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PAPER

Copper-catalyzed synthesis of substituted indazoles from 2-chloroarenes at low catalyst-loading†

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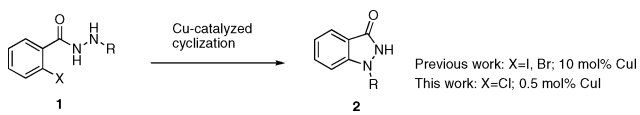
An efficient and convenient access to 1-substituted indazol-3-ones **2** has been achieved throughout the intramolecular C–N bond formations of 2-chloro-benzoic acid-*N′*-aryl and alkyl-hydrazides employing 0.5 mol% of cuprous (I) iodide and 20 mol% of L-proline as catalyst precursors under mild conditions in moderate to excellent yields.

Introduction

Substituted indazol-3-ones are present in many important pharmaceutically active molecules.[1] For instance, the indazole compounds and their derivatives have been reported to exhibit analgesic,[2] antitumor,[3] anticancer,[4] anti-inflammatory,[5] and antifertility activities.[6] We previously reported the synthesis of 1-substituted indazol-3-ones from 2-iodo- and 2-bromo-benzoic acid-*N′*-aryl and alkylhydrazides, which employed 10 mol% of cuprous(I) iodide and 20 mol% of L-proline as the pre-catalysts at room temperature for 3 h in good to excellent yields (Scheme 1).[7,8] However, decreasing the catalyst-loading under 10 mol% and also the use of chloroarenes as substrates afforded unsatisfactory results.[7]



Scheme 1 Strategy to synthesize indazolones.

The employment of 2-chlorobenzohydrazides as starting materials would represent some benefits. Economically, 2-chlorobenzoic acids and derivatives, precursors of 2-chlorobenzohydrazides, are usually less expensive than the corresponding iodo- and bromo-derivatives. Moreover, the rich existence of their analogues with a variety of substituents should also be attractive for diversity-oriented synthesis. Ordinarily, iodo- and bromoarenes have been utilized as coupling partner for the copper-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions and choroarenes were not nearly employed due to their significantly low reactivity.[9] Moreover, lowering the catalyst loading is also highly desirable from a green chemistry viewpoint. Mostly, 5 to 20 mol% of catalysts have been frequently exploited for the complete consumption of starting materials, in the copper-catalyzed systems.[9] After the several examinations based on our previous report,[7] it was eventually found that the 2-chlorobenzohydrazides **1** were also suitable substrates to be converted smoothly into 1-substituted indazol-3-ones **2** with only 0.5 mol% of copper catalyst in practical efficiency. Details of the results are reported below.

Results and discussions

Synthesis

Table 1 shows the summary for optimization studies of the reaction conditions to improve our previous system.[7] The reaction of 2-chlorobenzoic acid-*N′*-phenylhydrazide **1a** in the presence of 1 mol% of cuprous (I) iodide with L-proline[9d] (2 mol%)[10] and potassium carbonate (2 equiv.) in dimethylsulfoxide at 70 °C for 15 h gave a ring-closed product **2a** in 31% yield (entry 1). The reaction did not perform under ligand free conditions (not shown). Gratifyingly, when 5 mol% L-proline was employed with 1 mol% of cuprous (I) iodide, the yield was increased to 67% in the same reaction conditions (entry 2). To our delight, the satisfactory results were observed when excess amount of L-proline (10 and 20 mol% based on substrates) was introduced with 1 mol% CuI to afford desired product in 75 and 79% yields, respectively (entry 3 and 4). Organic base DBU should also be a good base for this transformation, although prolonged reaction time was required to accomplish the complete consumption of the starting material (entry 5). The reaction with cesium carbonate afforded a lower yield (62%, entry 7) and sodium *t*-butoxide provided complex mixture (not shown). A more efficient and economical conversion was realized with the use of 0.5 mol% copper catalyst and large excess L-proline (20 mol%) to produce indazolone **2a** in 80% yield after 24 h at 90 °C (entry 8).[11] To our knowledge, these results would be the first cases for copper-mediated coupling reactions to achieve efficient and practical carbon-heteroatom bond formations utilizing less reactive chloroarene as coupling partner along with a lower catalyst loading (<1 mol%) under the mild conditions. The role of excess L-proline based on the loading

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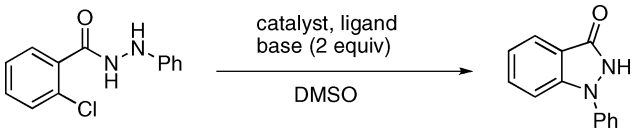
Table 1 The intramolecular cyclization of **1a** under various reaction conditions[a]



