Arava Veerareddy,[a]* Surendrareddy Gogireddy,[a] and P. K. Dubey[b]

[a]R&D Centre, Suven Life Sciences Ltd., Plot No. 18, Phase III, Jeedimetla, Hyderabad 500055, India
[b]Department of Chemistry, JNT University, Hyderabad 500072, India
*E-mail: reddyvenis@rediffmail.com

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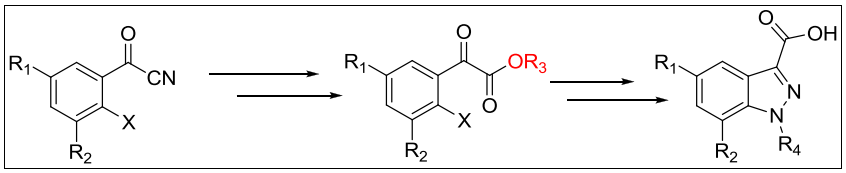
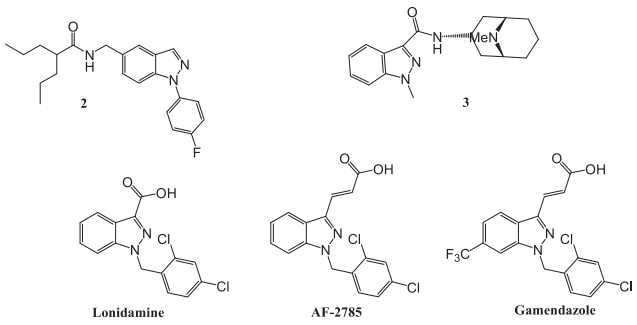


In this article, we study the synthesis of 1-substituted indazole-3-carboxylic acids from 2-halobenzoic acids.

J. Heterocyclic Chem., **51**, 1311 (2014).

INTRODUCTION

The last decade (2001–2010) has witnessed an unprecedented explosion of research on the diverse biological properties of compounds having an indazole moiety. The recent synthetic approaches to 1H and 2H indazoles were reviewed by Cankarova et al. [1]. The wide variety of interesting biological activities of indazoles attracted the attention of many synthetic groups. For example, compound **2** is an interesting lead molecule effective smoothened antagonist and inhibitor of the hedgehog pathway [2]. 1-Methyl indazole-3-carboxylic acid **1** forms part of the antiemetic drug granisetron **3**. The other interesting biologically active molecules are lonidamine **4**, AF-2785 **5**, and gamendazole **6**. These are potent spermatogenesis compounds [3].



2 3 4 5 6

Indazole-3-carboxylic acids are originally synthesized from isatin [4]. This strategy is useful to synthesize only aromatic-substituted indazole-3-carboxylic acids. Recently, the *N*-aryl indazoles are reported from anilino ketoximes [5] in good yields. A wide range of indazole-3-carboxylic acid derivatives is prepared by the [3 + 2] cycloaddition of diazo compounds with *O*-(trimethylsilyl)aryl triflate **7** in the presence of CsF or tetrabutylammoniumfluoride at room temperature [6], as shown in Scheme 1.

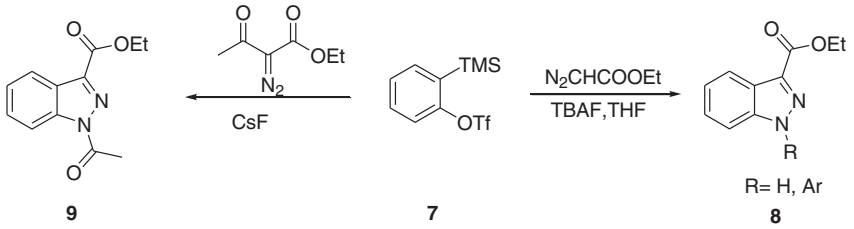
In general, the regioselective preparation of 1-substituted indazoles is difficult to achieve, as 2-substituted product will always form as a side product. To achieve regioselectivity, Vina et al. [7] reported a general Ullmann method in the presence of 0.2 mol% of CuO and K_2CO_3 in good yields (16–83%). Huat et al. [8] reported selective 1-functionalization with Cs_2CO_3 (3 equiv) and DMF with 50–95% yields. But to achieve 100% regioselectivity, we need to start with substituted hydrazines.

RESULTS AND DISCUSSION

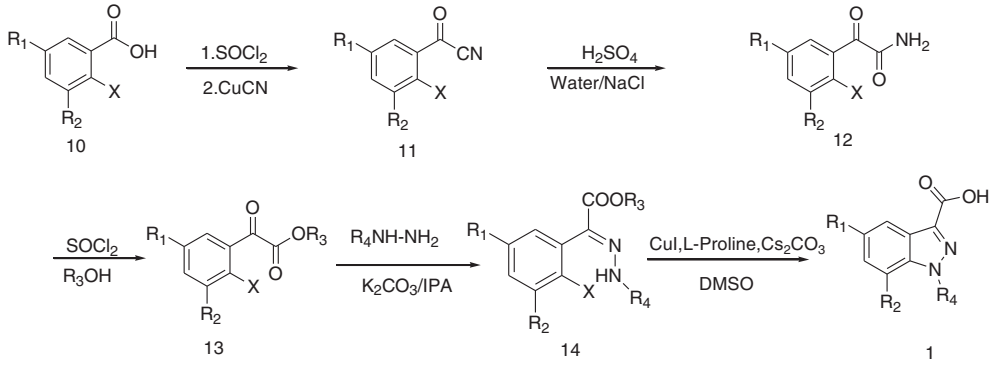
We herein report a general and novel synthesis of 1-substituted indazole-3-carboxylic acids in good yields. Our synthesis starts from 2-halobenzoic acid, converting it to acid chloride and to aroyl cyanides to amides and to α-ketoesters, which [9] are reacted with substituted hydrazines to obtain the corresponding 1-substituted indazole-3-carboxylic acids in good yields. The reaction strategy is depicted in Scheme 2.

The conversion of aroyl chlorides to aroyl cyanides is well documented [10]. Conversions of aroyl cyanides to aroyl esters (α-ketoesters) are reported in patented literature [11]. We modified the process and isolated the amides as crystalline solids, and all amides are fully characterized by spectral data. Amides are converted to α-ketoesters in the presence of thionyl chloride and alcohols. All α-ketoesters are characterized by spectral data. The ketoesters are reacted with hydrazine derivatives in the presence of K_2CO_3 and alcohols [in some cases, ester exchange is observed (e.g. **14c** and **14d**)], which are later converted to corresponding 1-substituted indazole-3-carboxylic acids in the presence of CuI, Cs_2CO_3, and L-proline as a promoter [12] in DMSO.

Scheme 1. Synthesis of 1-substituted indazole-3-carboxylic acid.



Scheme 2. Synthesis of 1-substituted indazole-3-carboxylic acid.



Both methyl and ethyl hydrazines are reacted with different α-ketoesters to give 1-methyl/ethyl indazole-3-carboxylic acids. Even though cyclized esters are isolated in some cases during the work up, the esters are allowed to hydrolyze completely. Acids are isolated and characterized. The results are tabulated in Table 1.

To study the generality of the method, different substituted aryl hydrazines are reacted with α-ketoesters, and we found that yields are usually good (>60%). The results of 1-aryl indazole-3-carboxylic acids are tabulated in Table 2.

In conclusion, we have developed a general and high yielding procedure for regioselective 1-substituted indazole-3-carboxylic acids.

EXPERIMENTAL

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. The purity of all compounds was routinely checked by TLC on Merck silica gel coated plates. IR spectra were recorded on a PerkinElmer model 2000 instrument in KBr phase. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or DMSO by using Brucker 400 MHz instrument, and mass spectra were recorded on a PerkinElmer mass spectrometer operating at 70 eV. C, H, and N analysis was recorded on Thermo Finnigan FLASH EA 1112 CHNS analyzer, and HRMS was recorded on Waters Micromass ESI-ToF MS.

General procedure for the preparation of α-oxo-2-phenylacetamides (12a–k). To a solution of water (8.2 mL, 0.458 mol) and sodium chloride (2.7 g, 0.0458 mol), conc. H_2SO_4 (45.0 g, 0.458 mol) was added at 10–15°C over a period of 30 min and was heated to 40°C. 2-Chlorobenzoyl cyanide (76.0 g, 0.458 mol) was added at 40–45°C by maintaining the temperature with external cooling over a period of 30 min. The reaction mixture was stirred for 1 h at 40–45°C, and after completion of the reaction, the mass was quenched into ice water (250.0 mL) at 5–15°C and stirred for 30 min at 10–15°C. The precipitated product was filtered and washed with chilled demineralized water (2 × 100 mL) to yield 67.0 g (80%), mp 134.5–136.2°C.

2-(2-Chlorophenyl)-2-oxoacetamide (12a) [16]. mp 134–136°C; IR (KBr): 3376.54, 3177.86, 1695.50, 1662.71, 1273.07, 750.0 cm^{-1}; ^{1}H NMR (DMSO): δ 7.46 (t, J = 6.52 Hz, 1H), 7.57–7.60 (m, 2H), 7.67 (dd, nJ = 7.50 Hz, nJ = 1.32 Hz, 1H), 7.99 (s, 1H), 8.3 (s, 1H); ^{13}C NMR: δ 127.6, 130.5, 131.5, 131.9, 133.9, 134.6, 165.1, 191.4; ms: m/z 184.2 (M^+) and 186.1 (M + 2).

