7.95 (dd, *J* = 14.2, 3.15 Hz, 1 H), 7.61 (d, *J* = 3.15 Hz, 1 H), 7.31 (d, *J* = 14.4 Hz, 1 H), 3.83 (s, 3 H), 3.33 (s, 3 H), 2.90 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 180.2, 176.4, 167.3, 165.9, 144.5, 130.8, 127.1, 125.8, 124.1, 116.6, 52.6, 47.4, 42.7, 38.4, 29.8.

MS (EI$^+$): *m*/*z* (%) = 302 (M^+, 96), 231 (100), 200 (49).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_2O_5$: 303.0981; found: 303.0987.

Spiro[indolin-2-one-glutarimides] 6a–e; General Procedure

Step 1: Carbamoyl radical generation using the photo-Fenton reaction under continuous flow conditions

The same protocol described above to obtain compounds **5a–o** was employed. However, prior to the imidation reaction, 3,3-disubstituted indolin-2-ones **4** were purified as follows: Formamide was removed by vacuum distillation. The crude product was mixed with silica gel and $CHCl_3$. The solvent was removed under reduced pressure, and the crude material adsorbed onto silica gel was transferred to a glass column for chromatography ($CHCl_3$/MeOH, 95:5).

Step 2: Imidation reaction

NaH (9.6 mg, 0.4 mmol) was added carefully to a stirred solution of 3,3-disubstituted indolin-2-one **4** (0.4 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and 2 M aq HCl (5 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 5 mL). The organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The spiro[indolin-2-one-glutarimides] were purified by silica gel column chromatography ($CHCl_3$/MeOH, 95:5).

1-Methylspiro[indoline-3,4′-piperidine]-2,2′,6′-trione (6a)[32]

White solid; yield: 88.9 mg (79%); mp 199–200 °C; R_f = 0.22 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3209, 3078, 2953, 2918, 1707, 1681, 1652, 1610, 1265, 1128, 738 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.47 (br s, 1 H), 7.37 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.10 (td, *J* = 7.6, 0.9 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 3.26 (s, 3 H), 2.99 (d, *J* = 17.2 Hz, 2 H), 2.66 (d, *J* = 17.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.2, 169.9 (2 C), 142.6, 129.8, 129.7, 123.6, 122.5, 109.1, 45.0, 38.7 (2 C), 26.7.

MS (EI$^+$): m/z (%) = 244 (M^+, 100), 159 (39), 130 (61).

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{12}N_2O_3$: 245.0926; found: 245.0920.

1-Benzylspiro[indoline-3,4′-piperidine]-2,2′,6′-trione (6b)

White solid; yield: 29.4 mg (46%); mp 181–183 °C; R_f = 0.54 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3199, 2943, 2899, 2841, 1710, 1697, 1647, 1610, 1351, 1267, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (br s, 1 H), 7.35–7.22 (m, 7 H), 7.05 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 4.93 (s, 2 H), 3.04 (d, J = 17.2 Hz, 2 H), 2.72 (d, J = 17.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.4, 169.8 (2 C), 141.7, 135.1, 129.8, 129.6, 129.0, 128.0, 127.2, 123.6, 122.5, 110.2, 45.0, 44.1, 38.8 (2 C).

MS (EI$^+$): m/z (%) = 320 (M^+, 5), 91 (100).

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{16}N_2O_3$: 321.1239; found: 321.1238.

1,1′-Dimethylspiro[indoline-3,4′-piperidine]-2,2′,6′-trione (6c)

White solid; yield: 64.0 mg (62%); mp 215–217 °C; R_f = 0.58 ($CHCl_3$/MeOH, 95:5).

IR (neat): 2956, 2918, 2912, 2841, 1710, 1703, 1672, 1610, 1257, 1089, 794 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 1 H), 7.09–7.03 (m, 2 H), 6.92 (d, J = 7.7 Hz, 1 H), 3.32 (s, 3 H), 3.24 (s, 3 H), 3.05 (d, J = 16.9 Hz, 2 H), 2.74 (d, J = 16.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3, 170.1 (2 C), 142.7, 130.0, 129.6, 123.4, 122.3, 109.1, 44.2, 39.5 (2 C), 26.7, 26.5.

MS (EI$^+$): m/z (%) = 258 (M^+, 100), 159 (76), 130 (63).

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_3$: 259.1083; found: 259.1083.

1-Methyl-5-(trifluoromethyl)spiro[indoline-3,4′-piperidine]-2,2′,6′-trione (6d)

White solid; yield: 108.7 mg (87%); mp 190–192 °C; R_f = 0.36 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3208, 3061, 2936, 2911, 2898, 1776, 1715, 1649, 1580, 1503, 1039, 799 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (br s, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.44 (m, 1 H), 7.02 (d, J = 8.2 Hz, 1 H), 3.29 (s, 3 H), 2.98 (d, J = 17.2 Hz, 2 H), 2.73 (d, J = 17.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 170.1 (2 C), 145.7, 130.3, 127.6 (q, J = 3.9 Hz), 125.9 (q, J = 32.9 Hz), 123.8 (q, J = 270 Hz), 119.6 (q, J = 3.6 Hz), 109.0, 44.9, 38.4 (2 C), 26.9.

MS (EI$^+$): m/z (%) = 312 (M^+, 100), 227 (38), 198 (39).

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_2O_3$: 313.0800; found: 313.0803.

5-Methoxy-1-methylspiro[indoline-3,4′-piperidine]-2,2′,6′-trione (6e)

White solid; yield: 39.5 mg (36%); mp 208–210 °C; R_f = 0.45 ($CHCl_3$/MeOH, 95:5).

IR (neat): 3174, 3074, 2956, 2912, 2839, 1714, 1681, 1629, 1600, 1257, 1029, 798, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H), 6.88–6.82 (m, 3 H), 3.78 (s, 3 H), 3.22 (s, 3 H), 2.98 (d, J = 17.2 Hz, 2 H), 2.65 (d, J = 17.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8, 169.7 (2 C), 156.6, 135.9, 131.1, 113.3, 110.6, 109.5, 55.9, 45.3, 38.7 (2 C), 26.7.

MS (EI$^+$): m/z (%) = 274 (M^+, 100), 259 (65), 174 (18).

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_4$: 275.1032; found: 275.1037.

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