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Tetrahedron 61 (2005) 8218–8225
Tetrahedron

New and efficient synthesis of bi- and trisubstituted indazoles

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Received 7 March 2005; revised 30 May 2005; accepted 9 June 2005

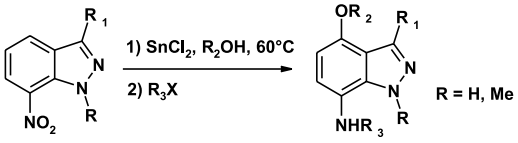
Available online 11 July 2005

Abstract—In this paper, the synthesis of bi- and trisubstituted indazoles was described. 4-Alkoxy-7-aminoprotected-indazole or 7-aminoprotected-indazole derivatives were prepared selectively using $SnCl_2$ in alcohol or $SnCl_2$ in ethyl acetate, respectively. The effects of the halogen atom in position 3 and of the *N*-alkylation in *N*-1 position of 7-nitroindazoles were investigated.

1. Introduction

Recently, considerable importance has been attached to synthetic methods leading to indazole derivatives because of their biological activities.[1–9] Various indazole derivatives, such as 3-substituted indazoles obtained via different cross-coupling reactions,[10–15] are common components of drugs and are generally found to be of pharmaceutical interest in a variety of therapeutic areas.[16]

One of our research targets is to develop simple and inexpensive synthetic procedures for heterocyclic compounds that are of interest for medical purpose. Here, we present the simple and efficient synthetic procedures developed to obtain 4- and 7-bisubstituted indazole derivatives. During the synthesis of sulfonamides from 7-nitroindazoles, we noticed that the conversion of the nitro group into a corresponding amino group with $SnCl_2$ in the presence of ethanol gave a product functionalized in the 4-position. Afterward we generalized this sequence by using other alcohols as solvent followed by a coupling reaction of amines achieved with various protecting groups (Scheme 1), in order to prepare new bi-and trisubstituted indazoles.



Scheme 1.

Keywords: Indazoles; Cross-coupling reaction; Alcohols; Nucleophilic addition.
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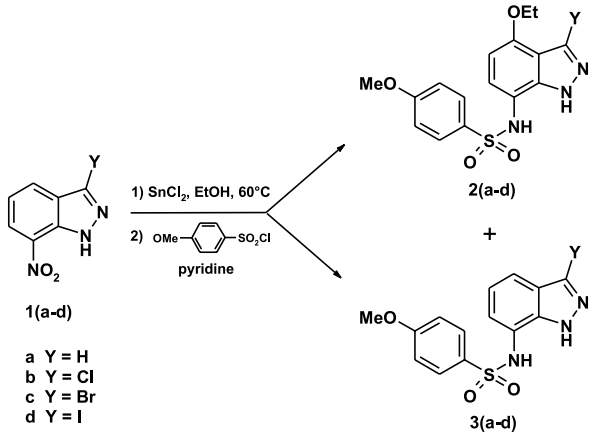
doi:10.1016/j.tet.2005.06.038

2. Results and discussion

One of the simplest ways to prepare 7-aminoindazole derivatives consists of the reduction of 7-nitroindazole derivatives with $SnCl_2$ in alcoholic solution. However, we observed that reduction of the compounds **1**(**a**–**d**) with $SnCl_2$ in ethanol as solvent gave two different compounds, that is, the desired amine and the amine substituted with ethoxy group in the 4-position, according to ^1H NMR of crude product. It is noteworthy that significant degradation of aromatic primary amine was observed. Consequently, we immediately protected this amine by using 4-methoxybenzenesulfonyl chloride in pyridine. This reaction afforded a mixture of *N*-(3-substituted-7-indazolyl)-benzenesulfonamides **3**(**a**–**d**) with the corresponding 4-ethoxysubstituted derivatives **2**(**a**–**d**) (Scheme 2).



Scheme 2.

The structure of the *N*-(4-ethoxy-3-iodo-7-indazolyl)-4-methoxybenzenesulfonamide **2d**, was unambiguously established by X-ray crystallography (Fig. 1). Indeed, the ethoxy group is bound to the C-4 of the aromatic ring. Moreover, a chelate was found between N(1) bound to H(1) and O(16) with N(1)–O(16)=2.994(5) Å and the angle N(1)–H(1)···O(16)=114.8°, inducing a bent shape for **2**. On the other hand, bond lengths and angles do not show surprising features.

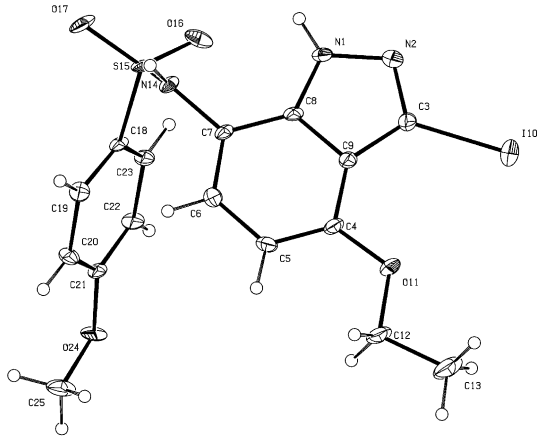


Figure 1. X-ray crystal structure of **2d**.

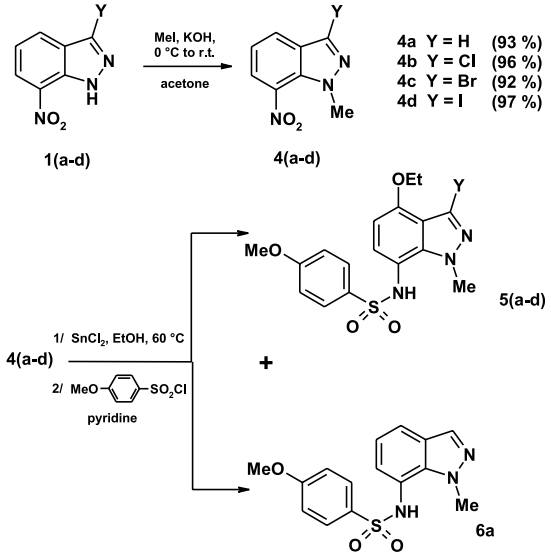
As it was noticed in Table 1, the nature of the substituent in the 3-position on the indazolyl ring in **1** led to different ratios of *N*-(4-ethoxy-1*H*-7-indazolyl)benzenesulfonamides **2**(**a**–**d**) and of corresponding 4-unsubstituted derivatives **3**(**a**–**d**). From the iodine-substituted **1d**, only the *N*-(4-ethoxy-1*H*-7-indazolyl)benzenesulfonamide **2d** was isolated, whereas **1a**, **1b** and **1c** afforded a mixture of compounds **2**(**a**–**c**) and **3**(**a**–**c**) (Table 1).

