JOC The Journal of Organic Chemistry

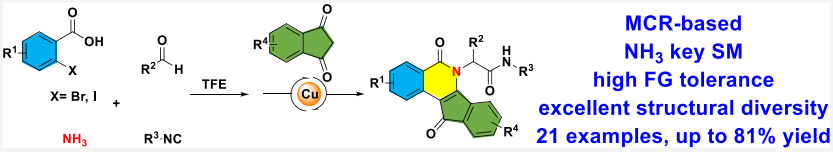
pubs.acs.org/joc Article

Copper-Catalyzed Modular Assembly of Polyheterocycles

Qian Wang, Jesse Tuinhof, Kumchok C. Mgimpatsang, Katarzyna Kurpiewska, Justyna Kalinowska-Tluscik, and Alexander Dömling*

Cite This: J. Org. Chem. 2020, 85, 9915−9927 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Easy operation, readily accessible starting materials, and short syntheses of the privileged scaffold indeno[1,2-*c*]isoquinolinone were achieved by an multicomponent reaction (MCR)-based protocol via an ammonia−Ugi-four component reaction (4CR)/copper-catalyzed annulation sequence. The optimization and scope and limitations of this short and general sequence are described. The methodology allows an efficient construction of a wide variety of indenoisoquinolinones in just two steps.

INTRODUCTION

The quest for novel synthetic routes for nitrogen (N)-containing heterocycles using atom-economical and efficient pathways is an active field in synthetic chemistry nowadays. This is due to widespread applications of N-containing heterocycles in almost all branches of organic chemistry including active pharmaceutical research,[1] functional materials,[2] catalysis,[3] and coordination chemistry.[4] Among the N-containing heterocycles, the indenoisoquinoline is a highly valuable scaffold, endowed with inhibition activities against topoisomerase I (Topo1)[5] in clinical testing with improved physicochemical and biological properties as compared to the clinically used camptothecin anticancer drugs, topotecan and irinotecan.[6] Several indenoisoquinolines, such as indotecan (LMP400, Figure 1A), have entered phase I clinical trials.[7]

The Ugi reaction is one of the most prominent multicomponent reaction (MCR) families.[8] It has attracted much attention due to the possibility of introducing versatile functional groups in the Ugi adducts, which can undergo further condensations or cyclization reactions, leading to an array of structurally diverse scaffolds.[9] Specifically, the Ugi four-component reaction (Ugi-4-CR) utilizing ammonia as the amine component can be an extremely valuable approach because it is inexpensive, is easily available, and permits reduced waste. However, relatively fewer studies have focused on it, most of which report an excessive byproduct formation and low yield (Figure 1B−D).[10]

Nowadays, introducing cleaner, safer, and easier accessible nitrogen donors to N-containing organic compounds is an extensively studied topic.[11] In 2009, the Chen group reported a simple, one-step assembly of Ugi adducts suitable for elaboration into a variety of 5-aminoazole compounds through postcondensation modifications by employing concentrated aqueous ammonia as a convenient source (Figure 1B).[10] Hutton et al. synthesized ustiloxin D utilizing an ammonia−Ugi reaction (Figure 1C).[12] Recently, Polindara-García and his colleagues developed a novel protocol for the fast introduction of the picolinamide directing group in aliphatic ketones using the ammonia−Ugi 4-CR reaction and the subsequent Pd-mediated γ-C(sp^3)−H bond activation (Figure 1D).[13]

Ullmann−Hurtley condensations are powerful tools for the formation of carbon−heteroatom and carbon−carbon bonds in the construction of a wide variety of heterocycles.[14] In 2012, Zhao et al. reported the synthesis of indolo[2,1-*b*]quinazoline derivatives via copper-catalyzed Ullmann-type intermolecular C−C and intramolecular C−N couplings.[14c] In 2016, a series of isoquinoline derivatives were synthesized, with high chemo- and regioselectivities, via the copper-catalyzed cascade reaction of 2-haloaryloxime acetates with β-diketones, β-keto esters, and β-keto nitriles.[14f] In addition, an Ugi-type MCR/copper-catalyzed annulation sequence has been an important strategy, leading to high structural diversity and molecular complexity.[15] Inspired by the remarkable progress of this key reaction achieved and based on our ongoing interest in MCR chemistry,[9,16] we envisioned that indeno[1,2-*c*]isoquinolinone derivatives could be alternatively synthesized in a concise manner by an Ugi reaction of *o*-halobenzoic acids and ammonia, followed by a Cu-catalyzed annulation reaction with 1,3-indandione (Figure 1E).

Received: May 22, 2020
Published: July 3, 2020

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

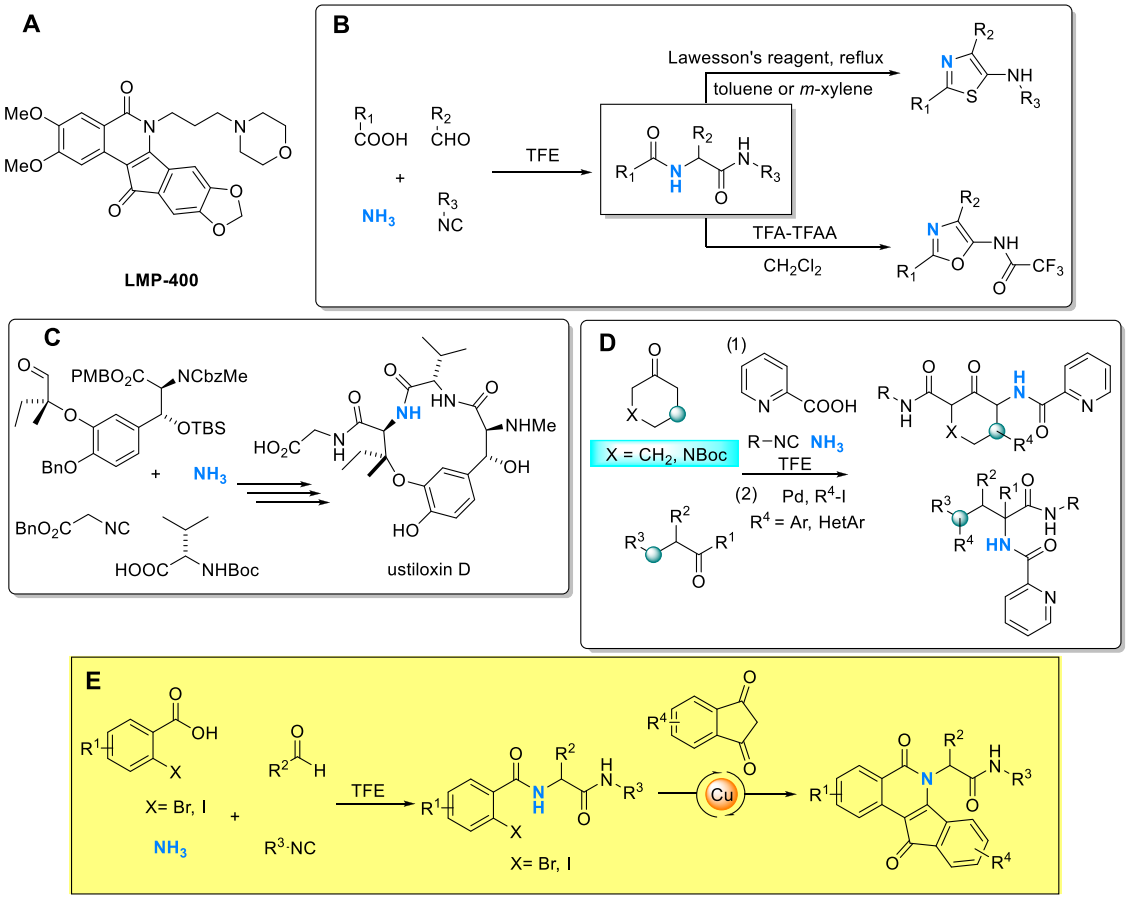


Figure 1. (A) Clinical Topo1 inhibitor LMP-400; (B) Ugi reactions with ammonia, yielding 5-aminothiazole and oxazole derivatives; (C) synthesis of ustiloxin D utilizing an ammonia–Ugi reaction; (D) Pd-mediated C(sp^3)–H bond activation in ammonia–Ugi 4-CR adducts; and (E) *our work*: copper-catalyzed arylation of 1,3-indandione of ammonia–Ugi 4-CR adducts.

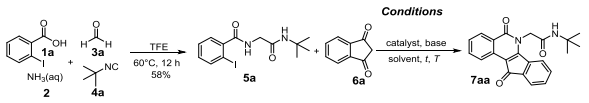
RESULTS AND DISCUSSION

The Ugi adduct model **5a** was readily obtained in 58% yield by reacting equimolar quantities of 2-iodobenzoic acid **1a**, paraformaldehyde **3a**, and *tert*-butyl isocyanide **4a** with an excess of an aqueous ammonia solution (1.2 equiv) **2** in 2,2,2-trifluoroethanol (TFE) under 60 °C for 12 h in a closed vial. Thereafter, we investigated the copper-catalyzed tandem reaction and optimized the reaction conditions by variation of the Cu source, base, solvent, time, and temperature (Table 1). When the reaction was carried out with 1,3-indandione **6a** (1 equiv) in the presence of 5 mol % $CuCl_2$ using 2.0 equiv of K_2CO_3 as the base in MeCN at 90 °C for 3 h, the desired product **7aa** was obtained in 61% yield (entry 1). Cs_2CO_3 (65% yield, entry 2) was superior to K_2CO_3 and was selected as the base for further studies. To our delight, the desired product **7aa** was formed in 70% yield with the addition of 1.5 equiv of 1,3-indandione **6a** (entry 3). Increasing the amount of **6a** to 2.0 equiv afforded **7aa** in 68% yield (entry 4). However, replacing the catalyst with CuI, $CuSO_4$, CuCl, CuBr, $CuBr_2$, $Cu(NO_3)_2$, Cu_2O, and CuCN resulted in lower yields of **7aa** of 49, 32, 44, 23, 25, 36, 64, and 57%, respectively (entries 5–12). The yield of **7aa** decreased to 62% at a temperature of 80 °C (entry 13). Also, a higher temperature of 100 °C did not increase the yield (entry 14). Variation of solvents yielded the following: a moderate yield of the product was obtained (42%) when dioxane was chosen as the solvent (entry 15), while no reaction at all occurred when toluene was used (entry 16). Moreover, a trace amount of products was produced in polar aprotic solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (entries 17 and 18). Finally, MeCN was the best solvent for this reaction among the selected solvents (entry 3 vs entries 15–18). Decreasing and increasing the reaction time did not help in improving the outcome of the product (entries 19 and 20). Notably, 35% yield was obtained when the reaction was run in the microwave irritation for 1 h (entry 21). Finally, the optimized reaction conditions were concluded to be the Ugi intermediate **5a** (0.3 mmol), 1,3-indandione **6a** (0.45 mmol), 5 mol % $CuCl_2$, and 2.0 equiv of Cs_2CO_3 in MeCN (4 mL) at 90 °C for 3 h (entry 3).

With the optimal conditions in hand, a set of Ugi products were synthesized in moderate to good yields and were examined to determine the scope of the tandem reaction to furnish the corresponding products **7a–t** (Scheme 1). All of the substrates **1–6** led to the expected indeno[1,2-*c*]-isoquinolinone products **7a–t** in just two simple steps. We initially replaced 1,3-indanedione with 5,6-dimethoxy-1,3-indanedione, and the reaction proceeded smoothly to afford the corresponding indenoisoquinoline derivatives in good yield (**7ab**). Paraformaldehyde was utilized in many cases and resulted in moderate to good yields (**7a–e**, **7n**, **7t**). Further, various aliphatic aldehydes including acetaldehyde (**7f**), isobutyraldehyde (**7g**), butyraldehyde (**7h**), 3-methylbutanal (**7i**), cyclopentanecarbaldehyde (**7j**), 3-phenylpropanal (**7k**), and 3-(methylthio)propanal (**7r**) proceeded well in this MCR

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915–9927

Table 1. Optimization of Reaction Conditions[a,b]



entry	6a (eq.)	catalyst	base	solvent	time (h)	t (°C)	yield 7aa[c] (%)
1	1.0	$CuCl_2$	K_2CO_3	MeCN	3	90	61
2	1.0	$CuCl_2$	Cs_2CO_3	MeCN	3	90	65
3	1.5	$CuCl_2$	Cs_2CO_3	MeCN	3	90	70
4	2.0	$CuCl_2$	Cs_2CO_3	MeCN	3	90	68
5	1.5	CuI	Cs_2CO_3	MeCN	3	90	49
6	1.5	$CuSO_4$	Cs_2CO_3	MeCN	3	90	32
7	1.5	CuCl	Cs_2CO_3	MeCN	3	90	44
8	1.5	CuBr	Cs_2CO_3	MeCN	3	90	23
9	1.5	$CuBr_2$	Cs_2CO_3	MeCN	3	90	25
10	1.5	$Cu(NO_3)_2$	Cs_2CO_3	MeCN	3	90	36
11	1.5	Cu_2O	Cs_2CO_3	MeCN	3	90	64
12	1.5	CuCN	Cs_2CO_3	MeCN	3	90	57
13	1.5	$CuCl_2$	Cs_2CO_3	MeCN	3	80	62
14	1.5	$CuCl_2$	Cs_2CO_3	MeCN	3	100	65
15	1.5	$CuCl_2$	Cs_2CO_3	dioxane	3	90	42
16	1.5	$CuCl_2$	Cs_2CO_3	toluene	3	90	N.D.[d]
17	1.5	$CuCl_2$	Cs_2CO_3	DMF	3	90	trace
18	1.5	$CuCl_2$	Cs_2CO_3	DMSO	3	90	trace
19	1.5	$CuCl_2$	Cs_2CO_3	MeCN	2	90	58
20	1.5	$CuCl_2$	Cs_2CO_3	MeCN	4	90	66
21[e]	1.5	$CuCl_2$	Cs_2CO_3	MeCN	1	90	35

[a]Reaction conditions: **5a** (0.3 mmol), **6a**, catalyst (5 mmol %), base (0.6 mmol), solvent (4 mL). [b]TFE = 2,2,2-trifluoroethanol. [c]Isolated yields. [d]N.D. = not detected. [e]Microwave. Green color indicates best condition screened.

and tandem reaction. We found that aromatic aldehydes bearing weak electron-withdrawing groups such as 4-Br and 4-Cl led to derivatives **7o** and **7s** in good yields. Similarly, the use of benzaldehyde and an electron-donating group 4-OMe in the aromatic aldehyde was compatible in this process to deliver the products in good yields (**7p**, **7m**). Heterocyclic pyridine aldehydes demonstrated good behavior in the Cu-mediated reaction and furnished **7q** in good yield (65%). In addition, commercially available 5-methoxy-, 4-methoxy-, 5-methyl-, 4-methyl-, and 4-nitro-substituted 2-bromobenzoic acid reacted to give the expected product **7n**–**t** in moderate to good yields.