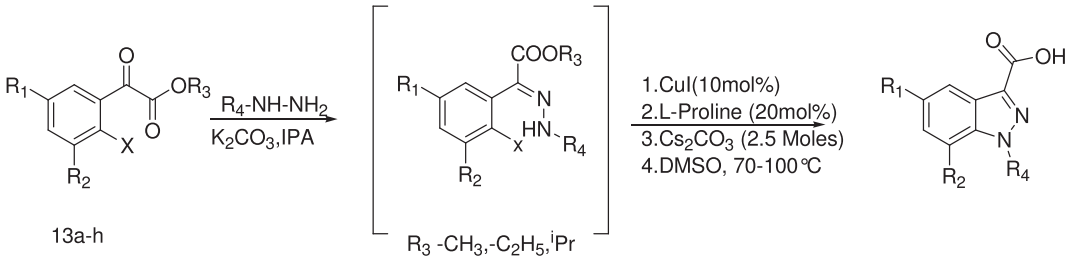
2-(2-Bromophenyl)-2-oxoacetamide (12b). mp 134–137°C; IR (KBr): 3378.47, 3177.86, 1700.32, 1662.71, 1271.14, 627.66 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48–7.51 (m, 2H), 7.58 (dd, nJ = 7.13 Hz, nJ = 2.42 Hz, 1H), 7.70 (t, J = 4.40 Hz, 1H), 8.00 (s, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 120.0, 128.0, 131.4, 133.6, 133.7, 136.7, 164.4, 192.0; ms: m/z 229.9 (M^+).

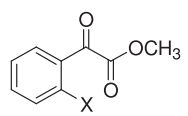
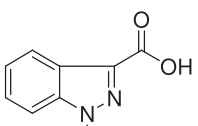
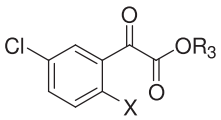
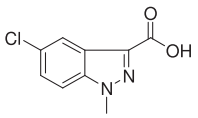
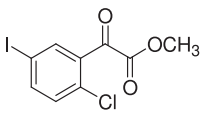
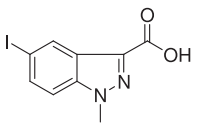
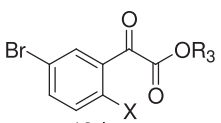
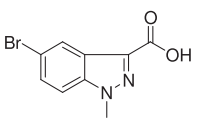
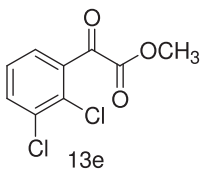
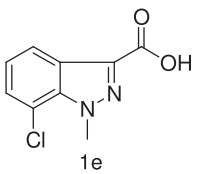
2-(2-Iodophenyl)-2-oxoacetamide (12c). mp 140–144°C; IR (KBr): 3415.12, 3219.33, 1720.58, 1690.63, 1227.74, 744.55 cm^{-1}; ^{1}H NMR (DMSO): δ 7.28 (m, 1H), 7.50 (m, 2H), 7.96 (d, J = 7.84 Hz, 1H), 8.0 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (DMSO): δ 93.5, 128.3, 131.2, 133.4, 139.5, 140.3, 164.1, 193.0; ms: m/z 276.0 (M^+).

2-(2-Chloro-5-iodophenyl)-2-oxoacetamide (12d). mp 177–178°C; IR (KBr): 3413.19, 3214.51, 1730.22, 1695.50,

Table 1

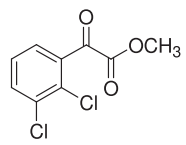
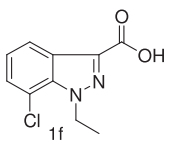
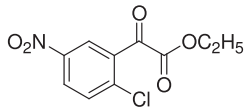
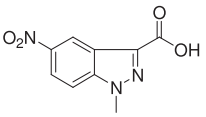
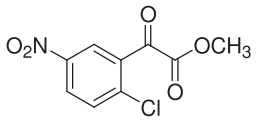
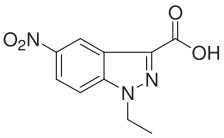
Synthesis of 1-alkyl indazole-3-carboxylic acid.



S. no.	Substrate	Product	Reaction conditions		mp (°C)	Yield (%)	Elemental analysis found % (calcd)/HRMS (calcd)
			Temp. (°C)	Time (h)			
1	 13a X=Cl,Br,I	 1a	95–100	7	215–216	83 (Cl), 81 (Br), 84 (I)	[13]
2	 13b X= Cl,Br,I $R_3 = CH_3, C_2H_5$.	 1b	95–100	7	252–254	73 (Cl), 73 (Br), 78 (I)	233.0095 (233.0094)
3	 13c	 1c	95–100	7	225–228	68	C, 36.14; H, 2.46; N, 9.04 (C, 35.79; H, 2.34; N, 9.27)
4	 13d X=Cl,I R_3=CH_3, C_2H_5.	 1d	95–100	7	232–233	78 (Cl), 82 (I)	276.9589 (276.9588)
5	 13e	 1e	95–100	7	223–224	82	C, 51.30; H, 3.49; N, 13.51 (C, 51.32; H, 3.35; N, 13.8)

(*Continued*)

Table 1
(*Continued*)

S. no.	Substrate	Product	Reaction conditions: Temp. (°C)	Reaction conditions: Time (h)	mp (°C)	Yield (%)	Elemental analysis found % (calcd)/HRMS (calcd)
6	 13e	 1f	75–80	7	212–216	70	247.0250 (247.0250)
7	 13f	 1g	95–100	7	242–244	78	244.0331 (244.0334)
8	 13g	 1h	70–75	5	226–228	72	[14]

1217.14, 804.35 cm^{-1}; ^1H NMR (DMSO): δ 7.34 (d, $J = 8.31$ Hz, 1H), 7.91–7.95 (m, 2H), 8.13 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (DMSO): δ 92.8, 131.6, 132.3, 136.7, 139.1, 142.0, 164.1, 189.8; ms: *m/z* 310.1.

2-(2,3-Dichlorophenyl)-2-oxoacetamide (12e) *[17].* mp 214–216°C; IR (KBr): 3417.33, 3209.06, 1728.16, 1694.15, 1244.22, 769.59 cm^{-1}; ^1H NMR (DMSO): δ 7.46 (t, $J = 7.83$ Hz, 1H), 7.59 (d, $J = 6.85$ Hz, 1H), 7.81 (d, $J = 7.21$ Hz, 1H), 8.08 (s, 1H), 8.44 (s, 1H); ^{13}C NMR (DMSO): δ 128.9, 129.4, 129.5, 132.7, 133.7, 137.5, 164.1, 190.6; ms: *m/z* 218.1 (M^+) and 220.1 (M + 2).

2-(5-Bromo-2-chlorophenyl)-2-oxoacetamide (12f). mp 191–193°C; IR (KBr): 3415.49, 3223.53, 1727.60, 1696.58, 1219.20, 806.69 cm^{-1}; ^1H NMR (DMSO): δ 7.51 (d, $J = 8.54$ Hz, 1H), 7.77 (dd, $nJ = 8.53$ Hz, $nJ = 2.36$ Hz, 1H), 7.84 (d, $J = 2.29$ Hz, 1H), 8.05 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (DMSO): δ 120.3, 130.8, 132.3, 133.4, 136.1, 136.8, 163.9, 189.9; ms: *m/z* 262.1 and 264.1 (M + 2).

2-(5-Bromo-2-iodophenyl)-2-oxoacetamide (12g). mp 150–155°C; IR (KBr): 3417.22, 3225.36, 1721.46, 1694.86, 1213.54, 982.35 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.78 (s, 1H), 6.96 (s, 1H), 7.34 (dd, $nJ = 8.38$ Hz, $nJ = 2.30$ Hz, 1H), 7.72 (d, $J = 2.26$ Hz, 1H), 7.77 (d, $J = 8.41$ Hz, 1H); ^{13}C NMR (DMSO): δ 92.0, 121.6, 132.9, 135.7, 141.7, 142.5, 162.8, 191.7; ms: *m/z* 354.0.

2-(2,5-Dichlorophenyl)-2-oxoacetamide (12h). mp 184–186°C; IR (KBr): 3415.71, 3220.27, 1727.95, 1693.15, 1221.27, 810.0 cm^{-1}; ^1H NMR (DMSO): δ 7.58 (d, $J = 11.6$ Hz, 1H), 7.67 (dd, $nJ = 5.70$ Hz, $nJ = 2.55$ Hz, 1H), 7.73 (d, $J = 2.51$ Hz, 1H), 8.05 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (DMSO): δ 130.3, 130.6, 132.1, 132.2, 133.2, 136.6, 163.9, 189.8; ms: *m/z* 218.1 (M^+) and 220.1 (M + 2).

2-(2-Bromo-5-chlorophenyl)-2-oxoacetamide (12i). mp 188–192°C; IR (KBr): 3413.51, 3220.69, 1727.38, 1697.40, 1220.45, 813.00 cm^{-1}; ^1H NMR (DMSO): δ 7.55 (dd, $nJ = 8.50$ Hz, $nJ = 2.48$ Hz, 1H), 7.68 (d, $J = 2.45$ Hz, 1H), 7.72 (d, $J = 8.55$ Hz, 1H), 8.0 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (DMSO): δ 118.2, 130.5, 132.8, 133.0, 135.0, 139.0, 163.2, 190.6; ms: *m/z* 263.0 (M^+).

