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Nucleophilic reactions in the indole series: displacement of bromine under phase transfer catalysis

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ABSTRACT

A novel synthetic approach for the synthesis of 3-substituted indoles by nucleophilic substitution of 3-bromo derivatives under phase transfer catalysis (PTC) was reported.

1. Introduction

The chemistry of indoles is characterized by their strong tendency to undergo ready electrophilic substitution in the five-membered ring, preferentially at position 3 but also at position 2.[1]

Instead, nucleophilic substitutions on the indole system are much less common and generally involve replacement of the hydrogen from the indole five-membered ring. Such substitutions are made possible by the presence of a group on nitrogen such as hydroxyl, methoxy and phenylsulfonyl, which can act as leaving group. In some cases, competing substitution of hydrogen on the six-membered ring can take place. Thus, nucleophilic substitutions on 1-methoxyindole-3-carboxyaldehyde by nitrogen and carbon nucleophiles gave 2-substituted indole-3-carboxyaldehydes in low to excellent yields.[2] The same substrate as well as 1-methoxyindole-2-carboxyaldehyde gave, upon reaction with methoxide or ethoxide ions, the 2-alkoxyindole-3-carboxyaldehydes and 3-alkoxyindole-2-carboxyaldehydes, respectively, in high yields.[3] The reactivity of 1-methoxy-6-nitroindole towards nucleophiles was somehow different; in fact its reaction with methoxide gave 2- and 3-methoxy-6-nitroindoles in 22 and 6% yield, respectively. Whereas, the same substrate reacted with sodium cyanide giving 7-cyano-6-nitroindole in 15% yield and with diethylmalonate, in the presence of potassium *tert*-butoxide, gave a methylene homologation reaction at position 3, instead of simple nucleophilic substitution reaction, and diethyl 2-(6-nitroindol-3-yl)methylmalonate was isolated in 38% yield.[4]

Reaction of 1-hydroxyindole with 2,3-dihydroindole gave, together with many other products, 5-(2,3-dihydroindol-1-yl)indole in poor yield.[3a] Reaction of *Nb*-acyl-1-hydroxy-tryptophan methylester and tryptamine, in the presence of mesyl chloride and triethylamine, gave the corresponding pyrrolo[2,3-*b*]indole derivatives in 47 and 45% yields, respectively, by an intramolecular nucleophilic substitution at the position 2 of the indole system.[3a]

Indoles substituted at position 1 by aryl sulfonates gave variable results from the preparative point of view. In fact reaction of 1-tosyloxyindole-3-carboxaldehyde with sodium methoxide gave 3-tosyloxyindole, 3-methoxyindole and 2-methoxyindole-3-carboxaldehyde in 16, 12 and 8% yields, respectively;[5] whereas, reaction of 2-nitro-1-phenylsulfonylindole with enolates of diethylmalonates, lithium dimethylcuprate and indole anion gave the corresponding 3-substituted 2-nitroindoles in low to high yields.[6] Cyclizing nucleophilic substitutions at position 3 of 1-phenylsulfonylindoles, bearing at position 2 suitable substituents having nitrogen, oxygen or sulfur nucleophiles, led to six- or seven-membered heterocycles annelated to the indole system, with elimination of the phenylsulfinate moiety, mainly in good yields.[7]

A further example of a formal nucleophilic replacement of hydrogen is furnished by the reaction of 2-carboxyindoles with thiols and with *N*-chlorosuccinimide that gave generally good yields of the corresponding 3-sulfenylindoles.[8]

Classical nucleophilic substitution involving replacement of a halogen atom from the five-membered ring of indole was verified only in a couple of reports related to replacement of halogen from position 2. In both cases the halogen replacement was assisted by an electron-withdrawing group in position 3 and by the presence of a substituent on the indole nitrogen. Thus, 2-chloro-1-methoxymethylindole-3-carboxaldehyde reacted with a range of nitrogen, oxygen and sulfur nucleophiles to give the corresponding 2-substituted indoles in 60–78% yield;[9] and 2-iodo-3-nitro-1-(phenylsulfonyl)indole underwent efficient amination under mild condition (43–96% yields).[10]

We have previously reported aromatic nucleophilic substitutions on halogenated pyrroles bearing suitable substituents as

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useful method to introduce a wide range of functional groups into the five-membered ring.[11] Such reactions proved to be a versatile instrument to obtain synthons for the synthesis of polycyclic systems.[12–14]

Considering that nucleophilic substitution at C-3 of indoles was verified only in the case of 1-methoxyindole-2-carboxaldehyde, which is not readily available as it involves a three steps synthesis, through some extremely unstable intermediates,[5] and considering our interest also in the indole chemistry we approached the study of nucleophilic substitution as displacement of the bromine atom at the 3-position of the indole ring. In this paper we wish to describe the reactivity of 2-substituted-3-bromo indoles towards nitrogen, oxygen and sulfur nucleophiles.

2. Results and discussion

Thus, 2-aryl or heteroaryl indoles **1a**,**b**,**d**, conveniently prepared according to known procedures,[15a–c] and the commercially available 2-phenylindole (**1c**) and 2-ethoxycarbonyl indole (**1e**) were selected as substrates for this study, in order to investigate the effect produced by the substituent adjacent to the reaction centre. Smooth bromination of the 3-position of indoles **1b**,**e** with *N*-bromosuccinimide in dimethylformamide, the same procedure that allowed the isolation of bromo derivatives **2a**,**c**,**d**,[15a,b] gave the corresponding bromoindoles **2b**,**e** in 92–95% yield.

In our first attempts, the experimental conditions used in the pyrrole series, i.e., dimethylformamide as a solvent, an excess of the proper nucleophile and stoichiometric amount of triethylamine, to neutralize the hydrobromic acid produced from the substitution reactions, were applied (Method A),[11] but poor results were obtained. In fact 3-bromo indoles **2a**–**e**, under these conditions, reacted with 4-methoxybenzenethiol, selected as sulfur nucleophile, to afford compounds **4a**–**e** in moderate yields (30–40%) and **2a**–**e** reacting with amines (benzylamine, pyrrolidine, morpholine and aniline) gave no direct nucleophilic substitution products. However, 2-(2-nitrophenyl)-1*H*-indole (**2a**) reacted with pyrrolidine, used as solvent (Method B), furnishing **7a** in very poor yields (4%). Moreover, upon melting a mixture of 3,5-dimethoxyaniline and the 2-substituted indoles **2a**–**e** (Method C) only the (3,5-dimethoxyphenyl)-2-(2-nitrophenyl)-1*H*-indol-3-amine (**7b**) was obtained in poor yields (5%). Phenols did not react at all with our substrates **2a**–**e** even with an excess of the nucleophile, and the starting material was recovered from reaction mixtures almost entirely.

In order to investigate the effect of the substitution of the pyrrole nitrogen on the nucleophilic substitution, 2-(2-nitrophenyl)-1*H*-indole **2a**, which proved to be the most reactive among the selected 2-substituted indoles, was methylated with iodomethane using sodium hydride as the base giving the corresponding 1-methylindole **3a** in excellent yields. This latter was reacted with 4-methoxybenzenethiol according to the previously described Method A furnishing only 12% yield of 3-[(4-methoxyphenyl) sulfanyl]-1-methyl-2-(2-nitrophenyl)-1*H*-indole (**5a**).

A more promising and versatile approach for aromatic nucleophilic substitutions on 3-bromoindoles appeared to us was the phase transfer catalysis (PTC). Many reports exist on the application of phase transfer catalysis for the displacement of halogens in aromatic and heteroaromatic compounds by carbon, nitrogen, oxygen and sulfur nucleophiles.[16] These reactions can be performed either in a monophasic solvent system or in a biphasic one. These latter are generally conducted in benzene or toluene and an aqueous sodium hydroxide solution (50:50 by weight) at room temperature or under slight heating, in the presence of tetrabutylammonium chloride as a catalyst. However, reaction of **2a**–**e** under these conditions, using thiophenols or amines as nucleophiles, did not prove successful, even when another ammonium salt, such as 2-methoxyethoxy-*N*,*N*-bis[2-(2-methoxyethoxy) ethyl]ethanamine (TDA-1), was used.

