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# An efficient synthesis of 1-arylindazole-3-carboxamides using nitrile imines, isocyanides and 2-hydroxymethylbenzoic acid, followed by a chemoselective Buchwald–Hartwig intramolecular cyclization†

M. Giustiniano,*[a] V. Mercalli,[b] E. Novellino[a] and G. C. Tron*[b]

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A convergent and efficient two-step synthesis of pharmaceutically relevant 1-arylindazole-3-carboxamides is reported. These molecules have been obtained in good to excellent yields (up to 98%) starting from a strategic reaction between isocyanides, 2-iodo-*N*-arylbenzohydrazonoyl chlorides and 2-hydroxymethylbenzoic acid followed by a chemoselective Buchwald–Hartwig intramolecular cyclization. This novel strategy provides an additional indazole synthesis to those already reported in literature both in the type of substrate as well as the substitution pattern obtainable in the products. Furthermore benzylisocyanide is herein reported for the first time as a convertible isocyanide providing an expeditious access to *N*-arylindazole-3-carbonitriles.

## Introduction

Several naturally occurring alkaloids and many bioactive synthetic compounds share as a common element the indazole nucleus.[1] According to their pattern of substitution, molecules containing the indazole ring have shown to possess different biological profiles spanning from anticancer compounds to serotonin 5-HT3 receptor antagonists.[2] In particular, substituted indazole-3-carboxamides have been disclosed as inhibitors of human neutrophil elastase,[3] DNA intercalating agents,[4] kinase inhibitors,[5] selective sodium channel blockers,[6] DGAT inhibitors,[7] and NAMPT inhibitors[8] (Fig. 1).

Due to the pharmaceutical relevance of indazoles several methods of preparations have been reported in literature which depend on the pattern of substitution of the indazole ring.[9] In particular 1-arylindazole-3-carboxamides **3** are prepared starting from the corresponding 1*H*-indazole-carboxylic acids **1** which are coupled with amines and then subjected to a Pd or Cu *N*-arylation. One disadvantage of this synthetic plan is that aryl substituted 1*H*-indazole-carboxylic acids require a multistep synthesis with poor overall efficiency[10] (Scheme 1).

For this reason an efficient synthetic strategy based on the preparation of substituted indazoles without using 1*H*-indazole-carboxylic acids is welcomed.

Recently, in our on-going studies aimed at the discovery of novel multicomponent reactions, we reported the use of hydrazonoyl chlorides as imine aza-analogue in isocyanide-mediated multicomponent reactions.[11] Continuing our interest in this chemistry, we recognized that α-aminocarbonyl hydrazones **7**, obtainable using the synthetic approach developed by us,[11a] thanks to their atom connectivity and the presence of the hydrazone functional group can be exploited in a post-condensation modification using a Buchwald–Hartwing

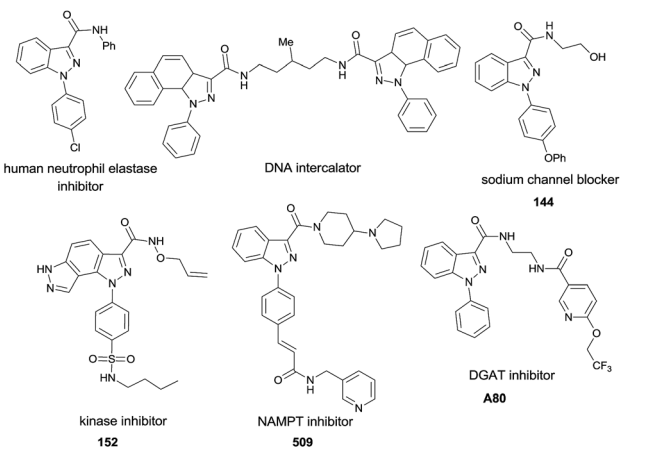


Fig. 1 Pharmaceutically relevant *N*-arylindazoles-3-carboxamides (numbers correspond to those reported in the patents).

[a]*Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", via D. Montesano 49, 80131 Napoli, Italy. E-mail: mariateresa.giustiniano@unina.it*

[b]*Dipartimento di Scienze del Farmaco, Università degli Studi del Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100 Novara, Italy. E-mail: giancesare.tron@pharm.unipmn.it*

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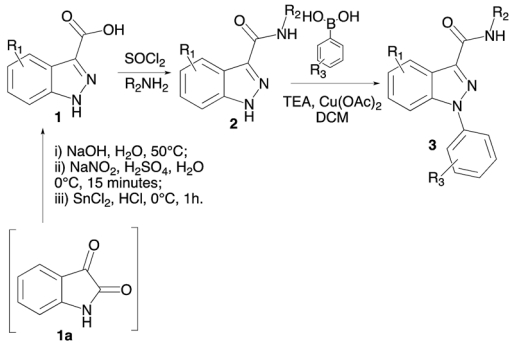
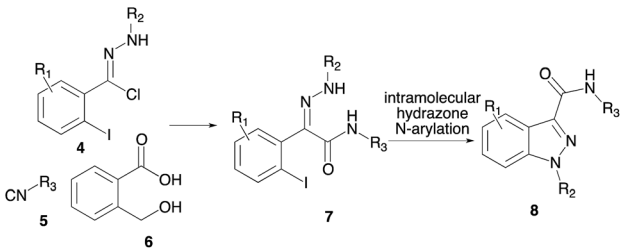



Scheme 1 Conventional synthesis of *N*-arylindazoles-3-carboxamides.



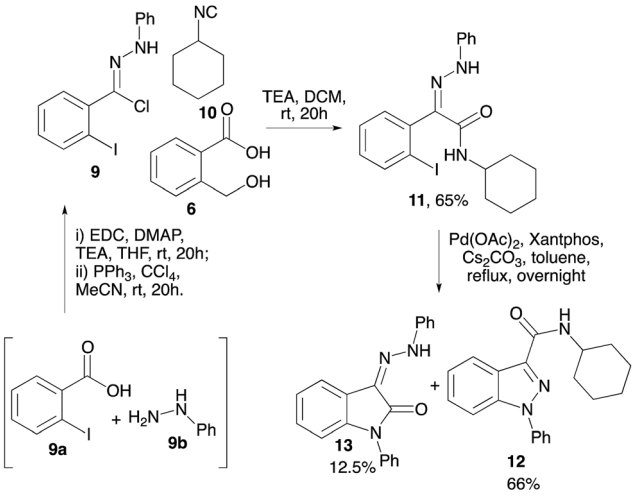

Scheme 2 General structure of α-aminocarbonyl hydrazones and cyclic indazole derivatives.

intramolecular amination to generate the substituted indazole ring **8** in two operationally simple reaction steps (Scheme 2).