1a **2a**

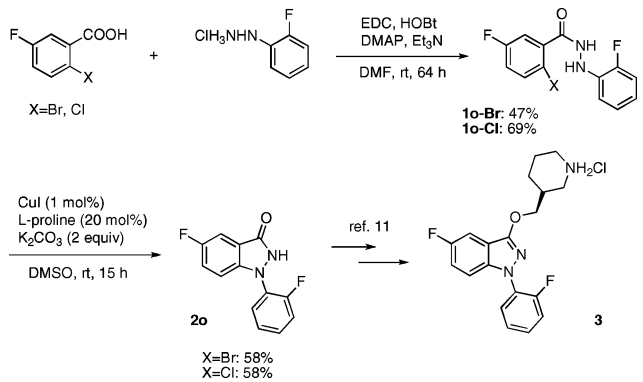
Entry	Catalyst	Ligand	Base	Temp (° C)	Time (h)	Yield[b] (%)
1	CuI (1)	L-Proline (2)	K_2CO_3	70	15	31
2	CuI (1)	L-Proline (5)	K_2CO_3	70	15	67
3	CuI (1)	L-Proline (10)	K_2CO_3	70	15	75
4	CuI (1)	L-Proline (20)	K_2CO_3	70	15	79
5	CuI (1)	L-Proline (20)	DBU	70	48	84
6	CuI (0.5)	L-Proline (20)	K_2CO_3	70	15	71
7	CuI (0.5)	L-Proline (20)	Cs_2CO_3	70	15	62
8	CuI (0.5)	L-Proline (20)	K_2CO_3	90	24	80

[a] All of the reactions were carried out using benzhydrazide **1a** (1.0 mmol), catalyst (0.5 and 1 mmol), ligand (2–20 mmol), and base (2.0 mmol) in DMSO (10 mL). [b] Isolated yield.

of copper catalyst for this system could be explained by considering the competitive role of the hydrazide moiety in complexating the copper ion. Such a complexation would inhibit the intramolecular coupling. Therefore a large excess of proline is needed to ensure the complexation of copper. The closely related phenomenon has been argued in our previous report, where DMEDA (20 mol%) and cuprous (I) chloride (1 mol%) were exploited as pre-catalysts for the coupling of 2-haloaniline with α–amino acids to form quinoxaline-2-ones.[12] A control experiment without the use of catalyst gave no desired product (not shown).

As the optimized reaction conditions were in hand, we next investigated the cyclization reactions with a series of substituted 2-chlorobenzohydrazides to examine the generality of the conditions (Table 2). Both electron-donating and electron-withdrawing groups on aromatic rings of corresponding benzoic acid and hydrazine moieties are feasible for this cyclization reaction. Alkyl-substituted hydrazides also reacted effectively at the same procedure (entries 7, 8 and 10). Although nitro-substituted hydrazides **1c** and **1d** provided complex mixtures under the optimized conditions, to our delight, the cyclization proceeded smoothly at room temperature to afford indazolone **2c** and **2d** in 93% and 55% yields, respectively (entries 3 and 4). In the latter case, a strong electron-donating methoxy group would destabilize the intermediacy nucleophilic nitrogen anion in the cyclization step. The pyridine containing substrates **1k**, **1l** and **1m** were also accessible for this transformation to provide a novel class of pyrazolo[3,4-b]pyridin-3-ones **2k**, **2l** and **2m** in moderate to good yields (entries 11, 12 and 13). Sulfonamide **1n** also reacted to give multi-substituted indazolone **2n** without the use of protecting group. Moreover, the comparable efficiencies were observed by a comparison of Br/I and Cl as leaving groups as shown in entries 1 and 7. The scalability of this transformation has also been demonstrated with the use of hydrazide **1a** (1.30 g, 5.25 mmol) to provide indazolone **2a** (1.00 g, 90%) under the optimal conditions (see experimental section).

As shown in Scheme 2, indazolone **2o**,[13] a key intermediate for the synthesis of (*S*)-5-fluoro-1-(2-fluorophenyl)-3-(piperidin-3-ylmethoxy)-1*H*-indazole **3**, a norepinephrine/serotonin reuptake inhibitor for the treatment of fibromyalgia,[14] has been



Scheme 2 Simple synthesis of the key intermediates for a pharmaceutical.

synthesized easily from commercial starting materials utilizing our protocol. The copper-mediated cyclization of hydrazides **1o**, derived from 5-fluoro-2-bromo and chlorobenzoic acids with 2-fluorophenylhydrazine, underwent to form desired indazolone **2o** in both 58% yields. The moderate efficiency for the cyclization step would attribute to steric bulk of *ortho*-substitution on hydrazine aromatic ring. This strategy avoids a hazardous reagent and unstable intermediate required for previous route.[13]

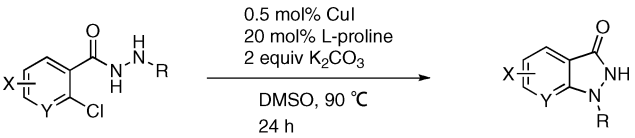
Pharmacology

In the course of our continuing study directed toward the discovery of anti-cancer drugs,[15] we tested the cytotoxic activity of all synthesized compounds (hydrazides **1** and indazolones **2**) against HeLaS3 cell line. Most of compounds did not show significant inhibition under 30 μM (IC_{50}) except for hydrazides **1n** (0.25 μM) and **1o-Br** (2.9 μM). Other biological studies are now under investigation.

