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Iminium Ion and *N*-hydroxyimide as the Surrogate Components in DEAD-Promoted Oxidative Ugi Variant

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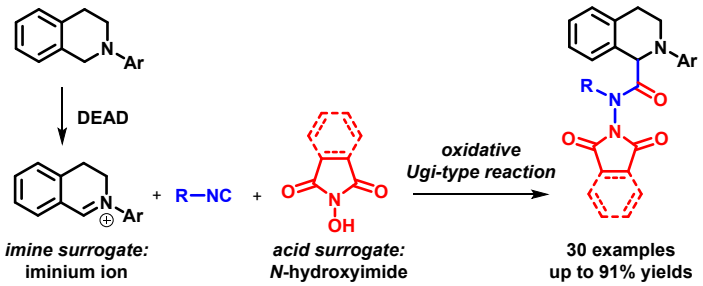


ABSTRACT

A practical metal-free oxidative Ugi-type three-component assembly has been achieved efficiently, employing tertiary amine-derived iminium ion as an imine surrogate, *N*-hydroxyimide as an acid surrogate, and DEAD as an oxidant. This dual-surrogate Ugi variant proceeded with a broad substrate scope and desired functional group tolerance, leading to a wide range of *N*-alkyl-*N*-acyl aminophthalimide and *N*-alkyl-*N*-acylaminosuccinimide derivatives in good isolated yields.

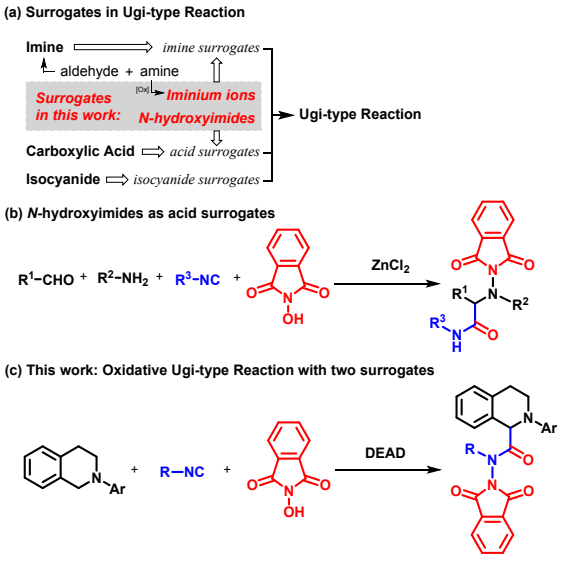
INTRODUCTION

Ugi reaction is considered as one of the most well-known multicomponent reactions (MCRs), because of its practical application for the construction of chemical libraries and pharmaceutical scaffolds for drug research.[1,2] As the demand for molecular diversity grew considerably, exploration of novel multicomponent Ugi reactions has become a pivotal solution, involved in unearthing novel surrogates for the indispensible components in traditional Ugi processes, including imines, carboxylic acids and isocyanides (Scheme 1a).

Since isocyanide is the core component in Ugi reaction, surrogates for isocyanide are less common than the ones for imine and acid. The first "isocyanide-free" Ugi reaction was revealed by El Kaïm in 2009. [3] In this reaction, precursors of isocyanide such as benzyl halide were regarded as the isocyanide surrogate, reaching the *in situ* isocyanide formation with the treatment of AgCN. In 2015, Dömling introduced a second practical "isocyanide-less" strategy, in which the isocyanide was yielded via the trisphosgene-promoted dehydration of the formamide. [4] Both of the above transformations were compatible with the subsequent Ugi reaction.

Extensive researches, perusing for novel Ugi component's functional equivalents, have been performed and various workable replacements to imine and carboxylic acid have been summarized in an excellent book and some reviews. [2,5] Among the existing imine surrogates, iminium ions, directly transformed from secondary or tertiary amines

through the action of various oxidants, have seduced many organic chemists in oxidative Ugi-type reaction over recent years. [6,7] For example, in 2007, Zhu's group pioneered the first oxidative Ugi-type reaction, in which 1,2,3,4-tetrahydroisoquinolines (THIQs) were converted into the corresponding cyclic imines, using IBX (2-iodoxybenzoic acid) as a mild and efficient oxidant. [6b] Ugi-type three-component assemblies, employing copper and peroxides as oxidants, were accomplished by Xie in 2010. [7a] Alternatively, the first photoredox-catalyzed oxidative Ugi-type reactions were reported by Rueping's group in 2013. [7c] The surrogate iminium ions could also be formed through the cascade event involving sequential imine formation and decarboxylation. [6g] Subsequently, taking advantage of the redox-neutral iminium ions formation and amine C–H functionalization of pyrrolidines and THIQs, Seidel performed a new variant of Ugi reaction. [6h] We recently reported a Brønsted-acid-catalyzed three-component reaction involving the oxidation of tertiary amines triggered by a 1,5-hydride shift. [8] In addition, we also described a metal-free oxidative Ugi-type reaction, in which the tertiary amines, oxidized by DEAD, were converted into the corresponding iminium ions. [9,10,11]



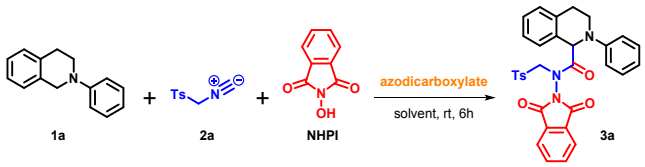
Scheme 1. Surrogate components in Ugi-type Reaction.

Well-studied acid surrogates, such as hydrazoic acids, cyanates, thiocyanates, thioacetic acid, phenols, thiophenol and even mineral acids and CO_2, have expanded the diversity of the Ugi reaction outcomes. [12] Notably, the above reactions employing carboxylic acids or their surrogates always underwent a N-C bond formation in the Mumm-type rearrangement. Recently, the first two examples of N-N bond formation in the Mumm-type rearrangement were illustrated successively by El Kaïm and Dömling. [13,14] The Dömling's work verified *N*-hydroxyimide as a new acid surrogate in the Ugi reaction, and provided straightforward access to α-hydrazino amides in the presence of Lewis acid (Scheme 1b). To expand the application of this strategy further, we initially supposed that the DEAD-promoted oxidative Ugi-type reaction of tertiary amines could allow the efficient unification with the iminium ion (imine surrogate), the *N*-hydroxyimide (acid surrogate) and isocyanide (Scheme 1c). In addition, we also focused on the feasibility of the Mumm-like migration of the phthalimide or succinimide

to the isocyanide nitrogen atom.

RESULTS AND DISCUSSION

Table 1. Optimization of Reaction Conditions. [a]

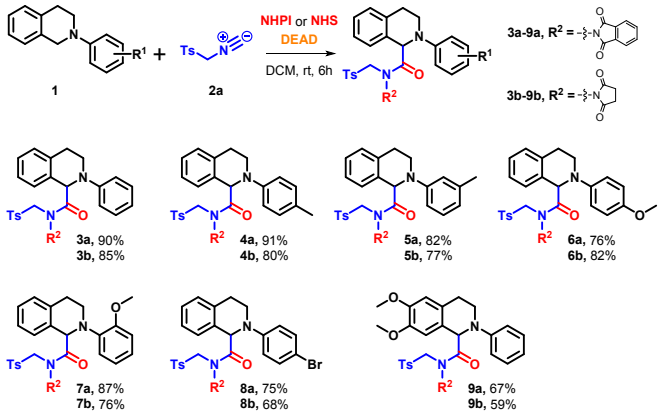


entry	azodicarboxylate	solvent	yield[b]
1	DEAD	THF	60
2	DIAD	THF	43
3	DBAD	THF	13
4	DEAD	DCM	90
5	DEAD	DCE	88
6	DEAD	toluene	34
7	DEAD	CH_3CN	65
8	DEAD	DMF	52
9[c]	DEAD	DCM	87
10[d]	DEAD	DCM	88
11[e]	DEAD	DCM	82
12[f]	DEAD	DCM	83

