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Cascade Couplings of *N*-Alkyl-*N*-methacryloyl Benzamides with Ethers and Benzenesulfonohydrazides To Generate Isoquinoline-1,3(2*H*,4*H*)-dione Derivatives

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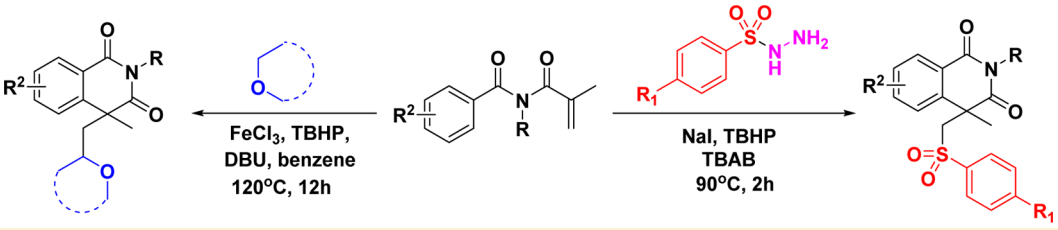
Supporting Information



ABSTRACT: Two radical-mediated cascade couplings of *N*-alkyl-*N*-methacryloylbenzamides with different ethers and arylsulfonohydrazides to generate ether- and arylsulfonyl-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives were developed. Both casccades proceeded via initially triggered functionalization of the alkene functions of the *N*-alkyl-*N*-methacryloylbenzamides, followed by ortho radical cyclizations onto the aromatic ring to give isoquinoline-1,3(2*H*,4*H*)-dione derivatives in good yields. These highly functionalized drug-like molecules will be valuable in drug discovery in the future.

Small molecules have played an important role in drug discovery.[1] Most drugs currently on the market are small molecules, which regulate biological processes by binding to such biomacromolecules as enzymes, proteins, DNA, etc. Therefore, powerful methodologies for the syntheses of highly functionalized small molecules for high-throughput screening (HTS) are very valuable,[2] especially those for preparing isoquinoline-1,3(2*H*,4*H*)-dione derivatives which are highly valued in drug discovery. This class of compounds has demonstrated several important biological activities. In Figure 1, four representative bioactive isoquinoline-1,3(2*H*,4*H*)-dione derivatives are shown.[3] These bioactivities include HIV-1 integrase inhibitors,[3a] antitumor activity against a human pancreatic carcinoma cell line,[3b] potent and selective inhibitors of cyclin-dependent kinase 4,[3c] and a potent caspase-3 inhibitor.[3d] Developing convenient syntheses of such molecules has attracted considerable attention from medicinal chemists. Producing these functionalized molecules efficiently is both an opportunity and a challenge.

Several methods to make isoquinoline-1,3(2*H*,4*H*)-dione derivatives have already been reported.[4] A few cascade methods employing oxidative cross-couplings to bifunctionalize alkene substrates, followed by cyclization to produce these derivatives, have been achieved.[5] They generated highly functionalized molecular structures in one-pot processes with good yields. Despite this early progress, large openings exist for further progress. In this paper, two new cascade couplings using *N*-alkyl-*N*-methacryloylbenzamide, arylsulfonohydrazides, and ethers as starting materials were developed. These reactions afforded ether- or arylsulfonyl-substituted isoquinoline-1,3-(2*H*,4*H*)-dione derivatives in good yields efficiently under mild conditions. Generating these highly functionalized

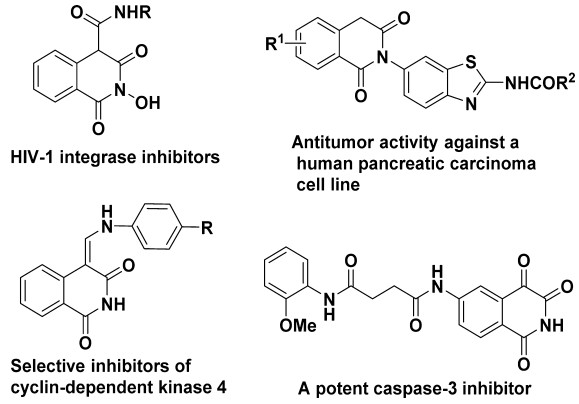


Figure 1. Biologically active isoquinoline-1,3(2*H*,4*H*)-dione derivatives.

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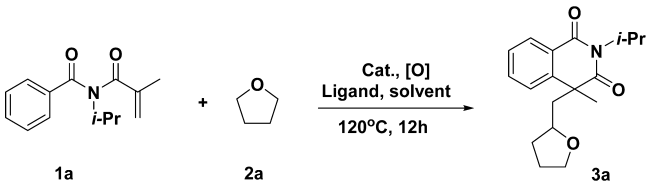
structures in simple, atom-efficient, one-pot reactions is a distinct improvement over traditional methods.

To search for suitable reaction conditions for these two multistep reactions, various metal catalysts, oxidants, and solvents were screened based on previous research results[6] (Table 1). Here, *N*-isopropyl-*N*-methacryloylbenzamide, which

Table 1. Screening for Suitable Reaction Conditions[a]



entry	cat.	oxidant/ligand	solvent	yield (%)
1	$FeCl_3$	–	benzene	trace
2	$FeCl_3$	TBHP/–	benzene	50
3	$CuCl_2$	TBHP/–	benzene	trace
4	$Cu(OAc)_2$	TBHP/–	benzene	trace
5	$FeCl_3$	TBHP/DBU	–	trace
6	$FeCl_3$	TBHP/DBU	benzene	65
7	$FeCl_3$	TBHP/DABCO	–	20
8	$FeCl_3$	TBHP/DABCO	benzene	15
9	$CuCl_2$	–	benzene	trace
10	$FeCl_3$	TBHP/DBU	EtOAc	<5
11	$FeCl_3$	TBHP/DBU	CH_3CN	20
12	$Cu(OAc)_2$	TBHP/DABCO	benzene	51