## Results and discussion

In order to test our hypothesis, we reacted 2-iodo-*N*′-phenylbenzohydrazonoyl chloride **9**, cyclohexylisocyanide **10** and 2-hydroxymethylbenzoic acid (sacrificial acid) **6** in DCM at room temperature overnight to obtain α-aminocarbonyl hydrazone **11** in 65%. The reaction is triggered by the *in situ* generation of nitrile imine by a base-induced dehydrochlorination of hydrazonoyl chloride. The 2-hydroxymethylbenzoic acid behaves like a pseudo water molecule in order to overpass the poor reactivity of water on the nitrilium ion.[12] Subsequently, this linear intermediate was then reacted in classic Buchwald–Hartwing conditions to evaluate indazole **12** formation (Scheme 3). It is important to highlight that *a priori* both the hydrazone and the amide function could cyclize to give either the indazole or the indolone derivatives,[13] both being at a suitable distance (5 centers) from the aromatic iodine atom of intermediate **11**. Refluxing **11** in toluene, and in the presence of palladium acetate, Xantphos and cesium carbonate gave indeed the desired indazole **12** in 66% yield (entry 1, Table 1), and 12.5% of indolone derivative **13** coming from intramolecular amidation.

In order to optimize indazole formation we screened different palladium sources (entries 2, 4–6), ligands (entries 3–6), and solvents (entry 6), and we also tried copper catalyst in place of palladium (entry 3). With palladium catalysts (entries 1, 2 and 4–6) 1 equivalent of cesium carbonate has been used as base. With our satisfaction, we were able to obtain indazole **12** in 97% yields,

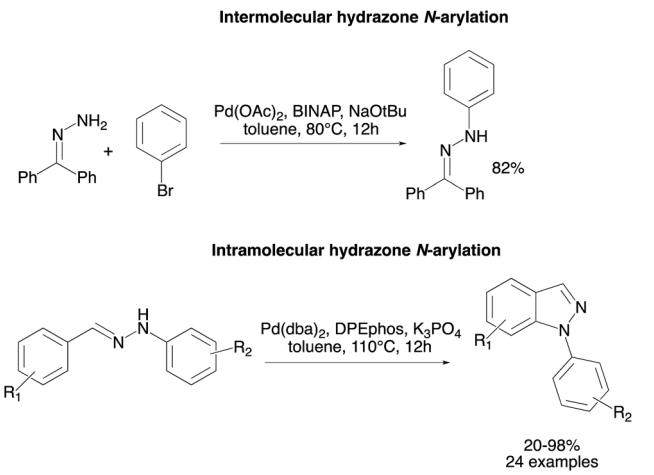



Scheme 3 3-CR affording α-aminocarbonyl hydrazones and test reaction for the formation of indazole derivatives.

Table 1 Optimization of indazole cyclization conditions

| Entry | Solvent | Catalyst 10% mol | Ligand 7% mol | Yield of 12 (yield of 13) |
|---|---|---|---|---|
| 1 | Toluene | $Pd(OAc)_2$ | Xantphos | 66% (12.5%) |
| 2 | Toluene | $Pd(dppf)Cl_2$ | Xantphos | 48% (4%) |
| 3 | Toluene | CuI | *N*,*N*′-dimethylethylene diamine | 22% (10%) |
| 4 | Toluene | $Pd(dppf)Cl_2$ | XPhos | 38% (20%) |
| 5 | Toluene | $Pd(PPh_3)_2Cl_2$ | Tri-*o*-tolyl-phosphine | 78% (traces) |
| 6 | 1,4-Dioxan | $Pd(PPh_3)_2Cl_2$ | Tri-*o*-tolyl-phosphine | 97% (traces) |

which means a highly regioselective formation of indazole derivatives over indolone one, when intermediate **11** was refluxed in 1,4-dioxan in the presence of tri-*o*-tolylphosphine (0.1 equiv.), cesium carbonate (1 equiv.) and bis(triphenylphosphine)palladium(II) dichloride (0.07 equiv.).




Scheme 4 Examples of inter- and intra-molecular hydrazine *N*-arylation reported in literature.

Despite the reported examples of both intermolecular[14] and intramolecular[9b] hydrazone *N*-arylation (Scheme 4), to our knowledge this is the first example of a regioselective hydrazone palladium catalyzed cyclization in the presence of an amide bond.

To evaluate the scope of this cyclization, we synthesized five different hydrazonoyl chlorides[11a] (**9**, **14–17**) and we selected six isocyanides (**10**, **18–22**) as starting inputs (Fig. 2), to form a library of α-aminocarbonyl hydrazones (31–74% yields) (Fig. 3). Aliphatic hydrazonoyl chlorides are much less stable than aromatic ones and did not react successfully in this reaction (poor yield, by-products formation and difficult purification procedure).

We then reacted the intermediate hydrazones using the optimized conditions to get eleven different substituted 1-arylindazole-3-carboxamides in good to excellent yields (48–98%) (Fig. 4).

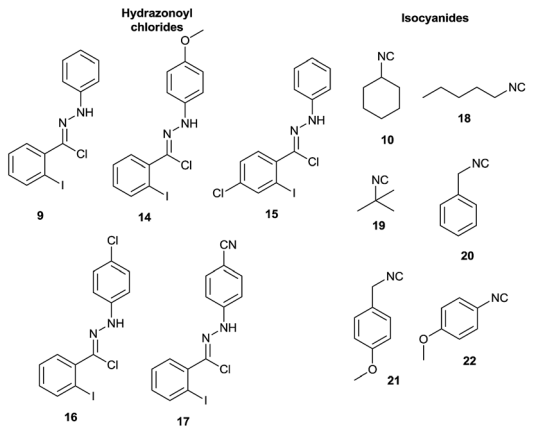



Fig. 2 Starting materials for the synthesis of α-aminocarbonyl hydrazones.