After successfully demonstrating the cyclization reactions with different aldehydes and 2-halogenbenzoic acids, we then examined indandione with various Ugi adducts by simply changing the isocyanide pool in the MCR and then studying the subsequent annulation. Benzyl isocyanide (**7d**, **7j**, **7n**) and substituted benzyl isocyanides with electron-donating and -withdrawing groups like 4-chloro (**7e**), 2,3-dimethoxy (**7i**) and 4-cyano (**7p**) reacted smoothly with 40, 75, 62, 80, 72, and 35% yields, respectively. Isocyanobenzene containing valuable functional groups such as ethyl and anisole was also applied and gave the corresponding products in good yields (**7h**, **7f**). Similarly, (2-isocyanoethyl)benzene (**7o**) and methyl 2-isocyanoacetate (**7l**) also furnished the different indeno[1,2-*c*]isoquinolinone products in 49 and 59% yields, respectively. In addition, aliphatic linear (**7b**), cyclic (**7c**) and branched isocyanides like *tert*-butyl isocyanide (**7a**, **7g**, **7m**, **7q**–**t**) and *tert*-octyl isocyanide (**7k**) also yielded different tetraheterocycles. Scheme 1 clearly indicates that there are no electronic or steric effects on the outcome of the reaction.

We also introduced ortho halo heterocyclic carboxylic acids such as 2-chloroquinoline-3-carboxylic acid and 2-bromothiophene-3-carboxylic acid in the Ugi reaction, which reacted with 25% ammonia solution **2**, paraformaldehyde **3a**, and *tert*-butyl isocyanide **4a** instead of a benzoic acid component to deliver products **5u** and **5v**. Following the present protocol, it is interesting that under optimized reaction conditions, the former substrate **5u** provided the corresponding pentacyclic multiheterocyclic compound *N*-(*tert*-butyl)-2-(6,13-dioxo-6,13-dihydro-5*H*-benzo[*b*]indeno[1,2-*h*][1,6]naphthyridin-5-yl)acetamide (**7u**) in good yield. However, the latter substrate **5v** afforded the tetracyclic compound *N*-(*tert*-butyl)-2-(4,10-dioxo-4,10-dihydro-5*H*-indeno[1,2-*b*]thieno[2,3-*d*]pyridin-5-yl)acetamide (**7v**) in moderate yield (Scheme 2).

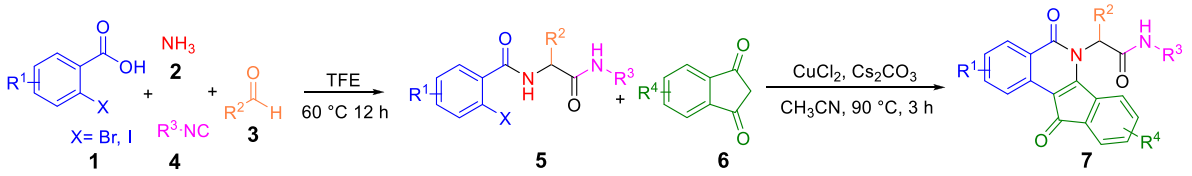
Furthermore, the scalability of this method was investigated (Scheme 3A). A four-component reaction of 2-iodobenzoic acid, ammonia, cyclopentanecarbaldehyde, and benzyl isocyanide was conducted on a 5 mmol scale, which further reacted with 1,3-indandione, while the polyheterocyclic product **7j** could be obtained in 40% overall yield (0.93 g). To further underscore the usefulness of the herein described indeno[1,2-*c*]isoquinolinones, we performed several late-stage functionalizations (Scheme 3). The bromo group of **7o** was coupled with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid to give the derivate **8** by a Suzuki reaction (Scheme 3B). In another application, product **7p** was reacted with sodium azide to afford tetrazole **9** in good yield (Scheme 3C). Finally, while reducing the nitro group of product **7t** with Pd/C, a mixture of **10** and the major overreductive product **11** (Supporting Information) was obtained. Therefore, we chose $SnCl_2$ for the selective reduction of a nitro group to deliver **10** in excellent yield (96%) and used it for further coupling (Scheme 3D). The intriguing scaffold urea **12** was successfully achieved by reacting **10** with (isocyanatomethyl)benzene in a cosolvent system.[17] In addition, we also coupled **10** with Boc-L-phenylalanine to afford a starting point for peptide synthesis. This effort was initially hindered by the lack of reactivity of **10** under standard amide coupling conditions (*N*,*N*′-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU), 1′-carbonyldiimidazole (CDI), etc.). A phosphorous oxychloride-mediated amide-bond-forming protocol was utilized for the formation of the desired product **13** in good yield.[18] Such kind of derivatives could be potentially useful as fluorescent tags to follow a peptide in biological material.

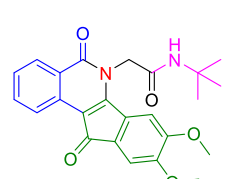
The crystal structure of compound **7aa** is shown in Figure 2, which unambiguously supports our chemistry (Figure 2). The structure features the high planarity of the tetracyclic structure and an intermolecular hydrogen bonding between two adjacent molecules.

A plausible mechanism of this tandem reaction is hypothesized and shown in Scheme 4. The reaction is presumably initiated with the reaction of Cu(I) active species, which was present in copper salts and 1,3-indandione **6a** to produce intermediate **A**, and the oxidative addition of the Ugi adduct 2-iodo-*N*-phenylbenzamide **5a** to this copper(I) complex results in the formation the Cu(III) intermediate **B**, which is further converted into intermediate **C** via reductive elimination. The intramolecular addition of the amide nitrogen to the carbonyl group in intermediate **C** gives intermediate **D**, which is then converted into **7aa** by dehydration.

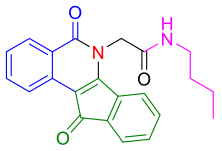
https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

Scheme 1. Ammonia–Ugi Reaction and the Subsequent Copper-Catalyzed Tandem Reaction[a,b,c]