Conclusions

In conclusion, we have established a general and practical access to substituted indazolones from readily available starting materials. The substrate scope for this synthesis has been expanded to even less reactive chloroarenes in this study. The improved reaction

Table 2 Synthesis of substituted indazolone derivatives[a]



1 **2**

X=substituents; Y=CH or N; R=alkyl, aryl

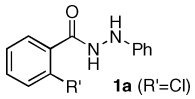
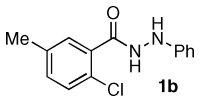
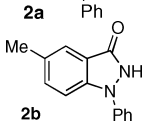
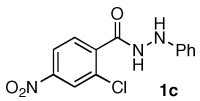
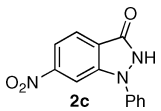
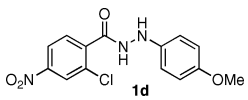
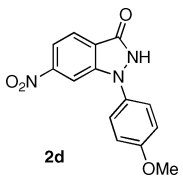
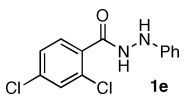
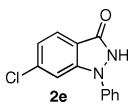
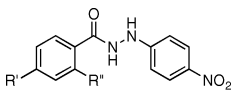
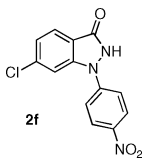
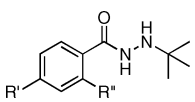
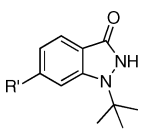
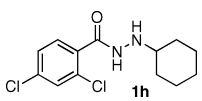
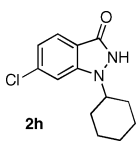
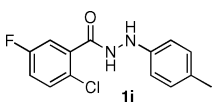
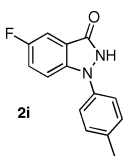
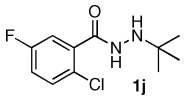
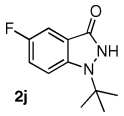
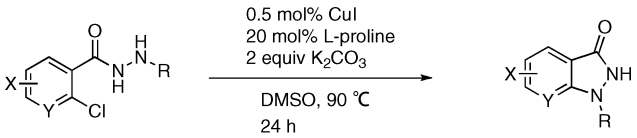
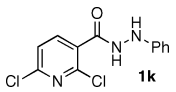
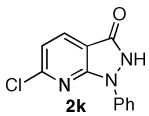
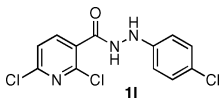
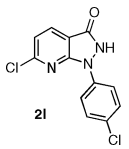
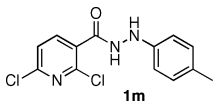
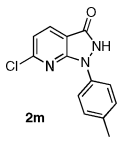
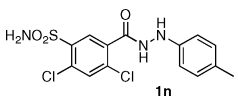
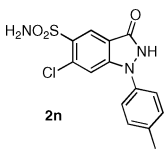
Entry	Hydrazide **1**	Indazolone **2**	Yield[b] (%)
1	 **1a** (R'=Cl)	 **2a**	80 (R′═Cl) 82 (R′═I) 59 (R′═Br)
2	 **1b**	 **2b**	87
3[c]	 **1c**	 **2c**	93
4[c]	 **1d**	 **2d**	55
5	 **1e**	 **2e**	91
6	 **1f**	 **2f**	86
7	 **1g** R'=R"=Cl	 **2g** R=Cl	83 (R′═R″═Cl) 66 (R′═H, R″═I) 80 (R′═H, R″═Br) 86 (R′═H, R″═Cl)
8	 **1h**	 **2h**	82
9	 **1i**	 **2i**	79
10	 **1j**	 **2j**	90

Table 2 (*Contd.*)



1 **2**

X=substituents; Y=CH or N; R=alkyl, aryl

Entry	Hydrazide **1**	Indazolone **2**	Yield[b] (%)
11	 **1k**	 **2k**	66
12	 **1l**	 **2l**	80
13	 **1m**	 **2m**	77
14	 **1n**	 **2n**	65

[a] All the reactions were carried out using hydrazide **1** (1.0 mmol), CuI (0.0050 mmol, 0.5 mol%), L-proline (0.020 mmol, 20 mol%), K_2CO_3 (2.0 mmol) in DMSO (10 mL). [b] Isolated yield. [c] The reaction was performed at room temperature.

conditions with lower copper catalyst loading (0.5 mol%) have been realized by carefully controlled ligand loading (20 mol%). The success of the key low loading of copper-catalyst in this transformation would partially attributed to the use of excess ligand. Bolm suggests that the ligand shifts equilibria away from favorable low-coordinated copper species which otherwise would be deactivated by aggregation.[12] Structurally diverse indazolones together with benzhydrazides as the precursors have been synthesized efficiently by this process to prepare two series of small chemical libraries. The simple synthesis of a key intermediate **2o** for a drug **3** was conducted by this protocol in mild conditions. Finally, the novel class of strong cytotoxic compound **1n** has appeared among the libraries.

Experimental

Chemistry

General methods. Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using hexane and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in DMSO-d6 solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as the internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined by using a Büchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HR-MS was determined using JEOL JNM-AX 500 mass spectrometer.

General procedure for the preparation of acid hydrazides 1a–o by the condensation of acid with hydrazine. To a stirred solution of acid (5.0 mmol) in DMF (10 mL) were added EDC·HCl (1.1 g, 5.5 mmol), HOBt·H_2O (0.74 g, 5.5 mmol), DMAP (31 mg, 0.25 mmol), and hydrazine (5.0 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature over 24 h, and it was diluted with EtOAc and poured into saturated NH_4Cl solution. Extractive workup with EtOAc and purification by column chromatography afforded acid hydrzide as a white solid.