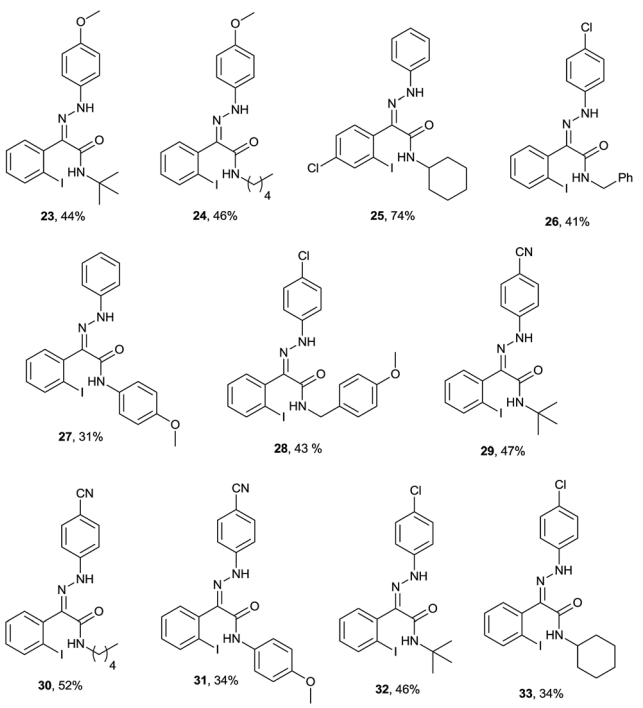



Fig. 3 Synthesized library of linear α-aminocarbonyl hydrazones.

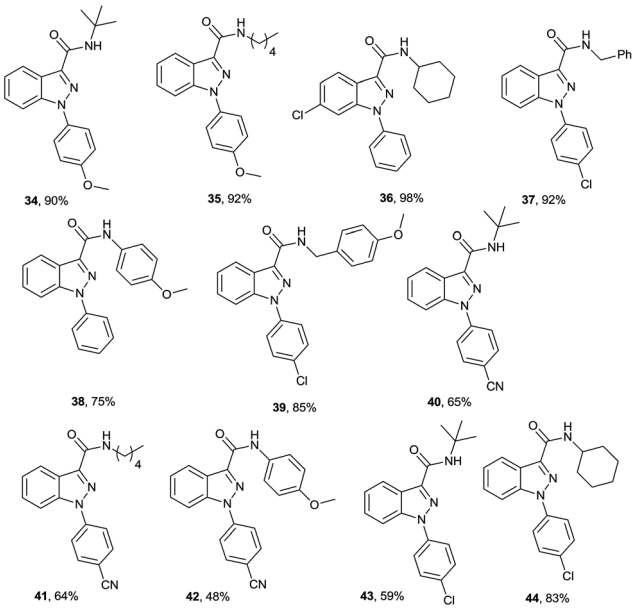
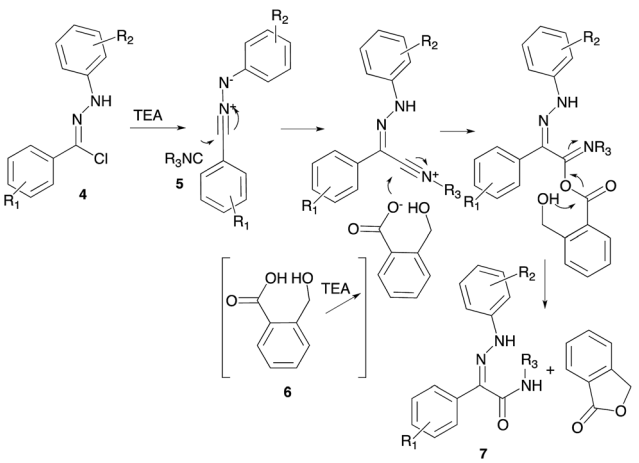


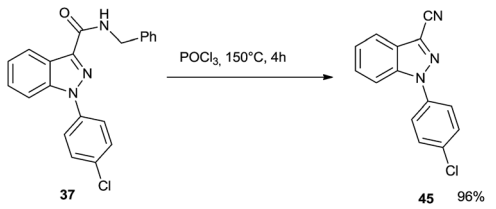

Fig. 4 Synthesized library of indazole cyclic derivatives.

The reaction proved to be quite general in scope as the presence of both aliphatic (**34–37**, **39–41**, **43** and **44**) and aromatic (**38**, **42**) carboxamides gave good yields. Only electron-withdrawing nitrile group on the hydrazone aromatic ring in derivatives **40**, **41** and **42** showed to decrease yields to 65, 64 and 48%, respectively.

A working hypothesis for the formation of hydrazone derivatives is depicted in Scheme 5. The hydrazonoyl chlorides **4** readily form the nitrilimine, which is the active 1,3-dipolar species and is attacked by the isocyanide carbon atom to form a nitrilium ion. The latter is then attacked by the carboxylate function of sacrificial acid **6** to give an unstable imidate: the hydroxy-function cyclize into the C=O carbonyl to give the *N*-arylhydrazono-acetamides **7** and phthalide. In this reaction




Scheme 5 Proposed reaction mechanism for the synthesis of hydrazono-acetamide derivative **7**.




Scheme 6 Conversion of *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitriles.

sacrificial acid **6** enables to overcome the poor nucleophilicity of water towards the nitrilium ion. **6** behaves indeed like a pseudo water molecule, as it traps the nitrilium ion and then undergoes an intramolecular cyclization to deliver one oxygen atom to the product, as water would, and the aromatic lactone phthalide.

In order to further expand the scope of the reaction we tried a direct conversion of *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitriles. The synthesis of such derivatives is usually accomplished in two or more steps, with overall yields of 26–44% and the use of harsh reaction conditions, with Zn- or Cu-containing waste[15] or promoted by tri-*n*-butyltin chloride and palladium.[16] An alternative two-step route, based on a primary amide formation and subsequent dehydration to nitrile (overall yield 63%) has been reported for the synthesis of p38 kinase inhibitors.[5] Dealing with their biological activities, *N*-arylindazole-3-carbonitrile derivatives have been described also as xanthine oxidase inhibitors[15] and as low nanomolar bradykinin receptor antagonists.[16] We speculated indeed that a one-step conversion of the reported *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitrile could be useful to further enlarge the size and the variability of the synthesizable libraries. So, by reacting *N*-arylindazole-3-carboxamide **37** in $POCl_3$ at 150 °C in a sealed tube for 4 h we were able to get *N*-arylindazole-3-carbonitrile **45** in 96% yield (Scheme 6).[17]

To our knowledge, this transformation accounts for the first application of benzylisocyanide as a convertible isocyanide.

