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Proline-Mediated Transition Metal-Free Access to 1*H*-Indazolones from 2-Halobenzohydrazides

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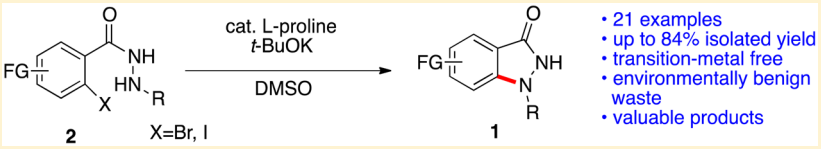
Supporting Information

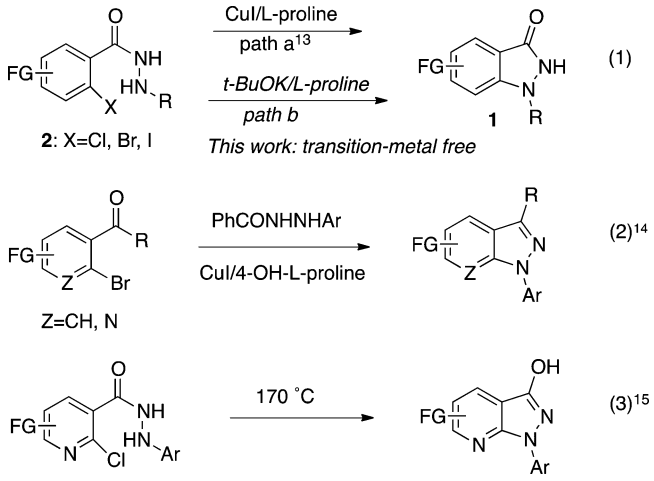


ABSTRACT: Transition metal-free access to 1*H*-indazolones **1** has been achieved on the basis of base-mediated intramolecular C−N bond formation. Reactions of 2-halobenzohydrazides **2** with potassium *tert*-butoxide in the presence of catalytic proline provided indazolones **1** in moderate to good yields. This transformation may proceed primarily via the radical pathway according to the control experiment with a radical scavenger.

1*H*-Indazolones and their congeners make up an important structural core for the development of pharmaceuticals, agrochemicals, and materials.[1] For pharmaceuticals, the indazolones and their derivatives have been represented to exhibit analgesic,[2] antitumor,[3] anticancer,[4] anti-inflammatory,[5] and antifertility activities.[6] Some indazolone derivatives exhibit excellent fluorescence properties.[1d] For these reasons, a huge amount of work dealing with the methods for synthesizing indazolones and derivatives has been published,[1a] which consists of palladium-catalyzed intramolecular amination reaction,[7] N−N bond formation through a PIFA {[bis-(trifluoroacetoxy)iodo]benzene}-mediated oxidative cyclization,[8] copper-catalyzed cyclization of 2-haloarylcarbonylic compounds,[9] cyclization of *O*-aminobenzoxime by selective activation of the oxime,[10] the [3+2] cycloaddition of diazo compounds with arynes and subsequent acyl migration,[11] and N−N bond-forming heterocyclization.[12]

One of the straightforward ways to access 1*H*-indazolones **1** would be the cyclization of 2-halobenzohydrazides **2** under transition metal-catalyzed conditions, which affords substituted 1*H*-indazolones **1**, regioselectively (Scheme 1, eq 1). We previously reported the Cu(I)-catalyzed cyclization (eq 1, path a) of hydrazides **2** to 1*H*-indazolones **1**.[13] The one-pot reaction process for the copper-catalyzed assembly of 1-aryl-1*H*-indazoles has also been achieved (eq 2).[14] Intramolecular aromatic substitution reaction provided 1*H*-indazoles in the case of 2-chloropyridine as substrates under harsh reaction conditions (eq 3).[15] However, the use of toxic transition metal catalysis, harsh reaction conditions, and a somewhat limited substrate scope reduce the attractiveness of these methods. We envisioned that hydrazides **2** would cyclize to 1*H*-indazolones **1** under the radical pathway[16] when intramolecular C−N bond formation occurs preferentially over cleavage of the amide bond. To the best of our knowledge, such a transformation has not yet been achieved. In this paper, we report the successful

Scheme 1. Synthesis of Indazolones via Intramolecular C−N Coupling



conversion of hydrazides **2a** to indazolones **1** under transition metal-free conditions with the use of catalytic proline[17] and alkali base (eq 1, path b).

Reaction of model substrate **2aa** (X = I) in the presence of potassium carbonate (2 equiv) and L-proline (20 mol %) in DMSO at 70 °C for 24 h did not take place (Table 1, entry 1). However, the trace amount of desired product **1a** was observed at an elevated temperature of 100 °C (entry 2). Potassium hydroxide instead of potassium carbonate provided a 9% yield of the cyclized product (entry 3). The reactivity was increased when potassium *tert*-butoxide was applied (33%, entry 4). Fortunately, the yield was dramatically improved by increasing

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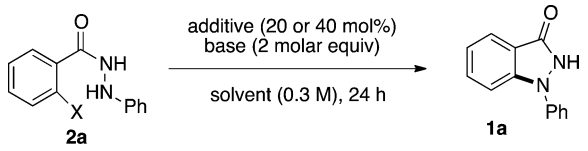
Table 1. Optimization of the Reaction Conditions[a]



entry	X	additive (mol %)	base	solvent	T (°C)	yield of **1a** (%)[b]
1	I (**2aa**)	L-proline (20)	K_2CO_3	DMSO	70	0
2	I (**2aa**)	L-proline (20)	K_2CO_3	DMSO	100	trace
3	I (**2aa**)	L-proline (20)	KOH	DMSO	100	9
4	I (**2aa**)	L-proline (20)	*t*-BuOK	DMSO	100	33
5	**I (2aa)**	**L-proline (40)**	***t*-BuOK**	**DMSO**	**100**	**84 (50)**[d]
6	Br (**2ab**)	L-proline (40)	*t*-BuOK	DMSO	100	56
7	Br (**2ab**)	L-proline (40)	*t*-BuOK	DMSO	120	80
8	Cl (**2ac**)	L-proline (40)	*t*-BuOK	DMSO	100	trace
9	F (**2ad**)	L-proline (40)	*t*-BuOK	DMSO	100	trace
10	I (**2aa**)	–	*t*-BuOK	DMSO	100	trace
11	I (**2aa**)	$Me_2NCH_2CO_2H$ (40)	*t*-BuOK	DMSO	100	10
12	I (**2aa**)	1,10-Phen[c] (40)	*t*-BuOK	DMSO	100	11
13	I (**2aa**)	L-proline (40)	*t*-BuOK	DMF	100	26
14	I (**2aa**)	L-proline (40)	*t*-BuOK	dioxane	100	23
15	I (**2aa**)	L-proline (40)	*t*-BuOK	PhMe	100	29
16	I (**2aa**)	L-proline (40)	*t*-BuOK	MeCN	100	33
17	I (**2aa**)	L-proline (20)	*t*-BuONa	DMSO	120	42

[a]Reaction conditions: **2a** (0.5 mmol), L-proline (20 or 40 mol %), and *t*-BuOK (2 mol equiv) were reacted in DMSO (1.5 mL) at the desired temperature and time. [b]After column chromatography. [c]1,10-Phenanthroline. [d]Result with 1.60 g of starting material (unoptimized).

