## Direct Access to 3-Aminoindazoles by Buchwald–Hartwig C–N Coupling Reaction

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Received 21 April 2011

**Abstract:** An efficient synthesis of various N-substituted 3-aminoindazoles using Buchwald–Hartwig C–N coupling reaction is described. Several parameters were varied, including the nature of the halogen atom and the protecting group of the starting materials, as well as the effects of the catalyst system, base, solvent, and reaction time. The efficiency of microwave versus conventional heating was also compared to test the outcome of the reaction. Thus, by applying this recent knowledge about metal-catalyzed aminations, an alternative for the direct synthesis of primary 3-aminoindazoles has been provided.

**Key words:** indazoles, amination, cross-coupling, palladium, copper, microwave promoted amination

To prepare new valuable building blocks in medicinal chemistry, design and synthesis of new polyfunctionalized indazole libraries<sup>1</sup> have been developed since a few years in our laboratory, particularly those corresponding to 2-aza bioisosteres of tryptophan, tryptamine, serotonine, and melatonine.<sup>2</sup> Indeed, the indazole scaffold seems to be able to interact with a variety of targets and is already found in a great number of products displaying a wide range of biological activities including, for example, kinase inhibitors,<sup>3</sup> HIV protease inhibitors,<sup>4</sup> MCH receptor 1 antagonists,<sup>5</sup> sodium channel modulators,<sup>6</sup> nitric oxide synthase inhibitors like 7-NI,7 and 4-NI,8 and also in lead compounds like granisetron,<sup>9</sup> a 5-HT<sub>3</sub> receptor antagonist, YC-1,<sup>10</sup> a guanylyl cyclase activator or lonidamine,<sup>11</sup> and a mitochondrial hexokinase inhibitor.

We have also been interested for a long time in the development of metal-catalyzed cross coupling reactions. Suzuki,<sup>10b,12</sup> Heck,<sup>2a,13</sup> and Sonogashira<sup>14</sup> reactions have been carried out at position 3 of the indazole nucleus, and also on its benzene ring. Recently, our attention was turned to the synthesis of various N-substituted 3-aminoindazoles using Buchwald–Hartwig C–N coupling reaction. Indeed, to the best of our knowledge, only a few 3-*N*-alkyl or *N*-arylamino derivatives have been described in the literature despite the fact that such compounds could have a very interesting potential – notably antineoplastic,<sup>3</sup> antiviral,<sup>4</sup> anorexigen,<sup>5</sup> and neuroprotective<sup>6</sup> properties. However, because of the lack of reactivity in traditional nucleophilic substitution reactions at the 3 position of this heterocycle, only one example of such direct amination starting from 3-nitroindazole was found,<sup>15</sup> but it required very hard conditions. Thus, the preparation of such products typically involved an aromatic nucleophilic substitution between hydrazine and benzonitriles or thioamides<sup>16</sup> substituted in *ortho* position by a leaving group like fluorine,<sup>3b,4,17</sup> or also sometimes by chlorine<sup>18</sup> or a nitro group.<sup>19</sup> Moreover, finally using similar cyclization conditions, introduction of the amino group could also result from the reaction of different amines on the 2halobenzyl chloroimidates, which were synthesized by the addition of a protected hydrazine on 2-halobenzyl acids followed by chlorination.<sup>20</sup> A new approach, which allows the direct incorporation of elaborated amines at the 3 position of the indazole nucleus, is therefore needed.

In the past few years, the metal-catalyzed Buchwald-Hartwig amination<sup>21</sup> of aryl halides has become an important method for the synthesis of arylamines, which offers considerable advantages over the classical processes like the Ullmann-type C-N bond formation,<sup>22</sup> since nonactivated substrates can be used in relatively mild reaction conditions. However, application of this coupling to various heterocyclic structures is still a relatively unexplored process<sup>23</sup> and only a few isolated examples using this reaction from 3-chloro-<sup>24</sup> or 3-bromoindazoles were found.<sup>5,25</sup> Consequently, it was envisaged that it would be interesting to carry out and report a general procedure for this kind of C-N cross-coupling at the 3-position of the indazole ring. With this in mind, the applicability of palladium- and copper-catalyzed amination protocols were evaluated on various 3-halogenoindazoles (Scheme 1). Several reaction parameters were varied, including the nature of halogen atom and protecting group, as well as the effects of catalyst system, base, solvent, and reaction time. The efficiency of microwave versus conventional heating was also compared to test the outcome of the reaction. Thus, by applying this recent knowledge about metal-catalyzed aminations, an alternative has been provided for the direct synthesis of primary 3-aminoindazoles by C-N cross-coupling of the corresponding bromo compounds



Scheme 1

SYNTHESIS 2011, No. 16, pp 2651–2663 Advanced online publication: 21.07.2011 DOI: 10.1055/s-0030-1260110; Art ID: Z42211SS © Georg Thieme Verlag Stuttgart · New York

 Table 1
 Synthesis of Protected 3-Halo-1H-indazoles 4 and 5a-h

Х	R	Indazoles 2 and 3 (%) Indazoles 4 and 5 (%)			
Ι	Н	2	68	4	55
Br	Н	3a	64	5a	88
Br	4-O <sub>2</sub> N	3b	77	5b	99
Br	4-C1	3c	68	5c	88
Br	5-MeO	3d	45	5d	63
Br	5-O <sub>2</sub> N	3e	91	5e	59
Br	5-Cl	3f	60	5f	69
Br	6-O <sub>2</sub> N	3g	81	5g	79
Br	6-C1	3h	54	5h	42

with benzophenone imine followed by an acidic hydrolysis of the obtained imino derivatives.

### Synthesis of New Protected 3-Halogenoindazoles

First, indazoles 1a-h were prepared from the corresponding 2-methylanilines according to a previously successful method developed in our laboratory.8,26 Then, iodination or bromination reactions<sup>10b,27</sup> were selectively carried out at the 3 position of these derivatives with iodine or bromine in DMF at room temperature to provide the 3-iodoindazole 2 and the different 3-bromoindazoles 3a-h in moderate to high yields. In addition, it was required to protect the nitrogen atom of the indazole nucleus at this stage to avoid a possible catalyst poisoning during the Buchwald–Hartwig C–N coupling. Indeed, a first attempt of metal-catalyzed amination carried out on the unprotected 3-bromoindazole failed. Accordingly, taking into account a previously described work about indazole protection by a tetrahydropyran-2-yl (THP) group,<sup>12b</sup> optimization of this procedure was tried starting from 3-halogenoindazoles synthesized by us and using dihydropyran and a catalytic amount of PTSA in ethyl acetate under reflux conditions.<sup>28</sup> Thus, this protocol provided THP-protected indazoles 4 and 5a-h in good yields. Moreover, THP was used as N-protecting group instead of classical 2-(trimethylsilyl)ethoxymethyl the (SEM) group,<sup>12b</sup> particularly because of its lower cost and its easier deprotection step (Scheme 2 and Table 1).



Scheme 2 Reagents and conditions: i)  $I_2$  (2 equiv), KOH (3.75 equiv), DMF, r.t., 1 h, 68%; ii)  $Br_2$  (1.5 equiv), DMF, r.t., 2–72 h, 45–77%; iii) DHP (2 equiv), PTSA (cat.), EtOAc, reflux, 3–48 h, 42–99%.

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## Copper-Catalyzed and Microwave-Promoted Amination of a 3-Iodoindazole Derivative

One of our initial attempts was the investigation of the application of microwave-promoted<sup>21k,29</sup> C-N bond-forming methodology to our protected 3-halogenoindazoles. A number of literature methods were examined using a variety of state of the art ligands for both Pd and Cu. Unfortunately, among our disappointing preliminary attempts, particularly starting from 3-bromo derivatives by reacting with various palladium catalyst systems in different solvents (toluene, DMF, 1,4-dioxane),<sup>30</sup> we had to modify our strategy to obtain the expected N-substituted 3-aminoindazoles. Thus, taking into account the important development of catalytic Ullmann-type amination, the coupling reaction of N-methylpiperazine with the 3-iodoindazole 4 was carried out in the presence of copper(I) iodide<sup>31</sup> as the catalyst, proline as the ligand, potassium carbonate as the base, and DMSO as the solvent at 140 °C in a microwave reactor for 30 minutes.<sup>32</sup> Using this protocol, 6 was first obtained in only 33% yield after purification by column chromatography on silica gel, but this result was improved by preparing this compound with a yield of 49%, using aluminum oxide instead of the more acidic silica gel for chromatography. In a likewise fashion, N-benzylpiperazine, N-benzyloxycarbonylpiperazine, and morpholine were combined with 4 leading to compounds 7–9, respectively, in good yields. In contrast, only traces of the desired product 10 were recovered from the reaction with aniline, which is a poor reagent for this coupling. In summary, we have successfully demonstrated the efficiency of the CuI/proline amination system on a 3-iodoindazole derivative and secondary cyclic amines under microwave irradiation (Scheme 3 and Table 2). However, in order to compare other reaction conditions, and to expand the range of the N-substituted 3-aminoindazoles to primary amines, we decided in the second part of this project, to investigate the new palladium-catalyzed Buchwald-Hartwig C-N coupling protocols under conventional oil-bath heating conditions in a sealed tube.



