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PAPER

Aerobic Thiyl Radical Addition/Cyclization of N-Methacryloyl Benzamides for the Synthesis of Isoquinoline-1,3(*2H*,*4H*)‐dione Derivatives

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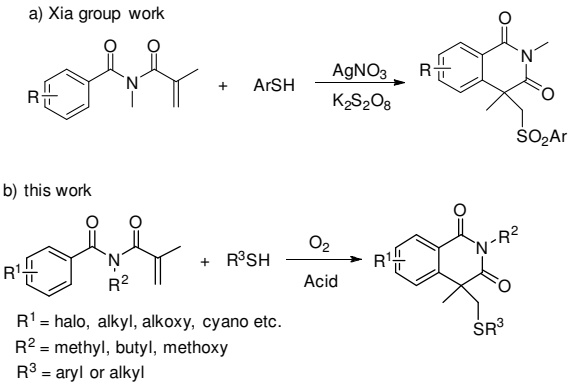
A highly effective oxidative thiyl radical addition/cyclization of N-methacryloylbenzamides was explored using dioxygen as the solely terminal oxidant without the use of precious and/or toxic transition-metal catalysts. This method provides convenient access to a variety of useful sulfide-containing 4,4-disubstituted isoquinoline-1,3-diones by constructing C-S and C-C bonds in one step.

The moiety of isoquinoline-1,3(*2H*,*4H*)-dione exhibits important functions found in a wide range of biologically active natural products and pharmaceuticals,[1] such as antiviral agent targeting HIV-I enzyme,[1a-b] antitumor activity against a human pancreatic carcinoma cell line,[1c] potent and selective cyclin-dependent kinase 4 inhibitors[1d] and so on.[1e-1g] The introduction of new functional groups into such a structural motif would offer more opportunities to discover new intriguing bioactive molecules. In the past decade, considerable advances were achieved in synthesis of the functionalized isoquinoline-1,3-diones via the tandem cyclization strategy due to its high step- and atom-economy,[2] especially using the strategy of difunctionalization of acrylamides with diverse radicals.[3, 4] In 2014, Liu demonstrated a tandem radical cyclization of N-alkyl-N-methacryloyl benzamides with $TMSCF_3$ using $PhI(OAc)_2$ as the oxidant.[3a] In 2015, Zhou developed a radical cascade reaction between N-alkyl-N-methacryloylbenzamide and aryl aldehyde providing a series of isoquinoline-1,3(*2H*,*4H*)-dione derivatives in good yields under mild reaction conditions.[3b-c] In addition, this radical addition–cyclization protocol was also suitable to construct other aza-heterocycles such as oxindoles,[5] quinolines[6] and quinolinones.[7]

The formation of C–S bond represents a key step in the synthesis of a broad range of biologically active molecules and functional materials, many efficient C–S bond formation methods were developed.[8] In 2015, Tian and co-workers disclosed a tandem sulfenylation/cyclization reaction of N-arylacrylamides with sulfonyl hydrazides, affording a wide range of 3-(sulfenylmethyl)-oxindole and 3-sulfenyl-3,4-dihydroquinolin-2(*1H*)-one derivatives in the present of iodine via radical process[9]. Very recently, Xia established an elegant protocol for the synthesis of sulfone-containing isoquinolinonediones using sulfide or sulfonyl chloride as sulfonylating precursors (Scheme 1a).[10] Taking inspiration of those recent works, Herein we report an aerobic oxidative acid-mediated difunctionalization of activated alkenes via cascade C–S and C–C bond formation to rapidly build sulfide-containing isoquinoline-1,3-diones structure (Scheme 1b). To the best of our knowledge, the similar protocol using aerobic oxidative thiyl radical to construct sulfide substituted isoquinoline-1,3-diones is not well-documented.

Scheme 1. Cyclization of N-methacryloyl-N-methylbenzamide with Thiols



We began our investigation using N-methyl-N-methacryloylbenzamide (**1a**, 0.5 mmol) and thiophenol (**2a**, 0.6 mmol) as substrates under various conditions and the result was summarized in Tables 1. When using DTBP, AIBN and TBHP (3 equiv.) as oxidant in DCE at 100 °C for 12 h under air atmosphere respectively, the diphenyl disulfide and S-phenyl benzenesulfonothioate were observed (entries 1-3). Pleasingly, the substrate of N-methyl-N-methacryloylbenzamide **1a** was consumed up in the parallel-blank experiment without oxidant under the air atmosphere and afforded the desired product **3aa** in 16% isolated yield (entry 4). It was found that the reaction

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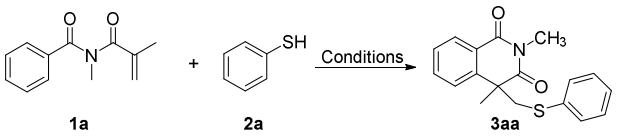
proceeded with a reasonable rate (75 % conversion after 12 h) giving a 42 % moderate yield when reducing the reaction temperature to 60 °C using air as oxidant (entry 5). Those results show that the dioxygen plays a vital role in this process and the reaction maybe involved in a radical pathway. Then the model reaction was carried out under pure oxygen balloon or air balloon atmosphere without other oxidants and additives, the yields increase to 55 % and 45 % slightly respectively (entries 6-7). Gratefully, the desired product **3aa** was isolated in 67 % yield when CH_3COOH (20 mol %) was introduced as an additive (entry 8). To further improve the yield, several acidic additives such as CF_3SO_3H, CH_3SO_3H, $TsOH·H_2O$ and $PhCO_2H$ were evaluated, revealing that $TsOH·H_2O$ provides the best yield of 89% (entries 9-12). A significant rise or drop of yield was not noticed when the amount of $TsOH·H_2O$ was increased to 1 equiv. or decreased to 0.1 equiv. (entries 13-14). Unfortunately, the Michael addition reaction was observed when using alkaline additives such as DMAP and pyridine (entries 15-16). Lastly, the other solvents such as DMF, DMSO, CH_3CN, THF and toluene were also scanned, DCE is the best solvent for this tandem reaction, additionally, and it does not require dry DCE solvent.

