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Synthesis of Bis(3-indolyl)methanes Mediated by Potassium *tert*-Butoxide

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The indole moiety is an important *N*-heterocycle found in natural products, and a key structural component of many value-added chemicals including pharmaceuticals. In particular, bis(3-indolyl)methanes (BIMs) are an important subgroup of indoles, composed of two indole units. Herein, we report the development of a simple method to access BIMs derivatives in yields of up to 77% by exploiting a *t*BuOK-mediated coupling reaction of indoles and benzyl alcohols.

Introduction

Nitrogen heterocycles are one of the most frequently occurring structures in pharmaceuticals.[1] Access to a wide variety of functionalized *N*-heterocyclic compounds is of critical importance to drive more efficient drug discovery programs. The indole scaffold is a privileged structure with potential applications in the medicinal chemistry field. It is found in natural products, and a key structural component of many value-added chemicals including pharmaceuticals. When properly functionalized, indole can exhibit a wide range of pharmacological properties including anticancer,[2] antioxidant[3] and anti-inflammatory activities.[4] In particular, bis(3-indolyl)methanes (BIMs) are an important subgroup of indoles, composed of two indole units, that is present in several natural products like arundine, streptindole, arsindoline A, barakacin and vibrindole A (Figure 1).

Preparation of these compounds is usually done by addition of aldehydes or ketones to two molecules of indole via acid[5,6] or base catalysis.[7] Furthermore, alternative and more sustainable methods have emerged, based on metal-catalysed[8,9] and metal-free reactions.[10] This includes metal-catalysed carbonylation and alkylation reactions[11–13] and organocatalysed reactions.[14] Other examples also include the use of metal-free oxidative reactions.[15,16] Recently, several examples have been reported using aryl amines (**1**),[17] aldehydes (**2**),[18–22] ketones (**3**),[23,24] benzyl amines (**4**)[16,25] and benzyl alcohols (**5**)[26–28] as starting materials (Scheme 1).

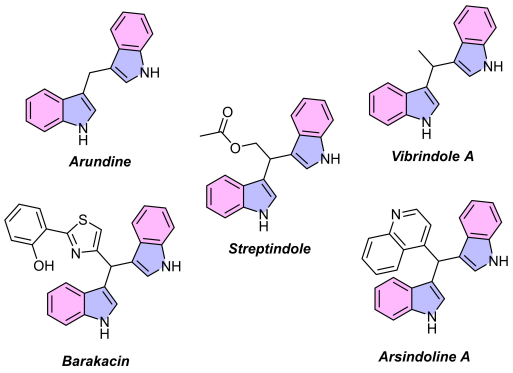

Figure 1. Examples of bis(3-indolyl)methanes (BIMs) present in different natural products.

Despite of the efficiency of metal-catalysed methods employing abundant metals, which constitute a key advance in this field, some catalysts are sensitive to air and not so easy to handle or prepare. Furthermore, removal of metal impurities and secondary products originating from metal-catalysed methods can lead to complex work-up procedures and purifications. Thus, the development of a method that allows simple access to BIMs derivatives is of great interest.

In the last few years, the use of potassium *tert*-butoxide has been reported for many chemical reactions,[30] including acceptorless dehydrogenative transformations,[31] oxidations[32] and radical pathways.[33]

Recently, Yu and co-workers reported the acceptorless dehydrogenation of *N*-heterocycles using potassium *tert*-butoxide.[31] Furthermore, *t*BuOK has been reported as the sole additive in a novel radical condensation reaction[34] for the transamidation of primary and tertiary amides at room temperatures, giving access to secondary amides.[35] In continuation of our interest in developing synthetic methodologies to access *N*-heterocycles, such as azaindoles and indoles,[36–40] we envisaged to investigate the synthesis of BIMs.