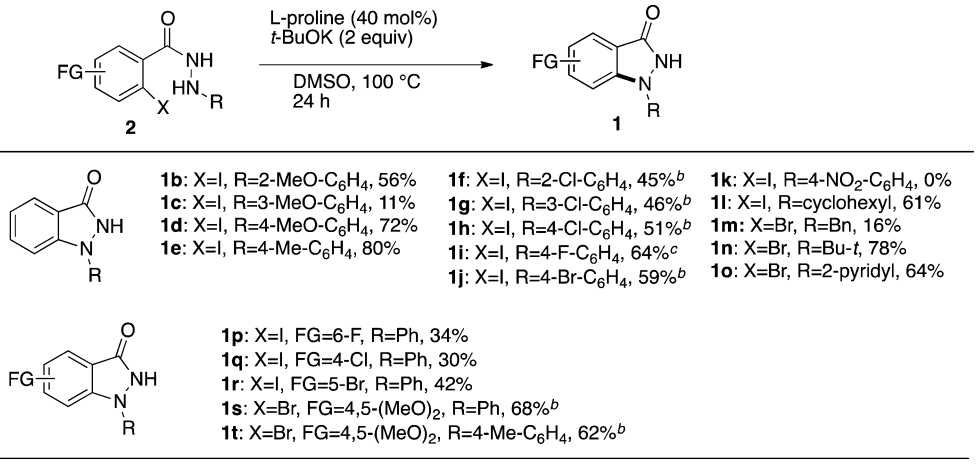


Figure 1. Substrate scopes of proline-catalyzed intramolecular C–N bond formation for indazolone synthesis. Footnote a: reaction conditions of **2** (0.5 mmol), L-proline (0.2 mmol, 40 mol %), and *t*-BuOK (2.0 molar equiv) reacted in DMSO at 100 °C for 24 h. Footnote b: at 120 °C. Footnote c: under microwatt irradiation at 160 °C for 20 min.

the amount of L-proline to 40 mol % (84%, entry 5). Bromoarene **2ab** (X = Br) was also found to be a good substrate for displaying an excellent yield at higher temperatures [56% at 100 °C and 80% at 120 °C (entries 6 and 7, respectively)]. A trace amount of product was observed with chloro- and fluoroarenes [**2ac** and **2ad** (X = Cl and F)] as substrates (entries 8 and 9, respectively) and also in the absence of L-proline (entry 10). Reactions with other additives, bases, and solvents were found to be less effective (entries 11–17). As a result, we chose entries 5 (X = I) and 7 (X = Br) as the optimized reaction conditions.

To examine the substrate scope, a variety of hydrazides **2** were used under the optimized reaction conditions (Figure 1). From Figure 1, it was evident that the electronic environments influence the reaction yields. Hydrazides with electron-rich aromatics at position N′ (**2b–2e**) afforded cyclized products (**1b–1e**) in moderate to good yields except for the substrate with a 3-methoxyphenyl group, **1c**; this phenomenon was attributed to the decrease in the nucleophilicity of the N′ atom by the inducing effect. Benzohydrazides with electron-poor aromatics at position N′ (**2f–2k**) provided the desired products (**1f–1j**) in moderate yields except for the substrate with a strongly withdrawing nitro group, **2k**, which did not afford the desired product **1k** to recover the starting material. These reactions required an elevated temperature (120 °C). The substitution at positions 4–6 with halogens (**2p–2r**) diminished the reactivity to give corresponding indazolones (**1p–1r**) in moderate yields. Conversions of 4,5-dimethoxy-substituted hydrazides (**2s** and **2t**), hydrazides with alkyl substitutions (**2l** and **2n**), and a hydrazide with a hetero-

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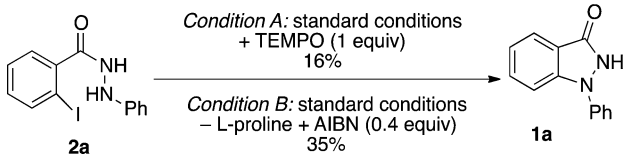
aromatic group (**2o**) represented acceptable efficiency in giving indazolones **1s**, **1t**, **1l**, **1n**, and **1o**, respectively, in 61−78% yields. Hydrazide with a primary alkyl group (**2m**) displayed a lower level of conversion to give indazolones (**1m**) in a 16% yield.[18]

Considering the previous reports,[16] the reaction presented here would proceed through a radical process. To assume this hypothesis, we performed the reaction in the presence of a radical scavenger. The reaction of **2a** under standard conditions with 1 equiv of TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] afforded product **1a** in 16% yield (condition A, Scheme 2), which indicates that the present transformation

Scheme 2. Control Experiments in the Presence of TEMPO and AIBN

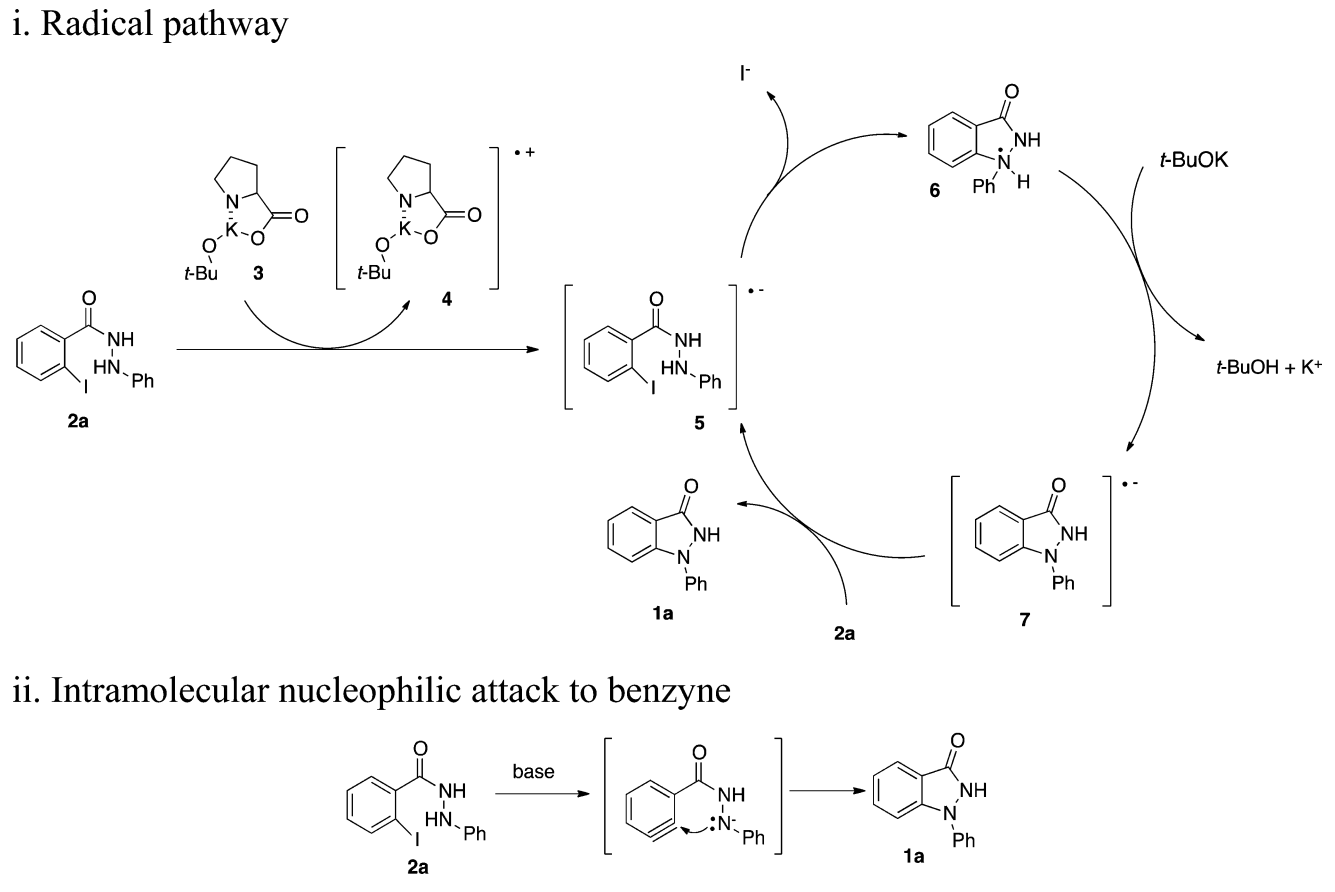


would constitute mainly the radical pathway along with another minor path(s). Indeed, the presence of AIBN [azobis(isobutyronitrile), 0.4 equiv], known as a thermal-free radical initiator, promoted the conversion in the absence of proline (condition B, Scheme 2). The initiator did not work as a catalyst considering the yield (35%). A probable mechanism with radical species is depicted in Scheme 3. An electron transfer from chelate **3** derived from *t*-BuOK and proline would afford radical anion **5**, which would be transferred to radical intermediate **6** by the release of halonium ion followed by intramolecular C−N coupling. The deprotonation of **6** by base would convert radical **6** to radical anion **7**, which would form final product **1a** by electron transfer to substrate **2a** to regenerate radical anion **5**. The probable minor pathways to indazolone are also depicted as eq 1 in Scheme 3. By the action of base, the formation of benzyne seems to be possible via intramolecular nucleophilic attack by **1a** (eq 1). The contribution of the intramolecular S_NAr mechanism would be smaller because the yields of the reactions have been decreasing in the following order: I > Br > Cl (Table 1, entries 5, 6, and 8).

