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ALKYLATION AND REDUCTION OF *N*-ALKYL-4-NITROINDAZOLES WITH ANHYDROUS $SnCl_2$ IN ETHANOL: SYNTHESIS OF NOVEL 7-ETHOXY-*N*-ALKYLINDAZOLE DERIVATIVES

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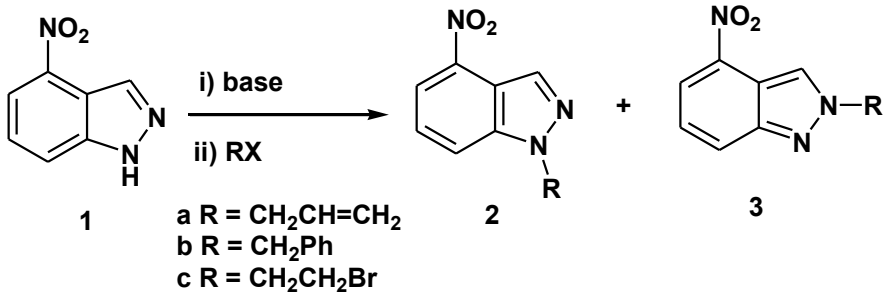
Abstract – New series of indazoles substituted at the *N*-1 and *N*-2 positions and their 7-ethoxy derivatives have been synthesis starting from alkylation of 4-nitroindazole and reduction of alkyl-nitro-derivatives with anhydrous $SnCl_2$ in ethanol. The structures of the products obtained were characterized using ^{1}H NMR, ^{13}C NMR, MS spectrometry and elemental analysis; the NMR spectroscopic data were used for structural assignment of the *N*-1 and *N*-2 isomers.

Substituted indazoles are recently being increasingly reported as bioactive molecules. Some recent examples of substituted indazoles are granisetron used in CNS disorder,[1] 7-substituted indazoles developed as neuronal-NOS inhibitors,[2] 5-nitroindazole and its derivatives have been found to possess wide spectrum of activities like antiprotozoal,[3] antimalarial[4] and cytotoxic,[5] *N*2-(substituted benzyl)-3-(4-methylphenyl)-2*H*-indazoles exhibit antiangiogenic activity[6] and *N*-[4-(3-amino-1*H*-indazol-4-yl)-phenyl]-*N*'-(3-methylphenyl)-urea (ABT-869) has shown significant tumor growth inhibition in multiple preclinical animal models.[7] Moreover, other indazole derivatives are found to exhibit significant levels of activity as HIV protease inhibitors, serototonin 5-$HT_{1\alpha}$, 5-HT_2 and 5-HT_3 receptor antagonists and aldol reductase inhibitors.[8,9] Recently, our research group has reported the synthesis and the antiproliferative activities of new *N*-(7-indazolyl) benzenesulfonamide derivatives.

Some of these compounds exhibited significant cytotoxicity against human (colon and prostate) and murine (leukemia) cell lines.[10] In our ongoing research programme for new polyfunctionalised indazoles,[10-13] we report herein the synthesis of new series of di- and trisubstituted indazole derivatives, which were obtained by alkylation of 4-nitroindazole followed by reduction of alkyl-nitro-derivatives with anhydrous $SnCl_2$ in ethanol.

The indazole ring has two nitrogen atoms (*N*-1, *N*-2) and presents annular tautomerism with regards to the position of the NH hydrogen atom. Several studies concerning the alkylation of 1*H*-indazole reveal that the acidity or basicity of the medium, use of protic or aprotic solvents, as well as electronic and steric effects all affect the ratio of *N*-1 and *N*-2 alkylated isomers formed. Generally, the *N*-1 isomers are thermodynamically more stable, whereas the *N*-2 isomers are kinetically favoured.[14] In the present work we examined alkylation of 4-nitroindazole by different alkylating conditions. These reactions gave a mixture of isomers **2** and **3**, with a moderate selectivity in favour of compound **2** (Scheme 1). The use of *t*-BuOK /THF instead of KOH/acetone led to the more interesting result, with a smooth selectivity in favour of the isomer **2**. The benzylation of 4-nitroindazole in the presence of *t*-BuOK /THF give only *N*-1 isomers.