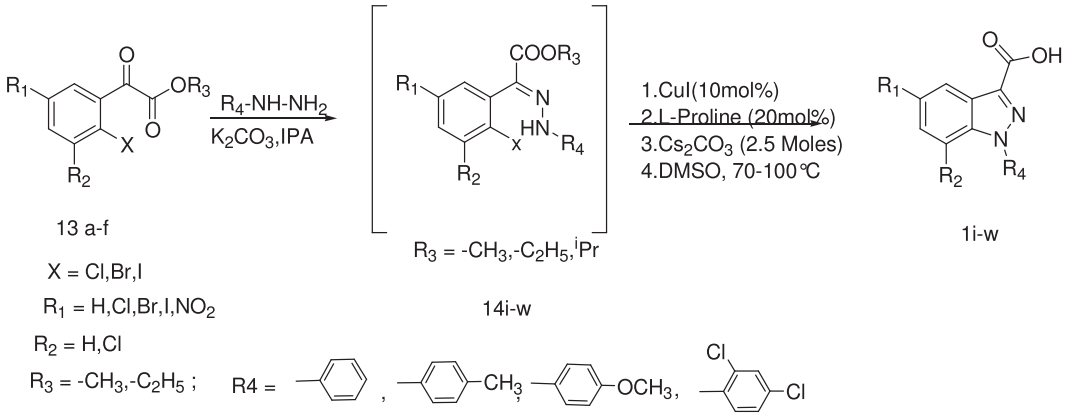
2-(5-Chloro-2-iodophenyl)-2-oxoacetamide (12j). mp 165–166°C; IR (KBr): 3415.98, 3223.33, 1721.81, 1697.33, 1215.75, 811.24 cm^{-1}; ^1H NMR (DMSO): δ 7.36 (dd, $nJ = 8.50$ Hz, $nJ = 2.50$ Hz, 1H), 7.60 (d, $J = 2.45$ Hz, 1H), 7.93 (d, $J = 8.41$ Hz, 1H), 8.07 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (DMSO): δ 91.4, 130.2, 132.8, 133.4, 141.4, 142.3, 162.8, 191.8; ms: *m/z* 310.1 (M^+).

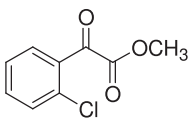
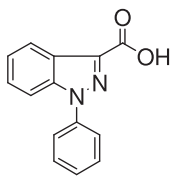
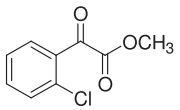
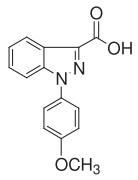
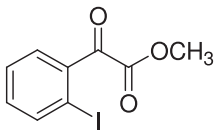
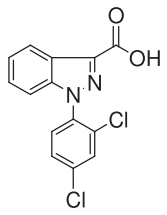
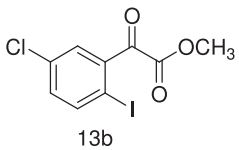
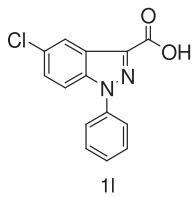
2-(2-Chloro-5-nitrophenyl)-2-oxoacetamide (12k). mp 183–185°C; IR (KBr): 3414.82, 3220.44, 1729.44, 1729.41, 1697.63, 1529.37, 1351.58, 589.28 cm^{-1}; ^1H NMR (DMSO): δ 7.86 (d, $J = 8.80$ Hz, 1H), 8.13 (s, 1H), 8.29 (dd, $nJ = 8.78$ Hz, $nJ = 2.75$ Hz, 1H), 8.40 (s, 1H), 8.50 (d, $J = 2.72$ Hz, 1H); ^{13}C NMR (DMSO): δ 126.0, 127.8, 132.0, 136.1, 138.1, 146.4, 163.3, 189.0.

General procedure for the preparation of substituted phenylglyoxalic acid esters (13a–k). To a solution of methanol/ethanol (100.0 mL) and 2-(2,3-dichlorophenyl)-2-oxoacetamide (20.0 g, 0.090 mol), thionyl chloride (26.2 g, 0.135 mol) was added at 40–45°C in 30 min and stirred for 4 h at 60–64°C. After completion of the reaction, the solvent was distilled off under atmospheric pressure to obtain the crude product. To the cooled mass, water (25.0 mL) and methylene chloride (100.0 mL) were added at room temperature and stirred for 30 min; the organic layer was separated and washed with water (25.0 mL), dried over sodium sulfate and concentrated in

Table 2

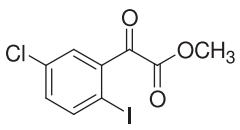
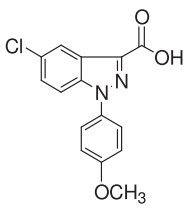
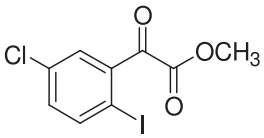
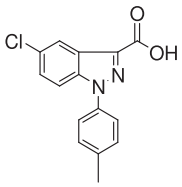
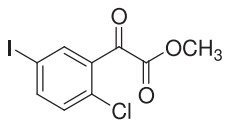
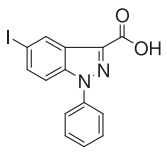
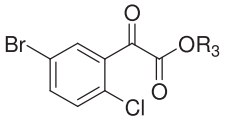
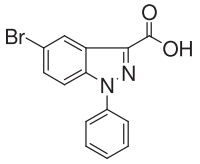
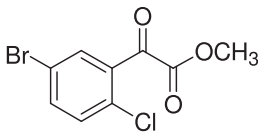
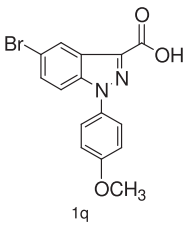
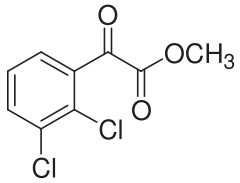
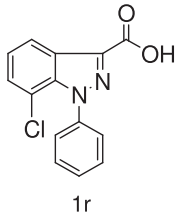
Synthesis of 1-aryl indazole-3-carboxylic acid.



S. no.	Substrate	Product	Reaction conditions		mp (°C)	Yield (%)	Elemental analysis found % (calcd)/HRMS (calcd)
			Temp (°C)	Time (h)			
1	 13a	 1i	75–80	6	192–194	71	[15]
2	 13a	 1j	70–75	5	200–202	66	291.0745 (291.0746)
3	 13a	 1k	95–100	3	256–258	65	C, 54.62; H, 2.89; N, 9.01 (C, 54.75; H, 2.62; N, 9.12)
4	 13b	 1l	75–80	6	249–250	70	295.0251 (295.0250)

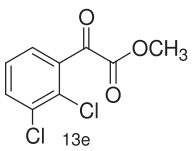
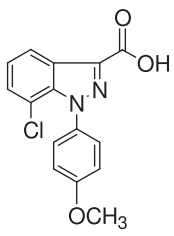
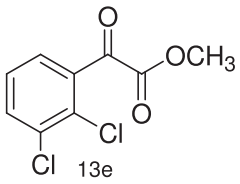
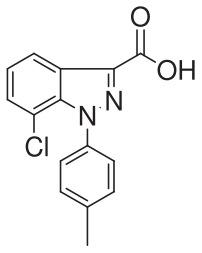
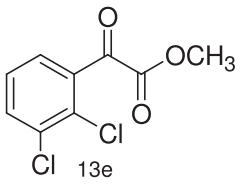
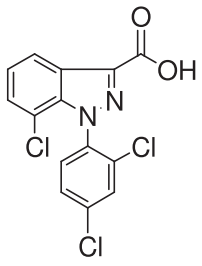
(*Continued*)

Table 2
(*Continued*)

S. no.	Substrate	Product	Reaction conditions		mp (°C)	Yield (%)	Elemental analysis found % (calcd)/HRMS (calcd)
			Temp (°C)	Time (h)			
5	 13b	 1m	70–75	5	228–230	72	C, 59.42; H, 3.66; N, 9.15 (C, 59.52; H, 3.66; N, 9.25)
6	 13b	 1n	60–65	7	265–268	70	309.0408 (309.0407)
7	 13c	 1o	75–80	6	235–237	62	386.9605 (386.9606)
8	 13d	 1p	75–80	6	248–250	68	C, 53.20; H, 2.90; N, 8.92 (C, 53.02; H, 2.86; N, 8.83)
9	 13d	 1q	65–70	7	227–230	69	C, 51.59; H, 3.30; N, 8.16 (C, 51.89; H, 3.19; N, 8.07)
10	 13e	 1r	75–80	6	272–274	68	C, 61.87; H, 3.43; N, 9.96 (C, 61.66; H, 3.33; N, 10.27)

(*Continued*)

Table 2
(*Continued*)

S. no.	Substrate	Product	Reaction conditions: Temp (°C)	Reaction conditions: Time (h)	mp (°C)	Yield (%)	Elemental analysis found % (calcd)/HRMS (calcd)
11	 13e	 1s	70–75	6	265–267	69	C, 59.49; H, 4.01; N, 9.34 (C, 59.52; H, 3.66; N, 9.25)
12	 13e	 1t	75–80	6	265–268	65	C, 62.53; H, 4.03; N, 9.41 (C, 62.83; H, 3.86; N, 9.77)
13	 13e	 1u	95–100	6	258–260	62	C, 49.2; H, 2.44; N, 8.23 (C, 49.22; H, 2.06; N, 8.20)

vacuum to obtain the desired (2,3-dichlorophenyl)-oxoacetic acid methyl/ethyl ester to yield 20.0 g (95%).

