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ORIGINAL PAPER

An efficient, general synthesis of 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles involving one-pot Sonogashira coupling and cyclisation

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Abstract A number of 2-substituted 3,6-dihydropyrrolo-[3,2-*e*]indoles were synthesised efficiently by the reaction of 4-iodo-1-(phenylsulfonyl)-5-(trifluoroacetamido)indole with terminal acetylenes in the presence of a palladium(0) catalyst and a copper(I) co-catalyst. The reaction involved one-pot Sonogashira coupling/heteroannulation, the first one of its kind in the synthesis of the title compounds. The required amido-iodoindole was prepared smoothly from 5-nitroindole by successive N-protection, reduction of the nitroarene, iodination of the resulting aminoarene and *N*-trifluoroacetylation.

Keywords 3,6-Dihydropyrrolo[3,2-*e*]indoles · One-pot synthesis · Palladium(0) catalyst · Sonogashira coupling · Cyclisation

Introduction

Condensed heterocycles continue to be an important arena for drug development. We have been working on the synthesis of condensed heterocycles for the last few decades [1–8]. Our attention was recently drawn to a relatively small group of compounds, viz. pyrroloindoles whose chemistry, including synthesis, has been reviewed [9]. Of the various isomeric pyrroloindole nuclei, the 3,6-dihydropyrrolo[3,2-*e*]-indole nucleus became the focus of efforts because it is present in a number of bioactive natural products, viz. the antitumour antibiotics CC-1065 [10–12], duocarmycin A [13–15], duocarmycin B2 [16], duocarmycin C [14] (identified as pyrindamycin A [17]), duocarmycins D and S [15], duocarmycin SA [15, 18, 19], gilvusmycin [20], yatakemycin (also antifungal) [21–23] and the cAMP phosphodiesterase inhibitors PDE-I (**1**) and PDE-II (**2**) [24, 25] (Fig. 1).

The synthesis and biological studies (antitumour, mainly DNA alkylation) of these compounds have been undertaken successfully by various groups. Several syntheses of the parent nucleus with or without substitution at one or both the pyrrole nuclei have also been reported using mostly Fischer mono- and bis-indolisations besides Bischler cyclisation [26–32]. But in nearly all these cases, the substrates had to be prepared from commercially available starting materials in several steps, a mixture of linear and angular regioisomers was always formed, the final 3,6-dihydropyrrolo[3,2-*e*]indoles were isolated in very poor to low yields and, more importantly, none of these methods was a general synthesis of substituted pyrroloindoles. Thus, there existed a need for the development of a short, efficient and general synthesis of only one type of substituted regioisomers, which should be free of the aforementioned shortcomings.

Our overall strategy was to construct the pyrrole ring on the benzenoid ring of the indole nucleus following protocols available for the synthesis of the indole ring by a two-step process, viz. Sonogashira coupling [33–35] of *o*-iodoanilines with terminal alkynes, followed by cyclisation of the resulting *o*-alkynylanilines.

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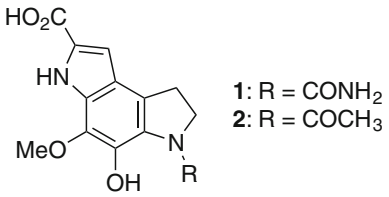


Fig. 1 Pyrrolo[3,2-*e*]indoles as cAMP phosphodiesterase inhibitors

A perusal of the literature, including a review on the application of Sonogashira coupling in the synthesis of heterocycles [36], revealed that a number of one-pot, two-step procedures for the synthesis of 2-substituted indoles have been recently developed from *N*-H/alkyl/acyl *o*-iodoanilines and terminal acetylenes by tandem Sonogashira coupling/5-*endo-dig* cyclisation [37–44]. These tandem reactions were brought about by using a Pd(0) catalyst (e.g. Pd/C-PPh_3, $Pd(OAc)_2$, Pd-zeolite, $(PPh_3)_2PdCl_2$), CuI as the co-catalyst and a base (e.g. Et_3N, Et_2NH, $NH_2CH_2CH_2OH$, NaOH, Cs_2CO_3) as the cyclising agent in a solvent (usually DMF) at ambient temperature, under reflux or under microwave or ultrasound irradiation.

We applied a similar methodology for our purpose. As a result, we have now been able to develop the first one-pot, two-step synthesis of 2-substituted 3,6-dihydropyrrolo[3,2-*e*]-indoles involving a Sonogashira coupling/5-*endo-dig* cyclisation route. The details of our work are briefly presented in this report.

