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A Convenient Synthesis of 1-Aryl- and 2-Aryl-Substituted Indazolones via Intramolecular C–N Coupling Promoted by KO*t*-Bu

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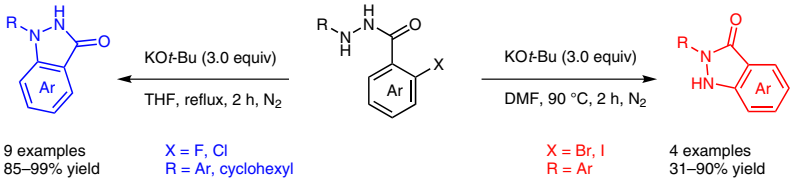

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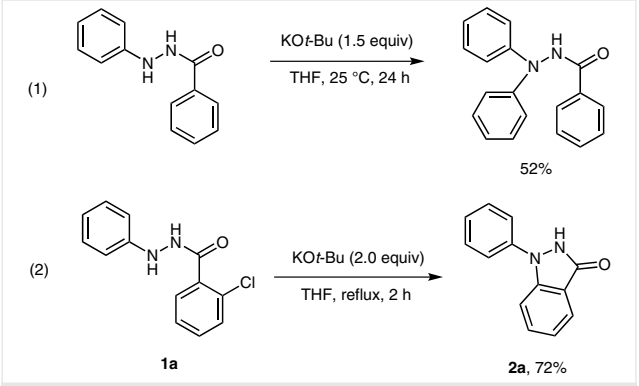
Abstract A new method for the synthesis of 1-arylindazolones and 2-arylindazolones from *N*′-aryl-2-halobenzohydrazides promoted by KO*t*-Bu was developed. The difference of 2-halogen substituent exerted a significant effect on the distribution of the products. Two distinct reaction pathways are proposed for the generation of 1-arylindazolones and 2-arylindazolones, respectively.

Key words indazolone, C–N coupling, potassium *tert*-butoxide, radical reaction, 2-halobenzohydrazide

Indazolone, an isomer of 3-OH indazole, is an important class of heterocyclic compounds that widely exists in natural products and synthetic drugs.[1] Indazolone derivatives possess many interesting bioactivities such as anticancer,[2] anti-inflammation,[3] antidiabete,[4] antivirus,[5] antiprotozoan,[6] antipsychosis,[7] bradykinin B1 receptor antagonists,[8] activators of the nitric oxide receptor,[9] and so on.[10] So far there are more than twenty indazolone derivatives on market as drugs or at the clinical research stage.[11] The methods for the synthesis of indazolone derivatives have been extensively studied.[12] In 2008 and 2012, Tanimori and co-workers reported CuI/proline-catalyzed intramolecular coupling of 2-halobenzohydrazide;[13] a variety of 1-alkyl- and 1-aryl-substituted indazolones were synthesized. In 2012, Ma and co-workers reported CuI-catalyzed intermolecular coupling of *N*-acyl-*N*′-substituted hydrazines with aryl iodides.[14] These methods still suffer from several disadvantages, such as the requirements for transition-metal catalysts, multistep reactions, harsh reaction conditions, expensive starting materials, or carcinogenic reagents. Thus, there is an unmet need for the development of a simple and general synthesis of indazolones from readily available starting materials, especially without a transition-metal catalyst.

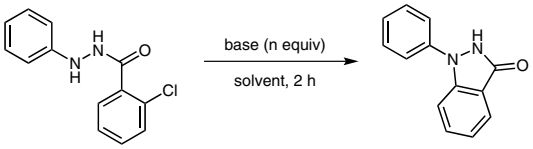
Recently we found that KO*t*-Bu/THF could promote homocoupling and decomposition of *N*′-arylacylhydrazines.[15] A series of *N*′,*N*′-diarylacylhydrazines were synthesized [Scheme 1 (1)]. During the study, we found that the reaction of 2-chlorobenzohydrazide **1a** under the refluxing condition did not give the expected *N*′,*N*′-diarylacylhydrazine, instead 1-phenylindazolone **2a** was obtained in good yield [Scheme 1 (2)]. Based on these findings, a new synthetic method for 1-arylindazolones and 2-arylindazolones from 2-halobenzohydrazides was explored and the results are disclosed herein.



Scheme 1 KO*t*-Bu promoted reactions of benzohydrazide and 2-chlorobenzohydrazide

Initially, we optimized the reaction conditions of 2-chlorobenzohydrazide **1a**. We found that the reaction with 3.0 equivalents of KO*t*-Bu gave the product **2a** in almost quantitative yield (Table 1, entry 1). The replacement of THF with DMF and DMSO also provided excellent yields (Ta-

Table 1 Optimization of Reaction Conditions[a]