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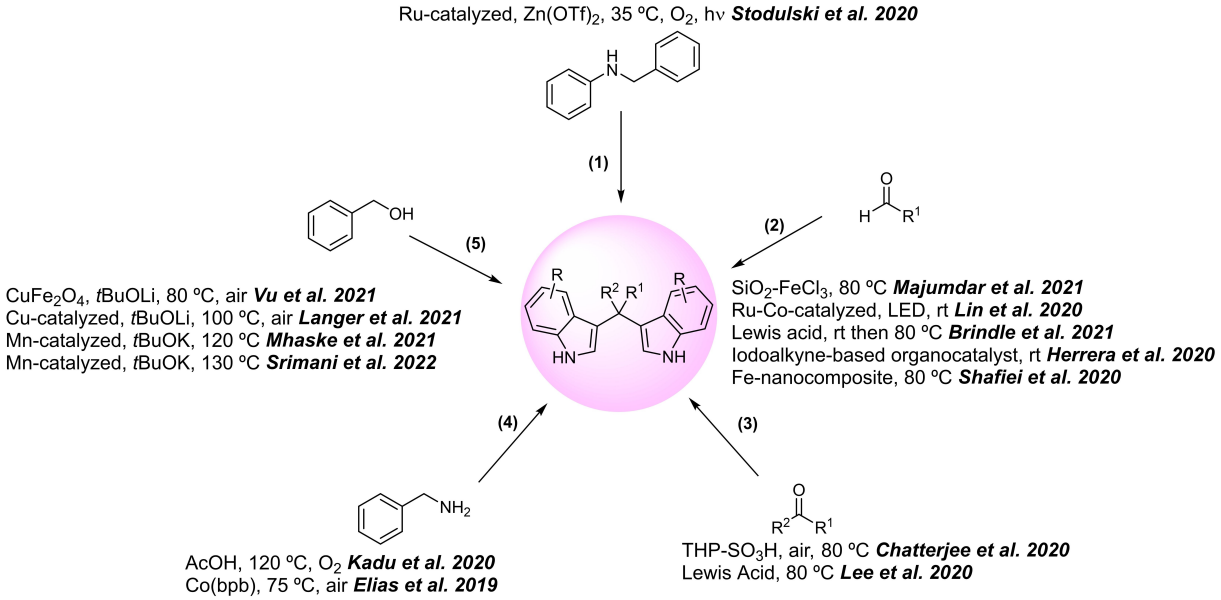


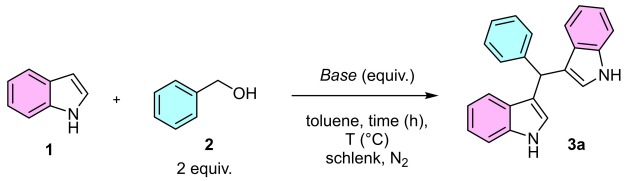
Scheme 1. Reported methods to prepare BIMs.[29] bpb: 1,2-Bis(pyridine-2-carboxamido)benzenate.

Results and Discussion

Herein, we developed a novel approach based on a *t*BuOK-mediated synthesis of several BIMs derivatives with a wide range of substrates and functional group compatibility.

A model reaction was chosen, where indole **1**, benzyl alcohol **2** and *t*BuOK were mixed in toluene to afford the corresponding BIM compound **3 a** (Table 1).

Table 1. Optimization of the synthesis of BIMs.[a]



Entry	Base [equiv.]	Time [h]	T [°C]	**3 a** [%][d]
1	*t*BuOK (0.1)	24	50–80	*trace*
2	*t*BuOK (0.1)	24	110	53
3	*t*BuOK (0.1)	6	110	22
4	*t*BuOK (0.5)	6	110	24
5	*t*BuOK (0.75)	6	110	54
6	***t*BuOK (1)**	**6**	**110**	**77**
7	*t*BuOK (1.5)	6	110	59
8	*t*BuOK (2)	6	110	40
9	*t*BuOK (2)	6	130	67
10	KOH (1)	6	110	63
11	*t*BuONa (1)	6	110	31
12	NaH (1)	6	110	53
13[b]	*t*BuOK (1)	6	110	64
14[c]	*t*BuOK (1)	6	110	55
15	*t*BuOK (1)	18	110	62