Results and discussion

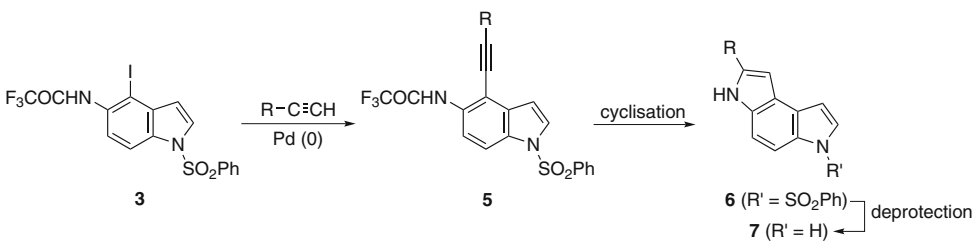
The crucial step of our synthetic strategy was the palladium(0)-catalysed Sonogashira coupling of *N*(1)-protected 5-amino-4-haloindoles with terminal alkynes, followed by cyclisation of the resulting 4-alkynyl-5-aminoindoles. Since aryl iodides commonly show higher reactivity than aryl bromides, a 5-amino-4-iodoindole was chosen as the target. Also, the amine must be protected by an electron-withdrawing group to promote subsequent cyclisation, and the best results had earlier been reported in this regard in other classes of heteroarenes using carbamates and, more usefully, trifluoroacetamides [45–49]. Our modified synthetic strategy, therefore, involved 4-iodo-1-(phenylsulfonyl)-5-(trifluoroacetamido)indole (**3**) as the substrate (Scheme 1).

Accordingly, the required precursor **3** was prepared efficiently, following standard protocols, from commercially available 5-nitroindole by successive *N*-phenylsulfonylation, reduction of the *N*-protected nitroarene to the corresponding arylamine, regioselective iodination at C-4, and trifluoroacetylation of the resulting 5-amino-4-iodo-1-(phenylsulfonyl)indole (Scheme 2).

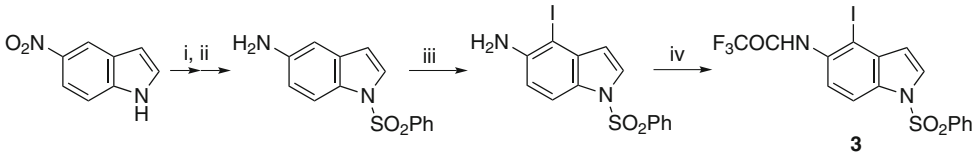
Initially, we tried the alkynylation of **3** with phenylacetylene (**4a**, Ar = Ph). Although several palladium catalysts, co-catalysts, bases and solvents have been widely used in Sonogashira reactions with varying degrees of success [50–52], we employed $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ (10 mol% each) as catalysts because these two compounds continue to be by far the most frequently used catalysts in copper-mediated (CuI, 5 mol% in our case) practical Sonogashira applications [53]. We also used piperidine (excess) and triethylamine (2, 5 and 10 equiv.) as the base and, in most cases, DMF as the solvent. The reactions were carried out (at room temperature or at 110 °C) in argon atmosphere in order to block homocoupling of the terminal alkynes through a copper-mediated Hay/Glaser reaction [54–57]. The outcome of our trial experiments, not detailed in the "Experimental", is presented in Table 1.

A critical analysis of the results is as follows. When piperidine was used as the base without the presence of a co-catalyst, only the alkynylindole **5a** was obtained, irrespective of the nature of the palladium catalyst and the temperature (entries 1–3). In subsequent experiments, 5 mol% of cuprous iodide was used as the co-catalyst. Whereas the use of 2 equiv. of triethylamine also furnished only **5a** (entry 4), the use of 5 equiv. of this base led to the formation of both **5a** and the corresponding cyclised product **6a** with increasing yields of the cyclised product with increasing periods of heating (**5a** 59 %, **6a** 4 % after 3 h; **5a** 51 %, **6a** 13 % after 6 h) (entries 5, 6). The optimal conditions were found to be 10 equiv. of triethylamine and heating for a period of 6 h when only the cyclised product **6a** was isolated in 65 % yield (entry 8). The structures of both **5a** and **6a** were ascertained by analysing their spectroscopic data (IR, ^1H and ^{13}C NMR).