Finally, to demonstrate the utility of this reaction, the intermediate for NSR (norepinephrine/serotonin reuptake) inhibitor **1u**[19] has been synthesized smoothly in two steps via the cyclization of hydrazide **2u** from commercially available starting materials in good yield (Scheme 4). Previous synthesis of **1u** required four steps (44% overall yield) with the use of a hazardous reagent (phosgene) via an unstable diazonium salt.[19]

In conclusion, we have demonstrated facile access to 1*H*-indazolones **1** from readily accessible 2-halobenzohydrazides **2** under transition metal-free conditions. The reactions have proceeded smoothly using a cheap and nontoxic amino acid, L-proline, as an additive with moderate functional group compatibility. The addition of proline was found to be essential for the efficiency of the reaction. The control experiments suggested the conversion took place mainly via the radical pathway. Using this method, we were able to prepare a synthetic precursor for (*S*)-5-fluoro-1-(2-fluorophenyl)-3-(piperidin-3-ylmethoxy)-1*H*-indazole, a known MSR inhibitor.

Scheme 3. Plausible Mechanisms



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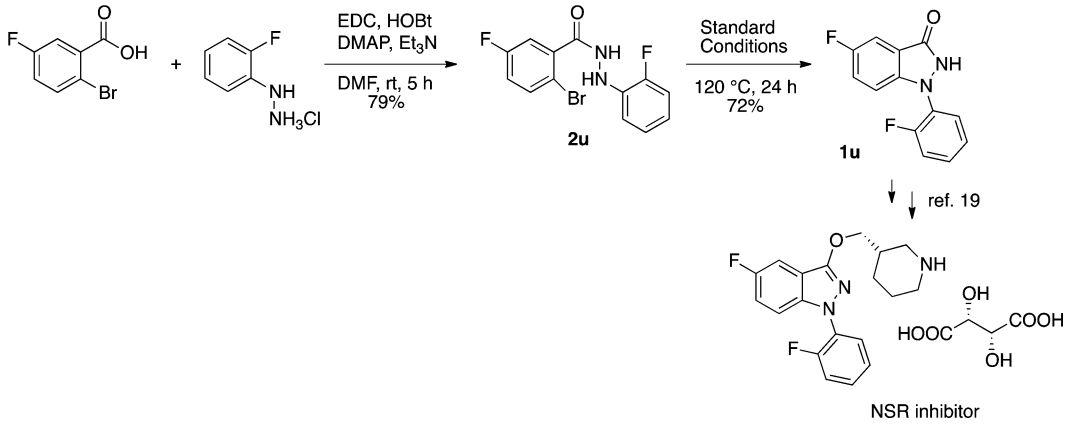
Scheme 4. Facile Formal Synthesis of the NSR Inhibitor



EXPERIMENTAL SECTION

General Information. All reactions were conducted under an Ar atmosphere. DMSO and DMF were distilled from calcium hydride. All other commercial reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz in DMSO-d_6 as a solvent. High-resolution mass measurement was performed with a fast atom bombardment (FAB) method on a quadrupole mass spectrometer operating in positive ion mode.

General Procedure for the Synthesis of 2-Halobenzohydrazides. *Condition A.* To a stirred solution of hydrazine (4.0 mmol, 1.0 equiv) and benzoic acid (4.0 mmol, 1.0 equiv) in dry DMF (10 mL) were added EDC·HCl (4.4 mmol, 1.1 equiv), HOBt·H_2O (4.4 mmol, 1.1 equiv), and DMAP (0.2 mmol, 5.0 mol %), and the mixture was stirred for 5 h at room temperature. The reaction was quenched with water and the mixture diluted with AcOEt and extracted with AcOEt. The organic layers were washed with water and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by recrystallization with AcOEt to afford 2-halobenzohydrazides **2**.

Condition B. Et_3N (4.0 mmol, 1.0 equiv) was added to a solution of hydrazine (4.0 mmol, 1.0 equiv) and benzoic acid (4.0 mmol, 1.0 equiv) in dry DMF (10 mL) and the mixture stirred for 10 min at ambient temperature; then to the mixture were added EDC·HCl (4.4 mmol, 1.1 equiv), HOBt·H_2O (4.4 mmol, 1.1 equiv), and DMAP (0.2 mmol, 5.0 mol %), and the mixture was stirred for 5 h at room temperature. The reaction was quenched with water and the mixture diluted with AcOEt and extracted with AcOEt. The organic layers were washed with water and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by recrystallization with AcOEt to afford 2-halobenzohydrazides **2**.

*2-Iodobenzoic Acid N′-Phenylhydrazide (**2aa**).*[13] Following condition A: milky white solid; 1.10 g, 85% yield; R_f = 0.44 (1:1 hexane/AcOEt); mp 204−206 °C (lit.[13] 199−201 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H, CONH), 7.96 (s, 1H, PhNH), 7.92 (d, J = 8.0 Hz, 1H), 7.50 (dd, 1H, J = 7.6, 7.3 Hz), 7.45 (dd, 1H, J = 7.6, 1.7 Hz), 7.22 (dt, J = 7.3, 1.7 Hz, 1H), 7.17 (dd, J = 8.0, 7.3 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.7 (C═O), 149.1, 141.1, 139.4, 131.2, 128.7 (2C), 128.5, 128.1, 118.6, 112.4 (2C), 93.7.

*2-Bromobenzoic Acid N′-Phenylhydrazide (**2ab**).*[13] Following condition A: milky white solid; 0.94 g, 84% yield; R_f = 0.40 (1:1 hexane/AcOEt); mp 170−172 °C (lit.[13] 170−172 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, CONH), 8.01 (s, 1H, PhNH), 7.71 (dd, J = 7.8, 7.3 Hz, 1H), 7.58−7.45 (m, 2H), 7.41 (dd, J = 7.8, 6.8 Hz, 1H), 7.17 (dd, J = 7.6, 7.3 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 6.73 (t, J = 7.3 Hz); ^{13}C NMR (100 Hz, DMSO-d_6) δ 167.2 (C═O), 149.1, 137.4, 132.9, 131.4, 129.2, 128.8 (2C), 127.8, 119.3, 119.7, 112.4 (2C).

*2-Chlorobenzoic Acid N′-Phenylhydrazide (**2ac**).*[13] Following condition A: white solid; 0.88 g, 89% yield; R_f = 0.40 (1:1 hexane/AcOEt); mp 163−165 °C (lit.[13] 152−154 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, CONH), 8.01 (s, 1H, PhNH), 7.58−7.40 (m, 4H), 7.17 (dd, J = 7.3, 7.0 Hz, 2H), 6.85 (d, J = 7.8 Hz, 2H), 6.73 (dd, J = 7.1, 6.8 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 166.3 (C═O), 149.1, 135.3, 131.3, 130.2, 129.8, 129.2, 128.8 (2C), 127.3, 118.7, 112.3 (2C).