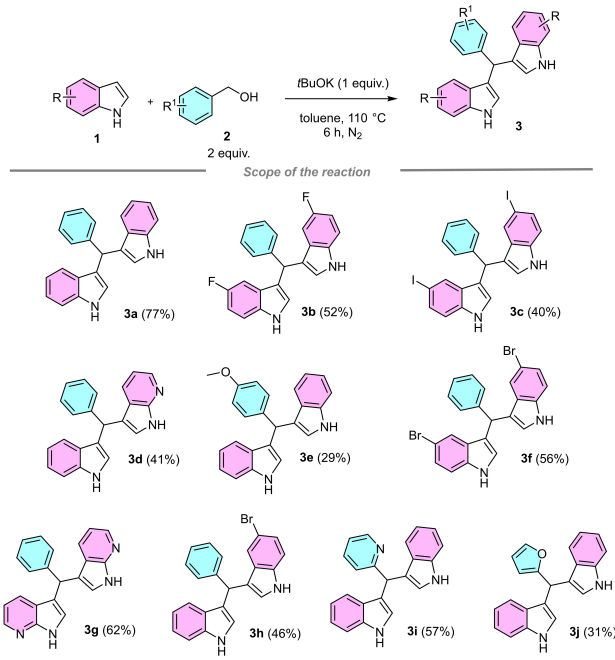
[a] Schlenk tube, under N_2; [b] Schlenk tube, under air; [c] 1 equiv. of benzyl alcohol; [d] yield quantified by quantitative NMR (qNMR) using 1,3,5-trimethoxybenzene as the standard.

Initial experiments involved the use of 0.1 equiv. of *t*BuOK at 50 °C (entry 1). Since the reaction did not seem to progress, as no starting material consumption was observed, the temperature was increased to 80 °C (entry 1). Even after 24 h, these conditions only allowed formation of the desired product **3 a** in 3% yield. Wondering whether the increase in temperature could be a crucial factor, the reaction was performed at 110 °C for 24 h (entry 2). Indeed, a great increase in yield was observed and the product **3 a** was obtained in 53% yield. Next, the amount of base was studied, and experiments were carried out with 0.1, 0.5, 0.75, 1, 1.5 and 2 equiv. of *t*BuOK at 110 °C (entries 3–8). After 6 h, using either 0.1 equiv. or 0.5 equiv., the product **3 a** was obtained in low yields (22% and 24% yield, respectively, entries 3 and 4). A significant increase in yield was observed when 0.75 equiv. of were used (54%, entry 5). Finally, experiments using 1 equiv. (entry 6), 1.5 equiv. (entry 7) and 2 equiv. of *t*BuOK (entry 8) were performed. Increasing the amount of base to 1 equiv. improved the yield to 77%; above these values, the yield decreased (entries 6–8). This shows that the amount of base is crucial for product formation, as higher conversion was obtained with an equimolar amount of base. Still, the use of an increasing excess (entries 7 and 8) seems to compromise the reaction outcome, probably due to a rapid formation of side products, as the reaction mixture revealed to be more complex.

Furthermore, experiments with 2 equiv. of *t*BuOK at 130 °C were carried out and the reaction seemed to progress smoother with a total yield of 67% (entry 9). Since these conditions were harsher and involved an excess of base, we decided to focus our efforts on using milder conditions. Subsequently, different bases were tested such as KOH, *t*BuONa and NaH, with corresponding yield of 63%, 31% and 53% (entries 10–12). These results suggest that the use of potassium *tert*-butoxide as base seems to be essential for the reaction mechanism (entry 7).

The reaction was also carried out in open air to access the influence of the presence of oxygen. Under these conditions, a slightly lower yield was obtained (64%, entry 13) when compared with the same reaction carried out in nitrogen atmosphere (77%, entry 6). Next, 1 equiv. of benzyl alcohol was used and a decrease in yield was observed, suggesting that an excess of alcohol is needed to promote the formation of the imine intermediate (entry 14; see intermediate **1c** in mechanistic proposal below Scheme 4). Additionally, leaving the reaction for 18 h did not significantly influence the product formation (entry 15). The best conditions found involved 1 equiv. of *t*BuOK for 6 h at 110 °C (entry 7).

Next, the reaction scope was investigated while applying the optimal reaction conditions (Table 1, entry 5), using different *N*-heterocycles and benzyl alcohol derivatives (Scheme 2). The use of different indole derivatives bearing halogen atoms at the aromatic ring seemed to, in general, decrease the reaction yield (see compounds **3b**, **3c** and **3f**), but still the reaction proceeded smoothly with the best yield obtained for 5-bromo-indole (**3f**, 56%). The use of 7-azaindole was also effective under the described conditions, with the corresponding bis-azaindole **3g** obtained in 62% yield. Comparing the reactivity of 7-azaindole with indole (**3a** vs. **3g**), the slight decrease in yield of product **3g** can be justified by the electron-deficient nature of the pyridine ring which can decrease the reactivity of the conjugated system in the pyrrole ring. Next, different benzyl alcohols were tested, one bearing an electron-donating group on the aromatic ring (-OCH_3) and the other bearing a pyridine ring, which possesses electron-withdrawing properties. The best yield was observed when the pyridine ring was present in the alcohol moiety (**3i**, 57%), most likely due to the electron-withdrawing nature of the pyridine that allows an easier attack of the second unit of indole, since a more reactive imine-like intermediate is formed (see mechanistic considerations below). The use of furfuryl alcohol also led to the desired product **3j** in 31% yield, which shows the versatility of the proposed methodology.