In the case of palladium-catalyzed reactions achieved with indazole, it was demonstrated the necessity of a protecting group in the *N*-1 position.[12,13] In order to optimize this sequence and considering that the presence of the NH group in 3-substituted-7-nitroindazoles **1**(**a**–**d**) could be the limiting factor, we decided to investigate the reactivity of the *N*-methyl-3-substituted-7-nitroindazoles **4**(**a**–**d**). Hence, the preliminary protection of compounds **1**(**a**–**d**) by iodomethane gave the corresponding 1-methyl-3-substituted-7-nitroindazoles **4**(**a**–**d**).[17,18] Then, compounds **4**(**a**–**d**) were reduced as previously described, and subsequent coupling was achieved with 4-methoxybenzenesulfonyl chloride. We noticed that **4**(**b**-**d**) afforded only the *N*-(4-ethoxy-3-halogeno-1-methyl-7-indazolyl)benzene-sulfonamides **5**(**b**–**d**) functionalized in position 4 (Table 2). Conversely, **4a** gave a mixture of the compound **5a** with the C(4)-nonsubstituted indazole (**6a**) (Scheme 3). In this last case, by comparing the **2/3** and **5/6** ratios, it is clear that S_NH is improved by *N*-alkylation of the *N*-1 position (see Tables 1 and 2).

Table 2. Effect of atom nature in 3-position on the synthesis of *N*-(4-ethoxy-1*H*-1-methyl-7-indazolyl)benzenesulfonamides **5** and C(4) nonsubstituted indazole **6**

Y	Time of reduction	Ratio **5/6**[a]	Yield of **5**[b]
H	4 h	67/33[c]	—
Cl	2 h	100/0	76%
Br	2 h 15 min	100/0	78%
I	1 h 50 min	100/0	80%

[a] Ratio determined by ^{1}H NMR spectroscopy of the reaction mixture.
[b] Compounds **5**(**b**–**d**) were isolated by flash chromatography.
[c] Compounds **5a** and **6a** were not separable by flash chromatography, global yield: 76%.



Scheme 3.

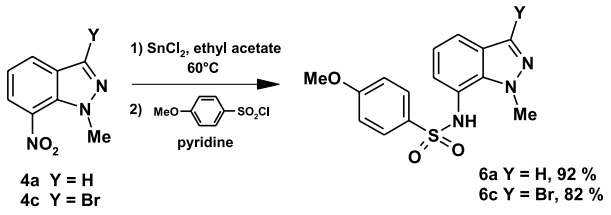
Finally, the reduction-protection of 7-nitro-indazole **4a** and 3-bromo-1-methyl-7-nitro-1*H*-indazole (**4c**) was performed with $SnCl_2$ by using ethyl acetate as solvent. As expected, we obtained exclusively the corresponding amines **6a** and **6c** in 92 and 82% yields, respectively. No trace of S_NH substitution was observed (Scheme 4).

These results could be related to the important role played by nitro groups of 7-nitro-indazole with regards to the introduction of the substituent in 4-position. Due to its

Table 1. Influence of the atom nature in the 3-position in **1**(**a**–**d**) on the synthesis of *N*-(4-ethoxy-1H-7-indazolyl)benzenesulfonamides **2**(**a**–**d**) and 4-unsubstituted derivatives **3**(**a**–**d**)

Y	Time of reduction (h)	Ratio **2/3**[a]	Yield of **2**[b]	Yield of **3**[b]	Yield of **2**+**3**[c] (%)
H	4	52/48	[c]	[c]	72
Cl	5	44/56	28%	37%	65
Br	9	63/37	56%	22%	78
I	2	100/0	76%	0%	76

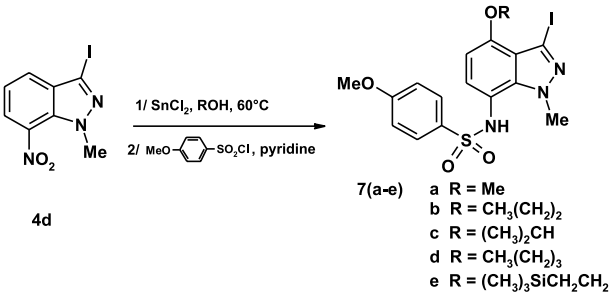
[a] Ratio determined by ^{1}H NMR spectroscopy of the reaction mixture.
[b] Yields of isolated products after flash chromatography.
[c] Compounds **2a** and **3a** were not separable by flash chromatography.



Scheme 4.

electron-withdrawing effect the nitro group in nitroarene activates in *ortho* and *para* for addition of nucleophilic agents.[19–23] Thus, the formation of the compound substituted by an ethoxy group in 4-position could be explained by the presence of the $C_2H_5O^-$ anion in the reaction mixture, followed by the S_NH on 7-nitroindazole. To study this hypothesis we performed reactions between compounds **1a** or **4a** and $C_2H_5O^-$ in ethanol at 60 °C. Unfortunately, no reaction was observed, and we isolated only the starting substances **1a** or **4a** in 92 and 95%, respectively. In addition to the mechanism proposed, we can supposed that the introduction of ethoxy group proceeds on the intermediate stage in reduction of NO_2 namely protonated hydroxylamine compound. Introduction of nucleophilic substituents via reactions of protonated arylhydroxylamines is a well known process.[24]

The reduction of the 3-iodo-7-nitroindazole **4d** was achieved with $SnCl_2$ in different alcohols, in order to introduce various alkoxy groups in the 4-position. In all cases, only compounds **7**(**a**–**e**) were obtained in good yields, illustrating the ability to introduce various alkoxy groups (Scheme 5). The results are collected in Table 3.



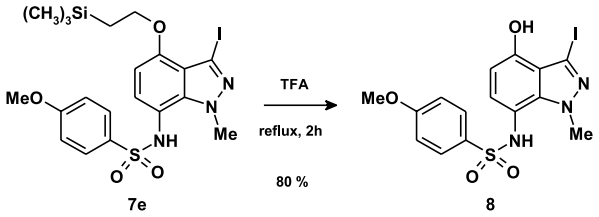
Scheme 5.

