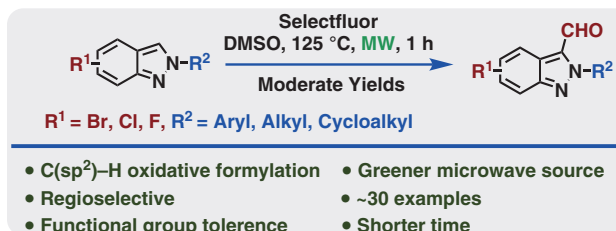


# Regioselective C3-Formylation of 2H-Indazoles Using Selectfluor under Microwave-Assisted Conditions

Manivel Pitchai<sup>\*a</sup>Mahammed Kaspady<sup>a</sup>Gopikumar Indasi<sup>a</sup>Rajesh Krishnan<sup>a</sup>Gururaju Sannakki Maheswarappa<sup>a</sup>Muthalagu Vetrichelvan<sup>\*a</sup> Arvind Mathur<sup>b</sup>Anuradha Gupta<sup>b</sup>

<sup>a</sup> Department of Discovery Synthesis, Biocon Bristol Myers Squibb R&D Centre, Syngene International Ltd., Biocon Park, Plot No. 2 & 3, Jigani Link Road, Bommasandra IV, Bangalore 560 099, India  
manivel.pitchai@syngeneintl.com  
muthalagu.vetrichelvan@syngeneintl.com

<sup>b</sup> Small Molecule Drug Discovery, Bristol Myers Squibb Research and Early Development, P.O. Box 5400, Princeton, NJ 08543-4000, USA



Received: 18.08.2023

Accepted after revision: 09.02.2024

Published online: 12.02.2024 (Accepted Manuscript), 04.03.2024 (Version of Record)

DOI: 10.1055/a-2266-3213; Art ID: SO-2023-12-0093-OP

License terms:

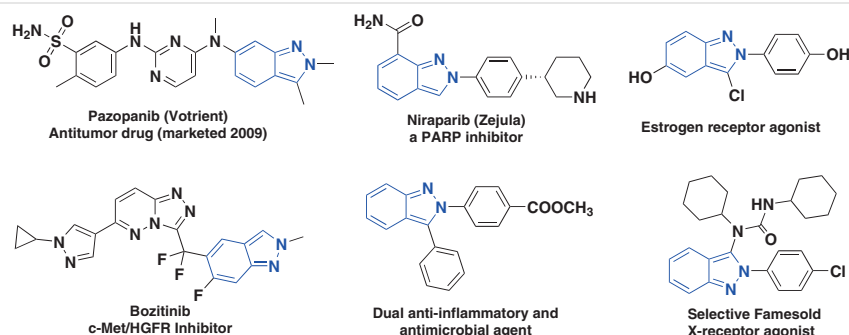
© 2024. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution and reproduction, so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

**Abstract** An efficient microwave-assisted Selectfluor-mediated regioselective C3-formylation of 2H-indazoles bearing a variety of alkyl and aryl substituents using DMSO as the formylating agent has been developed. This methodology provides access to 3-formyl 2H-indazoles with moderate to excellent yields. These functionalized indazoles are potentially useful as templates for drug discovery. Control experimental results suggest that this formylation probably proceeds through a radical pathway.

**Key words** 2H-indazoles, Selectfluor, C3-formylation, microwave, radical pathways

Indazoles are important heterocyclic scaffolds in the pharmaceutical field owing to their various biological properties such as anti-inflammatory, antibacterial, anti-HIV, antiarrhythmic, antifungal, and antitumor activities.<sup>1</sup> In particular, 2H-indazoles have received a great deal of attention as they are important moieties in fragment-based drug discovery (FBDD) and in scaffold hopping exercises for protein kinase inhibitors.<sup>2</sup> 2H-Indazole derivatives are an essential pharmacophore that display diverse pharmacological activity; compounds containing this group include the antitumor drug Pazopanib, Niraparib (a PARP inhibitor), an estrogen receptor agonist, Bazitinib (c-Met/HGFR inhibitor), a dual anti-inflammatory and antimicrobial agent, and a selective Famesold X-receptor agonist (Figure 1).<sup>3,4</sup>

Considering the significant importance of indazole and its derivatives in drug discovery research, the past decade was witness to tremendous research on the synthesis and functionalization of indazoles. Therefore, direct C3-functionalization on 2H-indazoles is worth pursuing as it would



