

An expedient general synthesis of pyrrolo[3,2-*e*]indazoles: domino Sonogashira/Cacchi coupling-heteroannulation reactions

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Abstract

A one-pot Sonogashira coupling-heteroannulation of 4-iodo-1-phenylsulfonyl-5-trifluoroacetamidindazole with terminal acetylenes using bis(triphenylphosphine)palladium(II) dichloride as the catalyst, cuprous iodide as the co-catalyst and triethylamine as the base in DMF furnished, after *N*(3)-deprotection, 7-H/substituted 3,6-dihydropyrrolo[3,2-*e*]indazoles in high yields. This is the first general synthesis of pyrrolo[3,2-*e*]indazoles. Uncatalyzed hydrodesilylation was observed during reaction with trimethylsilylacetylene, leading to the 7-unsubstituted parent pyrrolo[3,2-*e*]indazole.

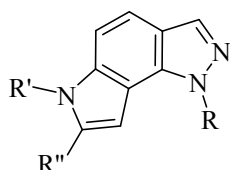
Keywords: Pyrrolo[3,2-*e*]indazoles, Sonogashira coupling/5-*endo-dig* cyclisation, palladium(II) catalyst, domino reactions

Introduction

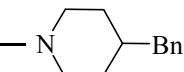
The indole ring constitutes the structural core of a host of bioactive compounds of natural and synthetic origins.^{1,2} More than 10,000 bioactive indoles are known, of which over 200 are either used as drugs or are in clinical trials.³ Substituted indazoles too are of considerable pharmaceutical importance because of their therapeutic potential and use,⁴ amongst which benzydamine is a notable anti-inflammatory agent.^{5,6} In continuation of our ongoing interest in the development of general synthetic routes to potentially bioactive condensed nitrogen heterocycles,⁷⁻¹⁴ we recently focused our attention on a relatively less studied class of heterocycles which incorporate both the indole and the indazole nuclei, *viz.* pyrazoloindoles which may also be regarded as pyrroloindazoles. A report on the study of indazole-containing polycyclic compounds in search of antitumor agents¹⁵ strengthened our motivation.

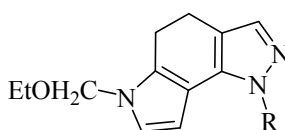
The extant literature on the synthesis and bioactivity of pyrroloindazoles revealed that eight isomeric classes of pyrroloindazoles have so far been synthesised.¹⁶⁻³³ Of these, only the [2,3-*g*]-

isomers¹⁸⁻²⁷ and the [3,2-*e*]-isomers^{22,24,25} display various biological activities. Thus, the [2,3-*g*]-isomers **1-4** and the [3,2-*e*]-pyrroloindazole **5** were bioactive. While **1** showed analgesic and antiinflammatory activity,¹⁸ **2** showed NMDA (*N*-methyl D-aspartate)-receptor antagonistic property with potential for the treatment of neuropathic pain,²² **3** and **4** displayed inhibition of sGC (soluble guanylate cyclase) with potential for treating hypertension²³ whereas **5** proved to be an antagonist of NMDA-receptor.²²



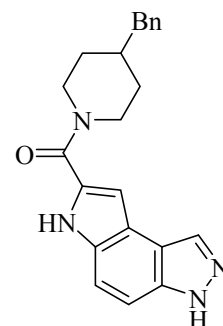
1. R = alkyl; R' = H; R'' = Me

2. R = R' = H; R'' = CO — 



3. R = Me

4. R = Ph



5

Among these two classes of pyrroloindazoles, only the [2,3-*g*]-types have already been subjected to rather thorough synthetic investigations.¹⁸⁻²⁷ But the [3,2-*e*]-types were synthesized only twice, neither of which was a general route.

In the first synthesis of pyrrolo[3,2-*e*]indazoles, only one member, *viz.* the 5-carbethoxy derivative was prepared from 5-aminoindazole using Fischer/Japp-Klingemann procedure. The derived 4-benzylpiperidinylcarboxamide proved to be a good antagonist of NMDA-receptor.²² In the second synthesis,^{24,25} two substrates, *viz.* 6-H- and 6-bromo-4,5-indolynes, generated *in situ*, were separately treated with ethyl diazoacetate when a mixture of two isomeric pyrroloindazoles, *viz.* the [3,2-*e*]-type and the [2,3-*g*]-type were formed in each case. Thus, 4-H-1-carbethoxypyrrolo[3,2-*e*]indazole and 8-H-1-carbethoxypyrrolo[2,3-*g*]indazole were formed from the 6-H-indolyne, whereas 4-bromo-1-carbethoxypyrrolo[3,2-*e*]indazole and 8-bromo-1-carbethoxypyrrolo[2,3-*g*]indazole were formed from the 6-bromoindolyne.

The reported bioactivity, hence the bioactive potential of pyrrolo[3,2-*e*]indazoles and particularly the absence of a general synthetic route to this particular isomeric class called for the development of a general synthesis of pyrrolo[3,2-*e*]indazoles, which we have now accomplished and is reported herein.

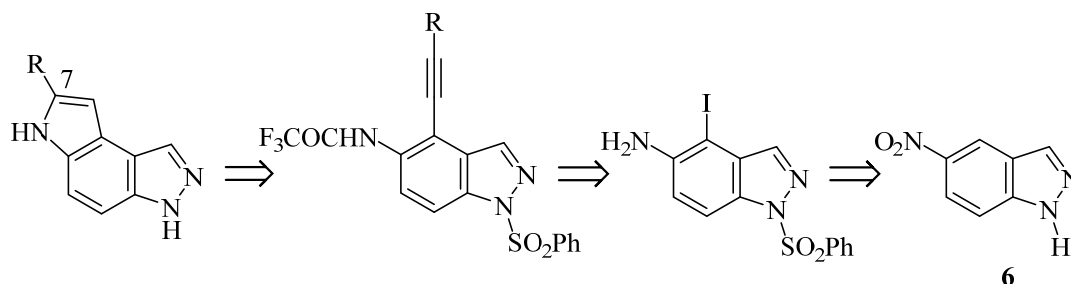
Several classical routes to the synthesis of indoles are known.^{34,35} Indazoles too have been the subject of synthetic efforts during the past decades.³⁶ Our plan was to utilize one of the recently developed palladium-catalyzed synthetic routes to indoles^{37,38} because of the mild reaction conditions involved, tolerance of a wide variety of functional groups (thereby avoiding the use of protecting groups), high regioselectivities and high yields.