Scheme 1. Synthesis of 1-alkyl- and 2-alkyl-4-nitroindazole derivatives

Table 1. Synthesis of 4-nitroindazole derivatives substituted at *N*-1 and *N*-2 (**2** and **3**)

Alkyl halide RX	**Base(solvent)**	Ratio **2/3**[a]	Yield of **2**[b]	Yield of **3**[b]	Yield of **2+3**
a $BrCH_2CH=CH_2$	KOH/acetone	68/32	49%	24%	73%
	t-BuOK /THF	80/20	57%	15%	72%
b $ClCH_2Ph$	KOH/acetone	62/38	52%	31%	83%
	t-BuOK /THF	100/0	78%	0	78%
c $BrCH_2CH_2Br$	KOH/acetone	58/42	33%	25%	58%
	t-BuOK /THF	60/40	45%	29%	74%

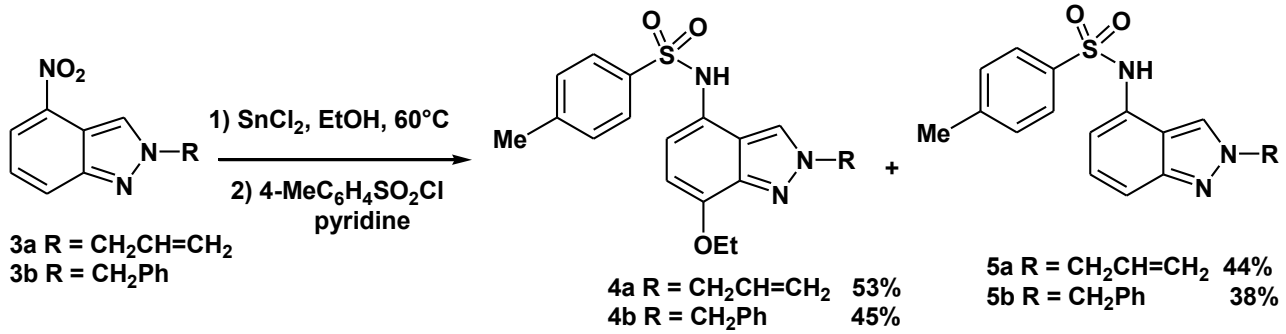
[a] Ratio determined by ^{1}H NMR spectroscopy of the reaction mixture.

[b] Yields of isolated products after flash chromatograph

The 1-alkyl and 2-alkyl isomers could be differentiated from their ^{13}C chemical shifts. The chemical shifts of CH-3 could differentiate between the two alkyl isomeric classes. Thus, the related signals appeared at δ 132.8-133.7 ppm for the 1-alkyl isomers **2**, whereas the values were δ 124.2-125.5 ppm for

the 2-alkyl derivatives **3**. ^{13}C-NMR spectroscopy is usually a particularly good method to perform this assignment.

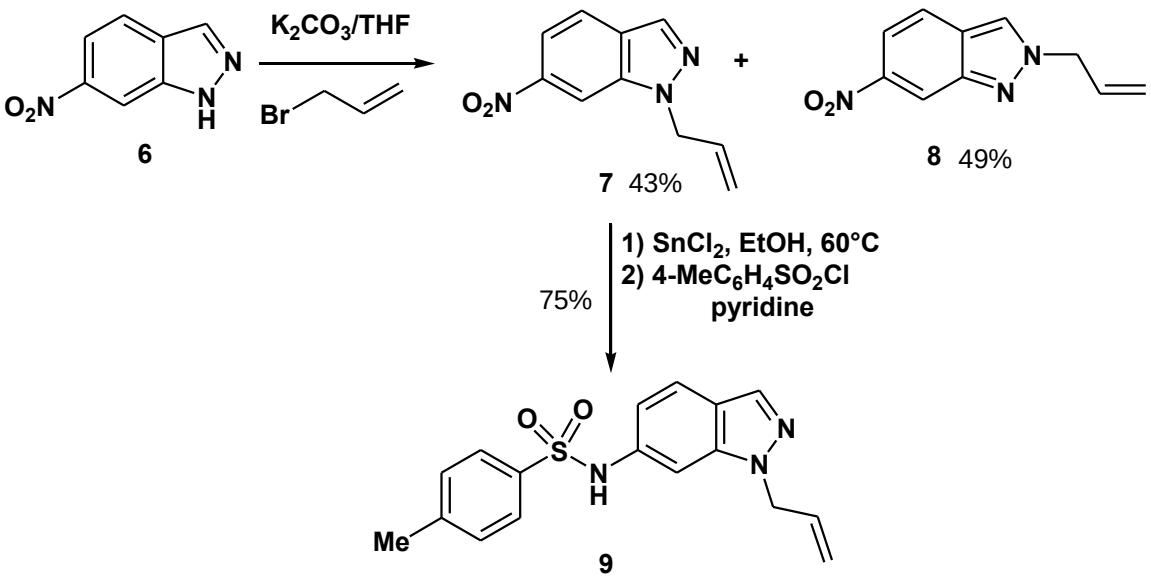
After separation of compounds **2** and **3** by column chromatography, we studied the reduction of the nitro group of *N*-alkylindazoles. Thus, we observed that reduction of the compound **3a** with $SnCl_2$ in ethanol as solvent gave two different compounds, that is, the desired amine and the amine substituted with ethoxy group in the 7-position, according to ^{1}H 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-methylbenzenesulfonyl chloride in pyridine. This reaction afforded a mixture of *N*-(4-indazolyl)-benzenesulfonamide **5a** with the corresponding 7-ethoxysubstituted indazole **4a**. The same method was used to obtain compounds **4b** and **5b** from isomer **3b** (Scheme 2). The 7-ethoxyindazoles **4a** and **4b** were obtained in 53% and 45% yields respectively.