To evaluate the efficiency and generality of this protocol, we then explored the scope and functional group of this transformation, a wide range of aryl thiols were subjected to the optimized reaction conditions. As shown in Table 2, aryl thiols bearing both electron-withdrawing (halogen, CF_3) and electron-donating (Me, OMe, $(CH_3)_3C$) groups presented great compatibility with **1a** affording a

Table 1. Optimization of Reaction Conditions [a]



1a **2a** **3aa**

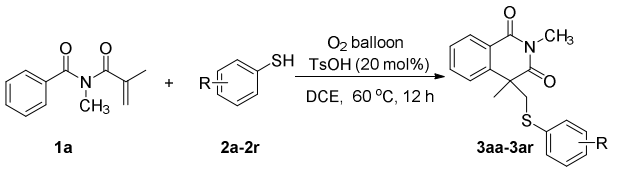
Entry	Conditions	Yield [b]
1	DTBP (3 equiv.), DCE, air, 100 °C,12h	0 %
2	AIBN (3 equiv.), DCE, air, 100 °C,12h	0 %
3	TBHP (3 equiv.), DCE, air, 100 °C,12h	0 %
4	DCE, air, 100 °C,12h	16 %
5	DCE, air, 60 °C,12h	42 %
6	DCE, O_2 balloon, 60 °C,12h	55 %
7	DCE, air balloon, 60 °C,12h	45 %
8	CH_3CO_2H (20 mol%), DCE, O_2 balloon, 60 °C,12h	67 %
9	CF_3SO_3H (20 mol%), DCE, O_2 balloon, 60 °C,12h	60
10	CH_3SO_3H (20 mol%), DCE, O_2 balloon, 60 °C,12h	75
11	$TsOH·H_2O$ (20 mol%), DCE, O_2 balloon, 60 °C,12h	89
12	$PhCO_2H$ (20 mol%), DCE, O_2 balloon, 60 °C,12h	50
13	$TsOH·H_2O$ (100 mol%), DCE, O_2 balloon, 60 °C,12h	86
14	$TsOH·H_2O$ (10 mol%), DCE, O_2 balloon, 60 °C,12h	84
15	DMAP (20 mol%), DCE, O_2 balloon, 60 °C,12h	0
16	Pyridine (20 mol%), DCE, O_2 balloon, 60 °C,12h	0

[a] reaction condition: **1a** (0.5 mmol), **2a** (0.6 mmol, 1.2 equiv.) and solvent (2 mL) for 12 h. DTBP = di-tert-butyl peroxide. TBHP = tert-butyl hydrogenperoxide (anhydrous, about 5 M in decane). AIBN = azodiisobutyronitrile. DMAP = 4-dimethylaminopyridine. [b] Isolated yield.

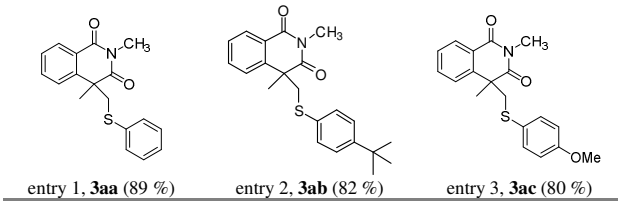
series of desired difunctionalization products in moderate to good yields (**3aa–3ap**). Variations of the substituents on the aromatic core were well tolerated but it should be noted that the aryl thiols possessing electron-withdrawing groups gave the desired products in higher yields than the substrates with electron-donating groups slightly. Generally, substitutents in the para position on the aryl group of thiols proceeded well (entries 1–8). Meta-substituted thiols were also excellent substrates under standard conditions (entries 9–11). But this procedure is sensitive to steric effects only with a moderate yield when using ortho-substituted thiols as substrates (entries 12–13). The 2-naphthalenethiol was viable substrate as well, giving a moderate 52% yield for this difunctionalization of the alkene (entry 14). Furthermore, this aerobic, radical-mediated tandem reaction is also compatible with aliphatic thiols affording moderate yield (entries 15-16). However the hetero aromatic 2-thiophenethiol was failed to participate in the reaction (entry 17).

With the thiols coupling partner scope established, we next turned our attention to probe the substrate scope of N-methacryloylbenzamides under the optimal conditions (Table 3). The effect of various groups on the aromatic ring was examined, varying the electronic properties of the substrate from electron-donating (methyl and methoxy) to moderate electron-withdrawing substituents (chloro and fluoro) in the para position, and all of them worked comparatively well with excellent yields (entries 1–8). The strong electron-withdrawing group such as CF_3 and CN resulted in slightly lower yields (entries 9 and 10). As was anticipated, meta-substituted substrates gave a mixture of two regioselective products, a mixture of 3bk + 3bk´(1:1) and 3bl + 3bl´(1:1) isomers was observed (entries 11–13). A strong steric effect of the substituents was not observed when ortho-substituted N-arylacrylbenzamides were used. A moderate yield was obtained when using ortho-methyl substituted N-arylacrylbenzamides as substrate (entries 14–16). It was found that various N-protected substrates, such as butyl and methoxy are also the effective substituent groups for this transformation.

Table 2. Substrate Scope of Thiols [a,b]



1a **2a-2r** **3aa-3ar**



entry 1, **3aa** (89 %) entry 2, **3ab** (82 %) entry 3, **3ac** (80 %)

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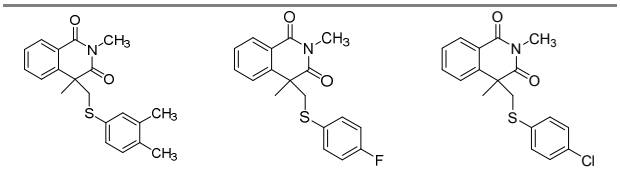
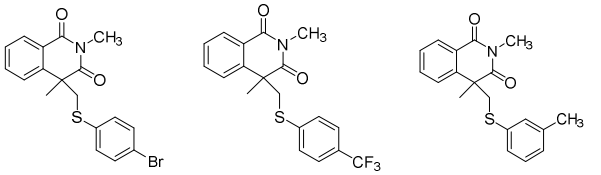
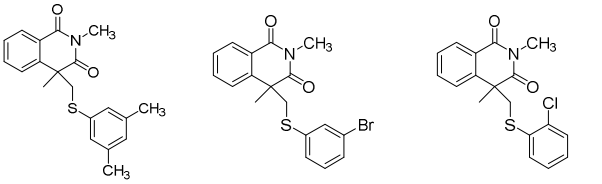