Scheme 1

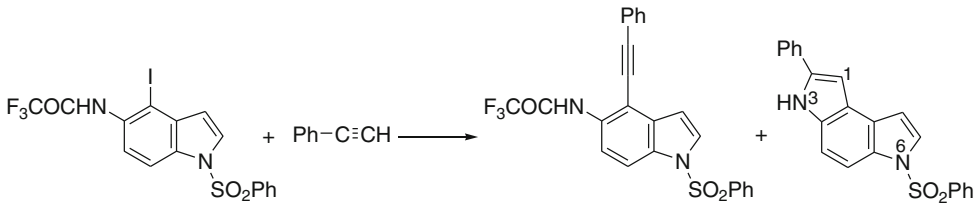


Scheme 2



Reagents and conditions: (i) $PhSO_2Cl$, NaOH, n-$Bu_4N^+HSO_4^-$ (cat.), CH_2Cl_2, rt, 4 h; 95%; (ii) $NH_2NH_2{\cdot}H_2O$ (98%), 10% Pd-C, MeOH, reflux, 6 h; 89%; (iii) *N*-Iodosuccinimide, CH_2Cl_2, -5 °C, 1.5 h; 70%; (iv) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 2 h; 91%.

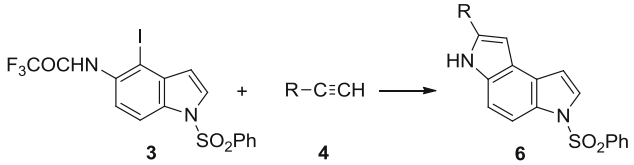
Table 1 Optimisation studies



Entry	Pd catalyst	Base (equiv.)	Solvent	Temp./°C	Time/h	Yield/%	
						5a	**6a**
1	$Pd(PPh_3)_4$	Piperidine	–	r.t.	6	50	–
2	$Pd(PPh_3)_4$	Piperidine	–	100	4	50	–
3	$PdCl_2(PPh_3)_2$	Piperidine	–	100	4	60	–
4	$PdCl_2(PPh_3)_2$	Et_3N (2)	DMF	110	4	65	–
5	$PdCl_2(PPh_3)_2$	Et_3N (5)	DMF	110	3	59	4
6	$PdCl_2(PPh_3)_2$	Et_3N (5)	DMF	110	6	51	13
7	$PdCl_2(PPh_3)_2$	Et_3N (10)	DMF	110	3	20	39
8	$PdCl_2(PPh_3)_2$	Et_3N (10)	DMF	110	6	–	65

All reactions were carried out in argon atmosphere using 10 mol% of Pd catalyst. In entries 4–8, 5 mol% of CuI was additionally used

Since the outcome of the reaction presented in entry 8 unveiled a novel synthetic route to 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles, we next explored the generality of this procedure. Accordingly, **3** was treated with a number of terminal acetylenes bearing a *p*-tolyl group (**4b**), alkyl groups (**4c**–**4e**), alkyl groups attached to an electron-withdrawing group (**4f**, **4g**), a methoxycarbonyl group (**4h**) and a trimethylsilyl group (**4i**) using the conditions



Scheme 3

employed in entry 8 of Table 1 (Scheme 3). All the reactions were complete in 3–9 h. The results are presented in Table 2.

As expected, all the products were identified spectroscopically as the novel 6-phenylsulfonyl derivatives of the corresponding cyclised products (**6a**–**6f**, **6h**), i.e. the corresponding 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles, except for those arising from **4g** and **4i**. The product from propargyl propionate (**4g**) was identified as 3,6-dihydro-2-(hydroxymethyl)pyrrolo[3,2-*e*]indole (**6g**), suggesting that either the initially formed, unisolated coupling product (**5g**) or the corresponding cyclised product underwent hydrolysis during the reaction. The product from TMS-acetylene (**4i**), on the other hand, underwent hydrosilylation either before or after the cyclisation, furnishing **6i** as the only isolated product. Noticeably, except for these two cases

Table 2 One-pot synthesis of *N*(6)-protected 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles **6a–6i** (Scheme 3)

