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,$^5$ N2-(substituted benzyl)-3-(4-methylphenyl)-2H-indazoles exhibit antiangiogenic activity$^6$ and N-[4-(3-amino-1H-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$_{1A}$, 5-HT$_2$ and 5-HT$_3$ receptor antagonists and aldol reductase inhibitors.$^8$ 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. In our ongoing research programme for new polyfunctionalised indazoles, 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 SnCl₂ 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 1H-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. In the present work we examined alkylation of 4-nitroindazole by different alkylation 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](image-url)

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

<table>
<thead>
<tr>
<th>Alkyl halide RX</th>
<th>Base(solvent)</th>
<th>Ratio 2/3</th>
<th>Yield of 2</th>
<th>Yield of 3</th>
<th>Yield of 2+3</th>
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<tbody>
<tr>
<td>a BrCH₂CH=CH₂</td>
<td>KOH/acetone</td>
<td>68/32</td>
<td>49%</td>
<td>24%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>t-BuOK/THF</td>
<td>80/20</td>
<td>57%</td>
<td>15%</td>
<td>72%</td>
</tr>
<tr>
<td>b ClCH₂Ph</td>
<td>KOH/acetone</td>
<td>62/38</td>
<td>52%</td>
<td>31%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>t-BuOK/THF</td>
<td>100/0</td>
<td>78%</td>
<td>0</td>
<td>78%</td>
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<tr>
<td>c BrCH₂CH₂Br</td>
<td>KOH/acetone</td>
<td>58/42</td>
<td>33%</td>
<td>25%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>t-BuOK/THF</td>
<td>60/40</td>
<td>45%</td>
<td>29%</td>
<td>74%</td>
</tr>
</tbody>
</table>

*a Ratio determined by 1H 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 13C 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 $\delta$ 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$_2$CO$_3$ in THF.
To generalize our results obtained in the series of 4-nitroindazole to other analogue structure, we investigated the reduction of 4-nitroindole 10 with SnCl₂ 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

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 SnCl₂ 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. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-ᵈ and solution (unless otherwise specified) with TMS as an
internal reference using a Bruker AC 300 (1H) or 75MHz (13C) instruments. Chemical shifts are given in δ parts per million (ppm). Multiplicities of 13C 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 SiO2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO2 (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)15. 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 NaNO2 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. 1H NMR (DMSO-d6): 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). 13C NMR (DMSO-d6): 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 MgSO4 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 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 MgSO4 and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc/hexane 3/7).

1-Allyl-4-nitro-1H-indazole (2a). This compound was obtained as yellow solid, mp 63-65 °C. 1H NMR (CDCl3): δ 5.07-5.10 (m, 2H, NCH2), 5.15-5.26 (m, 2H, =CH2), 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). 13C NMR (CDCl3): δ 52.2 (NCH2), 116.5 (CH-5), 117.1 (C-3a), 118.2 (CH-7), 118.5 (=CH2), 125.4 (CH-6), 132.0 (=CH), 132.8...
2-Allyl-4-nitro-2H-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$_9$N$_3$O$_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.03; H, 4.52; N, 20.56.

1-Benzyl-4-nitro-1H-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$_3$O$_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.62; H, 4.27; N, 16.52.

2-Benzyl-4-nitro-2H-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$_3$O$_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.62; H, 4.27; N, 16.52.

2-(2-Bromoethyl)-4-nitro-1H-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$_9$H$_8$BrN$_3$O$_2$: C, 40.02; H, 2.99; N, 15.56. Found: C, 40.24; H, 3.14; N, 15.45.

2-(2-Bromoethyl)-4-nitro-2H-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$_9$H$_8$BrN$_3$O$_2$: 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-2H-indazol-4-yl)-4-methylbenzenesulfonamide (4a).** Yield: 53%, colorless solid, mp 143-145 °C. ¹H NMR (DMSO- d₆): δ 1.33 (t, 3H, CH₃, J = 7.0 Hz), 2.28 (s, 3H, CH₃), 4.05 (q, 2H, CH₂O, J = 7.0 Hz), 4.95-4.98 (m, 2H, NCH₂), 5.08-5.24 (m, 2H, =CH₂), 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). After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/hexane 1/9). MS: m/z 372 (M + 1)⁺. Anal. Calcd for C₁₉H₂₁N₃O₃S: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.70; H, 5.54; N, 11.51.

**N-(2-allyl-2H-indazol-4-yl)-4-methylbenzenesulfonamide (5a).** Yield: 44%, colorless solid, mp 150-152 °C. ¹H NMR (DMSO- d₆): δ 2.28 (s, 3H, CH₃), 4.96-5.01 (m, 2H, NCH₂), 5.13-5.23 (m, 2H, =CH₂), 5.95-6.06 (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), 7.82 (s, 1H, NH). MS: m/z 328 (M + 1)⁺. Anal. Calcd for C₁₇H₁₇N₃O₂S: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.52; H, 5.08; N, 12.95.

**N-(2-benzyl-7-ethoxy-2H-indazol-4-yl)-4-methylbenzenesulfonamide (4b).** Yield: 45%, colorless solid, mp 156-158 °C. ¹H NMR (CDCl₃): δ 1.47 (t, 3H, CH₃, J = 7.1 Hz), 2.32 (s, 3H, CH₃), 4.15 (q, 2H, CH₂O, J = 7.1 Hz), 5.54 (s, 2H, NCH₂), 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). ¹³C NMR (CDCl₃): δ 14.6 (CH₃), 21.5 (CH₃), 57.5 (NCH₂), 64.0 (CH₂O), 103.3 (CH), 118.4 (CH), 120.3 (C), 121.2 (C), 122.9 (CH-3), 127.4 (CH), 128.2 (CH), 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 C₂₃H₂₃N₃O₃S: C, 65.54; H, 5.50; N, 9.97. Found: C, 65.68; H, 5.42; N, 10.11.

**N-(2-Benzyl-2H-indazol-4-yl)-4-methylbenzenesulfonamide (5b).** Yield: 38%, colorless solid, mp 180-182 °C. ¹H NMR (CDCl₃): δ 2.31 (s, 3H, CH₃), 5.60 (s, 2H, NCH₂), 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). ¹³C NMR (CDCl₃): δ 21.5 (CH₃), 57.3 (NCH₂), 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_{3}O_{2}S: 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$_2$CO$_3$ (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-1H-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 = 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$_9$N$_3$O$_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.23; H, 4.58; N, 20.61.

**2-Allyl-6-nitro-1H-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), 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$_9$N$_3$O$_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.18; H, 4.50; N, 20.57.

**Synthesis of N-(1-allyl-1H-indazol-6-yl)-4-methylbenzenesulfonamide (9).** This compound was prepared from 1-Allyl-6-nitro-1H-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$_3$O$_2$S: 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-1H-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
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. 1H NMR (DMSO-d6): δ 2.35 (s, 3H, CH3), 4.01 (s, 2H, NH2), 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). 13C NMR (DMSO-d6): δ 13.8 (CH3), 96.9 (CH), 106.7 (CH), 108.8 (CH), 116.1 (C), 121.0 (CH), 129.6 (C), 135.4 (C), 137.5 (C).

REFERENCES
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