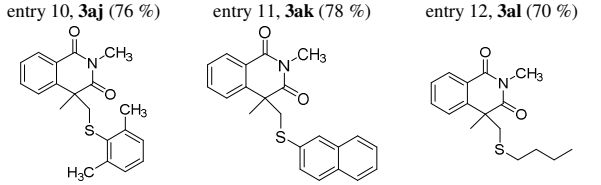
entry 4, **3ad** (80 %) entry 5, **3ae** (86 %) entry 6, **3af** (80 %)



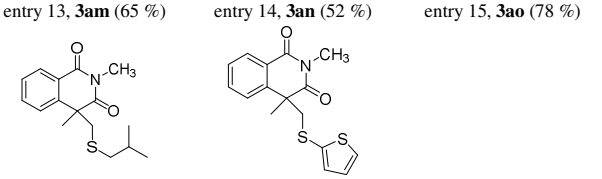
entry 7, **3ag** (85 %) entry 8, **3ah** (90 %) entry 9, **3ai** (80 %)



entry 10, **3aj** (76 %) entry 11, **3ak** (78 %) entry 12, **3al** (70 %)

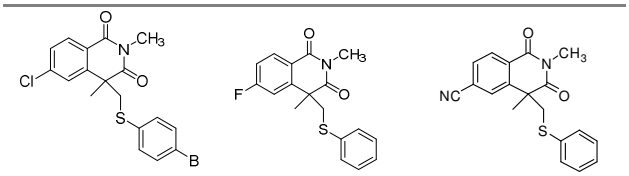


entry 13, **3am** (65 %) entry 14, **3an** (52 %) entry 15, **3ao** (78 %)

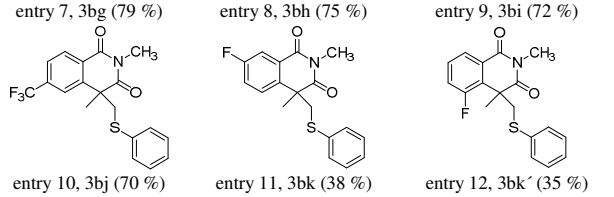


entry 16, **3ap** (75 %) entry 17, **3aq** (0%)

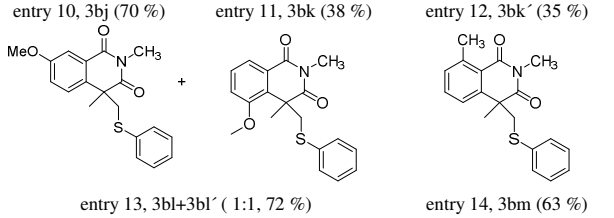
a reaction condition: 1a (0.5 mmol), 2 (0.6 mmol, 1.2 equiv.), TsOH (20 mol%), and DCE (2 mL) at 60 oC under oxygen balloon atmosphere for 12 h. b Isolated yield.



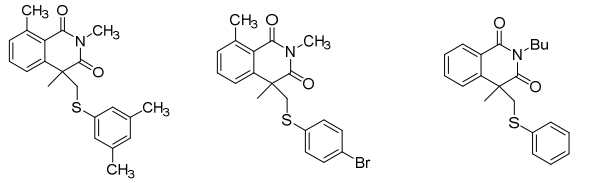
entry 7, 3bg (79 %) entry 8, 3bh (75 %) entry 9, 3bi (72 %)



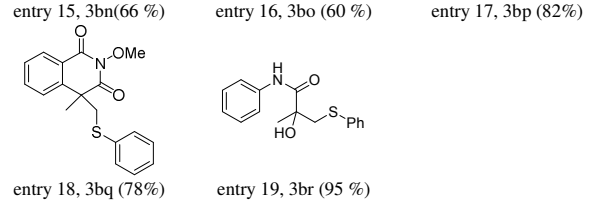
entry 10, 3bj (70 %) entry 11, 3bk (38 %) entry 12, 3bk´ (35 %)



entry 13, 3bl+3bl´ (1:1, 72 %) entry 14, 3bm (63 %)



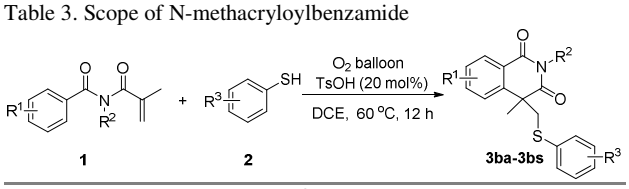
entry 15, 3bn(66 %) entry 16, 3bo (60 %) entry 17, 3bp (82%)



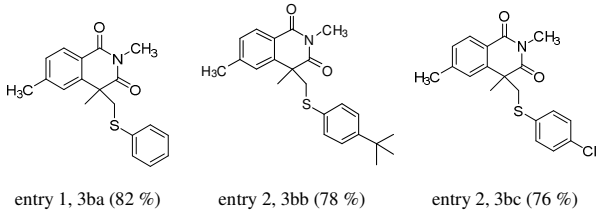
entry 18, 3bq (78%) entry 19, 3br (95 %)

a reaction condition: 1 (0.5 mmol), 2 (0.6 mmol, 1.2 equiv.), TsOH (20 mol%), and DCE (2 mL) at 60 oC under oxygen balloon atmosphere for 12 h. b Isolated yield.

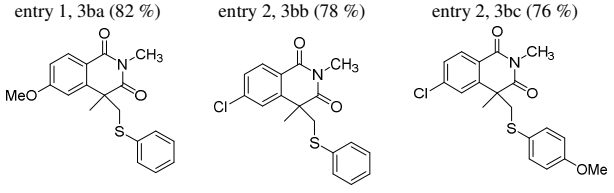
Table 3. Scope of N-methacryloylbenzamide



1 2 3ba-3bs



entry 1, 3ba (82 %) entry 2, 3bb (78 %) entry 2, 3bc (76 %)



entry 4, 3bd (82 %) entry 5, 3be (76 %) entry 6, 3bf (72 %)

(entries 17–18). Lastly, hydroxysulfenylation of double bond was observed when we transfer this protocol to the N-phenylmethacrylamide under the optimal conditions (entry 19). Unfortunately, when using N-methyl-N-phenylmethacrylamide as substrate, the radical cyclization or the hydroxysulfenylation could not be observed.