[a] **1a** (0.3 mmol), azodicarboxylate (0.33 mmol), **2a** (0.33 mmol), NHPI (0.33 mmol), solvent (3.0 mL). azodicarboxylate and **2a** were added at the same time. [b] Isolated yield. [c] DEAD (0.66 mmol). [d] **2a** (0.66 mmol). [e] NHPI (0.66 mmol). [f] **1a** was treated with DEAD for 1 h,

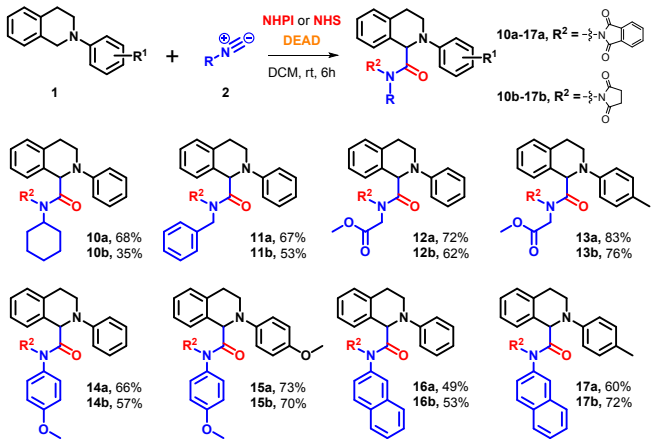
and subsequently **2a** and NHPI were added. NHPI = *N*-Hydroxyphthalimide. DIAD = diisopropyl azodicarboxylate. DBAD = di-*tert*-butyl azodicarboxylate.

The optimization of reaction conditions was initially carried out, with 2-phenyl-1,2,3,4-tetrahydro-isoquinoline **1a**, *p*-toluene sulfonyl isocyanide **2a** and *N*-hydroxyphthalimide (NHPI) as standard substrates. At the outset, DEAD was selected as the oxidant in this Ugi-type reaction, which was performed in THF at room temperature (25 ^{o}C), and the anticipated acyl hydrazide **3a** was rapidly obtained within 6 hours in 60% yield (Table 1, entry 1). When the oxidant was changed to DIAD or DBAD, the conversion of **3a** sharply decreased to 43% and 13%, respectively (Table 1, entries 2−3). Although NHPI was slightly soluble in DCM and DCE, the reaction processed smoothly, affording the desired products in excellent yields (Table 1, entries 4−5). However, yield improvements were not attained when toluene, acetonitrile or DMF were used as solvent (Table 1, entries 6−8). Next, the influence of the equivalents was investigated. When the equivalent of DEAD, **2a** or NHPI was doubled respectively, the isolated yields of **3a** were almost constant (Table 1, entries 9−11). The adjustment of additive sequencedid not improve the reaction yield (Table 1, entries 12). According to the above results, the oxidative Ugi-type reaction of **1a** (1.0 equiv), **2a** (1.1 equiv) and NHPI (1.1 equiv), with DEAD (1.1 equiv) as the oxidant, was optimally carried out in DCM (0.1 M) at room temperature.



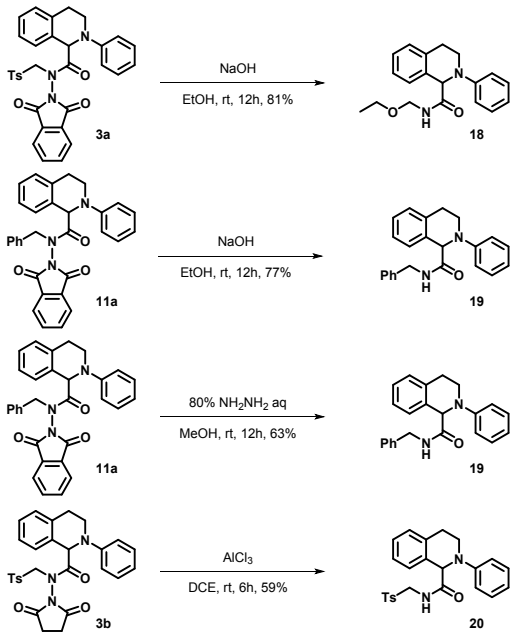
Scheme 2. Scope of the reaction in terms of substrates **1**.

With optimized conditions in hand, we next probed the scope of substrate **1** to confirm the generality of this protocol (Scheme 2). Both NHPI and *N*-hydroxysuccinimide (NHS) were employed as the acid component in these reactions, which provided **3a**-**9a** and **3b**-**9b** in the presence of **1**, **2a** and DEAD. The nitrogen-linked benzene rings with both electron-donating such as methyl, methoxyl (**3a**-**7a**, **3b**-**7b**) and electron-withdrawing bromide (**8a** and **8b**) were well tolerated under the DEAD-promoted system, affording the desired products in good to excellent yields. Notably, little influence of substituent position was observed when the *o*-, *m*-, and *p*-methyl or methoxyl-substituted tetrahydro-isoquinoline substrates were used. Similarly, the substrate carrying 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety provided **9a** and **9b** in 67% and 59% yields, respectively. In addition, most reactions with NHPI provided slightly higher yields than the one with NHS.



Scheme 3. Scope of the reaction in terms of isocyanides.

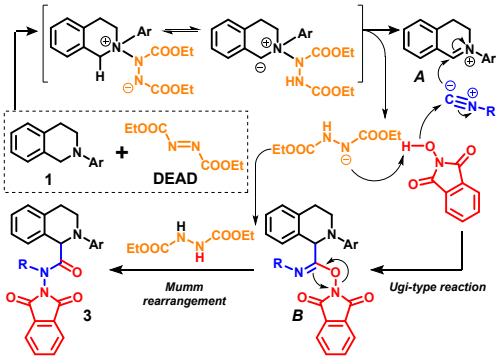
As shown in Scheme 3, a diverse range of isocyanides **2** were next subjected to this transformation to survey the reaction compatibility. The isocyanides bearing alkyl groups such as cyclohexyl and benzyl gave the corresponding products (**10a**, **10b**, **11a**, **11b**) in moderate yields. Methyl isocyanoacetate, combined with the standard substrate and the methyl-substituted derivative, provided four desired products (**12a**, **12b**, **13a**, **13b**) in moderate to good yields. Several aryl isocyanides, including 4-anisyl and 2-naphthyl group, could serve as tolerable substrates in the transformation for the successful production of the corresponding products (**14a-17a**, **14b-17b**).



Scheme 4. Further experiments.

To explore the synthetic utility of this methodology, two gram scale reactions employing NHPI and NHS were carried out respectively in the presence of **1a**, **2a** and DEAD for 12 h, affording **3a** in 86% yield and **3b** in 82% yield (the average of three runs). Moreover, further structural derivatization of **3a** and **3b** was conducted (Scheme 4). The substitution of the tosyl group of **3a** by ethoxy group was achieved with the aid of NaOH, affording alkoxymethylamide **18** in 81% yield. In this reaction, to our surprise, the imide group was spontaneously removed by the strong basic condition. When compound **11a** was treated as the reactant, the cleavage of the imide group also occurred, affording compound **19** in 77% yield. [15] Similarly, the amide compound **19** was obtained in 63% yield by the direct cleavage of imide group of **11a**, but not by the deprotection of phthaloyl group via hydrazinolysis.[14] The cleavage of the succinimide moiety in **3b** was achieved with the treatment of Lewis acid such as $AlCl_3$, affording amide **20** in 59%

yield.



Scheme 5. Proposed mechanism.