(2-Chlorophenyl)-oxoacetic acid methyl ester (13a) *[18].* IR (neat): 2955.13, 1739.52, 1699.90, 1590.18, 1207.68, 761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H), 7.27–7.39 (m, 2H), 7.45 (m, 1H), 7.69 (dd, $nJ = 7.68$ Hz, $nJ = 1.48$ Hz, 1H); ^{13}C NMR (CDCl3): δ 52.5, 127.1, 130.0, 131.3, 132.8, 133.5, 134.3, 163.2, 185.9; ms: *m/z* 198.1 (M^+) and 200.1 (M + 2).

(2-Bromophenyl)-oxoacetic acid methyl ester (13a) *[18].* IR (neat): 2954.09, 1735.62, 1702.29, 1586.76, 1207.27, 756.08 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (s, 3H), 7.43–7.46 (m, 2H), 7.63–7.70 (m, 2H); ^{13}C NMR (CDCl3): δ 52.7, 121.4, 127.6, 131.6, 133.6, 134.0, 135.2, 162.6, 186.8; ms: *m/z* 183 (M–$COOCH_3$).

(2-Iodophenyl)-oxoacetic acid methyl ester (13a). IR (neat): 2953.17, 1736.74, 1704.46, 1579.74, 1210.83, 721.63 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.97 (s, 3H), 7.26 (dt, 1H), 7.49 (t, $J = 7.50$ Hz, 1H), 7.62 (dd, $nJ = 7.72$ Hz, $nJ = 1.46$ Hz, 1H), 7.96 (d, $J = 7.87$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 52.8, 93.0, 128.2, 131.6, 133.7, 138.0, 140.6, 161.9, 187.6; ms: *m/z* 231.1 (M–$COOCH_3$).

(2,5-Dichlorophenyl)-oxoacetic acid ethyl ester (13b). mp 63–65°C; IR (KBr): 2991.13, 1730.64, 1692.99, 1458.85, 1196.18, 835.86 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, $J = 7.09$ Hz, 3H), 4.41 (q, 2H), 7.35 (d, $J = 8.52$ Hz, 1H), 7.45 (dd, $nJ = 8.45$ Hz, $nJ = 1.94$ Hz, 1H), 7.69 (d, $J = 1.76$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 62.9, 131.0, 131.5, 131.7, 133.4, 133.9, 134.5, 162.2, 185.1; ms: *m/z* 247.1

(2-Bromo-5-chlorophenyl)-oxoacetic acid ethyl ester (13b). mp 57–59°C; IR (KBr): 2985.71, 1730.95, 1696.50, 1454.58, 1189.99, 733.08 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, $J = 7.14$ Hz, 3H), 4.42 (q, 2H), 7.38 (dd, $nJ = 5.84$ Hz, $nJ = 2.85$ Hz, 1H), 7.55 (d, $J = 8.48$ Hz, 1H), 7.62 (d, $J = 2.48$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 63.0, 119.0, 131.2, 133.7, 134.1, 134.6, 136.9, 161.5, 185.9; ms: *m/z* 291.13 (M^+) and 293.1 (M + 2).

(5-Chloro-2-iodophenyl)-oxoacetic acid methyl ester (13b). IR (neat): 2953.13, 1735.80, 1696.28, 1451.98, 1202.86, 823.45 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.97 (s, 3H), 7.24 (dd, nJ = 8.40 Hz, nJ = 2.44 Hz, 1H), 7.55 (d, J = 2.42 Hz, 1H), 7.85 (d, J = 8.41 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 53.5, 89.6, 131.2, 133.6, 134.9, 139.8, 141.4, 161.1, 186.4; ms: m/z 264.90 (M–$COOCH_3$).

(2-Chloro-5-iodophenyl)-oxoacetic acid methyl ester (13c). IR (neat): 2955.26, 1742.80, 16936.36, 1466.98, 1229.15, 854.45 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (s, 3H), 7.17 (d, J = 8.42 Hz, 1H), 7.82 (dd, nJ = 8.42 Hz, nJ = 2.02 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 53.4, 91.5, 131.9, 133.4, 134.7, 139.6, 142.8, 162.5, 184.5.

(5-Bromo-2-chlorophenyl)-oxoacetic acid ethyl ester (13d). mp 59–62°C; IR (KBr): 2986.04, 1731.99, 1697.38, 1455.37, 1188.58, 738.69 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, J = 4.3 Hz, 3H), 4.41 (q, 2H), 7.30 (d, J = 8.52 Hz, 1H), 7.62 (dd, nJ = 8.50 Hz, nJ = 2.44 Hz, 1H), 7.85 (d, J = 2.36 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 63.0, 120.9, 131.8, 132.4, 133.9, 134.8, 136.9, 162.2, 185.1; ms: m/z 291.1 (M^+) and 293.2 (M + 2).

(5-Bromo-2-iodophenyl)-oxoacetic acid methyl ester (13d). IR (neat): 2953.27, 1732.78, 1690.28, 1455.35, 1199.61, 842.42 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.94 (s, 3H), 7.32 (dd, nJ = 8.36 Hz, nJ = 2.23 Hz, 1H), 7.65 (d, J = 2.20, 1H), 7.74 (d, J = 8.38 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 53.5, 90.8, 122.6, 134.0, 136.5, 140.1, 141.6, 161.0, 186.2; ms: m/z 311.2 (M–$COOCH_3$).

(2,3-Dichlorophenyl)-oxoacetic acid methyl ester (13e). IR (neat): 2955.43, 1741.18, 1708.05, 1414.01, 1222.38, 733.58 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H), 7.29 (t, J = 7.88 Hz, 1H), 7.54 (dd, nJ = 7.68 Hz, nJ = 1.20 Hz, 1H), 7.59 (dd, nJ = 8.0 Hz, nJ = 1.22 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 53.3, 127.9, 129.3, 131.4, 133.9, 134.5, 135.5, 162.5, 185.2; ms: m/z 231.2 (M^+) and 234.0 (M + 2).

(2-Chloro-5-nitrophenyl)-oxoacetic acid ethyl ester (13f). IR (neat): 1927.69, 1735.30, 1608.87, 1533.64, 1348.49, 1196.94, 1067.92, 757.58 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (t, J = 6.78 Hz, 3H), 4.46 (q, 2H), 7.65 (d, J = 8.78 Hz, 1H), 8.36 (dd, nJ = 8.74 Hz, nJ = 2.71 Hz, 1H), 8.57 (d, J = 2.68 Hz, 1H).

General procedure for the preparation of hydrazones (14a–w). To a solution of IPA (100.0 mL), (2-chlorophenyl)-oxoacetic acid methyl ester (10.0 g, 0.050 mol), and K_2CO_3 (10.3 g, 0.075 mol), hydrazine (methyl, ethyl, and phenyl; 0.055 mol) was added at room temperature. Reaction mass was heated to 60°C and stirred for 6 h at 60–65°C. After completion of the reaction, solvent was distilled off under vacuum, and water (25.0 mL) and ethyl acetate (50.0 mL) were added at room temperature and stirred for 30 min. The organic layer was separated and washed with water (10.0 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum to obtain the crude product, with a yield of 10.0 g (87.6%), which was purified by silica gel column chromatography [hexane:ethyl acetate (3:1)] to give 6.0 g of hydrazone as a colorless solid, mp 113.9–115.8°C.

Methyl 2-(2-chlorophenyl)-2-(2-methylhydrazono)acetate (14a). mp 114–116°C; IR (KBr): 3280.71, 3249.70, 2949.70, 1696.12, 1542.57, 1316.13, 1162.54, 752.10 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.14 (d, J = 3.67 Hz, 3H), 3.72 (s, 3H), 5.92 (d, J = 2.73 Hz, 1H), 7.12–7.44 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 37.8, 52.05, 127.5, 128.8, 129.6, 130.0, 130.6, 131.0, 133.6, 164.2; ms: m/z 167.2 (M–$COOCH_3$).

Methyl 2-(2-bromophenyl)-2-(2-methylhydrazono)acetate (14a). mp 116–120°C; IR (KBr): 3261.38, 2947.36, 1690.21, 1545.1313.89, 1134.25 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.22 (d, J = 4.0 Hz, 3H), 3.82 (s, 3H), 5.8 (s, 1 Hz), 7.18–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 37.8, 52.1, 123.3, 128.2, 130.5, 130.7, 131.1, 131.9, 133.2, 164.1; ms: m/z 213.2 (M–$COOCH_3$).

Methyl 2-(2-iodophenyl)-2-(2-methylhydrazono)acetate (14a). mp 140–142°C; IR (KBr): 3268.80, 2946.96, 1706.48, 1524.27, 1316.00, 1148.54 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.22 (d, J = 3.92 Hz, 3H), 3.8 (s, 3H), 5.84 (s, 1H), 7.11–7.96 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 37.8, 52.1, 98.3, 129.0, 130.4, 130.7, 133.3, 136.4, 139.6, 163.8; ms: m/z 259.1 (M–$COOCH_3$).