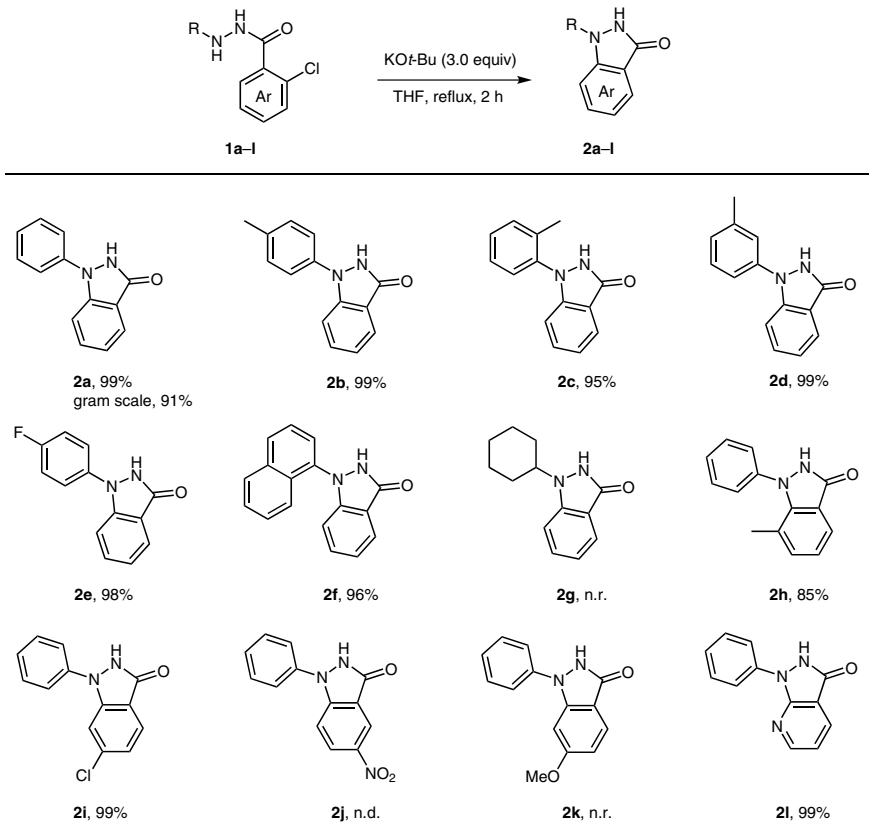
1a **2a**

Entry	Base (equiv)	Solvent	Temp (°C)	Yield[b] (%)
1	KO*t*-Bu (3.0)	THF	reflux	99
2	KO*t*-Bu (3.0)	DMF	90	99
3	KO*t*-Bu (3.0)	DMSO	90	92
4	KO*t*-Bu (3.0)	DMA	90	78
5	KO*t*-Bu (3.0)	toluene	90	67
6	NaO*t*-Bu (3.0)	THF	reflux	trace
7	KOMe (3.0)	THF	reflux	trace
8	NaOMe (3.0)	THF	reflux	trace
9	KOH (3.0)	THF	reflux	0
10	KO*t*-Bu (3.0)	THF	50	29

[a] Reaction conditions: **1a** (0.2 mmol), base, solvent (4.0 mL), under N_2, 2 h.
[b] Isolated yields.

ble 1, entries 2 and 3). Other solvents such as *N*,*N*-dimethylacetamide (DMA) and toluene gave lower yields (Table 1, entries 4 and 5). The influence of bases was also examined. NaO*t*-Bu, KOMe, NaOMe, and KOH were found to be ineffective (Table 1, entries 6–9). Lower reaction temperature (50 °C) led to a significantly lower yield (Table 1, entry 10).

With the optimized reaction conditions in hand, the substrate scope was then examined and the results are listed in Scheme 2. The *N*′-phenyl groups substituted with methyl and halogen were well tolerated. Excellent yields were obtained for the products **2a**–**e**. 2-Chloro-*N*′-1-naphthylbenzohydrazide (**1f**) also provided the product **2f** in excellent yields. 2-Chloro-*N*′-cyclohexylbenzohydrazide (**1g**) was found to be inactive. The result implicated that *N*′-aryl substitution is indispensable for the reaction. The influence of the benzoyl group was also examined. The benzo groups substituted with methyl and chloride **1h**,**i** were tolerated and the products **2h**,**i** were obtained in excellent yields. The result excluded the aryne reaction pathway because **1h** could not generate an aryne intermediate via E2 elimination. The reaction of substrate **1j** with a nitro group afforded complicated products. Although complete decomposition of **1j** was observed, no expected indazolone product could be isolated. The decomposition pathways are still elu-

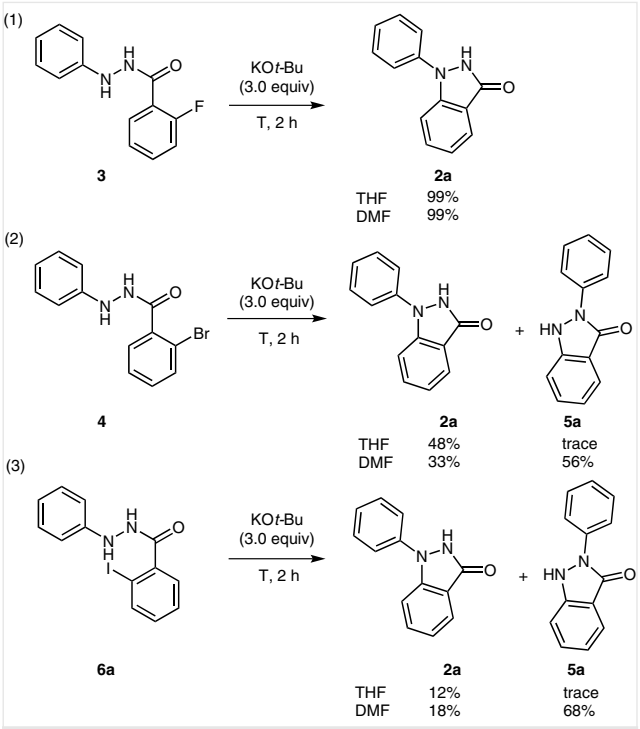


Scheme 2 Intramolecular coupling of 2-chlorobenzohydrazides **1** promoted by KO*t*-Bu in THF. *Reagents and conditions*: **1a–l** (0.2 mmol), KO*t*-Bu (0.6 mmol), THF (4.0 mL), reflux, under N_2, 2 h.