Spectral data of acid hydrazides (1a–o)

2-Chloro-*N*′-phenylbenzohydrazide (1a)[7]. Yield 90%; R_f 0.53 (hexane : AcOEt = 1 : 1); mp 152.2 °C; ^1H NMR (400 MHz,

DMSO-d6) δ 10.21 (d, 1H, J = 2.7 Hz, CONH), 8.03 (d, 1H, J = 2.7 Hz, PhNH), 7.38–7.60 (m, 4H, Ar), 7.17 (dd, 2H, J = 7.3, 7.6 Hz, Ar), 6.84 (d, 2H, J = 7.6 Hz, Ar), 6.72 (t, 1H, J = 7.3 Hz, Ar).

2-Chloro-4-methyl-benzoic acid *N′*-phenyl-hydrazide (1b). Yield 68%; mp 178.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.14 (s, 1H, CONH), 7.96 (s, 1H), 7.41 (d, 1H, J = 8.3 Hz), 7.35 (s, 1H), 7.31 (d, 1H, J = 8.0 Hz), 7.17 (t, 2H, J = 7.3 Hz), 6.86 (d, 2H, J = 7.8 Hz), 6.73 (t, 1H, J = 7.3 Hz), 2.35 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6)δ 166.3, 149.1, 136.8, 135.0, 131.7, 129.5, 129.4, 128.7 (2×C), 127.2, 118.6, 112.3 (2×C), 20.4; HRMS-EI calcd for $C_{14}H_{13}N_2OCl$: 260.0717, Found: 260.0699.

2-Chloro-4-nitro-benzoic acid *N′*-phenyl-hydrazide (1c)[16]. Yield 68%; R_f 0.63 (hexane : AcOEt = 1 : 1); mp 169.1 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.53 (s, 1H, CONH), 8.46 (d, 1H, J = 1.7 Hz, Ar), 8.34 (d, 1H, J = 8.5 Hz, Ar), 8.19(s, 1H, PhNH), 7.90 (d, 2H, J = 8.5 Hz, Ar), 7.25 (t, 2H, J = 7.8 Hz, Ar), 6.92 (d, 2H, J = 7.8 Hz, Ar), 6.81 (t, 1H, J = 6.8 Hz, Ar); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.9 (C═O), 148.8, 148.6, 141.0, 131.5, 130.4, 128.9 (2×C, Ar), 124.8, 122.5, 118.9, 112.4 (2×C, Ar).

2-Chloro-4-nitro-benzoic acid *N′*-4-methoxyphenyl-hydrazide (1d). Yield 59%; R_f 0.54 (hexane : AcOEt = 1 : 1); mp: 183.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.42 (s, 1H, CONH), 8.39 (d, 1H, J = 2.0 Hz, ArNH), 8.27 (dd, J = 6.0, 2.2 Hz, 1H, Ar), 7.78–7.82 (m, 2H, Ar), 6.78–6.88 (m, 4H, Ar), 3.67 (s, 3H, MeO); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.9 (C═O), 152.9, 148.5, 142.6, 141.1, 131.4, 130.4, 124.7, 122.5, 114.3 (2×C, Ar), 113.9 (2×C, Ar), 55.3; IR (neat): 3256 (NH), 2837 (Me), 1660 (C═O), 1518, 1351 (NO_2), 1239, 1037, 832 cm^{-1}; HRMS Calcd for $C_{14}H_{12}O_4N_3Cl$: 321.0516, Found: 321.0338.

2,4-Dichloro-benzoic acid *N′*-phenyl-hydrazide (1e)[17]. Yield 84%; mp 169.1 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H, CONH), 8.03 (s, 1H), 7.75 (d, 1H, J = 1.7 Hz), 7.52–7.62 (m, 2H), 7.17 (t, 2H, J = 7.6 Hz), 6.84 (d, 2H, J = 7.6 Hz), 6.73 (t, 1H, J = 7.3 Hz); ^{13}C NMR (136 Hz, DMSO-d6) δ 165.5, 149.0, 135.0, 134.1, 131.5, 130.6, 129.4, 128.8 (2×C), 127.5, 118.8, 112.3 (2×C).

2,4-Dichloro-benzoic acid *N′*-(4-nitro-phenyl)-hydrazide (1f)[18]. Yield 84%; R_f 0.43 (hexane : AcOEt = 1 : 1); mp 247.6 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.63 (s, 1H, CONH), 9.35 (s, 1H, Ar), 8.10 (d, 2H, J = 7.8 Hz,Ar), 7.79 (d, 1H, J = 1.7 Hz, ArNH), 7.66 (d, 1H, J = 8.3 Hz, Ar), 7.57 (dd, 1H, J = 1.7, 8.3 Hz, Ar), 6.90 (d, 2H, J = 7.8 Hz, Ar); ^{13}C NMR (136 Hz, DMSO-d6) δ 165.4 (C═O), 154.5, 138.3 (2×C, Ar), 135.5, 133.4, 131.6, 130.7, 129.5, 127.6, 126.0 (2×C, Ar), 110.9.

2,4-Dichloro-benzoic acid *N′*-*t*-butyl-hydrazide (1g)[19]. Yield 91%; mp 112.9 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.80 (br s, 1H), 7.70 (d, 2H, J = 2.0 Hz), 7.49 (dd, 1H, J = 2.0, 8.3 Hz), 7.44 (d, 1H, J = 8.3 Hz), 1.06 (s, 9H); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.2, 134.6, 134.5, 131.5, 130.7, 129.1, 127.3, 54.7, 27.3 (3×C).