Ethyl 2-(2,5-dichlorophenyl)-2-(2-methylhydrazono)acetate (14b). mp 82–84°C; IR (KBr): 3315.66, 2979.15, 1701.51, 1680.65, 1558.15, 1324.94, 1171.69, 817.12 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (t, J = 6.98 Hz, 3H), 3.2 (d, J = 3.52 Hz, 3H), 4.24 (q, 2H), 5.94 (s, 1H), 7.26 (s, 1H), 7.30 (d, J = 6.92 Hz, 1H), 7.40 (d, J = 8.56 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 37.9, 61.0, 127.8, 130.5, 130.8, 131.1, 131.5, 132.2, 133.2, 163.4; ms: m/z 275.2 (M^+) and 277.2 (M + 2).

Ethyl 2-(2-bromo-5-chlorophenyl)-2-(2-methylhydrazono) acetate (14b). mp 104–106°C; IR (KBr): 3315.30, 2979.28, 1699.31, 1680.27, 1557.93, 1324.30, 1171.33, 815.71 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (s, 3H), 3.19 (s, 3H), 4.23 (d, J = 7.11 Hz, 2H), 5.9 (s, 1H), 7.13 (s, 1H), 7.22 (d, J = 7.70 Hz, 1H), 7.56 (d, J = 8.03 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 37.9, 61.0, 121.4, 129.3, 130.7, 130.9, 133.8, 134.0, 134.6, 163.2; ms: m/z 319.2 and 321.2 (M + 2).

Ethyl 2-(5-chloro-2-iodophenyl)-2-(2-methylhydrazono)acetate (14b). mp 116–118°C; IR (KBr): 3322.86, 2930.25, 1704.90, 1541.53, 1307.31, 1155.59, 826.49 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (t, J = 7.09 Hz, 3H), 3.27 (d, J = 3.94 Hz, 3H), 4.30 (q, 2H), 5.83 (d, J = 3.06 Hz, 1H), 7.10–7.87 (m, 3H); ms: m/z 367.2 (M + 2).

Isopropyl 2-(2-chloro-5-iodophenyl)-2-(2-methylhydrazono) acetate (14c). mp 105–110°C; IR (KBr): 3298.89, 2978.16, 1674.60, 1543.03, 1458.23, 1081.84, 812.32 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (d, J = 6.10 Hz, 6H), 3.22 (d, J = 3.99 Hz, 3H), 5.13 (m, 1H), 5.86 (s, 1H), 7.24 (t, J = 9.31 Hz, 1H), 7.50 (d, J = 1.96 Hz, 1H), 7.67 (dd, nJ = 8.45 Hz, nJ = 1.99 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 21.7, 37.9, 68.4, 91.7, 128.1, 131.6, 132.3, 133.9, 139.2, 139.3, 162.9; ms: m/z 381.0 and 383.2 (M + 2).

Ethyl 2-(5-bromo-2-chlorophenyl)-2-(2-methylhydrazono) acetate (14d). mp 96–98°C; IR (KBr): 3293.71, 2983.72, 1677.86, 1541.82, 1321.91, 1172.63, 1086.28, 815.70 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (t, J = 6.78 Hz, 3H), 3.23 (d, J = 3.32 Hz, 3H), 4.2 (q, 2H), 5.91 (s, 1H), 7.27–7.38 (m, 2H), 7.48 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 37.9, 61.0, 120.8, 127.7, 131.4, 131.8, 132.9, 133.5, 133.6, 163.4; ms: m/z 319.2 and 321.1 (M + 2).

Isopropyl 2-(5-bromo-2-iodophenyl)-2-(2-methylhydrazono) acetate (14d). mp 125–127°C; IR (KBr): 3308.08, 2930.23, 1683.66, 1556.59, 1272.02, 1177.75, 812.01; ^1H NMR ($CDCl_3$): δ 1.26 (d, J = 6.26 Hz, 6H), 3.23 (d, J = 3.95 Hz, 3H), 5.15 (m, 1H), 5.79 (d, J = 3.47 Hz, 1H), 7.25 (m, 2H), 7.78 (dd, nJ = 5.42 Hz, nJ = 3.86 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.6, 21.8, 37.9, 68.4, 96.6, 123.0, 132.4, 133.0, 133.5, 138.9, 140.9, 162.5; ms: m/z 424.9 and 427.0 (M + 2).

Methyl 2-(2,3-dichlorophenyl)-2-(2-methylhydrazono)acetate (14e). mp 135–137°C; IR (KBr): 3275.15, 2948.65, 1702.27, 1530.77, 1317.88, 1162.98, 768.29 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.22 (d, J = 4.0 Hz, 3H), 3.81 (s, 3H), 5.88 (d, J = 2.92 Hz, 1H), 7.12 (dd, nJ = 7.61 Hz, nJ = 1.38 Hz, 1H), 7.31 (t, J = 7.82 Hz, 1H), 7.53 (dd, nJ = 8.06 Hz, nJ = 1.38 Hz, 1H); ^{13}C NMR

($CDCl_3$): δ 37.9, 52.1, 128.2, 128.3, 129.2, 131.3, 131.9, 132.1, 134.0, 163.9; ms: *m/z* 261.2.

Ethyl 2-(2-chloro-5-nitrophenyl)-2-(2-methylhydrazono)acetate (14f). mp 146–148°C; IR (KBr): 3308.59, 2992.70, 1688.36, 1562.17, 1346.59, 1169.51, 769.91 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, *J* = 3.54 Hz, 3H), 3.25 (d, *J* = 3.96 Hz, 3H), 4.29 (q, 2H), 5.93 (d, *J* = 3.36 Hz, 1H), 7.62 (d, *J* = 4.32 Hz, 1H), 8.10 (d, *J* = 2.68 Hz, 1H), 8.23 (dd, *nJ* = 5.96 Hz, *nJ* = 2.68 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2, 38.0, 61.2, 125.2, 126.4, 126.5, 131.0, 131.6, 141.2, 146.8, 163.2; ms: *m/z* 286.0 and 288.5 (M + 2).

Methyl 2-(2,3-dichlorophenyl)-2-(2-ethylhydrazono)acetate (14g). mp 104–106°C; IR (KBr): 3261.42, 2982.67, 1708.74, 1528.69, 1312.35, 1148.52, 761.78 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.18 Hz, 3H), 3.53 (m, 2H), 3.81 (s, 3H), 5.93 (s, 1H), 7.11 (d, *J* = 7.52 Hz, 1H), 7.33 (t, *J* = 7.79 Hz, 1H), 7.53 (d, *J* = 7.99 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.0, 45.7, 52.1, 128.2, 128.3, 129.2, 131.2, 132.0, 132.0, 134.0, 164.0; ms: *m/z* 275.1 (M^+) and 277.2 (M + 2).

Methyl 2-(2-chloro-5-nitrophenyl)-2-(2-ethylhydrazono)acetate (14h). IR (KBr): 3269.49, 2951.49, 1708.90, 1523.02, 1347.91, 1156.86, 742.08 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (t, *J* = 8.24 Hz, 3H), 3.58 (m, 2H), 3.83 (s, 3H), 5.99 (s, 1H), 7.68 (d, *J* = 8.81 Hz, 1H), 8.11 (d, *J* = 2.60 Hz, 1H), 8.23 (dd, n*J* = 8.80 Hz, *nJ* = 2.64 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.9, 45.9, 52.3, 125.3, 126.0, 126.7, 131.1, 131.5, 141.0, 146.9, 163.8.

Methyl 2-(2-chlorophenyl)-2-(2-phenylhydrazono)acetate (14i). IR (KBr): 3298.68, 2981.44, 1702.27, 1562.93, 1313.22, 1107.45, 747.14 cm^{-1}; ^1H NMR (DMSO): δ 3.70 (s, 3H), (t, *J* = 5.62 Hz, 1H), 7.30 (m, 4H), (dd, *nJ* = 7.38 Hz, *nJ* = 1.52 Hz, 1H), 7.47 (m, 2H), 7.58 (d, *J* = 7.71 Hz, 1H), 9.89 (s, 1H).

Methyl 2-(2,3-dichlorophenyl)-2-(2-phenylhydrazono)acetate (14j). mp 119–121°C; IR (KBr): 3265.38, 2947.76, 1411.37, 1541.66, 1432.69, 1225.41, 1086.87, 749.70 cm^{-1}; ^1H NMR (DMSO): δ 3.71 (s, 3H), 6.92 (t, *J* = 6.26 Hz, 1H), 7.24 (m, 4H), 7.54 (d, *J* = 8.60 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *nJ* = 8.54 Hz, *nJ* = 2.28 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 52.2, 114.7, 120.6, 122.2, 128.7, 129.3, 131.8, 132.9, 133.3, 134.0, 134.4, 144.1, 164.2; ms: *m/z* 367.2 and 369.2 (M + 2).

Methyl 2-(5-chloro-2-iodophenyl)-2-(2-phenylhydrazono) acetate (14k). mp 145–147°C; IR (KBr): 3264.41, 2945.44, 1708.36, 1540.92, 1229.64, 1154.35, 750.41 cm^{-1}; ^1H NMR (DMSO): δ 3.71 (s, 3H), 6.92 (t, *J* = 6.62 Hz, 1H), 7.26 (m, 5H), 7.38 (s, 1H), 7.94 (d, *J* = 8.44 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (DMSO): δ 52.2, 98.0, 114.7, 122.1, 129.3, 131.1, 131.2, 133.3, 134.0, 139.5, 140.7, 144.0, 163.8; ms: *m/z* 415.2 (M^+) and 417.2 (M + 2).