[a]Reaction conditions: catalysts (10 mol %), tetrahydrofuran (0.5 mL), *N*-methyl-*N*-phenylacrylamide (1.0 equiv), TBHP (*tert*-butyl hydroperoxide 70 wt % in water, 2.0 equiv), DABCO (1,4-Diazabicyclo-[2.2.2]octane) or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 0.1 equiv), benzene (1.0 mL), 120 °C. Isolated yield of product **3a** was based on the reactant *N*-methyl-*N*-phenylacrylamide **1a**. The reaction time, 12 h.

contains an alkene function, tetrahydrofuran, and benzenesulfonohydrazide were selected as representative starting reactants. Previous reports[7] demonstrated that copper and iron are possible catalysts for activating ethers in the presence of oxidants.[8] When $FeCl_3$ was selected as a catalyst (entry 1, Table 1) with no oxidant or ligand and benzene was used as a solvent, product **3a** was observed. The introduction of TBHP (*tert*-butyl hydroperoxide) into the reaction greatly changed the situation, and the cascade reaction occurred to give a 50% yield of ether-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivative **3a** (entry 2). $CuCl_2$ or $Cu(OAc)_2$ catalysts afforded only traces of **3a** (entry 5). The combination of TBHP/DBU in benzene with $FeCl_3$ as the catalyst gave a 65% yield (entry 6), but TBHP/DABCO with or without benzene solvent only generated 15% and 20% yields of **3a**, respectively (entries 7 and 8). Using $CuCl_2$ in benzene produced a trace of **3a** (entry 9). A TBHP/DBU combination in EtOAc with $FeCl_3$ afforded less than a 5% yield of **3a** (entry 10). When the solvent was switched to CH_3CN, a 20% yield of **3a** was achieved (entry 11). Using $Cu(OAc)_2$ as a catalyst in benzene with a combination of TBHP/DABCO gave a 51% yield of **3a** (entry 12). Based on reaction condition screening, the optimal conditions selected for this cascade reaction are $FeCl_3$ (10 mol %), ether (0.5 mL), *N*-methyl-*N*-phenylacrylamide (1.0 equiv), TBHP (70 wt % in water, 2.0 equiv), and DBU (0.1 equiv) in benzene (1.0 mL) at 120 °C for 12 h.

Using these optimal reaction conditions, different ethers were reacted with different *N*-alkyl-*N*-phenylacrylamides. All reactions proceeded well. The cascade couplings gave ether-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives **3a**–**j** in isolated yields ranging from 60% to 70%. Since products **3a**–**h** have two stereocenters, they were each obtained as diastereoisomer mixtures (Table 2). Their *dr* values were determined based on their ^1H NMR spectra.

To determine if radicals are involved in these cascade couplings, TEMPO (2,2,6,6-tetramethylpiperidine) was used as a radical scavenger in the reactions to prepare **3a**. In the presence of TEMPO, no coupling products were formed. This implicates that radical mechanisms are involved in each cascade reaction. So a plausible reaction mechanism is proposed in Scheme 1. TBHP is split to give a *tert*-butoxy radical under the action of Fe^{2+} and heat, and the *tert*-butoxy radical abstracts a hydrogen atom from ether to generate radical A. This radical adds to the double bond of reactant **1** to give conjugated tertiary radical intermediate B, which adds to the aromatic ring to give radical intermediate C. Finally radical C is oxidized by Fe^{3+} and loses a proton to afford product **3**.

Reaction condition screening was also carried out for the coupling of benzenesulfonylhydrazine with *N*-methyl-*N*-phenylacrylamide (Table 3) based on previous reports. In entry 1, when TBAB (tetrabutylammonium bromide) was used with TBHP, less than a 5% yield of expected product **5a** was produced. Using KI and NaI with TBHP generated no detectable **5a** (entries 2, 3). When KI was used with TBAB (serves as a phase transfer catalyst) and TBHP, a 10% yield of **5a** was achieved (entry 4). When solvent was changed to CH_3CN, a combination of NaI with TBAB and TBHP generated 75% yield of **5a** (entry 5). CuBr, $CuCl_2$, and $Cu(OAc)_2$ with TBHP gave the expected product **5a** in yields of 45%, 60%, and 55%, respectively (entries 6, 7, 8). The combination of NaI with TBAB and TBHP generated **5a** in 78% yield (entry 9). When CuBr, $CuCl_2$, and $Cu(OAc)_2$ were used with TBAB and TBHP, respectively, each reaction produced 25%, 45%, and 75% yields of **5a** (entries 10, 11, 12). After this screening, the conditions selected for further application of this benzenesulfonyl hydrazine-triggered cascade reaction were as follows: catalyst (20 mol %), *N*-methyl-*N*-phenylacrylamide (1.0 equiv), benzenesulfonylhydrazine (2.0 equiv), TBHP (70 wt % in water, 2.0 equiv), and TBAB (0.5 equiv) at 90 °C for 2 h.

Using the optimal reaction conditions found above, different benzenesulfonylhydrazines were reacted with different *N*-alkyl-*N*-phenylacrylamides (Table 4). All reactions proceeded well. These cascade couplings gave arylsulfonyl-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives **5a**–**j** in isolated yields, ranging from 55% to 85%. The benzenesulfonylhydrazine cascade proceeded faster than those of ethers, giving arylsulfonyl-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives in better yields at lower temperatures. Unlike the ether cascade reaction, the reaction products were not diastereoisomers.

To determine if a radical pathway is also involved in benzenesulfonylhydrazine cascade reactions, TEMPO (2,2,6,6-tetramethylpiperidine) was used as a radical scavenger in the reaction to produce **5a**. In the presence of TEMPO, no reaction product **5a** was formed. This demonstrates that a radical mechanism sequence occurs. While similar mechanisms have been proposed by others,[4g,h] a possible mechanism is proposed in Scheme 2. *tert*-Butoxyl and *tert*-butylperoxy radicals are