2,4-Dichloro-benzoic acid *N′*-cyclohexyl-hydrazide (1h). Yield 60%; mp 164.7 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.83 (d, 1H, J = 2.7 Hz, CONH), 7.68 (d, 1H, J = 1.7 Hz), 7.48 (dd, 1H, J = 1.7, 8.3 Hz), 7.43 (1H, d, J = 8.3 Hz), 4.94 (br s, 1H), 2.72–2.84 (m, 1H), 1.83 (d, 2H, J = 11.5 Hz), 1.63–1.76 (m, 2H), 1.50–1.59 (d, 2H, J = 8.8 Hz), 1.02–1.28 (m, 5H); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.3, 134.6, 134.5, 131.5, 130.5, 129.1, 127.3, 57.8, 30.9 (2×C), 25.7, 23.9 (2×C); HRMS Calcd for $C_{13}H_{16}N_2OCl_2$: 286.0640, Found: 286.0640.

2-Chloro-5-fluoro-benzoic acid *N′*-4-methylphenyl-hydrazide (1i). Yield 69%; mp 167.0 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.25 (d, 1H, J = 2.9 Hz), 7.85 (d, 1H, J = 2.4 Hz), 7.60 (dd, 1H, J = 4.9, 9.0 Hz), 7.44 (dd, 1H, J = 2.9, 8.3 Hz), 7.38 (1H, dt, J = 2.9, 8.3 Hz), 6.98 (d, 2H, J = 8.3 Hz), 6.77 (d, 2H, J = 8.3 Hz), 2.19 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6) δ 155.8, 137.6, 136.2, 134.4, 129.9 (3C), 120.8 (3×C), 117.3, 111.9, 104.5, 20.5; HRMS Calcd for $C_{14}H_{12}N_2OClF$: 278.0622, Found: 278.0605.

2-Chloro-5-fluoro-benzoic acid *N′*-*t*-butyl-hydrazide (1j). Yield 79%; mp 103.3 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.91 (br s, 1H), 7.63 (dd, 1H, J = 4.9, 8.3 Hz), 7.36–7.46 (m, 2H), 4.93 (br s, 1H), 1.14 (s, 9H); ^{13}C NMR (136 Hz, DMSO-d6) δ 163.8 (C═O), 161.6 (159.1), 137.34 (137.26), 131.6 (131.5), 125.72 (125.70), 118.0 (117.8), 116.5 (116.2), 54.7, 27.3 (3×C); HRMS Calcd for $C_{11}H_{14}N_2OClF$: 244.0779, Found: 244.0829.

2,6-Dichloro-nicotinic acid *N′*-phenyl-hydrazide (1k). Yield 93%; R_f 0.45 (hexane : AcOEt = 1 : 1); mp 147.4. °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.40 (s, 1H, CONH), 8.12 (d, 1H, J = 8.0 Hz, Ar), 8.09 (br s, 1H, ArNH), 7.71 (d, 1H, J = 8.0 Hz, Ar), 7.17 (t, 2H, J = 7.6 Hz, Ar), 6.85 (d, 2H, J = 7.8 Hz, Ar), 6.68–6.80 (m, 1H, Ar); ^{13}C NMR (136 Hz, DMSO-d6)δ 164.2 (C═O), 149.8, 148.7, 146.2, 141.6, 130.7, 128.9 (2×C, Ar), 123.8, 119.0, 112.4 (2×C, Ar); IR (neat): 3256 (NH), 3055 (Ar), 1653 (C═O), 1492, 1341, 1144, 912, 756, 691 cm^{-1}; HRMS Calcd for $C_{12}H_9N_3OCl_2$: 281.0122, Found: 281.0216.

2,6-Dichloro-nicotinic acid *N′*-4-chlorophenyl-hydrazide (1l). Yield 77%; mp 180.3 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.45 (s, 1H, CONH), 8.13 (dd, 1H, J = 1.5, 8.0 Hz), 7.71 (dd, 1H, J = 1.5, 8.0 Hz), 7.21 (d, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 7.6 Hz); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.2, 149.9, 147.7, 146.2, 141.6, 130.5, 128.7 (2×C), 123.8, 122.3, 113.9 (2×C); HRMS Calcd for $C_{12}H_8N_3OCl_3$: 314.9733, Found: 314.9837.

2,6-Dichloro-nicotinic acid *N′*-4-methylphenyl-hydrazide (1m). Yield 78%; mp 145.5 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.34 (d, 1H, J = 2.4 Hz, CONH), 8.09 (d, 1H, J = 8.0 Hz), 7.91 (br s, 1H), 7.70 (d, 1H, J = 8.0 Hz), 6.99 (d, 2H, J = 8.5 Hz), 6.76 (d, 2H, J = 8.5 Hz), 2.18 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.1, 149.7, 146.4, 146.2, 141.6, 130.7, 129.2 (2×C), 127.6, 123.7, 112.6 (2×C), 20.2; HRMS Calcd for $C_{13}H_{11}N_3OCl_2$: 295.0279, Found: 295.0259.