Methyl 2-(5-bromo-2-chlorophenyl)-2-(2-phenylhydrazono) acetate (14l). mp 119–121°C; IR (KBr): 3265.38, 1947.76, 1711.37, 1541.66, 1225.41, 1153.59, 749.70 cm^{-1}; ^1H NMR (DMSO): δ 3.71 (s, 3H), 6.92 (t, *J* = 6.26 Hz, 1H), 7.30 (m, 4H), 7.54 (d, *J* = 8.60 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.70 (dd, *nJ* = 8.56 Hz, *nJ* = 2.28 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (DMSO): δ 52.2, 114.7, 120.6, 122.2, 128.7, 129.3, 131.8, 132.9, 133.3, 134.0, 134.4, 144.1, 164.2; ms: *m/z* 367.2 and 369.2.

Methyl 2-(2-chlorophenyl)-2-(2-(4-methoxyphenyl)hydrazono) acetate (14o). mp 128–129°C; IR (KBr): 3256.23, 2956.10, 1679.65, 1516.95, 1157.16, 1036.42, 786.16 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.80 (s, 6H), 6.87 (d, *J* = 8.92 Hz, 2H), 7.19 (d, *J* = 8.92 Hz, 2H), 7.42 (m, 2H), 7.47 (m, 2H), 12.42 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 51.6, 55.5, 114.5, 115.3, 125.3, 126.6, 129.1, 129.2, 131.6, 134.5, 135.6, 136.6, 155.5, 163.7; ms: *m/z* 319.3 (M^+) and 321.2 (M + 2).

Methyl 2-(5-chloro-2-iodophenyl)-2-(2-(4-methoxyphenyl) hydrazono)acetate (14p). mp 155–157°C; IR (KBr): 3268.03, 2947.78, 1709.44, 1514.67, 1229.27, 1031.67, 823.05, 529.21 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.87 (s, 3H), 6.84 (d, *J* = 8.85 Hz, 2H), 7.14 (m, 4H), 7.67 (s, 1H), 7.90 (d, *J* = 8.25 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 52.3, 55.5, 95.5, 114.5, 115.7, 130.6, 131.3, 132.9, 135.4, 136.0, 137.6, 140.9, 155.6, 163.5; ms: *m/z* 445.0 and 447.2 (M + 2).

Methyl 2-(5-bromo-2-chlorophenyl)-2-(2-(4-methoxyphenyl) hydrazono)acetate (14q). mp 140–141°C; IR (KBr): 3260.54, 2945.86, 1706.29, 1516.12, 1222.79, 831.40, 501.66 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.85 (s, 3H), 6.83 (d, *J* = 8.87 Hz, 2H), 7.11 (d, *J* = 8.88 Hz, 2H), 7.42 (t, *J* = 4.11 Hz, 2H), 7.56 (dd, *nJ* = 8.57 Hz, *nJ* = 2.16 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 52.3, 55.4, 114.5, 115.6, 121.1, 128.6, 131.1, 131.6, 133.0, 133.8, 134.0, 135.9, 155.6, 163.9; ms: *m/z* 397.1 and 399.2 (M + 2).

Methyl 2-(2-chloro-5-iodophenyl)-2-(2-(4-methoxyphenyl) hydrazono)acetate (14r). mp 138–141°C; IR (KBr): 3247.40, 2948.68, 1707.71, 1516.22, 1222.00, 1033.04, 833.36 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H), 3.88 (s, 3H), 6.85 (d, *J* = 8.94 Hz, 2H), 7.12 (d, *J* = 8.95 Hz, 2H), 7.29 (d, *J* = 8.46 Hz, 1H), 7.60 (d, *J* = 1.99 Hz, 1H), 7.71 (s, 1H), 7.75 (dd, *nJ* = 8.46 Hz, *nJ* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 52.3, 55.5, 92.0, 114.5, 115.6, 128.6, 131.3, 131.8, 133.9, 135.9, 139.5, 139.9, 155.6, 164.00; ms: *m/z* 445.2.

Methyl 2-(2,3-dichlorophenyl)-2-(2-(4-methoxyphenyl)hydrazono) acetate (14s). mp 119–121°C; IR (KBr): 3247.57, 2954.38, 1674.83, 1514.00, 1155.20, 794.72 cm^{-1}; ^1H NMR (DMSO): δ 3.70 (s, 3H), 3.75 (s, 3H), 6.88 (d, *J* = 8.96 Hz, 2H), 7.25 (d, *J* = 8.92 Hz, 2H), 7.40 (t, *J* = 7.94 Hz, 1H), 7.46 (dd, *nJ* = 7.58 Hz, *nJ* = 1.36 Hz, 1H), 7.62 (dd, *nJ* = 7.94 Hz, *nJ* = 1.36 Hz, 1H), 12.21 (s, 1H); ^{13}C NMR (DMSO): δ 52.2, 55.6, 114.9, 116.0,124.9, 128.5, 130.5, 131.0, 131.9, 131.9, 136.7, 138.1, 155.7, 162.7.

Methyl 2-(5-chloro-2-iodophenyl)-2-(2-p-tolylhydrazono) acetate (14t). mp 180–182°C; IR (KBr): 3270.07, 2947.22, 1712.51, 1539.93, 1223.61, 1159.42, 810.21 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H), 3.87 (s, 3H), 7.10 (m, 4H), 7.20 (m, 2H), 7.72 (s, 1H), 7.91 (d, *J* = 8.32 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6, 52.4, 95.3, 114.3, 129.7, 130.6, 131.3, 132.4, 133.3, 135.5, 137.5, 139.8, 140.9, 163.5; ms: *m/z* 369.1 (–COOCH3).

Methyl 2-(2,3-dichlorophenyl)-2-(2-p-tolylhydrazono)acetate (14u). mp 119–121°C; IR (KBr): 3236.69, 2920.47, 1672.14, 1532.59, 1232.04, 1053.24, 791.54 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H), 3.86 (s, 3H), 7.08 (m, 4H), 7.21 (d, *J* = 7.58 Hz, 1H), 7.38 (t, *J* = 7.82 Hz, 1H), 7.40 (d, *J* = 8.02 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6, 52.3, 114.3, 128.3, 129.2, 129.7, 129.9, 131.4, 131.7, 132.2, 132.3, 134.3, 139.9, 164.0; ms: *m/z* 336.7.

Methyl 2-(2,3-dichlorophenyl)-2-(2-(2,4-dichlorophenyl) hydrazono)acetate (14v). mp 113–117°C; IR (KBr): 3320.74, 2951.37, 1727.55, 1566.01, 1499.06, 1158.78, 829.14 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.87 (s, 3H), 7.22 (m, 2H), 7.27 (s, 1H), 7.42 (t, *J* = 7.84 Hz, 1H), 7.63 (dd, *nJ* = 8.08 Hz, *nJ* = 1.31 Hz, 1H), 7.70 (t, *J* = 4.7 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (CDCl3): δ 52.6, 116.3, 119.0, 127.1, 128.2, 128.3, 128.4, 128.6, 130.7, 131.9, 132.1, 134.0, 134.6, 137.0, 163.4; ms: *m/z* 391.2 (M^-).

Methyl 2-(2-(2,4-dichlorophenyl)hydrazono)-2-(2-iodophenyl) acetate (14w). mp 122–124°C; IR (KBr): 3306.39, 1944.80,

1727.10, 1542.36, 1131.52, 777.54 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H), 7.21–7.26 (m, 4H), 7.56 (t, $J = 7.42$ Hz, 1H), 7.72 (t, $J = 4.69$ Hz, 1H), 8.02 (d, $J = 8.01$ Hz, 1H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 52.6, 96.9, 116.3, 118.9, 126.8, 128.1, 128.6, 129.2, 129.8, 131.4, 135.2, 137.2, 138.7, 140.0, 163.3.

General procedure for the preparation of 1-subtituted indazole-3-carboxylic acid (1a–w). To a solution of hydrazone (**3a**) (5.0 g, 0.022 mol), CuI (0.42 g, 0.0022 mol), L-proline (0.5 g, 0.0044 mol), and Cs_2CO_3 (18.0 g, 0.055 mol) in DMSO (15.0 mL) were heated to 95°C and stirred for 7 h at 95–100°C. After completion of the reaction, the solvent is distilled under reduced pressure and cooled to room temperature; water (50.0 mL) and toluene (10.0 mL) were added and stirred for 30 min. We filtered the mass through Celite pad and washed it with water (10.0 mL). The filtrate was separated, and we adjusted the pH to 2.0–2.5 with dil. HCl to obtain the desired compound, which was purified by crystallization in ethyl acetate to yield 3.2 g (83%), mp 216–217°C.

1-Methyl-1H-indazole-3-carboxylic acid (1a). mp 215–216°C; IR (KBr): 3024.75, 2938.01, 1687.17, 1487.63, 1230.90, 748.76 cm^{-1}; ^1H NMR (DMSO): δ 4.14 (s, 3H), 7.30 (t, $J = 7.46$ Hz, 1H), 7.47 (t, $J = 7.58$ Hz, 1H), 7.75 (d, $J = 8.44$ Hz, 1H), 8.0 (d, $J = 8.12$ Hz, 1H) 12.98 (s, 1H); ^{13}C NMR (DMSO): δ 36.5, 110.9, 121.6, 123.1, 123.3, 126.8, 134.7, 141.1, 163.7; ms: *m/z* 177 (M^+).