*2-Fluorobenzoic Acid N′-Phenylhydrazide (**2ad**).*[20] Following condition A: pale yellow solid; 0.77 g, 84% yield; R_f = 0.43 (1:1 hexane/AcOEt); mp 137−139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H, CONH), 8.02 (s, 1H, PhNH), 7.64 (dd, J = 7.3, 7.0 Hz, 1H), 7.61−7.50 (m, 1H), 7.37−7.27 (m, 2H), 7.17 (dd, J = 8.3, 7.6 Hz, 2H), 6.81 (d, J = 8.3 Hz, 2H), 6.73 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 164.1 (C═O), 159.2 (d, $^1J_{CF}$ = 247.8 Hz), 149.2, 132.7 (d, $^3J_{CF}$ = 8.2 Hz), 130.0 (d, $^3J_{CF}$ = 3.3 Hz), 128.8 (2C), 124.6 (d, $^4J_{CF}$ = 3.3 Hz), 123.0 (d, $^2J_{CF}$ = 14.8 Hz), 118.7, 116.2 (d, $^2J_{CF}$ = 21.4 Hz), 112.3 (2C).

*2-Iodobenzoic Acid N′-(2-Methoxyphenyl)hydrazide (**2b**).*[13] Following condition B: pale brown solid; 0.69 g, 71% yield; R_f = 0.42 (1:1 hexane/AcOEt); mp 167−169 °C (lit.[13] 154−155 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H, CONH), 7.92 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.23 (d, J = 7.3, 6.6 Hz, 1H), 7.07 (dd, J = 3.4 Hz, 1H, PhNH), 6.95 (d, J = 7.8 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.84 (dd, J = 7.3, 7.0 Hz, 1H), 6.77 (dd, J = 7.6, 6.6 Hz, 1H), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.4 (C═O), 146.5, 140.9, 139.4, 137.8, 131.3, 128.6, 128.1, 120.7, 119.3, 112.0, 110.4, 93.8, 55.5 (OCH_3).

*2-Iodobenzoic Acid N′-(3-Methoxyphenyl)hydrazide (**2c**).* Following condition B: white solid; 1.0 g, 69% yield; R_f = 0.54 (1:1 hexane/AcOEt); mp 180−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H, CONH), 8.00 (s, 1H, PhNH), 7.93 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 7.6, 7.3 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.23 (dd, J = 7.8, 7.6 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 6.31 (d, J = 8.0 Hz, 1H), 3.71 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.7 (C═O), 160.1, 150.6, 141.1, 139.4, 131.3, 129.5, 128.5, 128.1, 105.2, 104.3, 98.0, 93.7, 54.9 (OCH_3); IR (KBr) ν 3233, 3049, 3004, 1642, 1560, 1284, 1039 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{14}H_{14}IN_2O_2$ 369.0100, found 369.0100.

*2-Iodobenzoic Acid N′-(4-Methoxyphenyl)hydrazide (**2d**).* Following condition B: pale brown solid; 1.0 g, 72% yield; R_f = 0.23 (1:1 hexane/AcOEt); mp 187−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H, CONH), 7.92 (d, J = 7.8 Hz, 1H), 7.66 (s, 1H, PhNH), 7.49 (dd, J = 7.8, 7.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 7.6, 7.3 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 3.67 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.6 (C═O), 152.7, 143.0, 141.2, 139.3, 131.2, 128.5, 128.1, 114.2 (2C), 113.9 (2C), 93.8, 55.3 (OCH_3); IR (KBr) ν 3274, 3068, 3000, 1649, 1540, 1243, 1025 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{14}H_{14}IN_2O_2$ 369.0100, found 369.0088.

*2-Iodobenzoic Acid N′-(p-Tolyl)hydrazide (**2e**).* Following condition B: white solid; 1.1 g, 75% yield; R_f = 0.43 (1:1 hexane/AcOEt); mp 165−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H, CONH), 7.92 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H, PhNH), 7.50 (dd, J = 7.6, 7.3 Hz, 1H), 7.43 (dd, J = 7.6, 1.7 Hz, 1H), 7.22

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(ddd, J = 7.8, 7.3, 1.7 Hz, 1H), 6.98 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 2.19 (s, 3H, CH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.7 (C═O), 146.9, 141.2, 139.4, 131.2, 129.1 (2C), 128.5, 128.1, 127.2, 112.7 (2C), 93.8, 20.2 (CH_3); IR (KBr) ν 3273, 3052, 3020, 2918, 2862, 1650, 1555 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{14}H_{14}IN_2O$ 353.0151, found 353.0163.

*2-Iodobenzoic Acid N′-(2-Chlorophenyl)hydrazide (**2f**).* Following condition B: beige solid; 0.82 g, 55% yield; R_f = 0.42 (1:1 hexane/AcOEt); mp 176−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H, CONH), 7.94 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H, PhNH), 7.52 (dd, J = 7.6, 6.8 Hz, 1H), 7.49 (ddd, J = 5.7, 5.1, 1.9 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.24 (ddd, J = 5.7, 5.1, 1.9 Hz, 1H), 7.20 (dd, J = 7.3, 6.3 Hz, 1H), 7.10 (d, J = 6.8 Hz, 1H), 6.80 (ddd, J = 7.3, 6.3, 1.5 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.6 (C═O), 144.4, 140.7, 139.5, 131.5, 129.2, 128.7, 128.1, 127.7, 119.7, 117.3, 113.4, 93.2; IR (KBr) ν 3196, 3079, 1635, 1555, 1040 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}ClIN_2O$ 372.9604, found 372.9586.

*2-Iodobenzoic Acid N′-(3-Chlorophenyl)hydrazide (**2g**).* Following condition B: white solid; 0.78 g, 52% yield; R_f = 0.43 (1:1 hexane/AcOEt); mp 203−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H, CONH), 8.32 (s, 1H, PhNH), 7.94 (d, J = 7.8 Hz, 1H), 7.52 (dd, J = 7.6, 7.3 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.24 (dd, J = 7.8, 7.6 Hz, 1H), 7.19 (dd, J = 7.8, 8.0 Hz, 1H), 6.89 (dd, J = 1.7 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.8 (C═O), 150.7, 140.9, 139.4, 133.5, 131.4, 130.4, 128.5, 128.2, 118.1, 111.7, 111.0, 93.7; IR (KBr) ν 3282, 2997, 2808, 1637, 1507, 1081 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}ClIN_2O$ 372.9604, found 372.9611.

*2-Iodobenzoic Acid N′-(4-Chlorophenyl)hydrazide (**2h**).* Following condition B: white solid; 0.75 g, 50% yield; R_f = 0.57 (1:1 hexane/AcOEt); mp 183−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H, CONH), 8.21 (s, 1H, PhNH), 7.93 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 7.6, 7.2 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.26−7.17 (m, 3H), 6.89 (d, J = 6.6 Hz, 2H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.8 (C═O), 148.1, 141.0, 139.4, 131.4, 128.5 (3C), 128.1, 121.9, 113.9 (2C), 93.8; IR (KBr) ν 3234, 2991, 2853, 1647, 1534, 1091 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}ClIN_2O$ 372.9604, found 372.9586.

*2-Iodobenzoic Acid N′-(4-Fluorophenyl)hydrazide (**2i**).* Following condition B: white solid; 0.80 g, 56% yield; R_f = 0.57 (1:1 hexane/AcOEt); mp 205−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H, CONH), 7.98 (d, J = 2.0 Hz, 1H, PhNH), 7.93 (d, J = 8.0 Hz, 1H), 7.57−7.42 (m, 2H), 7.22 (ddd, J = 7.6, 7.2, 1.7 Hz, 1H), 7.02 (dd, J = 9.0, 8.8 Hz, 2H), 6.95−6.85 (m, 2H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.8 (C═O), 155.9 (d, $^1J_{CF}$ = 232.2 Hz), 145.7, 141.1, 139.3, 131.3, 128.5, 128.1, 115.1 (d, $^2J_{CF}$ = 22.2 Hz, 2C), 113.7 (d, $^3J_{CF}$ = 7.4 Hz, 2C), 93.8; IR (KBr) ν 3258, 2994, 2834, 1649, 1509, 1215 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}FIN_2O$ 356.9900, found 356.9889.