The plausible reaction pathway was illustrated in Scheme 5. The iminium ion **A** was obtained through two tandem steps: The nucleophilic addition initially occured between **1** and DEAD, and then the corresponding two intermediates in the bracket could be in equilibrium with each other by an intramolecular hydrogen transfer and furnish the iminium ion **A,** pairing with its basic counter anion (1H-DEAD anion). Next, the actived iminium ion **A** readily paticipated the Ugi-type reaction with isocyanides and NHPI (NHPI could be deprotonated by the 1H-DEAD anion), affording the intermediate **B**. The subsequent Mumm rearrangement occured at the nitrogen of the imide, but not the tertiary amine, which completed the oxidative Ugi-type reaction effectively and gave rise to acyl hydrazide **3**. Notably, during these transformations, DEAD served as the oxidant and 1H-DEAD anion served as the base.

CONCLUSIONS

In conclution, we have developed a novel protocol for the preparation of *N*-alkyl-*N*-acylaminophthalimide/*N*-alkyl-*N*-acylaminosuccinimide via oxidative Ugi

reaction upon DEAD promotion, employing tertiary amine-derived iminium ion as an imine surrogate, *N*-hydroxyimide as an acid surrogate. Under the mild conditions, this surrogate-combined Ugi reaction proceeded with a broad substrate scope and desired functional group tolerance, giving the target compounds in good yields and extending the skeletal diversity of the products. The *N*-alkyl-*N*-acylaminophthalimide products and the *N*-alkyl hydrazine derivatives, demonstrating potential for further applications in medicinal research, are now involved in the ongoing project in our laboratory.

EXPERIMENTAL SECTION

General Methods

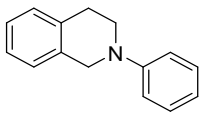
^{1}H and ^{13}C NMR spectra were recorded on an ACF* 300Q and 500Q Bruker spectrometer. High resolution mass spectra were recorded in electrospray ionization mass spectrometry measurements. Reactions were monitored by TLC on silica gel 60 F254 plates. Column chromatography was carried out on silica gel (200-300 mesh). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad singlet, coupling constant (s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

General procedure for synthesis of substrate 1:

2-phenyl-1,2,3,4-tetrahydroisoquinoline (1a): A two-neck flask was charged with copper (I) iodide (1.30 g, 6.70 mmol) and potassium phosphate (28.30 g, 133.30 mmol).

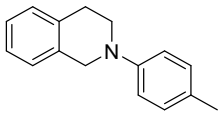
After the two-neck flask was evacuated and back filled with argon, a solution of 1,2,3,4-tetrahydroisoquinoline (12.52 mL, 100 mmol) and iodobenzene (7.43 mL, 66.70 mmol) in isopropanol (100 mL) and ethylene glycol (7.42 mL, 133.30 mmol) was added. The mixture was heated at 90 °C for 60~90 h and then allowed to cool to room temperature. Diethyl ether (50 mL) and water (50 mL) were added to the reaction. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The mixture was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 500:1-10:1) to give 2-phenyl- 1,2,3,4-tetrahydroisoquinoline (**1a**) (4.30 g, 31% yield). The other substrates **1b-g** could be prepared with the above mentioned method. The ^{1}H NMR data were identical with those reported in the literature.[16-18]

2-phenyl-1,2,3,4-tetrahydroisoquinoline (1a):



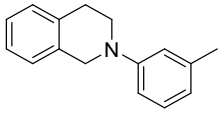
Off-white solid, 4.30 g, 31% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 8.5, 7.5 Hz, 2H), 7.23–7.15 (m, 4H), 7.01 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 4.44 (s, 2H), 3.59 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 5.8 Hz, 2H).

2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline (1b):



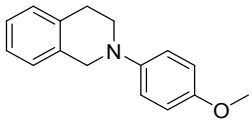
Light yellow solid, 261 mg, 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.08 (m, 6H), 6.95 (d, J = 8.4 Hz, 2H), 4.39 (s, 2H), 3.54 (t, J = 5.8 Hz, 2H), 3.02 (t, J = 5.7 Hz, 2H), 2.32 (s, 3H).

2-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline (1c):



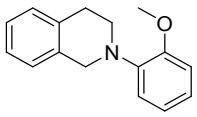
Brown oil, 187 mg, 28% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.12 (m, 6H), 6.88-6.79 (m, 2H), 6.68-6.63 (m, 1H), 4.43 (s, 2H), 3.58-3.55 (m, 2H), 3.10-3.02 (m, 2H), 2.37 (s, 3H).

2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1d):



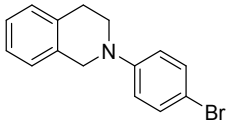
White solid, 315 mg, 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 4H), 6.97 (d, J = 8.8 Hz,, 2H), 6.85 (d, J = 8.8 Hz,, 2H), 4.28 (s, 2H), 3.77 (s, 3H), 3.45-3.40 (m, 2H), 3.01-2.96 (m, 2H).

2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1e):



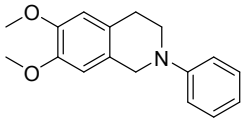
White solid, 142 mg, 20% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 4H), 7.24 – 7.15 (m, 2H), 7.15 – 7.03 (m, 2H), 4.48 (s, 2H), 4.07 (s, 3H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.16 (t, *J* = 5.9 Hz, 2H).

2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinoline (1f):



White solid, 104 mg, 12% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 2H), 7.25–7.09 (m, 4H), 6.84 (d, J = 8.9 Hz, 2H), 4.38 (s, 2H), 3.54 (t, J = 5.8 Hz, 2H), 2.99 (t, J = 5.8 Hz, 2H).

6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (1g):

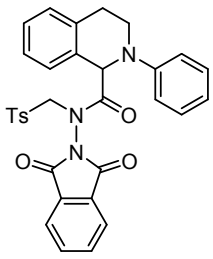


Yellow solid, 121 mg, 15% yield.. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 7.8 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 6.84 (t, J = 7.2 Hz, 1H), 6.66 (d, J = 3.0 Hz, 2H), 4.35 (s, 2H), 3.88 (s, 3H), 3.88 (s, 3H), 3.56 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 5.7 Hz, 2H).

General Procedure for the Synthesis of Compounds 3a-17a and 3b-17b

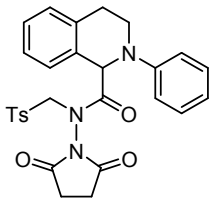
Compound **1** (0.3 mmol), isocyanide **2** (0.33 mmol), NHPI or NHS (0.33 mmol), and CH_2Cl_2 (3.0 mL) were added to a 10 mL flask. DEAD (52 μL, 58 mg, 0.33 mmol, 1.1 equiv.) was then added, and the resulting mixture was stirred at room temperature. The reaction was monitored by TLC until complete consumption of the starting material was observed. The solvent was directly extracted with ethyl acetate (3 x 5 mL) and the combined organic layer was washed with saturated $NaHCO_3$ solution (3 x 10 mL) and brine and dried over Na_2SO_4. After the organic phase removed under reduced pressure, the resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1–2:1) to give the desired product **3a-17a** and **3b-17b**, which was further purified by trituration with diethyl ether or diethyl ether/hexane.

***N*-(1,3-dioxoisoindolin-2-yl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline -1-carboxamide (3a)**:



White solid, 152 mg, 90%. m.p. 185–186°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.75 (m, 4H), 7.61 – 7.49 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.26 – 7.19 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 2H), 5.61 (s, 1H), 4.78 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.89 – 3.76 (m, 1H), 3.58 – 3.40 (m, 1H), 3.23 – 3.07 (m, 1H), 3.07 – 2.90 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 151.5, 146.6, 137.4, 137.0, 136.5, 132.7, 132.1, 131.8, 131.6, 131.6, 131.5, 131.2, 130.5, 130.1, 129.5, 126.2, 125.1, 122.2, 70.8, 62.2, 50.4, 31.1, 24.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{27}N_3O_5S$ 566.1744; Found 566.1767.