Entry	Alkyne	Product	Time/h	Yield/%	M.p./°C
1	**4a**, R = C_6H_5	**6a**, R = C_6H_5	6	65	200–202
2	**4b**, R = 4-MeC_6H_4	**6b**, R = 4-MeC_6H_4	5	65	204–206
3	**4c**, R = *n*-C_4H_9	**6c**, R = *n*-C_4H_9	4	64	98–100
4	**4d**, R = *n*-C_5H_{11}	**6d**, R = *n*-C_5H_{11}	4	60	80–82
5	**4e**, R = *n*-C_6H_{13}	**6e**, R = *n*-C_6H_{13}	4	58	60–62
6	**4f**, R = $(CH_2)_3CN$	**6f**, R = $(CH_2)_3CN$	4	66	160–162
7	**4g**, R = *n*-$C_3H_7CO_2CH_2$	**6g**, R = CH_2OH	9	35	166–168
8	**4h**, R = COOMe	**6h**, R = COOMe	3	45	151–153
9	**4i**, R = TMS	**6i**, R = H	3	80	108–110

Conditions: **3** (0.5 mmol), CuI (5 mol%), $PdCl_2(PPh_3)_2$ (10 mol%), alkynes **4a–4i** (1.5 equiv), Et_3N (10 equiv), 5 cm^3 DMF, 110 °C, 3–9 h

and for methyl propiolate (**4h**), the yields of the pyrroloindoles ranged from 58–66 %. Whereas TMS-acetylene (**4i**) led to a higher yield (80 %) of the desilylated pyrroloindole (**6i**), propargyl propionate (**4g**) and methyl propiolate (**4h**) furnished **6g** and **6h** in inexplicably lower yields, viz. 35 and 45 %, respectively. In the last two cases, no other product was found (TLC monitoring) to be formed.

The *N*-deprotection of the products **6** was not expected to pose any problem. Yet, in order to verify this notion, each of **6a**, **6c** and **6i**, chosen arbitrarily, was separately refluxed in methanol solution with magnesium and ammonium chloride [58–60] to afford the corresponding *N*-deprotected 3,6-dihydropyrrolo[3,2-*e*]indoles **7a**, **7c** and **7i** in 64, 55 and 67 % yields, respectively. The ^{1}H NMR data of both **7a** [26] and **7i** [31] agreed well with those reported earlier for them. Pertinently, compound **7a** had earlier been prepared from acetophenone and (1-acetyl-5-indolinyl)hydrazine in four steps in an overall yield of 0.4 % [26], which is clearly of no synthetic significance.

Conclusion

We have developed an expedient synthesis of 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles from 4-iodo-1-(phenylsulfonyl)-5-(trifluoroacetamido)indole and terminal acetylenes involving one-pot Sonogashira coupling/heteroannulation as the key step. The indolic substrate was efficiently prepared from 5-nitroindole in a four-step procedure. Noticeably, the use of trimethylsilylacetylene furnished the 2-unsubstituted 3,6-dihydropyrroloindole directly. To our knowledge, the present synthesis constitutes the first one-pot Sonogashira coupling/heteroannulation route to 2-substituted 3,6-dihydropyrrolo[3,2-*e*]indoles. This general synthesis of only one type of regioisomeric pyrroloindole is short yet efficient and devoid of the difficulties encountered in earlier routes to this class of condensed heterocycles.

Experimental

All reactions were carried out using oven-dried glassware. Commercial grade reagents were used without further purification. Solvents were dried prior to use following standard literature procedures. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C. DMF was dried, distilled and stored over molecular sieves (4 Å). Tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, *N*-iodosuccinimide and all alkynes were purchased from Sigma-Aldrich (USA). Trifluoroacetic anhydride was purchased from Alfa Aesar (Lancaster). Melting points were recorded in open capillaries. Infrared spectra were obtained as thin films on KBr pellets using a Shimadzu Fourier transform (FT–IR) 8300 spectrophotometer. ^{1}H (500 MHz) and ^{13}C (125 MHz, PND and DEPT-135) NMR spectra were recorded on a Bruker AVANCE III 500 MHz NMR spectrometer using tetramethylsilane as the internal standard. HR-MS spectra were taken using a TRACE GC ULTRA POLARIS Q mass spectrometer. Precoated silica gel 60 F254 TLC sheets (Merck) were used for thin-layer chromatography (TLC). All new compounds were also subjected to elemental analysis (C, H, N) in a Perkin Elmer 2400 Series II Analyser, and the results were in good agreement (±0.3 %) with the calculated values. Purification by column chromatography (CC) was done using 100–200 mesh silica gel (Merck). Anhydrous sodium sulfate was used for drying solutions. 1-(Phenylsulfonyl)indol-5-amine was prepared from 5-nitroindole, procured commercially, on 10 mmol scale, following a procedure [61] reported earlier from this laboratory.