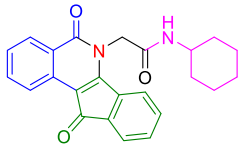




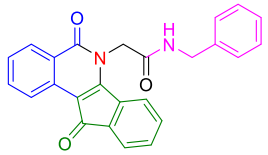
5a, 58%;
7ab, 64%



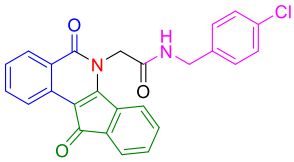
5b, 49%;
7b, 68%



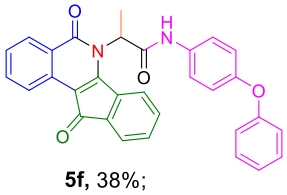
5c, 45%;
7c, 52%



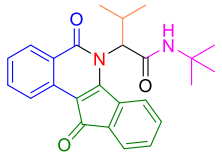
5d, 36%;
7d, 40%



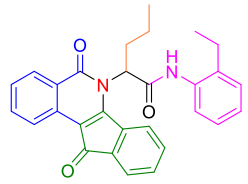
5e, 60%;
7e, 80%



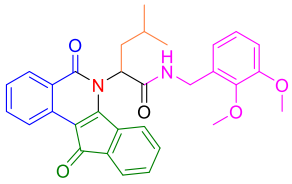
5f, 38%;
7f, 66%



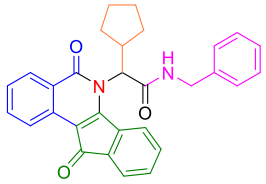
5g, 40%;
7g, 61%



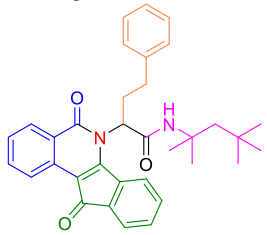
5h, 54%;
7h, 69%



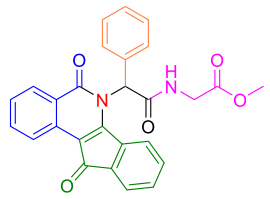
5i, 39%;
7i, 72%



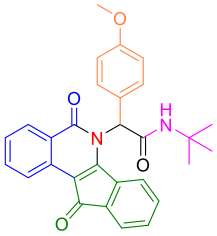
5j, 62%;
7j, 75%



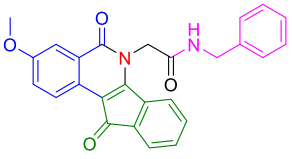
5k, 55%;
7k, 65%



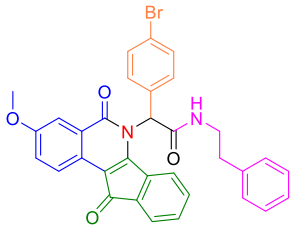
5l, 34%;
7l, 59%



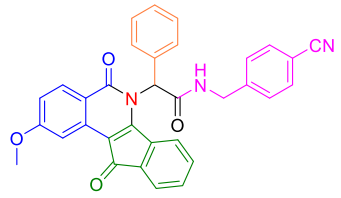
5m, 38%;
7m, 56%



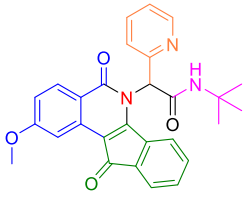
5n, 42%;
7n, 62%



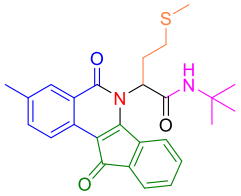
5o, 51%;
7o, 49%



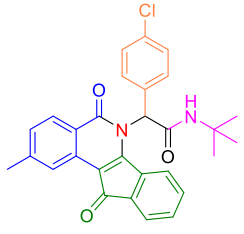
5p, 64%;
7p, 35%



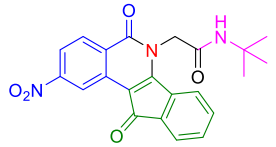
5q, 28%;
7q, 65%



5r, 32%;
7r, 63%



5s, 40%;
7s, 59%

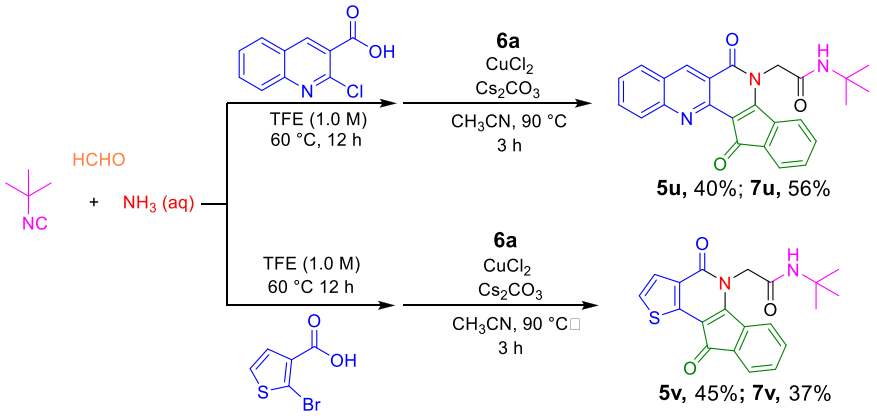


5t, 30%;
7t, 81%

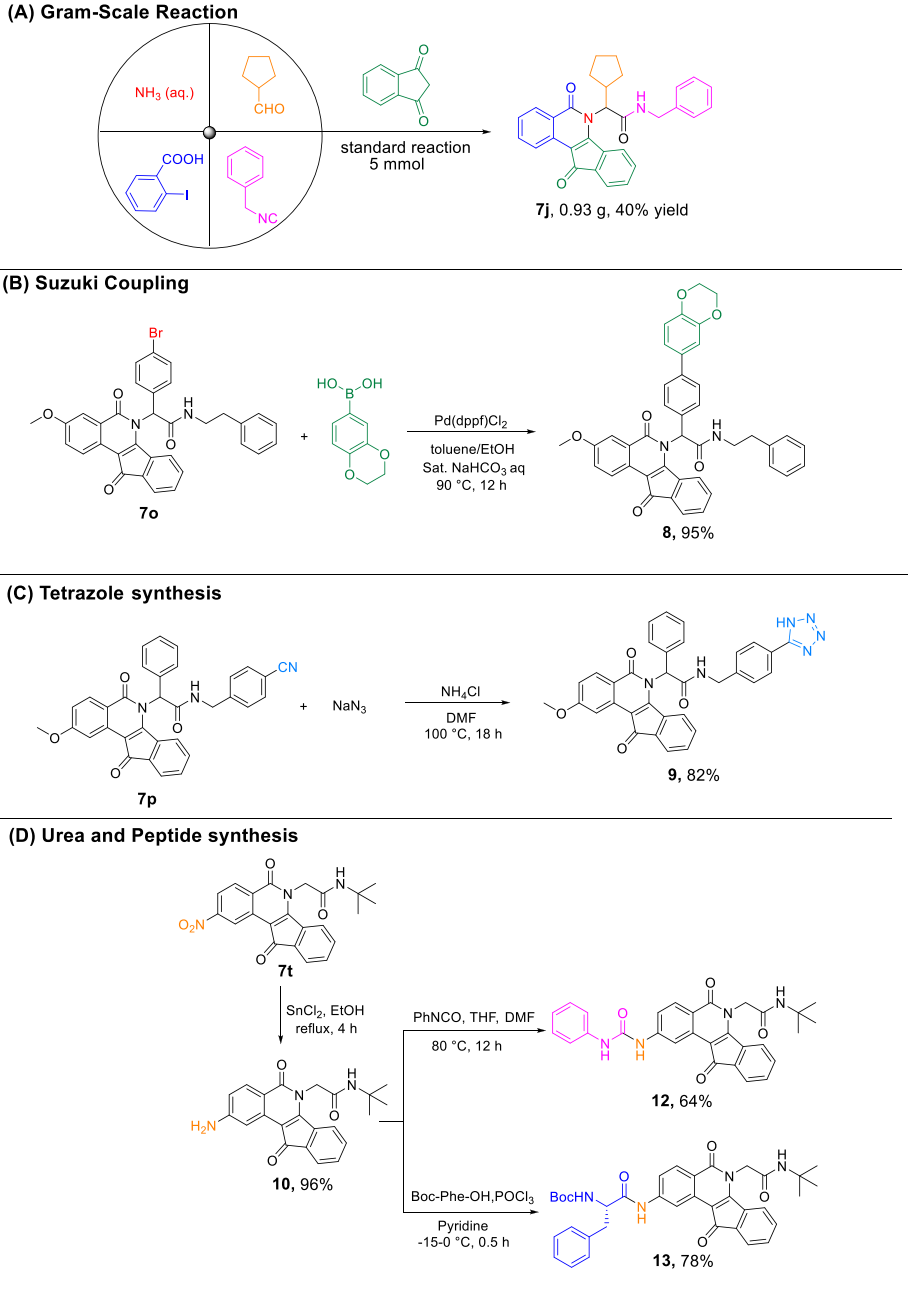
[a]The Ugi reaction was carried out using **1** (2.0 mmol), **2** (2.4 mmol), **3** (2.0 mmol), and **4** (2.0 mmol) in CF_3CH_2OH (1.0 M) for 12 h at 60 °C. [b]Reaction conditions: **5** (0.3 mmol), **6** (0.45 mmol), Cs_2CO_3 (0.6 mmol), $CuCl_2$ (0.015 mmol), CH_3CN (4 mL), 90 °C, 3 h. [c]Yield refers to the purified products. First yield refers to the Ugi reaction and second yield to the cyclization.

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915–9927

Scheme 2. Synthesis of Heterocyclic Fused Indenopyridone Derivatives



Scheme 3. Gram-Scale Reaction and Synthetic Applications



https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

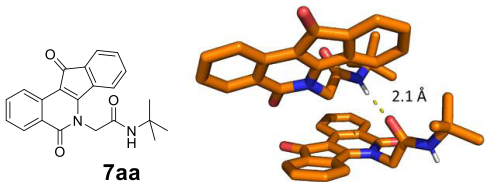


Figure 2. Crystal structure of **7aa** (CCDC 1991899) featuring a dimer and an intermolecular hydrogen bond between the NH of one molecule and the CO of the neighboring molecule of 2.1 Å length.

CONCLUSIONS

Our work features the development of an efficient route for the synthesis of a bioactive indenoisoquinoline library by incorporating a copper-catalyzed tandem reaction with the step-economical, high-yielding ammonia–Ugi MCR. Diversity can be achieved through the aldehyde, isocyanide, and 2-halogen benzoic acid components. This protocol offers a rapid approach to the indenoisoquinolinone scaffold, along with the achievement of remarkable structural diversity and brevity. The process is a simple operation, which uses readily available starting materials and provides good scalability. Furthermore, the current protocol was successfully extended to the synthesis of other benzo-1,4-dioxane-, urea-, and peptide-containing and tetrazolo indenoisoquinolinone cores, thus aiding future structure–activity relationship (SAR) studies for discovering potent and selective Topo1 inhibitors.

EXPERIMENTAL SECTION

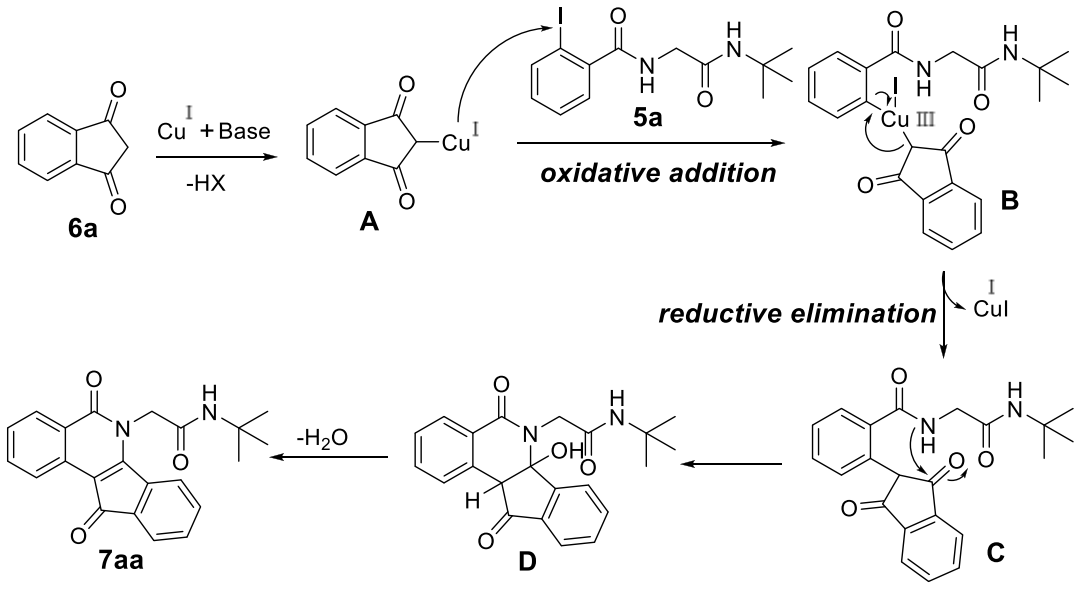
General Information. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts for ^{1}H NMR are reported relative to tetramethylsilane (TMS) (δ 0 ppm) or an internal solvent peak ($CDCl_3$ δ 7.26 ppm, CD_3OD δ 3.31 ppm or D_2O δ 4.79 ppm), and coupling constants are in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dt = double triplet, ddd = doublet of double doublet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in parts per million (ppm) relative to the solvent peak ($CDCl_3$ δ 77.23 ppm, DMSO δ 39.52 ppm, CD_3OD δ 49.00 ppm). Filtrations were performed on a silica bed (Screening Devices BV, 60–200 μm, 60 Å). Flash chromatography was performed on a Grace Reveleris X2 using Grace Reveleris silica columns (12 g), and a gradient of petroleum ether/ethyl acetate (0–100%) or dichloromethane/methanol (0–20%) was applied. Thin-layer chromatography (TLC) was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Reagents were available from commercial suppliers and used without any purification unless otherwise noted. All isocyanides were made in house by performing the Ugi procedure. Other reagents were purchased from Sigma-Aldrich, ABCR, Acros, Fluorochem, and AK Scientific and were used without further purification. Mass spectra were recorded on a Waters investigator supercritical fluid chromatograph with a 3100 MS detector (electrospray ionization (ESI)) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 × 250 mm^2, 5 μm particle size) and are reported as (m/z). High-resolution mass spectra (HRMS) were recorded using an LTQ-Orbitrap-XL (Thermo Fisher Scientific; ESI pos. mode) at a resolution of 60 000@m/z400. Melting points were obtained on a melting point apparatus and were uncorrected. Yields given refer to chromatographically purified compounds unless otherwise stated.

General Experimental Procedure and Characterization. *General Procedure A.* A calculated volume of a 25% ammonia solution (2.4 mmol) was added to a stirred solution or suspension of the carboxylic acid (2 mmol) in 2,2,2-trifluoroethanol (2 mL). The aldehyde (2 mmol) and isocyanide (2 mmol) were then introduced, and stirring was continued at 60 °C in a close screwed vial in a heating metal block overnight. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography to give the desired product **5**.

General Procedure B. Ugi adduct **5** (0.3 mmol), indandione **6** (0.45 mmol), and Cs_2CO_3 (0.6 mmol) were added to a 10 mL round-bottom flask equipped with a magnetic stir bar, and 4 mL of acetonitrile was added. The mixture was heated to 90 °C in an oil bath for 5 min, and then $CuCl_2$ (0.0015 mmol) was added and reacted for 3 h. The progress of the reaction was monitored by TLC for the disappearance of **5**. After the reaction was completed, the solvent was removed by rotary evaporation and the crude was product purified by column chromatography to give the desired product **7**.

Gram-Scale Synthesis of 7j. An oven-dried 50 mL flask equipped with a magnetic stirrer bar was charged with a calculated volume of a 25% ammonia solution (5.5 mmol) and 2-iodobenzoic acid (5 mmol) in 2,2,2-trifluoroethanol (5 mL). Then, cyclopentanecarbaldehyde (5 mmol) and benzyl isocyanide (5 mmol) were added to the solution and the reaction mixture was stirred at 60 °C in an oil bath overnight. The Ugi adduct **5j** was filtered and was then added to indandione **6a**

Scheme 4. Plausible Reaction Mechanism



https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915–9927

(1.5 equiv) and Cs_2CO_3 (2 equiv) in acetonitrile (1.3 M) and heated to 90 °C in an oil bath for 5 min. Then, $CuCl_2$ (10 mol %) was added and reacted for 5 h. The progress of the reaction was monitored by TLC for the disappearance of **5j**. After the reaction was completed, the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:2) to afford the product **7j** (0.93 g, 40% yield).

Procedure C. Compound **7o** (0.1 mmol) and (2,3-dihydrobenzo-[*b*][1,4]dioxin-6-yl)boronic acid (0.15 mmol) were placed in a 25 mL round-bottom flask, and toluene/ethanol (v/v = 5:1) (3 mL) and sat. $NaHCO_3$ (3 mL) were added. The mixture was flushed by N_2 for 10 min. Then, Pd(dppf)Cl_2 (0.01 mmol) was added and the reaction mixture was allowed to react at 90 °C in an oil bath for 12 h. Then, the reaction mixture was cooled to room temperature and treated with H_2O and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After the removal of EtOAc, the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:1) to afford the product **8**.

Procedure D. Compound **7p** (0.1 mmol), NaN_3 (0.12 mmol), and NH_4Cl (0.12 mmol) in DMF (1 mL) were placed in a closed 4 mL screwcap glass vial and heated in a heating metal block at 100 °C for 18 h. DMF was removed under vacuum, and the residue was purified by column chromatography (silica gel, methanol/dichloromethane = 1:4) to afford the product **9**.

Procedure E. To a flask were added **7t** (0.2 mmol), $HCOONH_4$ (2 mmol), and 10% Pd/C (10 mg). Anhydrous ethanol (4 mL) was added as a solvent, and the reaction mixture was stirred at room temperature for 8 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (v/v, 3:2) as an eluent to give product **10** (26 mg, 35% yield) as a red solid, and 2-(2-amino-5,11-dioxo-5,6a,11,11a-tetrahydro-6*H*-indeno[1,2-*c*]-isoquinolin-6-yl)-*N*-(*tert*-butyl)acetamide **11** (44 mg, 58% yield) was obtained using ethyl acetate/petroleum ether (v/v, 4:1) as an eluent as a white solid.