It was reported that in some experiments in which prolonged heating was requested, better results were obtained performing reactions with solid potassium hydroxide as the base and a crown ether as the catalyst.[17] In this light our reactions were conveniently carried out by heating under reflux a mixture of 2-substituted-3-bromoindoles, an excess of the nucleophile, solid potassium hydroxide and dibenzo-18-crown-6 as phase transfer catalyst. Thus, sulfur nucleophiles readily reacted with substrates **2a**–**e** and **3a** in acetonitrile (Method D) to give the 3-substituted indoles **4a**–**e** and **5a** with a satisfactory increase of the yields (56–80%) if compared with those obtained under the classical reaction conditions (Method A). Moreover when 3-bromoindoles **2a**–**d** were reacted under PTC conditions (Method D) with 3-methyl benzenethiol, compounds **6a**–**d** were obtained (56–74%) (Scheme 1).

These results encouraged us to prepare other *N*-methylated products and 2-substituted indoles **2b**–**e** were methylated as described above to give the corresponding 1-methyl derivatives **3b**–**e** in very good yields (80–92%). These latter easily reacted with 4-methoxy-benzenethiol under PTC conditions (Method D) yielding the corresponding products of direct nucleophilic substitution **5b**–**e** (52–62%).

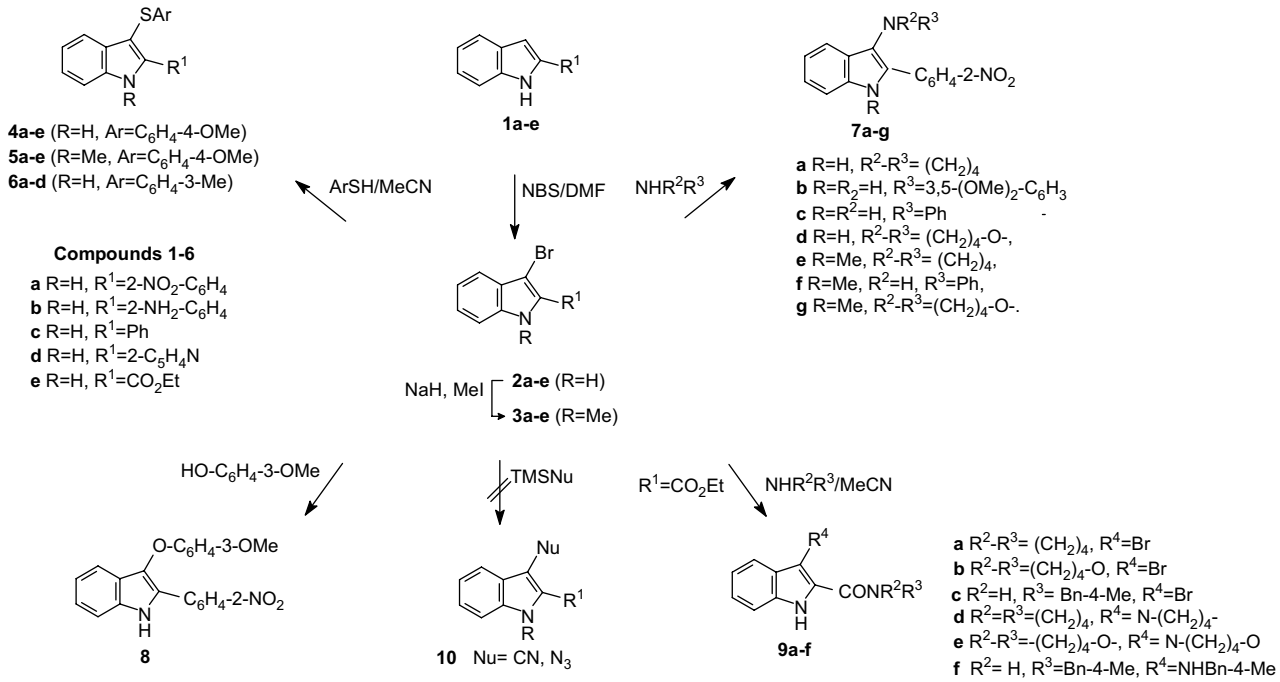
Nitrogen and oxygen nucleophiles needed more severe conditions to react with indoles **2**. In fact the displacement of the bromine generally took place after long refluxing time (24–48 h) only when the amines themselves were used as solvent under PTC conditions (Method E). In particular pyrrolidine, aniline and morpholine reacted either with 2-(2-nitrophenyl)-1*H*-indole (**2a**), giving derivatives **7a**,**c**,**d** in moderate to good yields (30–60%), and with the *N*-methyl derivative **3a** to afford **7e**–**g** in moderate yields (22–42%). Moreover, **2a** reacted with 3-methoxyphenol used as solvent (Method E), affording 40% yield of the corresponding direct substitution product **8**. All the other substrates gave tars and very complex mixtures from which it was not possible to isolate the desired compounds (Table 1).

The 2-ethoxycarbonylindole (**2e**) reacted with pyrrolidine, morpholine and 4-methylbenzylamine at 60 °C under PTC conditions using acetonitrile as solvent (Method D) furnishing the amide derivatives **9a**–**c** (40–55%), respectively, as main products, thus indicating that the displacement of bromine atom at the 3-position is disfavoured with respect to reaction of the ethoxycarbonyl functionality. Moreover using the required amines as solvent and heating under reflux (Method E), a mixture of compounds was obtained from which it was possible to isolate the amides **9a**–**c** (20–35%) and their substitution products **9d**–**f** as main products (45–60%). It seems that more severe reaction conditions forced the first formed amides **9a**–**c** to further react with nucleophiles to give **9d**–**f**.

Phase transfer catalysis reactions of **2a**–**e**, with charged nucleophiles such as azido or cyanide ions either using solid reactives, i.e., sodium azide or sodium cyanide, or using liquid ones to be used as solvent like trimethylsilyl azide or trimethylsilyl cyanide did not produce the desired derivatives **10**.

3. Conclusions

In conclusion, we have reported a method to have access to nucleophilic substitution at C-3 of the indole ring, offering an instrument to prepare functionalized indoles, as useful synthons for the synthesis of polycyclic heterocycles. From our studies it turns out that the displacement of bromine by sulfur, nitrogen or oxygen nucleophiles takes place under phase transfer catalysis even if not assisted by an electron withdrawing group on the α-carbon. Moreover it seems that substitution on the indole nitrogen reduces the reactivity towards nucleophilic substitution.



Scheme 1. Nucleophilic substitutions of 3-bromoindoles **2a**–**e** and **3a**–**e**.

4. Experimental

4.1. General

All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz, respectively, in DMSO-d_6 or $CDCl_3$ using a Bruker Avance II 200 spectrometer (TMS as internal reference). Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with a BÜCHI SEPACORE chromatography module. 2-(2-Nitrophenyl)-1*H*-indole **1a**,[15a] 2-(2-aminophenyl)-1*H*-indole **1b**,[15a] 2-pyridinyl indole **1d**[15c] were prepared according to procedure previously reported. 2-Phenyl-1*H*-indole **1c** and 2-ethoxycarbonylindole **1e** were supplied from Aldrich.

The 3-bromoderivatives **2a**,[15a] **2b**,[15a] **2c**[15b] and **2d**[15b] were prepared according to procedures earlier published.

Table 1
Direct nucleophilic substitution products of bromoindoles

Substrate	Nucleophile	Product	Method (% yields)				
			A	B	C	D	E
2a	HS-C_6H_4-4-OMe	**4a**	35	—	—	76	—
2a	HS-C_6H_4-3-Me	**6a**	—	—	—	74	—
2a	Pyrrolidine	**7a**	0	4	—	—	40
2a	H_2N-C_6H_3-3,5-$(OMe)_2$	**7b**	—	—	5	—	0
2a	Aniline	**7c**	0	—	—	—	30
2a	Morpholine	**7d**	0	—	—	—	60
2a	HO-C_6H_4-3-OMe	**8**	0	—	—	—	40
2b	HS-C_6H_4-4-OMe	**4b**	35	—	—	80	—
2b	HS-C_6H_4-3-Me	**6b**	—	—	—	56	—
2c	HS-C_6H_4-4-OMe	**4c**	35	—	—	70	—
2c	HS-C_6H_4-3-Me	**6c**	—	—	—	58	—
2d	HS-C_6H_4-4-OMe	**4d**	40	—	—	70	—
2d	HS-C_6H_4-3-Me	**6d**	—	—	—	72	—
2e	HS-C_6H_4-4-OMe	**4e**	30	—	—	56	—
2e	Pyrrolidine	**9d**	0	—	—	0	60
2e	Morpholine	**9e**	0	—	—	0	52
2e	H_2N-Bn-4-Me	**9f**	—	—	—	0	45
3a	HS-C_6H_4-4-OMe	**5a**	12	—	—	56	—
3a	Pyrrolidine	**7e**	0	—	—	—	42
3a	Aniline	**7f**	0	—	—	—	25
3a	Morpholine	**7g**	0	—	—	—	22
3b	HS-C_6H_4-4-OMe	**5b**	—	—	—	52	—
3c	HS-C_6H_4-4-OMe	**5c**	—	—	—	56	—
3d	HS-C_6H_4-4-OMe	**5d**	—	—	—	60	—
3e	HS-C_6H_4-4-OMe	**5e**	—	—	—	62	—

Methods: A (Nu/DMF/TEA, reflux, 24 h), B (Nu, reflux, 24 h), C (Nu, 160 °C, 24 h), D (Nu/KOH/18-crown-6 ether/CH_3CN, 60 °C, 6–8 h), E (Nu/KOH/18-crown-6 ether, reflux, 24 h).