The aminopalladation/reductive elimination domino reaction of alkynes containing a proximate nitrogen nucleophile, first observed by Yamanaka and subsequently by Cacchi,³⁹ has

proved to be very useful for the formation of a pyrrole ring incorporated into an indole nucleus. To be precise, Cacchi's novel approach to 2,3-disubstituted indoles through a palladium-catalyzed cyclisation of *ortho*-alkynyl-trifluoroacetanilides with aryl, heteroaryl and alkenyl halides, specially iodides, or triflates^{40,41} was of interest to us. Later, Flynn modified conditions to develop a one-pot, two-step synthesis of only one 2,3-disubstituted indole using bis(triphenylphosphine)palladium(II) dichloride as the catalyst.⁴²

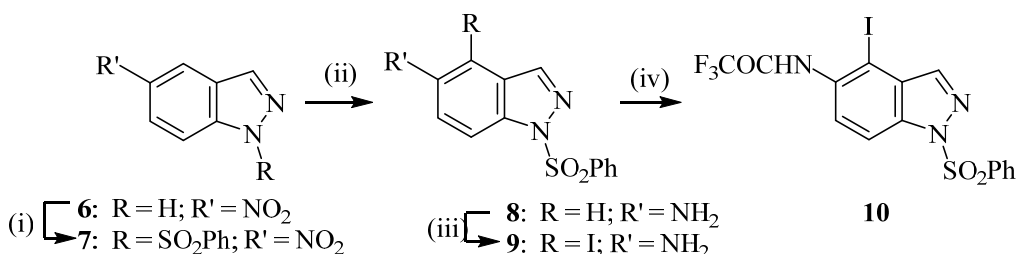
Results and Discussion

Our plan was to utilize the Sonogashira-Hagihara protocol (more often simply called Sonogashira reaction)⁴³⁻⁴⁶/Cacchi procedure for the construction of the pyrrole ring on the indazole framework. Our retrosynthetic analysis of the envisaged title molecules, shown in Scheme 1, involved 5-amino-*N*(1)-phenylsulfonylindazole¹¹ as the starting material and it was prepared from 5-nitroindazole **6**.



Scheme 1. Retrosynthesis of 7-substituted pyrrolo[3,2-*e*]indazoles.

Accordingly, the desired starting amine **8** was prepared from commercially available indazole **6** by successive *N*(1)-phenylsulfonylation (PTC-mediated) and reduction (hydrazine hydrate and palladized charcoal) of the resulting protected nitroindazole **7**. It was then iodinated exclusively at C-4 by *N*-iodosuccinimide (NIS) to efficiently furnish **9**. The site of iodination received support from the appearance of ¹H NMR signals at δ 7.09 and *ca.* 7.84 ppm (1H, d each *J* 9 Hz) in the ¹H NMR spectrum of **9**, which corresponded to H-6 and H-7. The amino-iodoindazole **9** was trifluoroacetylated to furnish the Sonogashira/Cacchi substrate, *ortho*-iodo-trifluoroacetamidoindazole **10** in very good yield (Scheme 2).



Reaction conditions and yields: (i) $PhSO_2Cl$, $NaOH$, $n-Bu_4N^+HSO_4^-$, THF, rt, 1 h; (**7**): 84%; (ii) NH_2NH_2 , Pd/C , MeOH, reflux, 3 h; (**8**): 82%; (iii) NIS, CH_3CN , rt, 2 h; (**9**): 81%; (iv) TFAA, Et_3N , THF, 0 °C, 2 h; (**10**): 83%.

Scheme 2. Preparation of the key precursor **10**.

The reaction of the Sonogashira/Cacchi substrate **10** was first tried with TMSA **11a** since TMSAs can be hydrodesilylated using a fluoride source, mostly TBAF, or an inorganic base, usually aq. KOH -MeOH. We used bis(triphenylphosphine)palladium(II) dichloride [$Pd(Ph_3P)_2Cl_2$] (10 mol %) as the catalyst in our experiments. Thus, **10** was treated with **11a** (1.4 equiv) and $Pd(Ph_3P)_2Cl_2$ (10 mol %) in DMF in the presence cuprous iodide (10 mol %) as the co-catalyst and Et_3N (10 equiv) as the base and stirred at 100-110 °C in an argon atmosphere (to avoid Hay-Glaser homocoupling of terminal acetylenes⁴⁷) until the substrate was consumed. The optimal concentrations of the catalyst, the co-catalyst and the base were determined by trial experiments which have not been described in the Experimental Section. A usual work-up of the reaction mixture, followed by purification of the crude product by column chromatography over silica gel, furnished a single product. Though expected to be the corresponding 7-TMS-pyrroloindazole, the sole product was indeed identified as 7-unsubstituted 3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole **12a** by combined spectroscopic (IR, 1H and ^{13}C NMR, MS) and elemental analyses. The presence of two 1H NMR signals at δ 7.71 and 7.87 ppm (1H, each d, J 9 Hz), corresponding to H-4 and H-5 of the pyrrolo[3,2-*e*]indazole nucleus, lent support to its type of isomer. It thus transpired that the tandem Sonogashira/Cacchi coupling-heteroannulation as well as hydrodesilylation had occurred in one pot.