Table 3. Synthesis of *N*-(4-alkoxy-3-iodo-1-methyl-7-indazolyl)benzenesulfonamides **7**(**a**–**e**)

R	Time of reduction	Yield (%)[a]
CH_3	3 h	67
$CH_3(CH_2)_2$	1 h 30 min	77
$(CH_3)_2CH$	1 h	79
$CH_3(CH_2)_3$	1 h	75
$(CH_3)_3SiCH_2CH_2$	45 min	78

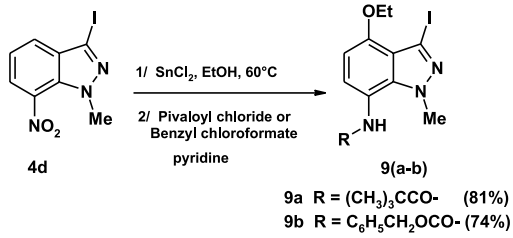
[a] Yields of isolated products after flash chromatography.

Moreover, it is noteworthy that the method developed here, permits, after simple transformation, to obtain other types of functionalization, which presents a potential utility for further developments in medicinal chemistry. For example, after a simple treatment in refluxing TFA, the ether function of compound **7e** was transformed into the corresponding phenol group (product **8**) in good yield (Scheme 6).



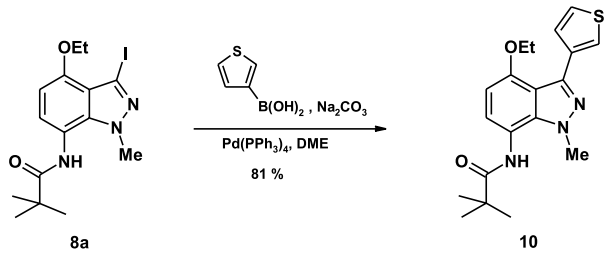
Scheme 6.

In order to use other secondary amine protecting groups, we also studied the coupling reaction with pivaloyl chloride or benzyl chloroformate achieved in pyridine, with **4d** as an example. The desired products **9**(**a**–**b**) were obtained in good yields (Scheme 7).



Scheme 7.

For deep investigations, we used the *N*-(4-ethoxy-3-iodo-1-methyl-1*H*-indazol-7-yl)-2,2-dimethyl-propionamide **9a** for Suzuki cross-coupling reaction with 3-thiopheneboronic acid in presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0). As expected, the sequence gave the *N*-(4-ethoxy-1-methyl-3-thiophen-3-yl-1*H*-indazol-7-yl)-2,2-dimethylpropionamide **10** in a very good yield (Scheme 8).



Scheme 8.

In conclusion, we present simple and efficient synthetic procedures of reduction-protection reaction developed to obtain bi- and tri-bisubstituted indazole derivatives. We determined experimental conditions to generate selectively 4-alkoxy-7-aminoprotected-indazoles by using various alcohols as solvent and different reactants in presence of $SnCl_2$. A selective way to 3-, 4-, 7-trisubstituted indazoles was developed through *N*-alkylation of *N*-1 position and by substitution of hydrogen in the 3-position by various halogens.

The reduction-protection conducted with ethyl acetate as solvent allowed us to generate exclusively 7-aminoprotected-indazoles. No trace of S_NH substitution was observed. Finally, potentiality of the functionalization ability in the

3-position of 3-iodoindazolylbenzenamide by a Suzuki cross-coupling reaction with various aromatic derivatives was established. This appears to be a general method to prepare new building blocks of interest in medicinal chemistry.

3. Experimental

3.1. General

Melting points were determined with Büchi SMP-20 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) using tetramethylsilane as the internal standard, multiplicities were determined by the DEPT 135 sequence. Chemical shifts were reported in parts per million (ppm, δ units). Coupling constants were reported in units of hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet, t, triplet. IR spectra were obtained on Perkin-Elmer Paragon 1000 PC FT-IR. Infrared spectra were recorded using NaCl film or KBr pellets. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. All commercial solvents were used without further purification. The following solvents and reagents have been abbreviated: dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), methanol (MeOH), trifluoroacetic acid (TFA), ethylene glycol dimethyl ether (DME) and petroleum ether (EP). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F$_{254}$ precoated plates. Visualization was made with ultraviolet light.

3.2. Crystal structure analysis of 2d

The crystal structure of compound **2d** has been determined by single-crystal X-ray diffraction techniques and refined by full-matrix least-squares procedures, to give a final R value of 0.0479. The crystals are triclinic, space group P-1, with $a=7.924(1)$ Å, $b=9.130(2)$ Å, $c=12.3056(1)$ Å, $\alpha=90.23(2)°$, $\beta=92.89(1)°$, $\gamma=96.71(2)°$, and $Z=2$. A crystal $0.25\times0.10\times0.05$ mm was chosen. The data were collected on a CAD4 Enraf-Nonius diffractometer with graphite monochromatized Cu Kα radiation. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC), UK, as Supplementary Materials.[25a] The position of non-H atoms were determined by the program SHELXS[25b] and the position of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined.

3.2.1. 7-Nitro-1*H*-indazole (1a). This compound was prepared according to method described in the lit.[26] (65% yield): mp 185–186 °C (lit.[26] mp 186 °C). IR (KBr, cm^{-1}): 3180 (NH), 1620 (CN), 1500, 1290 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.32 (t, $J=7.8$ Hz, 1H), 8.32 (d, $J=7.8$ Hz, 1H), 8.35 (d, $J=7.8$ Hz, 1H), 8.41 (s, 1H), 13.94 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 120.2, 123.5, 129.9, 135.6 (4CH), 127.1, 131.9, 132.1 (3C). MS $m/z=164$ [M+1]$^+$.

3.2.2. 3-Chloro-7-nitro-1*H*-indazole (1b). 7-Nitroindazole (1 g, 6.13 mmol) was dissolved in 25 mL of MeOH and 2 N aqueous sodium hydroxide (20 mL), and then sodium hypochlorite (6 mL, 98.2 mmol) was added to the solution. The mixture was refluxed for 1 h. After cooling, the solution acidified with acetic acid. The solid was filtered, washed with water and dried in vacuo to give a yellow solid (98% yield): mp 167–168 °C (lit.[23] mp 166–168 °C). IR (KBr, cm^{-1}): 3210 (NH), 1610 (CN), 1520, 1310 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.45 (t, $J=7.8$ Hz, 1H), 8.20 (d, $J=7.8$ Hz, 1H), 8.44 (d, $J=7.8$ Hz, 1H), 14.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 121.3, 125.1, 127.8 (3CH), 123.4, 132.5, 133.2, 134.7 (4C). MS $m/z=198$ (^{35}Cl) [M+1]$^+$, 200 (^{37}Cl) [M+3]$^+$.