**Figure 1** Representative examples of biologically active APIs encompassing 2H-indazoles

provide an efficient route for the synthesis of various 2*H*-indazole derivatives. Very recently, some remarkable breakthroughs related to C3-functionalization of 2*H*-indazoles through acylation, arylation, alkylation, alkenylation, trifluoromethylation, selenylation, and phosphorylation using different approaches including visible-light-mediated reactions were reported.<sup>3b,5</sup> In our quest to synthesize fluoro derivatives of 2*H*-indazoles, the use of Selectfluor was explored. Selectfluor is a widely used electrophilic fluorinating reagent in organic synthesis and has been employed not only as an electrophilic fluorinating reagent but also as an oxidant in many chemical transformations.<sup>6</sup> Our recent ef-

forts include the late-stage functionalization of APIs with fluorination, trifluoromethylation and other CH-functionalization.<sup>7</sup> In a continuation of our interest, we began our investigation of fluorination on 2*H*-indazoles using Selectfluor in DMSO solvent; contrary to our expectation, the formylated product was observed instead of fluorination. In an extension of the literature precedence of such formylation on 2*H*-indazole by Hajra *et al.*<sup>8</sup> using potassium persulfate oxidant, herein we report the scope and limitations of Selectfluor-mediated microwave-assisted C3-formylation of 2*H*-indazoles.

**Table 1** Optimization of Reaction Conditions<sup>a</sup>

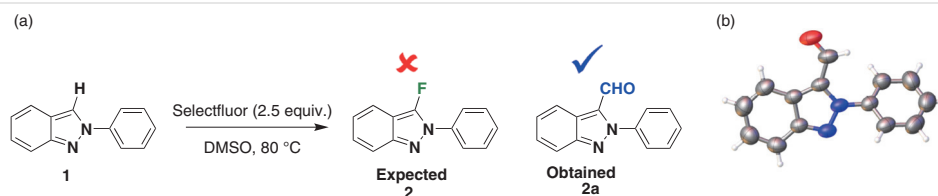


Entry	Oxidant (equiv)	Solvent (2 mL)	Temp (°C)	Time (h)	Conv. (%) <sup>b</sup>
1	Selectfluor (2.5)	DMSO	80 <sup>c</sup>	1	20
2	Selectfluor (2.5)	DMSO	100 <sup>c</sup>	1	26
3	Selectfluor (2.5)	DMSO	120 <sup>c</sup>	1	31
4	Selectfluor (2.5)	DMSO	125 (MW)	1	55
5	Selectfluor (1)	DMSO	125 (MW)	1	trace
6	Selectfluor (2)	DMSO	125 (MW)	1	trace
<b>7</b>	<b>Selectfluor (3)</b>	<b>DMSO</b>	<b>125 (MW)</b>	<b>1</b>	<b>80</b>
8	Selectfluor (3)	DMSO/H <sub>2</sub> O	125 (MW)	1	nr
9	Selectfluor (3)	HFIP	80 (MW)	1	nr
10	Selectfluor (3)	DMF	125 (MW)	1	nr
11	Selectfluor (3)	DMA	125 (MW)	1	nr
12	Oxone (3)	DMSO	125 (MW)	1	nr
13	diacetoxyiodobenzene (3)	DMSO	125 (MW)	1	nr
14	hydroquinone (3)	DMSO	125 (MW)	1	nr
15	sodium persulfate (3)	DMSO	125 (MW)	1	7
16	<i>tert</i> -butylhydroperoxide (3)	DMSO	125 (MW)	1	nr
17	Cu(OAc) <sub>2</sub> (3)	DMSO	125 (MW)	1	nr
18	Selectfluor-II (3)	DMSO	125 (MW)	1	28
19	(Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbpy))PF <sub>6</sub> /Selectfluor (0)	DMSO	100 W blue LED r.t.	12	nr
20	(Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbpy))PF <sub>6</sub> /Selectfluor (3)	DMSO	100 W blue LED r.t.	12	nr
21	Selectfluor (3)	DMSO	100 W blue LED r.t.	12	nr
22	Vilsmeier–Haack	DMF/POCl <sub>3</sub>	125 <sup>c</sup>	1	trace
23	–	DMSO	125 (MW)	1	trace
24	hexamethylenetetramine/acetic acid	–	110 <sup>c</sup>	3	trace

<sup>a</sup> Reaction conditions: All reactions were carried out with **1a** (0.2 mmol) and oxidant in DMSO (2 mL) for 1 h.

<sup>b</sup> Determined by LCMS.

<sup>c</sup> Reaction under conventional heating.