For understanding the mechanism of the tandem reaction, some control experiments were carried out (Scheme 2). Only trace amount of the desired product was detected by GC-MS under argon atmosphere (Scheme 2a), thus suggesting that this transformation was triggered by O_2 absolutely. Then a radical inhibition experiment was examined with the addition of TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl), no the desired product was obtained and only the coupling product **4** was obtained in 45% yield, suggesting that this transformation involved a radical process (Scheme 2b). It is well known that thiols can easily be oxidized into disulfides by the air, so we suspected the disulfides maybe potential thiyl radical source. Only the by-product S-phenyl benzenesulfonothioate was observed by the GC-MS analysis, when diphenyl disulfide was investigated under standard conditions without thiophenol **2a** (Scheme 2c). Moreover, treatment of **1a** with

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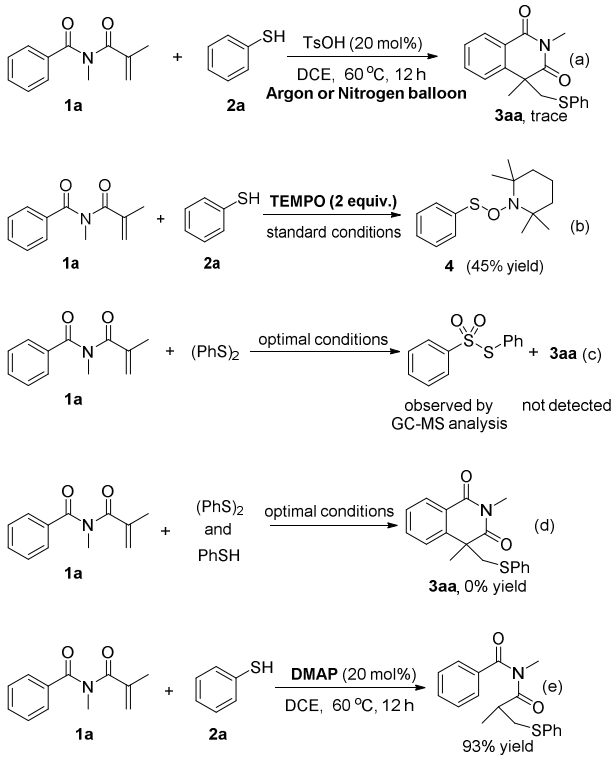
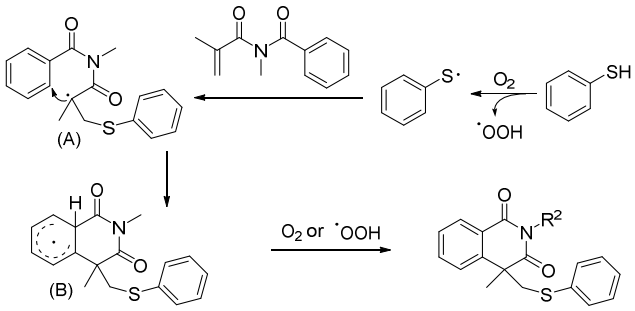
1.0 equiv of thiophenol and 0.1 equiv of diphenyl disulphide also failed to give the product **3aa** under the standard condition (Scheme 2d). These results illustrate that the thiyl radicals are from thiosl and this transformation is sensitive to the presence of impurity of disulfide. Interestingly, only Michael addition product was obtained in 93% yield when using DBU as base without acid (Scheme 2e), combination with the results of table 1, acid greatly accelerated this transformation, Those results indicate that the acidic environment maybe play a vital role in suppressing the Michael addition and accelerating the thiyl radical addition although it is still in unclear.

Scheme 2. Control experiments for mechanism



On the basis of existing precedent [11] and our experimental results, a possible mechanism is depicted in Scheme 3. Thiyl radical, generated from the corresponding thiols by the auto-oxidation reaction with molecular oxygen under acidic condition, attacks the terminal position of the C=C double bond to afford carbon-centered radical intermediate A. Then this radical species A, followed by the intramolecular addition to the aromatic ring, generates a cyclic radical intermediate B. Deprotonation of B by the oxygen or a hydroperoxide radical forms the desired isoquinoline-1,3-diones.

Scheme 3. Proposed cascade coupling reaction mechanism:



Conclusions

In conclusion, we have developed an aerobic radical tandem method which is applicable to a variety of thiols and N-methacryloylbenzamides. The reaction proceeds without the use of precious and/or toxic transition-metal catalysts common to related radical tandem processes and uses molecular oxygen as the sole oxidant. This process focus on the synthetic versatility of the thiyl radical, which is formed from simple aliphatic or aromatic thiols under mild conditions and can serve as a useful source of S-centered radicals for chemical synthesis. Preliminary mechanism revealed that a radical process is involved. Notably, The broad substrate scope and the aerobic nature of this method represent a major advance over existing conditions for the synthesis of the highly valuable sulfide-containing 4,4-disubstituted isoquinoline-1,3-diones and holds significant potential for the applications to a series of novel organic reactions. Our further efforts in this area are currently underway.

Experimental section

All reagents were purchased from commercial suppliers and used without further purification. Flash chromatography was carried out with silica gel (200-300 mesh). Analytical TLC was performed with silica gel 60 F_{254} plates. ^{1}H NMR and ^{13}C NMR (300 MHz and 75 MHz, respectively) spectra were recorded in $CDCl_3$. Chemical shifts (δ) are reported in ppm using TMS as internal standard, and spin-spin coupling constants (J) are given in Hz. HRMS were recorded on an Agilent 6210 TOF LC/MS mass spectrometer.

Typical procedure for synthesis of Sulfide-Containing 4,4-Disubstituted isoquinoline-1,3-diones

A 15-mL Schlenk tube was charged with N-methacryloyl-N-methylbenzamide (0.5mmol), thiol (0.6 mmol), $TsOH{\cdot}H_2O$ (20 mol %) in Dichloroethane (2 mL). The resultant mixture was stirred at 60 °C for 12 h under oxygen balloon. After the reaction was completed by TLC monitoring, the reaction mixture was cooled to room temperature, poured into NH_4Cl (aq. 20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The resulting residue was purified by flash silica gel column chromatography (eluent: hexane/EtOAc, v/v = 10/1) to afford the desired products.

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2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3aa): Isolated yield = 89% (138.4 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25-8.22 (m, 1H), 7.42-7.37 (m, 1H), 7.30-7.26 (m, 1H), 7.33-7.22 (m, 1H), 7.12 (br, 5H), 3.85 (d, J = 13.0 Hz, 1H), 3.40 (d, J = 13.0 Hz, 1H), 3.22 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 141.5, 134.8, 133.8, 131.0, 128.7, 127.8, 126.9, 125.5, 48.7, 47.6, 28.4, 27.1. LRMS (EI) m/z: 310.95, 122.95 (100), 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{18}NO_2S$ $(M+H)^+$: 312.1058, found 312.1054.