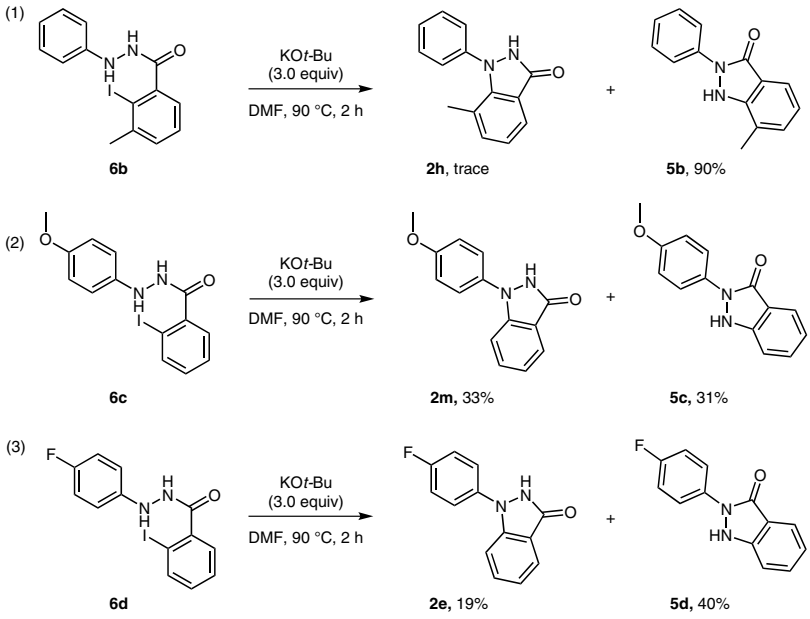
sive so far. On the other hand, the substrate with a methoxy group **1k** was found to be unreactive, as most of the substrate was recovered after the reaction. The replacement of the phenyl with a pyridyl group was also examined and the product **2l** was obtained in an excellent yield. A gram-scale reaction of 2-chlorobenzohydrazide **1a** is successful and demonstrates the practicability of this method.

The effect of different 2-halogen substituents was studied and the results are summarized in Scheme 3. The reaction of 2-fluorobenzohydrazide **3** in THF provided **2a** in an excellent yield. The reaction of 2-bromobenzohydrazide **4** gave **2a** in 48% yield. The reaction of 2-iodobenzohydrazide **6a** gave **2a** in only 12% yield. Furthermore the reactions of **3**, **4**, and **6a** in DMF were also examined. **2a** was obtained in excellent yield from 2-fluorobenzohydrazide **3**, however the reaction of 2-bromobenzohydrazide **4** gave 33% yield of **2a** together with 56% yield of 2-phenylindazolone **5a**. The further examination of 2-iodobenzohydrazide **6a** gave 18% yield of **2a** and 68% yield of **5a**.

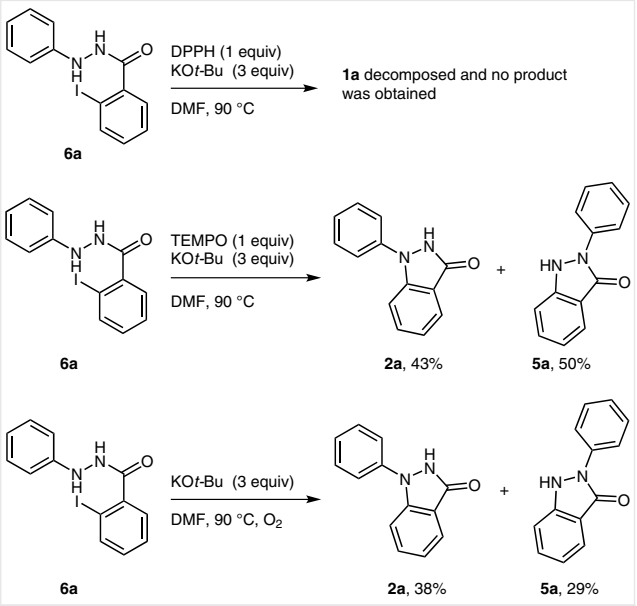
2-Phenylindazolone **5a** is possibly generated by the rearrangement of the β-lactam intermediate[12c] or by nucleophilic addition of the aryne intermediate.[16] Several 2-iodobenzohydrazides were prepared and examined (Scheme 4). The 2-iodo-3-methylbenzohydrazide **6b** gave exclusively 2-phenylindazolone **5b** in 90% yield. The result excluded the aryne pathway because **6b** could not generate an aryne intermediate. The 4-methoxyphenyl derivative **6c** gave a mixture of **2m** and **5c** in nearly 1:1 ratio. The reaction 4-fluorophenyl derivative **6d** led to a mixture of **2e** and **5d** in a nearly 1:2 ratio. The electronic properties of the substituent seems to exert a profound effect on the distribution of the products. The 2-iodonaphthohydrazide and the 2-iodobenzohydrazides with methoxy, chloride, fluoride, and nitro group on the benzoyl group were also examined. All the re-



Scheme 3 Intramolecular coupling of 2-halobenzohydrazides; solvent = THF, *T* = reflux, solvent = DMF, *T* = 90 °C



Scheme 4 Intramolecular coupling of 2-iodobenzohydrazide **6** promoted by KO*t*-Bu in DMF