3.2.3. 3-Bromo-7-nitro-1*H*-indazole (1c). To a solution of 7-nitroindazole (1 g, 6.13 mmol), (1.2 g, 6.74 mmol) of *N*-bromosuccinimide in acetonitrile was heated at reflux for 30 min. The solvent was removed in vacuo and the residue was taken up in 50 mL of ethyl acetate, washed with 2× 100 ml of water, 100 mL of 10% sodium thiosulfate, brine and then dried. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane to provide 1.3 g (90%) of **3** as a yellow solid: mp 175–176 °C (lit.[18] mp 176–178 °C). IR (KBr, cm^{-1}): 3180 (NH), 1620 (CN), 1500, 1310 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.46 (t, $J=7.9$ Hz, 1H); 8.13 (d, $J=7.9$ Hz, 1H); 8.45 (d, $J=7.9$ Hz, 1H), 14.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 121.3, 124.9, 128.3, (3CH), 123.1, 126.1, 133.3, 133.1 (4C). MS $m/z=242$ (^{79}Br) [M+1]$^+$, 244 (^{81}Br) [M+3]$^+$.

3.2.4. 3-Iodo-7-nitro-1*H*-indazole (1d). Iodine (3.1 g, 12.26 mmol) and potassium hydroxide pellets (1.28 g, 23 mmol) were successively added into a DMF solution (60 mL) of 7-nitroindazole (1 g, 6.13 mmol) at room temperature under stirring. After 1 h, the reaction mixture was poured into 10% aqueous NaHSO$_3$ (200 mL) and extracted with Et$_2$O (2×150 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$ and the solvent evaporated to give a light yellow solid (95% yield): mp 188–189 °C. IR (KBr, cm^{-1}): 3110 (NH), 1600 (CN), 1520, 1300 (NO$_2$). ^{1}H NMR (DMSO-d_6) δ 7.44 (t, $J=7.8$ Hz, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 8.46 (d, $J=7.8$ Hz, 1H), 14.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 120.9, 124.6, 130.8 (3CH), 96.8, 130.8, 132.1, 132.6 (4C). MS $m/z=290$ [M+1]$^+$. Anal. Calcd for C$_7$H$_4$IN$_3$O$_2$; C, 29.09; H, 1.39; I, 43.91; N, 14.54. Found: C, 29.16; H, 1.53; I, 44.08; N, 14.46.

3.3. General method for alkylation of 7-nitroindazole derivatives

To a solution of 7-nitroindazole derivatives (6.13 mmol) in acetone (15 mL) cooled at 0 °C was added potassium hydroxide (9.2 mmol). After 15 mn at 0 °C, iodomethane (6.13 mmol) was added dropwise. Upon disappearance of the starting material as indicated by TLC, the resulting mixture was evaporated. The crude material was dissolved with EtOAc (50 mL), washed with water and brine, dried over MgSO$_4$ and the solvent removed in vacuo to give the corresponding compounds. Spectral data for representative compounds are as follows:

3.3.1. 1-Methyl-7-nitro-1*H*-indazole (4a). Chromatography using EtOAc/hexane give a yellow solid (93% yield): mp 99–100 °C (lit.[26] mp 98 °C). IR (KBr, cm^{-1}): 1620 (CN), 1510, 1290 (NO_2). ^1H NMR (DMSO-d_6) δ 4.16 (s, 3H, CH_3), 7.40 (t, $J=7.7$ Hz, 1H), 7.90 (d, $J=7.7$ Hz, 1H), 8.29 (d, $J=7.7$ Hz, 1H), 8.32 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 40.3 (NCH_3), 120.1, 124.5, 128.6, 134.3 (4CH), 125.4, 128.4, 130.4 (3C). MS $m/z=178$ $[M+1]^+$.

3.3.2. 3-Chloro-1-methyl-7-nitro-1*H*-indazole (4b). This compound was similarly prepared from 3-chloro-7-nitroindazole in 96% yield as a yellow solid: mp 150–151 °C (lit.[18] mp 148–150 °C). IR (KBr, cm^{-1}): 1615 (CN), 1490, 1300 (NO_2). ^1H NMR (DMSO-d_6) δ 4.11 (s, 3H, CH_3), 7.42 (t, $J=7.8$ Hz, 1H), 8.11 (d, $J=7.8$ Hz, 1H), 8.28 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.9 (NCH_3), 121.2, 126.1, 126.5 (3CH), 124.6, 132.0, 132.8, 135.1 (4C). MS $m/z=212$ (^{35}Cl) $[M+1]^+$, 214 (^{37}Cl) $[M+3]^+$.

3.3.3. 3-Bromo-1-methyl-7-nitro-1*H*-indazole (4c). This compound was similarly prepared from 3-bromo-7-nitroindazole in 92% yield as a yellow solid: mp 158–159 °C (lit.[18] mp 160–162 °C). IR (KBr, cm^{-1}): 1610 (CN), 1520, 1310 (NO_2). ^1H NMR (DMSO-d_6) δ 4.22 (s, 3H, CH_3), 7.45 (t, $J=7.8$ Hz, 1H), 8.02 (d, $J=7.8$ Hz, 1H), 8.27 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 41.4 (NCH_3), 121.8, 126.6, 126.7 (3CH), 122.0, 127.8, 128.8, 130.1 (4C). MS $m/z=256$ (^{79}Br) $[M+1]^+$, 258 (^{81}Br) $[M+3]^+$.

3.3.4. 3-Iodo-1-methyl-7-nitro-1*H*-indazole (4d). This compound was similarly prepared from 3-iodo-7-nitroindazole in 97% as a yellow solid: mp 171–172 °C. IR (KBr, cm^{-1}): 1610 (CN), 1530, 1300 (NO_2). ^1H NMR (DMSO-d_6) δ 4.16 (s, 3H, CH_3), 7.40 (t, $J=7.7$ Hz, 1H), 7.9 (d, $J=7.7$ Hz, 1H), 8.29 (d, $J=7.7$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.8 (NCH_3), 120.8, 125.7, 128.6 (3CH), 95.1, 131.4, 132.1, 134.7 (4C). MS $m/z=304$ $[M+1]^+$. Anal. Calcd for $C_8H_6IN_3O_2$; C, 31.71; H, 2.00; I, 41.87; N, 13.87. Found: C, 31.80; H, 2.13; I, 41.77; N, 13.72.