4-Iodo-1-(phenylsulfonyl)indol-5-amine ($C_{14}H_{11}IN_2O_2S$) *N*-Iodosuccinimide (2.70 g, 12 mmol) was added in portions to a solution of 2.72 g 1-(phenylsulfonyl)indol-5-amine (10 mmol) in 50 cm^3 dry CH_2Cl_2 at −5 °C, and the solution was stirred until the reaction was complete (1.5 h). The mixture was poured into 10 % aqueous $Na_2S_2O_3$ solution, and the organic layer was separated, washed with

water, dried, filtered and the solvent removed under vacuum. A dark coloured residue was obtained, which was purified by CC using EtOAc/PE (1:9) as the eluent to furnish the product as a yellow solid. Yield: 2.78 g (70 %); m.p.: 138–140 °C; IR (KBr): $\bar{\nu}$ = 3,428, 3,325, 1,447, 1,370, 1,168, 1,137 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.04 (br s, 2H), 6.49 (dd, J = 3.5 Hz, 0.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 7.41 (tt, J = 7.5 Hz, 1.5 Hz, 2H), 7.51 (tt, J = 7.5 Hz, 1.5 Hz, 1H), 7.52 (d, J = 3.5 Hz, 1H), 7.76 (dd, J = 9.0 Hz, 1.0 Hz, 1H), 7.82 (dd, J = 8.5 Hz, 1.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$): δ = 75.7, 127.7, 136.4, 138.5, 143.9 (all Ar–C), 113.0, 113.4, 114.8, 127.0, 127.3, 129.6, 134.2 (all Ar–CH) ppm; HR-MS: calcd for $C_{14}H_{11}IN_2O_2S$ 397.9586 (M^+), found 397.9584.

N-[4-Iodo-1-(phenylsulfonyl)indol-5-yl]trifluoroacetamide (**3**, $C_{16}H_{10}F_3IN_2O_3S$)

Et_3N (2 cm^3) and 1.95 cm^3 $(CF_3CO)_2O$ were successively added to a solution of 3.98 g 4-iodo-1-(phenylsulfonyl) indol-5-amine (10 mmol) in 50 cm^3 dry CH_2Cl_2 at 0 °C, and the solution was stirred until the reaction was complete (2 h). The reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extract was washed with water, dried and the solvent removed. The residue was crystallised from CH_2Cl_2/PE to furnish **3** as a light brown solid. Yield: 4.5 g (91%); m.p.: 218–220 °C; IR (KBr): $\bar{\nu}$ = 3,355, 1,716, 1,376, 1,170, 1,135 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.67 (dd, J = 3.5 Hz, 0.5 Hz, 1H), 7.50 (tt, J = 7.5 Hz, 1.5 Hz, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.61 (tt, J = 7.5 Hz, 1.5 Hz, 1H), 7.70 (d, J = 3.5 Hz, 1H), 7.89 (dd, J = 8.5 Hz, 1.0 Hz, 2H), 7.98 (d, J = 9.0 Hz, 1H), 10.01 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ = 84.7, 132.3, 132.9, 136.3, 137.9 (all Ar-C), 113.1, 114.1, 122.8, 127.0, 127.9, 129.9, 134.7 (all Ar-CH) ppm; HR-MS: calcd for $C_{16}H_{10}F_3IN_2O_3S$ 493.9409 (M^+), found 493.9412.

N-[4-(Phenylethynyl)-1-(phenylsulfonyl)indol-5-yl]-trifluoroacetamide (**5a**, $C_{24}H_{15}F_3N_2O_3S$)

White solid; yield: 120 mg (51%); m.p.: 194–196 °C; IR (KBr): $\bar{\nu}$ = 3,382, 2,174, 1,724, 1,368, 1,347, 1,155, 1,140 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.88 (d, J = 3.5 Hz, 1H), 7.38–7.43 (m, 3H), 7.47 (t, J = 7.5 Hz, 2H), 7.51–7.60 (m, 3H), 7.67 (d, J = 3.5 Hz, 1H), 7.88 (dd, J = 8.0 Hz, 1.5 Hz, 2H), 8.03 (d, J = 9.0 Hz, 1H), 8.31 (d, J = 9.5 Hz, 1H), 8.80 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ = 80.9, 101.4, 106.3, 114.8, 121.7, 128.4, 132.1, 132.2, 138.0, 154.4, 154.7 (all Ar–C), 108.6, 114.7, 117.0, 126.9, 127.0, 128.8, 129.60, 129.63, 131.6, 134.3 (all Ar–CH) ppm; HR-MS: calcd for $C_{24}H_{15}F_3N_2O_3S$ 468.0755 (M^+), found 468.0760.