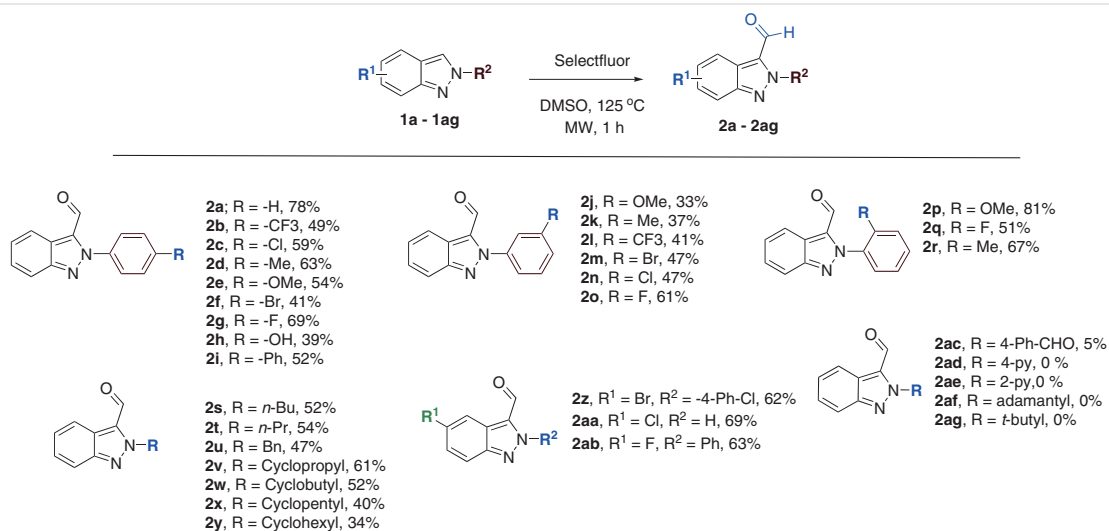
**Scheme 1** (a) C3-functionalization of 2H-indazoles. (b) Single-crystal X-ray structure of compound **2a** (CCDC 2315017, see the Supporting Information for full single-crystal X-ray details).<sup>9</sup>

As part of our drug discovery program, we were interested in late-stage functionalization of fluoro/trifluoromethyl group on indazoles. Hence, the fluorination of indazoles by using Selectfluor was proposed, which can act as both fluorinating reagent as well as an oxidant. When the reaction was performed using 2.5 equivalent of Selectfluor in DMSO at 80 °C for one hour, to our surprise, 3-formylated indazole was formed as a major product (20%) rather than the expected 3-fluorinated indazole, as shown in Scheme 1a. The formylated compound was characterized thoroughly and the structure of compound **2a** was confirmed by single-crystal X-ray crystallography as presented in Scheme 1b.<sup>9</sup>

As the aldehyde functional group can be utilized for the formation of a wide variety of C–C and C–hetero bonds, we believed that the 3-formylated 2H-indazoles can serve as a key precursor for indazole-based drug discovery. With this, an investigation was initiated to optimize the reaction conditions (Table 1). Increasing the temperature from 80 to 120 °C furnished only a marginal improvement in the yield (entries 2 and 3). To optimize the reaction further, microwave conditions were studied and, to our delight, the yield was improved to 55% (entry 4). Attention then turned towards

the number of equivalents of oxidant, and the experiments suggested that the reaction requires three equivalents for better yields (entries 5–7). The negative results shown in entries 8–11 suggested that DMSO was the only suitable solvent for the present transformation. Further screening with different oxidants such as oxone, diacetoxyiodobenzene, hydroquinone, sodium persulphate, TBHP, and copper acetate (entries 12–17) did not show the formation of the product, except in the case of sodium persulfate, with which 7% product formation was observed along with multiple impurities. The reaction with Selectfluor II yielded 28% of the product under standard conditions (entry 18). Attempts to conduct a photochemical reaction using Ir photoredox catalyst such as Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbpy)PF<sub>6</sub> under blue LED conditions (entries 19–21) were not successful. Formylation performed under classical Vilsmeier–Haack reaction conditions using POCl<sub>3</sub> and DMF, unfortunately, gave no product (entry 22). Similarly, only a trace amount of product was observed when Duff's formylation conditions were used with hexamethylene tetramine / AcOH under heating (entry 24).

After extensive screening of the reaction with different parameters, the optimal reaction conditions were estab-

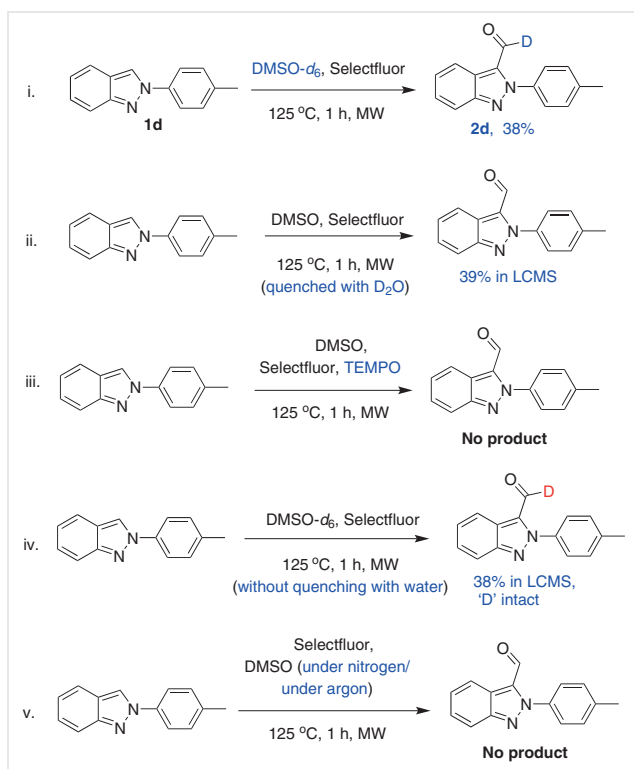


**Scheme 2** Substrate scope of Selectfluor-mediated formylation. Reagents and conditions: **1** (0.2 mmol) and Selectfluor (3.0 equiv) in DMSO (2 mL) for 1 h under microwave irradiation at 125 °C. Isolated yields given.