5-Chloro-1-methyl-1H-indazole-3-carboxylic acid (1b). mp 252–254°C; IR (KBr): 3423.75, 2924.07, 1687.92, 1476.73, 1222.17, 1040.74, 742.76 cm^{-1}; ^1H NMR (DMSO): δ 4.14 (s, 3H), 7.50 (d, $J = 6.93$ Hz, 1H), 7.82 (d, $J = 8.33$ Hz, 1H), 8.02 (s, 1H), 13.01 (s, 1H); ^{13}C NMR (DMSO): δ 36.9, 112.9, 120.4, 124.2, 127.2, 127.9, 134.3, 139.5, 163.1; ms: *m/z* 211 (M^+) and 213.2 (M + 2); HRMS: *m/z* calcd for $C_9H_7ClN_2O_2$ (M + Na): 233.0094. Found: 233.0095.

5-Iodo-1-methyl-1H-indazole-3-carboxylic acid (1c). mp 225–228°C; IR (KBr): 3431.64, 2943.54, 1724.43, 1485.98, 1223.41, 1120.94, 796.60 cm^{-1}; ^1H NMR (DMSO): δ 4.12 (s, 3H) 7.62 (d, $J = 8.80$ Hz, 1H), 7.40 (d, $J = 8.86$ Hz, 1H), 8.4 (s, 1H), 13.10(s, 1H); ^{13}C NMR (DMSO): δ 36.7, 88.0, 113.4, 125.6, 130.0, 133.8, 134.8, 140.2, 163.4; ms: *m/z* 303.2 (M^+). Anal. calcd for $C_9H_7IN_2O_2$: C, 35.79; H, 2.34; N, 9.27. Found: C, 36.14; H, 2.46; N, 9.04.

5-Bromo-1-methyl-1H-indazole-3-carboxylic acid (1d). mp 232–233°C; IR (KBr): 3663.60, 2915.59, 1690.49, 1497.07, 1215.89, 1038.37, 824.15 cm^{-1}; ^1H NMR (DMSO): δ 4.14 (s, 3H), 7.6(dd, $nJ = 8.82$ Hz, $nJ = 1.68$ Hz, 1H), 7.77 (d, $J = 8.92$ Hz, 1H), 8.18 (d, $J = 1.48$ Hz, 1H), 13.18 (s, 1H); ^{13}C NMR (DMSO): δ 36.8, 113.3, 116.0, 123.7, 124.8, 129.6, 134.2, 139.9, 163.3; ms: *m/z* 255.1 (M^+) and 257.1 (M + 2); HRMS: *m/z* calcd for $C_9H_7BrN_2O_2$ (M + Na): 276.9589. Found: 276.9588 and 278.9597.

7-Chloro-1-methyl-1H-indazole-3-carboxylic acid (1e). mp 223–224°C; IR (KBr): 3037.44, 2615.47, 1704.90, 1479.77, 1202.46, 1069.24, 720.67 cm^{-1}; ^1H NMR (DMSO): δ 4.39 (s, 3H), 7.2 (t, $J = 7.82$ Hz, 1H), 7.52 (d, $J = 7.44$ Hz, 1H), 8.0 (d, $J = 8.12$ Hz, 1H), 13.22 (s, 1H); ^{13}C NMR (DMSO): δ 39.9, 115.9, 121.0, 123.9, 126.1, 127.7, 134.9, 136.7, 163.2; ms: *m/z* 211.5 (M^+). Anal. calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.80. Found: C, 51.30; H, 3.49; N, 13.51.

7-Chloro-1-ethyl-1H-indazole-3-carboxylic acid (1f). mp 212–216°C; IR (KBr): 3034.14, 2937.41, 1696.55, 1479.23, 1260.15, 1192.75, 772.40 cm^{-1}; ^1H NMR (DMSO): δ 1.44 (t, $J = 7.14$ Hz, 3H), 4.8 (q, 2H), 7.27 (t, $J = 5.25$ Hz, 1H), 7.5 (d, $J = 7.4$ Hz, 1H), 8.07 (d, $J = 8.12$ Hz, 1H), 13.26 (s, 1H); ^{13}C NMR (DMSO): δ 16.7, 47.2, 115.7, 121.2, 124.0, 126.3, 128.1, 135.5, 136.0, 163.2; ms: *m/z* 225.2 (M^+) and 227.2 (M + 2); HRMS: *m/z* calcd for $C_{10}H_9ClN_2O_2$ (M + Na): 247.0250. Found: 247.0250.

5-Nitro-1-methyl-1H-indazole-3-carboxylic acid (1g). mp 242–244°C; IR (KBr): 3422.76, 2925.01, 1697.70, 1529.78, 1344.87, 1222.44, 781.06 cm^{-1}; ^1H NMR (DMSO): δ 4.19 (s, 3H), 7.9 (d, $J = 9.26$ Hz, 1H), 8.23 (t, $J = 8.13$ Hz, 1H), 8.83 (s, 1H), 13.8 (s, 1H); ^{13}C NMR (DMSO): δ 37.0, 112.3, 118.8, 121.4, 122.2, 137.7, 142.7, 143.5, 162.93; ms: *m/z* 220.0 (M^-); HRMS: *m/z* calcd for $C_9H_7N_3O_4$ (M + Na): 244.0334. Found: 244.0331.

1-Ethyl-5-nitro-1H-indazole-3-carboxylic acid (1h). mp 226–228°C; IR (KBr): 3422.13, 2855.61, 1674.94, 1524.11, 13339.88, 1196.85, 729.10 cm^{-1}; ^1H NMR (DMSO): δ 1.4 (t, $J = 7.0$ Hz, 3H), 4.5 (q, 2H), 7.9 (d, $J = 9.20$ Hz, 1H), 8.2 (d, $J = 9.25$ Hz, 1H), 8.80 (s, 1H), 13.8 (s, 1H); ^{13}C NMR (DMSO): δ 15.0, 44.9 112.1, 119.0, 121.4, 122.3, 137.8, 141.9, 143.5, 162.9; ms: *m/z* 234.1 (M^-).

1-Phenyl-1H-indazole-3-carboxylic acid (1i). mp 192–194°C; IR (KBr): 3421.10, 3057.70, 2611.16, 1689.60, 1479.49, 1201.03, 752.11 cm^{-1}; ^1H NMR (DMSO): δ 7.4 (t, $J = 7.8$ Hz, 1H), 7.51–7.56 (m, 2H), 7.62 (t, $J = 7.8$ Hz, 2H), 7.8 (d, $J = 7.26$ Hz, 1H), 7.86 (d, $J = 8.56$ Hz, 2H), 8.2 (d, $J = 8.12$ Hz, 1H), 13.34 (s, 1H); ^{13}C NMR (DMSO): δ 114.3, 122.5, 127.3, 128.7, 129.3, 129.6, 129.9, 132.1, 133.6, 136.40, 143.3, 164.6; ms: *m/z* 239.2 (M^+).

1-(4-Methoxyphenyl)-1H-indazole-3-carboxylic acid (1j). mp 200–202°C; IR (KBr): 3007.72, 1688.91, 1519.71, 1258.43, 1197.36, 739.71 cm^{-1}; ^1H NMR (DMSO): δ 3.84 (s, 3H), 7.14 (d, $J = 8.84$ Hz, 2H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.51 (t, $J = 7.64$ Hz, 1H), 7.66–7.71 (m, 3H), 8.18 (d, $J = 8.12$ Hz, 1H), 13.27 (s, 1H); ^{13}C NMR (DMSO): δ 55.8, 111.3, 115.1, 122.1, 123.8, 124.0, 125.4, 127.9, 132.1, 136.9, 140.1, 159.1, 163.7; ms: *m/z* 269.1 (M^+); HRMS: *m/z* calcd for $C_{15}H_{12}N_2O_3$ (M + Na): 291.0746. Found: 291.0745.

1-(2,4-Dichlorophenyl)-1H-indazole-3-carboxylic acid (1k). mp 256–258°C; IR (KBr); 3422.41, 2611.52, 1698.39, 1474.39, 1203.67, 749.05 cm^{-1}; ^1H NMR (DMSO): δ 7.35 (d, $J = 8.4$ Hz, 1H), 7.41 (t, $J = 7.45$ Hz, 1H), 7.52 (t, $J = 7.59$ Hz, 1H), 7.70 (d, $J = 8.47$ Hz, 1H), 7.90 (d, $J = 8.47$ Hz, 1H), 8.03 (s, 1H), 8.2 (d, $J = 8.0$ Hz, 1H), 13.5 (s, 1H); ^{13}C NMR (DMSO): δ 111.2, 122.1, 123.2, 124.0, 128.3, 129.1, 130.6, 131.6, 132.1, 135.0, 135.6, 138.0, 141.6, 163.5; ms: *m/z* 307.2 (M^+) and 309.2 (M + 2). Anal. calcd for $C_{14}H_8Cl_2N_2O_2$: C, 54.75; H, 2.62; N, 9.12. Found: C, 54.62; H, 2.89; N, 9.01.