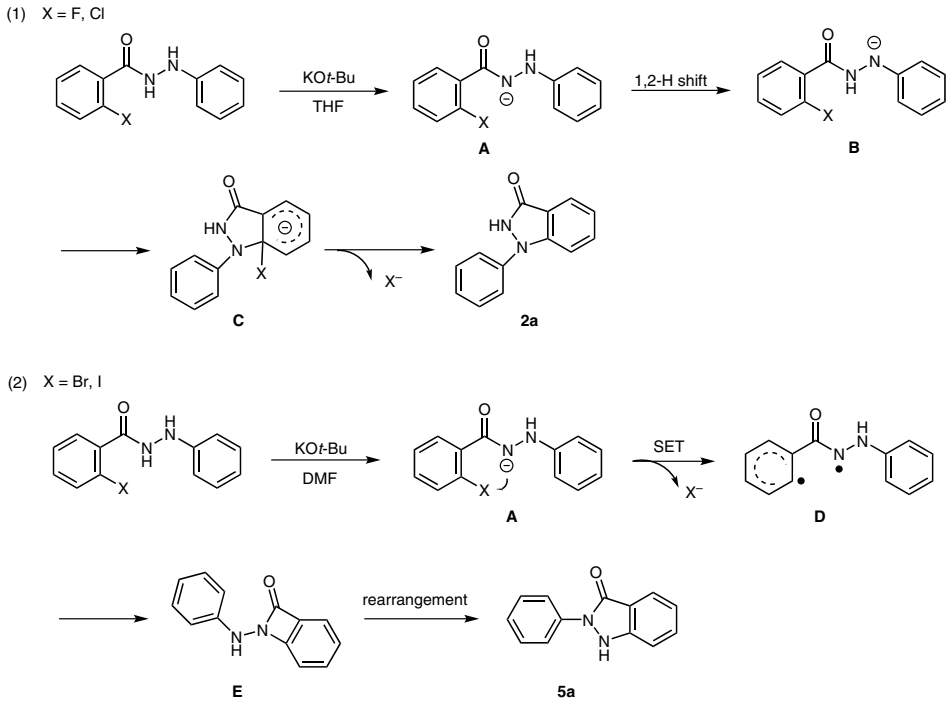
Scheme 5 Reactions in the presence of radical scavengers

actions gave messy products and the expected product was not obtained.

The reactions in the presence of radical scavengers such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), TEMPO, and O_2 were also examined (Scheme 5). DPPH totally inhibited the reaction. However, TEMPO and O_2 reduced the yield of 2-arylindazolones **5a** and increased the yield of 1-arylindazolones **2a**. These results indicate that the reaction has two competitive reaction pathways.

Two different reaction pathways of 2-halobenzohydrazides are proposed (Scheme 6). For the reaction of 2-chlorobenzohydrazide **1a** and 2-fluorobenzohydrazide **3**, a typical S_NAr reaction occurs (Scheme 6, pathway 1). The deprotonation of the substrate **1a** generates an amide anion **A**. After subsequent 1,2-hydrogen transfer, the *N*′-centered acylhydrazine anion **B** is formed. The anion attacks the phenyl ring to give a cyclohexadiene anion **C**. After elimination of the halogen anion, the product **2a** is obtained. For the reaction of 2-bromobenzohydrazide **4** and 2-iodobenzohydrazides **6a**, a competitive radical pathway also exists besides the above S_NAr pathway (Scheme 6, pathway 2). The amide anion **A** can transfer an electron to the halogen. After elimination of the halogen anion, a double radical intermediate **D** is formed. The subsequent radical coupling gives a β-lactam **E**. The further rearrangement of **E** provides 2-arylindazolone **5a**.

In conclusion, we have developed a new synthetic method for 1-arylindazolones and 2-arylindazolones from 2-halobenzohydrazides. The reaction was promoted efficiently by KO*t*-Bu. The distribution of the products was effected by the different 2-halogen substituents. Two distinct reaction pathways were proposed for the generation of 1-arylindazolones and 2-arylindazolones, respectively. The excellent yields, readily available substrates, and the exclu-



Scheme 6 Tentative reaction pathways

sion of transition-metal catalysts make this method attractive for the synthesis of 1-arylindazolones and 2-arylindazolones.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer, ^{1}H NMR are referenced to TMS and ^{13}C NMR are referenced to the carbon resonances of the solvent ($CDCl_3$: δ = 77.0). Melting points were determined with a commercially available WRS-2A melting point apparatus. The IR spectra were recorded as thin films with KBr using a Bruker Tensor 37 spectrophotometer. HRMS were acquired using a Shimadzu electron spray ionization time-of-flight (ESI-TOF) mass spectrometer in positive mode. Copies of the ^{1}H and ^{13}C NMR spectra are provided (see the Supporting Information). All reagents were used without further purification as received from commercial suppliers unless otherwise noted. All solvents were dried and distilled prior to use according to the standard protocols. HCTU = *O*-(6-chlorobenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

2-Chloro-*N*′-(*p*-tolyl)benzohydrazide (1b); Typical Procedure

To a solution of *p*-tolylhydrazine hydrochloride (0.79 g, 5 mmol), 2-chlorobenzoic acid (0.78 g, 5 mmol), and HCTU (2.28 g, 5.5 mmol) in DMF (10.0 mL), Et_3N (2.08 mL, 15 mmol) was added. The mixture was stirred at r.t. overnight. Then the mixture was washed with sat. aq NH_4Cl, aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) to give **1b** (0.78 g, 60%) as a white solid; mp 161.3–162.4 °C.

IR (KBr): 3259, 2997, 1653, 1488, 1319, 916, 819, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 7.82 (br s, 1 H), 7.56–7.42 (m, 4 H), 6.99 (d, *J* = 8.2 Hz, 2 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.7, 147.4, 135.8, 131.7, 130.7, 130.2, 129.7, 129.6, 127.8, 127.7, 113.1, 20.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0789; found: 261.0776.

2-Chloro-*N*′-(*o*-tolyl)benzohydrazide (1c)

White solid; yield: 0.65 g (50%); mp 144.2–145.2 °C.