Procedure F. To a solution of **7t** (0.3 mmol) in EtOH (1 mL) was added $SnCl_2$ (1.5 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 10 min and then refluxed in an oil bath for 4 h. After the completion of the reaction, ice-cold water was added to the reaction mixture. The obtained residue was diluted with a 20% NaOH solution, and the aqueous layer was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated to provide the product **10** (108 mg, 96% yield).

Procedure G. Compound **10** (0.1 mmol) was dissolved in a solvent mixture of dry DMF and THF (1:4 v/v) (1 mL) in a 10 mL round-bottom flask. To this solution was added phenyl isocyanate (0.15 mmol), and the mixture stirred under an inert atmosphere at 90 °C in an oil bath for 8 h. The reaction mixture was cooled to room temperature. Solvents was removed under vacuum, and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:7) to afford the product **12** (32 mg, 64% yield).

Procedure H. Boc-L-phenylalanine (0.1 mmol) and compound **10** (0.1 mmol) were dissolved in dry pyridine (0.3 mL). The solution was cooled to −15 °C, and phosphorus oxychloride (0.11 mmol) was added dropwise with vigorous stirring. The reaction was completed after 30 min (monitored by TLC). The reaction mixture was then quenched with crushed ice/water (10 mL) and extracted with EtOAc (three times, 10 mL). The combined EtOAc layers were washed with saturated $NaHCO_3$ and NaCl (three times, 10 mL each). After being dried on Na_2SO_4, the EtOAc layer was filtered and evaporated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:1) to afford the product **13** (49 mg, 78% yield).

*N-(2-(tert-Butylamino)-2-oxoethyl)-2-iodobenzamide (**5a**).* It was synthesized according to procedure A on a 2 mmol scale (418 mg, 58%) as a white solid; mp: 178−179 °C; R_f = 0.58 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.82 (dd, *J* = 13.1, 7.6 Hz, 1H), 7.42−7.30 (m, 3H), 7.08 (ddd, *J* = 10.8, 6.6, 2.7 Hz, 1H), 6.89−6.70 (m, 1H), 4.08 (t, *J* = 4.7 Hz, 2H), 1.33 (d, *J* = 12.3 Hz, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 167.9, 141.3, 139.9, 131.3, 128.4, 128.1, 92.6, 51.6, 44.6, 28.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{18}IN_2O_2$, 361.0408; found, 361.0407.

*N-(2-(Butylamino)-2-oxoethyl)-2-iodobenzamide (**5b**).* It was synthesized according to procedure A on a 2 mmol scale (353 mg, 49%) as a yellow solid; mp: 195−196 °C; R_f = 0.38 (50% EtOAc/dichloromethane). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.40 (q, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.98 (s, 1H), 6.75 (s, 1H), 4.17 (d, *J* = 5.2 Hz, 2H), 3.29 (q, *J* = 6.8 Hz, 2H), 1.56−1.48 (m, 2H), 1.36 (q, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 168.4, 141.1, 139.9, 137.7, 131.5, 128.7, 128.4, 128.2, 128.0, 127.6, 92.5, 43.9, 43.7. ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.7, 168.3, 141.2, 140.0, 131.5, 128.4, 128.2, 92.5, 43.9, 39.5, 31.5, 20.1, 13.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{18}IN_2O_2$, 361.0408; found, 361.0407.

*N-(2-(Cyclohexylamino)-2-oxoethyl)-2-iodobenzamide (**5c**).* It was synthesized according to procedure A on a 2 mmol scale (347 mg, 45%) as an off-white solid; mp: 160−161 °C; R_f = 0.32 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.46−7.33 (m, 2H), 7.12 (ddt, *J* = 9.4, 7.2, 3.6 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.13 (d, *J* = 5.2 Hz, 2H), 3.84−3.54 (m, 1H), 1.96−1.82 (m, 2H), 1.70 (dt, *J* = 13.5, 3.9 Hz, 2H), 1.60 (dt, *J* = 12.9, 3.9 Hz, 1H), 1.38−1.25 (m, 3H), 1.24−1.11 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 167.4, 141.3, 139.9, 131.4, 128.4, 128.2, 92.6, 48.6, 44.0, 32.9, 25.5, 24.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{20}IN_2O_2$, 387.0564; found, 387.0565.

*N-(2-(Benzylamino)-2-oxoethyl)-2-iodobenzamide (**5d**).* It was synthesized according to procedure **A** on a 2 mmol scale (284 mg, 36%) as a yellow solid; mp: 143−144 °C; R_f = 0.34 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 2H), 7.33−7.24 (m, 5H), 7.12 (dt, *J* = 8.4, 4.3 Hz, 2H), 6.92 (s, 1H), 4.46 (d, *J* = 4.7 Hz, 2H), 4.28−3.95 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 168.4, 141.1, 139.9, 137.7, 131.5, 128.7, 128.4, 128.2, 128.0, 127.6, 92.5, 43.9, 43.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{16}IN_2O_2$, 395.0251; found, 395.0246.

*N-(2-((4-Chlorobenzyl)amino)-2-oxoethyl)-2-iodobenzamide (**5e**).* It was synthesized according to procedure **A** on a 2 mmol scale (512 mg, 60%) as a yellow solid; mp: 166−167 °C; R_f = 0.22 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.33 (p, *J* = 7.3 Hz, 2H), 7.24−7.15 (m, 5H), 7.10 (t, *J* = 7.2 Hz, 1H), 4.36 (s, 2H), 4.30−3.93 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.9, 168.6, 140.9, 140.0, 136.4, 133.2, 131.5, 129.2, 128.7, 128.3, 128.2, 92.6, 43.9, 42.9. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{15}ClIN_2O_2$, 428.9861; found, 428.9860.

*2-Iodo-N-(1-oxo-1-((4-phenoxyphenyl)amino)propan-2-yl)-benzamide (**5f**).* It was synthesized according to procedure **A** on a 2 mmol scale (369 mg, 38%) as a yellow solid; mp: 178−179 °C; R_f = 0.65 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.36 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.45−7.37 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.17−7.05 (m, 3H), 6.97 (dd, *J* = 20.7, 8.3 Hz, 4H), 5.11 (t, *J* = 7.2 Hz, 1H), 1.64 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 170.0, 169.7, 157.6, 153.4, 141.0, 140.0, 133.5, 131.6, 129.7, 128.3 (d, *J* = 3.2 Hz), 123.0, 121.7, 119.6, 118.4, 92.5, 50.3, 18.4. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{20}IN_2O_3$, 487.0513; found, 487.0512.

*N-(1-(tert-Butylamino)-3-methyl-1-oxobutan-2-yl)-2-iodobenzamide (**5g**).* It was synthesized according to procedure **A** on a 2 mmol scale (322 mg, 40%) as a white solid; mp: 234−235 °C; R_f = 0.51 (20% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.48−7.36 (m, 2H), 7.12 (ddd, *J* = 8.0, 6.3, 2.9 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 5.92 (s, 1H), 4.29 (dd, *J* = 8.8, 7.1 Hz, 1H), 2.19 (h, *J* = 6.8 Hz, 1H), 1.39 (s, 9H), 1.06 (dd, *J* = 10.8, 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.7, 169.2, 141.8, 140.0, 131.2, 128.3, 128.1, 92.4, 59.7, 51.8, 31.3, 28.8, 19.3,

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

18.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}IN_2O_2$, 403.0877; found, 403.0872.

*N-(1-((2-Ethylphenyl)amino)-1-oxopentan-2-yl)-2-iodobenzamide (**5h**).* It was synthesized according to procedure **A** on a 2 mmol scale (486 mg, 54%) as a yellow solid; mp: 190−191 °C; R_f = 0.48 (30% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.10 (s, 1H), 7.93−7.89 (m, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.44−7.37 (m, 2H), 7.24 (t, J = 7.7 Hz, 2H), 7.19−7.12 (m, 2H), 6.45 (d, J = 8.0 Hz, 1H), 4.83 (td, J = 7.7, 6.4 Hz, 1H), 2.69 (qd, J = 7.5, 3.3 Hz, 2H), 2.19−2.05 (m, 1H), 1.93−1.80 (m, 1H), 1.61−1.55 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H), 1.05 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 169.4, 141.3, 140.0, 135.3, 134.7, 131.5, 128.7, 128.3, 126.6, 125.7, 123.5, 92.3, 54.4, 33.7, 24.4, 19.1, 14.1, 13.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}IN_2O_2$, 451.0877; found, 451.0876.

*N-(1-((2,3-Dimethoxybenzyl)amino)-4-methyl-1-oxopentan-2-yl)-2-iodobenzamide (**5i**).* It was synthesized according to procedure **A** on a 2 mmol scale (398 mg, 39%) as a yellow solid; mp: 156−157 °C; R_f = 0.45 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.97−7.68 (m, 1H), 7.38−7.31 (m, 2H), 7.08 (ddd, J = 8.0, 6.5, 2.6 Hz, 1H), 7.03−6.95 (m, 2H), 6.90 (dd, J = 7.7, 1.6 Hz, 1H), 6.86 (dd, J = 8.2, 1.5 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 4.73 (td, J = 8.4, 8.0, 5.0 Hz, 1H), 4.48 (d, J = 5.7 Hz, 2H), 3.87 (d, J = 1.7 Hz, 6H), 1.86−1.71 (m, 2H), 1.72−1.63 (m, 1H), 0.97 (dd, J = 10.4, 6.2 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 171.3, 169.3, 152.6, 147.2, 141.7, 139.8, 131.5, 131.2, 128.2, 128.1, 124.2, 121.4, 112.0, 92.4, 60.8, 55.8, 52.2, 41.1, 38.8, 24.9, 23.0, 22.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}IN_2O_4$, 511.1088; found, 511.1083.

*N-(2-(Benzylamino)-1-cyclopentyl-2-oxoethyl)-2-iodobenzamide (**5j**).* It was synthesized according to procedure **A** on a 2 mmol scale (573 mg, 62%) as a yellow solid; mp: 205−206 °C; R_f = 0.54 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J = 8.4 Hz, 1H), 8.50 (t, J = 6.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38−7.28 (m, 5H), 7.27−7.22 (m, 1H), 7.17 (td, J = 7.6, 1.7 Hz, 1H), 4.38 (d, J = 6.0 Hz, 1H), 4.35−4.29 (m, 2H), 2.28 (q, J = 8.2 Hz, 1H), 1.79 (m, J = 13.8, 4.8 Hz, 1H), 1.70−1.55 (m, 3H), 1.49 (m, J = 7.1, 3.0 Hz, 2H), 1.45−1.37 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.5, 169.1, 143.3, 139.9, 139.5 (d, J = 3.9 Hz), 131.2, 128.7, 128.3, 127.7, 127.2, 93.9, 57.8 (d, J = 3.9 Hz), 42.5, 42.0, 29.7, 29.4, 25.4, 25.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}IN_2O_2$, 463.0877; found, 463.0876.

*2-Iodo-N-(1-oxo-4-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)butan-2-yl)benzamide (**5k**).* It was synthesized according to procedure **A** on a 2 mmol scale (572 mg, 55%) as a yellow solid; mp: 157−158 °C; R_f = 0.46 (20% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.87 (dt, J = 8.0, 1.4 Hz, 1H), 7.41−7.27 (m, 4H), 7.22 (d, J = 7.3 Hz, 3H), 7.11 (ddd, J = 7.6, 5.6, 1.8 Hz, 1H), 6.95 (t, J = 18.8 Hz, 1H), 6.48 (d, J = 36.1 Hz, 1H), 4.98−4.49 (m, 1H), 2.80 (dt, J = 9.4, 6.2 Hz, 2H), 2.37−2.16 (m, 1H), 2.18−2.00 (m, 1H), 1.86 (dd, J = 14.8, 1.2 Hz, 1H), 1.79−1.55 (m, 1H), 1.43 (t, J = 3.3 Hz, 6H), 1.00 (d, J = 2.0 Hz, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 169.1, 141.5, 141.2, 140.0, 131.3, 128.6, 128.5, 128.3, 128.1, 126.1, 92.6 (d, J = 3.2 Hz), 55.6, 54.0, 51.7, 34.3 (d, J = 3.6 Hz), 31.9, 31.7, 31.5, 29.3 (d, J = 2.7 Hz), 28.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}IN_2O_2$, 521.1665; found, 521.1655.

*Methyl (2-(2-Iodobenzamido)-2-phenylacetyl)glycinate (**5l**).* It was synthesized according to procedure **A** on a 2 mmol scale (307 mg, 34%) as a yellow solid; mp: 159−160 °C; R_f = 0.32 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.88 (dd, J = 8.0, 1.1 Hz, 1H), 7.57−7.52 (m, 2H), 7.47−7.35 (m, 5H), 7.18 (d, J = 6.9 Hz, 1H), 7.12 (td, J = 7.6, 1.8 Hz, 1H), 6.49 (t, J = 5.4 Hz, 1H), 5.76 (d, J = 6.7 Hz, 1H), 4.20−3.99 (m, 2H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.9, 169.7, 168.6, 141.0, 140.0, 137.1, 131.4, 129.1, 128.7, 128.6, 128.1, 127.7, 92.4, 57.6, 52.5, 41.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}IN_2O_4$, 453.0306; found, 453.0304.