3.4. Synthesis of compounds 2(a–d) and 3(a–d)

General method. A mixture of 3-halogeno-7-nitroindazole **1**(**a**–**d**) (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of absolute ethanol is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methoxybenzenesulfonyl chloride (0.15 g, 0.72 mmol) at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.4.1. *N*-(3-Chloro-4-ethoxy-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2b). Rose solid, yield 28%: mp 104–105 °C. IR (KBr, cm^{-1}): 3342, 3229 (NH), 1596 (CN), 1341, 1160 (SO_2), 1244, 1025 (ArOCH). ^1H NMR (acetone-d_6) δ 1.43 (t, $J=6.9$ Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.12 (q, 2H, $J=6.9$ Hz, CH_2O), 6.38 (d, $J=8.1$ Hz, 1H), 6.76 (d, $J=8.1$ Hz, 1H), 7.00 (d, $J=8.9$ Hz, 2H), 7.62 (d, $J=8.9$ Hz, 2H), 8.52 (s, 1H, NH), 12.08 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 56.0 (OCH_3), 64.7 (CH_2O), 101.7, 114.8, 126.5, 130.3 (4CH), 113.1, 114.3, 131.8, 133.4, 141.2, 152.6, 163.9 (7C). MS $m/z=382$ (^{35}Cl) $[M+1]^+$, 384 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{16}H_{16}ClN_3O_4S$; C, 50.33; H, 4.22; Cl, 9.29; N, 11.00, S, 8.40. Found: C, 50.30; H, 4.16; Cl, 9.45; N, 11.17, S, 8.49.

3.4.2. *N*-(3-Bromo-4-ethoxy-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2c). Violet solid, yield 56%: mp 114–115 °C. IR (KBr, cm^{-1}): 3342, 3142 (NH), 1596 (CN), 1342, 1160 (SO_2), 1258, 1018 (ArOCH). ^1H NMR (acetone-d_6) δ 1.44 (t, $J=7.2$ Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.12 (q, $J=7.2$ Hz, 2H, CH_2O), 6.38 (d, $J=8.1$ Hz, 1H), 6.76 (d, $J=8.1$ Hz, 1H), 6.99 (d, $J=9.1$ Hz, 2H), 7.61 (d, $J=9.1$ Hz, 2H), 8.53 (s, 1H, NH), 12.25 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 56.0 (OCH_3), 64.7 (CH_2O), 101.8, 114.8, 126.4, 130.3 (4CH), 109.7, 114.2, 131.8, 152.5, 153.0, 154.8, 164.0 (7C). MS $m/z=426$ (^{79}Br) $[M+1]^+$, 428 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{16}H_{16}BrN_3O_4S$; C, 45.08; H, 3.78; Br, 18.74; N, 9.86, S, 7.52. Found: C, 45.20; H, 3.70; Br, 18.60; N, 10.09, S, 7.66.

3.4.3. *N*-(3-Chloro-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (3b). Colorless solid, yield 37%: mp 201–202 °C. IR (KBr, cm^{-1}): 3338, 3242 (NH), 1596 (CN), 1337, 1170 (SO_2), 1254, 1017 (ArOCH). ^1H NMR (DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 6.95 (d, $J=7.5$ Hz, 1H), 7.01 (dd, $J=7.5$, 7.8 Hz, 1H), 7.07 (d, $J=8.7$ Hz, 2H), 7.24 (d, $J=7.8$ Hz, 1H), 7.67 (d, $J=8.7$ Hz, 2H), 10.02 (s, 1H, NH), 13.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 55.6 (OCH_3), 114.3, 115.7, 120.0, 121.8, 129.2 (5CH), 120.1, 121.5, 130.5, 132.5, 136.2, 162.6 (6C). MS $m/z=338$ (^{35}Cl) $[M+1]^+$, 340 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{14}H_{12}ClN_3O_3S$; C, 49.78; H, 3.58; Cl, 10.50; N, 12.44; S, 9.49. Found: C, 49.86; H, 3.44; Cl, 10.75; N, 12.40; S, 9.39.

3.4.4. *N*-(3-Bromo-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (3c). Colorless solid, yield 22%: mp 193–194 °C. IR (KBr, cm^{-1}): 3317, 3228 (NH), 1596 (CN), 1340, 1146 (SO_2), 1252, 1002 (ArOCH). ^1H NMR (acetone-d_6) δ 3.83 (s, 3H, OCH_3), 7.01 (d, $J=9.1$ Hz, 2H), 7.10 (d, $J=7.2$ Hz, 1H), 7.43 (dd, $J=7.2$, 8.8 Hz, 1H), 7.53 (d, $J=8.8$ Hz, 1H), 7.66 (d, $J=9.1$ Hz, 2H), 8.90 (s, 1H, NH), 12.33 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 56.0 (OCH_3), 115.0, 118.1, 122.7, 122.8, 130.3 (5CH), 114.4, 122.2, 125.4, 126.7, 131.6, 164.1 (6C). MS $m/z=382$ (^{79}Br) $[M+1]^+$, 384 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{14}H_{12}BrN_3O_3S$; C, 43.99; H, 3.16; Br, 20.90; N, 10.99; S, 8.39. Found: C, 43.90; H, 3.25; Br, 20.85; N, 11.18; S, 8.21.

3.4.5. *N*-(4-Ethoxy-3-iodo-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (2d). Violet solid, yield 76%: mp 171–172 °C. IR (KBr, cm^{-1}): 3304, 3260 (NH), 1600 (CN), 1338, 1156 (SO_2), 1270, 1024 (ArOCH). ^1H NMR (acetone-d_6) δ 1.38 (t, $J=6.9$ Hz, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.05 (q, $J=6.9$ Hz, 2H, OCH_2), 6.33 (d, $J=8.4$ Hz, 1H), 6.58 (d, $J=8.4$ Hz, 1H), 7.03 (d, $J=8.7$ Hz, 2H), 7.60 (d, $J=8.7$ Hz, 2H), 9.56 (s, 1H, NH), 13.20 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.3 (CH_3), 55.6 (OCH_3), 63.5 (CH_2O), 100.8, 114.1, 123.8, 129.1 (4CH), 88.2, 112.9, 116.9, 130.8,

138.9, 150.4, 162.3 (7C). MS $m/z=474$ $[M+1]^+$. Anal. Calcd for $C_{16}H_{16}IN_3O_4S$; C, 40.60; H, 3.41; I, 26.81; N, 8.88; S, 6.77. Found C, 40.42; H, 3.66; I, 26.76; N, 8.94; S, 6.59.

3.5. Synthesis of 5(a–d) and 6a

These compounds were prepared from 3-halogeno-1-methyl-7-nitroindazole **4**(**a**–**d**) by using the same procedure applied to **1**(**a**–**d**).