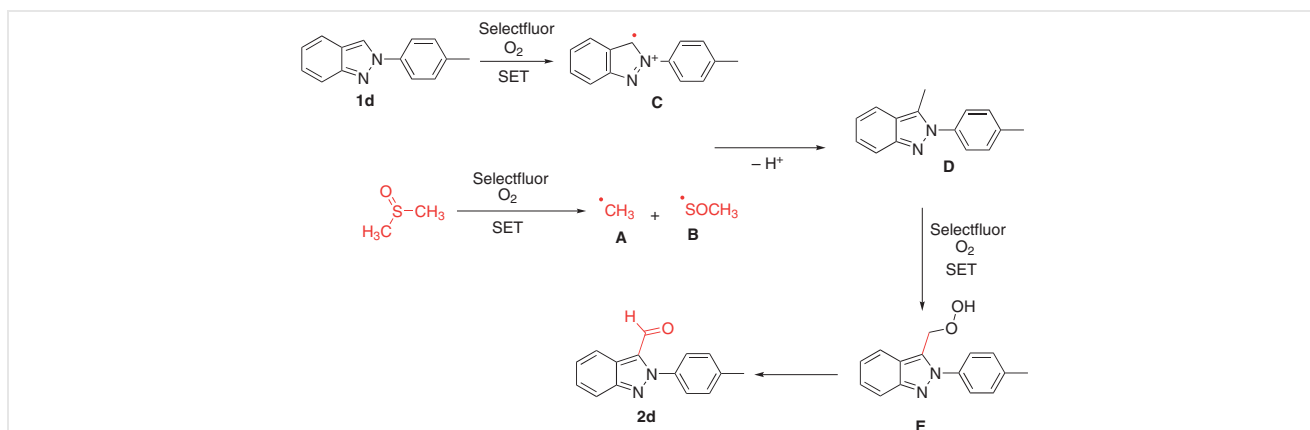
lished as microwave irradiation of a solution of Selectfluor (3 equiv) in DMSO as a solvent at 125 °C, which produced 80% conversion into the desired product (Table 1, entry 7). The substrate scope was explored with 2*H*-indazoles bearing a variety of aryl/alkyl/heteroaryl substituents on the indazole part. The 2*H*-indazoles were then subjected to formylation under the optimized conditions. The yields of the formylated 2*H*-indazoles **2a–ac** are summarized in Scheme 2. Aryl substituents with electron-donating and -withdrawing groups afforded the desired formylated prod-

uct **2a–ac** with moderate to good yields of 40–80%. Halogen-substituted indazoles **2b**, **2c**, **2f**, **2g**, **2l–o**, **2q**, **2aa**, and **2ab** also afforded moderate yields of 41–69%. Fortunately, *N*-alkyl (**2s**, **2t**) and *N*-cycloalkyl (**2v–y**) derivatives also gave moderate yield of 40–60%. Such derivatives were not successfully synthesized with the recently reported K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>-mediated formylation of 2*H*-indazoles.<sup>8</sup> One more advantage of the current method compared to the reported approach is the duration of reaction, with the present method requiring only 1 h compared to 24 h. Unfortunately, heteroaryl and hindered 2*H*-indazoles **2ad–ag** failed to produce the desired 3-formylated products.

To probe the mechanistic pathway of the reaction, several control experiments using **1d** as a model substrate were carried out. First, the reaction was performed with DMSO-*d*<sub>6</sub> instead of DMSO under standard conditions, which resulted in the product with –CDO mass and not a –CHO mass in LCMS. This clearly indicated that the source of aldehydic hydrogen was the solvent DMSO. A further control experiment was performed to confirm the source of aldehydic proton; the reaction was conducted under standard conditions with DMSO and quenched with D<sub>2</sub>O (Scheme 3, equation ii). Under these conditions the deuterated aldehyde mass was not observed in LCMS or NMR analyses. This result again suggests that the aldehydic proton comes from DMSO. Such type of formylation using DMSO as a C1-source has been reported previously.<sup>8</sup> To understand the reaction pathway, a reaction was performed in the presence of TEMPO, which acts as a radical scavenger (Scheme 3, equation iii). Under these conditions, no product formation was observed, thereby supporting a free-radical pathway for the reaction. The product mass was clearly observed by LCMS even without quenching the reaction mass with external water (Scheme 3, equation iv). Two parallel reactions were performed under inert conditions by using nitrogen and argon. In both cases the solvent and the reaction mixtures were thoroughly purged with nitrogen and argon prior to



Scheme 3 Control experiments



Scheme 4 Plausible reaction mechanism

starting the reaction under microwave conditions (Scheme 3, equation v). In neither case was the desired product mass observed in LCMS, indicating that dissolved  $O_2$  plays an important role in generating the aldehyde.