4.1.1. *Procedure for the bromination of 2-(2-aminophenyl)-1H-indole (**1b**) and 2-ethoxycarbonyl-indole (**1e**)*

To a solution of **1b** or **1e** (5.3 mmol) in anhydrous DMF (10 mL), a solution of NBS (0.94 g, 5.3 mmol) in anhydrous DMF (4 mL) was added at room temperature. After 2 h stirring the reaction mixture was poured onto crushed ice and the precipitate was filtered off and recrystallized from ethanol to give **2b**,**e**. *2-(2-Aminophenyl)-3-bromoindole (**2b**)*, obtained in 92% yield showed analytical and spectral data in agreement to those previously reported.[15b]

*4.1.1.1. 3-Bromo-2-ethoxycarbonylindole (**2e**).* Yield 95%; white solid, mp 153–156 °C; IR cm^{-1}: 3296 (NH), 1688 (CO), 1619 and 1518 (C=C). ^{1}H NMR (DMSO-d_6): δ 1.39 (3H, t, J=6.6 Hz, CH_3), 4.40 (2H, q, J=6.6 Hz, CH_2), 7.21 (1H, t, J=7.3 Hz, H-5), 7.38 (1H, t, J=7.3 Hz, H-6), 7.52 (1H, d, J=7.3 Hz, H-7), 7.56 (1H, d, J=7.3 Hz, H-4), 12.25 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 14.2 (q), 60.7 (t), 95.9 (s), 113.0 (d), 120.0 (d), 121.1 (d), 123.9 (s), 125.9 (d), 126.8 (s), 135.8 (s), 160.1 (s). Anal. Calcd for $C_{11}H_{10}NO_2Br$ (268.11): C, 49.28; H, 3.76; N, 5.22. Found: C, 49.00; H, 4.00; N, 5.52.

4.1.2. *General procedure for the synthesis of 3-bromo-1-methyl-2-substituted indoles **3a**–**e***

To a solution of the bromoderivatives **2a**–**e** (25 mmol) in anhydrous DMF (30 mL), NaH (25 mmol) was added. After 1 h stirring at room temperature, MeI (1.55 mL, 25 mmol) was added and stirred for further 2 h at room temperature. The reaction mixture was then poured onto crushed ice and the solid filtered off and dried. Recrystallization from ethanol gave the desired 1-methyl 3-bromo derivatives **3a**–**e**.

*4.1.2.1. 3-Bromo-1-methyl-2-(2-nitrophenyl)-indole (**3a**).* Yield 95%; orange solid, mp 108–110 °C; IR cm^{-1}: 1614 and 1573 (C=C), 1527 (NO_2). ^1H NMR (DMSO-d_6): δ 3.64 (3H, s, CH_3), 7.26 (1H, t, J=7.5 Hz, H-5), 7.38 (1H, t, J=7.5 Hz, H-6), 7.52 (1H, d, J=7.5 Hz, H-7), 7.66 (1H, d, J=7.5 Hz, H-4), 7.76 (1H, dd, J=7.2, 1.3 Hz, H-6′), 7.89 (1H, dt, J=7.2, 1.3 Hz, H-4′), 7.99 (1H, dd, J=7.2, 1.3 Hz, H-5′), 8.31 (1H, dd, J=7.2, 1.3 Hz, H-3′). ^{13}C NMR (DMSO-d_6): δ 31.2 (q), 89.1 (s), 110.6 (d), 118.3 (d), 120.5 (d), 123.0 (d), 124.4 (s), 124.7 (d), 125.9 (s), 131.2 (d), 132.0 (s), 133.6 (d), 133.7 (d), 136.2 (s), 149.4 (s). Anal. Calcd for $C_{15}H_{11}BrN_2O_2$ (331.17): C, 54.40; H, 3.35; N, 8.46. Found: C, 54.58; H, 3.02; N, 8.30.

*4.1.2.2. 2-(2-Aminophenyl)-3-bromo-1-methylindole (**3b**).* Yield 82-%; grey oil; IR cm^{-1}: 3467 and 3376 (NH_2), 1616 and 1577 (C=C). ^1H NMR (DMSO-d_6): δ 3.55 (3H, s, CH_3), 4.96 (2H, s, NH_2), 6.67 (1H, dt, J=7.6, 1.5 Hz, H-5′), 6.83 (1H, dd, J=7.6, 1.5 Hz, H-3′), 7.05 (1H, dd, J=7.6, 1.5 Hz, H-6′), 7.14–7.30 (3H, m, H-5, H-6, H-4′), 7.48 (1H, d, J=7.7 Hz, H-7), 7.53 (1H, d, J=7.7 Hz, H-4). ^{13}C NMR (DMSO-d_6): δ 30.9 (q), 89.1 (s), 110.6 (d), 113.4 (s), 114.9 (d), 115.8 (d), 118.1 (d), 120.0 (d), 122.2 (d), 126.5 (s), 130.2 (d), 131.9 (d), 133.7 (s), 136.4 (s), 147.4 (s). Anal. Calcd for $C_{15}H_{13}BrN_2$ (301.19): C, 59.82; H, 4.35; N, 8.46. Found: C, 60.01; H, 4.10; N, 8.64.

*4.1.2.3. Bromo-1-methyl-2-phenylindole (**3c**).* Yield 80%; grey solid, mp 70–72 °C; IR cm^{-1}: 1606 and 1574 (C=C). ^1H NMR (DMSO-d_6): δ 3.66 (3H, s, CH_3), 7.21 (1H, t, J=7.0 Hz, H-5), 7.30 (1H, t, J=7.0 Hz, H-6), 7.48–7.58 (7H, m, H-4, H-7, Ph). ^{13}C NMR (DMSO-d_6): δ 31.5 (q), 88.6 (s), 110.6 (d), 118.3 (d), 120.5 (d), 122.7 (d), 126.3 (s), 128.5 (2×d), 128.8 (d), 129.7 (s), 130.5 (2×d), 136.4 (s), 137.6 (s). Anal. Calcd for $C_{15}H_{12}NBr$ (286.17): C, 62.96; H, 4.23; N, 4.89. Found: C, 63.24; H, 4.50; N, 4.54.

*4.1.2.4. 3-Bromo-1-methyl-2-(pyridin-2-yl)-indole (**3d**).* Yield 92%; yellow solid, mp 75–76 °C; IR cm^{-1}: 1589 and 1566 (C=C and C=N). ^1H NMR (DMSO-d_6): δ 3.82 (3H, s, CH_3), 7.23 (1H, t, J=7.3 Hz, H-5), 7.34 (1H, t, J=8.5 Hz, H-4′), 7.46–7.55 (2H, m, H-6, H-7), 7.61 (1H, d, J=7.3 Hz, H-4), 7.84 (1H, d, J=7.3 Hz, H-5′), 8.02 (1H, dt, J=8.5, 1.2 Hz, H-6′), 8.80 (1H, d, J=8.5 Hz, H-3′). ^{13}C NMR (DMSO-d_6): δ 31.7 (q), 89.7 (s), 110.7 (d), 118.8 (d), 120.6 (d), 123.2 (d), 123.5 (d), 126.1 (s), 126.3 (d), 135.8 (s), 136.7 (s), 136.8 (d), 149.1 (s), 149.6 (d). Anal. Calcd for $C_{14}H_{11}N_2Br$ (287.16): C, 58.56; H, 3.86; N, 9.76. Found: C, 58.76; H, 4.05; N, 9.55.