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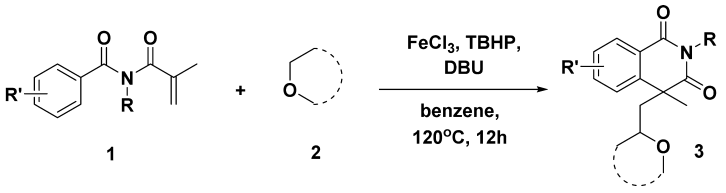
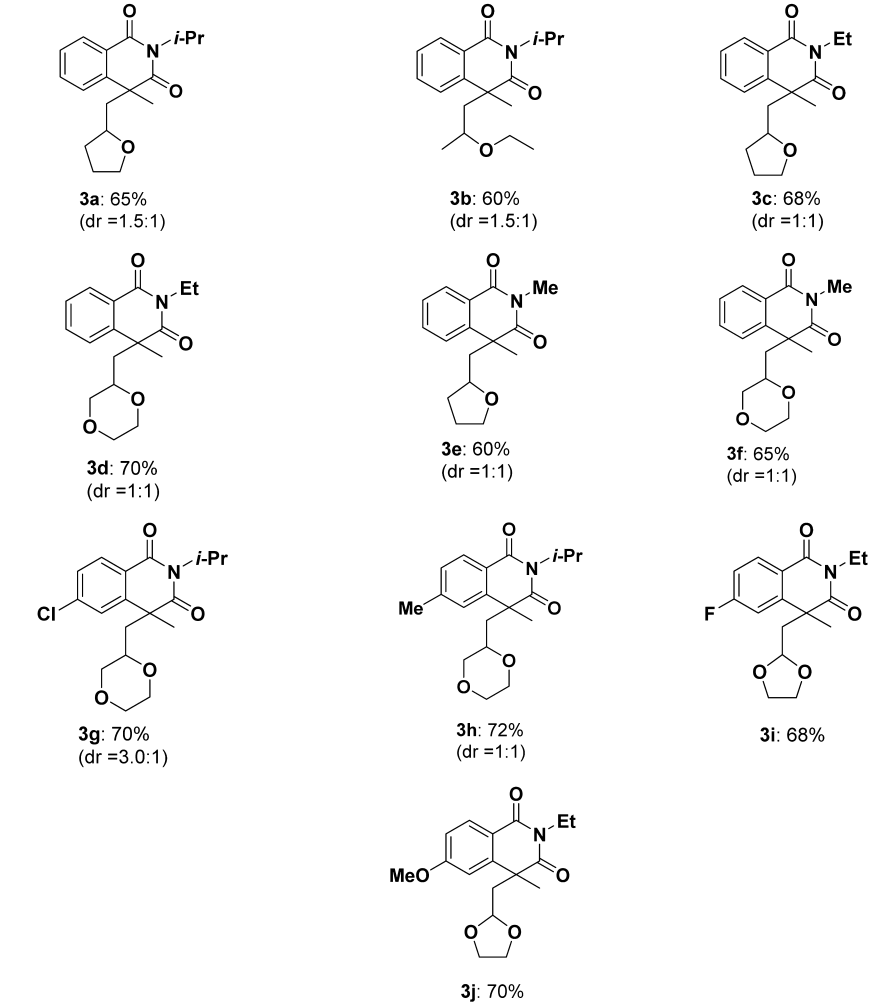
Table 2. Synthesis of Ether-Substituted Isoquinoline-1,3(2*H*,4*H*)-dione Derivatives[a]





[a]Reaction conditions: catalyst (10 mol %), tetrahydrofuran (0.5 mL), *N*-methyl-*N*-phenylacrylamide (1.0 equiv), TBHP (70 wt % in water, 2.0 equiv), and DBU (0.1 equiv) in benzene (1.0 mL) at 120 °C for 12 h. Isolated yield of product was based on the reactant *N*-methyl-*N*-phenylacrylamide.

Scheme 1. A Plausible Mechanism for the Cascade Coupling of an Ether with *N*-Alkyl-*N*-phenylacrylamide

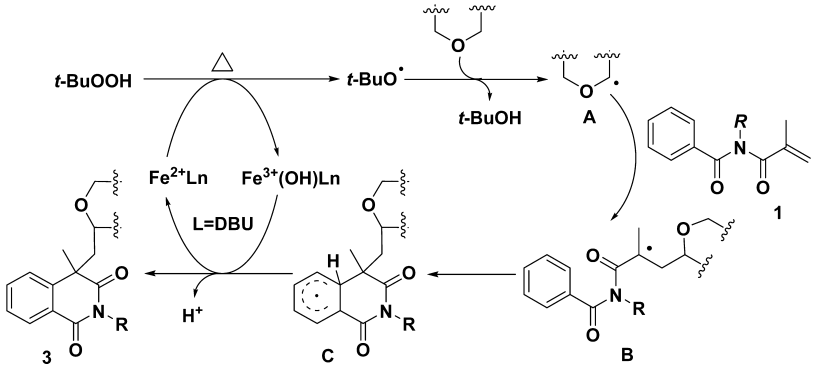


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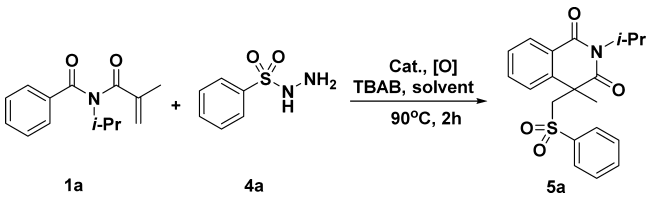
Table 3. Screening for Suitable Reaction Conditions[a]



1a 4a 5a

entry	cat.	oxidant	solvent	yield (%)
1	TBAB	TBHP	H_2O	<5
2	KI	TBHP	H_2O	trace
3	NaI	TBHP	H_2O	trace
4	KI + TBAB	TBHP	H_2O	10
5	NaI + TBAB	TBHP	MeCN	75
6	CuBr	TBHP	H_2O	45
7	$CuCl_2$	TBHP	H_2O	60
8	$Cu(OAc)_2$	TBHP	H_2O	55
9	NaI + TBAB	TBHP	–	78
10	CuBr + TBAB	TBHP	H_2O	25
11	$CuCl_2$ + TBAB	TBHP	H_2O	45
12	$Cu(OAc)_2$ + TBAB	TBHP	H_2O	75

[a]Reaction conditions: catalysts, KI or NaI (20 mol %), *N*-methyl-*N*-phenyl-acrylamide (1.0 equiv), benzenesulfonylhydrazine (2.0 equiv), TBHP (*tert*-butyl hydroperoxide 70 wt % in water, 2.0 equiv) and TBAB (tetrabutylammonium bromide, 0.5 equiv), 90 °C. Isolated yield of product **5a** was based on the reactant *N*-methyl-*N*-phenylacrylamide **1a**. The reaction time, 2 h.

generated under the action of I^- and I_2. *t*-BuOO$^\bullet$ and *t*-BuO$^\bullet$ transform sulfonylhydrazide **4** into a sulfonyl radical A. Sulfonyl radicals then add to the double bond of reactant **1** generating conjugated, tertiary radical B, which subsequently adds to the aromatic ring to give radical intermediate C. Hydrogen atom abstraction from radical C by *t*-BuO$^\bullet$ gives final product **5**.