## Conclusions

In conclusion we developed a novel, concise two-step synthesis for the construction of 1-aryl-indazoles-3-carboxamides performing a reaction between isocyanides, 2-iodo-*N*-arylbenzohydrazonoyl chlorides and 2-hydroxymethylbenzoic followed by a regioselective intramolecular hydrazone palladium catalyzed cyclization. Furthermore benzyl-isocyanide was unconventionally employed as a convertible isocyanide for the synthesis of biologically interesting *N*-arylindazole-3-carbonitriles. The present work step forward the consideration of post-condensation modifications of isocyanide-based reactions as a pass-holder to gain a direct access not only to medicinally relevant compounds, but still to the exploitation of the full potential of landmark transformations as the Buchwald–Hartwig reactions.

## Experimental section

### General

Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from $P_2O_5$ and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. $^1$H and $^{13}$C APT NMR were recorded on a 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts ($\delta$) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F254). When necessary they were developed with $KMnO_4$.

**General preparation of hydrazonoyl chlorides (9, 14–17).**[11a] The hydrazonoyl chlorides were readily synthesized in two steps:

*Preparation of acylhydrazines.* To a stirred solution of 2-iodobenzoic acids on a 5 mmol scale in THF (0.2 M, 10 mL) were added EDC HCl (1.05 g, 5.50 mmol, 1.1 eq.), DMAP (0.12 g, 1 mmol, 0.2 eq.), triethylamine (1.40 mL, 10 mmol, 2 eq.) and hydrazine (5 mmol, 1 eq.) at 0 °C. The resulting mixture was allowed to warm to room temperature over 24 h. The crude reaction mixture was washed with HCl 1 M sol. (x2), sat. $NaHCO_3$ (x2) and brine (x1), evaporated to dryness and used in the next step without further purification.

*Preparation of hydrazonoyl chlorides (**9, 14–17**).* The corresponding acylhydrazine (2.50 mmol) was dissolved in $CH_3CN$ (0.5 M, 5 mL) and triphenylphosphine (0.79 g, 3 mmol, 1.2 eq.) and carbon tetrachloride (0.29 mL, 3 mmol, 1.2 eq.) were added. The reaction was stirred at room temperature until all the acylhydrazine was consumed as judged by TLC (typically 8–12 hours). The reaction was concentrated under reduced pressure and purified by column chromatography (*n*-hexane/EtOAc) and stored below 0 °C.

**(*Z*)-2-Iodo-*N*′-phenylbenzohydrazonoyl chloride (9).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as a white solid (0.41 g, 46% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (br s, N*H*), 8.05 (d, $J$ = 7.88 Hz, 1H), 7.64 (br d, 1H), 7.48–7.41 (m, 3H), 7.35–7.33 (m, 2H), 7.14–7.07 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.3, 140.5, 139.9, 130.9, 130.7, 129.6, 128.3, 123.0, 121.6, 113.7, 96.8.

**(*Z*)-2-Iodo-*N*′-(4-methoxyphenyl)benzohydrazonoyl chloride (14).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as a yellowish solid (0.43 g, 44% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 7.96 Hz, 1H), 7.90 (br s, *NH*), 7.54 (d, $J$ = 7.72 Hz, 1H), 7.40 (t, $J$ = 7.52 Hz, 1H), 7.15 (d, $J$ = 8.88 Hz, 2H), 7.06 (t, $J$ = 7.52 Hz, 1H), 6.87 (d, $J$ = 8.92 Hz, 1H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz,

$CDCl_3$) $\delta$ 154.7, 140.5, 139.9, 137.2, 130.8, 130.5, 128.2, 122.0, 114.8 (4C), 96.6, 55.7.

**(*Z*)-4-Chloro-2-iodo-*N*′-phenylbenzohydrazonoyl chloride (15).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as a light yellow solid (0.69 g, 71% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (s, N*H*), 7.97 (s, 1H), 7.47 (br d, 1H), 7.39 (br d, AA′XX′, 1H), 7.33–7.29 (m, 2H), 7.22–7.20 (m, 2H), 6.96 (t, $J$ = 7.24 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 142.9, 139.8, 138.2, 135.5, 131.2, 129.4, 128.4, 121.6, 121.5, 113.5, 96.3.

**(*Z*)-*N*′-(4-Chlorophenyl)-2-iodobenzohydrazonoyl chloride (16).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as a light yellow solid (0.33 g, 34% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (br s, N*H*), 7. (br d, AA′XX′, 2H), 7.41 (br t, 1H), 7.26 (br d, AA′XX′, 2H), 7.15 (br d, AA′XX′, 2H), 7.08 (br t, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 141.8, 140.4, 139.6, 130.8, 130.7, 129.3, 128.2, 126.1, 123.7, 114.8, 96.5.

**(*Z*)-*N*′-(4-Cyanophenyl)-2-iodobenzohydrazonoyl chloride (17).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as a light orange solid (0.84 g, 88% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.44 (br s, N*H*), 7.98 (br d, 1H), 7.65 (br d, AA′XX′, 2H), 7.59 (br d, 1H), 7.49 (br t, 1H), 7.40 (br d, AA′XX′, 2H), 7.19 (br t, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 148.1, 140.3, 140.2, 134.0, 131.8, 131.0, 129.0, 125.0, 120.0, 114.2, 102.2, 97.5.

**General preparation of α-aminocarbonylhydrazones (11, 23–33).** The hydrazonoyl chloride (0.5 mmol, 1 eq.), the isocyanide (0.5 mmol, 1 eq.), 2-hydroxymethylbenzoic acid (0.5 mmol, 1 eq.) and TEA (1 mmol, 2 eq.) were one-pot mixed in DCM (0.5 M, 1 mL) and stirred at room temperature under a nitrogen atmosphere overnight. After evaporation of the solvent, the crude material was purified by column chromatography.

**(*Z*)-*N*-Cyclohexyl-2-(2-iodophenyl)-2-(2-phenylhydrazono)acetamide (11).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as yellow solid (0.15 g, 66% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.25 (br s, N*H*), 7.93 (br d, 1H), 7.46–7.45 (m, 2H), 7.29–7.10 (m, 5H), 6.93 (br t, 1H), 5.17 (br d, N*H*), 3.89–3.82 (m, 1H), 1.94–1.92 (m, 2H), 1.68–1.58 (m, 3H), 1.42–1.33 (m, 2H), 1.16–1.04 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.6, 143.5, 140.7, 140.0, 132.8, 131.8, 130.4, 129.2, 128.9, 121.7, 113.8, 100.6, 48.2, 32.7, 25.4, 24.8. IR (KBr) 3390, 2923, 2846, 1632, 1497, 1171, 760 $\nu_{max}$/$cm^{-1}$; mp 121.1–122.3 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{23}IN_3O$: 448.0886; found: 448.0895 (100%) [M + H]$^+$.