The observed cleavage of the TMS group occurring under the tandem Sonogashira-Hagihara/Cacchi cross-coupling-heteroannulation reactions requires explanation since we did not use any hydrodesilylating agent in our experiment. We believe, direct palladium-copper-catalyzed coupling of **10** with **11a** in a so-called “sila”-Sonogashira reaction⁴⁸ led to the elimination of trimethylsilyl iodide with the formation of *ortho*-ethynyl-trifluoroacetamidoindazole. It was immediately followed by 5-*endo-dig* cyclisation to form **12a**.

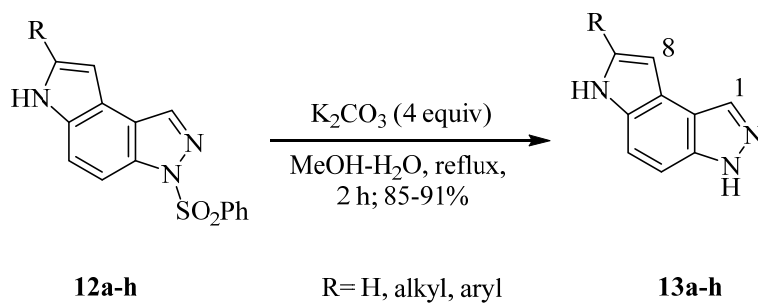
The occurrence of two reactions in tandem and the high yield of the product encouraged us to check the generality of the reaction. Hence, **10** was separately treated with seven other terminal acetylenes **11b-h** under the aforesaid conditions. Gratifyingly, the respective 7-substituted 3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazoles **12b-h** were isolated as the sole products in

82-94% yields in 5-8 h (Table 1). In the ^1H NMR spectra of all these products, the signals for H-4 and H-5 appeared as 1H, doublet each in the range δ 7.59-8.0 ppm showing, as expected, an *ortho*-coupling (J 8.5-9.5 Hz). The formation of [3,2-*e*]-type of pyrroloindazoles was thus confirmed. Pertinently, H-1 appeared at δ 8.6–8.9 ppm (s) in **12a-h**, whereas H-8 appeared at *ca.* δ 6.5 ppm (s) in the 7-alkyl derivatives **12b-e** and at δ 7.2-7.3 ppm (s) in the 7-aryl derivatives **12f-h**.

Table 1. Synthesis of 7-H/substituted 3,6-dihydropyrrolo[3,2-*e*]indazoles **12a-h** from terminal acetylenes using domino reactions

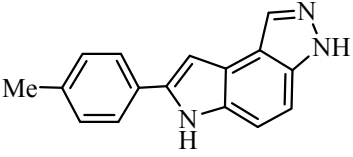
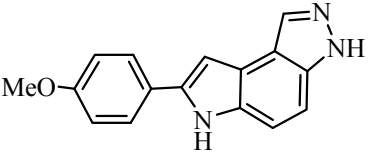
| Entry | Alkyne 11 | Product (R in str. 12) | Time (h) | Yield (%) | Mp (°C) |
|-------|---|---|----------|-----------|---------------|
| 1 | Me ₃ Si-C≡CH (11a) | 12a (H) | 10 | 83 | 204-206 (dec) |
| 2 | H ₃ C(CH ₂) ₃ -C≡CH (11b) | 12b (<i>n</i> -C ₄ H ₉) | 5 | 88 | 214-216 (dec) |
| 3 | H ₃ C(CH ₂) ₄ -C≡CH (11c) | 12c (<i>n</i> -C ₅ H ₁₁) | 7 | 82 | 186-188 (dec) |
| 4 | H ₃ C(CH ₂) ₅ -C≡CH (11d) | 12d (<i>n</i> -C ₆ H ₁₃) | 6 | 85 | 180-182 (dec) |
| 5 | NC(CH ₂) ₃ -C≡CH (11e) | 12e [(CH ₂) ₃ CN] | 6 | 94 | 258-260 (dec) |
| 6 | Ph-C≡CH (11f) | 12f (Ph) | 8 | 93 | 238-240 (dec) |
| 7 | <i>p</i> -MeC ₆ H ₄ -C≡CH (11g) | 12g (C ₆ H ₄ Me- <i>p</i>) | 7 | 88 | 222-224 (dec) |
| 8 | <i>p</i> -MeOC ₆ H ₄ -C≡CH (11h) | 12h (C ₆ H ₄ OMe- <i>p</i>) | 8 | 87 | 218-220 (dec) |

For *N*(3)-deprotection, each of **12a-h** was refluxed with aqueous methanolic potassium carbonate for 2 h, which generated the parent 7H/substituted 3,6-dihydropyrrolo[3,2-*e*]indazoles (**13a-h**) in 85-91% yields (Table 2). As expected, H-1 showed an upfield shift (to δ 8.1-8.3 ppm, s) in **13a-h**, whereas there was not much effect on the chemical shifts of H-8.

Table 2. Synthesis of 7-substituted 3,6-dihydropyrrolo[3,2-*e*]indazoles via *N*-deprotection of *N*-(3)-phenylsulfonylpyrroloindazoles

| Entry | 3-Phenylsulfonyl-pyrroloindazole | Product | Yield (%) | Mp (°C) |
|-------|----------------------------------|----------------|-----------|---------------|
| 1 | 12a | 13a | 87 | 162-164 (dec) |
| 2 | 12b | 13b | 86 | 134-136 (dec) |
| 3 | 12c | 13c | 85 | 168-170 |
| 4 | 12d | 13d | 88 | 134-136 |
| 5 | 12e | 13e | 90 | 130-132 |
| 6 | 12f | 13f | 87 | 246-248 |

Table 2 (continued)

| | | | | |
|---|------------|---|----|------|
| 7 | 12g |  | 91 | >250 |
| 8 | 12h |  | 86 | >250 |

Conclusions

An efficient, general synthesis of 7-H/substituted 3,6-dihydropyrrolo[3,2-*e*]indazoles has been developed by the reaction of 4-iodo-1-phenylsulfonyl-5-trifluoroacetamidoindazole with terminal alkynes using Sonogashira/Cacchi coupling-heteroannulation reactions, followed by *N*(3)-deprotection. To the best of our knowledge, this is the first general synthesis of this class of compounds, that too involving domino reactions. The overall procedure is simple, the yields are consistently high and both the indolic and the indazolic nitrogens are amenable to derivatization, thereby rendering our method even more useful. Furthermore, our work opens up the study of the reactions of **10** with internal alkynes, which is likely to unveil interesting results on 7,8-disubstituted pyrroloindazoles.