IR (KBr): 3305, 3207, 2877, 1635, 1492, 748 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.23 (s, 1 H), 7.57–7.44 (m, 4 H), 7.31 (s, 1 H), 7.09–7.03 (m, 2 H), 6.89 (d, *J* = 7.9 Hz, 1 H), 6.70 (t, *J* = 7.0 Hz, 1 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.1, 146.4, 135.3, 131.2, 130.3, 130.0, 129.8, 129.2, 127.2, 126.4, 122.0, 118.8, 111.2, 17.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0789; found: 261.0791.

2-Chloro-*N*′-(*m*-tolyl)benzohydrazide (1d)

White solid; yield: 0.72 g (55%); mp 185.0–185.8 °C.

IR (KBr): 3248, 3039, 1654, 1504, 1321, 1051, 771, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (s, 1 H), 7.90 (br s, 1 H), 7.56–7.43 (m, 4 H), 7.05 (t, *J* = 7.7 Hz, 1 H), 6.70–6.65 (m, 2 H), 6.56 (d, *J* = 7.4 Hz, 1 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2, 149.1, 137.8, 135.3, 131.2, 130.3, 129.8, 129.1, 128.6, 127.2, 119.5, 113.0 109.6, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0789; found: 261.0777.

2-Chloro-*N*′-(naphthalen-1-yl)benzohydrazide (1f)

White solid; yield: 0.89 g (60%); mp 172.5–174.5 °C.

IR (KBr): 3247, 3048, 1658, 1517, 1468, 1309, 1049, 773 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.39 (s, 1 H), 8.51 (br s, 1 H), 8.28–8.26 (m, 1 H), 7.86–7.83 (m, 1 H), 7.64–7.47 (m, 6 H), 7.34 (dd, *J* = 12.0, 7.3 Hz, 2 H), 6.97 (dd, *J* = 7.1, 1.1 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2, 143.8, 135.3, 133.8, 131.3, 130.3, 129.8, 129.3, 127.9, 127.3, 126.3, 125.8, 124.5, 122.2, 121.8, 118.6, 105.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}ClN_2O$: 297.0789; found: 297.0790.

2-Chloro-*N*′-cyclohexylbenzohydrazide (1g)

White solid; yield: 0.70 g (55%); mp 157.6–158.9 °C.

IR (KBr): 3304, 3226, 2926, 2854, 1649, 1542, 1485, 1313, 1051, 904, 742, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 1 H), 7.42–7.33 (m, 3 H), 2.99–2.93 (m, 1 H), 1.94 (d, *J* = 10.1 Hz, 2 H), 1.80–1.76 (m, 2 H), 1.64 (dd, *J* = 8.6, 2.9 Hz, 1 H), 1.34–1.16 (m, 5 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.2, 135.6, 130.9, 130.2, 129.5, 129.1, 127.0, 57.9, 30.9, 25.7, 24.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}ClN_2O$: 253.1102; found: 253.1092.

2-Chloro-3-methyl-*N*′-phenylbenzohydrazide (1h)

White solid; yield: 0.85 g (65%); mp 165.7–166.8 °C.

IR (KBr): 3248, 2865, 1655, 1599, 1493, 1319, 1051, 764, 690 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.14 (s, 1 H), 7.97 (br s, 1 H), 7.47–7.45 (m, 1 H), 7.36–7.33 (m, 2 H), 7.19–7.15 (m, 2 H), 6.86 (dd, *J* = 8.6, 1.0 Hz, 2 H), 6.73 (dd, *J* = 10.4, 4.2 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 149.1, 136.5, 135.9, 132.0, 130.2, 128.7, 126.8, 126.5, 118.6, 112.3, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0789; found: 261.0778.

2-Chloro-5-nitro-*N*′-phenylbenzohydrazide (1j)

White solid; yield: 0.85 g (58%); mp 159.9–161.6 °C.

IR (KBr): 3320, 3180, 1687, 1515, 1355, 945, 854, 744, 688 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (d, *J* = 1.6 Hz, 1 H), 8.36–8.32 (m, 2 H), 8.06 (d, *J* = 2.0 Hz, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.20 (t, *J* = 7.9 Hz, 2 H), 6.88 (d, *J* = 7.7 Hz, 2 H), 6.77 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 149.2, 146.6, 137.9, 136.6, 132.0, 129.3, 126.5, 124.4, 119.4, 112.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}ClN_3O_3$: 292.0483; found: 292.0480.

2-Chloro-*N*′-phenylnicotinohydrazide (1l)

White solid; yield: 0.62 g (50%); mp 156.0–156.2 °C.

IR (KBr): 3325, 1664, 1512, 1410, 756 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (d, *J* = 2.5 Hz, 1 H), 8.53 (dd, *J* = 4.8, 1.9 Hz, 1 H), 8.05–8.02 (m, 2 H), 7.55 (dd, *J* = 7.5, 4.8 Hz, 1 H), 7.21–7.17 (m, 2 H), 6.87 (dd, *J* = 8.6, 1.0 Hz, 2 H), 6.77–6.73 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.4, 151.2, 149.3, 147.3, 139.0, 132.1, 129.2, 123.6, 119.3, 112.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{11}ClN_3O$: 248.0585; found: 248.0577.

2-Iodo-3-methyl-*N*′-phenylbenzohydrazide (6b)

White solid; yield: 1.58 g (90%); mp 194.8–195.6 °C.

IR (KBr): 3242, 2970, 1651, 1493, 1313, 1014, 947, 762 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (d, J = 2.7 Hz, 1 H), 7.96 (d, J = 2.7 Hz, 1 H), 7.43–7.37 (m, 2 H), 7.20–7.15 (m, 3 H), 6.90 (d, J = 8.1 Hz, 2 H), 6.73 (t, J = 7.2 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 149.7, 143.3, 142.5, 130.9, 129.2, 128.6, 126.1, 119.0, 112.9, 100.7, 29.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{14}IN_2O$: 353.0145; found: 353.0143.