Scheme 2. Reduction of 2-alkyl-4-nitroindazole with $SnCl_2$ in ethanol

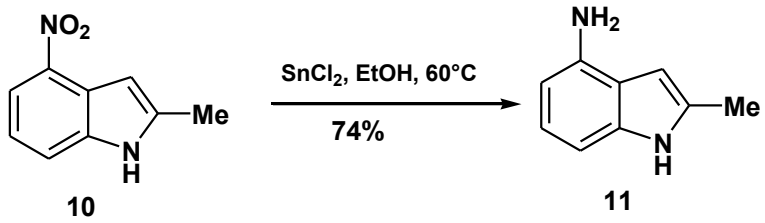
The yields of isolated products were determined after flash chromatography. The assignment of the structure of 7-ethoxy-*N*-(4-indazolyl)-4-methylbenzenesulfonamides **4a** and **4b** was unambiguously supported by the ^{1}H and ^{13}C NMR spectra, in particular by the evaluation of the multiplet pattern of the C-ring proton signals: two doublets were observed at δ 6.33-6.40 ppm and 6.55-6.56 ppm due to 6-H and 5-H protons of indazole. These results showed that the nitro group of indazole plays an important role for the orientation of the nucleophilic substitution of ethoxy group in indazole. Due to its electron-withdrawing effect the nitro group in nitroarene activates in ortho and para for addition of nucleophilic agents.[15–17] Thus, the formation of the compound substituted by an ethoxy group in 7-position could be explained by the presence of the ethoxy anion in the reaction mixture, followed by the nucleophilic substitution on 2-alkyl-4-nitroindazole.

When we applied the same condition of the reduction as previously described to 6-nitroindazole **7**, we obtained exclusively the corresponding sulfonamide **9** in 75% yield (Scheme 3). No trace of nucleophilic substitution was observed. This result show the important role played by position of nitro group in indazole for the preparation of ethoxyindazole derivatives. The *N*-alkylated indazoles **7** and **8** were obtained by alkylation of 6-nitroindazole **6** with allyl bromide in the presence of K_2CO_3 in THF.



Scheme 3. Alkylation and reduction of 1-allyl-6-nitroindazole **7** with $SnCl_2$ in ethanol

To generalize our results obtained in the series of 4-nitroindazole to other analogue structure, we investigated the reduction of 4-nitroindole **10** with $SnCl_2$ in ethanol. In this reaction, only the corresponding amine **11** was isolated in good yield (Scheme 4). No trace of the aminoethoxyindole was identified. Compound **10** was prepared according to method described in the literature.[18]



Scheme 4. Reduction of 4-nitroindole **10** with $SnCl_2$ in ethanol

These results show that the nature of the structure and the position of nitro group are factors important for the synthesis of the new series of alkoxyheterocycle derivatives.

In summary, we have developed an efficient method for the synthesis of new series of indazoles substituted at the *N*-1 and *N*-2 positions as well as their 7-ethoxyindazole derivatives starting from alkylation of 4-nitroindazole and reduction of alkyl-nitro-derivatives with anhydrous $SnCl_2$ in ethanol. This methodology of reduction is a valuable and general method for the preparation of new functionalized indazoles such as 7-alkoxy-4-aminoprotectedindazoles.