Scheme 3 Reagents and conditions: i)  $HNR^{1}R^{2}$  (2 equiv), CuI (0.2 equiv), proline (0.4 equiv),  $K_{2}CO_{3}$  (3 equiv), DMSO, microwave heating at 140 °C, 30 min (under argon), 27–51%.

### Palladium-Catalyzed Amination of Different 3-Bromoindazole Derivatives

The palladium-catalyzed amination of **3a** was first carried out with *N*-methylpiperazine using conditions developed by Buchwald  $[Pd_2(dba)_3, BINAP, and t-BuONa in reflux$ ing toluene],<sup>21b,c,23d</sup> but the corresponding C–N coupling

 Table 2
 Copper-Catalyzed and Microwave-Promoted Amination of

 3-Iodoindazole 4 with Various Amines



product **6** in this case was obtained only in 30% yield. With the aim of improving this procedure, a new monodentate ligand (dicyclohexylphosphinobiphenyl)<sup>30</sup> was tested under the same conditions in toluene instead of the BINAP bidentate in a polar solvent (1,4-dioxane). Unfortunately, these conditions provided the desired product **6** in a similar yield also along with a lot of starting material and a debrominated derivative. To decrease the formation of this by-product resulting from a  $\beta$ -elimination often observed with this kind of amines, it was decided to evaluate again another methodology using a different palladium catalyst system [Pd(OAc)<sub>2</sub>/Xantphos]<sup>33</sup> and above all Cs<sub>2</sub>CO<sub>3</sub> as a weaker base in 1,4-dioxane under reflux conditions.<sup>34</sup> Gratifyingly, with this protocol, **6** was finally

isolated in an excellent 73% yield. Next, with these optimized conditions, the palladium-catalyzed amination of the 3-bromoindazole derivative 3a was investigated with various secondary cyclic amines to synthesize the different 3-amino-substituted indazoles 7-9 and 11, which were still formed in the yields of 17-64%, considering the unfavorable negative charge at the 3 position of indazole. In fact, the poor result obtained with unprotected piperazine even in excess (1.5 equiv) was not surprising, taking into account the formation of a 3,3'-amino-substituted indazole dimer derivative. Subsequently, the coupling of 3a was successfully carried out with different primary aromatic amines to afford the expected amino compounds 10, 12-14 in moderate to excellent yields (19-87%) depending on the electron-withdrawing or electron-donating groups present in the anilines used (Scheme 4 and Table 3). In fact, it can be noted that the yields obtained with morpholine and aniline appear generally at least comparable to the few results available in the literature.<sup>24b,25</sup> Then, the use of benzylamine, a primary aliphatic amine for this C-N coupling gave us the amino derivative 15 in a yield of 23%. Furthermore, amination of the different 4-, 5-, or 6-substituted 3-bromoindazole derivatives 3b-f and 3h with N-benzyloxycarbonylpiperazine provided the corresponding N-substituted 3aminoindazoles 16-21 in 18-42% yields (Scheme 4 and Table 4).

**Table 3**Palladium-Catalyzed Amination of 3-Bromoindazole **3a**with Various Amines



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Table 3Palladium-Catalyzed Amination of 3-Bromoindazole 3awith Various Amines (continued)

Table 4Palladium-Catalyzed Amination of Different 3-Bromoin-<br/>dazole Derivatives 3b-f and 3h with Various Amines

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Scheme 4 Reagents and conditions: i)  $HNR^2R^3$  (1.2 equiv),  $Pd(OAc)_2$  (0.1 equiv), Xantphos (0.12 equiv),  $Cs_2CO_3$  (2.8 equiv), 1,4-dioxane, reflux, 6–24 h (under argon), 17–87%.

In addition, we found that treatment of the protected indazoles **7** and **10** with ethanolic HCl<sup>35</sup> at room temperature was able to cleave the THP in good yields to furnish the unprotected derivatives **22** and **23** (37 and 84%, respectively) (Scheme 5).



Scheme 5 *Reagents and conditions*: i) EtOH–HCl, r.t., 2–3 h, 37–84%.

Thus, we have successfully demonstrated that various Nsubstituted 3-aminoindazoles can be synthesized by a direct palladium-catalyzed Buchwald–Hartwig amination under conventional heating conditions starting from the corresponding 3-bromoindazole derivatives in a short time of 6–8 hours. However, the extension of reaction time to 24 hours<sup>23d</sup> sometimes allowed us to improve our results, for example, in 52, 65, and 21% yield for indazoles **9**, **13**, and **16**, respectively, instead of 38, 31, and 4% yield, respectively, after 6 hours of reaction. The amination conditions proposed in this paper result from a long and important devising and seem to be optimal for this position on this heterocycle with a good variety of tested amines, which could of course still be extended.

## Direct Synthesis of N-Unsubstituted 3-Aminoindazoles by C–N Cross-Coupling of the Corresponding Bromo Compounds with Benzophenone Imine

The classical synthesis of N-unsubstituted 3-aminoindazoles implicates the formation of the pyrazole moiety starting from 2-halobenzonitriles and hydrazine.<sup>3e,4,17c,18</sup> Moreover, Lefebvre and co-workers developed a similar cyclization avoiding the addition of hydrazine and including a palladium-catalyzed amination with the benzophenone hydrazone.<sup>36</sup> However, the major inconvenience of these methods is the poor availability of the starting materials. Then, it could perhaps be possible to obtain these compounds with a nitration at 3-position followed by a reduction, but it would need conditions not always compatible with different functions eventually present on the benzene ring. On the other hand, Wolfe and co-workers<sup>37a</sup> reported in 1997 the use of commercially available benzophenone imine<sup>37</sup> as a convenient surrogate for ammonia in palladium-catalyzed C–N couplings. With this in mind and starting directly from the variously substituted 3-bromoindazole derivatives **3a**, **3d**, and **3g**, the previously described optimum Buchwald–Hartwig reaction conditions were so applied using benzophenone imine. After acidic hydrolysis of the obtained, but not necessarily isolated imino compounds **24–26**, with ethanolic HCl at room temperature, this new procedure finally furnished us the expected unprotected primary 3-aminoindazoles **27–29** in good two-step yields (35, 67, and 49%, respectively) (Scheme 6).



Scheme 6 Reagents and conditions: i) Benzophenone imine (1.2 equiv),  $Pd(OAc)_2$  (0.1 equiv), Xantphos (0.12 equiv),  $Cs_2CO_3$  (2.8 equiv), 1,4-dioxane, reflux, 6–24 h (under argon); ii) EtOH–HCl, r.t., 0.5–72 h, 35–67% (over two steps).

To conclude, two efficient protocols for the synthesis of various 3-aminoindazoles in moderate to high yields have been developed both under microwave irradiation and traditional heating conditions. Thus, one of the most important advantages of the microwave-promoted coppercatalyzed amination method was of course the high-speed synthesis of the desired products, but better results were here in general obtained with the palladium-catalyzed C-N coupling procedure under conventional heating conditions. Considering the biological properties of indazole derivatives, this methodology allowing the facile introduction of indazole moiety on various scaffolds could be very useful for medicinal chemists to achieve new valuable building blocks. Further studies concerning development of new substituted indazole derivatives are currently in progress. In fact, taking into account our recent knowledge with regard to the synthesis of different primary 3aminoindazoles, we notably try to carry out the opposite C-N coupling considering the bigger availability of halogeno aromatic compounds.

All commercial reagents were used as received without further purification. Reaction mixtures were stirred magnetically and monitored by TLC using 0.2 mm Macherey-Nagel Polygram SIL G/UV<sub>254</sub> or ALOX N/UV<sub>254</sub> precoated plates. Column chromatography was performed using CarloErba-SDS 60A 70–200  $\mu$ m silica gel or Al<sub>2</sub>O<sub>3</sub>. Melting points were determined on a Kofler melting point apparatus. IR spectra were taken with a PerkinElmer spectrum X FT-IR spectrometer. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on a Jeol Lambda 400 Spectrometer. Chemical shifts ( $\delta$ ) are expressed in parts per million downfield from TMS as an internal standard and the coupling constants are in hertz. Mass spectra were recorded on a Jeol JMS GCMate with ionizing potential of 70 eV and with pfk as internal standard. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine', Rouen, France.