Pertinently, after the completion of our work, a report was published only a few months ago on a convenient synthesis of pyrrolo[3,4-*g*]indazoles by the annelation of the pyrazole ring on the isoindole moiety, and four members of the synthesized pyrroloindazoles showed modest antitumor activity against a host of human tumor cell lines.⁴⁹

Experimental Section

General. All melting points (in Celsius) were recorded on a Toshniwal apparatus. The IR spectra were recorded on KBr pellets using a Perkin-Elmer-782 spectrophotometer, the ¹H (500 MHz) and ¹³C (125 MHz) NMR spectra (PND, DEPT 135) (except in one case) on a Bruker DRX 500 NMR spectrometer unless otherwise mentioned, the LR EI-MS on a JEOL JMSAX505HA and HR ESI-MS(+) on a Waters Qtof Micro YA263 mass spectrometer. All elemental analyses were carried out on Perkin Elmer 2400 Series II C, H, N Analyzer. Analytical TLCs were carried out on silica gel G (Merck, India) plates. PE refers to petroleum ether, bp 60–80 °C. Column chromatography (CC) was performed using silica gel (100-200 mesh). DMF was dried, distilled

and stored over molecular sieves (4 Å). 5-Nitroindazole, Pd/C and all terminal alkynes were procured from Sigma-Aldrich. Phenylsulfonyl chloride, trifluoroacetic anhydride and hydrazine hydrate were purchased from Spectrochem, India. *N*-Iodosuccinimide (NIS) was purchased from Alfa-Aesar.

Synthesis of 5-amino-4-iodo-1-phenylsulfonylindazole (9). To a solution of 5-amino-1-phenylsulfonylindazole (**8**)¹¹ (2.73 g, 10 mmol) in dry MeCN (60 mL) at rt was gradually added NIS (2.70 g, 12 mmol) and the solution stirred until (2 h) the reaction was complete. The solution was poured into 10% aqueous Na₂S₂O₃ and MeCN distilled off. The solution was extracted with EtOAc (3 × 50 mL), the organic layer separated and washed with H₂O, dried (Na₂SO₄) and the solvent removed under vacuum. The resulting dark colored residue was purified by CC (10% EtOAc in PE) to furnish **9** as a colorless solid, yield 81%, 3.23 g, mp 182-184 °C; IR (ν_{\max} , cm⁻¹): 3468, 3375, 1614, 1505, 1366, 1176, 1058, 817, 725. ¹H NMR (CDCl₃): δ_{H} 5.46 (2H, s, NH₂), 7.09 (1H, d, *J* 9 Hz), 7.51 (2H, td, *J*₁ 7.5 Hz, *J*₂ 1.5 Hz), 7.67 (1H, tt, *J*₁ 7.5 Hz, *J*₂ 1 Hz), 7.84 (1H, d, *J* 9 Hz), 7.82-7.85 (2H, m), 8.06 (1H, d, *J* 1 Hz). ¹³C NMR (CDCl₃): δ_{C} 113.8, 119.3, 127.4, 130.2, 135.3, 144.7 (all CH_{arom}), 69.8, 131.4, 133.3, 136.6, 147.2 (all C_{arom}). MS (EI), *m/z* (%) = 399 (100) (M⁺), 258 (45) (M-SO₂Ph). Anal. Calcd for C₁₃H₁₀IN₃O₂S: C, 39.10; H, 2.51; N, 10.53%. Found: C, 39.15; H, 2.50; N, 10.56%.

Synthesis of 4-iodo-1-phenylsulfonyl-5-(trifluoroacetamido)indazole (10). To a solution of **9** (3.98 g, 10 mmol) in dry THF (75 mL) was added Et₃N (2 mL) and (CF₃CO)₂O (1.95 mL) at 0 °C, and the reaction mixture was stirred until (2 h) the reaction was complete. The solution was diluted with H₂O (40 mL), THF distilled off and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined solvent extracts were washed with H₂O, dried (Na₂SO₄) and the solvent removed to furnish a crude product which was purified by CC (10% EtOAc/PE) to furnish **10** as a brownish solid, yield 83%, 4.11 g, mp 164-166 °C; IR (ν_{\max} , cm⁻¹): 3320, 1727, 1542, 1369, 1282, 1171, 1156, 1088, 1077, 810, 725. ¹H NMR (CDCl₃): δ_{H} 7.50 (2H, td, *J*₁ 7.5 Hz, *J*₂ 1.5 Hz), 7.62 (1H, tt, *J*₁ 7.5 Hz, *J*₂ 1.5 Hz), 8.00 (2H, td, *J*₁ 8 Hz, *J*₂ 1.5 Hz), 8.06 (1H, s), 8.21 (1H, d, *J* 9 Hz), 8.24 (1H, d, *J* 9 Hz), 8.30 (1H, br s). ¹³C NMR (CDCl₃): δ_{C} 113.9, 124.3, 127.7, 129.4, 134.7, 143.7 (all CH_{arom}), 82.8, 130.5, 132.8, 137.0, 137.8 (all C_{arom}), 155.1 (NHCOCF₃). MS (ESI) calcd for C₁₅H₉IN₃O₃F₃S (M⁺) 494.9361; found 494.9340. MS (EI), *m/z* (%) = 495 (40) (M⁺), 368 (100) (M-I). Anal. Calcd for C₁₅H₉IN₃O₃F₃S: C, 36.36; H, 1.82; N, 8.48%. Found: C, 36.41; H, 1.80; N, 8.51%.