*N-(2-(tert-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-2-iodobenzamide (**5m**).* It was synthesized according to procedure **A** on a 2 mmol scale (354 mg, 38%) as a yellow solid; mp: 197−198 °C; R_f = 0.2 (30% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.85 (dd, J = 7.9, 1.1 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.41−7.30 (m, 3H), 7.15−7.04 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.40 (s, 1H), 5.76 (d, J = 7.2 Hz, 1H), 3.80 (s, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.0, 168.5, 159.4, 141.4, 139.9, 131.2, 130.5, 128.8, 128.4, 128.1, 114.2, 92.5, 57.0, 55.3, 51.7, 28.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}IN_2O_3$, 467.0826; found, 467.0824.

*N-(2-(Benzylamino)-2-oxoethyl)-2-bromo-5-methoxybenzamide (**5n**).* It was synthesized according to procedure **A** on a 2 mmol scale (316 mg, 42%) as a yellow solid; mp: 153−154 °C; R_f = 0.5 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.40 (dd, J = 14.2, 7.9 Hz, 3H), 7.33−7.14 (m, 5H), 6.96 (d, J = 3.1 Hz, 1H), 6.79 (dd, J = 8.8, 3.0 Hz, 1H), 4.38 (d, J = 5.7 Hz, 2H), 4.13 (d, J = 5.3 Hz, 2H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 168.5, 168.0, 158.8, 137.8, 137.6, 134.1, 128.6, 127.7, 127.5, 117.8, 114.6, 109.6, 55.6, 43.7, 43.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}BrN_2O_3$, 377.0495; found, 377.0496.

*2-Bromo-N-(1-(4-bromophenyl)-2-oxo-2-(phenethylamino)-ethyl)-5-methoxybenzamide (**5o**).* It was synthesized according to procedure **A** on a 2 mmol scale (555 mg, 51%) as a yellow solid; mp: 191−192 °C; R_f = 0.48 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.71 (d, J = 6.6 Hz, 1H), 7.54−7.43 (m, 3H), 7.37−7.26 (m, 2H), 7.21 (dd, J = 5.2, 1.9 Hz, 3H), 7.07 (d, J = 3.1 Hz, 1H), 7.00−6.93 (m, 2H), 6.86 (dd, J = 8.8, 3.1 Hz, 1H), 6.47 (t, J = 5.9 Hz, 1H), 5.66 (d, J = 6.6 Hz, 1H), 3.80 (s, 3H), 3.59 (dt, J = 13.3, 6.7 Hz, 1H), 3.36 (dtd, J = 12.2, 7.0, 5.2 Hz, 1H), 2.69 (td, J = 6.9, 2.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 168.9, 166.6, 158.9, 138.3, 137.1, 136.9, 134.4, 132.1, 129.1, 128.6, 128.6, 126.5, 122.5, 118.0, 115.1, 109.7, 57.2, 55.7, 41.0, 35.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{23}Br_2N_2O_3$, 545.0070; found, 545.0071.

*2-Bromo-N-(2-((4-cyanobenzyl)amino)-2-oxo-1-phenylethyl)-4-methoxybenzamide (**5p**).* It was synthesized according to procedure **A** on a 2 mmol scale (610 mg, 64%) as a white solid; mp: 193−194 °C; R_f = 0.58 (66% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.03 (t, J = 5.9 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.55 (dd, J = 6.6, 2.9 Hz, 2H), 7.40 (t, J = 8.5 Hz, 3H), 7.37−7.33 (m, 3H), 7.13−7.02 (m, 3H), 6.79 (dd, J = 8.7, 2.5 Hz, 1H), 6.13 (d, J = 7.4 Hz, 1H), 4.41 (dd, J = 15.8, 6.0 Hz, 1H), 4.27 (dd, J = 15.8, 5.6 Hz, 1H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 170.2, 166.8, 161.6, 143.4, 137.8, 132.2, 131.1, 129.0, 128.5, 128.1, 127.8, 127.2, 120.6, 119.0, 118.7, 113.3, 110.8, 57.5, 55.8, 43.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}BrN_3O_3$, 478.0761; found, 478.0760.

*2-Bromo-N-(2-(tert-butylamino)-2-oxo-1-(pyridin-2-yl)ethyl)-4-methoxybenzamide (**5q**).* It was synthesized according to procedure **A** on a 2 mmol scale (235 mg, 28%) as a brown solid; mp: 164−165 °C; R_f = 0.36 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.55 (d, J = 5.0 Hz, 1H), 8.15 (d, J = 5.9 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.25 (t, J = 6.3 Hz, 1H), 7.16 (s, 2H), 6.93−6.85 (m, 1H), 5.65 (d, J = 5.8 Hz, 1H), 3.83 (s, 3H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.2, 166.7, 161.4, 156.2, 148.6, 137.4, 131.5, 128.8, 123.0, 121.2, 120.5, 118.9, 113.4, 59.1, 55.7, 51.7, 28.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{23}BrN_3O_3$, 420.0917; found, 420.0916.

*2-Bromo-N-(1-(tert-butylamino)-4-(methylthio)-1-oxobutan-2-yl)-5-methylbenzamide (**5r**).* It was synthesized according to procedure **A** on a 2 mmol scale (256 mg, 32%) as a yellow solid; mp: 178−179 °C; R_f = 0.42 (30% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.43 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.06 (dd, J = 8.2, 2.2 Hz, 1H), 6.69 (s, 1H), 4.78 (dt, J = 8.1, 6.7 Hz, 1H), 2.61 (dddd, J = 41.8, 13.3, 8.7, 6.3 Hz, 2H), 2.30 (s, 3H), 2.21−2.03 (m, 5H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 169.8, 167.7, 137.6, 136.9, 133.1, 132.2, 130.0, 116.0, 53.2, 51.6, 31.9, 30.2, 28.7, 20.8, 15.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}BrN_2O_2S$, 401.0893; found, 401.0890.

*2-Bromo-N-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-methylbenzamide (**5s**).* It was synthesized according to procedure **A** on a 2 mmol scale (349 mg, 40%) as a yellow solid; mp: 199−200

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

°C; R_f = 0.49 (20% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.62 (d, *J* = 7.0 Hz, 1H), 7.49−7.41 (m, 4H), 7.35−7.30 (m, 2H), 7.18−7.13 (m, 1H), 6.35 (s, 1H), 5.74 (d, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 168.3, 166.8, 142.3, 136.9, 134.0, 133.7, 129.7, 129.0, 128.7, 128.2, 119.4, 57.2, 51.9, 28.5, 21.0. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{23}BrClN_2O_2$, 437.0626; found, 437.0625.

*2-Bromo-N-(2-(tert-butylamino)-2-oxoethyl)-4-nitrobenzamide (**5t**).* It was synthesized according to procedure **A** on a 2 mmol scale (214 mg, 30%) as a white solid; mp: 169−170 °C; R_f = 0.21 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.49 (d, *J* = 2.1 Hz, 1H), 8.23 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 4.8 Hz, 1H), 6.09 (s, 1H), 4.09 (d, *J* = 4.7 Hz, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.7, 166.1, 148.7, 142.8, 130.1, 128.5, 122.5, 120.3, 52.0, 44.1, 28.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{13}H_{17}BrN_3O_4$, 358.0397; found, 358.0398.

*N-(2-(tert-Butylamino)-2-oxoethyl)-2-chloroquinoline-3-carboxamide (**5u**).* It was synthesized according to procedure **A** on a 2 mmol scale (255 mg, 40%) as a white solid; mp: 187−188 °C; R_f = 0.56 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.45 (d, *J* = 12.3 Hz, 1H), 8.00 (t, *J* = 7.5 Hz, 1H), 7.89−7.74 (m, 3H), 7.64−7.51 (m, 1H), 6.45 (d, *J* = 43.1 Hz, 1H), 4.15 (d, *J* = 5.0 Hz, 2H), 1.39 (d, *J* = 3.8 Hz, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.2, 165.4, 147.9, 146.0, 139.7, 132.1, 128.4 (d, *J* = 4.1 Hz), 128.2, 127.9, 126.2, 51.8, 44.5, 28.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{19}ClN_3O_2$, 320.1160; found, 320.1160.

*2-Bromo-N-(2-(tert-butylamino)-2-oxoethyl)thiophene-3-carboxamide (**5v**).* It was synthesized according to procedure **A** on a 2 mmol scale (286 mg, 45%) as a white solid; mp: 165−166 °C; R_f = 0.65 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.62 (t, *J* = 4.3 Hz, 1H), 7.35 (d, *J* = 5.8 Hz, 1H), 7.25 (d, *J* = 5.8 Hz, 1H), 6.52 (s, 1H), 4.12 (d, *J* = 4.6 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.7, 162.4, 135.1, 129.2, 126.2, 113.6, 51.7, 44.2, 28.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{11}H_{16}BrN_2O_2S$, 319.0110; found, 319.0111.

*N-(tert-Butyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7aa**).* It was synthesized according to procedure B on a 0.3 mmol scale (76 mg, 70%) as a red solid; mp: 256−257 °C; R_f = 0.48 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.66 (t, *J* = 7.9 Hz, 1H), 8.31 (t, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.72 (q, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 6.9 Hz, 1H), 7.44 (dt, *J* = 12.1, 6.9 Hz, 2H), 7.38−7.31 (m, 1H), 6.47 (s, 1H), 5.05 (s, 2H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.6, 166.0, 164.1, 155.8, 137.0, 134.5, 134.3, 133.6, 132.5, 131.0, 128.5, 127.3, 123.6, 123.2, 123.1, 123.0, 109.1, 52.0, 49.5, 28.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{21}N_2O_3$, 361.1547; found, 361.1547.

*N-(tert-Butyl)-2-(8,9-dimethoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7ab**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (81 mg, 64%) as a red solid; mp: 262−263 °C; R_f = 0.50 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.58 (dt, *J* = 8.2, 0.8 Hz, 1H), 8.32−8.17 (m, 1H), 7.77 (s, 1H), 7.70 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.12 (s, 1H), 6.62 (s, 1H), 4.99 (s, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.4, 166.8, 164.4, 155.6, 152.5, 150.6, 134.3, 132.8, 130.5, 128.5, 127.6, 126.7, 123.1, 122.5, 108.5, 108.3, 107.3, 56.9, 56.3, 51.8, 50.6, 28.6. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{25}N_2O_5$, 421.1758; found, 421.1758.

*N-Butyl-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7b**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (73 mg, 68%) as a red solid; mp: 259−260 °C; R_f = 0.54 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.81−8.53 (m, 1H), 8.40−8.22 (m, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.75 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.59 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.54−7.41 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.69 (s, 1H), 5.14 (s, 2H), 3.30 (q, *J* = 6.8 Hz, 2H), 1.50 (dd, *J* = 8.5, 6.2 Hz, 2H), 1.37−1.29 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.6, 167.0, 164.3, 155.6, 136.9, 134.5, 134.4, 133.7, 132.5, 131.2, 128.5, 127.5, 123.7, 123.3, 123.2, 123.1, 109.3, 49.1, 39.6, 31.4, 20.0, 13.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{21}N_2O_3$, 361.1547; found, 361.1547.

*N-Cyclohexyl-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7c**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (60 mg, 52%) as a red solid; mp: 321−322 °C; R_f = 0.46 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, *J* = 8.1 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.64−7.40 (m, 5H), 5.18 (s, 2H), 3.58 (s, 1H), 1.85−1.50 (m, 4H), 1.54 (d, *J* = 9.3 Hz, 1H), 1.25 (q, *J* = 10.7 Hz, 5H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 190.5, 165.5, 162.9, 157.6, 137.4, 134.7, 134.7 (d, *J* = 24.1 Hz), 134.0, 132.3, 131.8, 128.7, 127.7, 123.3, 123.2, 123.1, 107.3, 48.4, 47.0, 32.7, 25.6, 24.9. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_3$, 387.1703; found, 387.1704.

*N-Benzyl-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7d**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (47 mg, 40%) as a red solid; mp: 289−290 °C; R_f = 0.55 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (t, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.91−7.81 (m, 1H), 7.63−7.54 (m, 2H), 7.48 (d, *J* = 2.5 Hz, 3H), 7.35−7.29 (m, 2H), 7.25 (d, *J* = 6.3 Hz, 3H), 5.27 (s, 2H), 4.35 (d, *J* = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 190.5, 166.8, 163.0, 157.5, 139.4, 137.3, 134.8 (d, *J* = 8.4 Hz), 134.6, 134.1, 132.4, 131.8, 128.8, 128.7, 127.7, 127.4, 123.4, 123.3, 123.1 (d, *J* = 5.1 Hz), 107.5, 47.4, 42.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{19}N_2O_3$, 395.1390; found, 395.1389.

*N-(4-Chlorobenzyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7e**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (103 mg, 80%) as a red solid; mp: 291−292 °C; R_f = 0.42 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (t, *J* = 6.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.58−7.52 (m, 2H), 7.49−7.43 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.23 (s, 2H), 4.32 (d, *J* = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 190.4, 166.9, 162.9, 157.3, 138.5, 137.2, 134.7 (d, *J* = 6.7 Hz), 134.5, 134.0, 132.3, 132.0, 131.7, 129.6, 128.7, 127.7, 123.3, 123.3, 123.2−122.9 (m), 107.5, 47.3, 42.2. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{18}ClN_2O_3$, 429.1001; found, 429.0999. [M + Na]$^+$ calcd for $C_{25}H_{17}ClN_2O_3Na$, 451.0820; found, 451.0819.