Based on these control experiments and on previous reports,<sup>10</sup> a possible mechanism was proposed as shown in Scheme 4. DMSO reacts with Selectfluor and is activated to generate methyl radical (**A**) and methylsulfone radical species (**B**) via single electron transfer (SET). 2*H*-Indazole **1d**, upon oxidation with Selectfluor, forms radical intermediate **C** through SET. Radical coupling of **C** with the methyl radical leads to the formation of intermediate **D**. Intermediate **D** undergoes SET and is trapped by  $O_2$  to form peroxy species **E**, which is converted into the desired aldehyde **2d**.

In summary, an efficient methodology for regioselective C3-formylation of 2*H*-indazoles bearing a variety of alkyl and aryl groups has been demonstrated. The advantages of this methodology include the greener microwave process, shorter time, extensive substrate scope including *N*-alkylated derivatives, and the use of DMSO as both solvent and formylating source. The deuterated labeling experiments indicate that this reaction may proceed through a radical pathway. This method thus provides rapid access to a variety of C3-formylated 2*H*-indazoles and related derivatives, which will generate a library of compounds on an important scaffold for drug discovery research in the pharmaceutical industry.

All starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. The starting materials were synthesized according to the reported procedures. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60  $F_{254}$  pre-coated plates and visualized with a UV lamp for reaction monitoring. All  $^1H$  NMR (400 MHz),  $^{13}C$  NMR (100 MHz), and  $^{19}F$  NMR spectra were recorded with a Bruker 300 or 400 MHz spectrometer, and chemical shifts are reported in ppm using TMS or the residual solvent peak as the reference. High-resolution mass spectra (HRMS) were recorded with LTQ XL Orbitrap Discovery-X caliber and Agilent-Q-TOF-Mass hunter instruments. LC-MS analyses were recorded with an Agilent 6140 quadrupole LCMS instrument using C18 columns (see the Supporting Information for more details on the respective spectra). A discover SP system microwave synthesizer (CEM Corporation) was used for the reaction. All 2*H*-indazole substrates were synthesized using reported procedures.<sup>11</sup>

### General Procedure

To a stirred solution of 2*H*-indazole (0.2 mmol) in DMSO (2 mL; 1 M) in a 10-mL microwave vial, Selectfluor (0.6 mmol) was added at room temperature, then the mixture was stirred for 1 h at 125 °C under microwave irradiation. The reaction mixture was diluted with water and extracted with EtOAc (2 × 20 mL), washed with water, dried over sodium sulfate, and concentrated under vacuum to afford the crude compound. The crude product was purified by ISCO (Red Sep,  $SiO_2$ ) using 15 to 20% EtOAc/hexane as eluant to give 2*H*-indazole-3-carbaldehyde derivatives **2a–ab**.

The analytical data for the reported aldehydes **2a**,<sup>8,12</sup> **2c–g**,<sup>8</sup> **2j**,<sup>8</sup> **2k**,<sup>8</sup> **2m–n**,<sup>8</sup> **2r**,<sup>8</sup> **2u**,<sup>13</sup> **2aa–ab**<sup>8</sup> matched the respective data.

### 2-(4-(Trifluoromethyl)phenyl)-2*H*-indazole-3-carbaldehyde (**2b**)

Yield: 49%; yellow solid; mp 136–139 °C.

$^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.06 (s, 1 H), 8.25 (d,  $J$  = 8.5 Hz, 1 H), 7.95 (d,  $J$  = 8.5 Hz, 1 H), 7.88–7.93 (m, 2 H), 7.74 (d,  $J$  = 8.5 Hz, 2 H), 7.46–7.57 (m, 2 H).

$^{13}C$  NMR (126 MHz, DMSO- $d_6$ ):  $\delta$  = 180.3, 147.9, 141.9, 131.87, 129.9 (q,  $J$  = 32.7 Hz, 1C), 128.0, 127.3, 127.0, 126.6 (q,  $J$  = 3.3 Hz, 1C), 123.2, 123.8 (q,  $J$  = 272.5 Hz, 1C), 120.5, 118.5.

$^{19}F$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  = 61.08 (s, 3F).

HRMS:  $m/z$   $[M + H]^+$  calcd for  $C_{15}H_9F_3N_2O$ : 291.0747; found: 291.0740.

### 2-(4-Hydroxyphenyl)-2*H*-indazole-3-carbaldehyde (**2h**)

Yield: 39%; brown liquid.

$^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.14 (s, 1 H), 9.99 (s, 1 H), 8.21 (d,  $J$  = 8.0 Hz, 1 H), 7.93 (d,  $J$  = 8.5 Hz, 1 H), 7.65 (d,  $J$  = 8.51 Hz, 2 H), 7.43–7.56 (m, 2 H), 7.00 (d,  $J$  = 8.5 Hz, 2 H).