Scheme 2. *t*BuOK-promoted coupling of alcohols and indole derivatives (the presence of an additional nitrogen atom in the aromatic moiety, forming the azaindole core, is highlighted in dark blue).

Additionally, experiments with *p*-trifluoromethyl and *p*-nitro benzyl alcohol were also carried out, but only trace amounts of both products were observed by TLC. Finally, competition experiments were performed using benzyl alcohol and two different indoles. Indeed, the synthesis of unsymmetrical BIMs is interesting and requires dedicated strategies.[41] When indole and 5-bromo indole were used as coupling partners, both products **3a** and **3h** were isolated from the reaction mixture in a 1:2.3 ratio, respectively. This distribution can be attributed to the formation of both indole and 5-bromo indole imine-like intermediates. When the imine-like product is formed from indole, two possible nucleophilic attacks (from indole and 5-bromo indole) can occur, leading to the formation of **3a** and **3h**, respectively. On the other hand, formation of the 5-bromo indole-derived imine-like product is only attacked by indole **3h**, since no formation of product **3f** was observed. This reinforces the higher reactivity of indole as a nucleophile in this reaction.

Furthermore, the use of indole and 7-azaindole with benzyl alcohol as coupling partners led to the formation of products **3g** and **3d** in a 1:1.5 ratio, respectively. These results suggest that the imine-like intermediate from azaindole might be more electrophilic, undergoing a subsequent nucleophilic attack by both indole and 7-azaindole. No formation of **3a** was observed.

Additional competitive experiments were also attempted with different benzyl alcohols. Experiments were performed with *p*-methoxybenzyl alcohol using indole and 6-bromoindole, and a mixture of 3 products was formed in a 1:1.8:0.9 ratio (identified by ^{1}H NMR spectroscopy). The major product contains both indole units (see Supporting Information).

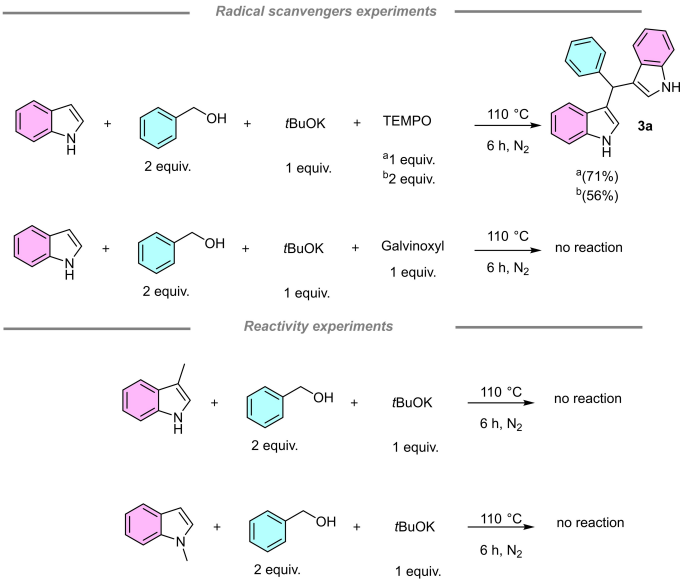
Furthermore, the same reaction was performed using pyridyl benzyl alcohol, indole and 6-bromoindole, and a similar result was observed, three compounds with a 1:1.7:0.6 ratio (see Supporting Information).

The results from these competition experiments suggest that functionalization of the benzyl moiety of the alcohol influences the reactivity of the intermediates generated. Indeed, simple benzyl alcohol leads to the formation of two products, while, when electron-withdrawing or electron-donating groups are present in the alcohol moiety, three compounds are formed. Interestingly, the major product contains both indole units, independently of the alcohol used.