EXPERIMENTAL

Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 and solution (unless otherwise specified) with TMS as an

internal reference using a Bruker AC 300 (^{1}H) or 75MHz (^{13}C) instruments. Chemical shifts are given in δ parts per million (ppm). Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light (254 nm). Commercial reagents were used without further purification unless stated.

4-Nitroindazole (1)[19]: In a 500 mL round bottomed flask were introduced (5 g, 33 mmol) of 2-methyl-3-nitroaniline and 200 mL of AcOH. The solution was warmed under stirring until completed dissolution. Addition drop by drop of a solution of (2.3 g, 37.70 mmol) of $NaNO_2$ in 5 mL of water led to diazonium salt precipitation. The solution was stirred until this precipitate redisolved and the mixture was concentrated to the third of its initial volume. Then hot water (250 mL) was added to yield an orange-yellow product. The mixture was warmed and filtered hot. After cooling the obtained precipitate was filtered, washed with cold water and dried to yield **1**: 85%, mp 198-200 °C. ^{1}H NMR (DMSO-d_6): δ 7.54 (t, 1H, H-6, J = 7.9 Hz), 7.87 (d, 1H, H-7, J = 7.5 Hz), 7.94 (d, 1H, H-5, J = 7.9 Hz), 8.46 (s, 1H), 13.98 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 110.6 (C-3a), 118.1 (CH-5), 119.3 (CH-7); 125.9 (CH-6), 141.4 (C-4), 143.4 (C-7a).

General procedure for the synthesis of 1-alkyl- and 2-alkyl-4-nitroindazole derivatives

General procedure 1 (using *t*-BuOK as base). To a solution of 4-nitroindazole **1** (6.13 mmol) in THF (30 mL) cooled at 0 °C was added potassium t-butoxide (9.2 mmol). After 15 min at 0 °C, RX (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 was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc/hexane 3/7).

General procedure 2 (using KOH as base). To a solution of 4-nitroindazole **1** (6.13 mmol) in acetone (15 mL) cooled at 0 °C was added potassium hydroxide (9.2 mmol). After 15 mn at 0 °C, RX (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 was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc/hexane 3/7).

1-Allyl-4-nitro-1*H*-indazole (2a). This compound was obtained as yellow solid, mp 63-65 °C. ^{1}H NMR ($CDCl_3$): δ 5.07-5.10 (m, 2H, NCH_2), 5.15-5.26 (m, 2H, $=CH_2$), 5.95-6.08 (m, 1H, =CH), 7.44 (t, 1H, J=7.8 Hz), 7.75 (d, 1H, J = 8.4 Hz), 8.04 (d, 1H , J = 7.8 Hz), 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 52.2 (NCH_2), 116.5 (CH-5), 117.1 (C-3a), 118.2 (CH-7), 118.5 ($=CH_2$), 125.4 (CH-6), 132.0 (=CH), 132.8

(CH-3), 140.6, 141.0 (C-4, C-7a). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.03; H, 4.52; N, 20.56.

2-Allyl-4-nitro-2*H*-indazole (3a).This compound was obtained as yellow solid, mp 68-70 °C. ^{1}H NMR ($CDCl_3$): δ 5.10-5.13 (m, 2H, NCH_2), 5.35-5.42 (m, 2H, $=CH_2$), 6.09-6.22 (m, 1H, =CH), 7.37 (t, 1H, *J*=7.8 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 8.56 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 56.7 (NCH_2), 115.0 (C-3a), 120.4 ($=CH_2$), 120.6 (CH-5), 124.2 (CH-3), 124.4 (CH-7), 126.0 (CH-6), 131.4 (=CH), 140.6 (C-4), 149.9 (C-7a). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.96; H, 4.50; N, 20.59.

1-Benzyl-4-nitro-1*H*-indazole (2b). This compound was obtained as yellow solid, mp 75-77 °C. ^{1}H NMR ($CDCl_3$): δ 5.69 (s, 2H, NCH_2), 7.20-7.24 (m, 2H, ArH), 7.28-7.36 (m, 3H, ArH), 7.43 (t, 1H, *J* = 7.8 Hz), 7.72 (d, 1H, *J* = 7.8 Hz), 8.11 (d, 1H, *J* = 8.1 Hz), 8.66 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 53.6 (NCH_2), 116.5 (CH-5), 117.4 (C-3a), 118.3 (CH-7), 125.6 (CH-6), 127.2 (2CH), 128.2 (CH), 129.0 (2CH), 133.0 (CH-3), 135.9 (C), 140.7, 141.1 (C-4, C-7a). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.56; H, 4.27; N, 16.52.