General Procedure for the synthesis of 7-H/substituted 3-phenylsulfonyl-3,6-dihydro-pyrrolo[3,2-*e*]indazoles (12a-h). A mixture of **10** (0.25 g, 0.5 mmol), the alkyne **11a-h** (0.7 mmol), Pd(Ph₃P)₂Cl₂ (35 mg; 10 mol %), CuI (19 mg; 10 mol %) and Et₃N (0.7 mL; 5 mmol) in DMF (3 mL) was stirred at 100 °C in argon atmosphere until (5-10 h) the reaction was complete (the reaction darkened in color). It was cooled to rt, filtered through a bed of Celite[®] and washed with EtOAc (3 × 15 mL). The combined organic layer was washed with brine and then H₂O,

dried (Na_2SO_4) and the solvent distilled off. The residue obtained was purified by CC and crystallized from EtOAc/PE mixture.

3-Phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12a). Pale yellow solid, yield 83%, 0.123 g, mp 204-206 °C (dec); IR (ν_{max} , cm^{-1}): 3307, 1584, 1480, 1447, 1375, 1185, 1117, 887, 771, 727, 682. ^1H NMR ($\text{DMSO}-d_6$): δ_{H} 6.75 (1H, d, J 2 Hz), 7.50 (2H, dd, J_1 7.5 Hz, J_2 2 Hz), 7.53 (1H, d, J 1 Hz), 7.62 (1H, t, J 7.5 Hz), 7.71 (1H, d, J 9 Hz), 7.85 (2H, dd, J_1 7.5 Hz, J_2 1.5 Hz), 7.87 (1H, d, J 9 Hz), 8.69 (1H, s), 11.65 (1H, s). ^{13}C NMR ($\text{DMSO}-d_6$): δ_{C} 100.7, 106.1, 115.6, 127.0, 127.2, 130.1, 135.0, 141.9 (all CH_{arom}), 118.8, 119.0, 132.9, 136.6, 137.0 (all C_{arom}). MS (ESI) calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) 320.0470; found: 320.0471.

7-*n*-Butyl-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12b). Colorless solid, yield 88%, 0.155 g, mp 214-216 °C (dec); IR (ν_{max} , cm^{-1}): 3359, 1589, 1370, 1186, 726. ^1H NMR ($\text{DMSO}-d_6$): δ_{H} 0.88 (3H, t, J 7.5 Hz), 1.31 (2H, sextet, J 7.5 Hz), 1.65 (2H, quintet, J 7.5 Hz), 2.74 (2H, t, J 7.5 Hz), 6.47 (1H, s), 7.52 (2H, t, J 7.5 Hz), 7.59 (1H, d, J 9 Hz), 7.63 (1H, t, J 7.5 Hz), 7.78 (1H, d, J 9 Hz), 7.84 (2H, d, J 8 Hz), 8.64 (1H, s), 11.48 (1H, s). ^{13}C NMR ($\text{DMSO}-d_6$): δ_{C} 14.1 (CH_3), 22.2, 27.7, 31.4 (all CH_2), 98.1, 104.8, 114.8, 127.2, 130.0, 135.0, 142.0 (all CH_{arom}), 118.3, 119.7, 132.7, 136.5, 137.0, 142.4 (all C_{arom}). MS (EI) m/z (%) 353 (100) (M^+), 311 (80) ($\text{M}-\text{C}_3\text{H}_6$), 310 (72) ($\text{M}-\text{C}_3\text{H}_7$), 212 (40) ($\text{M}-\text{SO}_2\text{Ph}$). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: C, 64.57; H, 5.42; N, 11.89%. Found: C, 64.52; H, 5.44; N, 11.88%.

7-*n*-Pentyl-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12c). Colorless solid, yield 82%, 0.151 g, mp 186-188 °C (dec); IR (ν_{max} , cm^{-1}): 3338, 1584, 1523, 1451, 1369, 1184, 1118, 808, 727. ^1H NMR (CDCl_3): δ_{H} 0.90 (3H, t, J 7.0 Hz), 1.32-1.40 (4H, m), 1.70 (2H, quintet, J 7.5 Hz), 2.83 (2H, t, J 7.5 Hz), 6.47 (1H, s), 7.41 (2H, t, J 8 Hz), 7.50 (1H, d, J 9 Hz), 7.52 (1H, t, J 7.5 Hz), 7.96 (2H, d, J 8.5 Hz), 8.03 (1H, d, J 9 Hz), 8.72 (1H, br s), 8.98 (1H, s). ^{13}C NMR (CDCl_3): δ_{C} 13.9 (CH_3), 22.4, 28.5, 28.9, 31.3 (all CH_2), 98.5, 107.0, 113.6, 127.3, 129.1, 133.9, 138.3 (all CH_{arom}), 105.9, 113.5, 129.0, 133.8, 140.5, 141.6 (all C_{arom}). MS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) 390.1252; found 390.1198. Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 65.40; H, 5.72; N, 11.44%. Found: C, 65.45; H, 5.74; N, 11.46%.