*4.1.2.5. 3-Bromo-2-ethoxycarbonyl-1-methylindole (**3e**).* Yield 90%; white solid, mp 67–69 °C; IR cm^{-1}: 1613 and 1504 (C=C), 1701 (CO). ^1H NMR (DMSO-d_6): δ 1.39 (3H, t, J=6.9 Hz, CH_3), 3.97 (3H, s, CH_3), 4.40 (2H, q, J=6.9 Hz, CH_2), 7.24 (1H, t, J=7.4 Hz, H-5), 7.42 (1H, t, J=7.4 Hz, H-6), 7.56 (1H, d, J=7.4 Hz, H-7), 7.60 (1H, d, J=7.4 Hz, H-4). ^{13}C NMR (DMSO-d_6): δ 13.9 (q), 32.4 (q), 60.8 (t), 96.8 (s), 111.1 (d), 120.3 (d), 121.2 (d), 125.3 (s), 125.6 (s), 125.9 (d), 137.5 (s), 160.3 (s). Anal. Calcd for $C_{12}H_{12}NO_2Br$ (282.14): C, 51.09; H, 4.29; N, 9.76. Found: C, 49.80; H, 4.00; N, 10.00.

4.1.3. General procedure for the preparation of 3-substituted indoles

Method A. To a solution of 2-substituted 3-bromoindoles **2a–e** (6.3 mmol) in anhydrous DMF (15 mL), stoichiometric amount of triethylamine (0.8 mL, 6.3 mmol) and the proper nucleophile (12.6 mmol) were added. The mixture was heated under reflux for 24 h then it was poured onto crushed ice. The aqueous phase was extracted with DCM, dried and purified by chromatography column using DCM/petroleum ether (1:1) as eluent.

Method B. A mixture of 2-substituted 3-bromoindoles **2a–e** (5 mmol) was heated under reflux for 24 h with an excess of the proper nucleophile (50 mmol). The mixture was cooled, washed with 1 N hydrochloric acid. Extraction with DCM afforded a crude material, which was purified by chromatography column using DCM/petroleum ether (1:1) as eluent.

Method C. A mixture of 2-substituted 3-bromoindoles **2a–e** (2.5 mmol), 3,5-dimethoxyaniline (0.76 g, 5 mmol) and sodium carbonate (0.52 g, 5 mmol) was heated at 160 °C for 24 h. The mixture was poured onto crushed ice and extracted with DCM. The oily residue was purified by chromatography column using DCM/petroleum ether (1:1) as eluent.

Method D. A mixture of powdered potassium hydroxide (0.84 g, 10 mmol), dibenzo 18-crown-6 ether (0.15 g, 0.5 mmol) and 2-substituted 3-bromoindoles **2a–e** or **3a–e** (5 mmol) in acetonitrile (20 mL) was stirred at room temperature for 30 min. The required nucleophile was added (10 mmol) and the reaction mixture was heated at 60 °C for 6–8 h. Hydrochloric acid (1 N) was added and the aqueous solution extracted with DCM. The residue was purified by chromatography column using DCM/petroleum ether (1:1) as eluent.

Method E. A mixture of 2-substituted 3-bromoindoles **2a** and **3a** (5 mmol), ten fold excess of the suitable nucleophile (50 mmol), powdered potassium hydroxide (0.84 g, 10 mmol) and dibenzo 18-crown-6 ether (0.15 g, 0.5 mmol) was heated under reflux for 24 h. The mixture was cooled, poured onto crushed ice and neutralized with 1 N hydrochloric acid. Extraction of the aqueous layer with DCM furnished an oil, which was purified by chromatography column using DCM/petroleum ether (1:1) as eluent.

*4.1.3.1. 3-[(4-Methoxyphenyl)sulfanyl]-2-(2-nitrophenyl)-indole (**4a**).* Yellow solid, mp 154–156 °C; IR cm^{-1}: 3269 (NH), 1595 and 1574 (C=C), 1527 (NO_2). ^1H NMR (DMSO-d_6): δ 3.64 (3H, s, CH_3), 6.75 (2H, d, J=8.3 Hz, H-3″, H-5′), 6.94 (2H, d, J=8.3 Hz, H-2″, H-6′), 7.09 (1H, t, J=7.6 Hz, H-5), 7.22 (1H, t, J=7.6 Hz, H-6), 7.43 (1H, d, J=7.6 Hz, H-7), 7.48 (1H, d, J=7.6 Hz, H-4), 7.66–7.88 (3H, m, H-4′, H-6′, H-5′), 8.17 (1H, d, J=8.3 Hz, H-3′), 12.07 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 55.0 (q), 100.6 (s), 112.0 (2×d), 114.5 (d), 118.8 (d), 120.3 (d), 122.7 (d), 124.7 (d), 126.2 (s), 127.8 (2×d), 128.2 (d), 129.0 (s), 130.2 (d), 133.1 (d), 133.5 (s), 136.3 (s), 138.7 (s), 148.8 (s), 157.4 (s). Anal. Calcd for $C_{21}H_{16}N_2O_3S$ (376.43): C, 67.01; H, 4.28; N, 7.44. Found: C, 66.78; H, 4.02; N, 7.70.

*4.1.3.2. 3-[(4-Methoxyphenyl)sulfanyl]-2-(2-aminophenyl)-indole (**4b**).* Brown solid, mp 76–78 °C; IR cm^{-1}: 3429 and 3392 (NH_2), 1616 and 1574 (C=C). ^1H NMR (200 MHz, DMSO-d_6): δ 3.65 (3H, s, CH_3), 4.98 (2H, s, NH_2), 6.61 (1H, t, J=7.3 Hz, H-5′), 6.77 (2H, d, J=8.7 Hz, H-3″, H-5″), 6.81 (2H, d, J=8.7 Hz, H-3′, H-6′), 6.98 (2H, d, J=8.7 Hz, H-2″, H-6″), 7.02–7.18 (3H, m, H-5, H-6, H-4′), 7.42 (1H, d, J=8.0 Hz, H-7), 7.46 (1H, t, J=8.0 Hz, H-4), 11.80 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 55.0 (q), 99.1 (s), 111.9 (d), 114.6 (2×d), 115.1 (d), 115.8 (d), 115.9 (s), 118.4 (d), 119.9 (d), 121.9 (d), 127.3 (2×d), 129.5 (s), 129.6 (d), 129.7 (d), 131.4 (d), 136.4 (s), 141.7 (s), 146.8 (s), 157.1 (s). Anal. Calcd for $C_{21}H_{18}N_2OS$ (346.45): C, 72.81; H, 5.24; N, 8.09. Found: C, 73.21; H, 5.03; N, 8.34.

*4.1.3.3. 3-[(4-Methoxyphenyl)sulfanyl]-2-phenylindole (**4c**).* White solid, mp 163–165 °C; IR cm^{-1}: 3326 (NH), 1592 and 1578 (C=C). ^1H NMR ($CDCl_3$): δ 3.69 (3H, s, CH_3), 6.75 (2H, d, J=8.4 Hz, H-3″, H-5″), 7.05 (2H, d, J=8.4 Hz, H-2″, H-6″), 7.15 (1H, t, J=7.8 Hz, H-5), 7.24 (1H, t, J=7.8 Hz, H-6), 7.35–7.47 (4H, m, H-7, H-3′, H-4′, H-5′), 7.64 (1H, d, J=7.8 Hz, H-4), 7.74 (2H, dd, J=8.1, 1.6 Hz, H-2′, H-6′), 8.47 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 55.3 (q), 100.9 (s), 111.1 (d), 114.6 (2×d), 119.9 (d), 121.0 (d), 123.2 (d), 127.7 (2×d), 128.1 (2×d), 128.6 (d), 128.7 (2×d), 129.7 (s), 131.2 (s), 131.5 (s), 135.8 (s), 141.5 (s), 157.5 (s). Anal. Calcd for $C_{21}H_{17}NOS$ (331.43): C, 76.10; H, 5.17; N, 4.23. Found: C, 76.44; H, 5.00; N, 4.58.