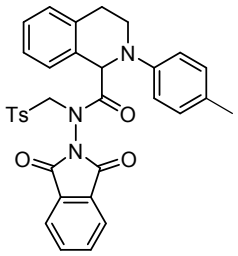
***N*-(2,5-dioxopyrrolidin-1-yl)-2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinolin e-1-carboxamide (3b)**:



White solid, 132 mg, 85% yield. m.p. 211–212°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.42 – 7.13 (m, 9H), 7.12 – 6.97 (m, 2H), 5.53 (s, 1H), 4.76 (d, *J* = 14.5 Hz, 1H), 4.49 (d, *J* = 14.5 Hz, 1H), 3.84 – 3.69 (m, 1H), 3.54 – 3.37 (m, 1H), 3.10 – 2.86

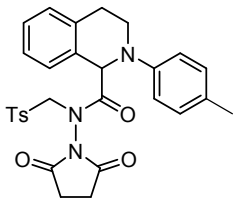
(m, 2H), 2.69 (s, 4H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 160.6, 148.7, 144.5, 134.8, 134.5, 130.0, 129.5, 128.8, 128.6, 127.9, 127.5, 126.7, 122.3, 119.3, 68.2, 59.2, 47.3, 28.1, 25.5, 21.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{27}N_3O_5SNa$ 540.1564; Found 540.1570.

***N*-(1,3-dioxoisoindolin-2-yl)-2-(p-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoli ne-1-carboxamide (4a)**:



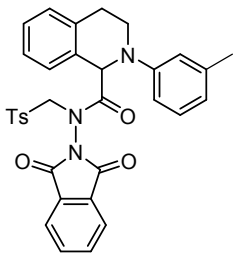
White solid, 158 mg, 91% yield. m.p. 184–186°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.76 (m, 4H), 7.61 – 7.49 (m, 1H), 7.39 – 7.26 (m, 4H), 7.25 – 7.14 (m, 3H), 7.08 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 7.9 Hz, 2H), 5.55 (s, 1H), 4.81 (d, J = 14.6 Hz, 1H), 4.40 (d, J = 14.6 Hz, 1H), 3.87 – 3.73 (m, 1H), 3.50 – 3.36 (m, 1H), 3.21 – 3.07 (m, 1H), 3.07 – 2.93 (m, 1H), 2.36 (d, J = 2.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 148.1, 145.3, 136.2, 135.8, 133.7, 131.6, 131.5, 130.5, 130.3, 130.0, 129.2, 128.8, 128.2, 125.0, 121.5, 69.6, 61.3, 49.6, 30.0, 23.0, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{30}N_3O_5S$ 580.1901; Found 580.1920.

***N*-(2,5-dioxopyrrolidin-1-yl)-2-(p-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoli ne-1-carboxamide (4b)**:



White solid, 127 mg, 80% yield. m.p. 186–187°C. ^{1}H NMR (300 MHz, DMSO) δ 7.52 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.07 (m, 7H), 6.99 (d, *J* = 8.1 Hz, 2H), 5.46 (s, 1H), 4.77 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 3.84 – 3.66 (m, 1H), 3.50 – 3.29 (m, 2H), 3.13 – 2.87 (m, 1H), 2.69 (s, 4H), 2.48 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 162.2, 147.8, 145.8, 136.2, 135.9, 133.5, 131.4, 130.8, 130.2, 130.0, 129.1, 128.8, 128.0, 121.2, 69.6, 60.9, 49.3, 29.6, 26.9, 23.0, 22.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{30}N_3O_5S$ 532.1901; Found 532.1914.

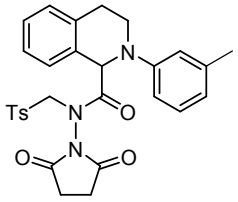
***N*-(1,3-dioxoisoindolin-2-yl)-2-(m-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5a)**:



White solid, 142 mg, 82% yield. m.p. 153–155°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.76 (m, 4H), 7.62 – 7.56 (m, 1H), 7.39 – 7.16 (m, 6H), 7.07 – 6.92 (m, 4H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.59 (s, 1H), 4.81 (d, *J* = 14.7 Hz, 1H), 4.45 (d, *J* = 14.7 Hz, 1H), 3.89 – 3.75 (m, 1H), 3.54 – 3.40 (m, 1H), 3.21 – 3.08 (m, 1H), 3.07 – 2.92 (m, 1H), 2.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.52, 148.85, 143.92, 139.41, 134.82, 134.36, 133.94, 130.19, 129.31, 129.15, 129.02, 128.81, 128.50, 127.88, 127.46, 126.83,

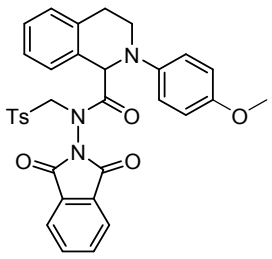
123.59, 123.34, 120.03, 116.44, 68.15, 59.63, 47.93, 28.58, 21.61, 21.55. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{30}N_3O_5S$ 580.1901; Found 580.1908.

***N*-(2,5-dioxopyrrolidin-1-yl)-2-(m-tolyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5b)**:



White solid, 122 mg, 77% yield. m.p. 175–176°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.12 (m, 6H), 6.98 – 6.76 (m, 3H), 5.50 (s, 1H), 4.79 (d, *J* = 14.6 Hz, 1H), 4.52 (d, *J* = 14.6 Hz, 1H), 3.83 – 3.69 (m, 1H), 3.50 – 3.34 (m, 1H), 3.12 – 2.87 (m, 2H), 2.69 (s, 4H), 2.48 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.99, 160.52, 148.62, 144.41, 139.36, 134.81, 134.45, 130.06, 129.44, 129.28, 128.74, 128.53, 127.79, 127.54, 126.68, 123.09, 119.68, 116.12, 68.11, 59.28, 47.51, 28.25, 25.52, 21.62, 21.57. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{30}N_3O_5S$ 532.1901; Found 532.1918.

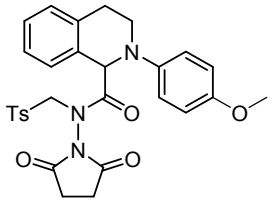
***N*-(1,3-dioxoisoindolin-2-yl)-2-(4-methoxyphenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (6a):**



White solid, 135 mg, 76% yield. m.p. 112–114°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 –

7.75 (m, 4H), 7.55 – 7.45 (m, 1H), 7.40 – 7.18 (m, 6H), 7.18 – 7.07 (m, 2H), 7.02 – 6.83 (m, 4H), 5.44 (s, 1H), 4.85 (d, *J* = 14.6 Hz, 1H), 4.25 (d, *J* = 14.6 Hz, 1H), 3.84 (s, 3H), 3.77 – 3.66 (m, 1H), 3.39 – 3.27 (m, 1H), 3.23 – 3.09 (m, 1H), 3.04 – 2.91 (m, 1H), 2.34 (d, *J* = 2.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 157.6, 145.3, 144.2, 136.0, 135.7, 135.4, 131.8, 130.5, 130.3, 130.0, 129.1, 128.6, 128.2, 125.0, 124.2, 116.2, 69.5, 62.4, 56.9, 50.6, 30.3, 22.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{30}N_3O_6S$ 596.1850; Found 596.1867.