4-(((4-(tert-butyl)phenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ab): Isolated yield = 82% (150.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 8.2 Hz, 1H), 7.51-7.32 (m, 2H), 7.25 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 3.81 (d, J = 13.2 Hz, 1H), 3.37 (d, J = 13.1 Hz, 1H), 3.21 (s, 3H), 1.68 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 150.2, 141.6, 133.6, 131.3, 131.0, 128.7, 127.7, 125.8, 125.6, 125.5, 48.8, 47.9, 34.5, 31.2, 28.5, 27.1. LRMS (EI) m/z: 367.10, 179.10 (100), 123.05, 91.05, 57.10, 41.05. HRMS (ESI+) *m/z* calculated for $C_{22}H_{26}NO_2S$ $(M+H)^+$: 368.1684, found 368.1680.

4-(((4-methoxyphenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ac): Isolated yield = 80% (136.6 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.6 Hz,, 1H), 7.52-7.47 (m, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 3.78 (d, J = 13.3 Hz, 1H), 3.73 (s, 3H), 3.32 (d, J = 13.2 Hz, 1H), 3.24 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 159.2, 141.8, 134.0, 133.7, 128.7, 127.7, 125.6, 125.2, 114.4, 55.3, 48.9, 28.8, 27.1. LRMS (EI) m/z: 341.00, 153.00 (100), 138.00, 109.10, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}NO_3S$ $(M+H)^+$: 342.1164, found 342.1160.

4-(((3,4-dimethylphenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ad): Isolated yield = 80% (135.8 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.8 Hz, 1H), 7.50-7.45 (m, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.91-6.85 (m, 2H), 6.79 (s, 1H), 3.80 (d, J = 13.1 Hz, 1H), 3.35 (d, J = 13.0 Hz, 1H), 3.23 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 141.7, 137.0, 135.8, 133.6, 132.9, 131.2, 130.1, 129.2, 128.6, 127.6, 125.6, 48.8, 48.2, 28.6, 27.1, 19.6, 19.3. LRMS (EI) m/z: 339.00, 150.95 (100), 107.05, 91.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1371 found 340.1367.

4-(((4-fluorophenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ae): Isolated yield = 86% (141.6 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.2 Hz, 1H), 7.49-7.40 (m, 2H), 7.25-7.22 (m, 1H), 7.08-7.03 (m, 2H), 6.82-6.72 (m, 2H), 3.79 (d, J = 13.2Hz, 1H), 3.37 (d, J = 13.6 Hz, 1H), 3.25 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 164.2, 163.7, 160.4, 141.53, 133.8, 133.7, 129.9, 128.8, 127.8, 125.5, 115.9 (d, J = 87.3 Hz), 48.96, 48.46, 28.68, 27.19. LRMS (EI) m/z: 329.00, 140.85 (100), 115.05, 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}FNO_2S$ $(M+H)^+$: 330.0964 found 330.0960.

4-(((4-chlorophenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3af): Isolated yield = 80% (138.3 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.8 Hz, 1H) 7.52 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 3.82 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 13.2 Hz, 1H), 3.26 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 164.2, 141.4, 133.8, 133.4, 133.0, 132.4, 128.9, 128.8, 127.8, 125.5, 48.8, 47.7, 28.6, 27.2. LRMS (EI) m/z: 347.00, 345.00, 157.00 (100), 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}ClNO_2S$ $(M+H)^+$: 346.0669 found 346.0665.

4-(((4-bromophenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ag): Isolated yield = 85% (144.2 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.5 Hz, 1H), 7.50-7.48 (m, 1H), 7.41-7.38 (m, 1H), 7.25-7.22 (m, 3H), 6.97-6.93 (m, 2H), 3.80 (d, J = 13.2 Hz, 1H), 3.39 (d, J = 13.1 Hz, 1H), 3.25 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 164.2, 141.3, 134.0, 133.8, 132.6, 131.8, 128.8, 127.8, 125.5, 125.4, 121.0, 48.8, 47.5, 28.6, 27.2. LRMS (EI) m/z: 391.90, 389.90, 247.85, 245.85, 202.80, 200.80, 121.95 (100), 75.00, 43.05. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}BrNO_2S$ $(M+H)^+$: 390.0163 found 390.0159.

2,4-dimethyl-4-(((4-(trifluoromethyl)phenyl)thio)methyl)isoquinoline-1,3(2H,4H)-dione (3ah): Isolated yield = 90% (170.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, J = 7.7 Hz, 1H), 7.46-7.23 (m, 7H), 3.86 (d, J = 13.1 Hz, 1H), 3.47 (d, J = 13.1 Hz, 1H), 3.29 (s, 3H), 1.70 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 164.1, 141.1, 136.5, 133.9, 131.2, 129.1, 128.8, 127.9, 127.3, 125.4, 123.5, 121.8, 118.2, 48.8, 47.2, 28.5, 27.1. LRMS (EI) m/z: 378.95, 190.95 (100), 170.95, 115.05, 91.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{17}F_3NO_2S$ $(M+H)^+$: 380.0932 found 380.0928.

2,4-dimethyl-4-((m-tolylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3ai): Isolated yield = 80% (130.1 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.8 Hz, 1H), 7.50 - 7.35 (m, 2H), 7.27 (d, J = 7.8 Hz, 1H), 7.05-6.89 (m, 3H), 6.84 (s, 1H), 3.84 (d, J = 13.1 Hz, 1H), 3.38 (d, J = 13.1 Hz, 1H), 3.24 (s, 3H), 2.21 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 141.6, 138.5, 134.4, 133.6, 131.8, 128.6, 128.1, 127.7, 125.5, 48.8, 47.7, 28.4, 27.1, 21.1. LRMS (EI) m/z: 325.10, 174.10, 216.00, 173.00, 137.05

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(100), 45.05. HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.1215 found 326.1211.