3.5.1. *N*-(3-Chloro-4-ethoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5b). Colorless solid, yield 76%: mp 168–169 °C. IR (KBr, cm^{-1}): 3261 (NH), 1590 (CN), 1340, 1154 (SO_2), 1260, 1054 (ArOCH). ^1H NMR (acetone-d_6) δ 1.39 (t, $J=6.9$ Hz, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.08 (q, $J=6.9$ Hz, 2H, CH_2O), 4.20 (s, 3H, NCH_3), 6.28 (d, $J=8.1$ Hz, 1H), 6.43 (d, $J=8.1$ Hz, 1H), 7.04 (d, $J=9.1$ Hz, 2H), 7.59 (d, $J=9.1$ Hz, 2H), 8.39 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.2 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.4, 114.9, 130.5, 130.6 (4CH), 113.8, 114.3, 126.7, 132.2, 141.1, 153.6, 164.1 (7C). MS $m/z=396$ (^{35}Cl) $[M+1]^+$, 398 (^{37}Cl) $[M+3]^+$. Anal. Calcd for $C_{17}H_{18}ClN_3O_4S$; C, 51.58; H, 4.58; Cl, 8.96; N, 10.61; S, 8.10. Found: C, 51.66; H, 4.48; Cl, 9.11; N, 10.51; S, 8.23.

3.5.2. *N*-(3-Bromo-4-ethoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5c). Colorless solid, yield 78%: mp 158–159 °C. IR (KBr, cm^{-1}): 3240 (NH), 1590 (CN), 1332, 1146 (SO_2), 1254, 1060 (ArOCH). ^1H NMR (acetone-d_6) δ 1.40 (t, $J=6.9$ Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.08 (q, $J=6.9$ Hz, 2H, CH_2O), 4.23 (s, 3H, NCH_3), 6.28 (d, $J=8.1$ Hz, 1H), 6.43, (d, $J=8.1$ Hz, 1H), 7.04 (d, $J=9.1$ Hz, 2H), 7.60 (d, $J=9.1$ Hz, 2H), 8.38 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.3 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.5 114.9, 130.3, 130.6 (4CH), 113.6, 116.4, 117.3, 132.1, 141.0, 153.5, 164.0 (7C). MS $m/z=440$ (^{79}Br) $[M+1]^+$, 442 (^{81}Br) $[M+3]^+$. Anal. Calcd for $C_{17}H_{18}BrN_3O_4S$; C, 46.37; H, 4.12; Br, 18.15; N, 9.54; S, 7.28. Found: C, 46.44; H, 4.03; Br, 18.32; N, 9.59; S, 7.40.

3.5.3. *N*-(4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (5d). Colorless solid, yield 80%: mp 183–184 °C. IR (KBr, cm^{-1}): 3290 (NH), 1590 (CN), 1332, 1154 (SO_2), 1260, 1018 (ArOCH). ^1H NMR (acetone-d_6) δ 1.47 (t, $J=7.2$ Hz, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.12 (q, $J=7.2$ Hz, 2H, CH_2O), 4.30 (s, 3H, NCH_3), 6.30 (d, $J=8.1$ Hz, 1H), 6.44 (d, $J=8.1$ Hz, 1H), 7.07 (d, $J=8.7$ Hz, 2H), 7.62 (d, $J=8.7$ Hz, 2H), 8.42 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.7 (CH_3), 39.3 (NCH_3), 56.1 (OCH_3), 64.8 (CH_2O), 101.4, 114.9, 130.0, 130.6 (4CH), 85.5, 113.4, 126.7, 132.2, 143.2, 153.2, 164.0 (7C). MS $m/z=488$ $[M+1]^+$. Anal. Calcd for $C_{17}H_{18}IN_3O_4S$; C, 41.90; H, 3.72; I, 26.04; N, 8.62; S, 6.58. Found: C, 41.96; H, 3.88; I, 26.00; N, 8.49; S, 6.43.

3.6. General procedure for the preparation of compounds 6a and 6c

A mixture of 3-halogeno-7-nitroindazole **4a**, **c** (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of ethyl acetate is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methoxybenzenesulfonyl chloride (0.15 g, 0.72 mmol) at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.6.1. 4-Methoxy-*N*-(1-methyl-1*H*-7-indazolyl)-benzenesulfonamide (6a). Colorless solid, yield 92%: mp 163–164 °C. IR (KBr, cm^{-1}): 3274 (NH), 1598 (CN), 1304, 1160 (SO_2), 1258, 1023 (ArOCH). ^1H NMR (DMSO-d_6) δ 3.48 (s, 3H, OCH_3), 4.23 (s, 3H, NCH_3), 6.43 (d, $J=7.5$ Hz, 1H), 6.90 (dd, $J=7.5$, 7.9 Hz, 1H), 7.10 (d, $J=8.5$ Hz, 2H), 7.59 (d, $J=8.5$ Hz, 2H), 7.65 (d, $J=7.9$ Hz, 1H), 8.06 (s, 1H), 9.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 38.7, (NCH_3) 55.7 (OCH_3), 114.0, 114.3, 120.2, 120.6, 123.1, 125.4, 127.6, 129.6, 133.7, 137.8, 162.8. MS $m/z=318$ $[M+1]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3S$; C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.58; H, 4.93; N, 13.36; S, 9.96.

3.6.2. *N*-(3-Bromo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (6c). Colorless solid, yield 82%: mp 184–185 °C. IR (KBr, cm^{-1}): 3440, 3232 (NH), 1644 (CN), 1318, 1154 (SO_2), 1278, 1076 (ArOCH). ^1H NMR (acetone-d_6) δ 3.90 (s, 3H, OCH_3), 4.33 (3H, NCH_3), 6.66 (dd, $J=1.6$, 7.2 Hz, 1H), 6.99–7.09 (m, 3H), 7.52 (dd, $J=1.6$, 7.2 Hz, 1H), 7.62 (d, $J=9.1$ Hz, 2H), 8.71 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 39.6 (NCH_3), 56.2 (OCH_3), 115.0, 119.8, 120.5, 121.7, 122.2 (5CH), 126.8, 130.7, 131.9, 139.4, 164.2 (5C). MS $m/z=396$ (^{79}Br) $[M+1]^+$, 398 (^{81}Br) $[M+1]^+$. Anal. Calcd for $C_{15}H_{14}BrN_3O_3S$; C, 45.47; H, 3.56; Br, 20.16; N, 10.60; S, 8.09. Found: C, 45.38; H, 3.69; Br, 20.04; N, 10.77; S, 8.23.

3.7. Synthesis of 7(a–e)

These compounds were synthesized as described for **1**(**a**–**d**) by using the appropriate alcohol.