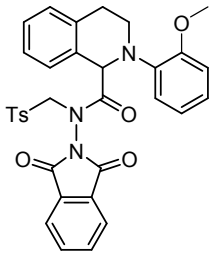
_N_-(2,5-dioxopyrrolidin-1-yl)-2-(4-methoxyphenyl)-_N_-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (6b):



White solid, 135 mg, 82% yield. m.p. 134–135°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.12 (m, 6H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.36 (s, 1H), 4.79 (d, *J* = 14.5 Hz, 1H), 4.34 (d, *J* = 14.5 Hz, 1H), 3.83 (s, 3H), 3.75 – 3.61 (m, 1H), 3.38 – 3.22 (m, 1H), 3.17 – 3.01 (m, 1H), 3.01 – 2.85 (m, 1H), 2.68 (s, 4H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 162.3, 157.4, 145.9, 144.0, 136.0, 135.9, 131.6, 130.8, 130.8, 130.2, 130.0, 129.1, 128.6, 128.0, 124.0, 116.1, 69.5, 61.9, 56.8, 50.3, 30.1, 26.9, 23.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{30}N_3O_6S$ 548.1850; Found 548.1865.

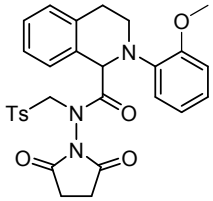
_N_-(1,3-dioxoisoindolin-2-yl)-2-(2-methoxyphenyl)-_N_-(tosylmethyl)-1,2,3,4-tetrahydro

isoquinoline-1-carboxamide (7a):



White solid, 155 mg, 87% yield. m.p. 180–181°C. ^{1}H NMR (300 MHz, DMSO) δ 7.81 (s, 4H), 7.43 (d, *J* = 6.8, 2.2 Hz, 1H), 7.36 – 7.22 (m, 6H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 3H), 5.86 (s, 1H), 4.87 (d, *J* = 14.5 Hz, 1H), 4.08 (d, *J* = 14.6 Hz, 1H), 3.95 (s, 3H), 3.89 – 3.76 (m, 1H), 3.42 – 3.28 (m, 1H), 3.25 – 3.12 (m, 1H), 3.11 – 2.98 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 155.0, 145.2, 138.9, 136.2, 135.6, 132.1, 130.5, 130.4, 130.0, 128.9, 128.6, 127.9, 126.7, 124.9, 124.8, 122.8, 113.0, 69.4, 59.2, 57.0, 48.6, 30.6, 22.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{33}H_{30}N_3O_6S$ 596.1850; Found 596.1860.

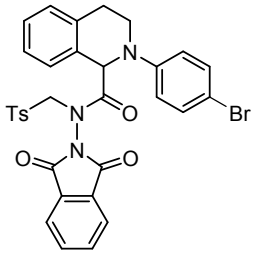
***N*-(2,5-dioxopyrrolidin-1-yl)-2-(2-methoxyphenyl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (7b):**



White solid, 124 mg, 76% yield. m.p. 168–169°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.37 – 7.06 (m, 8H), 7.02 – 6.85 (m, 2H), 5.75 (s, 1H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.13 (d, *J* = 14.4 Hz, 1H), 3.91 (s, 3H), 3.86 – 3.70 (m, 1H), 3.37 – 3.22 (m, 1H), 3.18 – 2.93 (m, 2H), 2.60 (s, 4H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5,

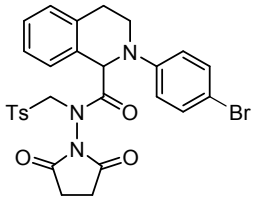
170.0, 162.3, 154.7, 145.8, 138.9, 136.2, 136.0, 131.9, 131.1, 130.8, 130.4, 130.1, 128.9, 128.6, 128.0, 127.8, 126.6, 124.7, 122.8, 112.9, 69.4, 58.7, 56.9, 48.3, 30.4, 26.9, 23.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{30}N_3O_6S$ 548.1850; Found 548.1859.

2-(4-bromophenyl)-*N*-(1,3-dioxoisoindolin-2-yl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (8a):



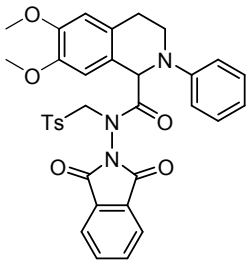
White solid, 145 mg, 75% yield. m.p. 162–164°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 4H), 7.62 – 7.55 (m, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.36 – 7.16 (m, 6H), 6.99 (dd, *J* = 17.0, 8.1 Hz, 4H), 5.55 (s, 1H), 4.78 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.5 Hz, 1H), 3.85 – 3.72 (m, 1H), 3.52 – 3.37 (m, 1H), 3.26 – 3.07 (m, 1H), 3.07 – 2.92 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 148.1, 144.5, 134.8, 132.7, 132.5, 130.0, 129.5, 129.2, 129.0, 128.8, 128.5, 128.4, 127.7, 127.4, 127.2, 124.0, 121.0, 68.4, 59.7, 48.1, 28.8, 21.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{27}N_3O_5SBr$ 644.0849; Found 644.0871.

2-(4-bromophenyl)-*N*-(2,5-dioxopyrrolidin-1-yl)-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (8b):



White solid, 121 mg, 68% yield. m.p. 167–168°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.46 – 7.33 (m, 3H), 7.32 – 7.07 (m, 5H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 4.77 (d, *J* = 14.5 Hz, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.82 – 3.62 (m, 1H), 3.48 – 3.32 (m, 1H), 3.12 – 2.86 (m, 2H), 2.69 (s, 4H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 161.5, 148.9, 146.1, 135.9, 135.7, 133.7, 131.0, 130.9, 130.2, 130.0, 129.4, 128.9, 128.3, 121.7, 69.5, 60.4, 48.8, 29.6, 26.9, 23.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{27}N_3O_5SBr$ 596.0849; Found 596.0855.

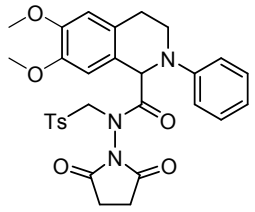
_N_-(1,3-dioxoisoindolin-2-yl)-6,7-dimethoxy-2-phenyl-_N_-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (9a):



Light yellow solid, 125 mg, 67% yield. m.p. 142–144°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 3.2 Hz, 4H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.11 – 7.01 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 2H), 6.64 (s, 1H), 5.45 (s, 1H), 4.70 (d, *J* = 14.8 Hz, 1H), 4.52 (d, *J* = 14.8 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.81 – 3.66 (m, 1H), 3.41 – 3.25 (m, 1H), 3.21 – 3.04 (m, 1H), 2.85 (d, *J* = 15.9 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 149.1, 148.7, 148.3, 144.0, 134.4, 133.8,

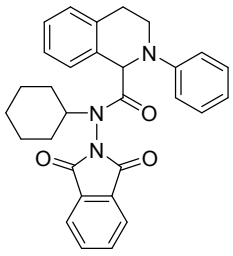
129.5, 129.1, 128.9, 128.3, 126.6, 123.7, 123.5, 123.0, 121.6, 120.3, 110.9, 109.4, 67.9, 59.6, 56.0, 55.8, 49.7, 28.8, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{32}N_3O_7S$ 626.1955; Found 626.1962.

_N_-(2,5-dioxopyrrolidin-1-yl)-6,7-dimethoxy-2-phenyl-_N_-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (9b):



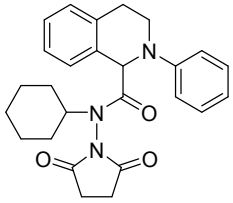
Light yellow solid, 102 mg, 59% yield. m.p. 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.26 (m, 5H), 7.17 (t, J = 8.7 Hz, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (s, 1H), 6.62 (s, 1H), 5.39 (s, 1H), 4.67 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.80 – 3.63 (m, 1H), 3.40 – 3.22 (m, 1H), 3.18 – 3.02 (m, 1H), 2.95 – 2.78 (m, 1H), 2.70 (s, 4H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.14, 162.22, 150.31, 150.04, 149.52, 145.92, 135.69, 130.84, 130.69, 129.60, 127.83, 124.33, 122.93, 121.61, 112.21, 110.74, 69.23, 60.77, 57.20, 57.19, 51.12, 30.09, 26.90, 22.97. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{32}N_3O_7S$ 578.1955; Found 578.1967.