4-(((3,5-dimethylphenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3aj) : Isolated yield = 76% (128.9 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 6.73 (s, 1H), 6.68 (s, 2H), 3.82 (d, J = 13.0 Hz, 1H), 3.37 (d, J = 13.0 Hz, 1H), 3.26 (s, 3H), 2.18 (s, 6H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 164.4, 141.6, 138.3, 134.1, 133.6, 128.9, 128.8, 128.5, 127.6, 125.6, 113.1, 48.8, 47.7, 28.4, 27.1, 21.1. LRMS (EI) m/z: 339.05, 151.00 (100), 107.10, 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1371 found 340.1367.

4-(((3-bromophenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ak): Isolated yield = 78% (152.2 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 7.5 Hz, 1H), 7.46 -7.36 (m, 2H), 7.26-7.20 (m, 2H), 7.15 (s, 1H), 7.07-6.94 (m, 2H), 3.82 (d, J = 13.1 Hz, 1H), 3.41 (d, J = 13.1 Hz, 1H), 3.30 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1 164.2, 141.2, 137.2 133.7, 133.3, 130.0, 129.9, 129.4, 128.8, 128.0, 125.5, 125.4, 122.4, 48.8, 47.4, 28.5, 27.2. LRMS (EI) m/z: 390.85, 388.85, 202.85, 200.90, 122.00 (100), 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}BrNO_2S$ $(M+H)^+$: 390.0163 found 390.0159.

4-(((2-chlorophenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3al): Isolated yield = 70% (121.0 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.221 (d, J = 7.4 Hz, 1H), 7.45-7.22 (m, 4H), 7.09-7.00 (m, 3H), 3.81 (d, J = 13.2 Hz, 1H), 3.52 (d, J = 13.1 Hz, 1H), 3.30 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.0, 164.2, 141.4, 136.1, 133.7, 133.5, 132.8, 129.7, 128.8, 128.2, 127.8, 126.9, 125.4, 125.3, 48.8, 45.7, 29.2, 27.2. LRMS (EI) m/z: 345.00, 156.95 (100), 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}ClNO_2S$ $(M+H)^+$: 346.0669 found 346.0665.

4-(((2,6-dimethylphenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3am): Isolated yield = 65% (110.3 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.03-6.95 (m, 3H), 3.61 (d, J = 12.2 Hz, 1H), 3.34 (s, 3H), 3.23 (d, J = 12.2 Hz, 1H), 2.24 (s, 6H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 142.5, 142.0, 133.9, 132.8, 128.9, 128.3, 128.0, 127.8, 125.3, 125.2, 48.6, 46.2, 29.9, 27.2, 21.6. LRMS (EI) m/z: 339.00, 151.00 (100), 105.05, 91.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{20}H_{22}NO_2S$ $(M+H)^+$: 340.1370 found 340.1366.

2,4-dimethyl-4-((naphthalen-2-ylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3an): Isolated yield = 52% (93.9 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 (d, J = 7.7 Hz, 1H), 7.71 (br, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.52-7.34 (m, 4H), 7.27 (dt, J = 11.6, 8.4 Hz, 3H), 3.95 (d, J = 13.1 Hz, 1H), 3.47 (d, J = 13.1 Hz, 1H), 3.18 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 164.3, 141.5, 133.7, 133.4, 132.1, 129.8, 128.7, 128.5, 128.4, 127.7, 127.6, 127.3, 126.5, 126.1, 125.5, 48.8, 47.3, 28.5, 27.1. LRMS (EI) m/z: 360.90, 215.95, 172.90 (100), 160.00, 129.05, 114.95, 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{22}H_{20}NO_2S$ $(M+H)^+$: 362.1215 found 362.1211.

4-((butylthio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ao): Isolated yield = 78% (113.6 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ : 8.26 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.48-7.40 (m, 2H), 3.40 (s, 3H), 3.32 (2, J = 13.6 Hz, 1H), 3.08 (d, J = 13.5 Hz, 1H), 2.11 (t, J = 7.2 Hz, 2H), 1.68 (s, 3H), 1.37-1.15 (m, 4H), 0.79 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.7, 164.4, 142.2, 133.8, 128.8, 127.7, 125.5, 125.4, 49.1, 45.0, 33.2, 31.6, 28.2, 27.2, 21.7, 13.6. LRMS (EI) m/z: 291.05, 103.05 (100), 61.05. HRMS (ESI+) *m/z* calculated for $C_{16}H_{22}NO_2S$ $(M+H)^+$: 292.1371 found 292.1367.

4-((isobutylthio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3ap): Isolated yield = 75% (109.2 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.48-7.40 (m, 2H), 3.40 (s, 3H), 3.30 (2, J = 13.2 Hz, 1H), 3.04 (d, J = 13.3 Hz, 1H),, 2.06-1.94 (m, 2H), 1.67 (s, 3H), 1.59-1.48 (m, 1H), 0.79 (dd, J = 6.5, 4.5 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.6, 164.4, 142.2, 133.8, 128.8, 127.7, 125.6, 125.4, 49.1, 45.6, 42.7, 28.5, 28.1, 27.2, 21.7. LRMS (EI) m/z: 291.05, 103.05 (100), 91.05, 57.10, 41.05. HRMS (ESI+) *m/z* calculated for $C_{16}H_{22}NO_2S$ $(M+H)^+$: 292.1371 found 292.1367.

2,4,6-trimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3ba): Isolated yield = 82% (133.4 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.8 Hz, 1H), 7.18-7.01(m, 7H), 3.84 (d, J = 13.2 Hz, 1H), 3. 40 (d, J = 13.2 Hz, 1 H), 3.22 (s, 3H), 2.30 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 164.3, 144.6, 141.4, 135.0, 131.1, 131.0, 128.8, 128.7, 126.8, 126.0, 123.0, 48.9, 47.5, 28.5, 27.1, 21.8. LRMS (EI) m/z: 324.95, 122.95 (100), 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.1215 found 326.1211.

4-(((4-(tert-butyl)phenyl)thio)methyl)-2,4,6-trimethylisoquinoline-1,3(2H,4H)-dione (3bb): Isolated yield = 78% (148.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 8.3 Hz, 3H), 7.02-6.95 (m, 3H), 3.81 (d, J = 13.2 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 3.22 (s, 3H), 2.29 (s, 3H), 1.65 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 164.4, 150.0, 144.5, 141.6, 131.3, 131.2, 128.7, 126.1, 125.7, 123.0,

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114.8, 48.9, 47.8, 34.4, 31.2, 28.5, 27.0, 21.9. LRMS (EI) m/z: 381.10, 179.10, 123.05, 57.10 (100). HRMS (ESI+) *m/z* calculated for $C_{23}H_{28}NO_2S$ $(M+H)^+$: 382.1841 found 382.1837.