*2-(5,11-Dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-N-(4-phenoxyphenyl)propanamide (**7f**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (96 mg, 66%) as a red solid; mp: 255−256 °C; R_f = 0.66 (40% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 8.15 (s, 1H), 7.94 (s, 1H), 7.83 (d, *J* = 7.1 Hz, 1H), 7.67−7.47 (m, 6H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 4H), 5.58 (s, 1H), 1.78 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 190.7, 167.1, 162.6, 157.8, 152.3, 137.4, 135.4, 134.8, 134.5 (d, *J* = 28.0 Hz), 132.4, 131.7, 130.4, 128.4, 127.7, 124.2 (d, *J* = 10.1 Hz), 123.8, 123.5, 123.2 (d, *J* = 20.1 Hz), 122.1, 119.7, 118.4, 108.5, 57.5, 15.4. HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{22}N_2O_4Na$, 509.1472; found, 509.1470.

*N-(tert-Butyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-3-methylbutanamide (**7g**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (74 mg, 61%) as a red solid; mp: 249−250 °C; R_f = 0.44 (10% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.77 (d, *J* = 8.1 Hz, 1H), 8.68 (s, 1H), 8.52 (d, *J* = 7.6 Hz, 1H), 8.36 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82−7.77 (m, 1H), 7.65 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.58−7.49 (m, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 4.67 (d, *J* = 10.8 Hz, 1H), 3.32−3.21 (m, 1H), 1.42 (s, 9H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.9, 168.7, 165.7, 157.3, 137.5, 134.5, 134.4, 134.1, 132.3, 130.8, 128.2, 127.5, 124.7, 124.1, 123.6, 123.2, 110.4, 75.3, 51.2, 29.7, 28.6, 19.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{27}N_2O_3$, 403.2016; found, 403.2015.

*2-(5,11-Dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-N-(2-ethylphenyl)pentanamide (**7h**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (93 mg, 69%) as a red solid; mp: 285−286 °C; R_f = 0.64 (30% EtOAc/petroleum ether). ^{1}H NMR

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

(500 MHz, chloroform-*d*) δ 10.24 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.41 (d, *J* = 8.2 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.55 (m, *J* = 7.7, 2.9 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 5.47 (dd, *J* = 9.2, 6.3 Hz, 1H), 2.82−2.76 (m, 1H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.55−2.44 (m, 1H), 1.36−1.31 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 190.8, 168.9, 165.8, 156.7, 137.3, 135.1, 135.0, 134.7, 134.3, 134.1, 133.6, 132.3, 131.1, 128.9, 128.2, 127.8, 126.6, 125.4, 124.1, 123.7, 123.5, 122.9, 110.7, 67.7, 31.5, 24.8, 19.8, 14.3, 13.4. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{29}H_{26}N_2O_3Na$, 473.1836; found, 473.1834.

*N-(2,3-Dimethoxybenzyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-4-methylpentanamide (**7i**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (110 mg, 72%) as a red solid; mp: 301−302 °C; R_f = 0.58 (50% EtOAc/petroleum ether). Mixture of rotamers (ratio, 3:2); ^1H NMR (500 MHz, chloroform-*d*) δ 8.71 (dd, *J* = 20.7, 6.9 Hz, 1H), 8.33 (dd, *J* = 20.5, 7.7 Hz, 1.6H), 8.14 (d, *J* = 7.2 Hz, 0.6H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 0.6H), 7.58−7.43 (m, 2H), 7.39 (t, *J* = 7.3 Hz, 0.6H), 7.33 (d, *J* = 7.5 Hz, 0.4H), 7.26 (t, *J* = 7.3 Hz, 0.4H), 7.19 (t, *J* = 7.6 Hz, 0.4H), 7.03 (t, *J* = 7.9 Hz, 0.6H), 6.94 (d, *J* = 7.6 Hz, 0.6H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.73 (t, *J* = 8.0 Hz, 0.8H), 6.63−6.54 (m, 0.8H), 5.43 (dd, *J* = 10.0, 5.1 Hz, 0.6H), 4.66 (dd, *J* = 15.4, 6.0 Hz, 0.6H), 4.56−4.43 (m, 1H), 4.39 (dd, *J* = 14.6, 5.3 Hz, 0.4H), 3.87 (d, *J* = 11.7 Hz, 3.6H), 3.75 (s, 1.2H), 3.62 (s, 1.2H), 2.71 (ddd, *J* = 14.3, 9.6, 5.0 Hz, 0.6H), 2.62−2.49 (m, 0.4H), 2.09 (td, *J* = 10.9, 8.2, 4.2 Hz, 0.6H), 1.94 (ddd, *J* = 14.3, 9.8, 4.5 Hz, 0.4H), 1.72 (s, 0.4H), 1.53 (d, *J* = 9.0 Hz, 0.6H), 1.39−1.31 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 1.2H), 0.87 (d, *J* = 6.6 Hz, 1.8H), 0.83 (d, *J* = 6.6 Hz, 1.2H), 0.78 (d, *J* = 6.5 Hz, 1.8H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*, major rotamer) δ 190.7, 170.1, 165.2, 156.9, 152.6, 147.2, 137.3, 134.4, 134.0, 133.2, 132.2, 131.5, 131.0, 130.4, 128.2, 127.5, 124.1, 123.7, 123.4, 122.6, 120.9, 111.9, 110.3, 64.4, 60.8, 55.8, 38.9, 37.6, 25.2, 22.9, 21.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{31}N_2O_5$, 511.2228; found, 511.2225.

*N-Benzyl-2-cyclopentyl-2-(5,11-dioxo-5,11-dihydro-6H-indeno-[1,2-c]isoquinolin-6-yl)acetamide (**7j**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (104 mg, 75%) as a red solid; mp: 262−263 °C; R_f = 0.81 (40% EtOAc/petroleum ether). ^1H NMR (500 MHz, chloroform-*d*) δ 8.87 (t, *J* = 6.0 Hz, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 7.7 Hz, 1H), 8.31 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.78 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 7.65 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.53 (dtd, *J* = 12.0, 7.4, 1.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.36 (s, 1H), 7.32−7.27 (m, 2H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.72 (dd, *J* = 15.1, 6.6 Hz, 1H), 4.39 (dd, *J* = 15.1, 5.2 Hz, 1H), 1.95 (ddd, *J* = 12.6, 7.6, 5.0 Hz, 1H), 1.78−1.35 (m, 8H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 190.8, 170.0, 165.7, 156.9, 138.2, 137.4, 134.5, 134.5, 134.1, 132.3, 131.0, 128.7, 128.1, 127.6, 127.5, 127.4, 124.2, 124.0, 123.6, 123.3, 110.3, 71.9, 43.5, 39.1, 30.6, 25.4, 24.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_3$, 463.2016; found, 463.2017.

*2-(5,11-Dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-4-phenyl-N-(2,4,4-trimethylpentan-2-yl)butanamide (**7k**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (101 mg, 65%) as a red solid; mp: 274−275 °C; R_f = 0.65 (20% EtOAc/petroleum ether). Mixture of rotamers (ratio, 3:1); ^1H NMR (500 MHz, chloroform-*d*) δ 8.75 (d, *J* = 8.1 Hz, 1H), 8.36 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.98 (s, 0.75H), 7.85 (d, *J* = 6.8 Hz, 0.75H), 7.80 (td, *J* = 7.0, 1.7 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 0.25H), 7.60 (ddd, *J* = 14.2, 6.6, 1.7 Hz, 1H), 7.56−7.50 (m, 1H), 7.46−7.31 (m, 2H), 7.13−6.88 (m, 5H), 6.39 (dd, *J* = 10.0, 3.3 Hz, 0.25H), 5.79 (s, 0.25H), 5.05 (dd, *J* = 9.9, 4.3 Hz, 0.75H), 3.06 (dq, *J* = 11.7, 6.8, 4.0 Hz, 1H), 2.80 (dt, *J* = 14.5, 7.4 Hz, 0.25H), 2.69 (dq, *J* = 9.4, 5.9, 3.1 Hz, 1.5H), 2.56 (dt, *J* = 14.7, 7.6 Hz, 0.25H), 2.42 (dq, *J* = 19.3, 7.8, 6.4 Hz, 1H), 1.95−1.71 (m, 1.5H), 1.68 (d, *J* = 10.3 Hz, 0.5H), 1.45 (d, *J* = 4.7 Hz, 4.5H), 1.38 (s, 1H), 1.27 (d, *J* = 5.5 Hz, 1.5H), 0.95 (s, 6.75H), 0.81 (s, 2.25H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*, major rotamer) δ 190.8, 168.7, 165.3, 157.1, 138.9, 137.2, 134.5, 134.2, 133.8, 132.3, 130.7, 128.4, 128.4, 128.2, 127.5, 126.3, 124.0, 123.7, 123.6, 123.1, 110.2, 66.3, 55.4, 51.5, 32.4, 31.4, 30.0, 29.2, 29.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{34}H_{37}N_2O_3$, 521.2799; found, 521.2795.

*Methyl (2-(5,11-Dioxo-5,11-dihydro-6H-indeno[1,2-c]-isoquinolin-6-yl)-2-phenylacetyl)glycinate (**7l**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (80 mg, 59%) as a red solid; mp: 255−256 °C; R_f = 0.50 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, chloroform-*d*) δ 8.76 (d, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 8.1, 1.3 Hz, 1H), 7.85−7.70 (m, 1H), 7.67−7.59 (m, 1H), 7.50 (m, *J* = 19.0, 7.4 Hz, 6H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.35−7.31 (m, 2H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.55 (s, 1H), 4.35 (dd, *J* = 18.3, 6.2 Hz, 1H), 4.01 (dd, *J* = 18.3, 4.1 Hz, 1H), 3.77 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 190.6, 170.0, 168.1, 164.3, 156.4, 137.1, 134.6, 134.5, 133.4, 133.2, 132.4, 131.0, 129.5, 129.1, 128.7, 127.6, 127.5, 124.1, 123.7, 123.5, 122.8, 110.2, 66.2, 52.5, 41.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_5$, 453.1445; found, 453.1446. $[M + Na]^+$ calcd for $C_{27}H_{20}N_2O_5Na$, 475.1264; found, 475.1263.

*N-(tert-Butyl)-2-(5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]-isoquinolin-6-yl)-2-(4-methoxyphenyl)acetamide (**7m**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (78 mg, 56%) as a red solid; mp: 259−260 °C; R_f = 0.38 (30% EtOAc/petroleum ether). ^1H NMR (500 MHz, chloroform-*d*) δ 8.76 (d, *J* = 8.1 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.78 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.66−7.60 (m, 1H), 7.57−7.52 (m, 1H), 7.50 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.40−7.31 (m, 4H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.48 (s, 1H), 3.83 (s, 3H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 190.7, 167.3, 164.4, 159.6, 156.9, 137.3, 134.6, 134.3, 133.4, 132.4, 130.9, 128.7, 128.6, 127.4, 125.9, 124.3, 123.7, 123.3, 123.1, 114.6, 109.9, 55.3, 52.0, 29.7, 28.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{27}N_2O_4$, 467.1965; found, 467.1959.

*N-Benzyl-2-(3-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7n**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (79 mg, 62%) as a red solid; mp: 299−300 °C; R_f = 0.72 (80% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 8.98 (t, *J* = 6.0 Hz, 1H), 8.45 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 2.8 Hz, 1H), 7.50 (dd, *J* = 5.5, 2.8 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.42−7.37 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 3H), 5.21 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 190.6, 166.8, 162.6, 158.8, 155.1, 139.5, 137.6, 134.4, 134.0, 131.3, 128.8, 127.7, 127.4, 126.2, 124.9, 124.8, 124.3, 123.0, 122.9, 109.3, 107.8, 55.9, 47.4, 42.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_4$, 425.1496; found, 425.1496.

*2-(4-Bromophenyl)-2-(3-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-N-phenethylacetamide (**7o**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (87 mg, 49%) as a red solid; mp: 274−275 °C; R_f = 0.51 (40% EtOAc/petroleum ether). ^1H NMR (500 MHz, chloroform-*d*) δ 8.67 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.61−7.55 (m, 1H), 7.47 (d, *J* = 7.7 Hz, 3H), 7.40 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.29 (s, 1H), 7.25−7.10 (m, 8H), 6.74 (s, 1H), 6.35 (s, 1H), 3.93 (s, 3H), 3.66 (s, 2H), 2.87 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 190.7, 167.5, 164.0, 159.3, 153.7, 138.3, 137.3, 134.2, 133.5, 132.8, 132.3, 130.6, 128.9, 128.7, 128.6, 126.6, 126.4, 125.4, 125.1, 123.5, 122.7, 122.5(d, *J* = 12.1 Hz), 110.6, 108.5, 55.7, 41.0, 35.2, 29.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{33}H_{26}BrN_2O_4$, 593.1071; found, 593.1070.