CONCLUSIONS

In summary, we have developed two new cascade reactions between *N*-alkyl-*N*-methacryloylbenzamides and ethers or arylsulfonylhydrazines. Both reactions proceeded as one-pot radical cascade processes via initially triggered radical addition to the terminal alkene carbon of *N*-alkyl-*N*-methacryloyl-benzamides. This was followed by radical cyclizations onto the aromatic ring to give isoquinoline-1,3(2*H*,4*H*)-dione derivatives in good yields. Ether- or arylsulfonyl-substituted isoquinoline-1,3(2*H*,4*H*)-dione derivatives are generated, which are difficult to achieve by traditional chemistry methods. Both cascade sequences are suitable for compound library production for the purpose of biological activity screening. This chemistry also enriches current isoquinoline chemistry.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compounds 3a–j. *N*-Methyl-*N*-phenylacrylamide (1.0 mmol, 1.0 equiv) was added to a dried sealed tube, followed by the addition of tetrahydrofuran (0.5 mL), $FeCl_3$ (0.1 mmol, 10 mol %), DBU (0.1 mmol, 0.1 equiv), and benzene (1 mL). Then aqueous TBHP (2.0 equiv, 70 wt % in water) was injected into the sealed tube under N_2. The reaction mixture was heated at 120 °C and stirred for 12 h. After the reaction was finished, the mixture was washed with brine. The aqueous phase was extracted with ethyl acetate. The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (petroleum ether/EtOAc = 20:1) to provide the title compound **3a** as a sticky solid in a 65% yield. The same procedure was applied for producing other compounds **3b–j**.

General Procedure for the Synthesis of Compounds 5a–j. *N*-Methyl-*N*-phenylacrylamide (1.0 mmol, 1.0 equiv) was added to a dried sealed tube, followed by the addition of benzenesulfonohydrazide (2.0 mmol, 2.0 equiv), NaI (0.2 mmol, 0.2 equiv), and TBAB (0.5 mmol, 0.5 equiv). Then aqueous TBHP (2.0 equiv, 70 wt % in water) was injected into the sealed tube under N_2, and the reaction mixture was heated at 90 °C and stirred for 2 h. After the reaction was finished, the mixture was washed with brine. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (Petroleum ether/EtOAc = 5:1) to give the title compound **5a** as a sticky solid in a 78% yield. The same procedure was applied for producing other compounds **5b–j**.

*2-Isopropyl-4-methyl-4-((tetrahydrofuran-2-yl)methyl)-isoquinoline-1,3(2H,4H)-dione (**3a**).* Following the general procedure gave the isolated yield (195.6 mg, 65%) as a colorless solid, mp 78–80 °C; **IR:** 2971, 7872, 1710, 1664, 1454, 1354, 769, 706 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.25 (m, 1H), 7.60 (m, 1H), 7.47–7.35 (m, 2H), 5.21 (m, 1H), 3.55–3.46 (m, 1H), 3.45 (m, 1.6H), 3.30 (m, 0.4H), 2.60 (dd, J = 14.0, 6.4 Hz, 0.4H), 2.45 (dd, J = 14.0, 6.4 Hz, 0.6H), 2.28 (dd, J = 14.0, 6.4 Hz, 0.6H), 2.00 (dd, J = 14.0, 3.2 Hz, 0.4H), 1.77–1.64 (m, 4H), 1.64(s, 2H), 1.59 (s, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.47 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.5, 176.5, 164.5, 164.5, 143.5, 143.1, 133.4, 133.2, 128.9, 128.8, 127.1, 127.0, 126.0, 125.5, 125.2, 125.1, 76.0, 75.2, 67.2, 67.0, 48.2, 47.6, 46.3, 45.8, 45.4, 45.1, 31.5, 31.4, 30.3, 29.7, 25.5, 25.4, 19.7, 19.5, 19.5, 19.3; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{23}NNaO_3$ 324.1576 (M + Na)$^+$, found 324.1552.

*4-(2-Ethoxypropyl)-2-isopropyl-4-methylisoquinoline-1,3(2H,4H)-dione (**3b**).* Following the general procedure gave the isolated yield (181.8 mg, 60%) as a colorless solid, mp 68–70 °C; **IR:** 2972, 2929, 1710, 1665, 1456, 1354, 769, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.24–8.20 (m, 1H), 7.58 (m, 1H), 7.44–7.33 (m, 2H), 5.24 (m, 1H), 3.25–3.18 (m, 1.6H), 2.80–2.72 (m, 1.4H), 2.55 (m, 0.4H), 2.33 (dd, J = 14.0, 3.2 Hz, 0.6H), 2.23 (m, 0.6H), 2.00 (m, 0.4H), 1.60 (s, 2H), 1.54 (s, 1H), 1.51 (d, J = 6.8 Hz, 3.6H), 1.48 (d, J = 6.8 Hz, 2.4H), 1.00 (m, 3H), 0.81 (t, J = 7.2 Hz, 1H), 0.65 (t, J = 7.2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.8, 176.7, 164.7, 164.7, 144.7, 143.2, 133.2, 133.0, 128.7, 128.4, 126.9, 126.6, 125.8, 125.7, 125.4, 124.8, 73.0, 71.5, 63.6, 63.5, 53.4, 50.0, 48.0, 46.4, 45.4, 45.3, 31.1, 30.2, 20.0, 19.8, 19.7, 19.7, 19.6, 19.0, 15.1, 14.8; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{25}NNaO_3$ 326.1732 (M + Na)$^+$, found 326.1726.