*4.1.3.4. 3-[(4-Methoxyphenyl)sulfanyl]-2-pyridin-2-yl-indole (**4d**).* White solid, mp 130–132 °C; IR cm^{-1}: 3419 (NH), 1594 and 1566 (C=C and C=N). ^1H NMR (DMSO-d_6): δ 3.65 (3H, s, CH_3), 6.81

(2H, d, *J*=8.5 Hz, H-3″, H-5″), 7.05 (2H, d, *J*=8.5 Hz, H-2″, H-6″), 7.10 (1H, t, *J*=7.7 Hz, H-5), 7.23 (1H, t, *J*=7.7 Hz, H-6), 7.40 (1H, t, *J*=8.5 Hz, H-4′), 7.55 (1H, d, *J*=7.7 Hz, H-7), 7.59 (1H, d, *J*=7.7 Hz, H-4), 7.91 (1H, t, *J*=8.5 Hz, H-5′), 8.58 (1H, d, *J*=8.5 Hz, H-6′), 8.73 (1H, d, *J*=8.5 Hz, H-3′), 12.21 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 55.0 (q), 99.8 (s), 112.6 (d), 114.9 (2×d), 118.9 (d), 120.4 (d), 122.1 (d), 123.1 (d), 123.3 (d), 127.6 (2×d), 128.2 (s), 130.8 (s), 135.9 (s), 137.0 (d), 139.1 (s), 149.2 (s), 149.3 (d), 157.5 (s). Anal. Calcd for $C_{20}H_{16}N_2OS$ (332.42): C, 72.26; H, 4.85; N, 8.43. Found: C, 72.42; H, 5.05; N, 8.55.

*4.1.3.5. 2-Ethoxycarbonyl-3-[(4-methoxyphenyl)sulfanyl]-indole (**4e**).* White solid, mp 128–130 °C; IR cm^{-1}: 3302 (NH), 1683 (CO), 1494 and 1572 (C═C). ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, *J*=7.2 Hz, CH_3), 3.73 (3H, s, CH_3), 4.42 (2H, q, *J*=7.2 Hz, CH_2), 6.74 (2H, d, *J*=8.5 Hz, H-3′, H-5′), 7.09 (1H, t, *J*=8.2 Hz, H-5), 7.23 (2H, d, *J*=8.5 Hz, H-2′, H-6′), 7.30 (1H, *J*=8.2 Hz, H-6), 7.40 (1H, d, *J*=8.2 Hz, H-7), 7.54 (1H, d, *J*=8.2 Hz, H-4), 9.50 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 55.2 (q), 61.4 (t), 95.2 (s), 112.0 (d), 114.4 (2×d), 114.4 (d), 121.1 (d), 121.7 (d), 125.9 (d), 127.8 (s), 127.9 (s), 129.7 (s), 130.5 (2×d), 130.5 (d), 135.8 (s), 158.2 (s), 161.5 (s). Anal. Calcd for $C_{18}H_{17}NO_3S$ (327.40): C, 66.04; H, 5.23; N, 4.28. Found: C, 66.35; H, 5.05; N, 4.55.

*4.1.3.6. 3-[(4-Methoxyphenyl)sulfanyl]-1-methyl-2-(2-nitrophenyl)-indole (**5a**).* Orange solid, mp 54–55 °C; IR cm^{-1}: 3269 (NH), 1601 and 1572 (C═C), 1525 (NO_2). ^{1}H NMR (DMSO-d_6): δ 3.62 (3H, s, CH_3), 3.64 (3H, s, CH_3), 6.74 (2H, d, *J*=6.9 Hz, H-3″, H-5″), 6.90 (2H, d, *J*=6.9 Hz H-2″, H-6″), 7.16 (1H, t, *J*=7.4 Hz, H-5), 7.32 (1H, t, *J*=7.4 Hz, H-6), 7.47 (1H, d, *J*=7.4 Hz, H-7), 7.65 (2H, m, H-4, H-6′), 7.84 (2H, m, H-4′, H-5′), 8.23 (1H, dd, *J*=7.8, 1.5 Hz, H-3′). ^{13}C NMR (DMSO-d_6): δ 31.2 (q), 55.0 (q), 100.5 (s), 110.7 (d), 114.5 (2×d), 118.7 (d), 120.7 (d), 122.7 (d), 124.6 (d), 125.1 (s), 127.9 (2×d), 128.0 (s), 128.4 (s), 131.0 (d), 133.5 (d), 133.6 (d), 137.1 (s), 140.9 (s), 149.3 (s), 157.4 (s). Anal. Calcd for $C_{22}H_{18}N_2O_3S$ (390.46): C, 67.68; H, 4.65; N, 7.17. Found: C, 68.08; H, 4.32; N, 7.50.

*4.1.3.7. 3-[(4-Methoxyphenyl)sulfanyl]-1-methyl-2-(2-aminophenyl)-indole (**5b**).* Yellow oil; IR cm^{-1}: 3467 and 3378 (NH_2), 1616 and 1576 (C═C). ^{1}H NMR (DMSO-d_6): δ 3.60 (3H, s, CH_3), 3.64 (3H, s, CH_3), 4.97 (2H, s, NH_2), 6.61 (1H, d, *J*=7.3 Hz, H-5′), 6.75 (2H, d, *J*=8.7 Hz, H-3″, H-5″), 6.83 (1H, d, *J*=7.3 Hz, H-3′), 7.00 (2H, d, *J*=8.7 Hz, H-2″, H-6″), 6.97–7.28 (7H, m, H-5, H-6, H-4′, H-6′), 7.46 (1H, d, *J*=8.1 Hz, H-7), 7.55 (1H, d, *J*=8.1 Hz, H-4). ^{13}C NMR (DMSO-d_6): δ 31.3 (q), 55.5 (q), 100.3 (s), 111.2 (d), 114.5 (s), 115.0 (2×d), 115.3 (d), 116.1 (d), 119.1 (d), 120.7 (d), 122.5 (d), 128.1 (2×d), 129.6 (s), 130.1 (s), 130.5 (d), 132.4 (d), 137.9 (s), 144.5 (s), 147.9 (s), 157.6 (s). Anal. Calcd for $C_{22}H_{22}N_2OS$ (362.49): C, 72.90; H, 6.12; N, 7.73. Found: C, 73.00; H, 5.92; N, 7.50.

*4.1.3.8. 3-[(4-Methoxyphenyl)sulfanyl]-1-methyl-2-phenylindole (**5c**).* Yellow oil; IR cm^{-1}: 1593 and 1574 (C═C). ^{1}H NMR (DMSO-d_6): δ 3.65 (3H, s, CH_3), 3.71 (3H, s, CH_3), 6.77 (2H, d, *J*=8.8 Hz, H-3″, H-5″), 6.96 (2H, d, *J*=8.7 Hz, H-2″, H-6″), 7.14 (1H, t, *J*=7.1 Hz, H-5), 7.29 (1H, t, *J*=7.1 Hz, H-6), 7.47–7.51 (6H, m, Ph, H-7), 7.61 (1H, d, *J*=7.1 Hz, H-4). ^{13}C NMR (DMSO-d_6): δ 31.6 (q), 50.1 (q), 99.5 (s), 110.8 (d), 114.6 (2×d), 118.6 (d), 120.7 (d), 122.5 (d), 127.4 (2×d), 128.1 (2×d), 128.7 (d), 128.8 (s), 129.3 (s), 130.1 (s), 130.5 (2×d), 137.1 (s), 145.2 (s), 157.2 (s). Anal. Calcd for $C_{22}H_{19}NOS$ (345.46): C, 76.49; H, 5.54; N, 4.05. Found: C, 76.20; H, 5.73; N, 4.30.

*4.1.3.9. 3-[(4-Methoxyphenyl)sulfanyl]-1-methyl-2-pyridin-2-yl-indole (**5d**).* Yellow oil; IR cm^{-1}: 1591 and 1566 (C═C and C═N). ^{1}H NMR ($CDCl_3$): δ 3.57 (3H, s, CH_3), 3.79 (3H, s, CH_3), 6.57 (2H, dd, *J*=8.7, 1.5 Hz, H-3″, H-5″), 6.90 (2H, d, *J*=8.7, 1.5 Hz, H-2″, H-6″), 7.06 (1H, t, *J*=8.2, H-5), 7.17 (1H, t, *J*=8.2 Hz, H-6), 7.20–7.24 (2H, m, H-7, H-4′), 7.32 (1H, d, *J*=8.2 Hz, H-4), 7.50–7.65 (3H, m, H-3′, H-5′, H-6′). ^{13}C NMR ($CDCl_3$): δ 31.9 (q), 55.2 (q), 102.2 (s), 110.0 (d), 114.4 (d), 114.5 (2×d), 120.0 (d), 120.1 (d), 120.9 (d), 123.3 (d), 123.4 (d), 127.6 (2×d), 129.4 (s), 129.7 (s), 136.2 (d), 137.9 (s), 142.0 (s), 149.9 (s), 157.4 (s). Anal. Calcd for $C_{21}H_{18}N_2OS$ (346.45): C, 72.81; H, 5.24; N, 8.09. Found: C, 72.60; H, 5.05; N, 8.52.