3.7.1. *N*-(3-Iodo-4-methoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7a). Green solid, yield 67%: mp 203–204 °C. IR (KBr, cm^{-1}): 3276 (NH), 1590 (CN), 1326, 1154 (SO_2), 1254, 1060 (ArOCH). ^1H NMR (acetone-d_6) δ 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.19 (s, 3H, NCH_3), 6.33 (d, $J=8.5$ Hz, 1H), 6.37 (d, $J=8.5$ Hz, 1H), 7.19 (d, $J=8.7$ Hz, 2H), 7.58 (d, $J=8.7$ Hz, 2H), 9.56 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 35.9 (NCH_3), 55.6, 55.7 (2OCH_3), 100.4, 114.3, 128.4, 129.2 (4CH), 86.4, 112.7, 118.7, 131.1, 139.1, 152.1, 162.4 (7C). MS $m/z=474$ $[M+1]^+$. Anal. Calcd for $C_{16}H_{16}IN_3O_4S$; C, 40.60; H, 3.41; I, 26.81; N, 8.88; S, 6.77. Found: C, 40.54; H, 3.61; I, 26.92; N, 8.70; S, 6.50.

3.7.2. *N*-(3-Iodo-4-propoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7b). Colorless solid, yield 77%: mp 139–140 °C. IR (KBr, cm^{-1}): 3226 (NH), 1582

(CN), 1326, 1146 (SO_2), 1254, 1026 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.10 (t, J=7.5 Hz, 3H, CH_3), 1.75–1.81 (m, 2H, CH_2); 3.84 (s, 3H, OCH_3), 3.97 (t, J=6.3 Hz, 2H, CH_2O), 4.18 (s, 3H, NCH_3), 6.29 (d, J=7.9 Hz, 1H), 6.34 (d, J=7.9 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 9.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 10.8 (CH_3), 38.4 (NCH_3), 21.8 (CH_2), 55.6 (OCH_3), 69.4 (CH_2O), 112.2, 114.4, 128.6, 129.2 (4CH), 86.6, 100.7, 114.7, 118.5, 131.0, 151.7, 162.4 (7C). MS m/z=502 $[M+1]^+$. Anal. Calcd for $C_{18}H_{20}IN_3O_4S$; C, 43.12; H, 4.02; I, 25.31; N, 8.38; S, 6.40. Found: C, 43.01; H, 4.23; I, 25.55; N, 8.19; S, 6.56.

3.7.3. *N*-(3-Iodo-4-isopropoxy-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7c). Colorless solid, yield 79%: mp 101–102 °C. IR (KBr, cm^{-1}): 3018 (NH), 1582 (CN), 1326, 1154 (SO_2), 1218, 1082 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.37 (d, J=6.0 Hz, 6H, $2CH_3$), 3.90 (s, 3H, OCH_3), 4.29 (s, 3H, NCH_3), 4.69–4.78 (m, 1H, $(CH_3)_2CH$–O), 6.33 (d, J=8.3 Hz, 1H), 6.44 (d, J=8.3 Hz, 1H), 7.08 (d, J=8.9 Hz, 2H), 7.63 (d, J=8.9 Hz, 2H), 8.41 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 21.5, 22.1 ($2CH_3$), 39.3 (NCH_3), 56.1 (OCH_3), 71.5 (CHO), 102.5, 114.9, 126.7, 130.0, 130.6 (5CH), 85.7, 113.0, 120.4, 132.3, 140.6, 152.1, 164.0 (7C). MS m/z=502 $[M+1]^+$. Anal. Calcd for $C_{18}H_{20}IN_3O_4S$; C, 43.12; H, 4.02; I, 25.31; N, 8.38; S, 6.40. Found: C, 43.01; H, 4.23; I, 25.55; N, 8.19; S, 6.56.

3.7.4. *N*-(4-Butoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxybenzenesulfonamide (7d). Colorless solid, yield 75%: mp 91–92 °C. IR (KBr, cm^{-1}): 3228 (NH), 1590 (CN), 1332, 1146 (SO_2), 1234, 1060 (ArOCH). ^{1}H NMR (acetone-d_6) δ 0.94 (t, J=7.2 Hz, 3H, CH_3), 1.52–1.61 (m, 2H, CH_2), 1.73–1.77 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.01 (t, J=6.6 Hz, 2H, CH_2O), 4.18 (s, 3H, NCH_3), 6.31 (d, J=8.3 Hz, 1H), 6.35 (d, J=8.3 Hz, 1H), 7.10 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 9.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 13.7 (CH_3), 38.4 (NCH_3), 18.8, 30.5 ($2CH_2$), 55.6 (OCH_3), 67.5 (CH_2O), 100.7, 112.2, 114.2, 129.2 (4CH), 119.5, 125.4, 128.6, 131.1, 139.0, 151.6, 162.4 (7C). MS m/z=516 $[M+1]^+$. Anal. Calcd for $C_{19}H_{22}IN_3O_4S$; C, 44.28; H, 4.30; I, 24.62; N, 8.15; S, 6.22. Found: C, 44.45; H, 4.21; I, 24.43; N, 8.38; S, 6.41.

3.7.5. *N*-(3-Iodo-4-(2-trimethylsilanyl-ethoxy)-1-methyl-1*H*-7-indazolyl)-4-methoxybenzene sulfonamide (7e). Colorless solid yield 78%: mp 172–173 °C. IR (KBr, cm^{-1}): 3254 (NH), 1590 (CN), 1334, 1146 (SO_2), 1246, 1040 (ArOCH). ^{1}H NMR (acetone-d_6) δ 0.10 (s, 9H, CH_3), 1.29 (t, J=8.5 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.19 (t, J=8.5 Hz, 2H, CH_2), 4.29 (s, 3H, NCH_3), 6.33 (d, J=8.1 Hz, 1H), 6.44 (d, J=8.1 Hz, 1H), 7.08 (d, J=8.9 Hz, 2H), 7.63 (d, J=8.9 Hz, 2H), 8.41 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ −1.3 ($3CH_3$), 18.0 (CH_2), 39.3 (NCH_3), 56.1 (OCH_3), 66.8 (CH_2O), 101.6, 114.9, 130.0, 130.6 (4CH), 85.5, 113.2, 119.8, 132.2, 140.4, 153.2, 164.0 (7C). MS m/z=560 $[M+1]^+$. Anal. Calcd for $C_{20}H_{26}IN_3O_4SSi$; C, 42.94; H, 4.68; I, 22.68; N, 7.51; S, 5.73, Si, 5.02. Found: C, 42.77; H, 4.51; I, 22.59; N, 7.73; S, 5.90, Si, 4.96.