*N-(4-Cyanobenzyl)-2-(2-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-2-phenylacetamide (**7p**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (55 mg, 35%) as a red solid; mp: 283−284 °C; R_f = 0.54 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 8.09 (s, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.50 (dd, *J* = 27.1, 7.3 Hz, 4H), 7.37 (m, *J* = 7.7 Hz, 5H), 7.31 (m, *J* = 7.3 Hz, 2H), 7.18 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.49 (dd, *J* = 15.8, 6.2 Hz, 1H), 4.24 (dd, *J* = 16.0, 5.5 Hz, 1H), 3.94 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 190.7, 167.5, 164.4, 162.8, 158.2, 145.7, 136.8, 134.6, 134.5, 134.4, 133.8, 132.5, 132.4, 131.65 (d, *J* = 4.5 Hz), 131.1, 128.6, 128.1, 124.4, 123.0, 119.4, 117.8, 117.0, 109.8, 108.7, 104.5, 56.2, 56.1, 43.1. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{33}H_{24}N_3O_4$, 526.1761; found, 526.1755. $[M + Na]^+$ calcd for $C_{33}H_{23}N_3O_4Na$, 548.1581; found, 548.1574.

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

*N-(tert-Butyl)-2-(2-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-2-(pyridin-2-yl)acetamide (**7q**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (91 mg, 65%) as a red solid; mp: 252−253 °C; R_f = 0.54 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.95 (s, 1H), 8.72 (s, 1H), 8.40−8.17 (m, 2H), 7.78 (s, 1H), 7.67−7.48 (m, 2H), 7.30 (d, *J* = 4.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 25.8, 7.9 Hz, 3H), 6.55 (d, *J* = 7.4 Hz, 1H), 4.03 (s, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 191.3, 164.6, 164.4, 163.3, 157.6, 155.9, 148.4, 138.2, 137.8, 134.9, 134.5, 132.0, 131.2, 130.2, 123.4, 122.7, 122.5, 120.3, 117.5, 116.8, 109.1, 104.0, 59.1, 55.8, 51.8, 28.8. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{28}H_{26}N_3O_4$, 468.1918; found, 468.1913.

*N-(tert-Butyl)-2-(3-methyl-5,11-dioxo-5,11-dihydro-6H-indeno-[1,2-c]isoquinolin-6-yl)-4-(methylthio)butanamide (**7r**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (85 mg, 63%) as a red solid; mp: 283−284 °C; R_f = 0.56 (30% EtOAc/petroleum ether). Mixture of rotamers (ratio, 1:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (dd, *J* = 20.7, 8.2 Hz, 1H), 8.06 (s, 0.5H), 7.97 (s, 0.5H), 7.86 (d, *J* = 7.7 Hz, 0.5H), 7.68 (dd, *J* = 18.6, 11.5 Hz, 1.5H), 7.59−7.27 (m, 4H), 6.37 (d, *J* = 10.0 Hz, 0.5H), 5.31 (s, 0.5H), 2.92 (s, 0.5H), 2.65 (s, 0.5H), 2.45 (d, *J* = 5.6 Hz, 5.5H), 2.16 (s, 0.5H), 1.96 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 16.5 Hz, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6, major rotamer) δ 190.7, 167.1, 162.8, 157.8, 138.1, 137.5, 135.8, 134.2, 133.4, 131.1, 129.9, 127.8, 124.9, 123.8, 123.0, 122.6, 108.6, 61.1, 56.1, 51.3, 31.9, 29.0, 21.6, 15.0. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{29}N_2O_3S$, 449.1893; found, 449.1893.

*N-(tert-Butyl)-2-(4-chlorophenyl)-2-(2-methyl-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7s**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (86 mg, 59%) as a red solid; mp: 261−262 °C; R_f = 0.58 (20% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.58 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.64 (dd, *J* = 6.4, 1.9 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 4H), 7.32 (dd, *J* = 13.0, 8.6 Hz, 4H), 6.43 (s, 1H), 2.56 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.8, 166.8, 164.3, 156.6, 145.8, 137.2, 134.4, 134.4, 133.6, 132.9, 132.4, 131.0, 129.4, 129.3, 129.2, 128.7, 128.6, 128.4, 123.4, 123.4, 110.1, 52.1, 29.7, 28.5, 22.2. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{29}H_{26}ClN_2O_3$, 485.1627; found, 485.1623.

*N-(tert-Butyl)-2-(2-nitro-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**7t**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (98 mg, 81%) as a red solid; mp: 239−240 °C; R_f = 0.40 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.45 (d, *J* = 2.2 Hz, 1H), 8.47 (d, *J* = 8.8 Hz, 1H), 8.18 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 6.28 (s, 1H), 5.11 (s, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 189.6, 165.0, 162.9, 157.5, 151.4, 136.5, 134.4, 133.8, 133.1, 131.9, 130.6, 126.3, 123.7, 123.4, 120.7, 119.1, 108.2, 52.3, 49.2, 28.7. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{20}N_3O_5$, 406.1398; found, 406.1397.

*N-(tert-Butyl)-2-(6,13-dioxo-6,13-dihydro-5H-benzo[b]indeno-[1,2-h][1,6]naphthyridin-5-yl)acetamide (**7u**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (69 mg, 56%) as a red solid; mp: 297−298 °C; R_f = 0.62 (75% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (s, 1H), 8.28 (d, *J* = 8.3 Hz, 1H), 8.25 (s, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.02−7.94 (m, 1H), 7.68 (dd, *J* = 13.5, 7.0 Hz, 2H), 7.63 (d, *J* = 4.1 Hz, 2H), 7.58 (dd, *J* = 7.3, 3.9 Hz, 1H), 5.25 (s, 2H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 188.0, 165.6, 163.7, 161.8, 151.5, 147.6, 139.8, 136.8, 134.5, 133.9, 132.5, 130.5, 129.1, 127.1, 126.3, 124.0, 123.1, 118.3, 108.2, 79.7, 55.4, 51.4, 28.9. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{22}N_3O_3$, 412.1656; found, 412.1653.

*N-(tert-Butyl)-2-(4,10-dioxo-4,10-dihydro-5H-indeno[1,2-b]-thieno[2,3-d]pyridin-5-yl)acetamide (**7v**).* It was synthesized according to procedure **B** on a 0.3 mmol scale (41 mg, 37%) as a red solid; mp: 268−269 °C; R_f = 0.55 (60% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.71−7.60 (m, 2H), 7.50 (td, *J* = 7.7, 1.3 Hz, 1H), 7.46−7.37 (m, 2H), 6.54 (s, 1H), 5.08 (d, *J* = 5.3 Hz, 2H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 188.3, 165.9, 160.3, 154.4, 141.8, 137.6, 134.4, 134.1, 131.2, 128.2, 127.1, 124.7, 123.9, 123.5, 110.4, 52.0, 49.4, 28.6. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{20}H_{19}N_2O_3S$, 367.1111; found, 367.1111.

*2-(4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-2-(3-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-N-phenethylacetamide (**8**).* It was synthesized according to procedure C on a 0.1 mmol scale (62 mg, 95%) as a red solid; mp: 305−306 °C; R_f = 0.42 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.70 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 2.7 Hz, 1H), 7.62−7.57 (m, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.47 (s, 1H), 7.41 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 3H), 7.24−7.13 (m, 5H), 7.11 (d, *J* = 2.1 Hz, 1H), 7.07 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.58 (s, 1H), 4.33 (s, 4H), 3.94 (s, 3H), 3.67 (q, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 190.8, 167.9, 164.0, 159.2, 154.1, 143.8, 143.6, 140.9, 138.6, 137.6, 134.4, 133.5, 133.4, 132.0, 130.4, 128.7, 128.6, 127.8, 127.4, 126.5 (d, *J* = 3.1 Hz), 125.7, 125.4, 125.0, 123.3, 122.5, 120.1, 117.7, 115.8, 110.5, 108.6, 64.5 (d, *J* = 5.1 Hz), 55.6, 41.1, 35.3. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{41}H_{33}N_2O_6$, 649.2333; found, 649.2332. [M + Na]$^+$ calcd for $C_{41}H_{32}N_2O_6Na$, 671.2153; found, 671.2152.

*N-(4-(1H-Tetrazol-5-yl)benzyl)-2-(2-methoxy-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)-2-phenylacetamide (**9**).* It was synthesized according to procedure D on a 0.1 mmol scale (47 mg, 82%) as a red solid; mp: 264−265 °C; R_f = 0.46 (15% MeOH/dichloromethane). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.21 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 2.5 Hz, 1H), 7.98−7.91 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.39 (dd, *J* = 7.6, 3.4 Hz, 3H), 7.36−7.33 (m, 1H), 7.31 (s, 1H), 7.22 (dd, *J* = 5.7, 2.6 Hz, 2H), 7.06 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.87 (s, 1H), 4.66 (d, *J* = 15.0 Hz, 1H), 4.37 (d, *J* = 15.0 Hz, 1H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, methanol-d_4) δ 190.8, 168.6, 164.6, 163.4, 161.2, 157.5, 138.9, 136.5, 134.5, 134.3, 133.6, 132.9, 130.8, 130.2, 128.6, 128.5, 128.1, 128.0, 127.7, 126.4, 123.4, 122.5, 117.4, 116.9, 109.1, 103.8, 54.8, 43.2, 35.2. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{33}H_{25}N_6O_4$, 569.1932; found, 569.1926. [M + Na]$^+$ calcd for $C_{33}H_{24}N_6O_4Na$, 591.1751; found, 591.1744.

*2-(2-Amino-5,11-dioxo-5,11-dihydro-6H-indeno[1,2-c]-isoquinolin-6-yl)-N-(tert-butyl)acetamide (**10**).* It was synthesized according to procedure F on a 0.3 mmol scale (108 mg, 96%) as a red solid; mp: 188−189 °C; R_f = 0.33 (50% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.55−7.47 (m, 2H), 7.42 (dt, *J* = 7.3, 3.4 Hz, 2H), 6.73 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.33 (s, 2H), 5.11 (s, 2H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 190.5, 166.1, 162.1, 157.9, 154.5, 137.6, 134.9, 134.3, 133.5, 131.4, 130.5, 123.0, 122.6, 115.7 (d, *J* = 4.9 Hz), 112.3, 106.7, 103.2 (d, *J* = 7.4 Hz), 51.2, 46.3, 28.9 (d, *J* = 5.2 Hz). HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{22}N_3O_3$, 376.1656; found, 376.1654.

*2-(2-Amino-5,11-dioxo-5,6a,11,11a-tetrahydro-6H-indeno[1,2-c]isoquinolin-6-yl)-N-(tert-butyl)acetamide (**11**).* It was synthesized according to procedure E on a 0.2 mmol scale (44 mg, 58%) as a white solid; mp: 155−156 °C; R_f = 0.22 (80% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.04 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 7.71−7.65 (m, 1H), 7.63−7.56 (m, 1H), 7.42−7.31 (m, 2H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.50 (s, 1H), 5.19 (s, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, methanol-d_4) δ 167.7, 163.8, 153.0, 147.8, 140.7, 136.5, 135.8, 129.7, 128.2, 127.5, 124.5, 120.7, 120.3, 115.4, 113.9, 104.3, 71.7, 51.0, 46.2, 29.4, 27.6. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{24}N_3O_3$, 378.1812; found, 378.1811.

*N-(tert-Butyl)-2-(5,11-dioxo-2-(3-phenylureido)-5,11-dihydro-6H-indeno[1,2-c]isoquinolin-6-yl)acetamide (**12**).* It was synthesized according to procedure G on a 0.1 mmol scale (32 mg, 64%) as a red solid; mp: 277−278 °C; R_f = 0.36 (70% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.77 (s, 1H), 8.57 (d, *J* = 2.6 Hz, 1H), 8.17 (s, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.74 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.53 (dd, *J* = 21.7, 7.5 Hz, 4H), 7.46 (d, *J* = 7.4 Hz, 2H),

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915−9927

7.33 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H), 5.15 (s, 2H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 190.3, 165.8, 162.2, 158.1, 152.6, 145.6, 139.7, 137.4, 134.7, 133.8, 133.4, 131.7, 130.1 (d, J = 11.0 Hz), 129.3, 123.3, 122.8, 118.9, 118.2, 118.0, 117.2, 109.4 (d, J = 10.7 Hz), 106.9, 51.3, 46.7, 28.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{27}N_4O_4$, 495.2027; found, 495.2026.

*tert-Butyl (S)-(1-((6-(2-(tert-Butylamino)-2-oxoethyl)-5,11-dioxo-6,11-dihydro-5H-indeno[1,2-c]isoquinolin-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**13**).* It was synthesized according to procedure H on a 0.1 mmol scale (49 mg, 78%) as a red solid; mp: 298−299 °C; R_f = 0.28 (50% EtOAc/petroleum ether). ^1H NMR (500 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.77 (s, 1H), 8.17 (d, J = 10.9 Hz, 2H), 7.88 (d, J = 9.1 Hz, 1H), 7.55 (dd, J = 19.9, 6.6 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.38 (d, J = 7.5 Hz, 2H), 7.34−7.19 (m, 4H), 5.16 (s, 2H), 4.43 (s, 1H), 3.07 (d, J = 14.1 Hz, 1H), 3.00−2.72 (m, 1H), 1.34 (s, 9H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 190.3, 172.2, 165.7, 162.2, 158.2, 156.0, 144.6, 138.4, 137.4, 134.7, 133.9, 133.2, 131.8, 130.0, 129.8, 128.6, 126.8, 123.4, 123.0 (d, J = 24.2 Hz), 119.3 (d, J = 25.5 Hz), 118.4, 111.4, 106.9, 78.7, 57.2, 51.3, 46.7, 37.7, 28.9 (d, J = 14.0 Hz), 28.7 (d, J = 16.4 Hz). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{39}N_4O_6$, 623.2864; found, 623.2863.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01238.