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#### 3-Iodo-1H-indazole (2)

Indazole (1a; 3.0 g, 25.3 mmol) was added to a stirred mixture of KOH (5.3 g, 94.9 mmol, 3.75 equiv) and I<sub>2</sub> (12.8 g, 50.6 mmol, 2 equiv) in DMF (40 mL). After 1 h at r.t., EtOAc (60 mL) was added, and the organic layer was washed successively with aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 × 30 mL) and brine (3 × 30 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc–cyclohexane, 1:3) to give **2** as a yellow solid; yield: 4.2 g (68%); mp 140 °C;  $R_f = 0.4$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 3435, 3153, 1619, 1471, 1314, 1237, 1013, 737, 600  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.23 (t, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 1 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 12.48 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 93.5, 111.0, 121.4, 122.0, 127.5, 128.2, 140.8.

Anal. Calcd for  $C_7H_5IN_2$ : C, 34.45; H, 2.07; N, 11.48. Found: C, 34.33; H, 2.22; N, 11.27.

#### 3-Bromo-1*H*-indazoles 3a-h; General Procedure

To a cooled solution of the chosen indazole **1a–h** in DMF (5–20 mL) was added at 0 °C dropwise  $Br_2$  (1.5 equiv). After the end of addition, the mixture was stirred for 2–72 h at r.t. The mixture was diluted with EtOAc (40 mL), the organic layer was washed successively with aq  $Na_2S_2O_3$  (3 × 20 mL) and brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc–cy-clohexane, 1:6 to 1:2) to give the expected 3-bromoindazoles **3a–h**.

#### 3-Bromo-1H-indazole (3a)

Starting from 1*H*-indazole (**1a**; 1.5 g, 12.7 mmol) and following the general procedure, the product **3a** was obtained as a yellow solid; yield: 1.6 g (64%); mp 124 °C;  $R_f = 0.4$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 3437, 2915, 1623, 1329, 1241, 1024, 733 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.21 (t, *J* = 6.8 Hz, 1 H), 7.44 (t, *J* = 6.8 Hz, 1 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 12.75 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 110.2, 120.2, 121.8, 122.9, 123.1, 128.1, 141.1.

HRMS (EI): m/z calcd for  $C_7H_5BrN_2$  [M<sup>+</sup>]: 195.9636; found: 195.9642.

#### 3-Bromo-4-nitro-1H-indazole (3b)

Starting from 4-nitro-1*H*-indazole (**1b**; 1.0 g, 6.0 mmol) and following the general procedure, the product **3b** was obtained as a yellow solid; yield: 1.1 g (77%); mp 228 °C,  $R_f = 0.2$  (silica gel; EtOAc–cyclohexane, 1:2).

IR (KBr): 3161, 2922, 1530, 1347, 1299, 1154, 1026, 998, 793, 730 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  = 7.61 (t, J = 7.8 Hz, 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 112.3, 117.2, 117.3, 118.6, 126.8, 141.3, 142.9.

HRMS (EI): m/z calcd for  $C_7H_4BrN_3O_2$  [M<sup>+</sup>]: 240.9486; found: 240.9488.

#### 3-Bromo-4-chloro-1*H*-indazole (3c)

Starting from 4-chloro-1*H*-indazole (**1c**; 0.6 g, 4.0 mmol) and following the general procedure, the product **3c** was obtained as a yellow solid; yield: 0.6 g (68%); mp 236 °C;  $R_f = 0.2$  (silica gel; EtOAc–cyclohexane, 1:4).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  = 7.21 (d, *J* = 6.8 Hz, 1 H), 7.37 (t, *J* = 6.8 Hz, 1 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 13.75 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 110.3, 118.0, 118.2, 122.0, 124.5, 128.2, 142.4.

HRMS (EI): m/z calcd for  $C_7H_4BrClN_2$  [M<sup>+</sup>]: 229.9246; found: 229.9238.

#### 3-Bromo-5-methoxy-1H-indazole (3d)

Starting from 5-methoxy-1*H*-indazole (**1d**; 3.0 g, 20.2 mmol) and following the general procedure, the product **3d** was obtained as a white solid; yield: 2.1 g (45%); mp 178 °C;  $R_f = 0.2$  (silica gel; EtOAc–cyclohexane, 1:4).

IR (KBr): 3161, 2944, 1634, 1514, 1489, 1295, 1217, 1179, 1014, 823, 728  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 3.89 (s, 3 H), 6.93 (s, 1 H), 7.12 (d, *J* = 8.8 Hz, 1 H), 7.40 (d, *J* = 9.8 Hz, 1 H), 10.42 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 55.7, 98.7, 111.2, 120.8, 122.0, 123.4, 136.8, 155.4.

Anal. Calcd for  $C_8H_7BrN_2O$ : C, 42.32; H, 3.11; N, 12.34. Found: C, 42.32; H, 3.09; N, 12.47.

#### 3-Bromo-5-nitro-1H-indazole (3e)

Starting from 5-nitro-1*H*-indazole (**1e**; 10.0 g, 61.0 mmol) and following the general procedure, the product **3e** was obtained as a white solid; yield: 13.5 g (91%); mp 226 °C;  $R_f = 0.2$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 3447, 3141, 2919, 1741, 1682, 1621, 1533, 1492, 1340, 1283, 1089, 787, 701 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  = 7.76 (d, *J* = 8.8 Hz, 1 H), 8.24 (dd, *J* = 8.8, 2.0 Hz, 1 H), 8.45 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 112.1, 117.1, 121.5, 122.2, 123.6, 142.2, 142.9.

HRMS (EI): m/z calcd for  $C_7H_4BrN_3O_2$  [M<sup>+</sup>]: 240.9486; found: 240.9490.

#### 3-Bromo-5-chloro-1H-indazole (3f)

Starting from 5-chloro-1*H*-indazole **1f** (1 g, 6.5 mmol) and following the general procedure, the product **3f** was obtained as a beige solid; yield: 0.9 g (60%); mp 212 °C;  $R_f = 0.1$  (silica gel; EtOAc–cyclohexane, 1:6).

IR (KBr): 3434; 3141, 1476, 1268, 920, 790, 615 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ = 7.54 (d, J = 10.8 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 7.71 (s, 1 H).

<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ = 112.9, 118.3, 119.7, 123.0, 126.1, 128.0, 139.6.

HRMS (EI): m/z calcd for  $C_7H_4BrClN_2$  [M<sup>+</sup>]: 229.9246; found: 229.9244.

### 3-Bromo-6-nitro-1*H*-indazole (3g)

Starting from 6-nitro-1*H*-indazole (**1g**; 1.0 g, 6.0 mmol) and following the general procedure, the product **3g** was obtained as a yellow solid; yield: 1.2 g (81%); mp 206 °C;  $R_f = 0.2$  (silica gel; EtOAc-cyclohexane, 1:3).

IR (KBr): 3349, 1591, 1526, 1339, 1019, 882, 786, 657 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  = 7.83 (d, J = 8.8 Hz, 1 H), 8.01 (dd, J = 8.8, 2.0 Hz, 1 H), 8.48 (s, 1 H), 14.07 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 107.8, 115.9, 120.8, 121.0, 125.2, 139.5, 146.9.

Anal. Calcd for  $C_7H_4BrN_3O_2$ : C, 34.74; H, 1.67; N, 17.36. Found: C, 34.45; H, 1.44; N, 16.86.

### 3-Bromo-6-chloro-1*H*-indazole (3h)

Starting from 6-chloro-1*H*-indazole (**1h**; 1.0 g, 6.5 mmol) and following the general procedure, the product **3h** was obtained as an orange solid; yield: 0.8 g (54%); mp 193 °C;  $R_f = 0.3$  (silica gel; EtOAc–cyclohexane, 1:4).

IR (KBr): 3168, 2925, 1624, 1459, 1325, 1023, 924, 798, 587 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.22 (d, *J* = 9.8 Hz, 1 H), 7.52 (s, 1 H), 7.71 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 109.9, 121.3, 121.9, 123.1, 123.3, 134.8, 141.4.

HRMS (EI): m/z calcd for  $C_7H_4BrClN_2$  [M<sup>+</sup>]: 229.9246; found: 229.9250.