3.7.6. *N*-(4-Hydroxy-3-iodo-1-methyl-1*H*-7-indazolyl)-4-methoxy-benzenesulfonamide (8). Compound **7e** (100 mg, 0.18 mmol) was dissolved in 5 mL of trifluoroacetic acid. The mixture was refluxed for 2 h. After cooling, solvent was removed. The crude material was dissolved with EtOAc, washed with sodium hydrogen carbonate and brine, dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with EtOAc/EP to provide 80% of **8** as colorless solid: mp 227–228 °C. IR (KBr, cm^{-1}): 3310 (OH), 3246 (NH), 1602 (CN), 1344, 1143 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.89 (s, 3H, OCH_3), 4.30 (s, 3H, NCH_3), 6.24 (d, J=7.9 Hz, 1H), 6.35 (d, J=7.9 Hz, 1H), 7.06 (d, J=8.9 Hz, 2H), 7.62 (d, J=8.9 Hz, 2H), 8.34 (s, 1H, NH), 9.26 (s, 1H, OH). ^{13}C NMR (acetone-d_6) δ 39.2 (NCH_3), 56.1 (OCH_3), 104.9, 114.8, 130.0, 130.6 (4CH), 85.5, 112.4, 119.7, 132.2, 140.9, 151.9, 163.9 (7C). SM: m/z=460 $[M+1]^+$. Anal. Calcd for $C_{15}H_{14}IN_3O_4S$; C, 39.23; H, 3.07; I, 27.63; N, 9.15; S, 6.98. Found: C, 39.36; H, 3.28; I, 27.43; N, 9.05; S, 6.84.

3.8. General procedure for the preparation of compounds 9(a,b)

A mixture of 3-halogeno-7-nitroindazole **1**(**a**–**d**) (0.66 mmol) and anhydrous $SnCl_2$ (0.62 g, 3.3 mmol) in 25 mL of absolute ethanol is heated at 60 °C. After reduction, the starting material has disappeared and the solution is allowed to cool down. The pH is made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before being extracted with ethyl acetate. The organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in CH_2Cl_2 (5 mL) and then Et_3N (1.5 equiv) and trimethylacethyl chloride(1.1 equiv) or benzyl chloroformate (1.1 equiv) were added. The reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/EP).

3.8.1. *N*-(4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-2,2-dimethyl-propionamide (9a). Colorless solid, yield 81%: mp 161–162 °C. IR (KBr, cm^{-1}): 3268 (NH), 1640 (CO), 1602 (CN), 1246, 1016 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.28 (s, 9H, $3CH_3$), 1.45 (t, J=6.9 Hz, 3H, CH_3), 4.04 (s, 3H, NCH_3), 4.12 (q, J=6.9 Hz, 2H, OCH_2), 6.40 (d, J=8.1 Hz, 1H), 6.92 (d, J=8.1 Hz, 1H), 8.57 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 27.8 ($3CH_3$), 38.3 (NCH_3), 39.5 ($C(CH_3)_3$), 64.6 (OCH_2), 101.6, 128.6 (2CH), 85.1, 115.5, 119.6, 139.8, 152.1 (5C), 179.2 (CO). SM m/z=402 $[M+1]^+$. Anal. Calcd for $C_{15}H_{20}IN_3O_2$; C, 44.90; H, 5.02; I, 31.63; N, 10.47. Found: C, 44.97; H, 4.89; I, 31.44; N, 10.56.

3.8.2. (4-Ethoxy-3-iodo-1-methyl-1*H*-7-indazolyl)-carbamic acid benzyl ester (9b). Colorless solid, yield 74%: mp 167–168 °C. IR (KBr, cm^{-1}): 3254 (NH), 1682 (CO), 1604 (CN), 1240, 1054 (ArOCH). ^{1}H NMR (acetone-d_6) δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 4.03 (s, 3H, NCH_3), 4.14 (q, J=7.2 Hz, 2H, OCH_2), 5.14 (s, 2H, CH_2), 6.44 (d, J=8.1 Hz, 1H), 7.08 (d, J=8.1 Hz, 1H), 7.34 (m, 5H), 8.25 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 38.1 (NCH_3), 64.7 (OCH_2), 67.2 (OCH_2), 101.7, 114.9, 121.4, 128.8, 129.2 (5CH), 85.4, 119.8, 138.0, 139.7, 152.4, 158.6 (6C), 177.1 (CO). SM m/z=452 $[M+1]^+$. Anal. Calcd for $C_{18}H_{18}IN_3O_3$; C, 47.91; H, 4.02; I, 28.12; N, 9.31. Found: C, 47.86; H, 3.92; I, 28.30; N, 9.15.

3.8.3. *N*-(4-Ethoxy-1-methyl-3-thiophen-3-yl-1*H*-7-indazolyl)-2,2-dimethyl-propionamide (10). Under argon atmosphere, a mixture of **9a** (100 mg, 0.24 mmol) and 3-thiopheneboronic acid ($m=40$ mg, 0.28 mmol) in DME (8 mL), sodium carbonate (80 mg, 0.72 mmol) in H_2O (4 mL) was added followed by the addition of $Pd(PPh_3)_4$ (30 mg, 0.043 mmol). The reaction mixture was refluxed with vigorous stirring for 2 h. It was then evaporated to dryness under reduced pressure. Ethyl acetate (5 mL) was added; the organic phase was washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (EtOAc/EP) yielding 72 mg (81%) of **10** as a colorless solid: mp 132–133 °C. IR (KBr, cm^{-1}): 3320 (NH), 1644 (CO), 1602 (CN), 1258, 1048 (ArOCH). ^1H NMR (acetone-d_6) δ 1.36 (s, 9H, $3CH_3$), 1.48 (t, $J=7.2$ Hz, 3H, CH_3), 4.13 (s, 3H, NCH_3), 4.20 (q, $J=7.2$ Hz, 2H, CH_2O), 6.98 (d, $J=8.1$ Hz, 1H), 7.22 (d, $J=8.1$ Hz, 1H), 7.58 (dd, $J=6.2$, 4.0 Hz, 1H), 7.90 (d, $J=6.2$ Hz, 1H), 8.34 (d, $J=4.0$ Hz, 1H), 8.60 (s, 1H, NH). ^{13}C NMR (acetone-d_6) δ 14.8 (CH_3), 27.9 ($3CH_3$), 38.2 (NCH_3), 39.6 ($C(CH_3)_3$) 64.7 (OCH_2), 101.2, 124.7, 126.7, 128.1, 129.7 (5CH), 114.7, 115.9, 135.8, 141.1, 153.0 (5C), 179.1 (CO). SM $m/z=358$ $[M+1]^+$. Anal. Calcd for $C_{19}H_{23}IN_3O_2S$; C, 63.84; H, 6.49; N, 11.75, S, 8.97. Found: C, 63.78; H, 6.30; N, 11.96, S, 9.18.

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