*2-Iodobenzoic Acid N′-(4-Bromophenyl)hydrazide (**2j**).* Following condition B: milky white solid; 0.88 g, 53% yield; R_f = 0.43 (1:1 hexane/AcOEt); mp 219−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H, CONH), 8.19 (s, 1H, PhNH), 7.92 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 7.6, 7.0 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.22 (dd, J = 7.8, 7.6 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.7 (C═O), 148.5 (2C), 140.9, 139.4, 131.3 (2C), 128.5, 128.1, 114.4 (2C), 109.4, 93.7; IR (KBr) ν 3231, 2994, 2857, 1646, 1534, 912 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}{}^{79}BrIN_2O$ 416.9099, $C_{13}H_{11}{}^{81}BrIN_2O$ 418.9080, found 416.9081, 418.9084.

*2-Iodobenzoic Acid N′-(4-Nitrophenyl)hydrazide (**2k**).*[13] Following condition B: pale yellow solid; 0.84 g, 55% yield; R_f = 0.31 (1:1 hexane/AcOEt); mp 226−228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H, CONH), 9.35 (s, 1H, PhNH), 8.10 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 4.4 Hz, 2H), 7.32−7.20 (m, 1H), 6.95 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.7 (C═O), 154.7, 140.6, 139.4, 138.2, 131.6, 128.6, 128.2, 125.9 (2C), 110.9 (2C), 93.8.

*2-Iodobenzoic Acid N′-Cyclohexylhydrazide (**2l**).*[13] Following condition B: white solid; 1.10 g, 81% yield; R_f = 0.23 (1:1 hexane/AcOEt); mp 161−163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H, CONH), 7.86 (d, J = 7.8 Hz, 1H), 7.42 (dd, J = 7.6, 7.3 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.16 (dd, J = 7.8, 7.6 Hz, 1H), 4.89 (s, 1H, PhNH), 2.90−2.62 (m, 1H), 1.97−1.78 (m, 2H), 1.76−1.61 (m, 2H), 1.60−1.47 (m, 1H), 1.28−1.02 (m, 4H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 167.9 (C═O), 141.7, 139.1, 130.9, 128.3, 128.0, 94.0, 57.8, 31.0 (2C), 25.7, 24.0 (2C).

*2-Bromobenzoic Acid N′-Benzylhydrazide (**2m**).*[21] Following condition B: pale yellow liquid; 0.72 g, 59% yield; R_f = 0.39 (1:1 hexane/AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, 1H, J = 7.3 Hz), 7.24−7.39 (m, 8H), 4.81 (s, 2H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 140.1, 136.1, 131.7, 129.4, 128.5, 128.3, 128.2, 127.9, 127.4, 127.22, 127.16, 118.6, 52.4.

*2-Bromo-N′-(tert-butyl)benzohydrazide (**2n**).*[13] Following condition B: colorless liquid; 0.47 g, 36% yield; R_f = 0.38 (1:1 hexane/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.34−7.45 (m, 3H), 4.81 (br s, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 137.8, 132.7, 131.0, 129.3, 127.5, 119.3, 54.7, 27.4.

*2-Bromo-N′-(pyridin-2-yl)benzohydrazide (**2o**).* Following condition A: white solid; 0.52 g, 44% yield; R_f = 0.15 (1:1 hexane/AcOEt); mp 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H, CONH), 8.51 (s, 1H, NHPy), 8.08 (ddd, J = 4.8, 2.0, 0.8 Hz, 1H), 7.70 (dd, J = 8.2, 0.8 Hz, 1H), 7.55 (ddd, J = 8.2, 7.6, 0.8 Hz, 1H), 7.54 (dd, J = 7.4, 0.8 Hz, 1H), 7.49 (ddd, J = 7.6, 7.4, 0.8 Hz, 1H), 7.41 (ddd, J = 8.2, 7.6, 2.0 Hz, 1H), 6.76 (dd, J = 8.2, 0.8 Hz, 1H), 6.72 (ddd, J = 7.6, 4.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 159.7, 147.6, 137.5, 137.2, 132.9, 131.4, 129.3, 127.6, 119.3, 114.6, 106.4; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{12}H_{11}{}^{79}BrN_3O$ 292.0083, $C_{12}H_{11}{}^{81}BrN_3O$ 294.0065, found 292.0055, 294.0046.

*6-Fluoro-2-iodobenzoic Acid N′-Phenylhydrazide (**2p**).* Following condition A: milky white solid; 0.81 g, 57% yield; R_f = 0.52 (1:1 hexane/AcOEt); mp 218−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H, CONH), 8.12 (d, J = 2.4 Hz, 1H, PhNH), 7.75 (d, J = 7.8 Hz, 1H), 7.38 (dd, J = 9.0, 8.5 Hz, 1H), 7.33−7.23 (m, 1H), 7.17 (dd, J = 7.8, 7.6 Hz, 2H), 6.91 (d, J = 6.9 Hz, 2H), 6.74 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 164.4 (C═O), 158.4 (d, $^1J_{CF}$ = 247.8 Hz), 148.8, 135.0 (d, $^3J_{CF}$ = 3.3 Hz), 132.5 (d, $^3J_{CF}$ = 8.2 Hz), 130.2 (d, $^2J_{CF}$ = 20.5 Hz), 128.7 (2C), 118.7, 115.6 (d, $^2J_{CF}$ = 21.4 Hz), 112.5 (2C), 95.1 (d, $^4J_{CF}$ = 2.4 Hz); IR (KBr) ν 3242, 3032, 2985, 1659, 1493, 1244 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}FIN_2O$ 356.9900, found 356.9903.

*4-Chloro-2-iodobenzoic Acid N′-Phenylhydrazide (**2q**).* Following condition A: white solid; 0.97 g, 65% yield; R_f = 0.49 (1:1 hexane/AcOEt); mp 199−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H, CONH), 8.08−7.97 (m, 2H, PhNH, Ar), 7.58 (dd, J = 8.0, 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 7.6, 7.3 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.0 (C═O), 149.0, 140.0,138.3, 134.7, 129.7, 128.7 (2C), 128.1, 118.7, 112.4 (2C), 94.9; IR (KBr) ν 3255, 3050, 2843, 1647, 1529, 1100 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}ClIN_2O$ 372.9604, found 372.9576.

*5-Bromo-2-iodobenzoic Acid N′-Phenylhydrazide (**2r**).* Following condition A: white solid; 1.10 g, 68% yield; R_f = 0.67 (1:1 hexane/AcOEt); mp 210−212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H, CONH), 7.98 (s, 1H, PhNN), 7.85 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 8.3, 2.4 Hz, 1H), 7.17 (dd, J = 7.8, 7.3 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 167.3 (C═O), 148.9, 143.1, 141.4, 134.1, 130.9, 128.8 (2C), 121.5, 118.7, 112.5 (2C), 92.8; IR (KBr) ν 3272, 3097, 3046, 1642, 1450, 915 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{11}BrIN_2O$ 416.9099, found 416.9116.

*4,5-Dimethoxy-2-bromobenzoic Acid N′-Phenylhydrazide (**2s**).* Following condition A: milky white solid; 1.10 g, 82% yield; R_f = 0.19 (1:1 hexane/AcOEt); mp 127−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H, CONH), 7.98 (d, J = 8.3 Hz, 1H, PhNH), 7.21 (s, 1H), 7.16 (dd, J = 7.6, 7.2 Hz, 2H), 7.05 (s, 1H), 6.86 (d, J = 7.6 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 3.82 (s, 6H, OCH_3); ^{13}C NMR (100 Hz,

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DMSO-d_6) δ 166.8 (C═O), 149.2, 128.8 (2C), 128.7, 127.8, 127.4, 118.6, 115.9, 112.4 (2C), 112.3, 110.0, 56.1 (OCH_3), 55.9 (OCH_3); HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{16}{}^{79}BrN_2O_3$ 351.0344, found 351.0321.