# 1-THP-3-halogeno-1*H*-indazoles 4 and 5a–h; General Procedure

To a solution of the chosen 3-halogenoindazole **2** or **3a–h** dissolved in EtOAc (20–50 mL) were added successively a catalytic amount of PTSA and 3,4-dihydro-2*H*-pyrane (DHP, 2 equiv). The reaction mixture was heated under reflux for 3–48 h and then neutralized with NH<sub>4</sub>OH ( $3 \times 20$  mL). After the addition of EtOAc (40 mL), the organic layer was washed with brine ( $3 \times 20$  mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc–cyclohexane, 1:6 to 1:3) to give the expected protected indazoles **4** and **5a–h**.

### 3-Iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (4)

Starting from 3-iodo-1*H*-indazole (**2**; 1 g, 4.1 mmol) and following the general procedure, the product **4** was obtained as an orange solid; yield: 0.7 g (55%); mp 75 °C;  $R_f = 0.7$  (silica gel; EtOAc–cyclohexane, 1:4).

IR (KBr): 2956, 1614, 1460, 1377, 1209, 1039, 1078, 746, 575  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.69–1.81 (m, 3 H), 2.05–2.16 (m, 2 H), 2.52–2.62 (m, 1 H), 3.73 (dt, *J* = 11.7, 3.0 Hz, 1 H), 4.03 (dd, *J* = 10.7, 2.0 Hz, 1 H), 5.69 (dd, *J* = 9.3, 3.0 Hz, 1 H), 7.23 (t, *J* = 6.8 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.4, 24.9, 29.4, 67.5, 85.6, 93.3, 110.2, 121.6, 121.9, 127.6, 128.9, 139.9.

Anal. Calcd for  $C_{12}H_{13}IN_2O$ : C, 43.92; H, 3.99; N, 8.54. Found: C, 43.62; H, 4.03; N, 8.63.

### 3-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (5a)

Starting from 3-bromo-1*H*-indazole (**3a**; 2 g, 10.1 mmol) and following the general procedure, the product **5a** was obtained as a yellow solid; yield: 2.5 g (88%); mp 65 °C;  $R_f = 0.6$  (silica gel; EtOAc-cyclohexane, 1:6).

IR (KBr): 2941, 1651, 1617, 1463, 1326, 1200, 1081, 911, 747  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.77 (m, 3 H), 2.09–2.14 (m, 2 H), 2.51–2.56 (m, 1 H), 3.73 (t, *J* = 10.8 Hz, 1 H), 4.02 (d, *J* = 11.7 Hz, 1 H), 5.68 (dd, *J* = 9.8, 2.9 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.4, 25.0, 29.3, 67.4, 85.4, 110.3, 120.4, 121.9, 122.1, 124.4, 127.7, 140.5.

HRMS (EI): m/z calcd for  $C_{12}H_{13}BrN_2O$  [M<sup>+</sup>]: 280.0211; found: 280.0208.

# 3-Bromo-4-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5b)

Starting from 3-bromo-4-nitro-1*H*-indazole (**3b**; 0.8 g, 3.3 mmol) and following the general procedure, the product **5b** was obtained as a beige solid; yield: 1.1 g (99%), mp 142 °C;  $R_f = 0.3$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 2947, 1737, 1529, 1447, 1362, 1249, 1189, 1079, 1040, 998, 726 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.75 (m, 3 H), 2.03–2.14 (m, 2 H), 2.50–2.54 (m, 1 H), 3.75 (dt, *J* = 10.3, 2.9 Hz, 1 H), 3.96 (d, *J* = 11.7 Hz, 1 H), 5.77 (dd, *J* = 8.8, 2.9 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.94 (d, *J* = 8.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.8, 24.8, 29.0, 67.1, 86.0, 115.2, 116.3, 118.4, 118.8, 126.5, 142.1, 142.4.

HRMS (EI): m/z calcd for  $C_{12}H_{12}BrN_3O_3$  [M<sup>+</sup>]: 325.0061; found: 325.0066.

# 3-Bromo-4-chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5c)

Starting from 3-bromo-4-chloro-1*H*-indazole (**3c**; 0.5 g, 2.2 mmol) and following the general procedure, the product **5c** was obtained as an orange solid; yield: 0.6 g (88%); mp 118 °C;  $R_f = 0.5$  (silica gel; EtOAc–cyclohexane, 1:5).

IR (KBr): 2937, 1607, 1491, 1439, 1245, 1183, 1079, 1041, 1004, 773, 731  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.66–1.74 (m, 3 H), 2.05–2.14 (m, 2 H), 2.50–2.54 (m, 1 H), 3.72 (t, *J* = 10.8 Hz, 1 H), 3.99 (d, *J* = 11.7 Hz, 1 H), 5.66 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.2, 24.9, 29.1, 67.3, 85.6, 109.4, 119.8, 120.5, 122.8, 126.8, 128.0, 141.9.

Anal. Calcd for  $C_{12}H_{12}BrClN_2O$ : C, 45.67; H, 3.83; N, 8.88. Found: C, 45.26; H, 3.71; N, 8.67.

# 3-Bromo-5-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5d)

Starting from 3-bromo-5-methoxy-1*H*-indazole (**3d**; 0.7 g, 3.1 mmol) and following the general procedure, the product **5d** was obtained as a white solid; yield: 0.6 g (63%); mp 104 °C;  $R_f = 0.7$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 2943, 1672, 1625, 1502, 1452, 1222, 1077, 1032, 913, 880, 813, 745, 619  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.65–1.79 (m, 3 H), 2.05–2.16 (m, 2 H), 2.47–2.55 (m, 1 H), 3.72 (dt, *J* = 11.2, 2.9 Hz, 1 H), 3.88 (s, 3 H), 4.01 (d, *J* = 11.7 Hz, 1 H), 5.63 (dd, *J* = 9.3, 2.0 Hz, 1 H), 6.90 (s, 1 H), 7.10 (dd, *J* = 9.3, 2.0 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.4, 25.0, 29.3, 55.7, 67.3, 85.6, 99.0, 111.5, 120.2, 121.0, 124.7, 136.2, 155.5.

HRMS (EI): m/z calcd for  $C_{13}H_{15}BrN_2O_2$  [M<sup>+</sup>]: 310.0316; found: 310.0311.

# **3-Bromo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole** (5e)

Starting from 3-bromo-5-nitro-1*H*-indazole (**3e**; 1 g, 4.1 mmol) and following the general procedure, the product **5e** was obtained as a white solid; yield: 0.8 g (59%); mp 121 °C;  $R_f = 0.5$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 2944, 1615, 1520, 1349, 1209, 1080, 1040, 913, 785  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.76 (m, 3 H), 2.11–2.17 (m, 2 H), 2.47–2.51 (m, 1 H), 3.76 (dt, *J* = 10.3, 2.9 Hz, 1 H), 4.00 (d,

*J* = 10.8 Hz, 1 H), 5.74 (dd, *J* = 10.3, 2.9 Hz, 1 H), 7.70 (d, *J* = 9.8 Hz, 1 H), 8.31 (dd, *J* = 10.7, 2.0 Hz, 1 H), 8.60 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.9, 24.8, 29.2, 67.3, 86.2, 111.4, 118.2, 122.6, 124.0, 124.4, 142.4, 143.2.

Anal. Calcd for  $C_{12}H_{12}BrN_3O_3$ : C, 44.19; H, 3.71; N, 12.88. Found: C, 44.33; H, 3.57; N, 12.96.

# 3-Bromo-5-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (5f)

Starting from 3-bromo-5-chloro-1*H*-indazole (**3f**; 0.4 g, 1.7 mmol) and following the general procedure, the product **5f** was obtained as a yellow solid; yield: 0.4 g (69%); mp 76 °C;  $R_f = 0.4$  (silica gel; EtOAc–cyclohexane, 1:6).

IR (KBr): 2943, 1483, 1443, 1261, 1199, 1080, 1041, 1006, 911, 800, 789  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.67–1.74 (m, 3 H), 2.08–2.15 (m, 2 H), 2.47–2.51 (m, 1 H), 3.73 (t, *J* = 10.8 Hz, 1 H), 3.99 (d, *J* = 9.8 Hz, 1 H), 5.65 (dd, *J* = 8.8, 2.9 Hz, 1 H), 7.38 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.53 (d, *J* = 9.8 Hz, 1 H), 7.59 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.1, 24.9, 29.2, 67.2, 85.8, 111.8, 119.6, 121.0, 125.3, 127.7, 128.4, 139.0.

Anal. Calcd for C<sub>12</sub>H<sub>12</sub>BrClN<sub>2</sub>O: C, 45.67; H, 3.83; N, 8.88. Found: C, 45.83; H, 3.80; N, 9.23.

## 3-Bromo-6-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5g)

Starting from 3-bromo-6-chloro-1*H*-indazole (**3g**; 1.5 g, 6.2 mmol) and following the general procedure, the product **5g** was obtained as a beige solid; yield: 1.6 g (79%); mp 134 °C;  $R_f = 0.5$  (silica gel; EtOAc–cyclohexane, 1:4).