**(*Z*)-*N*-(*tert*-Butyl)-2-(2-iodophenyl)-2-(2-(4-methoxyphenyl)-hydrazono)acetamide (23).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as sticky reddish solid (0.10 g, 44% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.20 (bs, N*H*), 7.92 (d, $J$ = 7.96 Hz, 1H), 7.45–7.44 (m, 2H), 7.14 (br d, AA′XX′, 2H), 7.12–7.07 (m, 1H), 6.83 (d, $J$ = 8.92 Hz, 2H), 5.05 (br s, N*H*), 3.76 (s, 3H), 1.35 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.5, 154.9, 141.2, 139.6, 137.6, 132.3, 131.8, 130.1, 128.9, 115.0, 114.6, 100.7, 55.6, 51.6, 28.6. IR (KBr) 3406, 2956, 1635, 1530, 1500, 1229, 1157 $\nu_{max}$/$cm^{-1}$; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{19}H_{23}IN_3O_2$: 452.0835; found: 452.0774 (100%) [M + H]$^+$.

**(*Z*)-2-(2-Iodophenyl)-2-(2-(4-methoxyphenyl)hydrazono)-*N*-pentylacetamide (24).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as reddish oil (0.11 g, 46% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.19 (br s, N*H*), 7.94 (d, $J$ = 7.96 Hz, 1H), 7.47–7.42 (m, 2H), 7.13 (br d, AA′XX′, 2H), 7.11–7.08 (m, 1H), 6.83 (d, $J$ = 8.88 Hz, 2H), 5.27 (br t, N*H*), 3.76 (s, 3H), 3.26 (q, $J$ = 6.56 Hz, 2H), 1.53–1.46 (m, 2H), 1.33–1.25 (m, 4H), 0.89–0.86 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.7, 155.0, 140.9, 140.0, 139.7, 137.5, 131.7, 130.2, 128.8, 115.0 (2C), 114.6 (2C), 101.0, 55.6, 39.2, 29.1, 29.0, 22.3, 14.0. IR (KBr) 3417, 2950, 2923, 1635, 1506, 1220, 1168, 823 $\nu_{max}$/$cm^{-1}$; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{25}IN_3O_2$: 466.0991; found: 466.0956 (100%) [M + H]$^+$.

**(*Z*)-2-(4-Chloro-2-iodophenyl)-*N*-cyclohexyl-2-(2-phenylhydrazono) acetamide (25).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as yellow solid (0.18 g, 74% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.20 (br s, N*H*), 7.45 (br d, AA′XX′, 1H), 7.37 (br d, AA′XX′, 1H), 7.28–7.24 (m, 2H), 7.17 (br d, AA′XX′, 2H), 6.94 (br t, 1H), 5.07 (br d, N*H*), 3.88–3.80 (m, 1H), 1.95–1.92 (m, 2H), 1.69–1.59 (m, 3H), 1.42–1.32 (m, 2H), 1.17–1.06 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.3, 143.3, 139.4, 139.0, 135.2, 132.3, 131.5, 129.2, 129.1, 122.0, 113.9, 100.6, 48.2, 32.8, 25.4, 24.8. IR (KBr) 3395, 2928, 2851, 1635, 1495, 1245, 1168, 990, 740 $\nu_{max}$/$cm^{-1}$; mp 132.6–133.2 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{22}ClIN_3O$: 482.0496; found: 482.0482 (100%) [M + H]$^+$.

**(*Z*)-*N*-Benzyl-2-(2-(4-chlorophenyl)hydrazono)-2-(2-iodophenyl)-acetamide (26).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 99 : 1) to give the product as yellowish solid (0.10 g, 41% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.24 (br s, N*H*), 7.92 (br d, 1H), 7.45–7.10 (m, 12H), 5.63 (br s, N*H*), 4.50 (d, $J$ = 5.92 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.4, 142.15, 140.4, 139.8, 137.3, 132.9, 131.5, 130.5, 129.2, 128.9, 128.7, 126.7, 115.2, 100.6, 43.3. IR (KBr) 3390, 1629, 1533, 1495, 1160, 823, 754 $\nu_{max}$/$cm^{-1}$; mp 110.4–111.7 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{21}H_{18}ClIN_3O$: 490.0183; found: 490.0152 (100%) [M + H]$^+$.

**(*Z*)-2-(2-Iodophenyl)-*N*-(4-methoxyphenyl)-2-(2-phenylhydrazono) acetamide (27).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as yellow solid (0.07 g, 31% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.22 (br s, N*H*), 7.99 (br d, 1H), 7.57–7.50 (m, 2H), 7.34–7.15 (m, 7H), 6.96 (br t, 1H), 6.88 (br d, AA′XX′, 2H), 6.83 (br s, N*H*), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.1, 157.2, 143.4, 140.5, 139.9, 132.4, 132.0, 130.6, 129.5, 129.1, 123.1, 122.2, 114.3, 114.1, 100.9, 55.5. IR (KBr) 3351, 1601, 1506, 1484, 1234, 1146, 998 $\nu_{max}$/$cm^{-1}$; mp 119.3–120.6 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{21}H_{19}IN_3O_2$: 472.0522; found: 472.0556 (100%) [M + H]$^+$.

**(*Z*)-2-(2-(4-Chlorophenyl)hydrazono)-2-(2-iodophenyl)-*N*-(4-methoxybenzyl)acetamide (28).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 99 : 1) to give the product as white solid (0.11 g, 43% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.24 (br s, N*H*), 7.91 (br d, 1H), 7.44–7.42 (m, 2H), 7.23–7.10 (m, 7H), 6.85 (br d, AA′XX′, 2H), 5.60–5.57 (m, 1H), 4.42 (br d, 2H), 3.78 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$)

$\delta$ 160.3, 159.1, 142.1, 140.3, 139.8, 132.9, 131.6, 130.5, 129.3, 129.2, 129.1, 128.9, 126.6, 115.1, 114.1, 100.6, 55.3, 42.8. IR (KBr) 3324, 3208, 1626, 1517, 1489, 1242, 1160, 1004, 825 $\nu_{max}$/cm$^{-1}$; mp 143.3–144.4 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{22}H_{20}ClIN_3O_2$: 520.0289; found: 520.0292 (100%) [M + H]$^+$.