$^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 180.6, 158.7, 147.3, 131.5, 130.0, 127.7, 127.3, 126.5, 120.4, 118.3, 115.7.

HRMS:  $m/z$   $[M + H]^+$  calcd for  $C_{14}H_{10}N_2O_2$ : 239.0822; found: 239.0820.

### 2-([1,1'-Biphenyl]-4-yl)-2*H*-indazole-3-carbaldehyde (**2i**)

Yield: 52%; yellow gummy solid.

$^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.12 (s, 1 H), 8.26 (d,  $J$  = 8.0 Hz, 1 H), 7.94–8.00 (m, 5 H), 7.82 (d,  $J$  = 7.5 Hz, 2 H), 7.43–7.58 (m, 5 H).

$^{13}C$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  = 180.3, 147.9, 141.8, 131.7, 127.9, 127.3, 127.0, 126.5, 123.1, 120.50, 18.5, 79.1.

HRMS:  $m/z$   $[M + H]^+$  calcd for  $C_{20}H_{14}N_2O$ : 299.1186; found: 299.1182.

### 2-(3-(Trifluoromethyl)phenyl)-2*H*-indazole-3-carbaldehyde (**2l**)

Yield: 41%; yellow solid; mp 120–123 °C.

$^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.04 (s, 1 H), 8.24 (d,  $J$  = 8.5 Hz, 1 H), 7.95 (d,  $J$  = 8.5 Hz, 1 H), 7.61–7.70 (m, 2 H), 7.43–7.58 (m, 4 H).

$^{13}C$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta$  = 180.1, 147.8, 139.4, 131.8, 130.7, 130.6, 130.1 (q,  $J$  = 32.7 Hz, 1C), 127.9, 126.9, 126.5 (q,  $J$  = 3.6 Hz, 1C), 123.3 (q,  $J$  = 4.4 Hz, 1C), 123.1, 123.5 (q,  $J$  = 273.2 Hz, 1C), 120.4, 118.5, 114.5, 15.1.

$^{19}F$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta$  = 61.0 (s, 3F).

HRMS:  $m/z$   $[M + H]^+$  calcd for  $C_{15}H_9F_3N_2O$ : 291.0747; found: 291.0743.

### 2-(3-Fluorophenyl)-2*H*-indazole-3-carbaldehyde (**2o**)

Yield: 61%; yellow solid; mp 91–93 °C.

$^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.08 (s, 1 H), 8.25 (d,  $J$  = 8.5 Hz, 1 H), 7.96 (d,  $J$  = 8.0 Hz, 1 H), 7.91–7.82 (m, 1 H), 7.78–7.68 (m, 2 H), 7.59–7.48 (m, 3 H), 3.40 (br d,  $J$  = 18.6 Hz, 1 H), 2.68 (s, 1 H), 2.59 (br d,  $J$  = 13.6 Hz, 1 H).

$^{13}C$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta$  = 180.9, 162.4 (d,  $J$  = 245.8 Hz, 1C), 148.2, 140.4 (d,  $J$  = 11.0 Hz, 1C), 132.3, 131.7 (br d,  $J$  = 8.8 Hz, 1C), 128.4, 127.4, 123.3, 121.0, 119.0, 117.4 (br d,  $J$  = 20.5 Hz, 1C), 114.6 (br d,  $J$  = 25.7 Hz, 1C).

$^{19}F$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta$  = 111.2 (s, 1F).

HRMS:  $m/z$   $[M + H]^+$  calcd for  $C_{14}H_9FN_2O$ : 241.0778; found: 241.0770.



**2-(2-Methoxyphenyl)-2H-indazole-3-carbaldehyde (2p)**

Yield: 81%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 9.82–9.80 (m, 1 H), 8.22–8.16 (m, 1 H), 7.94–7.90 (m, 1 H), 7.69–7.63 (m, 2 H), 7.54–7.45 (m, 2 H), 7.38–7.34 (m, 1 H), 7.26–7.20 (m, 1 H), 3.79 (s, 3 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 180.5, 153.2, 147.8, 132.2, 131.8, 128.4, 127.3, 127.1, 126.5, 121.8, 120.9, 120.2, 118.4, 112.7, 56.0.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: 253.0978; found: 253.0968.**2-(2-Fluorophenyl)-2H-indazole-3-carbaldehyde (2q)**

Yield: 51%; yellow solid; mp 92–95 °C.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.05 (d, *J* = 2.0 Hz, 1 H), 8.23–8.27 (m, 1 H), 7.94–7.98 (m, 1 H), 7.87 (dt, *J* = 1.7, 7.6 Hz, 1 H), 7.70–7.77 (m, 1 H), 7.48–7.63 (m, 4 H).<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): δ = 179.8 (d, *J* = 2.2 Hz, 1C), 155.9 (d, *J* = 250.9 Hz, 1C), 148.2, 132.4 (d, *J* = 8.1 Hz, 1C), 132.2, 129.2, 127.9, 127.0, 125.3 (d, *J* = 3.7 Hz, 1C), 122.7, 120.1, 118.5, 116.7 (d, *J* = 19.1 Hz, 1C).<sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>): δ = 124.1 (s, 1F).HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>9</sub>FN<sub>2</sub>O: 241.0778; found: 241.0777.**2-Butyl-2H-indazole-3-carbaldehyde (2s)**