General procedure for the synthesis of compounds ***6a–6i***

A mixture of **3** (0.5 mmol), alkyne **4** (0.75 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (5 mol%), Et_3N (5 mmol) and 5 cm^3 DMF was stirred at 110 °C for 3–9 h in an argon atmosphere. It was then cooled to rt, filtered through a bed of Celite and the Celite bed was washed with CH_2Cl_2 (3 × 15 cm^3). The combined organic extract was washed with brine and then water, dried and the solvent distilled off. Purification of the residue by CC and elution with EtOAc/PE afforded **6a–6i** in 35–80 % yields.

3,6-Dihydro-2-phenyl-6-(phenylsulfonyl)pyrrolo[3,2-e]-indole (**6a,** $C_{22}H_{16}N_2O_2S$)

Yellow solid; yield: 121 mg (65%); m.p.: 200–202 °C; IR (KBr): $\bar{\nu}$ = 3,432, 1,359, 1,182, 1,141, 1,124 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 7.15 (dd, J = 3.5 Hz, 0.5 Hz, 1H), 7.20 (d, J = 1.5 Hz, 1H), 7.37 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 2H), 7.71 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 3.5 Hz, 1H), 7.91 (dd, J = 8.5 Hz, 1.0 Hz, 2H), 8.00 (dd, J = 9.0 Hz, 1.0 Hz, 2H), 11.81 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ = 97.9, 108.1, 109.1, 109.7, 125.3, 126.0, 126.9, 127.8, 129.4, 130.1, 134.7 (all Ar–CH), 121.6, 123.0, 129.2, 132.6, 134.0, 137.8, 138.1 (all Ar–C) ppm; HR-MS: calcd for $C_{22}H_{16}N_2O_2S$ 372.0932 (M^+), found 372.0928.

3,6-Dihydro-2-(4-methylphenyl)-6-(phenylsulfonyl)pyrrolo-[3,2-e]indole (**6b**, $C_{23}H_{18}N_2O_2S$)

White solid; yield: 126 mg (65%); m.p.: 204–206 °C; IR (KBr): $\bar{\nu}$ = 3,449, 3,399, 1,364, 1,178, 1,136 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3H), 6.91 (d, J = 2.5 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 3.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 3H), 8.44 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.25 (CH_3), 97.8, 108.2, 108.5, 125.0, 125.4, 126.6, 128.4, 129.1, 129.4, 129.7, 133.5 (all Ar–CH), 121.8, 123.1, 129.3, 129.8, 133.1, 137.6, 138.4 (all Ar–C) ppm; HR-MS: calcd for $C_{23}H_{18}N_2O_2S$ 386.1089 (M^+), found 386.1085.

2-Butyl-3,6-dihydro-6-(phenylsulfonyl)pyrrolo[3,2-e]-indole (**6c**, $C_{20}H_{20}N_2O_2S$)

Light brown solid; yield: 113 mg (64%); m.p.: 98–100 °C; IR (KBr): $\bar{\nu}$ = 3,400, 1,364, 1,185, 1,166, 1,139 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.5 Hz, 3H), 1.39 (m, 2H), 1.68 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 6.39 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 4.0 Hz, 0.5 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 7.34 (tt, J = 7.5 Hz, 1.5 Hz, 2H), 7.43 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 7.57 (d, J = 4.0 Hz, 1H), 7.78 (dd, J = 9.0 Hz, 0.5 Hz, 1H), 7.84 (dd,

$J = 8.5$ Hz, 1.5 Hz, 2H), 8.03 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (CH_3), 22.7, 28.4, 31.8 (all CH_2), 98.4, 107.6, 108.6, 108.7, 125.5, 127.0, 129.4, 133.8 (all Ar–CH), 121.1, 123.1, 130.0, 132.4, 138.8, 140.4 (all Ar–C) ppm; HR-MS: calcd for $C_{20}H_{20}N_2O_2S$ 352.1245 (M^+), found 352.1240.