_N_-cyclohexyl-_N_-(1,3-dioxoisoindolin-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (10a):



White solid, 98 mg, 68% yield. m.p. 136–138°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.79 (m, 2H), 7.79 – 7.71 (m, 2H), 7.50 – 7.42 (m, 1H), 7.42 – 7.18 (m, 7H), 6.99 (t, *J* = 7.3 Hz, 1H), 5.78 (s, 1H), 4.01 (dt, *J* = 12.6, 6.5 Hz, 1H), 3.69 – 3.50 (m, 2H), 3.11 (t, *J* = 5.8 Hz, 2H), 1.54 – 0.60 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 152.4, 149.7, 135.1, 134.1, 132.1, 129.5, 129.0, 128.9, 127.4, 126.2, 123.3, 121.4, 119.5, 57.6, 55.5, 45.6, 33.8, 33.1, 28.8, 25.5, 23.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{30}N_3O_3$ 480.2282; Found 480.2296.

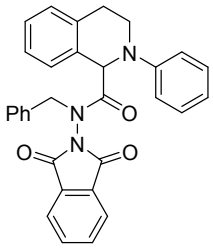
***N*-cyclohexyl-*N*-(2,5-dioxopyrrolidin-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (10b):**



White solid, 46 mg, 35% yield. m.p. 131–132°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.12 (m, 8H), 6.97 (t, *J* = 7.2 Hz, 1H), 5.72 (s, 1H), 4.07 – 3.88 (m, 1H), 3.73 – 3.43 (m, 2H), 3.23 – 2.88 (m, 2H), 2.69 (s, 4H), 1.75 – 1.61 (m, 1H), 1.57 – 1.38 (m, 3H), 1.37 – 1.00 (m, 4H), 0.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 151.7, 149.6, 135.1, 132.0, 129.2, 129.0, 128.8, 127.5, 127.3, 126.2, 121.3, 119.5, 57.5, 55.7, 45.3, 34.0, 33.3, 25.5, 23.8, 23.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{30}N_3O_3$ 432.2282;

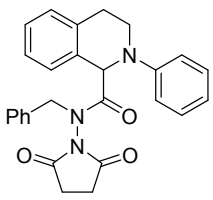
Found 432.2291.

_N_-benzyl-_N_-(1,3-dioxoisoindolin-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (11a):



White solid, 98 mg, 67% yield. m.p. 86–88°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.76 – 7.67 (m, 2H), 7.54 (d, J = 7.0 Hz, 1H), 7.39 – 7.26 (m, 4H), 7.26 – 7.14 (m, 3H), 7.14 – 7.04 (m, 3H), 6.98 (t, J = 7.3 Hz, 1H), 6.84 (s, 2H), 5.80 (s, 1H), 4.60 (d, J = 16.1 Hz, 1H), 4.43 (d, J = 16.2 Hz, 1H), 4.03 – 3.87 (m, 1H), 3.74 – 3.55 (m, 1H), 3.22 – 2.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 157.9, 150.8, 140.6, 136.6, 135.6, 132.9, 130.8, 130.7, 130.2, 129.3, 129.0, 128.8, 128.0, 128.0, 127.6, 124.9, 122.7, 120.0, 59.5, 51.9, 47.8, 30.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{26}N_3O_3$ 488.1969; Found 488.1983.

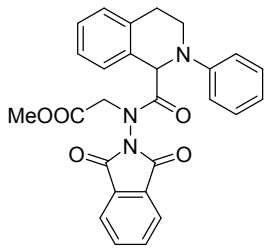
_N_-benzyl-_N_-(2,5-dioxopyrrolidin-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (11b):



White solid, 70 mg, 53% yield. m.p. 117–118°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.39 – 7.08 (m, 10H), 7.06 – 6.87 (m, 3H), 5.74 (s, 1H), 4.60 (d, J = 16.0 Hz, 1H),

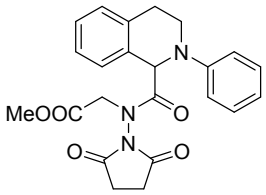
4.44 (d, J = 16.2 Hz, 1H), 4.01 – 3.82 (m, 1H), 3.72 – 3.50 (m, 1H), 3.11 – 2.95 (m, 2H), 2.68 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 157.2, 150.6, 140.9, 136.6, 132.8, 130.7, 130.2, 129.5, 129.0, 128.9, 128.2, 127.9, 127.8, 122.6, 120.0, 59.4, 52.0, 47.6, 29.7, 27.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}N_3O_3$ 440.1969; Found 440.1980.

Methyl *N*-(1,3-dioxoisoindolin-2-yl)-*N*-(2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)glycinate (12a):



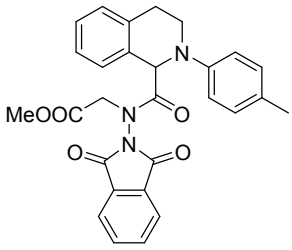
White solid, 102 mg, 72% yield. m.p. 114–116°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.80 (m, 2H), 7.80 – 7.54 (m, 3H), 7.52 – 7.14 (m, 7H), 7.02 (t, J = 7.3 Hz, 1H), 5.66 (s, 1H), 4.14 (d, J = 18.0 Hz, 1H), 4.05 – 3.82 (m, 2H), 3.65 – 3.50 (m, 1H), 3.39 (s, 3H), 3.22 – 3.08 (m, 1H), 3.08 – 2.93 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 170.0, 158.1, 149.4, 135.3, 134.6, 131.3, 129.7, 129.1, 128.1, 128.0, 127.0, 123.9, 122.1, 119.2, 59.2, 51.9, 48.9, 47.6, 28.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{24}N_3O_5$ 470.1710; Found 470.1730.

Methyl *N*-(2,5-dioxopyrrolidin-1-yl)-*N*-(2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)glycinate (12b):



White solid, 78 mg, 62% yield. m.p. 131–132°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 1H), 7.41 – 7.22 (m, 4H), 7.22 – 7.07 (m, 3H), 6.99 (t, *J* = 7.4 Hz, 1H), 5.60 (s, 1H), 4.15 (d, *J* = 18.5 Hz, 1H), 3.94 (d, *J* = 18.5 Hz, 1H), 3.90 – 3.78 (m, 1H), 3.59 (s, 4H), 3.17 – 2.90 (m, 2H), 2.78 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.2, 156.9, 149.3, 135.4, 131.1, 129.7, 129.1, 128.1, 127.0, 121.9, 118.9, 59.1, 52.1, 48.7, 47.3, 28.5, 26.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}N_3O_5$ 422.1710; Found 422.1719.

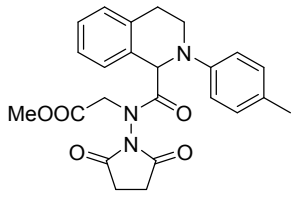
Methyl *N*-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl)glycinate (13a):



White solid, 120 mg, 83% yield. m.p. 140–141°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.81 (m, 2H), 7.81 – 7.63 (m, 3H), 7.50 – 6.99 (m, 7H), 5.61 (s, 1H), 4.15 (d, *J* = 17.9 Hz, 1H), 3.94 (d, *J* = 18.0 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.58 – 3.42 (m, 1H), 3.42 (s, 3H), 3.27 – 3.07 (m, 1H), 3.08 – 2.92 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 157.9, 147.0, 135.0, 134.2, 131.5, 131.0, 129.9, 129.4, 128.8, 127.6, 126.6, 123.5, 119.5, 59.2, 51.5, 48.5, 47.8, 28.6, 20.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd

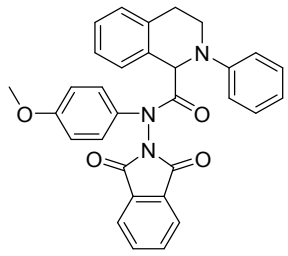
for $C_{28}H_{26}N_3O_5$ 484.1867; Found 484.1879.