IR (KBr): 3074, 2977, 1525, 1343, 1208, 1079, 1039, 1004, 807, 729  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.79 (m, 3 H), 2.12–2.15 (m, 2 H), 2.47–2.53 (m, 1 H), 3.80 (dt, *J* = 9.8, 3.9 Hz, 1 H), 4.03 (d, *J* = 11.7 Hz, 1 H), 5.77 (dd, *J* = 9.2, 2.0 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 8.10 (dd, *J* = 8.8, 2.0 Hz, 1 H), 8.56 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.0, 24.8, 29.3, 67.5, 86.2, 107.6, 116.7, 121.4, 122.1, 127.6, 139.2, 147.4.

Anal. Calcd for  $C_{12}H_{12}BrN_3O_3$ : C, 44.19; H, 3.71; N, 12.88. Found: C, 44.88; H, 3.73; N, 12.87.

# 3-Bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (5h)

Starting from 3-bromo-6-chloro-1*H*-indazole (**3h**; 0.7 g, 3.2 mmol) and following the general procedure, the product **5h** was obtained as a yellow solid; yield: 0.4 g (42%); mp 92 °C;  $R_f = 0.7$  (silica gel; EtOAc–cyclohexane, 1:4).

IR (KBr): 2924, 2837, 1613, 1465, 1333, 1208, 1083, 1041, 1004, 969, 793, 773 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.66–1.77 (m, 3 H), 2.05–2.13 (m, 2 H), 2.48–2.51 (m, 1 H), 3.73 (t, *J* = 9.8 Hz, 1 H), 4.01 (d, *J* = 11.7 Hz, 1 H), 5.62 (dd, *J* = 9.8, 2.9 Hz, 1 H), 7.20 (d, *J* = 9.8 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 7.60 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.2, 24.9, 29.2, 67.4, 85.8, 110.4, 110.5, 121.4, 122.0, 123.1, 134.4, 140.8.

HRMS (EI): m/z calcd for  $C_{12}H_{12}BrClN_2O$  [M<sup>+</sup>]: 313.9821; found: 313.9835.

### Buchwald–Hartwig C–N Coupling Synthesis of N-Substituted 3-Aminoindazoles 6–21; General Procedure

Method I; Copper-Catalyzed and Microwave-Promoted Amination of a 3-Iodoindazole Derivative: 3-Iodo-1-(tetrahydro-2H-pyran-2-

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yl)-1*H*-indazole (**4**) dissolved in DMSO (2–3 mL), CuI (0.2 equiv), proline (0.4 equiv),  $K_2CO_3$  (3 equiv), and the chosen amine (2 equiv) were combined in a microwave tube fitted with a crimped septum cap. The tube was evacuated and then filled with argon several times. The reaction mixture was heated in a microwave at 140 °C for 30 min. Then, after the addition of EtOAc (30 mL), the organic layer was washed with brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on Al<sub>2</sub>O<sub>3</sub> often using a solvent gradient (EtOAc–cyclohexane, 1:12 to 1:3 sometimes followed by CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 99.5:0.5 to 99:1) to give the desired N-substituted 3-aminoindazoles **6–10**.

Method II; Palladium-Catalyzed Amination of Different 3-Bromoindazole Derivatives: In a dry sealed tube, anhyd 1,4-dioxane (3 mL), Pd(OAc)<sub>2</sub> (0.1 equiv), Xantphos (0.12 equiv), and the chosen amine (1.2 equiv) were added under argon and the mixture was preheated at 100 °C in an oil bath for 5 min. After cooling, the desired 3-bromoindazole derivative **5a–f** or **5h** and Cs<sub>2</sub>CO<sub>3</sub> (2.8 equiv) were also combined under argon with the premixed solution. Then, the reaction mixture was heated under reflux for 6–24 h. After the addition of EtOAc (30 mL), the organic layer was washed with brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on Al<sub>2</sub>O<sub>3</sub> (EtOAc–cyclohexane, 1:12 to 1:2 or CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 99:1 to 95:5) to give the expected N-substituted 3-aminoindazoles **6–21**.

## 3-(4-Methylpiperazin-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (6)

Starting from 4 (0.2 g, 0.6 mmol) (method I) or **5a** (0.3 g, 1 mmol) (method II) and following the general procedure, the product **6** was obtained as a yellow oil with method I (0.09 g, 49%) and with method II (0.2 g, 73%);  $R_f = 0.3$  (Al<sub>2</sub>O<sub>3</sub>; CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 99:1).

IR (neat): 2931, 1611, 1519, 1445, 1262, 1220, 1143, 1037, 805, 742 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.73 (m, 3 H), 1.96–2.14 (m, 2 H), 2.38 (s, 3 H), 2.53–2.58 (m, 1 H), 2.64 (t, *J* = 4.9 Hz, 4 H), 3.48–3.50 (m, 4 H), 3.71 (t, *J* = 10.8 Hz, 1 H), 4.05 (d, *J* = 9.8 Hz, 1 H), 5.54 (dd, *J* = 9.8, 2.0 Hz, 1 H), 7.04 (t, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.9, 25.1, 29.3, 46.3, 49.3, 54.9, 67.6, 84.9, 109.8, 116.5, 119.4, 121.1, 126.5, 141.4, 151.6.

HRMS (EI): m/z calcd for  $C_{17}H_{24}N_4O$  [M<sup>+</sup>]: 300.1950; found: 300.1953.

## 3-(4-Benzylpiperazin-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (7)

Starting from 4 (0.2 g, 0.6 mmol) (method I) or **5a** (0.3 g, 1 mmol) (method II) and following the general procedure, the product **7** was obtained as a yellow oil with method I (0.1 g, 43%) and with method II (0.1 g, 29%);  $R_f = 0.4$  (Al<sub>2</sub>O<sub>3</sub>; CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 99.5:0.5).

IR (neat): 2937, 1611, 1451, 1219, 1039, 910, 740 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.72–1.75 (m, 3 H), 1.96–2.12 (m, 2 H), 2.50–2.58 (m, 1 H), 2.66 (t, *J* = 4.9 Hz, 4 H), 3.44–3.51 (m, 4 H), 3.60 (s, 2 H), 3.70 (t, *J* = 10.7 Hz, 1 H), 4.05 (d, *J* = 6.8 Hz, 1 H), 5.54 (dd, *J* = 9.8, 2.0 Hz, 1 H), 7.04 (t, *J* = 7.8 Hz, 1 H), 7.27–7.30 (m, 2 H), 7.34 (t, *J* = 6.8 Hz, 2 H), 7.38 (d, *J* = 6.8 Hz, 2 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H).

 $^{13}$ C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.8, 25.1, 29.2, 49.4, 52.7, 63.0, 67.5, 84.8, 104.4, 109.8, 116.2, 119.3, 121.1, 126.4, 127.0, 128.1, 129.1, 141.4, 151.7.

HRMS (EI): m/z calcd for  $C_{23}H_{28}N_4O$  [M<sup>+</sup>]: 376.2263; found: 376.2267.

### 4-[1-(Tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1carboxylic Acid Benzyl Ester (8)

Starting from **4** (0.2 g, 0.6 mmol) (method I) or **5a** (0.3 g, 1 mmol) (method II) and following the general procedure, the product **8** was obtained as a yellow oil with method I (0.1 g, 51%) and with method II (0.3 g, 64%);  $R_f = 0.1$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:8).

IR (neat): 2939, 1704, 1611, 1520, 1434, 1243, 1220, 1078, 1038, 911, 742  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.72–1.75 (m, 3 H), 1.96–2.12 (m, 2 H), 2.50–2.54 (m, 1 H), 3.42–3.44 (m, 4 H), 3.67–3.69 (m, 1 H), 3.72 (t, *J* = 4.9 Hz, 4 H), 4.04 (d, *J* = 9.8 Hz, 1 H), 5.18 (s, 2 H), 5.54 (dd, *J* = 9.8, 3.0 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 7.33–7.38 (m, 4 H), 7.38 (d, *J* = 3.9 Hz, 2 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.9, 25.1, 29.3, 43.5, 49.5, 67.2, 67.6, 84.8, 109.9, 116.4, 119.7, 120.8, 126.7, 127.9, 128.0, 128.5, 136.6, 141.4, 151.3, 155.32.

HRMS (EI): m/z calcd for  $C_{24}H_{28}N_4O_3$  [M<sup>+</sup>]: 420.2161; found: 420.2179.