*4.1.3.10. 2-Ethoxycarbonyl-3-[(4-methoxyphenyl)sulfanyl]-1-methyl-indole (**5e**).* Yellow oil; IR cm^{-1}: 1699 (CO), 1593 and 1574 (C═C). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, t, *J*=7.1 Hz, CH_3), 3.69 (3H, s, CH_3), 3.99 (3H, s, CH_3), 4.36 (2H, q, *J*=7.1 Hz, CH_2), 6.82 (2H, d, *J*=8.5 Hz, H-3″, H-5″), 7.10–7.19 (3H, m, H-5, H-2″, H-6″), 7.37 (1H, dt, *J*=8.2, 1.2 Hz, H-6), 7.47 (1H, d, *J*=8.2 Hz, H-7), 7.65 (1H, d, *J*=8.2 Hz, H-4). ^{13}C NMR (DMSO-d_6): δ 14.0 (q), 32.2 (q), 55.1 (q), 61.1 (t), 109.4 (s), 111.4 (d), 114.6 (2×d), 120.5 (d), 121.2 (d), 125.2 (d), 127.6 (s), 127.7 (s), 129.7 (2×d), 131.1 (s), 138.0 (s), 157.8 (s), 160.9 (s). Anal. Calcd for $C_{19}H_{19}NO_3S$ (341.42): C, 66.84; H, 5.61; N, 4.10. Found: C, 66.55; H, 5.48; N, 4.00.

*4.1.3.11. 3-[(3-Methylphenyl)sulfanyl]-2-(2-nitrophenyl)-indole (**6a**).* White solid, mp 119–121 °C; IR cm^{-1}: 3369 (NH), 1592 and 1574 (C═C), 1519 (NO_2). ^{1}H NMR (DMSO-d_6): δ 2.12 (3H, s, CH_3), 6.72 (1H, d, *J*=7.5 Hz, H-4″), 6.82 (1H, s, H-2″), 6.84 (1H, d, *J*=7.5 Hz, H-5″), 7.0 (1H, d, *J*=7.5 Hz, H-6″), 7.10 (1H, t, *J*=7.5 Hz, H-5), 7.25 (1H, t, *J*=7.5 Hz, H-6), 7.41 (1H, d, *J*=7.5 Hz, H-7), 7.50 (1H, d, *J*=7.5 Hz, H-4), 7.67–7.87 (3H, m, H-6′, H-4′, H-5′), 8.16 (1H, d, *J*=6.7 Hz, H-3′), 12.14 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 20.8 (q), 98.9 (s), 112.1 (d), 118.7 (d), 120.4 (d), 122.3 (d), 122.8 (d), 124.7 (d), 125.6 (d), 125.7 (d), 126.1 (s), 128.6 (d), 129.1 (s), 130.3 (d), 133.1 (d), 133.4 (d), 136.3 (s), 137.9 (s), 138.0 (s), 139.2 (s), 148.6 (s). Anal. Calcd for $C_{21}H_{16}N_2O_2S$ (360.43): C, 69.98; H, 4.47; N, 7.77. Found: C, 70.18; H, 4.64; N, 7.92.

*4.1.3.12. 3-[(3-Methylphenyl)sulfanyl]-2-(2-aminophenyl)-indole (**6b**).* Yellow oil; IR cm^{-1}: 3428, 3388, 3214 (NH and NH_2), 1616 and 1574 (C═C). ^{1}H NMR (DMSO-d_6): δ 2.16 (3H, s, CH_3), 4.98 (2H, s, NH_2), 6.59 (1H, t, *J*=7.6 Hz, H-5′), 6.70–6.87 (4H, m, H-2″, H-4″, H-5″, H-6″), 7.00 (1H, d, *J*=7.6 Hz, H-3′), 7.02–7.21 (4H, m, H-5, H-6, H-4′, H-6′), 7.38 (1H, d, *J*=6.8 Hz, H-7), 7.46 (1H, d, *J*=6.8 Hz, H-4), 11.81 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 20.9 (q), 97.5 (s), 112.0 (d), 115.1 (d), 115.7 (d), 117.9 (s), 118.3 (d), 119.9 (d), 122.0 (2×d), 125.3 (d), 125.4 (d), 128.6 (d), 129.6 (d), 129.7 (s), 131.3 (d), 136.4 (s), 138.0 (s), 139.0 (s), 142.1 (s), 147.0 (s). Anal. Calcd for $C_{21}H_{18}N_2S$ (330.45): C, 76.33; H, 5.49; N, 8.48. Found: C, 76.03; H, 5.58; N, 8.29.

*4.1.3.13. 3-[(3-Methylphenyl)sulfanyl]-2-phenylindole (**6c**).* Yellow oil; IR cm^{-1}: 3406 (NH), 1590 and 1573 (C═C). ^{1}H NMR ($CDCl_3$): δ 2.16 (3H, s, CH_3), 6.82 (2H, d, *J*=7.0 Hz, H-4″, H-6″), 6.95 (1H, s, H-2″), 6.99 (1H, t, *J*=7.6 Hz, H-5), 7.12 (1H, t, *J*=7.0 Hz, H-5″), 7.21 (1H, t, *J*=7.6 Hz, H-6), 7.30–7.35 (4H, m, H-7, H-3′, H-4′, H-5′), 7.64 (1H, d, *J*=7.6 Hz, H-4), 7.69 (2H, dt, *J*=8.2, 1.8 Hz, H-2′, H-6′), 8.41 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.3 (q), 99.3 (s), 111.1 (d), 119.9 (d), 121.8 (d), 122.5 (d), 123.2 (d), 125.5 (d), 126.0 (d), 128.0 (2×d), 128.5 (d), 128.6 (2×d), 128.7 (d), 131.2 (s), 131.3 (s), 135.7 (s), 138.5 (s), 138.9 (s), 141.9 (s). Anal. Calcd for $C_{21}H_{17}NS$ (315.43): C, 79.96; H, 5.43; N, 4.44. Found: C, 80.06; H, 5.12; N, 4.24.

*4.1.3.14. 3-[(3-Methylphenyl)sulfanyl]-2-pyridin-2-yl-indole (**6d**).* Yellow solid, mp 116–118 °C; IR cm^{-1}: 3422 (NH), 1592 and 1569 (C═C and C═N). ^{1}H NMR ($CDCl_3$): δ 2.13 (3H, s, CH_3), 6.76 (1H, d, *J*=6.9 Hz, H-6″), 6.80 (1H, t, *J*=6.9 Hz, H-5″), 6.92–7.30 (6H, m, H-5, H-6, H-7, H-2″, H-4′), 7.58 (1H, d, *J*=6.8 Hz, H-4), 7.61 (1H, t, *J*=7.5 Hz, H-5′), 8.52 (1H, d, *J*=7.5 Hz, H-6′), 8.64 (1H, d, *J*=7.5 Hz, H-3′), 10.6 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 21.9 (q), 100.8 (s), 112.0 (d), 120.7 (d), 121.4 (d), 123.0 (d), 123.2 (d), 123.3 (d), 124.5 (d), 126.3 (d), 126.7 (d), 129.2 (d), 132.5 (s), 136.0 (s), 137.4 (d), 138.5 (s), 139.1 (s), 139.4 (s), 149.3 (d), 149.8 (s). Anal. Calcd for $C_{20}H_{16}N_2S$ (316.42): C, 75.92; H, 5.10; N, 8.48. Found: C, 76.12; H, 5.33; N, 8.38.

*4.1.3.15. 2-(2-Nitrophenyl)-3-pyrrolidin-1-yl-indole (**7a**).* Brown solid, mp 203–205 °C; IR cm^{-1}: 3328 (NH), 1604 and 1587 (C=C and C=N), 1505 (NO_2). ^1H NMR ($CDCl_3$): δ 1.84–2.00 (2H, m, CH_2), 2.14–2.22 (2H, m, CH_2), 3.22–3.31 (2H, m, CH_2), 3.80–3.91 (2H, m, CH_2), 7.20–7.34 (3H, m, H-5, H-6, H-4′), 7.48 (1H, d, *J*=7.5 Hz, H-7), 7.58 (1H, d, *J*=7.5 Hz, H-5′), 8.01 (1H, d, *J*=7.5 Hz, H-4), 8.20 (1H, d, *J*=7.5 Hz, H-6′), 8.21 (1H, d, *J*=7.5 Hz, H-3′), 9.97 (1H, s, NH). ^{13}C NMR ($CDCl_3$): δ 24.7 (2×t), 49.8 (2×t), 111.1 (d), 112.6 (s), 116.7 (d), 121.2 (d), 121.7 (d), 121.9 (d), 122.1 (d), 124.5 (d), 125.2 (s), 129.6 (d), 137.5 (s), 139.6 (s), 141.2 (s), 159.7 (s). Anal. Calcd for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.34; H, 5.58; N, 13.67. Found: C, 70.20; H, 5.84; N, 13.60.