*2-Ethyl-4-methyl-4-((tetrahydrofuran-2-yl)methyl)isoquinoline-1,3(2H,4H)-dione (**3c**).* Following the general procedure gave the isolated yield (195.1 mg, 68%) as a colorless solid, mp 72–74 °C; **IR:** 2977, 2873, 1710, 1665, 1466, 1359, 769, 705 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.28–8.21 (m, 1H), 7.61–7.47 (m, 1H), 7.6–7.37 (m, 2H), 3.60 (m, 0.5H), 3.50 (m, 0.5H), 3.42–3.36 (m, 1.5H), 3.26 (m, 0.5H), 2.60 (dd, J = 14.0, 10.8 Hz, 0.5H), 2.44 (dd, J = 14.0, 6.8 Hz, 0.5H), 2.32 (dd, J = 14.0, 6.0 Hz, 0.5H), 2.00 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.73–1.62 (m, 4H), 1.62 (s, 1.5H), 1.55 (s, 1.5H), 1.40–1.25 (m, 2H), 1.25–1.20 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.1, 176.0, 164.0, 163.9, 143.6, 143.2, 133.6, 133.4, 128.9, 128.7, 127.1, 127.1, 125.6, 125.4, 125.3, 124.7, 76.0, 75.2, 67.1, 67.0, 48.2, 47.7, 45.9, 45.6, 35.7, 35.6, 31.4(2), 30.4, 30.1, 25.5, 25.4, 13.1, 12.7; **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{22}NO_3$ 288.1600 (M + H)$^+$, found 288.1599.

*4-((1,4-Dioxan-2-yl)methyl)-2-ethyl-4-methylisoquinoline-1,3-(2H,4H)-dione (**3d**).* Following the general procedure gave the isolated yield (208.6 mg, 70%) as a colorless solid, mp 74–76 °C; **IR:** 2959, 2854, 1711, 1665, 1467, 1359, 770, 705 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.29–8.22 (m, 1H), 7.64–7.63(m, 1H), 7.46–7.35 (m, 2H), 4.07–4.02 (m, 2H), 3.49–2.85 (m, 5.5H), 3.07 (m, 1H), 2.85 (m, 0.5H), 2.55 (dd, J = 14.0, 4.8 Hz, 0.5H), 2.30 (dd, J = 14.0, 3.2 Hz, 0.5H), 2.11 (dd, J = 14.0, 4.8 Hz, 0.5H), 1.87 (dd, J = 14.0, 3.2 Hz, 0.5H), 1.61 (s, 3H), 1.25–1.18 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 175.9, 175,8, 163.9(2), 143.6, 142.6, 133.6, 133.6, 128.8, 128.7, 127.4, 127.2, 125.6, 125.3, 124.7(2), 73.1, 72.6, 70.7, 70.5, 66.3(2), 66.2, 66.1, 45.6, 44.5, 43.8, 43.7, 35.7, 35.6, 30.1, 29.9, 13.2, 12.7;

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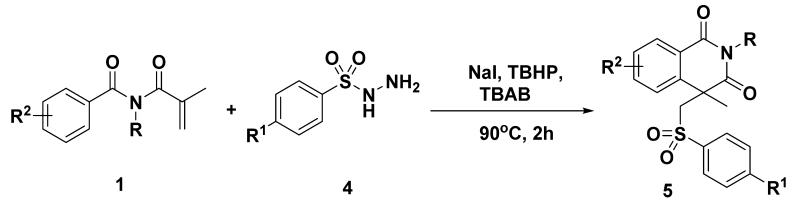
Table 4. Synthesis of Arylsuflonyl-Substituted Isoquinoline-1,3(2*H*,4*H*)-dione Derivatives[a]



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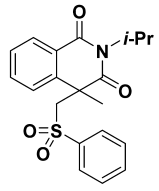
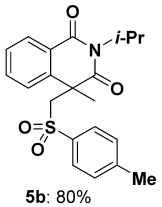
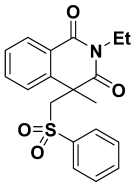
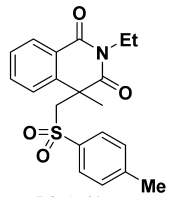
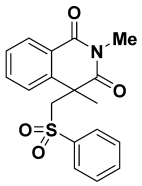

5a: 78%


5b: 80%


5c: 80%


5d: 85%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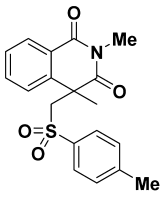
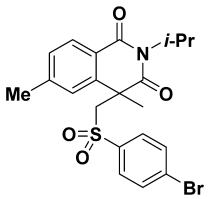

5f: 79%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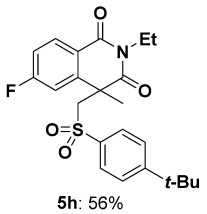
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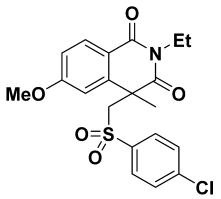
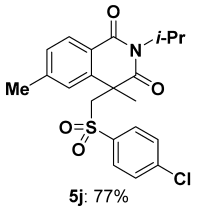
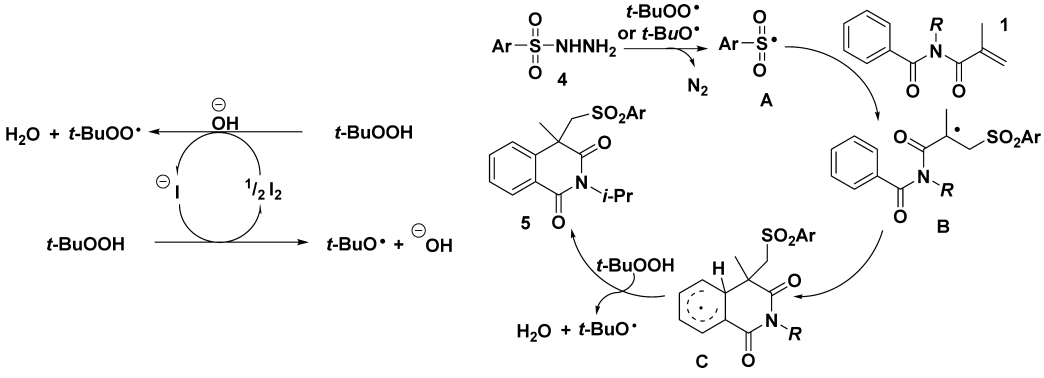

5i: 83%


5j: 77%

[a]Reaction conditions: NaI (0.2 equiv), *N*-methyl-*N*-phenylacrylamide (1.0 equiv), benzenesulfonylhydrazine (2.0 equiv), TBHP (70 wt % in water, 2.0 equiv) and TBAB (0.5 equiv) at 90 °C for 2 h. Isolated yield of product was based on the reactant *N*-methyl-*N*-phenylacrylamide.