7-*n*-Hexyl-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12d). Colorless solid, yield 85%, 0.162 g, mp 180-182 °C (dec); IR (ν_{max} , cm^{-1}): 3319, 1583, 1375, 1189, 1074, 726. ^1H NMR ($\text{DMSO}-d_6$): δ_{H} 0.80 (3H, t, J 7.0 Hz), 1.24 (6H, m), 1.63 (2H, quintet, J 7 Hz), 2.74 (2H, t, J 7.5 Hz), 6.46 (1H, s), 7.53 (2H, t, J 7.5 Hz), 7.64 (1H, t, J 7 Hz), 7.65 (1H, d, J 7.5 Hz), 7.87 (2H, d, J 7.5 Hz), 7.88 (1H, d, J 7.5 Hz), 8.93 (1H, s), 12.04 (1H, s). ^{13}C NMR ($\text{DMSO}-d_6$): δ_{C} 14.3 (CH_3), 22.4, 28.1, 28.5, 29.1, 31.3 (all CH_2), 98.0, 106.1, 115.3, 127.2, 130.1, 135.2, 138.5 (all CH_{arom}), 118.1, 121.7, 133.1, 136.9, 137.1, 142.9 (all C_{arom}). MS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_2\text{S}$ ($\text{M}+\text{H}$) 382.1589; found: 382.1592. Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: C, 66.14; H, 6.04; N, 11.02%. Found: C, 66.18; H, 6.07; N, 11.07%.

7-(3-Cyanopropyl)-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12e). Colorless solid, yield 94%, 0.171 g, mp 258-260 °C (dec); IR (ν_{max} , cm^{-1}): 3345, 2241, 1588, 1538, 1445, 1366, 1188, 1105, 728, 689. ^1H NMR ($\text{DMSO}-d_6$): δ_{H} 1.96 (2H, quintet, J 7 Hz), 2.51 (2H, t, J 7.5 Hz), 2.85 (2H, t, J 7.5 Hz), 6.52 (1H, s), 7.51 (2H, t, J 8 Hz), 7.60 (1H, d, J 8.5 Hz), 7.62

(1H, t, J 8 Hz), 7.79 (1H, d, J 9 Hz), 7.83 (2H, t, J 8 Hz), 8.64 (1H, s), 11.58 (1H, s). ^{13}C NMR (DMSO- d_6): δ_{C} 16.2, 25.0, 27.0 (all CH_2), 98.7, 105.2, 114.9, 127.2, 130.0, 132.9, 135.0 (all CH_{arom}), 118.4, 119.6, 120.8, 136.5, 137.0, 140.3, 142.0 (CN + rest C_{arom}). MS (ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) 387.0892; found: 387.0854. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$: C, 62.64; H, 4.39; N, 15.38%. Found: C, 62.69; H, 4.37; N, 15.40%.

7-Phenyl-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12f). Colorless solid, yield 93%, 0.174 g, mp 238-240 °C (dec); IR (ν_{max} , cm^{-1}): 3349, 1589, 1476, 1446, 1187, 1114, 766, 751, 726, 685. ^1H NMR (DMSO- d_6): δ_{H} 7.21 (1H, s), 7.31 (1H, t, J 7.5 Hz), 7.46 (2H, t, J 7.5 Hz), 7.53 (2H, t, J 7.5 Hz), 7.64 (1H, t, J 7 Hz), 7.71 (1H, d, J 9 Hz), 7.85 (2H, d, J 8.5 Hz), 7.87 (2H, d, J 9 Hz), 7.89 (1H, d, J 9.5 Hz), 8.70 (1H, s), 12.10 (1H, s). ^{13}C NMR (DMSO- d_6): δ_{C} 98.3, 106.7, 115.3, 125.6, 127.0, 128.3, 129.5, 130.1, 135.1, 141.8 (all CH_{arom}), 118.6, 120.1, 132.1, 134.1, 136.9, 137.0, 139.4 (all C_{arom}). MS (ESI) calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) 396.0783; found: 396.0773. Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$: C, 67.56; H, 4.02; N, 11.26%. Found: C, 67.52; H, 4.03; N, 11.29%.

7-(4-Methylphenyl)-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12g). Colorless solid, yield 88%, 0.170 g, mp 222-224 °C (dec); IR (ν_{max} , cm^{-1}): 3379, 1589, 1498, 1474, 1449, 1367, 1182, 1109, 807, 783, 727. ^1H NMR (DMSO- d_6): δ_{H} 2.47 (3H, s), 7.32 (1H, s), 7.43 (2H, d, J 8.0 Hz), 7.70 (2H, t, J 7.5 Hz), 7.80 (1H, t, J 7.5 Hz), 7.88 (1H, d, J 9 Hz), 7.92 (2H, d, J 8 Hz), 8.05 (2H, d, J 7.5 Hz), 8.06 (1H, d, J 9.5 Hz), 8.87 (1H, s), 12.22 (1H, s). ^{13}C NMR (DMSO- d_6): δ_{C} 21.2 (CH_3), 97.7, 106.3, 115.2, 125.5, 127.2, 130.0, 130.1, 135.0, 141.9 (all CH_{arom}), 118.8, 120.2, 129.4, 133.9, 136.9, 137.0, 137.7, 139.6 (all C_{arom}). MS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_2\text{SNa}$ ($\text{M}+\text{Na}$) 410.0939; found: 410.0932. Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$: C, 68.22; H, 4.39; N, 10.85%. Found: C, 68.16; H, 4.40; N, 10.89%.