### 3-(Morpholin-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (9)

Starting from **4** (0.2 g, 0.8 mmol) (method I) or **5a** (0.3 g, 1 mmol) (method II) and following the general procedure, the product **9** was obtained as a beige oil with method I (0.06 g, 27%) and with method II (0.1 g, 52%);  $R_f = 0.1$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:12).

IR (KBr): 2957, 1611, 1520, 1443, 1221, 1118, 1079, 1022, 909, 742 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.71–1.76 (m, 3 H), 1.97–2.17 (m, 2 H), 2.53–2.56 (m, 1 H), 3.39–3.50 (m, 4 H), 3.71 (t, *J* = 11.7 Hz, 1 H), 3.91 (t, *J* = 4.9 Hz, 4 H), 4.05 (d, *J* = 9.8 Hz, 1 H), 5.55 (dd, *J* = 9.8, 2.9 Hz, 1 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 7.34 (t, *J* = 6.8 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.9, 25.2, 29.3, 50.0, 66.8, 67.7, 84.9, 109.9, 116.4, 119.6, 121.0, 126.7, 141.5, 151.7.

HRMS (EI): m/z calcd for  $C_{16}H_{21}N_3O_2$  [M<sup>+</sup>]: 287.1634; found: 287.1632.

# Phenyl[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (10)

Starting from **4** (0.2 g, 0.6 mmol) (method I) or **5a** (0.4 g, 1.5 mmol) (method II) and following the general procedure, the product **10** was obtained as a yellow solid with method I (traces) and with method II (0.4 g, 87%); mp 166 °C;  $R_f = 0.3$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:10).

IR (neat): 3350, 2953, 1606, 1549, 1445, 1214, 1025, 743 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.74–1.79 (m, 3 H), 2.05–2.18 (m, 2 H), 2.60–2.63 (m, 1 H), 3.74 (t, *J* = 8.8 Hz, 1 H), 4.07 (d, *J* = 9.8 Hz, 1 H), 5.62 (dd, *J* = 9.3, 3.0 Hz, 1 H), 6.27 (s, 1 H), 6.92 (t, *J* = 6.8 Hz, 1 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 7.29 (t, *J* = 7.8 Hz, 2 H), 7.38–7.42 (m, 3 H), 7.49 (d, *J* = 8.8 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.8, 25.1, 29.4, 67.5, 84.8, 109.9, 116.3, 116.8, 119.6, 119.9, 120.3, 127.2, 129.0, 140.6, 142.4, 144.2.

HRMS (EI): m/z calcd for  $C_{18}H_{19}N_3O$  [M<sup>+</sup>]: 293.1528; found: 293.1527.

# 3-(Piperazin-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (11)

Starting from **5a** (0.3 g, 1 mmol) and following method II, the product **11** was obtained as a yellow oil (0.05 g, 17%);  $R_f = 0.1$  (Al<sub>2</sub>O<sub>3</sub>; CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 95:5).

IR (neat): 3420, 2921, 1610, 1520, 1222, 1037, 909, 803 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.71–1.76 (m, 3 H), 1.99–2.14 (m, 2 H), 2.52–2.56 (m, 1 H), 3.09 (t, *J* = 4.9 Hz, 4 H), 3.38–3.47 (m, 4 H), 3.71 (t, *J* = 10.8 Hz, 1 H), 4.05 (d, *J* = 9.8 Hz, 1 H), 5.30 (s, 1 H), 5.55 (dd, *J* = 9.8, 2.9 Hz, 1 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 7.33 (t, *J* = 6.8 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.9, 25.1, 29.3, 45.6, 50.5, 67.6, 84.9, 109.9, 116.5, 119.5, 121.1, 126.6, 141.5, 152.0.

HRMS (EI): m/z calcd for  $C_{16}H_{22}N_4O$  [M<sup>+</sup>]: 286.1793; found: 286.1786.

# (4-Bromophenyl)[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (12)

Starting from **5a** (0.3 g, 1 mmol) and following method II, the product **12** was obtained as an orange solid (0.07 g, 19%); mp 130 °C;  $R_f = 0.3$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:8).

IR (KBr): 3402, 2923, 1614, 1549, 1487, 1290, 1214, 1021, 803, 733  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.74–1.80 (m, 3 H), 2.05–2.18 (m, 2 H), 2.58–2.62 (m, 1 H), 3.74 (t, *J* = 8.8 Hz, 1 H), 4.08 (d, *J* = 11.7 Hz, 1 H), 5.62 (dd, *J* = 9.3, 2.0 Hz, 1 H), 6.27 (s, 1 H), 7.11 (t, *J* = 6.8 Hz, 1 H), 7.29–7.33 (m, 2 H), 7.38 (d, *J* = 9.8 Hz, 2 H), 7.42 (d, *J* = 6.8 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.53 (d, *J* = 7.8 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 22.8, 25.1, 29.4, 67.6, 84.8, 110.0, 112.5, 116.4, 118.3, 119.5, 120.2, 127.6, 131.9, 140.6, 141.2, 143.8.

HRMS (EI): m/z calcd for  $C_{17}H_{18}BrN_4O$  [M<sup>+</sup>]: 373.0663; found: 373.0652.

# (4-Methoxyphenyl)[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (13)

Starting from **5a** (0.3 g, 1 mmol) and following method II, the product **13** was obtained as a beige solid (0.2 g, 65%); mp 140 °C;  $R_f = 0.3$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:4).

IR (KBr): 3363, 2954, 1614, 1548, 1510, 1451, 1245, 1212, 1073, 1037, 911, 828, 743  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta = 1.75-1.80$  (m, 3 H), 2.00–2.09 (m, 2 H), 2.46–2.50 (m, 1 H), 3.75–3.78 (m, 1 H), 3.77 (s, 3 H), 3.91 (d, J = 8.8 Hz, 1 H), 5.72 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.14 (t, J = 6.8 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 2 H), 8.02 (d, J = 7.8 Hz, 1 H), 8.81 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 22.5, 24.9, 29.0, 55.2, 66.4, 83.5, 109.6, 114.0, 116.0, 117.2, 119.2, 120.2, 127.0, 136.2, 140.2, 145.0, 152.6.

HRMS (EI): m/z calcd for  $C_{19}H_{21}N_3O_2$  [M<sup>+</sup>]: 323.1634; found: 323.1633.

### (3,4-Dimethoxyphenyl)[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (14)

Starting from **5a** (0.3 g, 1 mmol) and following method II, the product **14** was obtained as a beige solid (0.2 g, 54%); mp 95 °C;  $R_f = 0.3$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:3).

IR (KBr): 3370, 2934, 1616, 1513, 1451, 1207, 1026, 910, 731  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.65–1.78 (m, 3 H), 2.04–2.18 (m, 2 H), 2.56–2.62 (m, 1 H), 3.73 (t, *J* = 10.8 Hz, 1 H), 3.87 (s, 6 H), 4.04 (d, *J* = 11.7 Hz, 1 H), 5.59–5.61 (m, 1 H), 6.25 (s, 1 H), 6.81 (d, *J* = 7.8 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 7.26 (s, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 22.8, 25.2, 29.3, 55.7, 56.3, 67.2, 84.6, 102.4, 108.6, 109.7, 112.1, 116.4, 119.6, 119.7, 127.2, 136.4, 140.7, 143.3, 145.0, 149.3.

HRMS (EI): m/z calcd for  $C_{20}H_{23}N_3O_3$  [M<sup>+</sup>]: 353.1739; found: 353.1744.

# Benzyl[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (15)

Starting from **5a** (0.3 g, 1 mmol) and following method II, the product **15** was obtained as a yellow oil (0.07 g, 23%);  $R_f = 0.2$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:12).

IR (neat): 3370, 2939, 2855, 1613, 1549, 1449, 1340, 1217, 1077, 1034, 742, 699  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.59$  (s, 2 H), 1.71–1.76 (m, 3 H), 1.98–2.12 (m, 2 H), 2.56–2.59 (m, 1 H), 3.71 (t, J = 10.7 Hz, 1 H), 4.07 (d, J = 9.8 Hz, 1 H), 4.17 (s, 1 H), 5.53 (dd, J = 9.8, J = 3.0 Hz, 1 H), 7.02 (t, J = 6.8 Hz, 1 H), 7.29 (t, J = 6.8 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 2 H), 7.39 (t, J = 8.8 Hz, 1 H), 7.46–7.48 (m, 3 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 23.1, 25.2, 29.5, 48.4, 67.7, 84.9, 109.5, 115.8, 119.2, 127.1, 127.3, 128.2, 128.5, 128.8, 139.8, 141.4, 149.6.

HRMS (EI): m/z calcd for  $C_{19}H_{21}N_3O$  [M<sup>+</sup>]: 307.1684; found: 307.1674.