Scheme 2. Plausible Reaction Mechanism of the Cascade Coupling of Arylsulfonylhydrazine with *N*-Alkyl-*N*-phenylacrylamide



HRMS (ESI-TOF) *m*/*z* calculated for $C_{17}H_{21}NNaO_4$ 326.1368 $(M + Na)^+$, found 326.1366.

*2,4-Dimethyl-4-((tetrahydrofuran-2-yl)methyl)isoquinoline-1,3-(2H,4H)-dione (**3e**).* Following the general procedure gave the isolated

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yield (163.8 mg, 60%) as a colorless solid, mp 68−70 °C; **IR:** 2951, 2850, 1712, 1667, 1467, 1363, 769, 702 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.27−8.21 (m, 1H), 7.60 (m, 1H), 7.47−7.37 (m, 2H), 3.55 (m, 0.5H), 3.49 (m, 0.5H), 3.37 (s, 1.5H), 3.34 (s, 1.5H), 2.6 (dd, J = 14.0, 10.8 Hz, 0.5H), 2.40 (dd, J = 14.0, 6.8 Hz, 0.5H), 2.30 (dd, J = 14.0, 6.8 Hz, 0.5H), 2.00 (dd, J = 14.0, 3,2 Hz, 0.5H), 1.85−1.65 (m, 4H), 1.62 (s, 1.5H), 1.58 (s, 1.5H), 1.40−1.22 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.7, 176.3, 164.5, 164.4, 143.6, 143.1, 133.7, 133.4, 128.8, 128.7, 127.2, 125.6, 125.3, 124.6, 75.9, 75.2, 67.3, 67.1, 48.6, 48.1. 46.0, 45.6, 31.2(2), 29.9, 29.3, 27.2, 27.1, 25.6, 25.2; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{19}NNaO_3$ 296.1263 $(M + Na)^+$, found 296.1256.

*4-((1,4-Dioxan-2-yl)methyl)-2,4-dimethylisoquinoline-1,3-(2H,4H)-dione (**3f**).* Following the general procedure gave the isolated yield (187.6 mg, 65%) as a colorless solid, mp 72−74 °C; **IR:** 2957, 2854, 1713, 1667, 1468, 1363, 770, 702 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.28−8.20 (m, 1H), 7.64−7.62 (m, 1H), 7.47−7.44 (m, 2H), 3.50−3.36 (m, 5H), 3.35 (s, 1.5H), 3.31 (s, 1.5H), 3.20−3.17 (m, 1H), 3.09−3.02 (m, 1H), 2.80 (m, 0.5H), 2.54 (dd, J = 14.0, Hz, 0.5H), 2.27 (dd, J = 14.0, 4.8 Hz, 0.5H), 2.09 (dd, J = 14.0, 2.4 Hz, 0.5H), 1.63 (s, 1.5H), 1.61 (s, 1.5H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.6, 176.3, 164.4, 143.4, 142.5, 133.7, 133.6, 128.8, 128.7, 127.5, 127.3, 125.6, 125.3, 125.2, 124.6, 73.1, 72.6, 70.6, 70.4, 66.5, 66.3, 66.1, 66.0, 65.9, 45.8, 44.6, 44.2, 44.0, 29.7, 29.5, 27.2, 27.1; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{19}NNaO_4$ 312.1212 $(M + Na)^+$, found 312.1215.

*(1,4-Dioxan-2-yl)methyl)-6-chloro-2-isopropyl-4-methyl-isoquinoline-1,3(2H,4H)-dione (**3g**).* Following the general procedure gave the isolated yield (245.7 mg, 70%) as a colorless solid, mp 82−84 °C; **IR:** 2929, 2854, 1716, 1663, 1457, 1344, 757, 706 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.17 (d, J = 8.4 Hz, 0.3H), 8.14 (d, J = 8.4 Hz, 0.7H), 7.43−7.36 (m, 1.3H), 7.31 (d, J = 1.6 Hz, 0.7H), 5.21 (m, 1H), 3.54 (m, 2.7H), 3.35 (m, 3H), 3.27 (m, 0.3H), 3.12 (m, 0.7H), 2.86 (m, 0.3H), 2.54 (m, 0.3H), 2.25 (dd, J = 14.0, 4.4 Hz, 0.7H), 2.01 (dd, J = 14.0, 4.4 Hz, 0.7H), 1.79 (m, 0.3H), 1.59 (s, 3H), 1.51−1.39 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 175.6(2), 163.7(2), 145.4(2), 139.8(2), 130.4, 130.3, 128.0, 127.7, 125.6, 125.3, 123.8(2), 72.9, 72.6, 70.7, 70.4, 66.3(2), 66.1(2), 45.9, 45.7, 43.8, 43.6, 29.7, 29.4, 19.7, 19.6, 19.4, 19.3; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{22}ClNNaO_4$ 374.1135 $(M + Na)^+$, found 374.1148.