This observation reinforces that the most electrophilic imine-like intermediate (generated from the most electrophilic indole) preferentially reacts with the most nucleophilic indole.

Next, we investigated the reaction mechanism and conducted several control experiments (Scheme 3).

First, 1.0 equiv. and 2.0 equiv. of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) were added, respectively, to the reaction system under the optimized conditions and the formation of the final product **3a** was supressed by the increasing amount of TEMPO as mirrored in the lowered yields.



Scheme 3. Control experiments for mechanistic insights.

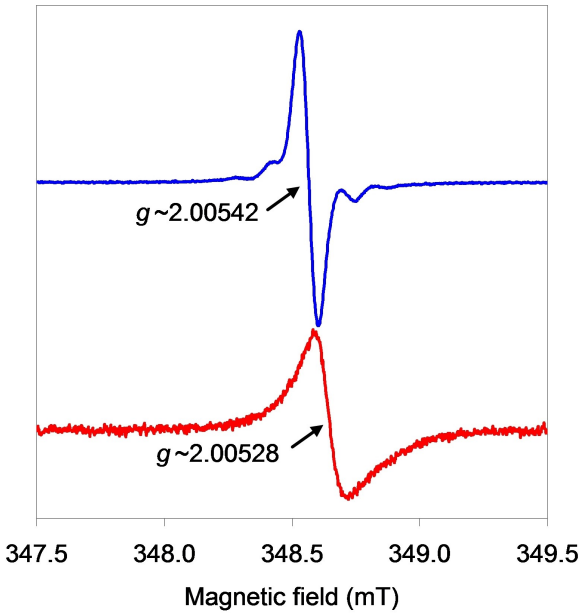


Figure 2. EPR spectra of the following reaction mixtures: blue - benzyl alcohol, *t*BuOK and toluene reacted at 110 °C, for 2 h; red - benzyl alcohol, *t*BuOK, toluene and indole reacted at 110 °C, for 2 h. Other reaction details are described in the Supporting Information. Spectra were acquired at room temperature (298 K) as described in the Supporting Information. To facilitate comparison between the two spectra, the blue one was multiplied by 0.1.

The use of a different radical scavenger like galvinoxyl (1.0 equiv.) completely inhibited the reaction. Furthermore, these control experiments suggested that a possible formation of radical intermediates might take place.

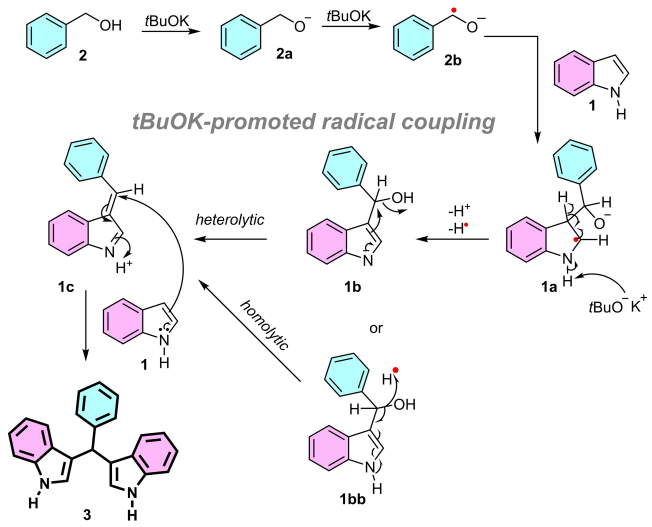
To confirm the formation of radical species, we used electron paramagnetic resonance (EPR) spectroscopy.

The reaction of indole (1.0 equiv.), benzyl alcohol (2.0 equiv.) and *t*BuOK (1.0 equiv.), in toluene, at 110 °C, for 2 h, yielded a broad, nearly isotropic EPR spectrum, probably originating from different radical species (Figure 2, red spectrum). To shed light on the components responsible for the formation of these radicals, the spectra of reaction mixtures without one of the three reagents (benzyl alcohol, *t*BuOK and indole) were also acquired. In the absence of benzyl alcohol or *t*BuOK, no radical species was detected (Figure S2, Supporting Information), suggesting that it is the reaction between these two components (benzyl alcohol and *t*BuOK) that generates the initiating radical species. In accordance, in the presence of only benzyl alcohol and *t*BuOK (absence of indole), a strong EPR spectrum was observed (Figure 2, blue spectrum), clearly supporting that the reaction of benzyl alcohol with *t*BuOK is able to generate radical species in high concentration. Even though the radical species responsible for this strong spectrum were not characterised, they are not likely to be the same as the ones formed in the presence of indole (as they do not have similar g-factor values; compare the red and blue spectra) and are present at a much higher concentration (i.e., display a higher intensity). Hence, it can be suggested that, in the presence of indole, the initiating radical species (blue spectrum) are consumed, and new ones are formed at the same time as the BIM is being produced (red spectrum).