2-Iodo-*N*′-(4-methoxyphenyl)benzohydrazide (6c)

White solid; yield: 1.75 g (95%); mp 141.2–143.4 °C.

IR (KBr): 3278, 2999, 2833, 1651, 1510, 1246, 1032, 829, 744 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.66 (s, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.43 (dd, J = 7.5, 1.5 Hz, 1 H), 7.22 (td, J = 7.7, 1.7 Hz, 1 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.79 (d, J = 9.0 Hz, 2 H), 3.67 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 153.2, 143.4, 141.7, 139.8, 131.7, 129.0, 128.6, 114.6, 114.4, 94.3, 55.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{14}IN_2O_2$: 369.0095; found: 369.0102.

***N*′-(4-Fluorophenyl)-2-iodobenzohydrazide (6d)**

White solid; yield: 1.42 g (80%); mp 204.2–205.6 °C.

IR (KBr): 3261, 3001, 1651, 1504, 1209, 910, 829, 721, 687 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.17 (s, 1 H), 7.93 (dd, J = 7.9, 0.8 Hz, 2 H), 7.48 (dtd, J = 9.3, 7.5, 1.4 Hz, 2 H), 7.23 (ddd, J = 7.9, 7.3, 1.9 Hz, 1 H), 7.00–6.89 (m, 2 H), 6.93–6.89 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.2, 157.6 (J = 232 Hz), 146.1, 141.5, 139.8, 131.7, 129.0, 128.5, 115.7 (J = 22 Hz), 114.2 (J = 8 Hz), 94.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{11}FIN_2O$: 356.9902; found: 356.9895.

1-Phenyl-1*H*-indazol-3(2*H*)-one (2a);[13b] Typical Procedure

To a dried 50-mL Radleys reaction tube were added **1a** (49.3 mg, 0.2 mmol), KO*t*-Bu (67.4 mg, 0.6 mmol), and THF (4 mL). The mixture was stirred at reflux for 2 h under N_2 atmosphere. The mixture was cooled to r.t., the solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) to give **2a** (41.7 mg, 99%) as a white solid; mp 213.5–214.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.24 (s, 1 H), 7.77 (d, J = 8.9 Hz, 2 H), 7.69 (d, J = 7.6 Hz, 2 H), 7.52 (t, J = 7.9 Hz, 2 H), 7.47–7.43 (m, 1 H), 7.26 (t, J = 7.4 Hz, 1 H), 7.16 (t, J = 7.7 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.8, 140.7, 139.7, 130.0, 128.8, 125.2, 121.1, 121.0, 120.8, 115.3, 110.8.

1-(*p*-Tolyl)-1*H*-indazol-3(2*H*)-one (2b)

White solid; yield: 44.4 mg (99%); mp 223.4–225.7 °C.

IR (KBr): 2918, 2582, 1546, 1311, 823, 738 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.17 (br s, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.70 (d, J = 8.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 2 H), 7.45–7.41 (m, 1 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.14 (t, J = 7.4 Hz, 1 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 139.2, 137.8, 134.1, 129.8, 128.1, 120.7, 120.4, 120.0, 114.5, 110.2, 20.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1024.

1-(*o*-Tolyl)-1*H*-indazol-3(2*H*)-one (2c)

White solid; yield: 42.6 mg (95%); mp 180.8–184.0 °C.

IR (KBr): 2924, 2582, 1618, 1544, 1313, 750 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.96 (s, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.45–7.41 (m, 1 H), 7.39–7.32 (m, 4 H), 7.09 (dd, J = 7.9, 7.1 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 2.13 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.6, 141.2, 138.2, 134.6, 131.4, 127.9, 127.7, 126.8, 126.7, 120.2, 119.5, 113.2, 109.6, 17.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1025.

1-(*m*-Tolyl)-1*H*-indazol-3(2*H*)-one (2d)

White solid; yield: 44.4 mg (99%); mp 178.3–179.3 °C.

IR (KBr): 2921, 2588, 1610, 1547, 1309, 1238, 789, 742 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (br s, 1 H), 7.78–7.74 (m, 2 H), 7.50–7.43 (m, 3 H), 7.39 (t, J = 7.7 Hz, 1 H), 7.15 (dd, J = 11.3, 4.2 Hz, 1 H), 7.07 (d, J = 7.4 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.2, 140.2, 139.2, 139.0, 129.2, 128.2, 125.5, 121.2, 120.4, 120.2, 117.7, 114.7, 110.4, 21.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1024.

1-(4-Fluorophenyl)-1*H*-indazol-3(2*H*)-one (2e)[13b]

White solid; yield: 44.7 mg (98%); mp 220.2–221.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.25 (br s, 1 H), 7.76 (d, J = 7.9 Hz, 1 H), 7.71–7.68 (m, 3 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.35 (t, J = 8.5 Hz, 2 H), 7.15 (t, J = 7.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.9 (J = 241 Hz), 156.8, 139.8, 137.1, 128.9, 123.2 (d, J = 8 Hz), 121.0, 120.8, 116.8 (J = 23 Hz), 115.1, 110.5.

1-(Naphthalen-1-yl)-1*H*-indazol-3(2*H*)-one (2f)

White solid; yield: 50.0 mg (96%); mp 237.1–239.7 °C.