2-Benzyl-4-nitro-2*H*-indazole (3b). This compound was obtained as yellow solid, mp 106-108 °C. ^{1}H NMR ($CDCl_3$): δ 5.69 (s, 2H, NCH_2), 7.35-5.41 (m, 6H, ArH), 8.10 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 8.57 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 58.2 (NCH_2), 115.2 (C-3a), 120.7 (CH-5), 124.3 (CH-7), 124.6 (CH-3), 126.2 (CH-6), 128.2 (2CH), 128.8 (CH), 129.2 (2CH), 134.9 (C), 140.7 (C-4), 150.0 (C-7a). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.62; H, 4.30; N, 16.48.

1-(2-Bromoethyl)-4-nitro-1*H*-indazole (2c). This compound was obtained as yellow solid, mp 78-80 °C. ^{1}H NMR ($CDCl_3$): δ 3.85 (t, 2H, *J* = 6.3 Hz, $BrCH_2$), 3.93 (t, 2H, *J* = 6.3 Hz, NCH_2), 7.51 (t, 1H, *J* = 7.8 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 7.8 Hz), 8.62 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.9 ($BrCH_2$), 50.6 (NCH_2), 116.3 (CH-5), 116.9 (C-3a), 118.5 (CH-7), 125.8 (CH-6), 133.7 (CH-3), 140.6, 141.7 (C-4, C-7a). Anal. Calcd for $C_9H_8BrN_3O_2$: C, 40.02; H, 2.99; N, 15.56. Found: C, 40.24; H, 3.14; N, 15.45.

2-(2-Bromoethyl)-4-nitro-2*H*-indazole (3c). This compound was obtained as yellow solid, mp 104-110 °C, ^{1}H NMR ($CDCl_3$): δ 3.93 (t, 2H, *J* = 6.3 Hz, $BrCH_2$), 4.88 (t, 2H, *J* = 6.3 Hz, NCH_2), 7.38 (t, 1H, *J* = 7.5 Hz), 8.04 (d, 1H, *J* = 8.3 Hz), 8.13 (d, 1H, *J* = 7.5 Hz), 8.61 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.7 ($BrCH_2$), 55.5 (NCH_2), 114.6 (C-3a), 120.3 (CH-5), 125.5 (CH-3), 125.8 (CH-7), 126.1 (CH-6), 141.7 (C-4), 150.2 (C-7a). Anal. Calcd for $C_9H_8BrN_3O_2$: C, 40.02; H, 2.99; N, 15.56. Found: C, 40.26; H, 3.22; N, 15.48.

General method for the synthesis of 7-ethoxy-*N*-(-2-alkyl-4-indazolyl)-4-methylbenzene sulfonamides and *N*-(2-alkyl-4-indazolyl)-4-methylbenzenesulfonamides. A mixture of 2-alkyl-4-nitroindazole **(3a-b)** (1.22 mmol) and anhydrous $SnCl_2$ (1.1 g, 6.1 mmol) in 25 mL of absolute EtOH 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 EtOAc. 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-methylbenzenesulfonyl chloride (0.26 g, 1.25 mmol) at room temperature for 24 h. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/hexane 1/9).

***N*-(2-Allyl-7-ethoxy-2*H*-indazol-4-yl)-4-methylbenzenesulfonamide (4a).** Yield: 53%, colorless solid, mp 143-145 °C. ^{1}H NMR (DMSO-d_6): δ 1.33 (t, 3H, CH_3, J = 7.0 Hz), 2.28 (s, 3H, CH_3), 4.05 (q, 2H, CH_2O, J = 7.0 Hz), 4.95-4.98 (m, 2H, NCH_2), 5.08-5.24 (m, 2H, $=CH_2$), 5.95-6.05 (m, 1H, =CH), 6.40 (d, 1H, H-6, J = 8.1 Hz), 6.55 (d, 1H, H-5, J = 8.1 Hz), 7.24 (d, 2H, ArH, J = 7.8 Hz), 7.53 (d, 2H, ArH, J = 7.8 Hz), 8.08 (s, 1H, H-3), 9.86 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 15.1 (CH_3), 21.4 (CH_3), 55.6 (NCH_2), 63.7 (CH_2O), 103.8 (CH), 115.5 (CH), 118.9 ($=CH_2$), 120.3 (C), 122.0 (C), 123.4 (CH-3), 127.2 (2CH), 129.8 (2CH), 133.8 (=CH), 137.4 (C), 142.0 (C), 143.3 (C), 147.3 (C). MS: *m/z* 372 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.70; H, 5.54; N, 11.51.