Yield: 52%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.38 (s, 1 H), 8.13–8.18 (m, 1 H), 7.83–7.88 (m, 1 H), 7.37–7.46 (m, 2 H), 4.81–4.87 (m, 2 H), 1.87–1.96 (m, 2 H), 1.25–1.35 (m, 2 H), 0.90 (s, 3 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 179.8, 146.7, 130.4, 126.4, 125.8, 123.5, 119.5, 118.1, 51.8, 32.3, 19.1, 13.3.LCMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: 203.1186; found: 203.1120.**2-Propyl-2H-indazole-3-carbaldehyde (2t)**

Yield: 54%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.38 (s, 1 H), 8.13–8.18 (m, 1 H), 7.83–7.88 (m, 1 H), 7.37–7.46 (m, 2 H), 4.81–4.87 (m, 2 H), 1.87–1.96 (m, 2 H), 1.25–1.35 (m, 2 H), 0.90 (s, 3 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 179.7, 146.6, 29.8, 126.3, 125.7, 123.6, 119.6, 118.3, 53.1, 22.7.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: 189.1029; found: 189.1025.**2-Cyclopropyl-2H-indazole-3-carbaldehyde (2v)**

Yield: 61%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.52 (s, 1 H), 8.08–8.14 (m, 1 H), 7.79–7.84 (m, 1 H), 7.37–7.45 (m, 2 H), 4.72 (td, *J* = 3.6, 7.4 Hz, 1 H), 1.43–1.48 (m, 2 H), 1.23–1.30 (m, 2 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 180.3, 147.9, 141.8, 131.7, 127.9, 127.3, 127.0, 126.5, 123.1, 120.5, 118.5, 79.1.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 187.0873; found: 187.0865.**2-Cyclobutyl-2H-indazole-3-carbaldehyde (2w)**

Yield: 52%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.35 (s, 1 H), 8.13 (td, *J* = 1.13, 8.3 Hz, 1 H), 7.88–7.92 (m, 1 H), 7.37–7.47 (m, 2 H), 5.88 (t, *J* = 8.3 Hz, 1 H), 2.69–2.82 (m, 2 H), 2.57 (ddt, *J* = 1.25, 3.13, 6.07 Hz, 2 H), 1.89–1.99 (m, 2 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 180.3, 147.9, 141.8, 131.7, 127.9, 127.3, 127.0, 126.5, 123.1, 120.5, 118.5, 79.1.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O: 201.1029; found: 201.1026.**2-Cyclopentyl-2H-indazole-3-carbaldehyde (2x)**

Yield: 40%; yellow gummy solid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.42 (s, 1 H), 8.14 (d, *J* = 7.0 Hz, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.35–7.45 (m, 2 H), 5.79–5.88 (m, 1 H), 2.25 (td, *J* = 6.3, 12.9 Hz, 2 H), 2.10–2.20 (m, 2 H), 1.93 (br dd, *J* = 5.8, 9.3 Hz, 2 H), 1.67–1.80 (m, 2 H), 1.22–1.29 (m, 1 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 179.9, 126.4, 125.8, 123.6, 119.6, 118.3, 61.929, 33.3, 24.4.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O: 215.1186; found: 215.1179.**2-Cyclohexyl-2H-indazole-3-carbaldehyde (2y)**

Yield: 34%; yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.42 (s, 1 H), 8.13–8.17 (m, 1 H), 7.84–7.89 (m, 1 H), 7.37–7.45 (m, 2 H), 5.26–5.35 (m, 1 H), 1.84–2.15 (m, 6 H), 1.74 (br d, *J* = 13.1 Hz, 1 H), 1.51 (td, *J* = 3.33, 12.9 Hz, 2 H), 1.29 (br d, *J* = 12.6 Hz, 1 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 180.3, 147.9, 141.8, 131.7, 127.9, 127.3, 127.0, 126.5, 123.1, 120.5, 118.5, 79.1.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O: 229.1343; found: 229.1335.**5-Bromo-2-(4-chlorophenyl)-2H-indazole-3-carbaldehyde (2z)**

Yield: 62%; pale-yellow solid; mp 144–146 °C.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 10.03 (s, 1 H), 8.44 (d, *J* = 2.0 Hz, 1 H), 7.97–7.93 (m, 1 H), 7.91–7.87 (m, 2 H), 7.76–7.71 (m, 1 H), 7.75 (s, 2 H), 7.67–7.63 (m, 1 H).<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 180.3, 146.1, 137.3, 134.7, 131.2, 131.0, 129.4, 128.1, 124.0, 122.5, 120.7, 119.9.HRMS: *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>8</sub>BrClN<sub>2</sub>O: 334.9588; found: 334.9547.**Conflict of Interest**

The authors declare no conflict of interest.