7-(4-Methoxyphenyl)-3-phenylsulfonyl-3,6-dihydropyrrolo[3,2-*e*]indazole (12h). Colorless solid, yield 87%, 0.175 g, mp 218-220 °C; IR (ν_{max} , cm^{-1}): 3448, 1608, 1545, 1497, 1379, 1254, 1183, 1111, 1077, 1023, 832, 790, 730, 683. ^1H NMR (DMSO- d_6): δ_{H} 3.94 (3H, s), 7.21 (2H, dd, J_1 8.0 Hz, J_2 1 Hz), 7.25 (1H, s), 7.70 (2H, t, J 8 Hz), 7.80 (1H, dt, J_1 7.5 Hz, J_2 1 Hz), 7.87 (1H, d, J 8.5 Hz), 7.96 (2H, d, J 8 Hz), 8.02-8.08 (3H, m), 8.87 (1H, s), 12.17 (1H, s). ^{13}C NMR (DMSO- d_6): δ_{C} 55.6 (OCH_3), 97.1, 106.0, 114.9, 115.1, 127.0, 127.2, 130.1, 135.0, 141.9 (all CH_{arom}), 118.5, 120.3, 124.8, 133.9, 136.9, 137.1, 136.9, 159.5 (all C_{arom}). MS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_3\text{SNa}$ ($\text{M}+\text{Na}$) 426.0889; found: 426.0889. Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$: C, 65.51; H, 4.22; N, 10.42%. Found: C, 65.57; H, 4.23; N, 10.44%.

General procedure for *N*(3)-deprotection of 12a-h. To a solution of **12a-h** (1 mmol) in MeOH (30 mL) was added an aqueous solution (10 mL) of K_2CO_3 (0.55 g; 4 mmol), and the solution was refluxed for 2 h. It was diluted with H_2O (40 mL), MeOH distilled off and the solution extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine and then H_2O , dried (Na_2SO_4) and the solvent distilled off. The residue was purified by CC to furnish **13a-h**. All the products were crystallised from EtOAc/PE.

3,6-Dihydropyrrolo[3,2-*e*]indazole (13a). Colorless solid, yield 87%, 0.137 g, mp 162-164 °C (dec); IR (ν_{max} , cm^{-1}): 3433, 3327, 1505, 937, 771. ^1H NMR (400 MHz, CDCl_3): δ_{H} 6.83 (1H, d,

J 2 Hz), 7.28 (1H, d, *J* 2 Hz), 7.29 (1H, d, *J* 8.8 Hz), 7.45 (1H, d, *J* 8.8 Hz), 8.23 (1H, s), 8.94 (1H, br s). ¹³C NMR (100 MHz, CDCl₃): δ_C 100.5, 104.6, 112.7, 123.2, 131.8 (all CH_{arom}), 115.8, 118.0, 130.3, 136.9 (all C_{arom}). MS (ESI) calcd for C₉H₈N₃ (M+H) 158.0712; found: 158.0710. Anal. Calcd for C₉H₇N₃: C, 68.78; H, 4.49; N, 26.74%. Found: C, 68.80; H, 4.48; N, 26.77%.

7-*n*-Butyl-3,6-dihydropyrrolo[3,2-*e*]indazole (13b). Colorless solid, yield 86%, 0.183 g, mp 134-136 °C (dec); IR (ν_{max}, cm⁻¹): 3371, 3202, 3178, 1546, 1344, 938, 780. ¹H NMR (CDCl₃): δ_H 0.96 (3H, t, *J* 7.5 Hz), 1.43 (2H, sextet, *J* 7.5 Hz), 1.73 (2H, quintet, *J* 7.5 Hz), 2.81 (2H, t, *J* 7.5 Hz), 6.54 (1H, s), 7.18 (1H, d, *J* 9 Hz), 7.34 (1H, d, *J* 8.5 Hz), 8.24 (1H, s), 8.34 (1H, s), 10.47 (1H, br s). ¹³C NMR (CDCl₃): δ_C 13.9 (CH₃), 22.4, 28.0, 31.5 (all CH₂), 98.7, 103.2, 112.3, 132.8 (all CH_{arom}), 115.8, 119.3, 129.8, 136.9, 139.4 (all C_{arom}). MS (ESI) calcd for C₁₃H₁₆N₃ (M+H) 214.1343; found: 214.1349. Anal. Calcd for C₁₃H₁₅N₃: C, 73.21; H, 7.09; N, 19.70%. Found: C, 73.25; H, 7.10; N, 19.73%.

7-*n*-Pentyl-3,6-dihydropyrrolo[3,2-*e*]indazole (13c). Colorless solid, yield 85%, 0.195 g, mp 168-170 °C; IR (ν_{max}, cm⁻¹): 3271, 3205, 1530, 1464, 1378, 945, 783. ¹H NMR (DMSO-*d*₆): δ_H 0.83 (3H, t, *J* 7 Hz), 1.27-1.29 (4H, m), 1.64 (2H, quintet, *J* 7 Hz), 2.72 (2H, t, *J* 7.5 Hz), 6.37 (1H, s), 7.23 (1H, d, *J* 9 Hz), 7.35 (1H, d, *J* 9 Hz), 8.46 (1H, s), 11.64 (1H, s), 13.04 (1H, s). ¹³C NMR (DMSO-*d*₆): δ_C 14.3 (CH₃), 22.2, 28.1, 29.0, 31.1 (all CH₂), 98.1, 104.7, 112.8, 129.3 (all CH_{arom}), 115.3, 121.1, 130.4, 137.3, 139.6 (all C_{arom}). MS (ESI) calcd for C₁₄H₁₈N₃ (M+H) 228.1500; found: 228.1500. Anal. Calcd for C₁₄H₁₇N₃: C, 74.00; H, 7.49; N, 18.5%. Found: C, 74.15; H, 7.47; N, 18.55%.