*4.1.3.16. 3-N-(3,5-Dimethoxyphenylamine)-2-(2-nitrophenyl)-indole (**7b**).* Red solid, mp 156–158 °C; IR cm^{-1}: 3391 (NH), 1591 and 1578 (C=C), 1527 (NO_2). ^1H NMR (DMSO-d_6): δ 3.73 (6H, s, 2×CH_3), 5.78 (1H, s, NH), 6.07 (2H, d, *J*=2.1 Hz, H-2″, H-6″), 6.44 (1H, *J*=2.1 Hz, H-4″), 6.85 (1H, d, *J*=7.1 Hz, H-7), 7.23 (1H, t, *J*=7.1 Hz, H-5), 7.63 (1H, t, *J*=7.1 Hz, H-6), 7.73 (1H, d, *J*=7.1 Hz, H-4), 7.83–7.99 (3H, m, H-4′, H-5′, H-6′), 8.23 (1H, d, *J*=7.8 Hz, H-3′), 12.35 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 55.4 (2×q), 95.5 (d), 97.3 (d), 112.6 (d), 120.5 (s), 122.0 (d), 124.3 (d), 125.5 (d), 126.5 (s), 127.9 (d), 128.0 (d), 131.6 (d), 131.8 (d), 134.0 (d), 135.2 (s), 149.4 (s), 150.8 (s), 157.8 (s), 161.2 (s), 161.6 (s), 167.8 (s). Anal. Calcd for $C_{22}H_{19}N_3O_4$ (389.41): C, 67.86; H, 4.92; N, 10.79. Found: C, 67.65; H, 5.15; N, 11.02.

*4.1.3.17. 3-N-Phenylamine-2-(2-nitrophenyl)-indole (**7c**).* Yellow oil; IR cm^{-1}: 3410 and 3403 (NH), 1604 and 1579 (C=C), 1498 (NO_2). ^1H NMR (DMSO-d_6): δ 5.25 (1H, s, NH), 6.52 (1H, d, *J*=8.8 Hz, H-7), 7.94–7.25 (3H, m, H-5, H-6, H-4″), 7.46 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 7.72–8.00 (6H, m, H-4, H-4′, H-5′, H-6′, H-3″, H-5″), 8.19 (1H, d, *J*=8.1 Hz, H-3′), 11.82 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 89.5 (s), 101.5 (d), 112.0 (d), 115.7 (d), 118.3 (d), 120.3 (d), 123.0 (2×d), 124.8 (d), 125.6 (s), 126.7 (s), 130.4 (2×d), 131.2 (d), 131.4 (s), 133.3 (d), 133.4 (d), 135.6 (s), 148.0 (s), 148.6 (s). Anal. Calcd for $C_{20}H_{15}N_3O_2$ (329.36): C, 72.94; H, 4.59; N, 12.76. Found: C, 73.08; H, 4.76; N, 12.50.

*4.1.3.18. 3-Morpholin-4-yl-2-(2-nitrophenyl)-indole (**7d**).* Yellow solid, mp 190–192 °C; IR cm^{-1}: 3353 (NH), 1602 and 1584 (C=C), 1501 (NO_2). ^1H NMR ($CDCl_3$): δ 3.41–3.43 (4H, m, 2×CH_2), 3.87–3.90 (4H, m, 2×CH_2), 6.91 (2H, d, *J*=7.3 Hz, H-4, H-7), 7.17–7.36 (4H, m, H-5, H-6, H-4′, H-5′), 7.58 (1H, d, *J*=8.5 Hz, H-6′), 8.13 (1H, d, *J*=8.5 Hz, H-3′), 8.49 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 47.1 (2×t), 66.3 (2×t), 92.3 (s), 111.4 (d), 113.2 (d), 117.9 (d), 119.5 (d), 120.9 (d), 123.8 (d), 127.5 (d), 127.8 (d), 128.6 (s), 131.9 (s), 135.4 (s), 138.8 (s), 153.5 (s). Anal. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.74; H, 5.00; N, 13.32.

*4.1.3.19. 1-Methyl-2-(2-nitrophenyl)-3-pyrrolidin-1-yl-indole (**7e**).* Orange solid, mp 186–187 °C; IR cm^{-1}: 1601 and 1580 (C=C), 1508 (NO_2). ^1H NMR ($CDCl_3$): δ 2.05 (4H, m, 2×CH_2), 3.38 (4H, m, 2×CH_2), 3.58 (1H, s, CH_3), 6.60 (1H, d, *J*=7.1 Hz, H-7), 7.16–7.36 (5H, m, H-4, H-5, H-6, H-4′, H-5′), 7.58 (1H, d, *J*=7.6 Hz, H-6′), 8.21 (1H, d, *J*=7.6 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 25.4 (2×t), 31.1 (q), 47.9 (2×t), 89.0 (s), 109.4 (d), 111.3 (d), 115.7 (d), 119.2 (d), 120.2 (d), 122.7 (d), 122.8 (d), 126.8 (s), 128.1 (d), 128.6 (s), 130.6 (s), 136.1 (s), 150.7 (s). Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.38): C, 71.01; H, 5.96; N, 13.07. Found: C, 71.20; H, 5.80; N, 13.36.

*4.1.3.20. 3-N-Phenylamine-1-methyl-2-(2-nitrophenyl)-indole (**7f**).* Orange oil; IR cm^{-1}: 3403 (NH), 1608 and 1578 (C=C), 1498 (NO_2). ^1H NMR (DMSO-d_6): δ 3.59 (1H, s, CH_3), 6.38 (1H, s, NH), 6.89 (1H, d, *J*=7.0 Hz, H-7), 6.89–7.41 (10H, m, Ph, H-4, H-5, H-6, H-4′, H-5′), 7.56 (2H, d, *J*=8.4 Hz, H-6′), 8.22 (1H, d, *J*=8.4 Hz, H-3′). ^{13}C NMR (DMSO-d_6): δ 31.2 (q), 89.7 (s), 109.6 (d), 114.6 (d), 118.6 (d), 119.3 (d), 120.4 (d), 121.9 (2×d), 123.0 (d), 124.8 (d), 124.9 (d), 126.8 (s), 127.9 (d), 128.7 (s), 129.8 (2×d), 134.9 (s), 136.5 (s), 139.1 (s), 149.5 (s). Anal. Calcd for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.08; H, 5.16; N, 12.46.

*4.1.3.21. 1-Methyl-3-morpholin-4-yl-2-(2-nitrophenyl)-indole (**7g**).* Orange solid, mp 182–183 °C; IR cm^{-1}: 1596 and 1567 (C=C), 1490 (NO_2). ^1H NMR ($CDCl_3$): δ 3.29–3.37 (4H, m, 2×CH_2), 3.80–3.84 (4H, m, 2×CH_2), 3.86 (1H, s, CH_3), 6.88 (1H, t, *J*=7.3 Hz, H-5′), 7.24–7.65 (7H, m, H-4, H-5, H-6, H-7, H-3′, H-4′, H-6′). ^{13}C NMR ($CDCl_3$): δ 31.9 (q), 47.8 (2×t), 66.5 (2×t), 91.1 (s), 109.6 (d), 115.8 (d), 117.5 (d), 119.2 (d), 120.2 (d), 122.5 (d), 127.2 (s), 130.1 (d), 132.7 (d), 136.7 (s), 143.9 (s), 151.5 (s), 152.6 (s). Anal. Calcd for $C_{19}H_{19}N_3O_3$ (337.38): C, 67.64; H, 5.68; N, 12.45. Found: C, 68.04; H, 5.20; N, 12.32.