***N*-(2-Allyl-2*H*-indazol-4-yl)-4-methylbenzenesulfonamide (5a).** Yield: 44% , colorless solid, mp 150-152 °C. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 4.96-5.01 (m, 2H, NCH_2), 5.13-5.23 (m, 2H, $=CH_2$), 5.96-6.06 (m, 1H, =CH), 6.77 (d, 1H, J = 7.2 Hz), 7.04 (t, 1H, J = 7.3 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.55 (d, 2H, ArH, J = 7.4 Hz), 7.65 (d, 2H, ArH, J = 7.4 Hz), 8.37 (s, 1H, H-3), 10.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.3 (CH_3), 55.7 (NCH_2), 111.0 (CH) 113.6 (CH), 119.1 ($=CH_2$), 120.3 (C), 122.0 (C), 123.2 (CH-3), 126.1 (CH), 127.2 (2CH), 129.8 (2CH), 133.8 (=CH), 137.3 (C), 142.0 (C), 149.4 (C). MS: *m/z* 328 $(M + 1)^+$. Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.52; H, 5.08; N, 12.95.

***N*-(2-Benzyl-7-ethoxy-2*H*-indazol-4-yl)-4-methylbenzenesulfonamide (4b).** Yield: 45%, colorless solid, mp 156-158 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, CH_3, J = 7.1 Hz), 2.32 (s, 3H, CH_3), 4.15 (q, 2H, CH_2O, J = 7.1 Hz), 5.54 (s, 2H, NCH_2), 6.33 (d, 1H, H-6, J = 7.9 Hz), 6.56 (d, 1H, H-5, J = 7.9 Hz), 7.10 (d, 2H, ArH, J = 7.7 Hz), 7.23-7.35 (m, 5H, ArH), 7.53 (d, 2H, ArH, J = 7.7 Hz), 7.82 (s, 1H, H-3), 8.96 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.6 (CH_3), 21.5 (CH_3), 57.5 (NCH_2), 64.0 (CH_2O), 103.3 (CH), 118.4 (CH), 120.3 (C), 121.2 (C), 122.9 (CH-3), 127.4 (2CH), 128.2 (2CH), 128.5 (CH), 128.9 (2CH), 129.4 (2CH), 135.2 (C), 136.0 (C), 142.0 (C), 143.6 (C), 148.2 (C). MS: *m/z* 422 $(M + 1)^+$. Anal. Calcd for $C_{23}H_{23}N_3O_3S$: C, 65.54; H, 5.50; N, 9.97. Found: C, 65.68; H, 5.42; N, 10.11.

***N*-(2-Benzyl-2*H*-indazol-4-yl)-4-methylbenzenesulfonamide (5b).** Yield: 38%, colorless solid, mp 180-182 °C, ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 5.60 (s, 2H, NCH_2), 6.84 (d, 1H, J = 7.8 Hz), 7.13 (d, 2H, ArH, J = 7.8 Hz), 7.28-7.41 (m, 7H, ArH), 7.66 (d, 2H, ArH, J = 7.8 Hz), 7.82 (s, 1H, H-3), 8.85 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3), 57.3 (NCH_2), 113.0 (CH), 114.1 (CH), 117.3 (C), 124.7

(CH-3), 126.4 (CH), 127.3 (2CH), 128.4 (2CH), 128.8 (CH), 129.0 (2CH), 129.6 (2CH), 129.7 (C), 134.2 (C), 135.8 (C), 144.0 (C), 147.1 (C). MS: *m/z* 378 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13. Found: C, 66.69; H, 5.12; N, 10.98.