2,4-Dichloro-5-sulfamoyl-benzoic acid *N′*-(1-methyl-phenyl)-hydrazide (1n). Yield 71%; R_f 0.40 (hexane : AcOEt = 1 : 1); mp 208.3 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ: 10.39 (d, 1H, J = 2.2 Hz, CONH), 8.00 (s, 1H, Ar), 7.99 (s, 1H, Ar), 7.92 (br s, 1H, ArNH), 7.89 (br s, 2H, SO_2NH_2), 6.99 (d, 2H, J = 8.0 Hz, Ar), 6.73 (d, 2H, J = 8.0 Hz, Ar), 2.18 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6) δ 164.5 (C═O), 146.5, 140.1, 134.4, 134.2, 132.4, 132.3, 129.3 (2×C, Ar), 129.0, 127.6, 112.6 (2×C, Ar), 20.2 (Me); HRMS Calcd for $C_{14}H_{13}N_3O_3Cl_2$: 373.0055, Found: 373.0059.

2-Chloro-5-fluoro-benzoic acid *N′*-2-fluorophenyl-hydrazide (1o-Cl). Yield 78%; mp 145.5 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.34 (br s, 1H), 7.89 (br s, 1H), 7.61 (dd, 1H, J = 4.9, 8.8 Hz), 7.35–7.46 (m, 2H), 6.96–7.14 (m, 3H), 6.71–6.79 (m,

1H); ^{13}C NMR (136 Hz, DMSO-d6) δ 165.04 (165.02), 161.6, 159.1, 136.55 (136.47), 136.41 (136.30), 131.84 (131.76), 125.77, (125.74), 124.60 (124.57), 119.05 (118.99), 118.50 (118.29), 116.38 (116.13), 114.97 (114.79), 113.88 (113.85); HRMS Calcd for $C_{13}H_9N_2OClF_2$: 282.0371, Found: 282.0374.

General procedures for the synthesis of indazole-3-ones 2a–o. The mixture of 2-chlorobenzoic acid hydrazide (1.0 mmol), CuI (0.95 mg, 0.005 mmol, 0.5 mol%), L-proline (23 mg, 0.20 mmol, 20 mol%), and K_2CO_3 (0.28 g, 2.0 mmol) in DMSO (10 mL) was stirred at 90 °C for 24 h under nitrogen atmosphere. The mixture was treated with water and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with water and brine and dried over magnesium sulfate. After filtration, solvent was evaporated *in vacuo* to *ca.* 1 mL and crystallization afforded indazole-3-ones.

1-Phenylindazol-3(2H)-one (2a)[7,20]. Yield 80%; R_f 0.45 (hexane : AcOEt = 7 : 3); mp 166.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.29 (br s, 1H, NH), 7.76 (t, 2H, J = Ar), 7.68 (d, 2H, J = 7.8 Hz, Ar), 7.51 (t, 2H, J = 7.8 Hz, Ar), 7.45 (t, 1H, J = 7.3 Hz, Ar), 7.25 (t, 1H, J = 7.3 Hz, Ar), 7.15 (t, 1H, J = 7.3 Hz, Ar); IR (KBr): ν 1554 (C═O), 1349 (NO_2), 1301, 1231, 885, 802, 753, 695 cm^{-1}.

A gram scale preparation of 2a. A mixture of 2-chlorobenzoic acid hydrazide **1a** (1.30 g, 5.25 mmol), CuI (5 mg, 0.026 mmol, 0.5 mol%), L-proline (120 mg, 1.05 mmol, 20 mol%), and K_2CO_3 (1.45 g, 10.5 mmol) in DMSO (15 mL) was stirred at 90 °C for 24 h under nitrogen atmosphere. After cooling, the mixture was treated with sat. $NaHCO_3$ aq. (100 mL) and the mixture was extracted eight times with ethyl acetate (30 mL×8). The combined organic layer was washed with water (50 mL×3) and brine (50 mL) and dried over magnesium sulfate. After filtration, solvent was evaporated *in vacuo* to afford a crude product which was recrystallized to provide pure **2a** (0.754 g, 68%). The mother liquid was concentrated *in vacuo* and the residue was subjected to column chromatography (chloroform) afforded additional pure **2a** (0.244 g, 22%).

5-Methyl-1-phenyl-2,3-dihydro-1*H*-indazol-3-one (2b). Yield 87%; mp 226.5 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.16 (br s, 1H), 7.63–7.72 (m, 3H), 7.46–7.56 (m, 3H), 7.29 (d, 1H, J = 8.8 Hz), 7.24 (t, 1H, J = 7.3 Hz), 2.41 (s, 3H); ^{13}C NMR (136 Hz, DMSO-d6) δ 155.9, 140.4, 137.9, 130.1, 129.4 (2×C), 129.3, 124.4, 120.1 (2×C), 119.5, 115.1, 110.2, 20.6; HRMS-EI Calcd for $C_{14}H_{12}N_2O$: 224.0949, Found: 224.0938.

6-Nitro-1-phenyl-2,3-dihydro-1*H*-indazol-3-one (2c). Yield 93%; R_f 0.31 (hexane : AcOEt = 7 : 3); mp 286.9 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.86 (br s, 1H, NH), 8.46 (s, 1H, Ar), 8.00 (d, 1H, J = 8.5 Hz), 7.94 (d, 1H, J = 8.5 Hz), 7.74 (d, 2H, J = 7.6 Hz, Ar), 7.59 (t, 2H, J = 7.6 Hz, Ar), 7.37 (t, 1H, J = 7.3 Hz, Ar); ^{13}C NMR (136 Hz, DMSO-d6) δ 156.4 (C═O), 147.7, 139.2, 137.8, 130.1 (2×C, Ar), 126.5, 122.1, 121.8 (2×C, Ar), 117.8, 114.9,106.8; IR (KBr): ν 3093, 1554, 1349, cm^{-1}; HRMS-EI Calcd for $C_{13}H_9N_3O_3$: 255.0644, Found: 255.0605.