### 4-[4-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (16)

Starting from **5b** (0.3 g, 1 mmol) and following method II, the product **16** was obtained as a red solid (0.1 g, 21%); mp 50 °C;  $R_f = 0.4$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:3).

IR (KBr): 2926, 1701, 1618, 1528, 1424, 1344, 1242, 1118, 1082, 1041, 731 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.68–1.72 (m, 3 H), 2.02–2.15 (m, 2 H), 2.48–2.52 (m, 1 H), 3.08–3.10 (m, 4 H), 3.70–3.72 (m, 5 H), 3.97 (d, *J* = 11.7 Hz, 1 H), 5.16 (s, 2 H), 5.65 (dd, *J* = 9.2, 2.9 Hz, 1 H), 7.32–7.38 (m, 5 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.2, 25.0, 26.9, 29.2, 43.5, 51.4, 67.1, 85.2, 108.3, 115.8, 117.4, 125.8, 127.8, 128.0, 128.5, 136.7, 142.6, 143.6, 150.2, 155.3.

HRMS (EI): m/z calcd for  $C_{24}H_{27}N_5O_5$  [M<sup>+</sup>]: 465.2012; found: 465.2026.

## 4-[4-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (17)

Starting from **5c** (0.3 g, 1 mmol) and following method II, the product **17** was obtained as a colorless oil (0.2 g, 40%);  $R_f = 0.2$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:4).

IR (neat): 2935, 1696, 1608, 1512, 1431, 1382, 1243, 1113, 1080, 1040 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.74 (m, 3 H), 1.95–2.12 (m, 2 H), 2.47–2.52 (m, 1 H), 3.30–3.34 (m, 4 H), 3.70–3.73 (m, 5 H), 4.01 (d, *J* = 10.7 Hz, 1 H), 5.17 (s, 2 H), 5.54 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.32–7.38 (m, 6 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.5, 25.0, 29.1, 43.7, 51.8, 67.1, 67.4, 84.8, 108.6, 115.5, 121.2, 126.4, 127.3, 127.8, 128.0, 128.5, 136.7, 142.5, 151.7, 155.4.

HRMS (EI): m/z calcd for  $C_{24}H_{27}CIN_4O_3$  [M<sup>+</sup>]: 454.1771; found: 454.1774.

# 4-[5-Methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (18)

Starting from **5d** (0.3 g, 1 mmol) and following method II, the product **18** was obtained as a yellow oil (0.08 g, 18%);  $R_f = 0.1$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:8).

IR (neat): 2939, 1701, 1624, 1521, 1489, 1431, 1240, 1122, 1078, 1036, 909, 811, 760, 699 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.74 (m, 3 H), 1.96–2.12 (m, 2 H), 2.48–2.52 (m, 1 H), 3.35–3.38 (m, 4 H), 3.69–3.71 (m, 1 H), 3.72 (t, *J* = 4.9 Hz, 4 H), 3.84 (s, 3 H), 4.02 (d, *J* = 6.8 Hz, 1 H), 5.17 (s, 2 H), 5.49 (d, *J* = 9.8 Hz, 1 H), 6.96 (s, 1 H), 7.04 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.33–7.39 (m, 6 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.8, 25.1, 29.3, 43.4, 50.0, 55.9, 67.2, 67.6, 85.2, 100.6, 111.1, 116.5, 118.6, 127.9, 128.0, 128.1, 128.5, 136.6, 137.2, 154.0, 155.3.

HRMS (EI): m/z calcd for  $C_{25}H_{30}N_4O_4$  [M<sup>+</sup>]: 450.2267; found: 450.2276.

### 4-[5-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (19)

Starting from **5e** (0.3 g, 1 mmol) and following method II, the product **19** was obtained as a red solid (0.2 g, 37%); mp 170 °C;  $R_f = 0.1$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:8).

IR (KBr): 2938, 1697, 1611, 1530, 1473, 1432, 1323, 1224, 1128, 1076, 1035, 739 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.60–1.74 (m, 3 H), 2.00–2.17 (m, 2 H), 2.45–2.50 (m, 1 H), 3.45–3.50 (m, 4 H), 3.70–3.72 (m, 1 H), 3.74 (t, *J* = 4.9 Hz, 4 H), 4.03 (d, *J* = 11.7 Hz, 1 H), 5.18 (s, 2 H), 5.57 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.33–7.39 (m, 5 H), 7.50 (d, *J* = 9.8 Hz, 1 H), 8.23 (dd, *J* = 8.8, 1.9 Hz, 1 H), 8.67 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.4, 25.0, 29.2, 43.4, 49.2, 67.3, 67.6, 85.3, 110.2, 115.6, 119.1, 121.9, 127.9, 128.1, 128.5, 136.6, 140.9, 143.1, 153.2, 155.3.

HRMS (EI): m/z calcd for  $C_{24}H_{27}N_5O_5$  [M<sup>+</sup>]: 465.2012; found: 465.2019.

# 4-[5-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (20)

Starting from **5f** (0.3 g, 1 mmol) and following method II, the product **20** was obtained as an orange solid (0.1 g, 29%); mp 98 °C;  $R_f = 0.5$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:5).

IR (KBr): 2926, 1704, 1533, 1469, 1430, 1221, 1078, 1034, 986, 910, 752, 695 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.69–1.72 (m, 3 H), 1.96–2.11 (m, 2 H), 2.48–2.50 (m, 1 H), 3.14–3.17 (m, 2 H), 3.36–3.40 (m, 2 H), 3.68– 3.70 (m, 1 H), 3.71 (t, *J* = 4.9 Hz, 4 H), 4.02 (d, *J* = 11.7 Hz, 1 H), 5.18 (s, 2 H), 5.50 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.33–7.38 (m, 5 H), 7.39 (d, *J* = 6.8 Hz, 1 H), 7.62 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 22.7, 25.1, 29.2, 43.5, 49.5, 67.2, 67.5, 85.0, 111.2, 117.3, 120.1, 125.1, 127.2, 128.0, 128.5, 129.3, 136.6, 139.9, 150.8, 155.3.

HRMS (EI): m/z calcd for  $C_{24}H_{27}ClN_4O_3$  [M<sup>+</sup>]: 454.1771; found: 454.1783.

## 4-[6-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]piperazin-1-carboxylic Acid Benzyl Ester (21)

Starting from **5h** (0.3 g, 1 mmol) and following method II, the product **21** was obtained as an orange oil (0.2 g, 42%);  $R_f = 0.4$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:2).

IR (neat): 2940, 1697, 1621, 1435, 1242, 1121, 1078, 1038, 910, 734, 698  $\text{cm}^{-1}$ .

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.70–1.72 (m, 3 H), 1.94–2.12 (m, 2 H), 2.48–2.50 (m, 1 H), 3.20–3.22 (m, 2 H), 3.39–3.41 (m, 2 H), 3.68–3.71 (m, 5 H), 4.01–4.04 (m, 1 H), 5.17 (s, 2 H), 5.46 (d, *J* = 6.8 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 7.32–7.38 (m, 6 H), 7.50 (d, *J* = 8.8 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 22.8, 25.1, 29.2, 43.7, 49.3, 49.9, 67.2, 67.4, 84.5, 95.3, 110.8, 112.8, 121.4, 128.0, 128.5, 136.5, 136.6, 142.9, 151.3, 155.2, 155.3.

HRMS (EI): m/z calcd for  $C_{24}H_{27}ClN_4O_3$  [M<sup>+</sup>]: 454.1771; found: 454.1780.

# Unprotected N-Substituted 3-Aminoindazoles 22 and 23; General Procedure

Indazole **7** or **10** was introduced in ethanolic HCl (5–6 mL) and the mixture was stirred for 2–3 h at r.t. Then, the acidic mixture was neutralized with aq 2 N NaOH and the EtOH was evaporated in vacuo. After addition of EtOAc (30 mL) to the residue, the organic layer was washed with brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. Finally, the expected unprotected N-substituted 3-aminoindazoles **22** and **23** were directly isolated.

## 3-(4-Benzylpiperazin-1-yl)-1H-indazole (22)

Starting from **7** (0.07 g, 0.2 mmol) and following the general procedure, the product **22** was obtained as an orange oil (0.02 g, 37%);  $R_f = 0.4$  (Al<sub>2</sub>O<sub>3</sub>; EtOAc–cyclohexane, 1:1).

IR (KBr): 3214, 2931, 2819, 1617, 1517, 1452, 1343, 1256, 1166, 1007, 738, 699 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 2.69 (t, *J* = 4.8 Hz, 4 H), 3.48 (t, *J* = 4.9 Hz, 4 H), 3.68 (s, 2 H), 7.02–7.07 (m, 1 H), 7.32–7.39 (m, 7 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 9.16 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 49.7, 52.9, 63.2, 109.9, 115.4, 119.2, 121.1, 126.8, 127.1, 128.3, 129.2, 138.1, 142.8, 153.4.