Preparation of *N*-alkylated indazoles (7) and (8). To a solution of 6-nitroindazole (**6)** (6.13 mmol) in THF (30 mL) cooled at 0 °C was added K_2CO_3 (9.2 mmol). After 15 mn at 0 °C, allyl bromide (6.13 mmol) was added dropwise. The solution was stirred for 16 h and 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 was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc/hexane 3/7).

1-Allyl-6-nitro-1*H*-indazole (7). Yield: 43%, yellow solid, mp 56-58 °C. ^{1}H NMR ($CDCl_3$): δ 5.10-5.13 (m, 2H, NCH_2), 5.16-5.30 (m, 2H, $=CH_2$), 6.01-6.10 (m, 1H, =CH), 7.84 (d, 1H, *J* = 9.1 Hz), 8.01 (dd, 1H, *J* = 9.1 Hz , 1.8 Hz), 8.13 (s, 1H), 8.37 (d, 1H , *J* = 1.6 Hz). ^{13}C NMR ($CDCl_3$): δ 52.3 (NCH_2), 106.1 (CH-7), 115.5 (CH-5), 118.7 ($=CH_2$), 121.9 (CH-4), 127.3 (C-3a), 131.9, 133.6 (CH-3, =CH), 138.2 (C-7a), 146.5 (C-6). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.23; H, 4.58; N, 20.61.

2-Allyl-6-nitro-1*H*-indazole (8). Yield: 49%, yellow solid, mp 48-50 °C. ^{1}H NMR ($CDCl_3$): δ 5.10-5.12 (m, 2H, NCH_2), 5.34-5.43 (m, 2H, $=CH_2$), 6.13-6.18 (m, 1H, =CH), 7.75 (d, 1H, *J* = 9.3 Hz), 7.88 (dd, 1H, *J* = 9.3 Hz , 2.1 Hz), 8.08 (s, 1H), 8.68 (d, 1H , *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$): δ 56.8 (NCH_2), 115.5, 115.9 (CH-5, CH-7), 120.7 ($=CH_2$), 121.5 (CH-4), 123.7 (CH-3), 124.4 (C-3a), 131.2 (=CH), 146.6, 146.8 (C-6, C-7a). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.18; H, 4.50; N, 20.57.

Synthesis of *N*-(1-allyl-1*H*-indazol-6-yl)-4-methylbenzenesulfonamide (9). This compound was prepared from 1-Allyl-6-nitro-1*H*-indazole **7** by using the same procedure applied to **(3a-b).**

Yield: 75%, colorless solid, mp 95-97 °C. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.97-5.00 (m, 2H, NCH_2), 5.06-5.22 (m, 2H, $=CH_2$), 5.91-5.97 (m, 1H, =CH), 6.82 (d, 1H, *J* = 8.4 Hz), 7.18 (d, 2H, ArH, *J* = 7.8 Hz), 7.28 (s, 1H), 7.55 (d, 1H, *J* = 8.4 Hz), 7.64 (s, 1H, NH); 7.70 (d, 2H, ArH, *J* = 7.8 Hz), 8.00 (s, 1H, H-3). ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3), 51.7 (NCH_2), 100.7 (CH), 116.3 (CH), 118.2 ($=CH_2$), 121.3 (C), 122.3 (CH), 127.4 (2CH), 129.7 (2CH), 132.1 (CH), 132.7 (CH), 135.8 (C), 136.0 (C), 139.7 (C), 144.1 (C); MS: *m/z* 328 $(M + 1)^+$; Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.48; H, 5.12; N, 13.01.

Synthesis of 4-Amino-2-methyl-1*H*-indole (11). A mixture of 2-methyl-4-nitroindole (**10**) (1.22 mmol) and anhydrous $SnCl_2$ (1.1 g, 6.1 mmol) in 25 mL of absolute EtOH 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 EtOAc. The

organic phase is washed with brine and dried over magnesium sulfate. The solvent was removed under vacuum and the residue was purified by flash chromatography (eluted with EtOAc/hexane 3/7). Yield: 74%, brown solid, mp 192-194 °C. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 4.01 (s, 2H, NH_2), 6.21 (s, 1H, H-3), 6.58 (d, 1H, J = 7.4 Hz), 6.88 (t, 1H, *J* = 7.4 Hz), 7.70 (d, 1H, *J* = 7.4 Hz), 11.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.8 (CH_3), 96.9 (CH), 106.7 (CH), 108.8 (CH), 116.1 (C), 121.0 (CH), 129.6 (C), 135.4 (C), 137.5 (C).

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