3,6-Dihydro-2-pentyl-6-(phenylsulfonyl)pyrrolo[3,2-e]-indole (**6d**, $C_{21}H_{22}N_2O_2S$)
Light brown solid; yield: 110 mg (60%); m.p.: 80–82 °C; IR (KBr): $\bar{\nu} = 3{,}406$, 1,363, 1,185, 1,139 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 7.0$ Hz, 3H), 1.34 (m, 4H), 1.69 (quintet, $J = 7.5$ Hz, 2H), 2.74 (t, $J = 7.5$ Hz, 2H), 6.38 (s, 1H), 6.85 (d, $J = 3.5$ Hz, 1H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 2H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.56 (d, $J = 3.5$ Hz, 1H), 7.78 (d, $J = 9.0$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 2H), 8.01 (br s, 1H), ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.0$ (CH_3), 22.3, 28.3, 29.1, 31.5 (all CH_2), 98.0, 107.3, 108.2, 108.3, 125.2, 126.6, 129.0, 133.5 (all Ar–CH), 121.2, 122.8, 129.7, 132.0, 138.5, 140.1 (all Ar–C) ppm; HR-MS: calcd for $C_{21}H_{22}N_2O_2S$ 366.1402 (M^+), found 366.1408.

2-Hexyl-3,6-dihydro-6-(phenylsulfonyl)pyrrolo[3,2-e]-indole (**6e**, $C_{22}H_{24}N_2O_2S$)
Light brown solid; yield: 110 mg (58%); m.p.: 60–62 °C; IR (KBr): $\bar{\nu} = 3{,}460$, 1,618, 1,399, 1,363, 1,140 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J = 7.0$ Hz, 3H), 1.32 (m, 4H), 1.71 (m, 2H), 1.38 (m, 2H), 2.76 (t, $J = 7.5$ Hz, 2H), 6.40 (s, 1H), 6.88 (d, $J = 3.5$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.58 (d, $J = 3.5$ Hz, 1H), 7.80 (d, $J = 9.0$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 2H), 8.05 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.2$ (CH_3), 22.7, 28.5, 29.1, 29.5, 31.7 (all CH_2), 98.1, 107.4, 108.4, 125.3, 126.7, 129.1, 133.6 (all Ar–CH), 121.3, 122.9, 129.8, 132.2, 138.6, 140.2 (all Ar–C) ppm; HR-MS: calcd for $C_{22}H_{24}N_2O_2S$ 380.1558 (M^+), found 380.1561.

4-[3,6-Dihydro-6-(phenylsulfonyl)pyrrolo[3,2-e]indol-2-yl]butanenitrile (**6f**, $C_{20}H_{17}N_3O_2S$)
White solid; yield: 120 mg (66%); m.p.: 160–162 °C; IR (KBr): $\bar{\nu} = 3{,}325$, 2,256, 1,382, 1,361, 1,185, 1,159, 1,133 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 2.00$ (quintet, $J = 7.5$ Hz, 2H), 2.60 (t, $J = 7.5$ Hz, 2H), 2.92 (t, $J = 7.5$ Hz, 2H), 7.42 (d, $J = 9.0$ Hz, 1H), 7.60 (dd, $J = 3.5$ Hz, 0.5 Hz, 1H), 7.61 (t, $J = 8.0$ Hz, 2H), 7.71 (tt, $J = 7.5$ Hz, 1.0 Hz, 1H), 7.81 (dd, $J = 9.0$ Hz, 0.5 Hz, 1H), 7.88 (d, $J = 3.5$ Hz, 1H), 7.98 (dd, $J = 8.5$ Hz, 1.0 Hz, 2H), 11.83 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 16.3$, 25.2, 27.3 (all CH_2), 106.5, 107.8, 109.9, 126.0, 126.9, 130.1, 134.8 (all CH), 120.7, 121.7, 122.6, 129.5, 133.1, 137.6, 139.5 (all Ar–C) ppm; HR-MS: calcd for $C_{20}H_{17}N_3O_2S$ 363.1041 (M^+), found 363.1048.

3,6-Dihydro-6-(phenylsulfonyl)pyrrolo[3,2-e]indole-2-methanol (**6g**, $C_{17}H_{14}N_2O_3S$)
White solid; yield: 57 mg (35 %); m.p.: 166–168 °C; IR (KBr): $\bar{\nu} = 3{,}362$, 3,213, 1,349, 1,165, 1,143 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 2.50$ (br, 1H), 2.86 (d, $J = 7.0$ Hz, 1H), 2.95 (d, $J = 7.0$ Hz, 1H), 6.64 (d, $J = 3.5$ Hz, 1H), 7.43 (q, $J = 7.0$ Hz, 2H), 7.52 (br, 1H), 7.53 (d, $J = 7.0$ Hz, 1H), 7.55 (d, $J = 3.5$ Hz, 1H), 7.83 (t, $J = 7.0$ Hz, 2H), 7.93 (t, $J = 7.5$ Hz, 1H), 7.98 (d, $J = 7.0$ Hz, 1H), 10.32 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 109.5$, 113.6, 113.9, 118.5, 126.6, 127.2, 129.3, 133.9 (all Ar–CH), 131.0, 132.2, 132.3, 137.8, 155.0, 155.5 (all Ar–C) ppm; HR-MS: calcd for $C_{17}H_{14}N_2O_3S$ 326.0725 (M^+), found 326.0721.