4-(((4-chlorophenyl)thio)methyl)-2,4,6-trimethylisoquinoline-1,3(2H,4H)-dione (3bc): Isolated yield = 76% (136.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J = 7.9 Hz, 1H), 7.25-7.15 (m, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.02-6.84 (m, 3H), 3.80 (d, J = 13.2 Hz, 1H), 3.38 (d, J = 13.3 Hz, 1H), 3.27 (s, 3H), 2.28 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 164.2, 144.6, 141.2, 133.6, 133.0, 132.6, 132.4, 128.8, 128.7, 126.0, 122.9, 49.0, 47.7, 28.7, 27.1, 21.7. LRMS (EI) m/z: 358.95, 157.00 (100), 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{19}ClNO_2S$ $(M+H)^+$: 360.0825 found 360.0821.

6-methoxy-2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bd): Isolated yield = 82% (139.9 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (d, J = 8.8 Hz, 1H), 7.12 (br, 5H), 6.87 (dd, J = 2.1 Hz, J = 8.8 Hz, 1H), 6.66 (d, J = 2.1 Hz, 1H), 3.86 (d, J = 13.2 Hz, 1H), 3.76 (s, 3H), 3.37 (d, J = 13.2 Hz, 1H), 3.22 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 163.9, 143.7, 135.0, 131.2, 131.0, 128.7, 126.8, 118.5, 113.6, 110.7, 55.4, 49.1, 47.6, 28.6, 27.0. LRMS (EI) m/z: 341.05, 123.05 (100), 103.00, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}NO_3S$ $(M+H)^+$: 342.1164 found 342.1160.

6-chloro-2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3be): Isolated yield = 76% (131.4 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.4 Hz, 1H), 7.38-7.28 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.17-7.03 (m, 4H), 3.83 (d, J = 13.4 Hz, 1H), 3.36 (d, J = 13.4 Hz, 1H), 3.22 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.6, 163.5, 143.1, 140.3, 134.3, 131.1, 130.2, 128.8, 128.4, 127.2, 126.0, 124.0, 49.1, 47.5, 28.2, 27.2. LRMS (EI) m/z: 344.95, 123.95 (100), 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}ClNO_2S$ $(M+H)^+$: 346.0669 found 346.0665.

6-chloro-4-(((4-methoxyphenyl)thio)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3bf): Isolated yield = 72% (135.2 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 7.14 (d, J = 1.6 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 3.80 (d, J = 13.1 Hz, 1H), 3.75 (s, 3H), 3.30 (d, J = 13.1 Hz, 1H), 3.26 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.7, 163.5, 159.2, 143.3, 140.3, 134.0, 130.2, 128.3, 126.1, 124.8, 124.0, 114.5, 55.3, 49.3, 48.6, 28.7, 28.7, 27.2. LRMS (EI) m/z: 374.95, 153.05 (100), 137.95, 109.05, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{19}ClNO_3S$ $(M+H)^+$: 376.0774 found 376.0770.

4-(((4-bromophenyl)thio)methyl)-6-chloro-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (3bg): Isolated yield = 79% (167.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 1.5 Hz, J = 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 1.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 3.80 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 13.2 Hz, 1H), 3.26 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.5, 163.4, 142.9, 140.4, 133.6, 132.7, 131.9, 130.3, 128.9, 126.0, 124.0, 121.4, 49.18, 47.51, 28.40, 27.27. LRMS (EI) m/z: 424.85, 422.85, 202.85, 200.85, 122.05 (100), 108.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{16}BrClNO_2S$ $(M+H)^+$: 423.9774 found 423.9770.

6-fluoro-2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bh): Isolated yield = 75% (123.5 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (dd, J = 2.1 Hz, J = 6.1 Hz, 1H), 7.13-7.03 (m, 6H), 6.92 (dd, J = 2.1 Hz, J = 9.0 Hz, 1H), 3.84 (d, J = 12.9 Hz, 1H), 3.34 (d, J = 12.9 Hz, 1H), 3.22 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.7, 167.8, 164.4, 163.4, 144.6, 134.4, 131.8, 131.1, 128.8, 127.1, 115.7, 112.6, 49.2, 47.6, 28.3, 27.1. LRMS (EI) m/z: 329.05, 123.05 (100), 109.00, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}FNO_2S$ $(M+H)^+$: 330.0964 found 330.0960.

2,4-dimethyl-1,3-dioxo-4-((phenylthio)methyl)-1,2,3,4-tetrahydroisoquinoline-6-carbonitrile (3bi): Isolated yield = 72% (121.1 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, J = 8.1 Hz, 1H), 7.56 (dd, J = 0.9 Hz, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.14-7.12 (m, 3H), 7.04-7.02 (m, 2H), 3.87 (d, J = 13.5 Hz, 1H), 3.38 (d, J = 13.4 Hz, 1H), 3.26 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 162.8, 162.87, 142.3, 134.1, 131.2, 130.8, 130.1, 129.4, 129.0, 128.8, 127.5, 117.4, 117.0, 49.2, 47.6, 28.1, 27.5, 27.4. LRMS (EI) m/z: 336.05, 123.00 (100), 109.00, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{17}N_2O_2S$ $(M+H)^+$: 337.1011 found 337.1007.

2,4-dimethyl-4-((phenylthio)methyl)-6-(trifluoromethyl)isoquinoline-1,3(2H,4H)-dione (3bj): Isolated yield = 70% (132.7 mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.10-7.02 (m, 5H), 3.87 (d, J = 13.8 Hz, 1H), 3.40 (d, J = 13.8 Hz, 1H), 3.27 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.5, 163.2, 142.2, 135.16, 134.2, 131.1, 129.5, 128.9, 128.4, 127.2, 124.6, 122.8, 121.44, 49.3, 47.8, 28.0, 27.3. LRMS (EI) m/z: 378.95, 122.95 (100), 77.00, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{17}F_3NO_2S$ $(M+H)^+$: 380.0932 found 380.0928.