^1H and $^{13}C\{^1H\}$ NMR spectra of compounds **5**, **7**, and **8**−**13**, along with X-ray crystallographic data for **7a** (PDF) Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Alexander Dömling − *Department of Drug Design, University of Groningen, 9713 AV Groningen, The Netherlands;* orcid.org/0000-0002-9923-8873; Email: a.s.s.domling@rug.nl

Authors

Qian Wang − *Department of Drug Design, University of Groningen, 9713 AV Groningen, The Netherlands*

Jesse Tuinhof − *Department of Drug Design, University of Groningen, 9713 AV Groningen, The Netherlands*

Kumchok C. Mgimpatsang − *Department of Drug Design, University of Groningen, 9713 AV Groningen, The Netherlands*

Katarzyna Kurpiewska − *Faculty of Chemistry, Jagiellonian University, 30-060 Krakow, Poland*

Justyna Kalinowska-Tluscik − *Faculty of Chemistry, Jagiellonian University, 30-060 Krakow, Poland;* orcid.org/0000-0001-7714-1651

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01238

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research has been supported (to A.D.) by the National Institute of Health (NIH) (2R01GM097082-05), the European Lead Factory (IMI) under grant agreement no. 115489, and the Qatar National Research Foundation (NPRP6-065-3-012). Also, funding was received through ITN "Accelerated Early stage drug dIScovery" (AEGIS, grant agreement no. 675555) and COFUND ALERT (grant agreement no. 665250), Hartstichting (ESCAPE-HF, 2018B012) and KWF Kankerbestrijding grant (grant agreement no. 10504). Moreover, this work was supported by the Ministry of Science and Higher Education, Warsaw, Poland (grant number 6903/IA/SP/2018). We thank Qiang Zheng (University of Groningen) for helpful discussion and Marcel de Vries (University of Groningen) for his help in HRMS analysis. Q.W. acknowledges the China Scholarship Council for supporting.

■ REFERENCES

(1) (a) Giraudo, A.; Krall, J.; Bavo, F.; Nielsen, B.; Kongstad, K. T.; Rolando, B.; Blasio, R. D.; Gloriam, D. E.; Löffler, R.; Thiesen, L.; Harpsøe, K.; Frydenvang, K.; Boschi, D.; Wellendorph, P.; Lolli, M. L.; Jensen, A. A.; Frølund, B. Five-Membered N-Heterocyclic Scaffolds as Novel Amino Bioisosteres at γ-Aminobutyric Acid (GABA) Type A Receptors and GABA Transporters. *J. Med. Chem.* **2019**, *62*, 5797−5809. (b) Hu, C. F.; Lu, L.; Wan, J.-P.; Wen, C. The Pharmacological Mechanisms and Therapeutic Activities of Hydroxychloroquine in Rheumatic and Related Diseases. *Curr. Med. Chem.* **2017**, *24*, 2241−2249.

(2) Smith, C. A.; Narouz, M. R.; Lummis, P. A.; et al. N-Heterocyclic Carbenes in Materials Chemistry. *Chem. Rev.* **2019**, *119*, 4986−5056.

(3) Crabtree, R. H. Homogeneous Transition Metal Catalysis of Acceptorless Dehydrogenative Alcohol Oxidation: Applications in Hydrogen Storage and to Heterocycle Synthesis. *Chem. Rev.* **2017**, *117*, 9228−9246.

(4) (a) Doddi, A.; Peters, M.; Tamm, M. N-Heterocyclic Carbene Adducts of Main Group Elements and Their Use as Ligands in Transition Metal Chemistry. *Chem. Rev.* **2019**, *119*, 6994−7112. (b) Huynh, H. V. Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, *118*, 9457−9492.

(5) Pommier, Y.; Cushman, M. The Indenoisoquinoline Noncamptothecin Topoisomerase I Inhibitors: Update and Perspectives. *Mol. Cancer Ther.* **2009**, *8*, 1008−1014.

(6) (a) Pommier, Y.; Sun, Y.; Shar-yin, N. H.; Nitiss, J. L. Roles of Eukaryotic Topoisomerases in Transcription, Replication and Genomic Stability. *Nat. Rev. Mol. Cell Biol.* **2016**, *17*, 703−721. (b) Kohlhagen, G.; Paull, K. D.; Cushman, M.; Nagafuji, P.; Pommier, Y. Protein-Linked DNA Strand Breaks Induced by NSC 314622, A Novel Noncamptothecin Topoisomerase I Poison. *Mol. Pharmacol.* **1998**, *54*, 50−58. (c) Strumberg, D.; Pommier, Y.; Paull, K.; Jayaraman, M.; Nagafuji, P.; Cushman, M. Synthesis of Cytotoxic Indenoisoquinoline Topoisomerase I Poisons. *J. Med. Chem.* **1999**, *42*, 446−457. (d) Cushman, M.; Jayaraman, M.; Vroman, J. A.; Fukunaga, A. K.; Fox, B. M.; Kohlhagen, G.; Strumberg, D.; Pommier, Y. Synthesis of New Indeno[1,2-c]isoquinolines: Cytotoxic Noncamptothecin Topoisomerase I Inhibitors. *J. Med. Chem.* **2000**, *43*, 3688−3698. (e) Pommier, Y. DNA Topoisomerase I Inhibitors: Chemistry, Biology, and Interfacial Inhibition. *Chem. Rev.* **2009**, *109*, 2894−2902. (f) Wang, P.; Elsayed, M. S. A.; Plescia, C. B.; Ravji, A.; Redon, C. E.; Kiselev, E.; Marchand, C.; Zeleznik, O.; Agama, K.; Pommier, Y.; Cushman, M. Synthesis and Biological Evaluation of the First Triple Inhibitors of Human Topoisomerase 1, Tyrosyl−DNA Phosphodiesterase 1 (Tdp1), and Tyrosyl−DNA Phosphodiesterase 2 (Tdp2). *J. Med. Chem.* **2017**, *60*, 3275−3288.

(7) Wang, K.; Elsayed, M. S. A.; Wu, G.; Deng, N.; Cushman, M.; Yang, D. Indenoisoquinoline Topoisomerase Inhibitors Strongly Bind and Stabilize the MYC Promoter G-Quadruplex and Downregulate MYC. *J. Am. Chem. Soc.* **2019**, *141*, 11059−11070.

(8) (a) Dömling, A.; Ugi, I. Multicomponent Reactions with Isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Ugi, I. The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem., Int. Ed.* **1962**, *1*, 8−21. (c) Marcaccini, S.; Torroba, T. The Use of the Ugi Four-Component Condensation. *Nat. Protoc.* **2007**, *2*, 632−639.

(9) (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing synthetic efficiency: Multi-Component Transformations Lead The Way. *Chem. – Eur. J* **2000**, *6*, 3321–3329. (b) Wang, Q.; Osipyan, A.; Konstantinidou, M.; Butera, R.; Mgimpatsang, K. C.; Shishkina, S. V.; Dömling, A. Pd-Catalyzed de Novo Assembly of Diversely Substituted Indole-Fused Polyheterocycles. *J. Org. Chem.* **2019**, *84*, 12148–12156.

(10) Thompson, M. J.; Chen, B. Ugi Reactions with Ammonia Offer Rapid Access to a Wide Range of 5-Aminothiazole and Oxazole Derivatives. *J. Org. Chem.* **2009**, *74*, 7084–7093.

(11) (a) Liu, J.; Zhang, C.; Zhang, Z.; Wen, X.; Dou, X.; Wei, J.; Qiu, X.; Song, S.; Jiao, N. Nitromethane as a Nitrogen Donor in Schmidt-type Formation of Amides and Nitriles. *Science* **2020**, *367*, 281–285. (b) Lv, Z. J.; Huang, Z.; Zhang, W. X.; Xi, Z. Scandium-Promoted Direct Conversion of Dinitrogen into Hydrazine Derivatives via N–C Bond Formation. *J. Am. Chem. Soc.* **2019**, *141*, 8773–8777.

(12) Brown, A. L.; Churches, Q. I.; Hutton, C. A. Total Synthesis of Ustiloxin D Utilizing an Ammonia–Ugi Reaction. *J. Org. Chem.* **2015**, *80*, 9831–9837.

(13) Alemán-Ponce de León, D.; Sánchez-Chávez, A. C.; Polindara-García, L. A. Pd-Mediated γ-C(sp3)–H Bond Activation in Ammonia–Ugi 4-CR Adducts by Using Picolinamide as Directing Group. *J. Org. Chem.* **2019**, *84*, 12809–12834.

(14) (a) Wang, Z. L.; Zhao, L.; Wang, M. X. Caryl–Calkyl Bond Formation from $Cu(ClO_4)_2$-mediated Oxidative Cross Coupling Reaction Between Arenes and Alkyllithium Reagents Through Structurally Well-Defined Ar–Cu(III) Intermediates. *Chem. Commun.* **2012**, *48*, 9418–9420. (b) Dohi, T.; Kita, Y. *Iodine Chemistry and Applications*; Wiley: Hoboken, 2014; pp 303–310. (c) Jiang, M.; Li, J.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. A Facile Copper-Catalyzed One-Pot Domino Synthesis of 5,12-Dihydroindolo[2,1-b]quinazolines. *Org. Lett.* **2012**, *14*, 1420–1423. (d) Yang, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. A Simple Copper-Catalyzed Cascade Synthesis of 2-Amino-1H-indole-3-carboxylate Derivatives. *Adv. Synth. Catal.* **2010**, *352*, 1033–1038. (e) Li, C.; Zhang, L.; Shu, S.; Liu, H. A Simple Copper-Catalyzed Two-Step One-Pot Synthesis of Indolo[1,2-a]quinazoline. *Beilstein J. Org. Chem.* **2014**, *10*, 2441–2447. (f) Jiang, H.; Yang, J.; Tang, X.; Wu, W. Divergent Syntheses of Isoquinolines and Indolo[1,2-a]quinazolines by Copper-Catalyzed Cascade Annulation from 2-Haloaryloxime Acetates with Active Methylene Compounds and Indoles. *J. Org. Chem.* **2016**, *81*, 2053–2061. (g) Kavala, V.; Wang, C. C.; Barange, D. K.; Kuo, C. W.; Lei, P. M.; Yao, C. F. Synthesis of Isocoumarin Derivatives via the Copper-Catalyzed Tandem Sequential Cyclization of 2-Halo-N-phenyl Benzamides and Acyclic 1,3-Diketones. *J. Org. Chem.* **2012**, *77*, 5022–5029.

(15) (a) An, Y.; He, H.; Liu, T.; Zhang, Y.; Lu, X.; Cai, Q. Diversified synthesis of 2-(4-Oxo [1, 2, 3] triazolo [1, 5-a] quinoxalin-5 (4H)-yl) acetamide derivatives through Ugi-4-CR and copper-catalyzed tandem reactions. *Synthesis* **2017**, *49*, 3863–3873. (b) Shi, J.; Wu, J.; Cui, C.; Dai, W. M. Microwave-Assisted intramolecular Ullmann diaryl etherification as the post-ugi annulation for generation of dibenz [b,f][1,4] oxazepine Scaffold. *J. Org. Chem.* **2016**, *81*, 10392–10403. (c) Tyagi, V.; Khan, S.; Bajpai, V.; Gauniyal, H. M.; Kumar, B.; Chauhan, P. M. Skeletal diverse synthesis of N-fused polycyclic heterocycles via the sequence of ugi-type MCR and CuI-catalyzed coupling/tandem Pictet–Spengler reaction. *J. Org. Chem.* **2012**, *77*, 1414–1421. (d) Zhou, F.; Liu, J.; Ding, K.; Liu, J.; Cai, Q. Copper-catalyzed tandem reaction of isocyanides with N-(2-haloaryl) propiolamides for the synthesis of pyrrolo [3,2-c] quinolin-4-ones. *J. Org. Chem.* **2011**, *76*, 5346–5353.

(16) Wang, Q.; Mgimpatsang, K. C.; Konstantinidou, M.; Shishkina, S. V.; Dömling, A. 1,3,4-Oxadiazoles by Ugi-Tetrazole and Huisgen Reaction. *Org. Lett.* **2019**, *21*, 7320–7323.

(17) Ghosh, A. K.; Brindisi, M. Urea Derivatives in Modern Drug Discovery and Medicinal Chemistry. *J. Med. Chem.* **2020**, *63*, 2751–2788.

(18) Ginn, J. D.; Bosanac, T.; Chen, R.; Cywin, C.; Hickey, E.; Kashem, M.; Kerr, S.; Kugler, S.; Li, X.; Prokopowicz, A., III; et al. Substituted 2H-Isoquinolin-1-ones as Potent Rho-Kinase Inhibitors: Part 2, Optimization for Blood Pressure Reduction in Spontaneously Hypertensive Rats. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5153–5156.

https://dx.doi.org/10.1021/acs.joc.0c01238
J. Org. Chem. 2020, 85, 9915–9927