*4.1.3.22. 3-(3-Methoxyphenoxy)-2-(2-nitrophenyl)-indole (**8**).* Orange solid, mp 129–131 °C; IR cm^{-1}: 3396 (NH), 1606 and 1588 (C=C), 1525 (NO_2). ^1H NMR ($CDCl_3$): δ 3.70 (3H, s, CH_3), 6.53 (2H, d, *J*=7.6 Hz, H-4″, H-6″), 6.56 (1H, s, H-2″), 7.05 (1H, t, *J*=8.2 Hz, H-5), 7.11 (1H, t, *J*=8.2 Hz, H-6), 7.18–7.47 (4H, H-4, H-7, H-5′, H-5″), 7.57 (1H, t, *J*=7.6 Hz, H-4′), 7.70 (1H, d, *J*=7.6 Hz, H-6′), 7.86 (1H, d, *J*=7.6 Hz, H-3′), 8.1 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 55.3 (q), 101.8 (d), 107.8 (s), 107.9 (d), 111.7 (d), 118.9 (d), 120.3 (d), 120.8 (s), 121.7 (s), 123.8 (d), 124.7 (d), 128.8 (d), 129.8 (d), 132.0 (d), 132.3 (d), 132.6 (d), 134.5 (s), 146.4 (s), 148.7 (s), 159.5 (s), 160.7 (s). Anal. Calcd for $C_{21}H_{16}N_2O_4$ (347.37): C, 69.99; H, 4.48; N, 7.77. Found: C, 70.24; H, 4.64; N, 8.01.

*4.1.3.23. 3-Bromo-2-(pyrrolidin-1-yl carbonyl)-indole (**9a**).* Yield 40% (Method D), 20% (Method E); white solid, mp 208–210 °C; IR cm^{-1}: 3125 (NH), 1607 (CO). ^1H NMR (DMSO-d_6): δ 1.20–1.23 (4H, m, 2×CH_2), 3.48–3.51 (4H, m, 2×CH_2), 7.16 (1H, t, *J*=6.8 Hz, H-5), 7.27 (1H, t, *J*=6.8 Hz, H-6), 7.43 (1H, d, *J*=6.8 Hz, H-7), 7.47 (1H, d, *J*=6.8 Hz, H-4), 11.90 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 23.8 (t), 25.5 (t), 45.6 (t), 47.6 (t), 88.6 (s), 112.3 (d), 118.7 (d), 120.5 (d), 123.7 (d), 126.0 (s), 130.9 (s), 134.8 (s), 160.7 (s). Anal. Calcd for $C_{13}H_{13}BrN_2O$ (293.16): C, 53.26; H, 4.47; N, 9.56. Found: C, 53.48; H, 4.84; N, 10.06.

*4.1.3.24. 3-Bromo-2-(morpholin-4-yl carbonyl)-indole (**9b**).* Yield 55% (Method D), 22% (Method E); white solid, mp 105–110 °C; IR cm^{-1}: 3246 (NH), 1610 (CO). ^1H NMR (DMSO-d_6): δ 3.50–3.74 (8H, m, 4×CH_2), 7.20 (1H, t, *J*=7.2 Hz, H-5), 7.28 (1H, t, *J*=7.2 Hz, H-6), 7.44 (1H, d, *J*=7.2 Hz, H-7), 7.48 (1H, d, *J*=7.2 Hz, H-4), 12.03 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 60.7 (t), 66.2 (2×t), 69.8 (t), 89.1 (s), 112.3 (d), 118.8 (d), 120.6 (d), 123.8 (d), 125.8 (s), 129.0 (s), 135.0 (s), 161.3 (s). Anal. Calcd for $C_{13}H_{13}BrN_2O_2$ (309.16): C, 50.51; H, 4.24; N, 9.06. Found: C, 50.66; H, 4.40; N, 9.24.

*4.1.3.25. 3-Bromo-N-(4-methylbenzyl)-indole-2-carboxamide (**9c**).* Yield 50% (Method D), 35% (Method E); white solid, mp 207–208 °C; IR cm^{-1}: 3392 and 3251 (NH), 1626 (CO), 1576 and 1556 (C=C). ^1H NMR (DMSO-d_6): δ 2.28 (3H, s, CH_3), 4.46 (2H, d, *J*=5.4 Hz, CH_2), 7.14–7.30 (6H, m, H-5, H-6, H-2′, H-3′, H-5′, H-6′), 7.47 (1H, d, *J*=8.2 Hz, H-7), 7.51 (1H, d, *J*=8.2 Hz, H-4), 8.40 (1H, t, *J*=5.4 Hz, NH), 12.03 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 20.6 (q), 42.4 (t), 90.4 (s), 112.7 (d), 119.4 (d), 120.8 (d), 124.7 (d), 126.6 (s), 127.2 (s), 127.3 (2×d), 128.5 (s), 128.8 (2×d), 134.9 (s), 135.9 (s), 160.0 (s). Anal. Calcd for $C_{21}H_{17}BrN_2O$ (343.22): C, 59.49; H, 4.41; N, 8.16. Found: C, 59.36; H, 4.25; N, 8.10.

*4.1.3.26. 3-Pyrrolidin-1-yl-2-(pyrrolidin-1-ylcarbonyl)-indole (**9d**).* White solid, mp 205–207 °C; IR cm^{-1}: 3254 (NH), 1601 (CO). ^1H NMR ($CDCl_3$): δ 1.84–1.99 (8H, m, 4×CH_2), 3.40–3.56 (8H, m, 4×CH_2), 6.90 (1H, t, *J*=8.3 Hz, H-5), 7.11 (1H, t, *J*=8.3 Hz, H-6), 7.30 (1H, d, *J*=8.3 Hz, H-7), 7.82 (1H, d, *J*=8.3 Hz, H-4), 9.50 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 23.4 (2×t), 25.9 (2×t), 46.7 (2×t), 52.4 (2×t), 112.0 (s), 112.1 (d), 117.4 (d), 118.1 (s), 121.7 (d), 123.3 (d), 129.2 (s), 135.4 (s), 164.7 (s). Anal. Calcd for $C_{17}H_{21}N_3O$ (283.37): C, 70.06; H, 7.47; N, 14.83. Found: C, 70.20; H, 7.84; N, 13.96.

*4.1.3.27. 3-Morpholin-4-yl-2-(morpholin-4-ylcarbonyl)-indole (**9e**).* White solid, mp 273–276 °C; IR cm^{-1}: 3254 (NH), 1589 (CO). ^1H NMR (DMSO-d_6): δ 3.07–3.11 (4H, m, 2×CH_2), 3.56–3.61 (8H, m, 4×CH_2), 3.70–3.75 (4H, m, 2×CH_2), 6.98 (1H, t, J=8.1 Hz, H-5), 7.13 (1H, t, J=8.1 Hz, H-6), 7.30 (1H, d, J=8.1 Hz, H-7), 7.67 (1H, d, J=8.1 Hz, H-4), 11.09 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 52.5 (2×t), 66.3 (4×t), 66.8 (2×t), 112.0 (d), 118.7 (d), 119.9 (d), 121.9 (s), 122.4 (s), 122.5 (d), 127.5 (s), 134.5 (s), 163.3 (s). Anal. Calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.74; H, 6.71; N, 13.31. Found: C, 64.50; H, 6.94; N, 13.60.

*4.1.3.28. N-(4-Methylbenzyl)-3-[(4-methylbenzyl)amino]-indole-2-carboxamide (**9f**).* White solid, mp 218–220 °C; IR cm^{-1}: 3261–3258 (NH), 1626 (CO), 1568 and 1515 (C=C). ^1H NMR (DMSO-d_6): δ 2.25 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.46 (2H, d, J=5.6 Hz, CH_2), 4.55 (2H, d, J=6.7 Hz, CH_2), 6.54 (1H, t, J=6.7 Hz, NH), 6.89 (1H, t, J=8.2 Hz, H-5), 7.05–7.34 (10H, m, H-6, H-7, H-2′, H-3′, H-5′, H-6′, H-2″, H-3″, H-5″, H-6″), 7.24 (1H, d, J=8.2 Hz, H-4), 8.37 (1H, t, J=5.6 Hz, NH), 10.60 (1H, br s, NH). ^{13}C NMR (DMSO-d_6): δ 20.6 (2×q), 41.7 (t), 50.3 (t), 112.4 (s), 113.8 (d), 118.0 (d), 120.1 (s), 121.3 (d), 124.4 (d), 127.2 (2×d), 127.5 (2×d), 128.8 (2×d), 128.9 (2×d), 133.4 (s), 135.1 (s), 135.6 (s), 135.7 (s), 136.3 (s), 137.6 (s), 162.5 (s). Anal. Calcd for $C_{25}H_{25}N_3O$ (383.49): C, 78.30; H, 6.57; N, 10.96. Found: C, 78.02; H, 6.14; N, 11.58.

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