**(*Z*)-*N*-(*tert*-Butyl)-2-(2-(4-cyanophenyl)hydrazono)-2-(2-iodophenyl)acetamide (29).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as white solid (0.11 g, 47% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.45 (br s, N*H*), 7.94 (br d, 1H), 7.53–7.41 (m, 4H), 7.21–7.16 (m, 3H), 5.18 (br s, N*H*), 1.35 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.7, 147.0, 140.2, 139.7, 136.7, 133.5, 131.5, 130.8, 129.0, 119.7, 113.8, 103.5, 99.6, 52.1, 28.4. IR (KBr) 3390, 3164, 2961, 2214, 1637, 1508, 1149, 990 $\nu_{max}$/cm$^{-1}$; mp 167.8–168.8 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{19}H_{20}IN_4O$: 447.0682; found: 447.0646 (100%) [M + H]$^+$.

**(*Z*)-2-(2-(4-Cyanophenyl)hydrazono)-2-(2-iodophenyl)-*N*-pentylacetamide (30).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as yellowish solid (0.12 g, 52% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.43 (br s, N*H*), 7.96 (br d, 1H), 7.54–7.41 (m, 4H), 7.22–7.15 (m, 3H), 5.42 (br s, N*H*), 3.30–3.25 (m, 1H), 1.55–1.48 (m, 2H), 1.33–1.25 (m, 4H), 0.88 (br t, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.1, 146.9, 139.9, 139.8, 135.9, 133.6, 131.4, 130.8, 129.0, 119.7, 113.9, 103.8, 99.9, 39.5, 29.1, 28.8, 22.3, 13.9. IR (KBr) 3329, 2923, 2214, 1646, 1508, 1149, 828 $\nu_{max}$/cm$^{-1}$; mp 91.0–92.4 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{22}IN_4O$: 461.0838; found: 461.0852 (100%) [M + H]$^+$.

**(*Z*)-2-(2-(4-Cyanophenyl)hydrazono)-2-(2-iodophenyl)-*N*-(4-methoxyphenyl)acetamide (31).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as reddish solid (0.08 g, 34% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.40 (br s, N*H*), 8.00 (br d, 1H), 7.56–7.54 (m, 5H), 7.34–7.21 (m, 4H), 6.92 (br s, N*H*), 6.89 (br s, AA′XX′, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.2, 157.6, 146.7, 140.0, 139.7, 135.7, 133.6, 131.8, 131.1, 129.2, 128.9, 123.1, 119.6, 114.3, 114.1, 104.2, 100.0, 55.5. IR (KBr) 3395, 2208, 1607, 1506, 1229, 1141, 825 $\nu_{max}$/cm$^{-1}$; mp 111.2–112.3 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{22}H_{18}IN_4O_2$: 497.0474; found: 497.0482 (100%) [M + H]$^+$.

**(*Z*)-*N*-(*tert*-Butyl)-2-(2-(4-chlorophenyl)hydrazono)-2-(2-iodophenyl)acetamide (32).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 97 : 3) to give the product as yellow solid (0.11 g, 46% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.26 (br s, N*H*), 7.93 (br d, 1H), 7.46–7.42 (m, 2H), 7.22–7.10 (m, 5H), 5.11 (br s, N*H*), 1.35 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.2, 142.3, 140.8, 139.7, 134.0, 131.7, 130.4, 129.1, 128.9, 126.2, 114.9, 100.2, 51.8, 28.5. IR (KBr) 3406, 2956, 1643, 1489, 1231, 1157, 987, 823 $\nu_{max}$/cm$^{-1}$; mp 139.4–140.6 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{18}H_{20}ClIN_3O$: 456.0340; found: 456.0304 (100%) [M + H]$^+$.

**(*Z*)-2-(2-(4-Chlorophenyl)hydrazono)-*N*-cyclohexyl-2-(2-iodophenyl)acetamide (33).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 97 : 3) to give the product as orange solid (0.08 g, 34% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.25 (br s, N*H*), 7.93 (br d, 1H), 7.46–7.41 (m, 2H), 7.20 (br d, AA′XX′, 2H), 7.14–7.09 (m, 4H), 5.16 (br d, N*H*), 3.87–3.79 (m, 1H), 1.92–1.89 (m, 2H), 1.67–1.63 (m, 3H), 1.38–1.31 (m, 2H), 1.12–1.05 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 142.2, 140.5, 139.7, 133.5, 131.7, 130.4, 129.2, 128.9, 126.3, 114.9, 100.4, 48.2, 32.7, 25.4, 24.7. IR (KBr) 3390, 2923, 2846, 1635, 1492, 1160, 993 $\nu_{max}$/cm$^{-1}$; mp 134.8–135.4 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{22}ClIN_3O$: 482.0496; found: 482.0472 (100%) [M + H]$^+$.

**General preparation of *N*-arylindazole-3-carboxamides (12, 34–44).** The $\alpha$-aminocarbonylhydrazone (0.1 mmol, 1 equiv.) is dissolved in dry 1,4-dioxan (0.3 M) and cesium carbonate (0.1 mmol, 1 equiv.), tri-*o*-tolylphosphine (0.01 mmol, 0.1 equiv.) and bis(triphenylphosphine)palladium(II) dichloride (0.007 mmol, 0.07 equiv.) were added. The reaction mixture was stirred at reflux temperature overnight, evaporated and purified by chromatographic column (*n*-hexane/ethyl acetate).

***N*-Cyclohexyl-1-phenyl-1*H*-indazole-3-carboxamide (12).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as yellow solid (0.03 g, 97% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.49 (d, $J$ = 8.12 Hz, 1H), 7.73–7.66 (m, 3H), 7.58–7.54 (m, 2H), 7.46–7.40 (m, 2H), 7.35–7.32 (m, 1H), 7.04 (br d, N*H*), 4.10–4.00 (m, 1H), 2.08–2.03 (m, 2H), 1.80–1.64 (m, 3H), 1.50–1.20 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.6, 140.4, 139.7, 139.5, 129.6 (2C), 127.6 (2C), 123.9, 123.4 (2C), 123.3, 123.2, 110.4, 48.0, 33.3 (2C), 25.6, 25.0 (2C). IR (KBr) 2923, 2851, 1662, 1555, 1363, 1245, 1171, 1056 $\nu_{max}$/cm$^{-1}$; mp 104.3–105.5 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{22}N_3O$: 320.1763; found: 320.1730 (100%) [M + H]$^+$.