*(1,4-Dioxan-2-yl)methyl)-2-isopropyl-4,6-dimethylisoquinoline-1,3(2H,4H)-dione (**3h**).* Following the general procedure gave the isolated yield (238.3 mg, 72%) as a colorless solid, mp 78−80 °C; **IR:** 2924, 2854, 1717, 1662, 1457, 1363, 721, 706 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.10−8.06 (dd, J = 14.0, 7.6 Hz, 1H), 7.24−7.05 (m, 2H), 5.18 (m, 1H), 3.52−3.18 (m, 5.5H), 3.15−3.05 (m, 1H), 2.85 (m, 0.5H), 2.53 (m, 0.5H), 2.43 (s, 3H), 2.27 (dd, J = 14.0, 5.2 Hz, 0.5H), 2.04 (dd, J = 14.0, 6.8 Hz, 0.5H), 1.78 (dd, J = 14.0, 2.4 Hz, 0.5H), 1.58 (s, 1.5H), 1.57 (s, 1.5H), 1.48−1.43 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 176.4, 176.4, 164.5, 164.4, 144.1, 143.3, 142.5, 129.1, 128.8, 128.4, 128.3, 126.8, 125.7, 125.4, 123.4, 122.8, 73.0, 72.8, 70.7, 70.5, 66.4, 66.3, 66.1, 66.0, 45.8, 45.4, 45.0, 44.6, 43.8(2), 29.9, 29.6, 22.0, 21.9, 19.7, 19.6, 19.5, 19.4; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{25}NNaO_4$ 354.1681 $(M + Na)^+$, found 354.1681.

*(1,3-Dioxolan-2-yl)methyl)-2-ethyl-6-fluoro-4-methyliso-quinoline-1,3(2H,4H)-dione (**3i**).* Following the general procedure gave the isolated yield (205.5 mg, 68%) as a colorless solid, mp 81−83 °C; **IR:** 2981, 2886, 1712, 1666, 1457, 1361, 781, 702 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.28−7.05 (aromatic H, 3H), 4.46 (dd, J = 7.6, 4.2 Hz, 1H), 4.05 (m, 1H), 3.76 (m, 1H), 3.63 (m, 1H), 3.56 (m, 1H), 2.75 (dd, J = 14.0, 7.2 Hz, 1H), 2.28 (dd, J = 14.0, 2.8 Hz, 1H), 1.21 (s, 3H), 1.20 (t, J = 7.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 175.2, 167.3, 164.8, 163.0, 145.8, 131.8, 121.3, 115.4, 112.7, 102.0, 64.9, 64.3, 45.6, 45.5, 44.6, 35.7, 30.5, 12.7; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{18}FNNaO_4$ 330.1118 $(M + Na)^+$, found 330.1119.

*(1,3-Dioxolan-2-yl)methyl)-2-ethyl-6-methoxy-4-methyliso-quinoline-1,3(2H,4H)-dione (**3j**).* Following the general procedure gave the isolated yield (223.3 mg, 70%) as a colorless solid, mp 80−82 °C; **IR:** 2926, 2360, 1717, 1663, 1473, 1396, 751, 705 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.20−6.80 (aromatic H, 3H), 4.44 (dd, J = 8.0, 2.8 Hz, 1H), 4.01 (m, 1H), 3.97 (s, 3H), 3.62 (m, 2H), 2.65 (dd, J = 14.0, 8.0 Hz, 1H), 2.24 (dd, J = 14.0, 2.8 Hz, 1H), 1.57 (s, 3H), 1.16 (t, J = 7.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 175.7, 163.8, 144.8, 131.1, 117.9, 113.2, 110.6, 101.5, 64.8, 64.3, 55.5, 45.6, 44.6, 35.5, 30.5, 12.8; **HRMS** (ESI/Q-TOF) m/z calculated for $C_{17}H_{21}NNaO_5$ 342.1317 $(M + Na)^+$, found 342.1314.

*2-Isopropyl-4-methyl-4-((phenylsulfonyl)methyl)isoquinoline-1,3-(2H,4H)-dione (**5a**).* Following the general procedure gave the isolated yield (232.4 mg, 78%) as a colorless solid, mp 170−172 °C; **IR:** 2977, 2360, 1711, 1663, 1448, 1304, 744, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.27−7.07 (aromatic H, 9H), 5.26 (m, 1H), 4.14 (d, J = 14.8 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 1.58 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.53 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 174.4, 163.9, 140.6, 139.0, 133.3, 133.2, 129.2, 129.1, 128.0, 127.4, 125.6, 125.4, 64.8, 45.9, 45.7, 31.3, 19.6, 19.3; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_4S$ 372.1270 $(M + H)^+$, found 372.1287.

*2-Isopropyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**5b**).* Following the general procedure gave the isolated yield (308.3 mg, 80%) as a colorless solid, mp 174−176 °C; **IR:** 2929, 2361, 1711, 1664, 1454, 1356, 758, 703 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.27−7.10 (aromatic H, 8H), 5.26 (m, 1H), 4.14 (d, J = 17.6 Hz, 1H), 3.90 (d, J = 17.6 Hz, 1H), 2.38 (s, 3H) 1.59 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.53 (d, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 174.4, 163.9, 144.3, 139.2, 137.7. 133.1, 129.7, 129.3, 127.9, 127.5, 125.6, 125.5, 64.8, 45.9, 45.7, 31.5, 21.6, 19.6, 19.2; **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{24}NO_4S$ 386.1426 $(M + H)^+$, found 386.1424.

*2-Ethyl-4-methyl-4-((phenylsulfonyl)methyl)isoquinoline-1,3-(2H,4H)-dione (**5c**).* Following the general procedure gave the isolated yield (285.5 mg, 80%) as a colorless solid, mp 168−170 °C; **IR:** 2981, 2361, 1712, 1666, 1449, 1303, 742, 704 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.28−7.13 (aromatic H, 9H), 4.47 (d, J = 17.6 Hz, 1H), 4.10 (m, 1H), 3.94 (d, J = 17.6 Hz, 1H), 1.58 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.9, 163.3, 140.4, 139.1, 133.4, 133.4, 129.2, 129.1, 128.1, 127.5, 125.8, 124.9, 64.7, 45.4, 36.1, 31.5, 12.7; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{19}NNaO_4S$ 380.0932 $(M + Na)^+$, found 380.0932.