5-Chloro-1-phenyl-1H-indazole-3-carboxylic acid (1l). mp 249–250°C; IR (KBr): 3424.56, 2925.11, 1710.56, 1686.91, 1491.84, 1201.14, 754.68 cm^{-1}; ^1H NMR (DMSO): δ 7.5–7.59 (m, 2H), 7.6 (t, $J = 7.5$ Hz, 2H), 7.70 (d, $J = 7.80$ Hz, 2H) 7.8 (d, $J = 9.0$ Hz, 1H), 8.17 (s, 1H), 13.56 (s, 1H); ^{13}C NMR (DMSO); 113.5, 121.1, 123.7, 125.2, 128.5, 128.6, 130.2, 137.0, 138.6, 138.8, 163.2; ms: *m/z* 273.3 (M^+) and 275.2 (M + 2); HRMS: *m/z* calcd for $C_{14}H_9ClN_2O_2$ (M + Na): 295.0250. Found: 295.0251.

5-Chloro-1-(4-methoxyphenyl)-1H-indazole-3-carboxylic acid (1m). mp 228–230°C; IR (KBr): 2940.16, 1714.56, 1690.11, 1490.10, 1260.86, 827.14 cm^{-1}; ^1H NMR (DMSO): δ 3.84 (s, 3H), 7.14 (d, $J = 11.0$ Hz, 2H), 7.52 (dd, $nJ = 8.99$ Hz, $nJ = 1.77$ Hz, 1H), 7.65 (d, $J = 8.84$ Hz, 1H), 7.74 (d, $J = 9.0$ Hz, 2H), 8.13 (d, $J = 1.52$ Hz, 1H), 13.50 (s, 1H); ^{13}C NMR (DMSO): δ 55.9, 113.3, 115.2, 121.0, 124.9, 125.4, 128.2, 128.4, 131.7, 136.4, 138.7, 159.3, 163.3; ms: *m/z* 303.4 and 305.2 (M + 2).

Anal. calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.42; H, 3.66; N, 9.15.

5-Chloro-1-p-tolyl-1H-indazole-3-carboxylic acid (1n). mp 265–268°C; IR (KBr): 2925.53,2573.68, 1686.74, 1500.04, 1200.39, 820.02 cm^{-1}; ^1H NMR (DMSO): δ 2.49 (s, 3H), 7.41 (d, $J = 8.13$ Hz, 2H), 7.54 (dd, $nJ = 9.0$ Hz, $nJ = 1.75$ Hz, 1H), 7.63 (d, $J = 8.22$ Hz, 2H), 7.79 (d, $J = 9.0$ Hz, 1H), 8.14 (d, $J = 1.52$ Hz, 1H), 13.50 (s, 1H); ^{13}C NMR (DMSO): δ 21.0, 113.5, 121.0, 123.5, 125.0, 128.3, 128.5, 130.5, 136.4, 136.7, 138.2, 138.6, 163.3; ms: *m/z* 287.3 (M^+) and 289.3 (M + 2); HRMS: *m/z* calcd for $C_{15}H_{11}ClN_2O_2$ (M + Na): 309.0407. Found: 309.0408.

5-Iodo-1-phenyl-1H-indazole-3-carboxylic acid (1o). mp 235–237°C; IR (KBr): 3423.27, 2920.34, 1688.96, 1485.32, 1199.96, 781.79 cm^{-1}; ^1H NMR (DMSO): δ 7.52 (t, $J = 7.36$ Hz, 1H), 7.62–7.68, (m, 3H), 7.7–7.8 (m, 3H), 8.85 (s, 1H), 13.54 (s, 1H); ^{13}C NMR (DMSO): δ 93.5, 118.5, 128.3, 130.1, 133.2, 134.9, 135.3,140.9, 141.2, 143.5, 143.8, 168.0; ms: *m/z* 365.2 (M^+); HRMS: *m/z* calcd for $C_{14}H_9IN_2O_2$ (M + Na): 386.9606. Found: 386.9605.

5-Bromo-1-phenyl-1H-indazole-3-carboxylic acid (1p). mp 248–250°C; IR (KBr): 3431.18, 2853.75, 1686.18, 1487.99, 1199.52, 781.05 cm^{-1}; ^1H NMR (DMSO): δ 7.53 (t, $J = 7.16$ Hz, 1H), 7.63–7.69 (m, 3H), 7.84 (m, 3H), 8.32 (s, 1H), 13.56 (s, 1H); ^{13}C NMR (DMSO): δ 113.7, 116.6, 123.6, 124.2, 125.7, 128.6, 130.2, 130.9, 136.8, 138.7, 163.2; ms: *m/z* 317.2 (M^+), 319.2 (M + 2), and 320.3 (M + 3). Anal. calcd for $C_{14}H_9BrN_2O_2$: C, 53.02; H, 2.86; N, 8.83. Found: C, 53.20; H, 2.90; N, 8.92.

5-Bromo-1-(4-methoxyphenyl)-1H-indazole-3-carboxylic acid (1q). mp 227–230°C; IR (KBr): 3435.42, 1686.81, 1518.21, 1259.53, 1198.28, 839.16; cm^{-1}; ^1H NMR (DMSO): δ 3.84 (s, 3H), 7.14 (d, $J = 8.64$ Hz, 2H), 7.59–7.67 (m, 4H), 8.28 (s, 1H), 13.44 (s, 1H); ^{13}C NMR (DMSO): δ 55.9, 113.6, 115.2, 116.4, 124.1, 125.4, 130.6, 131.7, 136.2, 138.9, 159.3, 163.3; ms: *m/z* 347.1 and 349.0 (M + 2). Anal. calcd for $C_{15}H_{11}BrN_2O_3$: C, 51.89; H, 3.19; N, 8.07. Found: C, 51.59; H, 3.30; N, 8.16.

7-Chloro-1-phenyl-1H-indazole-3-carboxylic acid (1r). mp 272–274°C; IR (KBr): 3481.21, 3056.67, 1697.20, 1501.65, 1266.93, 1193.73, 692.36 cm^{-1}; ^1H NMR (DMSO): δ 7.4 (t, $J = 7.88$ Hz, 1H), 7.57 7.62 (m, 6H), 8.19 (d, $J = 8.08$ Hz, 1H), 13.48 (s, 1H); ^{13}C NMR (DMSO): δ 116.2, 121.4, 124.7, 126.0, 128.3, 128.9, 129.8, 137.1, 137.3, 139.5, 163.2; ms: *m/z* 273.2 (M^+) and 275.2 (M + 2). Anal. calcd for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; N, 10.27. Found: C, 61.87; H, 3.43; N, 9.96.

7-Chloro-1-(4-methoxyphenyl)-1H-indazole-3-carboxylic acid (1s). mp 265–267°C; IR (KBr): 3420.15, 2836.63, 1691.73, 1519.79, 1249.32, 1179.85, 836.68 cm^{-1}; ^1H NMR (DMSO): δ 3.85 (s, 3H), 7.09 (d, $J = 8.8$ Hz, 2H), 7.35 (t, $J = 7.82$ Hz, 1H), 7.5 (d, $J = 8.76$ Hz, 2H), 7.5 (d, $J = 7.4$ Hz, 1H), 8.17 (d, $J = 8.08$ Hz, 1H), 13.43 (s, 1H); ^{13}C NMR (DMSO): δ 55.8, 113.9, 116.2, 121.3, 124.5, 125.9, 128.8, 129.6, 132.4, 137.0, 137.3, 160.1, 163.3; ms: *m/z* 303.3 (M^+) and 305.2 (M + 2). Anal. calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.49; H, 4.01; N, 9.34.

7-Chloro-1-p-tolyl-1H-indazole-3-carboxylic acid (1t). mp 265–268°C; IR (KBr): 3435.89, 2919.58, 1691.31, 1486.91, 1184.56, 1184.56, 824.71 cm^{-1}; ^1H NMR (DMSO): δ 2.42 (s, 3H), 7.35–7.38 (m, 3H) 7.45 (d, $J = 7.96$ Hz, 2H), 7.56 (d, $J = 7.4$, 1H) 8.17 (d, $J = 8.08$ Hz, 1H), 13.46 (s, 1H); ^{13}C NMR (DMSO): δ 21.1, 116.2, 121.3, 124.6, 126.0, 128.0, 128.9, 129.3, 137.1, 139.4, 163.2; ms: *m/z* 287.3 (M^+). Anal. calcd for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.86; N, 9.77. Found: C, 62.53; H, 4.03; N, 9.41.

7-Chloro-1-(2,4-dichlorophenyl)-1H-indazole-3-carboxylic acid (1u). mp 258–260°C; IR (KBr); 3429.72, 2890.69, 1690.89, 1472.22, 1181.43, 778.11 cm^{-1}; ^1H NMR (DMSO): δ 7.40 (t, $J = 7.15$ Hz, 1H), 7.62 (d, $J = 7.16$ Hz, 1H), 7.68 (d, $J = 8.41$ Hz, 1H), 7.8 (dd, $nJ = 8.7$ Hz, $nJ = 1.2$ Hz, 1H), 7.97 (s, 1H), 8.19 (d, $J = 7.84$ Hz, 1H), 13.7 (s, 1H); ^{13}C NMR (DMSO): δ 116.0, 121.5, 125.0, 125.5, 128.5, 129.0, 129.5, 132.4, 134.1, 136.1, 136.3, 137.9, 138.2, 163.0; ms: *m/z* 341.0 (M^+). Anal. calcd for $C_{14}H_7Cl_3N_2O_2$: C, 49.22; H, 2.06; N, 8.20. Found: C, 49.20; H, 2.44; N, 8.23.

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