6-Nitro-1-(4-methoxy-phenyl)-2,3-dihydro-1*H*-indazol-3-one (2d). Yield 55%; R_f 0.21 (hexane : AcOEt = 7 : 3); mp 281.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.70 (br s, 1H, CONH), 8.30 (s, 1H, Ar), 7.78–8.07 (m, 2H, Ar), 7.61 (d, 2H, J = 6.1 Hz, Ar), 7.13 (d, 2H, J = 6.3 Hz, Ar), 3.82 (s, 3H, OMe); ^{13}C NMR (136 Hz, DMSO-d6) δ 157.8 (C═O), 155.8, 147.3, 137.8, 132.1, 123.7 (2×C, Ar), 121.8, 116.9, 114.9 (2×C, Ar), 114.1, 106.4, 55.5 (OMe); HRMS Calcd for $C_{14}H_{11}N_3O_4$: 285.0749, Found: 285.0748.

6-Chloro-1-phenyl-2,3-dihydro-1*H*-indazol-3-one (2e)[18]. Yield 91%; mp 236.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.47 (br s, 1H), 7.77 (s, 1H), 7.76 (d, 1H, J = 8.5 Hz), 7.67 (d, 2H, J = 7.8 Hz), 7.52 (t, 2H, J = 7.6 Hz), 7.28 (1H, t, J = 7.3 Hz), 7.16 (d, 1H, J = 9.3 Hz); ^{13}C NMR (136 Hz, DMSO-d6) δ 156.2, 139.6, 139.3, 133.6, 129.6 (2×C), 125.4, 122.1, 121.0 (2×C), 120.9, 113.6, 109.9.

6-Chloro-1-(4-nitrophenyl)-2,3-dihydro-1*H*-indazol-3-one (2f). Yield 86%; colorless oil; R_f 0.20 (hexane : AcOEt = 7 : 3); ^{1}H NMR (400 MHz, DMSO-d6) δ 11.97 (br s, 1H, NH), 8.32 (d, 2H, J = 9.0 Hz, Ar), 8.04 (s, 1H, Ar), 7.95 (d, 2H, J = 9.0 Hz, Ar), 7.80 (d, 1H, J = 8.5 Hz, Ar), 7.28 (d, 1H, J = 8.5 Hz, Ar); ^{13}C NMR (136 Hz, DMSO-d6) δ 157.7 (C═O), 144.9, 143.0, 139.4, 134.6, 125.5, 125.4 (2×C, Ar), 122.4, 119.5 (2×C, Ar), 115.3, 111.1; HRMS-EI Calcd for $C_{13}H_8N_3O_3Cl$: 289.0254, Found: 289.0275.

1-*tert*-Butyl-6-chloro-2,3-dihydro-1*H*-indazol-3-one (2g). Yield 83%; mp 179.3 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.80 (br s, 1H, NH), 7.74 (s, 1H), 7.68 (d, 1H, J = 8.5 Hz), 7.05 (d, 1H, J = 8.5 Hz), 1.67 (s, 9H); ^{13}C NMR (136 Hz, DMSO-d6) δ 152.7, 139.2, 131.6, 121.6, 118.8, 112.6, 111.1, 58.8, 29.3 (3×C); HRMS-EI Calcd for $C_{11}H_{13}N_2OCl$: 224.0717, Found: 224.0707.

6-Chloro-1-cyclohexyl-2,3-dihydro-1*H*-indazol-3-one (2h). Yield 82%; mp 197.0; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.77 (br s, 1H, NH), 7.67 (d, 1H, J = 7.6 Hz), 7.59 (d, 1H, J = 8.5 Hz), 6.96 (1H, dd, J = 1.7, 7.6 Hz), 4.32–4.42 (1H, m, NCH), 1.63–1.88 (m, 7H), 1.38–1.53 (m, 2H), 1.12–1.26 (m, 1H); ^{13}C NMR (136 Hz, DMSO-d6) δ 153.9, 140.2, 131.9, 121.5, 118.9, 110.8, 108.8, 55.8, 32.0 (2×C), 25.1, 25.0 (2×C); HRMS-EI Calcd for $C_{13}H_{15}N_2OCl$: 250.0873, Found: 250.0873.

5-Fluoro-1-(4-methylphenyl)-2,3-dihydro-1*H*-indazol-3-one (2i). Yield 79%; mp 223.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.25 (br s, 1H, NH), 7.01 (br s, 1H), 7.43–7.60 (m, 3H), 7.24–7.28 (m, 3H), 2.34 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6) δ 155.8, 137.6, 136.2, 134.4, 129.9 (3×C), 120.8 (3×C), 117.3, 111.9, 104.5, 20.5; HRMS-EI Calcd for $C_{14}H_{11}N_2OF$: 242.0855, Found: 242.0854.