**Acknowledgment**

We thank Dr Li Jianqing and Dr James Kempson for their helpful suggestions and proofreading. The analytical support from the Discovery Analytical Department, Biocon Bristol Myers Squibb Research Centre (BBRC), Bangalore (India) is gratefully acknowledged.

**Supporting Information**

Supporting information for this article is available online at <https://doi.org/10.1055/a-2266-3213>. Spectral data for the new intermediates are presented.

**References**

- (1) Qin, J.; Cheng, W.; Duan, Y.-T.; Yang, H.; Yao, Y. *Anti-Cancer Agents Med. Chem.* **2021**, *21*, 839.

- (2) Zhang, S. G.; Liang, C. G.; Zhang, W. H. *Molecules* **2018**, *23*, 2783.
- (3) (a) Mal, S.; Malik, U.; Mahapatra, M.; Mishra, A.; Pal, D.; Paidesetty, S. K. *Drug Dev. Res.* **2022**, *83*, 1469. (b) Ghosh, S.; Mondal, S.; Hajra, A. *Adv. Synth. Catal.* **2020**, *362*, 3768. (c) Schoene, J.; Gazzi, T.; Lindemann, P.; Christian, M.; Volkamer, A.; Nazaré, M. *ChemMedChem* **2019**, *14*, 1514.
- (4) (a) Benson, G. M.; Bleicher, K.; Feng, S.; Grether, U.; Kuhn, K.; Martin, R. E.; Plancher, J. M.; Richter, H.; Rudolph, M.; Taylor, S. US 2010/0076026A1, **2010**. (b) Villanueva, J. P.; Mulia, L. Y.; Sánchez, I. G.; Espinosa, J. F. P.; Arteché, O. S.; Sainz-Españes, T. R.; Cerbón, M. A.; Villar, K. R.; Vicente, A. K. R.; Gines, M. C.; Galván, Z. C.; Estrada-Castro, D. B. *Molecules* **2017**, *22*, 1864. (c) Villar, K. R.; Campos, A. H.; Mulia, L. Y.; Sainz-Españes, T. R.; Arteché, O. S.; Espinosa, J. F. P.; Benitez, F. C.; Lugo, M. L.; Petrisans, B. V.; Quintana-Salazar, E. A.; Villanueva, J. P. *Pharmaceuticals* **2021**, *14*, 176.
- (5) (a) Vidyacharan, S.; Murugan, A.; Sharada, D. S. *J. Org. Chem.* **2016**, *81*, 2837. (b) Yang, Z.; Yu, J. T.; Pan, C. *Org. Biomol. Chem.* **2022**, *20*, 7746.
- (6) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192.
- (7) (a) Kempson, J.; Zhang, H.; Wong, M. K. Y.; Li, J.; Li, P.; Wu, D. R.; Rampulla, R.; Galella, M. A.; Dabros, M.; Traeger, S. C.; Muthalagu, V.; Gupta, A.; Arunachalam, P. N.; Mathur, A. *Org. Process Res. Dev.* **2018**, *22*, 846. (b) Panja, C.; Puttaramu, J. C.; Chandran, T. K.; Nimje, R. Y.; Kumar, H.; Gupta, A.; Arunachalam, P. N.; Corte, J. R.; Mathur, A. *J. Fluorine Chem.* **2020**, *236*, 109516. (c) Pitchai, M.; Premsai, R.; Mathur, A.; Gupta, A. *unpublished results*.
- (8) (a) Bhattacharjee, S.; Laru, S.; Ghosh, P.; Hajra, A. *J. Org. Chem.* **2021**, *86*, 10866. (b) Xiang, S.; Chen, H.; Liu, Q. *Tetrahedron Lett.* **2016**, *57*, 3870.
- (9) CCDC 2315017 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/structures](http://www.ccdc.cam.ac.uk/structures).
- (10) (a) Tashrifi, Z.; Khanaposhtani, M. M.; Larijani, B.; Mahdavi, M. *Adv. Synth. Catal.* **2020**, *362*, 65. (b) Cao, H.; Lei, S.; Li, N.; Chen, L.; Liu, J.; Cai, H.; Qiu, S.; Tan, J. *Chem. Commun.* **2015**, *51*, 1823. (c) Ma, X.; Du, W.; Liu, W.; Liu, Y.; Tiebo, X. T.; Jiang, Y. *J. Chem. Sci.* **2019**, *131*, 55.
- (11) Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, *13*, 3542.
- (12) Shortcliff, L. D.; Weakley, T. J. R.; Haley, M. M.; Kohler, F.; Herges, R. *J. Org. Chem.* **2004**, *69*, 6979.
- (13) Williams, S. J.; Jarrott, B. WO 2016/149765 A1, **2016**.