7-fluoro-2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bk): Isolated yield = 38% (62.5mg), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.29-

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7.19 (m, 1H), 7.21-6.99 (m, 6H), 3.84 (d, *J* = 13.3 Hz, 1H), 3.36 (d, *J* = 13.3 Hz, 1H), 3.22 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 174.9, 163.4, 160.2, 137.3, 134.6, 131.1, 128.8, 127.8, 127.6 127.0, 121.3, 114.7, 48.6, 47.9, 28.3, 27.3. LRMS (EI) m/z: 329.00, 123.00 (100), 109.00, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}FNO_2S$ $(M+H)^+$: 330.0964 found 330.0960.

5-fluoro-2,4-dimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bk´): Isolated yield = 35% (57.6mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.08 (d, *J* = 8.1 Hz, 1H), 7.37-7.29 (m, 1H), 7.08-7.00 (m, 6H), 3.82 (dd, *J* = 13.5 Hz, 2H), 3.22 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 175.0, 163.4, 161.4, 158.1, 134.0, 131.7, 129.4, 128.7, 127.0, 124.9, 121.1, 120.8, 48.2, 44.1, 27.3, 26.4. LRMS (EI) m/z: 329.00, 123.00 (100), 108.95, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{17}FNO_2S$ $(M+H)^+$: 330.0964 found 330.0960.

2,4,8-trimethyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bm): Isolated yield = 63% (102.5 mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.36 (t, *J* = 7.5 Hz, 1H), 7.22-7.13 (m, 7H), 3.82 (d, *J* = 12.9 Hz, 1H), 3.40 (d, *J* = 12.9 Hz, 1H), 3.20 (s, 3H), 2.78 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 174.8, 164.8, 142.8, 142.3, 135.0, 132.6, 131.8, 130.7, 128.7, 126.7, 124.0, 123.7, 48.6, 47.9, 28.7, 27.1, 24.0. LRMS (EI) m/z: 325.00, 174.00, 122.95 (100), 115.05, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}NO_2S$ $(M+H)^+$: 326.1215 found 326.1211.

4-(((3,5-dimethylphenyl)thio)methyl)-2,4,8-trimethylisoquinoline-1,3(2H,4H)-dione (3bn): Isolated yield = 66% (116.6 mg), ^{1}H NMR (300 MHz, $CDCl_3$) : *δ* 7.38-7.27 (m, 1H), 7.19-7.15 (m, 2H), 6.70-6.68 (m, 3H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.37 (d, *J* = 12.9 Hz, 1H), 3.24 (s, 3H), 2.78 (s, 3H), 2.19 (s, 6H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ:* 174.9, 164.9, 142.8, 142.2, 138.2, 134.2, 132.4, 131.7, 128.6, 123.9, 123.8, 48.7, 48.0, 28.6, 27.1, 24.0, 21.1. LRMS (EI) m/z: 353.10, 151.05(100), 107.10, 45.00. HRMS (ESI+) *m/z* calculated for $C_{21}H_{24}NO_2S$ $(M+H)^+$: 354.1528 found 354.1524.

4-(((4-bromophenyl)thio)methyl)-2,4,8-trimethylisoquinoline-1,3(2H,4H)-dione (3bo): Isolated yield = 60% (121.2 mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.38-7.33 (m, 1H), 7.23-7.05 (m, 4H), 6.97 (d, *J* = 8.3 Hz, 2H), 3.79 (d, *J* = 12.9 Hz, 1H), 3.40 (d, *J* = 12.9 Hz, 1H), 3.23 (s, 3H), 2.77 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 174.7, 164.7, 142.6, 142.4, 134.2, 132.7, 132.3, 131.7, 128.8, 123.9, 123.7, 120.8, 48.7, 47.8, 28.8, 27.1, 23.9. LRMS (EI) m/z: 404.90, 402.95, 202.90 (100), 200.95, 122.05, 91.05, 45.05. HRMS (ESI+) *m/z* calculated for $C_{19}H_{19}BrNO_2S$ $(M+H)^+$: 404.0320 found 404.0316.

2-butyl-4-methyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bp): Isolated yield = 82% (144.9 mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.23 (d, *J* = 7.5 Hz, 1H), 7.53-7.42 (m, 1H), 7.43-7.34 (m, 1H), 7.30-7.25 (m, 1H), 7.11 (s, 5H), 3.99-3.88 (m, 2H), 3.83 (d, *J* = 12.9 Hz, 1H), 3.45 (d, *J* = 12.9 Hz, 1H), 1.68 (s, 3H), 1.61-1.53 (m, 2H), 1.39-1.29 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 174.9, 164.0, 141.6, 135.3, 133.7, 130.8, 128.8, 128.7, 127.8, 127.7, 126.7, 125.5, 48.7, 47.4, 40.5, 30.0, 28.7, 20.3, 13.8. LRMS (EI) m/z: 353.05, 122.95 (100), 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{21}H_{24}NO_2S$ $(M+H)^+$: 354.1528 found 354.1524.

2-methoxy-4-methyl-4-((phenylthio)methyl)isoquinoline-1,3(2H,4H)-dione (3bq): Isolated yield = 78% (127.6 mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.22 (d, *J* = 7.5 Hz, 1H), 7.53-7.44 (m, 1H), 7.44-7.36 (m, 1H), 7.29-7.22 (m, 1H), 7.10 (s, 5H), 3.96 (s, 3H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.50 (d, *J* = 12.9 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 170.9, 160.5, 140.9, 134.9, 134.2, 134.1, 131.0, 128.9, 128.8, 127.0, 125.9, 125.2, 64.12, 64.0, 50.9, 47.5, 28.4. LRMS (EI) m/z: 326.95, 151.00, 123.00 (100), 115.00, 77.05, 45.00. HRMS (ESI+) *m/z* calculated for $C_{18}H_{18}NO_3S$ $(M+H)^+$: 328.1007 found 328.1003.

2-hydroxy-2-methyl-N-phenyl-3-(phenylthio)propanamide (3br): Isolated yield = 95% (136.5 mg), ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.66 (s, 1H), 7.43 (t, *J* = 8.1 Hz, 4H), 7.29-7.08 (m, 6H), 3.74 (d, *J* = 13.9 Hz, 1H), 3.51 (br, 1H), 3.23 (d, *J* = 13.9 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 172.2, 137.2, 134.6, 130.6, 129.1, 128.9, 127.1, 124.5, 119.7, 75.5, 45.0, 26.1. LRMS (EI) m/z: 289.05, 269.00(100), 177.00, 124.05, 94.05, 43.05. HRMS (ESI+) *m/z* calculated for $C_{16}H_{18}NOS$ $(M+H)^+$: 288.1058 found 288.1054.

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