*4,5-Dimethoxy-2-bromobenzoic Acid N′-(p-Tolyl)hydrazide (**2t**).* Following condition B: milky white solid; 1.10 g, 72% yield; R_f = 0.32 (1:1 hexane/AcOEt); mp 169−171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H, CONH), 7.71 (s, 1H, PhNH), 7.20 (s, 1H), 7.03 (s, 1H), 6.97 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.3 Hz, 2H), 3.80 (s, 6H, OCH_3), 2.18 (s, 3H, CH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 166.7 (C═O), 150.3, 147.8, 146.9, 129.1 (2C), 128.7, 127.2, 115.9, 112.7 (2C), 112.3, 110.0, 56.1 (OCH_3), 55.9 (OCH_3), 20.2 (CH_3); IR (KBr) ν 3263, 3002, 2947, 2843, 2593, 1647, 1599, 1210, 1031, 970, 854 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{18}BrN_2O_3$ 365.0501, found 365.0503.

*5-Fluoro-2-bromobenzoic Acid N′-(2-Fluoro)hydrazide (**2u**).* Following condition B: white solid; 0.98 g, 79% yield; R_f = 0.51 (1:1 hexane/AcOEt); mp 146−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H, CONH), 7.93 (s, 1H, PhNH), 7.78−7.70 (dd, J = 8.8, 4.9 Hz, 1H), 7.42 (dd, J = 8.4, 2.5 Hz, 1H), 7.33 (dt, J = 8.5, 2.9 Hz, 1H), 7.14−6.99 (m, 3H), 6.80−6.71 (m, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 166.0 (d, J_{CF} = 1.6 Hz, C═O), 161.0 (d, $^1J_{CF}$ = 245.4 Hz), 150.2 (d, $^1J_{CF}$ = 137.8 Hz), 138.7 (d, $^3J_{CF}$ = 7.4 Hz), 136.4 (d, $^3J_{CF}$ = 9.9 Hz), 135.0 (d, $^3J_{CF}$ = 8.3 Hz), 124.7 (d, $^4J_{CF}$ = 3.3 Hz), 119.1 (d, $^3J_{CF}$ = 6.6 Hz), 118.7 (d, $^2J_{CF}$ = 22.2 Hz), 116.5 (d, $^2J_{CF}$ = 23.9 Hz), 114.9 (d, $^2J_{CF}$ = 17.3 Hz), 114.1 (d, $^2J_{CF}$ = 13.1 Hz), 114.0 (d, $^4J_{CF}$ = 6.5 Hz); IR (KBr) ν 3260, 2958, 2841, 1647, 1598, 1261, 1210, 970, 857 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{13}H_{10}BrF_2N_2O$ 326.9944, found 326.9945.

General Procedure for the Synthesis of 1*H*-Indazolones. A mixture of 2-halobenzohydrazide **2** (0.5 mmol), L-proline (0.2 mmol, 40 mol %), and *t*-BuOK (1.0 mmol, 2.0 equiv) in dry DMSO (1.5 mL) was stirred at 100 °C for 24 h. The reaction was quenched with a saturated $NaHCO_3$ solution, and the mixture was extracted with AcOEt. The organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified by recrystallization with AcOEt to afford 1*H*-indazolones **1**.

*1-Phenylindazol-3(2H)-one (**1a**).*[13] Brown solid: 88 mg, 84% yield; R_f = 0.48 (1:1 hexane/AcOEt); mp 205−207 °C (lit.[13] 166−168 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H, CONH), 7.78−7.62 (m, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.47 (dd, J = 7.8, 7.3 Hz, 2H), 7.41 (dd, J = 8.3, 7.1 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.11 (dd, J = 8.0, 7.1 Hz); ^{13}C NMR (100 Hz, DMSO-d_6) δ 110.3 (C═O), 148.8, 120.3, 120.5, 120.6 (2C), 124.8, 128.4, 129.5 (2C), 139.2, 140.2, 156.3.

*1-(2-Methoxyphenyl)-2,3-dihydro-1H-indazol-3-one (**1b**).*[13] Brown solid: 67 mg, 56% yield; R_f = 0.19 (1:1 hexane/AcOEt); mp 185−187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H, CONH), 7.70 (d, J = 8.0 Hz, 1H), 7.46−7.29 (m, 3H), 7.25 (d, J = 8.3 Hz, 1H), 7.12−6.98 (m, 3H), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.0 (C═O), 153.4, 141.3, 128.5, 128.2, 127.6, 127.3, 120.7, 119.9, 119.3, 113.6, 112.8, 110.9, 55.5 (OCH_3).

*1-(3-Methoxyphenyl)-2,3-dihydro-1H-indazol-3-one (**1c**).* Pale red solid: 13 mg, 11% yield; R_f = 0.36 (1:1 hexane/AcOEt); mp 178−180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H, CONH), 7.82−7.71 (m, 2H), 0.7.52−7.37 (m, 2H), 7.28 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 168.72 (C═O), 160.2, 150.6, 141.1, 139.4, 131.3, 129.6, 128.5, 128.2, 105.2, 104.3, 98.0, 93.8, 54.9 (OCH_3); IR (KBr) ν 2958, 2828, 1510, 1308, 1239, 1172, 1015 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_2$ 241.0977, found 241.0969.

*1-(4-Methoxyphenyl)-2,3-dihydro-1H-indazol-3-one (**1d**).* Beige solid: 87 mg, 72% yield; R_f = 0.47 (1:1 hexane/AcOEt); mp 205−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H, CONH), 7.73 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.41 (dd, J = 8.5, 7.0 Hz, 1H), 7.11 (dd, J = 8.0, 7.0 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.7 (C═O), 155.8, 139.3, 133.4, 128.1, 122.7 (2C), 120.4, 119.9, 114.6 (2C), 114.1, 109.9, 55.4 (OCH_3); IR (KBr) ν 2960, 2837, 1513, 1320, 1240, 1174, 1019 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_2O_2$ 241.0977, found 241.0968.

*1-(p-Tolyl)-2,3-dihydro-1H-indazol-3-one (**1e**).*[22] Pale brown solid: 90 mg, 80% yield; R_f = 0.55 (1:1 hexane/AcOEt); mp 226−228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H, CONH), 7.62−7.74 (m, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 8.0, 7.6 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.12 (dd, J = 7.8, 7.6 Hz, 1H), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.1 (C═O), 139.2, 137.8, 134.1, 129.9 (2C), 128.2, 120.8 (2C), 120.5, 120.1, 114.5, 110.2, 20.5 (CH_3).

*1-(2-Chlorophenyl)-2,3-dihydro-1H-indazol-3-one (**1f**).* Brown solid: 55 mg, 45% yield; R_f = 0.52 (1:1 hexane/AcOEt); mp 204−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H, CONH), 7.74 (d, J = 8.1 Hz, 1H), 7.77−7.64 (m, 1H), 7.61−7.44 (m, 3H), 7.38 (t, J = 7.6 Hz), 7.12 (dd, J = 7.6, 7.3 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.4 (C═O), 141.4, 136.9, 130.6, 129.9, 129.5, 129.4, 128.3, 127.9, 120.3, 120.0, 113.9, 110.2; IR (KBr) ν 2959, 2806, 1548, 1360, 1318, 949 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{13}H_{10}ClN_2O$ 245.0482, found 245.0505.

*1-(3-Chlorophenyl)-2,3-dihydro-1H-indazol-3-one (**1g**).*[23] Milky white solid: 56 mg, 46% yield; R_f = 0.50 (1:1 hexane/AcOEt); mp 238−240 °C (lit.[23] 240 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H, CONH), 7.81 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.72−7.76 (m, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.49 (ddd, J = 7.2, 7.1, 1.2 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.19 (dd, J = 7.6, 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.8 (C═O), 141.5, 139.2, 133.9, 131.2, 128.8, 124.3, 120.9, 120.7, 119.9, 118.5, 115.3, 110.6.