IR (KBr): 3021, 2588, 1618, 1543, 1444, 1311, 771, 740 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.18 (s, 1 H), 8.08–8.03 (m, 2 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 8.4 Hz, 1 H), 7.67–7.58 (m, 3 H), 7.52 (t, J = 7.1 Hz, 1 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.09 (d, J = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.2, 142.1, 135.7, 134.2, 129.2, 128.3, 128.0, 127.9, 126.7, 126.6, 125.7, 123.8, 123.5, 120.4, 119.9, 113.7, 109.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022; found: 261.1029.

7-Methyl-1-phenyl-1*H*-indazol-3(2*H*)-one (2h)

White solid; yield: 40.8 mg (85%); mp 172.3–174.5 °C.

IR (KBr): 3021, 2588, 1618, 1543, 1444, 1311, 771, 740 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 10.94 (s, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.51–7.47 (m, 2 H), 7.43–7.39 (m, 3 H), 7.16 (d, *J* = 7.0 Hz, 1 H), 7.05–7.01 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.1, 141.2, 140.8, 129.6, 128.6, 127.4, 127.0, 120.4, 120.1, 118.0, 114.8, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1024.

6-Chloro-1-phenyl-1*H*-indazol-3(2*H*)-one (2i)[13b]

White solid; yield: 48.4 mg (99%); mp 234.6–235.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.48 (br s, 1 H), 7.78–7.76 (m, 2 H), 7.68 (d, *J* = 7.8 Hz, 2 H), 7.53 (t, *J* = 7.9 Hz, 2 H), 7.29 (t, *J* = 7.4 Hz, 1 H), 7.18 (dd, *J* = 8.5, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.7, 140.1, 139.8, 134.0, 130.1, 125.8, 122.6, 121.4, 121.3, 114.0, 110.3.

1-Phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-3(2*H*)-one (2l)

White solid; yield: 41.8 mg (99%); mp 198.2–200.3 °C.

IR (KBr): 2923, 1596, 1581, 1543, 1421, 1302, 1275, 1155, 771, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.67 (s, 1 H), 8.61 (dd, *J* = 4.5, 1.3 Hz, 1 H), 8.25–8.23 (m, 3 H), 7.49 (t, *J* = 7.9 Hz, 2 H), 7.25 (dd, *J* = 7.9, 4.6 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.8, 150.5, 150.4, 140.1, 130.8, 129.5, 124.6, 119.5, 117.2, 107.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}N_3O$: 212.0818; found: 212.0822.

1-(4-Methoxyphenyl)-1*H*-indazol-3(2*H*)-one (2m)

White solid; yield: 15.9 mg (33%); mp 204.2–206.7 °C.

IR (KBr): 2923, 1596, 1581, 1543, 1421, 1302, 1275, 1155, 771, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (br s, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.6 Hz, 1 H), 7.58–7.54 (m, 2 H), 7.43–7.39 (m, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 7.10–7.07 (m, 2 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.2, 139.8, 133.9, 128.5, 123.1, 120.9, 120.3, 115.1, 110.4, 55.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_2$: 241.0972; found: 241.0965.

2-Phenyl-1*H*-indazol-3(2*H*)-one (5a);[12a] **Typical Procedure**

To a dried 50-mL Radleys reaction tube was added **6a** (67.6 mg, 0.2 mmol), KO*t*-Bu (67.4 mg, 0.6 mmol), and DMF (8 mL). The mixture was stirred at 90 °C for 2 h under N_2 atmosphere. The mixture was cooled to r.t., then it was poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat. brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) to give **5a** (28.6 mg, 68%) as a white solid and **2a** (7.6 mg, 18%) respectively.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.64 (br s, 1 H), 7.93 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 147.1, 138.1, 133.0, 129.5, 125.4, 123.9, 122.3, 119.4, 118.6, 113.1.

7-Methyl-2-phenyl-1*H*-indazol-3(2*H*)-one (5b)

White solid; yield: 40.4 mg (90%); mp 172.9–174.0 °C.

IR (KBr): 3032, 2873, 1641, 1497, 1362, 1311, 881, 798, 748 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.40 (s, 1 H), 7.95 (dd, *J* = 8.7, 1.0 Hz, 2 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.53–7.49 (m, 2 H), 7.41 (d, *J* = 7.2 Hz, 1 H), 7.27–7.24 (m, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 146.0, 137.7, 132.6, 129.0, 124.9, 122.6, 122.1, 120.7, 119.2, 117.9, 15.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O$: 225.1022; found: 225.1024.

2-(4-Methoxyphenyl)-1*H*-indazol-3(2*H*)-one (5c)

White solid; yield: 14.9 mg (31%); mp 190.9–191.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.63 (s, 1 H), 7.80 (d, *J* = 9.0 Hz, 2 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2, 157.1, 146.8, 132.6, 131.2, 123.8, 122.2, 121.5, 118.6, 114.7, 113.0, 55.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_2$: 241.0972; found: 241.0968.

2-(4-Fluorophenyl)-1*H*-indazol-3(2*H*)-one (5d)

White solid; yield: 18.3 mg (40%); mp 207.5–208.2 °C.

IR (KBr): 3120, 1653, 1510, 1356, 1228, 833, 754 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.66 (br s, 1 H), 7.99–7.90 (m, 2 H), 7.75 (d, *J* = 7.7 Hz, 1 H), 7.61 (t, *J* = 7.6 Hz, 1 H), 7.37–7.34 (m, 3 H), 7.20 (t, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 160.6 (*J* = 234 Hz), 147.1, 134.5, 133.1, 123.9, 122.4, 121.5 (*J* = 8 Hz), 118.4, 116.4 (*J* = 23 Hz), 113.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}FN_2O$: 229.0772; found: 229.0767.

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Supporting Information

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References

(1) For a review, see: Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415.