HRMS (EI): m/z calcd for  $C_{18}H_{20}N_4$  [M<sup>+</sup>]: 292.1688; found: 292.1686.

### Phenyl(1*H*-indazol-3-yl)amine (23)

Starting from **10** (0.05 g, 0.2 mmol) and following the general procedure, the product **23** was obtained as a brown solid (0.03 g, 84%); mp 96 °C;  $R_f = 0.9$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (neat): 3412, 3251, 2924, 1619, 1603, 1555, 1497, 1446, 1338, 1261, 1077, 1026, 740, 686 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta = 6.78$  (t, J = 6.8 Hz, 1 H), 7.01 (t, J = 6.8 Hz, 1 H), 7.23 (t, J = 7.8 Hz, 2 H), 7.31 (t, J = 6.8 Hz, 1 H), 7.36 (d, J = 8.8 Hz, 1 H), 7.64 (d, J = 7.8 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 1 H), 8.73 (s, 1 H), 11.92 (s, 1 H).

<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ = 109.4, 114.5, 115.6, 118.1, 118.5, 119.5, 126.5, 128.5, 140.5, 143.1, 144.8.

HRMS (EI): m/z calcd for  $C_{13}H_{11}N_3$  [M<sup>+</sup>]: 209.0953; found: 209.0963.

# Two-Step Synthesis of Unprotected Primary 3-Aminoindazoles 27–29; General Procedure

Step I: Buchwald–Hartwig C–N Coupling of Different 3-Bromoindazole Derivatives with Benzophenone Imine: In a dry sealed tube, anhyd 1,4-dioxane (3 mL), Pd(OAc)<sub>2</sub> (0.1 equiv), Xantphos (0.12 equiv), and benzophenone imine (1.2 equiv) were added under argon and the mixture was preheated at 100 °C in an oil bath for 5 min. After cooling, the desired 3-bromoindazole derivative **5a**, **5e**, or **5g** and Cs<sub>2</sub>CO<sub>3</sub> (2.8 equiv) were also combined under argon with the premixed solution. Then, the reaction mixture was heated under reflux for 6–24 h. After the addition of EtOAc (30 mL), the organic layer was washed with brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc–cyclohexane, 1:8 to 1:3) to give the expected 3-iminoindazoles **24–26**.

Step II: Acidic Hydrolysis of the Previously Synthesized 3-Iminoindazole Derivatives: The chosen indazole **24–26** was introduced in ethanolic HCl (15–20 mL) and the mixture was stirred for 0.5–72 h at r.t. Then, the acidic mixture was neutralized with aq 2 N NaOH and the EtOH was evaporated in vacuo. The obtained residue was dissolved in EtOAc (30 mL) and a pH-dependent extraction was carried out. First, an acidic aqueous layer was used to hold the desired primary 3-aminoindazoles and eliminate the simultaneously synthesized benzophenone in the organic layer. Then, the expected compounds were extracted from an alkaline aqueous layer with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (3 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo. Finally, the expected unprotected primary 3-aminoindazoles **27–29** were directly isolated.

### 3-Amino-1*H*-indazole (27) Step I

# Benzhydrylidene[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (24)

Starting from **5a** (0.4 g, 1.5 mmol) and following the general procedure, the product **24** was obtained as a yellow solid (0.6 g, 99%); mp 115 °C;  $R_f = 0.5$  (silica gel; EtOAc–cyclohexane, 1:3).

IR (KBr): 2922, 1609, 1488, 1320, 1285, 1199, 1027, 746, 696  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.63–1.70 (m, 3 H), 1.86–2.00 (m, 2 H), 2.28–2.32 (m, 1 H), 3.47–3.61 (m, 1 H), 3.69–3.71 (m, 1 H), 5.62 (dd, *J* = 6.3, 2.9 Hz, 1 H), 6.99 (t, *J* = 7.8 Hz, 1 H), 7.22–7.30 (m, 7 H), 7.41 (d, *J* = 7.8 Hz, 4 H), 7.49 (d, *J* = 5.9 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H).

 $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  = 21.7, 25.1, 28.7, 65.9, 84.1, 109.7, 118.4, 120.5, 126.5, 127.8, 128.1, 128.6, 129.1, 129.8, 131.0, 137.3, 139.4, 140.6, 150.9, 171.8.

HRMS (EI): m/z calcd for  $C_{25}H_{23}N_{3}O$  [M^+]: 381.1841; found: 381.1851.

### Step II

### 3-Amino-1H-indazole (27)

Starting from **24** (0.6 g, 1.5 mmol) and following the general procedure, the product **27** was obtained as a beige solid (0.07 g, 35%); mp 164 °C;  $R_f = 0.2$  (silica gel; EtOAc).

IR (KBr): 3314, 1616, 1535, 1494, 1344, 1044, 744 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  = 5.32 (s, 2 H), 6.85–6.89 (m, 1 H), 7.18–7.21 (m, 2 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 11.35 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ): δ = 109.3, 114.0, 117.4, 120.2, 126.1, 141.4, 149.0.

HRMS (EI): m/z calcd for  $C_7H_7N_3$  [M<sup>+</sup>]: 133.0640; found: 133.0634.

### 3-Amino-5-nitro-1*H*-indazole (28)

#### Step I Benzhydrylidene[5-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (25)

Starting from **5e** (0.3 g, 1 mmol) and following the general procedure, the product **25** was synthesized, but not purified.

## Step II

### 3-Amino-5-nitro-1H-indazole (28)

Starting from the crude material obtained during step I and following the general procedure, the product **28** was obtained as an orange solid (0.1 g, 67% over two steps); mp 159 °C;  $R_f = 0.1$  (silica gel; EtOAc–cyclohexane, 1:1).

IR (KBr): 3438, 1617, 1521, 1473, 1325, 1261, 1066, 1023, 804, 740  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  = 3.56 (s, 2 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 8.13 (d, *J* = 10.8 Hz, 1 H), 8.97 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ): δ = 109.8, 113.2, 119.6, 121.3, 138.9, 142.7, 151.7.

HRMS (EI): m/z calcd for  $C_7H_6N_4O_2$  [M<sup>+</sup>]: 178.0490; found: 178.0487.

### 3-Amino-6-nitro-1*H*-indazole (29) Step I

#### Benzhydrylidene[6-nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-3-yl]amine (26)

Starting from **5g** (0.3 g, 1 mmol) and following the general procedure, the product **26** was obtained as a yellow solid (0.2 g, 59%); mp 142 °C;  $R_f = 0.4$  (silica gel; EtOAc–cyclohexane, 1:8).

IR (KBr): 2957, 2918, 2870, 1608, 1422, 1343, 1199, 1020, 738, 696  $\rm cm^{-1}$ 

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.62–1.65 (m, 3 H), 1.90–1.94 (m, 2 H), 2.26–2.30 (m, 1 H), 3.65–3.75 (m, 2 H), 5.69 (dd, *J* = 7.3, 3.9 Hz, 1 H), 7.22–7.26 (m, 4 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 10.7, 2.0 Hz, 1 H), 7.87 (d, *J* = 8.8 Hz, 2 H), 8.38 (s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.4, 24.9, 28.7, 66.1, 84.9, 107.0, 115.3, 121.2, 121.4, 128.0, 128.2, 129.0, 129.9, 131.5, 136.9, 138.8, 139.2, 146.6, 151.0, 173.3.

HRMS (EI): m/z calcd for  $C_{25}H_{22}N_4O_3$  [M<sup>+</sup>]: 426.1692; found: 426.1707.

### Step II

#### 3-Amino-6-nitro-1*H*-indazole (29)

Starting from **26** (0.2 g, 0.5 mmol) and following the general procedure, the product **29** was obtained as a red solid (0.07 g, 84%); mp 210 °C;  $R_f = 0.1$  (silica gel; EtOAc–cyclohexane, 1:1).

IR (KBr): 3370, 1711, 1627, 1518, 1347, 1057, 787, 730 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  = 5.72 (s, 2 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 8.11 (s, 1 H), 12.11 (s, 1 H).

<sup>13</sup>C NMR (DMSO- $d_6$ ):  $\delta$  = 105.9, 111.7, 116.7, 121.6, 139.6, 146.2, 149.7.

HRMS (EI): m/z calcd for  $C_7H_6N_4O_2$  [M<sup>+</sup>]: 178.0490; found: 178.0488.

### Acknowledgment

We thank Dr. Rémi Legay for the high-resolution mass spectrometry measurements.

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