1-*tert*-Butyl-5-fluoro-2,3-dihydro-1*H*-indazol-3-one (2j). Yield 90%; mp 172.8 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.53 (br s, 1H, NH), 7.64 (dd, 1H, J = 3.9, 9.3 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.15 (t, 1H, J = 9.3 Hz), 1.59 (s, 9H); ^{13}C NMR (136 Hz, DMSO-d6) δ 156.8, 154.4, 152.6, 136.5, 115.6, 113.4, 104.0, 58.5, 29.3 (3×C); HRMS-EI Calcd for $C_{11}H_{13}N_2OF$: 208.1012, Found: 208.0984.

6-Chloro-1-phenyl-1*H*,2*H*,3*H*-pyrazolo[3,4-b]pyridin-3-one (2k). Yield 66%; R_f 0.64 (hexane : AcOEt = 1 : 1); mp 236.4 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.90 (br s, 1H, CONH), 8.25 (dd, 1H, J = 8.4, 1.2 Hz Ar), 8.08 (d, 2H, J = 8.8 Hz, Ar), 7.51 (t, 2H, J = 7.6 Hz, Ar), 7.29 (dd, 1H, J = 8.3, 1.2 Hz, Ar), 7.57 (dt, 1H, J = 8.3, 1.3 Hz, Ar); ^{13}C NMR (136 Hz, DMSO-d6) δ 154.4 (C═O), 150.4, 148.5, 138.9, 133.4, 129.2 (2×C, Ar), 124.9, 119.4 (2×C, Ar), 116.8, 106.5; HRMS-EI Calcd for $C_{12}H_8N_3OCl$: 245.0356, Found: 245.0327.

6-Chloro-1-(4-chlorophenyl)-1*H*,2*H*,3*H*-pyrazolo[3,4-b]pyridin-3-one (2l). Yield 90%; mp 266.6 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.99 (br s, 1H, NH), 8.26 (d, 1H, J = 8.0 Hz), 8.12 (d, 2H, J = 7.6 Hz), 7.57 (d, 2H, J = 7.6 Hz), 7.31 (d, 1H, J = 8.0 Hz);^{13}C NMR (136 Hz, DMSO-d6) δ 154.6, 150.5, 148.6, 137.7, 133.5, 129.2 (2×C), 128.6, 120.6 (2×C), 117.1, 106.8; HRMS-EI Calcd for $C_{12}H_7N_3OCl_2$: 278.9966, Found: 278.9950.

6-Chloro-1-(4-methylphenyl)-1*H*,2*H*,3*H*-pyrazolo[3,4-b]pyridin-3-one (2m). Yield 77%; mp 222.5 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.89 (br s, 1H, NH), 8.26 (d, 1H, J = 8.3 Hz), 7.93 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 7.25 (d, 1H, J = 8.3 Hz), 2.32 (s, 3H, Me); ^{13}C NMR (136 Hz, DMSO-d6) δ 154.2, 150.3, 148.3, 136.5, 134.1, 133.4, 129.5 (2×C), 119.5 (2×C), 116.5, 106.2, 20.5; HRMS-EI Calcd for $C_{13}H_{10}N_3OCl$: 259.0512, Found: 259.0504.

6-Chloro-5-sulfamoyl-1-(4-methylphenyl)-2,3-dihydro-1*H*-indazol-3-one (2n). Yield 65%; R_f 0.63 (hexane : AcOEt = 1 : 3); mp 297.7 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.80 (br s, 1H, CONH), 8.45 (s, 1H, Ar), 7.84 (s, 1H, Ar), 7.58 (d, 2H, J = 6.6 Hz, Ar), 7.57 (s, 2H, SO_2NH_2), 7.35 (d, 2H, J = 8.3 Hz, Ar), 2.36 (s, 3H, OMe); ^{13}C NMR (136 Hz, DMSO-d6) δ: 156.8 (C═O), 139.3, 136.7, 135.6, 133.1, 130.2 (2×C, Ar), 130.1, 122.5, 121.6 (2×C, Ar), 112.6, 112.0, 20.6; IR (neat): 3382 (NH), 3277 (NH), 3032 (Ar), 1557 (C═O), 1337 (S═O), 1169, 997, 916, 810 cm^{-1}; HRMS-EI Calcd for $C_{14}H_{12}N_3O_3SCl$: 337.0268, Found: 337.0168.

5-Fluoro-1-(2-fluorophenyl)-2,3-dihydro-1*H*-indazol-3-one (2o)[13]. Yield 58%; R_f 0.35 (hexane : AcOEt = 7 : 3); mp 211.7 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 11.39 (br s, 1H, CONH), 7.59 (t, 1H, J = 7.8 Hz Ar), 7.40–7.54 (m, 3H, Ar), 7.36 (t, 1H, J = 7.3 Hz, Ar), 7.22–7.34 (m, 2H, Ar).

Pharmacology[21]

Cell Culture. HeLa S3 cells were cultured at 37 °C in a humidified atmosphere with 5% CO_2, in a RPMI 1640 cell culture medium supplemented with 10% fetal bovine serum.

***In vitro* cytotoxicity test.** The cells were plated at a density of 1.5 × 103 cells per 0.1 mL per well in 96-well flat-bottomed microplates. After overnight incubation, 0.1 mL aliquots of medium containing serially diluted test compounds were added to triplicate wells, and incubation was continued for 72 more hours. Cell growth was assessed using the crystal violet staining method.[22] The IC_{50} value was defined at the drug concentration needed to produce a 50% reduction of growth relative to the untreated control.

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