Methyl *N*-(2,5-dioxopyrrolidin-1-yl)-*N*-(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline -1-carbonyl)glycinate (13b):



White solid, 99 mg, 76% yield. m.p. 177–179°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.1 Hz, 1H), 7.38 – 7.24 (m, 2H), 7.24 – 7.13 (m, 3H), 7.08 (d, *J* = 8.3 Hz, 2H), 5.54 (s, 1H), 4.18 (d, *J* = 17.6 Hz, 1H), 3.94 (d, *J* = 18.6 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.61 (s, 3H), 3.54 – 3.40 (m, 1H), 3.18 – 2.91 (m, 2H), 2.79 (s, 4H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.9, 156.8, 146.8, 135.0, 131.3, 130.8, 129.9, 128.7, 127.6, 126.6, 119.2, 59.2, 51.7, 48.3, 47.6, 28.3, 25.6, 20.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}N_3O_5$ 436.1867; Found 436.1874.

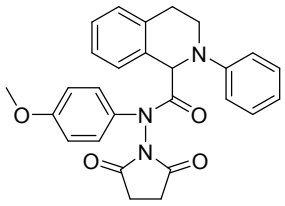
***N*-(1,3-dioxoisoindolin-2-yl)-*N*-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (14a):**



White solid, 100 mg, 66% yield. m.p. 116–117°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 2H), 7.76 – 7.66 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.25 (m, 4H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.10 – 6.88 (m, 3H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.27 (d, *J* = 8.4 Hz, 2H),

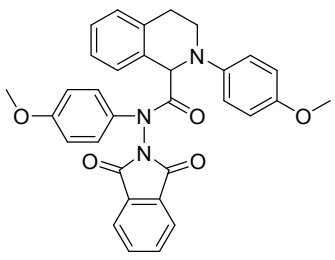
5.71 (s, 1H), 3.74 (s, 4H), 3.62 – 3.47 (m, 1H), 3.10 – 2.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 157.0, 156.4, 149.4, 138.0, 135.7, 134.6, 132.1, 129.5, 129.4, 129.2, 127.9, 127.6, 126.6, 123.9, 121.5, 121.3, 119.4, 114.2, 58.3, 55.8, 44.9, 28.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{26}N_3O_4$ 504.1918; Found 504.1929.

_N_-(2,5-dioxopyrrolidin-1-yl)-_N_-(4-methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (14b):



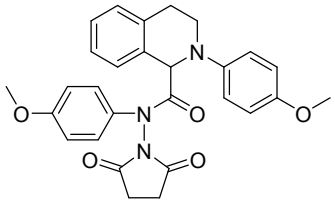
White solid, 78 mg, 57% yield. m.p. 129–131°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 1H), 7.33 – 7.22 (m, 4H), 7.22 – 7.15 (m, 1H), 7.02 – 6.88 (m, 3H), 6.69 (d, J = 8.4 Hz, 2H), 6.32 (d, J = 8.4 Hz, 2H), 5.66 (s, 1H), 3.77 (s, 3H), 3.75 – 3.67 (m, 1H), 3.61 – 3.46 (m, 1H), 3.05 – 2.81 (m, 2H), 2.71 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 156.5, 149.3, 138.0, 135.7, 132.0, 129.3, 129.2, 127.9, 127.7, 126.6, 121.5, 121.1, 119.9, 119.2, 114.3, 58.2, 55.9, 44.8, 28.6, 25.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}N_3O_4$ 456.1918; Found 456.1927.

_N_-(1,3-dioxoisoindolin-2-yl)-_N_,2-bis(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (15a):



White solid, 117 mg, 73% yield. m.p. 140–141°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 2H), 7.79 – 7.68 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.19 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 1H), 3.95 – 3.82 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.50 – 3.35 (m, 1H), 3.12 – 2.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 157.5, 157.0, 144.9, 139.2, 136.6, 135.7, 133.3, 130.6, 130.5, 128.8, 128.5, 127.5, 124.9, 122.7, 115.8, 115.3, 60.8, 57.0, 56.9, 47.6, 30.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{28}N_3O_4$ 518.2074; Found 518.2083.

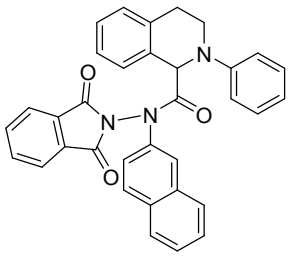
_N_-(2,5-dioxopyrrolidin-1-yl)-_N_,2-bis(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoli ne-1-carboxamide (15b):



White solid, 102 mg, 70% yield. m.p. 124–126°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 4H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.23 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 1H), 4.00 – 3.81 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.47 – 3.33 (m, 1H), 3.10 – 2.86 (m, 2H), 2.74 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 155.6, 155.0, 142.9, 137.2, 134.6, 131.2, 128.5, 126.8, 126.6, 125.5, 122.8, 120.7, 113.7, 113.4, 58.6, 55.0, 54.9, 45.4, 28.2, 25.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}N_3O_4$ 470.2074; Found 470.2080.

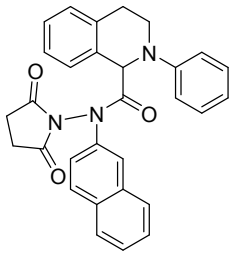
_N_-(1,3-dioxoisoindolin-2-yl)-_N_-(naphthalen-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoquin

oline-1-carboxamide (16a):



White solid, 77 mg, 49% yield. m.p. 92–94°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.79 (m, 2H), 7.78 – 7.66 (m, 3H), 7.65 – 7.56 (m, 2H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.26 (m, 6H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.13 – 7.02 (m, 3H), 6.56 (d, *J* = 8.0 Hz, 2H), 5.74 (s, 1H), 3.77 – 3.62 (m, 1H), 3.58 – 3.41 (m, 1H), 3.05 – 2.88 (m, 1H), 2.88 – 2.71 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 156.7, 149.1, 142.0, 135.6, 135.3, 134.3, 133.5, 131.7, 130.3, 129.1, 128.9, 128.2, 127.6, 127.5, 127.3, 127.2, 126.4, 126.1, 124.5, 123.6, 121.3, 121.0, 119.4, 116.0, 58.5, 44.9, 28.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{34}H_{26}N_3O_3$ 524.1969; Found 524.1983.

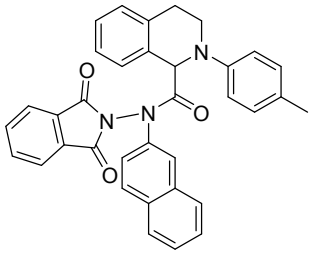
***N*-(2,5-dioxopyrrolidin-1-yl)-*N*-(naphthalen-2-yl)-2-phenyl-1,2,3,4-tetrahydroisoqui noline-1-carboxamide (16b):**



White solid, 76 mg, 53% yield. m.p. 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.35 (m, 4H), 7.39 – 7.20 (m, 4H), 7.18 (d, *J* = 6.1 Hz, 1H), 7.06 – 6.90 (m, 3H), 6.66 – 6.51 (m, 2H), 5.66 (s, 1H), 3.74 – 3.59

(m, 1H), 3.53 – 3.39 (m, 1H), 3.02 – 2.83 (m, 1H), 2.86 – 2.62 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.64, 156.04, 149.36, 142.34, 135.67, 133.88, 131.91, 130.71, 129.41, 129.18, 128.64, 127.97, 127.86, 127.70, 127.60, 126.64, 126.55, 124.94, 121.45, 121.31, 119.60, 116.42, 58.72, 45.02, 28.75, 25.93. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{26}N_3O_3$ 476.1969; Found 476.1977.