Methyl 3,6-dihydro-6-(phenylsulfonyl)pyrrolo[3,2-e]-indole-2-carboxylate (**6h**, $C_{18}H_{14}N_2O_4S$)
White solid; yield: 80 mg (45 %); m.p.: 151–153 °C; IR (KBr): $\bar{\nu} = 3{,}366$, 1,718, 1,370, 1,189, 1,164 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 3.86$ (s, 3H), 7.15 (d, $J = 3.5$ Hz, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.42 (d, $J = 9.0$ Hz, 1H), 7.54 (t, $J = 7.5$ Hz, 2H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.80 (d, $J = 3.5$ Hz, 1H), 7.91 (d, $J = 9.0$ Hz, 1H), 7.93 (d, $J = 7.5$ Hz, 2H), 12.14 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 52.6$ (CO_2CH_3), 107.3, 109.5, 111.0, 112.1, 126.9, 127.3, 130.6, 135.3 (all Ar–CH), 120.4, 124.4, 129.5, 130.8, 135.1, 138.1 (all Ar-C), 162.0 (CO_2Me) ppm; HR-MS: calcd for $C_{18}H_{14}N_2O_4S$ 354.0674 (M^+), found 354.0678.

3,6-Dihydro-3-(phenylsulfonyl)pyrrolo[3,2-e]indole (**6i**, $C_{16}H_{12}N_2O_2S$)
White solid; yield: 119 mg (80 %); m.p.: 108–110 °C; IR (KBr): $\bar{\nu} = 3{,}378$, 1,612, 1,365, 1,185, 1,135 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 6.69$ (t, $J = 2.0$ Hz, 1H), 6.91 (d, $J = 3.5$ Hz, 1H), 7.21 (t, $J = 2.5$ Hz, 1H), 7.32 (d, $J = 9.0$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.60 (d, $J = 3.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.87 (d, $J = 9.0$ Hz, 1H), 8.47 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 101.3$, 108.6, 108.8, 109.3, 124.4, 125.7, 127.0, 129.5, 133.9 (all Ar-CH), 120.7, 123.7, 130.0, 132.7, 138.8 (all Ar–C) ppm; HR-MS: calcd for $C_{16}H_{12}N_2O_2S$ 296.0619 (M^+), found 296.0622.

*General procedure for N-deprotection of **6a**, **6c**, and **6i***

A stirred mixture of compound **6a/6c/6i** (0.134 mmol), Mg turnings (2.68 mmol) and NH_4Cl (0.60 mmol) in 3 cm^3 dry MeOH was refluxed until the substrate was fully consumed (8–10 h) and then filtered hot. The filtrate was concentrated to a small volume, diluted with 20 cm^3 water and extracted with CH_2Cl_2 (3×15 cm^3). The combined organic extract was washed with water, dried and the solvent distilled off. The residue was purified by CC using EtOAc/PE as eluent to furnish pure **7a/7c/7i**.

3,6-Dihydro-2-phenylpyrrolo[3,2-e]indole (**7a**)
Light brown solid; yield: 20 mg (64 %); m.p.: 138–140 °C (140–141 °C [26]).

2-Butyl-3,6-dihydropyrrolo[3,2-e]indole (**7c**, $C_{14}H_{16}N_2$)
Light brown gum; yield: 16 mg (58 %); ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H), 1.44 (m, 2H), 1.74 (quintet, $J = 7.5$ Hz, 2H), 2.81 (t, $J = 7.5$ Hz, 2H), 6.48 (s, 1H), 6.73 (s, 1H), 7.16 (s, 2H), 7.19 (s, 1H), 7.94 (br s, 1H), 8.17 (br s, 1H) ppm; HR MS: calcd for $C_{14}H_{16}N_2$ 212.1313 (M^+), found 212.1319.

3,6-Dihydropyrrolo[3,2-e]indole (**7i**)
White solid; yield: 18 mg (67 %); m.p.: 90–92 °C (89–92 °C [31]).

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