7-*n*-Hexyl-3,6-dihydropyrrolo[3,2-*e*]indazole (13d). Colorless solid, yield 88%, 0.212 g, mp 134-136 °C; IR (ν_{max}, cm⁻¹): 3379, 3214, 1531, 1449, 1342, 1167, 1115, 1038, 943, 843, 776, 684. ¹H NMR (CDCl₃): δ_H 0.89 (3H, t, *J* 6.5 Hz), 1.27-1.36 (4H, m), 1.39 (2H, quintet, *J* 7 Hz), 1.70 (2H, quintet, *J* 7.5 Hz), 2.83 (2H, t, *J* 7.5 Hz), 6.54 (1H, s), 7.24 (1H, d, *J* 8.5 Hz), 7.34 (1H, d, *J* 8.5 Hz), 8.73 (1H, s), 8.83 (1H, s). ¹³C NMR (CDCl₃): δ_C 14.0 (CH₃), 22.4, 28.3, 28.7, 28.7, 31.4 (all CH₂), 97.8, 104.4, 112.3, 130.1 (all CH_{arom}), 115.3, 121.2, 129.8, 137.4, 139.5 (all C_{arom}). MS (ESI) calcd for C₁₅H₂₀N₃ (M+H) 242.1657; found: 242.1667. Anal. Calcd for C₁₅H₁₉N₃: C, 74.69; H, 7.88; N, 17.43%. Found: C, 74.60; H, 7.85; N, 17.46%.

7-(3-Cyanopropyl)-3,6-dihydropyrrolo[3,2-*e*]indazole (13e). Colorless solid, yield 90%, 0.202 g, mp 130-132 °C; IR (ν_{max}, cm⁻¹): 3381, 3330, 2251, 1626, 1600, 1551, 1437, 1327, 945, 783. ¹H NMR (DMSO-*d*₆): δ_H 2.16 (2H, t, *J* 7 Hz), 2.68 (2H, t, *J* 6.5 Hz), 3.02 (2H, t, *J* 6.5 Hz), 6.61 (1H, s), 7.32 (1H, d, *J* 8.5 Hz), 7.49 (1H, d, *J* 8.5 Hz), 8.24 (1H, s), 11.33 (1H, s), 13.00 (1H, s). ¹³C NMR (DMSO-*d*₆): δ_C 16.3, 25.2, 27.1 (all CH₂), 98.7, 103.6, 112.5, 132.0 (all CH_{arom}), 118.7, 115.7, 120.9, 130.3, 132.0, 137.5 (CN + rest C_{arom}). MS (ESI) calcd for C₁₃H₁₃N₄ (M+H) 225.1146; found: 225.1105. Anal. Calcd for C₁₃H₁₂N₄: C, 69.64; H, 5.36; N, 25.00%. Found: C, 69.60; H, 5.37; N, 24.95%.

7-Phenyl-3,6-dihydropyrrolo[3,2-*e*]indazole (13f). Pale yellow solid, yield 87%, 0.203 g, mp 246-248 °C; IR (ν_{max}, cm⁻¹): 3434, 3128, 1624, 1596, 1475, 1439, 1379, 1164, 952, 788, 754, 689. ¹H NMR (DMSO-*d*₆): δ_H 7.33 (1H, s), 7.44 (1H, d, *J* 8 Hz), 7.60 (2H, t, *J* 8 Hz), 7.61 (2H, t, *J* 7.5 Hz), 8.03 (2H, d, *J* 7.5 Hz), 8.33 (1H, s), 11.91 (1H, s), 13.13 (1H, s). ¹³C NMR (DMSO-

d_6): δ_C 98.5, 105.3, 112.8, 125.0, 127.4, 129.4, 131.8 (all CH_{arom}), 115.8, 119.4, 131.9, 132.9, 136.6, 137.0 (all C_{arom}). MS (ESI) calcd for $C_{15}H_{11}N_3$ (M^+) 233.0953; found: 233.0900. Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.25; H, 4.72; N, 18.03%. Found: C, 77.25; H, 4.70; N, 18.06%.

7-(4-Methylphenyl)-3,6-dihydropyrrolo[3,2-*e*]indazole (13g). Colorless solid, yield 91%, 0.225 g, mp > 250 °C; IR (ν_{max} , cm^{-1}): 3429, 3179, 1624, 1544, 1375, 1348, 1164, 1082, 951, 851, 790. 1H NMR (DMSO- d_6): δ_H 2.49 (3H, s), 7.25 (1H, s), 7.41 (1H, d, J 9 Hz), 7.42 (2H, d, J 8 Hz), 7.59 (1H, d, J 9 Hz), 7.91 (2H, d, J 8 Hz), 8.30 (1H, s), 11.83 (1H, s), 13.09 (1H, s). ^{13}C NMR (DMSO- d_6): δ_C 21.2 ($PhCH_3$), 97.9, 105.0, 112.7, 125.0, 129.9, 131.8 (all CH_{arom}), 115.7, 119.4, 130.2, 131.6, 136.7, 136.8, 137.0 (all C_{arom}). MS (ESI) calcd for $C_{16}H_{14}N_3$ ($M+H$) 248.1187; found: 248.1107. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.73; H, 5.26; N, 17.01%. Found: C, 77.77; H, 5.28; N, 17.04%.

7-(4-Methoxyphenyl)-3,6-dihydropyrrolo[3,2-*e*]indazole (13h). Colorless solid, yield 86%, 0.226 g, mp > 250 °C; IR (ν_{max} , cm^{-1}): 3425, 3163, 1607, 1546, 1495, 1253, 1180, 1025, 828, 785. 1H NMR (DMSO- d_6): δ_H 3.77 (3H, s), 7.00 (2H, d, J 8 Hz), 7.01 (1H, s), 7.20 (1H, d, J 9 Hz), 7.42 (1H, d, J 9 Hz), 7.76 (2H, d, J 8 Hz), 8.14 (1H, s), 11.62 (1H, s), 12.92 (1H, s). ^{13}C NMR (DMSO- d_6): δ_C 55.6 (OCH_3), 97.3, 104.6, 112.8, 114.8, 126.4, 131.9 (all CH_{arom}), 115.6, 119.5, 125.6, 131.4, 136.8, 137.0, 158.9 (all C_{arom}). MS (ESI) calcd for $C_{16}H_{14}N_3O$ ($M+H$) 264.1137; found: 264.1100. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94; N, 15.97%. Found: C, 73.05; H, 4.96; N, 15.99%.

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