*1-(4-Chlorophenyl)-2,3-dihydro-1H-indazol-3-one (**1h**).*[15] Pale brown solid: 69 mg, 51% yield; R_f = 0.47 (1:1 hexane/AcOEt); mp 266−268 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H, CONH), 7.81−7.73 (m, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.65 (t, J = 8.5 Hz, 2H), 7.17 (dd, J = 7.8, 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.6 (C═O), 139.1, 139.0, 129.4 (2C), 128.6, 128.5, 121.9 (2C), 120.6 (2C), 115.1, 110.4.

*1-(4-Fluorophenyl)-2,3-dihydro-1H-indazol-3-one (**1i**).*[24] Brown solid: 73 mg, 64% yield; R_f = 0.46 (1:1 hexane/AcOEt); mp 240−242 °C (lit.[24] 250 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H, CONH), 7.75 (d, J = 8.0 Hz, 1H), 7.77−7.64 (m, 3H), 7.44 (t, J = 7.6 Hz, 1H), 7.34 (dd, J = 8.5, 7.6 Hz, 2H), 7.15 (dd, J = 7.6, 7.3 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 159.2 (d, $^1J_{CF}$ = 240.6 Hz), 156.4 (C═O), 139.3, 136.7, 128.4, 122.7 (d, $^3J_{CF}$ = 7.4 Hz, 2C), 120.6, 120.3, 116.2 (d, $^2J_{CF}$ = 22.1 Hz, 2C), 114.6, 110.1.

*1-(4-Bromophenyl)-2,3-dihydro-1H-indazol-3-one (**1j**).* Orange solid: 84 mg, 59% yield; R_f = 0.53 (1:1 hexane/AcOEt); mp 273−275 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H, CONH), 7.77 (dd, J = 7.8, 6.8 Hz, 2H), 7.71−7.62 (m, 4H), 7.47 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.6 (C═O), 139.5, 139.1, 132.3 (2C), 128.6, 122.2 (2C), 120.7, 120.6, 116.6, 115.1, 110.4; IR (KBr) ν 2991, 2807, 1559, 1443, 1324, 815 cm^{-1}; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{13}H_{10}BrN_2O$ 288.9977, found 288.9995.

*1-Cyclohexylindazol-3(2H)-one (**1l**).*[13] Brown solid: 66 mg, 61% yield; R_f = 0.48 (1:1 hexane/AcOEt); mp 249−251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H, CONH), 7.57 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.27 (dd, J = 7.8, 7.6 Hz, 1H), 6.94 (dd, J = 7.6, 7.3 Hz, 1H), 4.36−4.25 (m, 1H), 1.87−1.62 (m, 7H), 1.50−1.36 (m, 2H), 1.24−1.12 (m, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 154.0 (C═O), 140.2, 126.6, 120.2, 118.4, 112.1, 109.2, 55.8 (2C), 32.0 (3C), 25.2.

*1,2-Dihydro-1-phenylmethyl-3H-indazol-3-one (**1m**).*[13] White solid: 18 mg, 16% yield; R_f = 0.50 (1:1 hexane/EtOAc); mp 160−161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.17−7.33 (m, 6H), 6.98 (dd, J = 7.6, 7.3 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.4, 141.2, 138.0, 128.4 (2C), 127.34 (2C), 127.26, 127.0, 120.0, 118.6, 112.6, 109.4, 51.1.

*1-(tert-Butyl)-1H-indazol-3(2H)-one (**1n**).*[13] Pale yellow solid: 74 mg, 78% yield; R_f = 0.62 (1:1 hexane/EtOAc); mp 124−127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 7.58−7.61 (m, 2H), 7.25 (dd, J = 8.5, 7.3 Hz, 1H), 7.00 (t, J = 7.6, 7.3 Hz, 1H), 1.60 (s,

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9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.8, 139.5, 126.3, 120.1, 118.1, 113.9, 111.9, 58.3, 29.3.

*1-(Pyridin-2-yl)-1H-indazol-3(2H)-one (**1o**).*[25] White solid: 67.9 mg, 64% yield; R_f = 0.28 (1:1 hexane/EtOAc); mp 186−188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (brs, 1H, CONH), 8.67 (d, J = 8.4 Hz, 1H), 8.46 (dd, J = 4.8, 0.8 Hz, 1H), 7.89 (ddd, J = 8.4, 8.0, 1.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.52 (ddd, J = 8.4, 8.0, 1.6 Hz, 1H), 7.23 (dd, J = 8.0, 7.6 Hz, 1H), 7.14 (ddd, J = 7.6, 4.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 153.7, 147.8, 139.4, 138.8, 128.9, 121.6, 120.1, 118.6, 116.0, 115.0, 111.5.

*6-Fluoro-1-phenyl-2,3-dihydro-1H-indazol-3-one (**1p**).* White solid: 39 mg, 34% yield; R_f = 0.55 (1:1 hexane/AcOEt); mp 231−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H, CONH), 7.75 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.61−7.52 (m, 3H), 7.32 (t, J = 7.3 Hz, 1H), 7.14 (dd, J = 8.3, 7.6 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 155.6 (d, $^1J_{CF}$ = 250.3 Hz), 154.4 (C═O), 141.8 (d, $^3J_{CF}$ = 7.4 Hz), 139.7, 129.8 (d, $^3J_{CF}$ = 7.4 Hz), 129.6 (2C), 125.5, 121.2 (2C), 106.7 (d, $^4J_{CF}$ = 4.1 Hz), 105.1 (d, $^2J_{CF}$ = 18.2 Hz), 103.9 (d, $^3J_{CF}$ = 20.6 Hz); IR (KBr) ν 2918, 2729, 1545, 1428, 1298, 1129 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{10}FN_2O$ 229.0777, found 229.0752.

*4-Chloro-1-phenyl-2,3-dihydro-1H-indazol-3-one (**1q**).*[13] Beige solid: 37 mg, 30% yield; R_f = 0.40 (1:1 hexane/AcOEt); mp 230−232 °C (lit.[13] 236 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H, CONH), 7.86−7.77 (m, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 7.6, 6.8 Hz, 1H), 7.50 (dd, J = 8.3, 7.1 Hz, 1H), 7.30 (dd, J = 7.3, 6.8 Hz, 1H), 7.21 (dd, J = 8.0, 7.1 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 165.4 (C═O), 140.2, 139.2, 129.5 (2C), 128.4, 124.8, 120.6 (2C), 120.5, 120.3, 114.8, 110.4.

*5-Bromo-1-phenyl-2,3-dihydro-1H-indazol-3-one (**1r**).* Pale brown solid: 61 mg, 42% yield; R_f = 0.45 (1:1 hexane/AcOEt); mp 242−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H, CONH), 7.94 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.62−7.97 (m, 3H), 7.28 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 155.4 (C═O), 139.8, 137.8, 130.9, 129.6 (2C), 125.3, 122.7, 120.9 (2C), 116.2, 112.5, 112.0; IR (KBr) ν 2979, 2905, 1550, 1442, 1267, 794 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{13}H_{10}{}^{79}BrN_2O$ 288.9977, $C_{13}H_{10}{}^{81}BrN_2O$ 290.9957, found 288.9964, 290.9935.

*4,5-Dimethoxy-1-phenyl-2,3-dihydro-1H-indazol-3-one (**1s**).* Pale brown solid: 92 mg, 68% yield; R_f = 0.17 (1:1 hexane/AcOEt); mp 235−237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H, CONH), 7.67 (d, J = 7.8 Hz, 2H), 7.49 (dd, J = 7.8, 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.1 (C═O), 151.5, 145.2, 140.5, 134.7, 129.5 (2C), 124.3, 120.3 (2C), 107.0, 100.3, 92.6, 55.7 (OCH_3), 55.6 (OCH_3); IR (KBr) ν 2950, 2826, 1480, 1352, 1288, 1249, 1171, 1087, 1017 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$ 271.1083, found 271.1080.