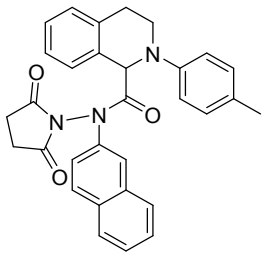
_N_-(1,3-dioxoisoindolin-2-yl)-_N_-(naphthalen-2-yl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (17a):



White solid, 97 mg, 60% yield. m.p. 151–153°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 – 7.68 (m, 3H), 7.58 (t, *J* = 8.3 Hz, 3H), 7.52 – 7.28 (m, 5H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.57 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.48 (s, 1H), 5.63 (s, 1H), 3.87 – 3.68 (m, 1H), 3.55 – 3.37 (m, 1H), 3.05 – 2.87 (m, 1H), 2.87 – 2.74 (m, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 156.4, 146.5, 141.5, 134.7, 133.8, 132.9, 131.2, 130.7, 129.8, 129.1, 128.6, 128.4, 127.6, 127.0, 126.9, 126.7, 126.6, 125.7, 125.5, 123.9, 123.1, 120.5, 120.0, 115.6, 58.5, 44.8, 28.2, 20.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{28}N_3O_3$ 538.2125; Found 538.2135.

_N_-(2,5-dioxopyrrolidin-1-yl)-_N_-(naphthalen-2-yl)-2-(p-tolyl)-1,2,3,4-tetrahydroisoqui

noline-1-carboxamide (17b):



White solid, 106 mg, 72% yield. m.p. 141–142°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.25 (m, 6H), 7.19 (d, *J* = 6.6 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.61 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.52 (s, 1H), 5.58 (s, 1H), 3.80 – 3.67 (m, 1H), 3.48 – 3.37 (m, 1H), 3.02 – 2.86 (m, 1H), 2.86 – 2.67 (m, 5H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.74, 157.36, 148.39, 143.48, 136.72, 134.96, 133.05, 132.48, 131.76, 131.03, 130.32, 129.64, 128.93, 128.69, 128.65, 127.61, 127.54, 125.96, 122.42, 121.77, 117.64, 60.26, 46.56, 29.96, 27.01, 22.09. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{28}N_3O_3$ 490.2125; Found 490.2131.

Gram-Scale Preparation of compound 3a and 3b

A 100 mL flask was charged with the **1a** (628 mg, 3 mmol), TosMIC (644 mg, 3.3 mmol), NHPI (538 mg, 3.3 mmol) and DCM (30 mL). To the flask was added DEAD (0.52 mL, 3.3 mmol) dropwise. The resulting mixture was then stirred at room temperature. The reaction was monitored by TLC until complete consumption (12h). The residue was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine and dried over Na_2SO_4. After the organic phase removed under reduced pressure, the resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1–2:1) to give

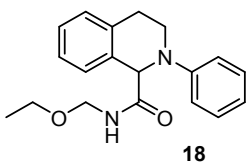
the desired product **3a** (three runs: 1.46 g, 86.0%; 1.42 g, 83.7%; 1.51 g, 89.0%; Average yield: 86%).

A 100 mL flask was charged with the **1a** (628 mg, 3 mmol), TosMIC (644 mg, 3.3 mmol), NHS (380 mg, 3.3 mmol) and DCM (30 mL). To the flask was added DEAD (0.52 mL, 3.3 mmol) dropwise. The resulting mixture was then stirred at room temperature. The reaction was monitored by TLC until complete consumption (12h). The residue was washed with saturated $NaHCO_3$ (3 x 20 mL) and brine and dried over Na_2SO_4. After the organic phase removed under reduced pressure, the resulting residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1–1:1) to give the desired product **3b** (three runs: 1.29 g, 83.1%; 1.31 g, 84.4%; 1.21 g, 77.9%; Average yield: 82%).

Synthesis of compound 18

A suspension of **3a** (170 mg, 0.3 mmol) in EtOH (6 mL) was added solid NaOH (24 mg, 0.6 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 24 h. The solvent was directly removed under vacuum. The residue was extracted with ethyl acetate and combined organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1-2:1) to give **18**.

***N*-(ethoxymethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (18):**



18

Colorless glass, 75 mg, 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.59 (m, 1H),

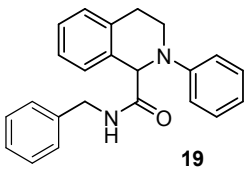
7.52 (t, J = 6.8 Hz, 1H), 7.42 – 7.24 (m, 4H), 7.24 – 7.14 (m, 1H), 7.07 – 6.89 (m, 3H), 5.08 (s, 1H), 4.84 – 4.60 (m, , 2H), 3.90 (dt, J = 11.3, 4.6 Hz, 1H), 3.51 – 3.27 (m, 3H), 3.22 – 2.92 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 149.2, 134.5, 132.3, 129.4, 128.8, 127.7, 127.5, 126.7, 119.9, 114.9, 69.9, 65.4, 63.8, 45.3, 28.8, 14.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}N_2O_2$ 311.1754; Found 311.1765.

Synthesis of compound 19

Method A: A suspension of **11a** (146 mg, 0.3 mmol) in EtOH (6 mL) was added solid NaOH (24 mg, 0.6 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 24 h. The solvent was directly removed under vacuum. The residue was extracted with ethyl acetate and combined organic phase was concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1-1:1) to give **19**.

Method B: A suspension of **11a** (146 mg, 0.3 mmol) in methanol (3 mL) was added 0.2 mL hydrazine hydrate (80%). The reaction was stirred at room temperature for 12 h. The solvent was directly removed under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1-1:1) to give **19**.

2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carbohydrazide (19):



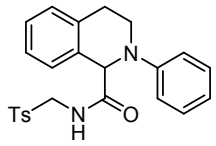
19

Brown glass, 79mg, 77% yield (method A); 65 mg, 63% yield (method B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.62 (m, 1H), 7.42 – 7.17 (m, 8H), 7.14 – 7.03 (m, 2H), 7.03 – 6.88 (m, 3H), 5.12 (s, 1H), 4.57 – 4.32 (m, 2H), 3.87 (dt, *J* = 11.1, 4.5 Hz, 1H), 3.35 (td, *J* = 10.7, 4.2 Hz, 1H), 3.20 – 2.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 148.8, 137.6, 133.9, 132.1, 128.8, 128.3, 128.0, 127.1, 126.9, 126.8, 126.7, 126.2, 119.2, 114.4, 65.0, 44.7, 42.9, 28.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O$ 343.1805; Found 343.1818.

Synthesis of compound 20

A solution of **3a** (170 mg, 0.3 mmol) in DCE (3 mL) was added $AlCl_3$ (120 mg, 0.9 mmol). The reaction was stirred at room temperature for 48 h. The suspention was quenched with 10% NaOH under ice cooling, and the aqueous layer was extracted with ethyl acetate and combined organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 5:1-2:1) to give **20**.

2-phenyl-*N*-(tosylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (20):



20

White solid, 74 mg, 59% yield. m.p. 110–112°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, *J* = 7.0 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.13 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 2H), 5.11 – 4.77 (m, 2H), 4.32 (dd, *J* = 14.2,

5.7 Hz, 1H), 4.09 – 3.88 (m, 1H), 3.39 – 3.11 (m, 2H), 3.11 – 2.94 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 150.5, 146.2, 136.2, 135.1, 133.2, 131.1, 130.9, 130.3, 129.7, 129.1, 129.0, 128.1, 121.4, 116.0, 66.9, 61.4, 46.2, 30.4, 23.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}N_2O_3S$ 421.1580; Found 421.1593.

ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for all compounds are prepared. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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