(2) (a) Hall, I. H.; Wong, O. T.; Hall, E. S.; Chen, L. K. *Anti-Cancer Drugs* **1993**, *4*, 389. (b) Das, S.; Chaudhari, S. S.; Thomas, A.; Pardeshi, S. R.; Deshmukh, V. G.; Wadekar, P. D.; Khairatkar-Joshi, N.; Shah, D. M.; Bajpai, M. WO 2015087234, **2015**.

(3) Magano, J.; Waldo, M.; Greene, D.; Nord, E. *Org. Process Res. Dev.* **2008**, *12*, 877.
(4) (a) Gibbs, A. C.; Abad, M. C.; Zhang, X. Q.; Tounge, B. A.; Lewandowski, F. A.; Struble, G. T.; Sun, W. M.; Sui, Z. H.; Kuo, L. C. *J. Med. Chem.* **2010**, *53*, 7979. (b) Zhang, X. Q.; Song, F. B.; Kuo, G.-H.; Xiang, A.; Gibbs, A. C.; Abad, M. C.; Sun, W. M.; Kuo, L. C.; Sui, Z. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4762.
(5) Leis, J.; Carter, C. US 20140179637, **2014**.
(6) Vega, M. C.; Rolón, M.; Montero-Torres, A.; Fonseca-Berzal, C.; Escario, J. A.; Gómez-Barrio, A.; Gálvez, J.; Marrero-Ponce, Y.; Arán, V. J. *Eur. J. Med. Chem.* **2012**, *58*, 214.
(7) Schelkun, R. M.; Yuen, P.-W. WO 2006056873, **2006**.
(8) Bodmer-Narkevitch, V.; Anthony, N. J.; Cofre, V.; Jollya, S. M.; Murphy, K. L.; Ransom, R. W.; Reiss, D. R.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G.; Kuduk, S. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7011.
(9) Selwood, D. L.; Brummell, D. G.; Budworth, J.; Burtin, G. E.; Campbell, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A. J.; Kling, M. R.; Liu, Q.; Madge, D. J.; Meillerais, S.; Powell, K. L.; Reynolds, K.; Spacey, G. D.; Stables, J. N.; Tatlock, M. A.; Wheeler, K. A.; Wishart, G.; Woo, C.-K. *J. Med. Chem.* **2001**, *44*, 78.
(10) (a) Bruneau, P.; Delvare, C. *J. Med. Chem.* **1991**, *34*, 1028. (b) Tachibana, S.; Fukano, A.; Sudo, K.; Tanaka, M. *J. Chromatogr. B: Biomed. Sci. Appl.* **1999**, *734*, 39. (c) Dees, E. C.; Whitfield, L. R.; Grove, W. R.; Rummel, S.; Grochow, L. B.; Donehower, R. C. *Clin. Cancer Res.* **2000**, *6*, 3885. (d) Zoja, C.; Corna, D.; Benedetti, G.; Morigi, M.; Donadelli, R.; Guglielmotti, A.; Pinza, M.; Bertani, T.; Remuzzi, G. *Kidney Int.* **1998**, *53*, 726.
(11) (a) Runti, C.; Baiocchi, L. *Int. J. Tissue React.* **1985**, *7*, 175. (b) Guglielmotti, A.; Capezzone de Joannon, A.; Cazzolla, N.; Marchetti, M.; Soldo, L.; Cavallo, G.; Pinza, M. *Pharmacol. Res.* **1995**, *32*, 369. (c) Inai, T.; Mancuso, M.; Hashizume, H.; Baffert, F.; Haskell, A.; Baluk, P.; Hu-Lowe, D. D.; Shalinsky, D. R.; Thurston, G.; Yancopoulos, G. D.; McDonald, D. M. *Am. J. Pathol.* **2004**, *165*, 35. (d) Karaman, M. W.; Herrgard, S.; Treiber, D. K.; Gallant, P.; Atteridge, C. E.; Campbell, B. T.; Chan, K. W.; Ciceri, P.; Davis, M. I.; Edeen, P. T.; Faraoni, R.; Floyd, M.; Hunt, J. P.; Lockhart, D. J.; Milanov, Z. V.; Morrison, M. J.; Pallares, G.; Patel, H. K.; Pritchard, S.; Wodicka, L. M.; Zarrinkar, P. P. *Nat. Biotechnol.* **2008**, *26*, 127.
(12) For synthetic methods for indazolone and its derivatives, see: (a) Bird, C. W.; Chng, J. C. W.; Rama, N. H.; Saeed, A. *Synth. Commun.* **1991**, *21*, 545. (b) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519. (c) Stadlbauer, W. In *Science of Synthesis*; Vol 12; Neier, R., Ed.; Thieme: Stuttgart, **2002**, 227. (d) Viña, D.; Olmo, E. D.; López-Pérez, J. L.; Feliciano, A. S. *Org. Lett.* **2007**, *9*, 525. (e) 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.
(13) (a) Tanimori, S.; Ozaki, Y.; Iesaki, Y.; Kirihata, M. *Synlett* **2008**, 1973. (b) Tanimori, S.; Kobayashi, Y.; Iesaki, Y.; Ozaki, Y.; Kirihata, M. *Org. Biomol. Chem.* **2012**, *10*, 1381.
(14) Xiong, X. D.; Jiang, Y. W.; Ma, D. W. *Org. Lett.* **2012**, *14*, 2552.
(15) Wang, W. J.; Zhang, T.; Duan, L. J.; Zhang, X. J.; Yan, M. *Tetrahedron* **2015**, *71*, 9073.
(16) For examples of the formation of arynes, see: (a) Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654. (b) Shi, L.; Wang, M.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. *Org. Lett.* **2003**, *5*, 3515.