*4,5-Dimethoxy-1-(p-tolyl)-2,3-dihydro-1H-indazol-3-one (**1t**).* Pale red solid: 88 mg, 62% yield; R_f = 0.55 (1:1 hexane/AcOEt); mp 245−247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H, CONH), 7.59 (d, J = 8.0 Hz, 2H), 7.37 (s, 1H), 7.35 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 Hz, DMSO-d_6) δ 155.9 (C═O), 151.4, 145.1, 138.1, 135.0, 133.7, 129.9 (2C), 120.5 (2C), 106.7, 100.3, 92.4, 55.7 (OCH_3), 55.6 (OCH_3), 20.5 (CH_3); IR (KBr) ν 2959, 2825, 2670, 2568, 1481, 1354, 1289, 1249, 1171, 1094, 1011 cm^{-1}; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1239, found 285.1244.

*5-Fluoro-1-(o-fluorophenyl)-2,3-dihydro-1H-indazol-3-one (**1u**).*[13,19] Brown solid: 87 mg, 72% yield; R_f = 0.28 (1:1 hexane/AcOEt); mp 219−221 °C (lit.[13] 212 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H, CONH), 7.59 (t, J = 7.8 Hz, 1H), 7.57−7.42 (m, 3H), 7.40−7.21 (m, 3H); ^{13}C NMR (100 Hz, DMSO-d_6) δ 156.7 (d, $^1J_{CF}$ = 234.6 Hz), 156.6 (d, J_{CF} = 5.0 Hz, C═O), 155.1 (d, $^1J_{CF}$ = 247.0 Hz), 138.0, 128.7 (d, $^3J_{CF}$ = 7.4 Hz), 127.3, 127.1 (d, $^3J_{CF}$ = 11.5 Hz), 125.4 (d, $^4J_{CF}$ = 3.3 Hz), 117.2 (d, $^2J_{CF}$ = 24.7 Hz), 117.0 (d, $^2J_{CF}$ = 19.8 Hz), 113.9 (d, $^3J_{CF}$ = 9.9 Hz), 111.9 (d, $^3J_{CF}$ = 5.7 Hz), 111.8 (d, $^4J_{CF}$ = 5.7 Hz), 104.6 (d, $^2J_{CF}$ = 24.7 Hz).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00651.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. *Eur. J. Med. Chem.* **2015**, *90*, 707−731. (b) Thangadurai, A.; Minu, M.; Wakode, S.; Agrawal, S.; Narasimhan, B. *Med. Chem. Res.* **2012**, *21*, 1509−1523. (c) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415−2437. (d) Mayakrishnan, S.; Arun, Y.; Balachandran, C.; Emi, N.; Muralidharan, D.; Perumal, P. T. *Org. Biomol. Chem.* **2016**, *14*, 1958−1968.

(2) Fletcher, S. R.; McIver, E.; Lewis, S.; Burkamp, F.; Leech, C.; Mason, G.; Boyce, S.; Morrison, D.; Richards, G.; Sutton, K.; Jones, A. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2872−2876.

(3) Wang, H.; Han, H.; Von Hoff, D. D. *Cancer Res.* **2006**, *66*, 9722−9730.

(4) Kawanishi, N.; Sugimoto, T.; Shibata, J.; Nakamura, K.; Masutani, K.; Ikuta, M.; Hirai, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122−5126.

(5) Abouzid, K. A. M.; El-Abhar, H. S. *Arch. Pharmacal Res.* **2003**, *26*, 1−8.

(6) (a) Silvestrini, B.; Cheng, C. Y. U.S. Patent 99-304042, 1999. (b) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; de Ocariz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869−878.

(7) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519−521.

(8) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501−3505.

(9) Viña, D.; Del Olmo, E.; López-Pérez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525−528.

(10) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021−1023.

(11) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219−226.

(12) (a) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687−2689. For some other references for the synthesis of indazolone analogues, see: (b) Baiocchi, L.; Corsi, G.; Palazzo, G. *Synthesis* **1978**, *1978*, 633−648. (c) Barton, D. H. R.; Lukacs, G.; Wagle, D. *J. Chem. Soc., Chem. Commun.* **1982**, 450−452. (d) Wyrick, S. D.; Voorstad, J.; Cocolas, G.; Hall, I. H. *J. Med. Chem.* **1984**, *27*, 768−772. (e) Bruneau, P.; Delvare, C.; Edwards, M. P.; McMillan, R. M. *J. Med. Chem.* **1991**, *34*, 1028−1036.

(13) (a) Tanimori, S.; Ozaki, Y.; Iesaki, Y.; Kirihata, M. *Synlett* **2008**, 1973−1976. (b) Tanimori, S.; Kobayashi, Y.; Iesaki, Y.; Ozaki, Y.; Kirihata, M. *Org. Biomol. Chem.* **2012**, *10*, 1381−1387.

(14) Xiong, X.; Jiang, Y.; Ma, D. *Org. Lett.* **2012**, *14*, 2552−2555.

(15) Schelkun, R. M.; Yuen, P.-W. PCT Appl. WO 2006/056873A2, 2006.

(16) (a) Gai, R.; Back, D. F.; Zeni, G. *J. Org. Chem.* **2015**, *80*, 10278−10287. (b) Baars, H.; Beyer, A.; Kohlhepp, S. V.; Bolm, C. *Org. Lett.*

DOI: 10.1021/acs.joc.6b00651
J. Org. Chem. 2016, 81, 6766−6773

2014, *16*, 536−539. (c) Thomé, I.; Besson, C.; Kleine, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7509−7513. (d) Li, P.; Ji, Y.; Chen, W.; Zhang, X.; Wang, L. *RSC Adv.* **2013**, *3*, 73−78. (e) Beyer, A.; Buendia, J.; Bolm, C. *Org. Lett.* **2012**, *14*, 3948−3951. (f) Thomé, I.; Bolm, C. *Org. Lett.* **2012**, *14*, 1892−1895. (g) Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654−660. (h) Kalugin, V. E.; Shestopalov, A. M. *Tetrahedron Lett.* **2011**, *52*, 1557−1560.

(17) Tanimoro, K.; Ueno, M.; Takeda, K.; Kirihata, M.; Tanimori, S. *J. Org. Chem.* **2012**, *77*, 7844−7849.

(18) Heteroaromatic substrates at the aromatic ring (3-bromo-*N*′-phenylpicolinohydrazide and 3-bromo-*N*′-phenylisonicotinohydrazide) did not afford desired indazolone under the stated conditions, which have resulted in the formation of complex mixtures of unknown byproducts. The difficulty in forming the pyridine radical can be seen in the results. The starting materials (∼10−30%) along with several unknown byproducts were recovered in the case of entries with lower yields (<50−60%) in Figure 1. The probable reasons for the lower conversions could partially be attributed to the decreased nucleophilicity of the nitrogen atom (substrates **2f**−**2h** and **2k**) and the instability of the aromatic radical formed after the release of iodide ion by the electron-withdrawing group (**2p** and **2r**).

(19) Magano, J.; Waldo, M.; Greene, D.; Nord, E. *Org. Process Res. Dev.* **2008**, *12*, 877−883.

(20) Zhang, C.-Y.; Liu, X.-H.; Wang, B.-L.; Wang, S.-H.; Li, Z.-M. *Chem. Biol. Drug Des.* **2010**, *75*, 489−493.

(21) Flagstad, T.; Petersen, M. T.; Nielsen, T. E. *Angew. Chem., Int. Ed.* **2015**, *54*, 8395−8397.

(22) Kametani, T.; Sota, K.; Shio, M. *J. Heterocycl. Chem.* **1970**, *7*, 815−820.

(23) GB 1214109 19701202, 1970.

(24) Palazzo, G. U. S. US 3470194A, 19690930, 1969.

(25) Schelkun, R. M.; Yuen, P.-W. PCT Int. Appl. 2006056873, 2006.

DOI: 10.1021/acs.joc.6b00651
J. Org. Chem. 2016, 81, 6766−6773