***N*-(*tert*-Butyl)-1-(4-methoxyphenyl)-1*H*-indazole-3-carboxamide (34).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as reddish oil (0.03 g, 90% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.48 (d, $J$ = 8.08 Hz, 1H), 7.60–7.56 (m, 3H), 7.42 (br t, 1H), 7.31 (br t, 1H), 7.08–7.04 (m, 3H), 3.89 (s, 3H), 1.53 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.0, 159.0, 140.7, 139.6, 132.4, 127.4, 125.2 (2C), 123.4, 123.3, 123.0, 114.7 (2C), 110.3, 55.7, 51.3, 29.1. IR (KBr) 3406, 2956, 1668, 1533, 1508, 1196, 1028, 751 $\nu_{max}$/cm$^{-1}$; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1712; found: 324.1728 (100%) [M + H]$^+$.

**1-(4-Methoxyphenyl)-*N*-pentyl-1*H*-indazole-3-carboxamide (35).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as an off-white solid (0.03 g, 92% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.47 (d, $J$ = 8.12 Hz, 1H), 7.59–7.56 (m, 3H), 7.41 (br t, 1H), 7.31 (br t, 1H), 7.14 (br t, N*H*), 7.06 (br d, AA′XX′, 2H), 3.87 (s, 3H), 3.52–3.47 (m, 2H), 1.66–1.61 (m, 2H), 1.39–1.35 (m, 4H), 0.92–0.88 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 159.1, 140.6, 139.0, 132.5, 127.4, 125.1 (2C), 123.5, 123.2, 123.1, 114.7 (2C), 110.3, 55.6, 39.1, 29.5, 29.2, 22.4, 14.0. IR (KBr) 3291, 2956, 1640, 1544, 1245, 1201, 1026 $\nu_{max}$/cm$^{-1}$; mp 58.7–59.8 °C; MS (ESI) $m/z$ (M + H)$^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1869; found: 338.1843 (100%) [M + H]$^+$.

**6-Chloro-*N*-cyclohexyl-1-phenyl-1*H*-indazole-3-carboxamide (36).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as an off-white solid (0.03 mg, 98% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.41 (d, $J$ = 8.60 Hz, 1H), 7.69–7.67 (m, 3H), 7.60–7.57 (m, 2H), 7.48–7.44 (m, 1H), 7.30 (d, $J$ = 8.64 Hz, 1H), 6.99 (br d, N*H*), 4.08–4.00 (m, 1H), 2.08–2.05 (m, 2H), 1.80–1.66 (m, 4H), 1.49–1.17 (m, 4H); $^{13}$C NMR

(100 MHz, $CDCl_3$) $\delta$ 161.1, 140.7, 139.8, 139.0, 134.2, 129.7 (2C), 128.0, 124.4 (2C), 123.5 (2C), 122.2, 110.2, 48.0, 33.2 (2C), 25.6, 25.0 (2C). IR (KBr) 3324, 2934, 2851, 1637, 1536, 1495, 1251, 751 $\nu_{max}/cm^{-1}$; mp 146.1–147.2 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{20}H_{21}ClN_3O$: 354.1373; found: 354.1349 (100%) $[M + H]^+$.

***N*-Benzyl-1-(4-chlorophenyl)-1*H*-indazole-3-carboxamide (37).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as white solid (0.03 g, 92% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (d, $J = 8.12$ Hz, 1H), 7.68–7.65 (m, 3H), 7.53–7.29 (m, 10H), 4.73 (br d, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 162.1, 140.2, 139.5, 138.2, 138.0, 133.2, 129.7 (2C), 128.7 (2C), 128.0, 127.9 (2C), 127.5, 124.4 (2C), 124.0, 123.6, 123.3, 110.3, 43.1. IR (KBr) 3302, 1648, 1539, 1492, 1196, 1086, 976 $\nu_{max}/cm^{-1}$; mp 101.3–102.6 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{21}H_{17}ClN_3O$: 362.1060; found: 362.1030 (100%) $[M + H]^+$.

***N*-(4-Methoxyphenyl)-1-phenyl-1*H*-indazole-3-carboxamide (38).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as red solid (0.03 g, 75% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.88 (br s, N*H*), 8.53 (d, $J =$ 7.00 Hz, 1H), 7.73–7.66 (m, 5H), 7.57–7.54 (m, 2H), 7.46–7.41 (m, 2H), 7.34 (br t, 1H), 6.91 (d, $J = 8.68$ Hz, 2H), 3.78 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.1, 156.3, 140.5, 139.4, 139.3, 131.0, 129.6, 127.8 (2C), 123.9, 123.5, 123.4, 123.2, 121.5, 114.2, 110.6, 55.5. IR (KBr) 3318, 2956, 1668, 1530, 1240, 1020, 823 $\nu_{max}/cm^{-1}$; mp 116.6–117.3 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found: 344.1407 (100%) $[M + H]^+$.

**1-(4-Chlorophenyl)-*N*-(4-methoxybenzyl)-1*H*-indazole-3-carboxamide (39).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as orange solid (0.03 g, 85% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (br d, 1H), 7.64–7.61 (m, 3H), 7.49–7.46 (m, 4H), 7.37–7.31 (m, 3H), 6.86 (br d, AA′XX′, 2H), 4.64 (br d, 2H), 3.77 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 162.0, 159.0, 140.2, 139.7, 138.0, 133.1, 130.4, 129.7, 129.3, 128.0, 124.3, 124.0, 123.5, 123.4, 114.1, 110.3, 55.3, 42.6. IR (KBr) 3313, 1646, 1541, 1492, 1086, 828 $\nu_{max}/cm^{-1}$; mp 135.0–136.1 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{22}H_{19}ClN_3O_2$: 392.1166; found: 392.1133 (100%) $[M + H]^+$.

***N*-(*tert*-Butyl)-1-(4-cyanophenyl)-1*H*-indazole-3-carboxamide (40).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as yellowish solid (0.02 g, 65% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (br d, 1H), 6.91 (br d, AA′XX′, 2H), 7.84 (br d, AA′XX′, 2H), 7.73 (br d, 1H), 7.49 (br t, 1H), 7.35 (br t, 1H), 6.99 (br s, N*H*), 1.53 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.3, 143.0, 141.7, 140.0, 133.6, 128.5, 124.4, 123.9 (2C), 122.7, 118.2, 110.3, 110.3, 51.5, 29.0. IR (KBr) 3340, 2967, 2230, 1651, 1541, 1363, 850 $\nu_{max}/cm^{-1}$; mp 131.7–133.0 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{19}H_{19}N_4O$: 319.1559; found: 319.1525 (100%) $[M + H]^+$.