*2-Ethyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**5d**).* Following the general procedure gave the isolated yield (315.1 mg, 85%) as a colorless solid, mp 169−171 °C; **IR:** 2981, 2360, 1712, 1666, 1466, 1318, 759, 703 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.28−7.14 (aromatic H, 8H), 4.45 (d, J = 14.4 Hz, 1H), 4.08 (m, 1H), 3.90 (d, J = 14.4 Hz, 1H), 2.38 (s, 3H) 1.57 (s, 3H), 1.29 (t, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.9, 163.3, 144.4, 139.2, 137.4, 133.3, 129.7, 129.2, 127.9, 127.5, 125.9, 124.9, 64.7, 45.4, 36.0, 31.6, 21.6, 12.7; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{22}NO_4S$ 372.1270 $(M + H)^+$, found 372.1287.

*2,4-Dimethyl-4-((phenylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**5e**).* Following the general procedure gave the isolated yield (264.1 mg, 77%) as a colorless solid, mp 164−166 °C; **IR:** 2925, 2360, 1715, 1667, 1468, 1308, 746, 702 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.30−7.15 (aromatic H, 9H), 4.46 (d, J = 14.8 Hz, 1H), 3.94 (d, J = 14.8 Hz, 1H), 3.42 (s, 3H), 1.59 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 174.3, 163.8, 140.1, 139.0, 133.5, 129.2, 129.1, 128.2, 127.5, 125.9, 124.8, 64.8, 53.3, 45.4, 31.5, 27.6; **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{17}NNaO_4S$ 366.0776 $(M + Na)^+$, found 366.0781.

*2,4-Dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**5f**).* Following the general procedure gave the isolated yield (278.2 mg, 79%) as a colorless solid, mp 165−167 °C; **IR:** 2972, 2361, 1714, 1667, 1468, 1316, 759, 701 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.29−7.13 (aromatic H, 8H), 4.43 (d, J = 14.8 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.39 (s, 3H), 2.38 (s, 3H), 1.58 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 174.3, 163.8, 144.5, 139.2, 137.2, 133.4, 129.7, 129.2, 128.5, 128.0, 127.6, 129.9, 125.9, 124.7, 64.8, 45.4, 31.6, 27.5, 21.6; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{19}NNaO_4S$ 380.0932 $(M + Na)^+$, found 380.0932.

*(4-Bromophenyl)sulfonyl)methyl)-2-isopropyl-4,6-dimethyl-isoquinoline-1,3(2H,4H)-dione (**5g**).* Following the general procedure gave the isolated yield (361.1 mg, 78%) as a colorless solid, mp 178−

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180 °C; **IR:** 2927, 2361, 1717, 1662, 1457, 1363, 692, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.14−6,67 (aromatic H, 7H), 5.25 (m, 4H), 4.47 (d, J = 14.8 Hz, 1H), 3.86 (d, J = 14.8 Hz, 1H), 2.16 (s, 3H), 1.55 (t, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.3, 162.9, 143.3, 138.6, 137.7, 131.3, 128.5, 128.2, 128.0, 127.7, 125.2, 122.3, 64.0, 45.0, 44.6, 30.5, 20.7, 18.7, 18.4; **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}BrNNaO_4S$ 486.0351 $(M + Na)^+$, found 486.0359.

*(4-(tert-Butyl)phenyl)sulfonyl)methyl)-2-ethyl-6-fluoro-4-methylisoquinoline-1,3(2H,4H)-dione (**5h**).* Following the general procedure gave the isolated yield (241.2 mg, 56%) as a colorless solid, mp 174−176 °C; **IR:** 2922, 2361, 1717, 1662, 1457, 1362, 690, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.30−6,71 (aromatic H, 7H), 4.47 (d, J = 14.4 Hz, 1H), 4.10 (m, 2H), 3.83 (d, J = 14.8 Hz, 1H), 1.57 (s, 3H), 1.30 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.4, 166.9, 164.4, 162.4, 157.5, 142.1, 142.0, 137.1, 132.2, 132.1, 127.2, 126.2, 121.4, 116.1, 115.9, 113.0, 112.8, 64.6, 45.4, 36.2, 35.2, 31.4, 30.9, 12.7; **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{26}FNNaO_4S$ 454.1464 $(M + Na)^+$, found 454.1463.

*(4-Chlorophenyl)sulfonyl)methyl)-2-isopropyl-4,6-dimethyl-isoquinoline-1,3(2H,4H)-dione (**5i**).* Following the general procedure gave the isolated yield (349.3 mg, 83%) as a colorless solid, mp 178−180 °C; **IR:** 2937, 2824, 1733, 1653, 1457, 1363, 690, 669 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.24−6,42 (aromatic H, 7H), 4.48 (d, J = 14.8 Hz, 1H), 4.25 (m, 2H), 3.84 (d, J = 14.8 Hz, 1H), 3.75 (s, 3H), 1.57 (s, 3H), 1.29 (t, J = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 172.9, 162.7, 162.0, 139.9, 139.2, 138.0, 130.9, 128.4, 128.1, 117.0, 112.4, 110.7, 63.9, 54.7, 44.6, 35.1, 30.7, 11.9; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{20}ClNNaO_5S$ 444.0648 $(M + Na)^+$, found 444.0657.

*(4-Chlorophenyl)sulfonyl)methyl)-2-isopropyl-4,6-dimethyliso-quinoline-1,3(2H,4H)-dione (**5j**).* Following the general procedure gave the isolated yield (322.09 mg, 77%) as a colorless solid, mp 172−174 °C; **IR:** 2925, 2834, 1721, 1661, 1457, 1364, 692, 667 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.13−6,67 (aromatic H, 7H), 5.26 (m, 1H), 4.46 (d, J = 14.8 Hz, 1H), 3.87 (d, J = 14.8 Hz, 1H), 2.13 (s, 3H), 1.54 (t, J = 6.8 Hz, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 173.3, 162.9, 143.3, 139.0, 138.0, 137.7, 128.5, 128.3, 128.2, 127.9, 125.2, 122.2, 63.9, 44.9, 30.4, 28.8, 20.5, 18.6, 18.4; **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{22}ClNNaO_4S$ 442.0856 $(M + Na)^+$, found 442.0855.

■ ASSOCIATED CONTENT

Supporting Information

Spectral characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Author Contributions

‖M.Z. and W.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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