**1-(4-Cyanophenyl)-*N*-pentyl-1*H*-indazole-3-carboxamide (41).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 95 : 5) to give the product as light pink solid (0.02 g, 64% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.51 (br d, 1H), 7.91 (br d, AA′XX′, 2H), 7.84 (br d, AA′XX′, 2H), 7.75 (br d, 1H), 7.51 (br t, 1H), 7.37 (br t, 1H), 7.12 (br t, N*H*), 3.53–3.48 (m, 2H), 1.76–1.65 (m, 2H), 1.39–1.38 (m, 4H), 0.92–0.89 (m, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.8, 143.1, 141.1, 140.0, 133.6, 128.5, 124.5, 124.0, 123.8, 122.7, 118.2, 110.4, 110.3, 39.2, 29.5, 29.1, 22.4, 14.0. IR (KBr) 3285, 2934, 2225, 1646, 1555, 1421, 1179, 842 $\nu_{max}/cm^{-1}$; mp 144.2–145.5 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{20}H_{21}N_4O$: 333.1715; found: 333.1728 (100%) $[M + H]^+$.

**1-(4-Cyanophenyl)-*N*-(4-methoxyphenyl)-1*H*-indazole-3-carboxamide (42).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 9 : 1) to give the product as pink solid (0.02 g, 48% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (br s, NH), 8.56 (br d, 1H), 7.96 (br d, AA′XX′, 2H), 7.88 (br d, AA′XX′, 2H), 7.78 (br d, 1H), 7.66 (br d, AA′XX′, 2H), 7.56 (br t, 1H), 7.43 (br t, 1H), 6.93 (br d, AA′XX′, 2H), 3.82 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.5, 156.5, 142.9, 141.0, 140.2, 133.7, 130.6, 128.7, 124.5, 124.3, 123.8, 122.9, 121.6, 118.1, 114.3, 110.7, 110.4, 55.5. IR (KBr) 3302, 2225, 1648, 1599, 1506, 1237, 1168, 836 $\nu_{max}/cm^{-1}$; mp 191.5–192.4 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{22}H_{17}N_4O_2$: 369.1352; found: 369.1341 (100%) $[M + H]^+$.

***N*-(*tert*-Butyl)-1-(4-chlorophenyl)-1*H*-indazole-3-carboxamide (43).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 98 : 2) to give the product as yellow solid (0.02 g, 59% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.49 (br d, 1H), 7.67–7.61 (m, 3H), 7.52 (br d, AA′XX′, 2H), 7.45 (br t, 1H), 7.33 (br t, 1H), 7.01 (br s, N*H*), 1.53 (s, 9H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.7, 140.5, 140.3, 138.0, 133.1, 129.7, 127.9, 124.5, 123.8, 123.6, 123.4, 110.1, 51.3, 29.1. IR (KBr) 3401, 3060, 2961, 1662, 1530, 1497, 1193, 1091 $\nu_{max}/cm^{-1}$; mp 47.1–48.7 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{18}H_{19}ClN_3O$: 328.1217; found: 328.1224 (100%) $[M + H]^+$.

**1-(4-Chlorophenyl)-*N*-cyclohexyl-1*H*-indazole-3-carboxamide (44).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 98 : 2) to give the product as yellow solid (0.03 g, 83% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.49 (br d, 1H), 7.67 (br d, AA′XX′, 2H), 7.63 (br d, 1H), 7.52 (br d, AA′XX′, 2H), 7.45 (br t, 1H), 7.34 (br t, 1H), 7.00 (br s, N*H*), 4.10–4.01 (m, 1H), 2.08–2.03 (m, 2H), 1.83–1.76 (m, 3H), 1.49–1.20 (m, 5H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.3, 140.2, 140.0, 138.0, 133.1, 129.7, 127.9, 124.4, 124.0, 123.5, 123.4, 110.1, 48.0, 33.3, 25.6, 25.0. IR (KBr) 3401, 2923, 2846, 1657, 1528, 1492, 1196, 1086, 831 $\nu_{max}/cm^{-1}$; mp 58.9–60.8 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{20}H_{21}ClN_3O$: 354.1373; found: 354.1384 (100%) $[M + H]^+$.

**General preparation of *N*-arylindazole-3-carbonitriles (45).** *N*-Benzyl-1-(4-chlorophenyl)-1*H*-indazole-3-carboxamide **37** (0.07 mmol, 1 equiv.) is dissolved in phosphorous oxychloride (0.03 M) stirred at 150 °C for 4 hours. The reaction mixture is cooled at room temperature and poured into ice/ammonium hydroxide. The product is then extracted with ethyl acetate (x3); the organic phase is washed with brine, dried over $Na_2SO_4$ and evaporated. The product is then purified by chromatographic column (*n*-hexane/ethyl acetate).

**1-(4-Chlorophenyl)-1*H*-indazole-3-carbonitrile (45).** The crude material was purified by column chromatography (*n*-hexane/EtOAc 98 : 2) to give the product as yellowish solid (0.02 g, 96% yield). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (br d, 1H), 7.75 (br d, 1H), 7.68 (br d, AA′XX′, 2H), 7.57–7.55 (m, 3H), 7.44 (br t, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 130.0, 137.4, 134.3, 130.0, 128.9, 126.1, 124.6, 124.4, 120.6, 120.1, 113.1, 111.2. IR (KBr) 2236, 1495, 1355, 1218, 1089, 834 $\nu_{max}/cm^{-1}$; mp 164.4–165.6 °C; MS (ESI) $m/z$ $(M + H)^+$ calcd for $C_{14}H_9ClN_3$: 254.0485; found: 254.0467 (100%) $[M + H]^+$.

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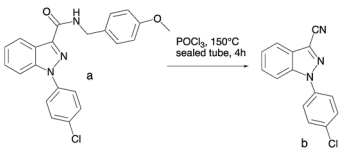
17 The conversion to carbonitrile has been successfully accomplished with high yield also with the *para*-methoxy analog of benzyl amide **37**:




however, as the synthesis of compound "**a**" needs *para*-methoxy-benzylisocyanide in place of the commercially available benzyl isocyanide used for benzyl amide **37**, and the yields of the conversion of both the benzyl amides are the same (96%), we reasoned that the best way to get such a carbonitrile was by using the commercially available benzyl isocyanide.