As the reaction proceeds, the concentration of radicals decreases, which is reflected in the much lower intensity of the red spectrum (note the scaling factor of 0.1 for the blue spectrum in Figure 2). Eventually, all radical species relevant to the reaction are consumed and the reaction stops. A similar role for the *t*BuOK/benzyl alcohol-derived radicals in the generation of 3-arylpropanamides was suggested by Azizi and Madsen,[34] who also used EPR spectroscopy to prove the generation of radicals.

Furthermore, 3-methyl indole and *N*-methyl indole were investigated to prove the crucial role of the free NH position and position C-3 of the indole moiety. Unsurprisingly, no reaction was observed when these substrates were used, since an NH group is needed as a precursor for the reaction mechanism. Besides that, the blockage of position 3 of the indole moiety hinders the reaction success since this is where the functionalization by benzyl alcohol takes place.

Based on the EPR spectra, that clearly showed the ability of the system *t*BuOK/benzyl alcohol to generate radical species in high concentrations, the following reaction mechanism is proposed (Scheme 4). First, benzyl alcohol is deprotonated by the base to form alkoxide **2a**, followed by initiation, generating radical anion **2b**. Radical **2b** then reacts with indole **1** in position C-3 to give radical anion intermediate **1a**. This intermediate **1a** then undergoes rapid homolytic cleavage of the C3 C–H bond forming a C–C double bond in **1b**. Next, two possible pathways can occur, either by heterolytic cleavage through an elimination reaction or by homolytic cleavage and capture of the previously generated H-atom (shown as**1bb**), leading to the formation of an imine-like intermediate **1c**. This highly reactive intermediate **1c** undergoes a second nucleophilic attack by indole to obtain the desired product **3** (Scheme 4). Our results demonstrate the important role of *t*BuOK in the generation of radical species.



Scheme 4. Proposed mechanism for the *t*BuOK-promoted radical coupling of indole **1** with benzyl alcohol **2**.

Conclusion

A novel base-mediated methodology and simple route to access BIMs derivatives was developed. This emerges as suitable and reliable alternative to the use of complex metal-catalysts that are not always stable and easy to handle. Taking advance of a potassium *tert*-butoxide-mediated coupling, several BIMs were synthesized with yields up to 77% in refluxing toluene. Furthermore, control experiments and EPR spectroscopic studies allowed conclusions regarding the role of the base in the reaction mechanism. The mechanistic studies revealed that a radical mechanism is involved in the C-3 alkylation of indoles and azaindoles, in which the *t*BuOK facilitates the reaction to proceed smoothly and to be complete after 6 h. This report constitutes a proof of concept on the relevance of *t*BuOK and its role in C–C bond.forming reactions involving benzyl moieties.

Experimental Section

Materials and methods

All reagents and solvents were acquired commercially and usually used without further purification. The solvents used during the reactions were dried and distilled using typical methods. Analytical TLC was performed on Merck Kieselgel GF 254, 0.2 mm plates supported on aluminium with the described eluent for each case.

NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers at NOVA School of Science and Technology. ^{1}H NMR and ^{13}C NMR spectra were measured at 400 and 101 MHz, respectively. The samples were prepared in 5 or 3 mm NMR tubes using $CDCl_3$ or DMSO-d_6 and the corresponding trace as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R–H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet, broad singlet (br s), doublet of doublets (dd), triplet of doublets (td), doublet (d), triplet (t) and multiplet (m) with the coupling constant (*J*) being given in Hz. X-band EPR spectra were acquired with a Bruker EMX 6/1 spectrometer and an ER 4102ST cavity (Bruker), at 298 K and with a modulation frequency of 100 kHz, modulation amplitude of 0.05 mT and microwave power of 635 μW.

General procedure for synthesis of BIMs derivatives

A Schlenk tube was equipped with a stirring bar was subjected to vacuum while heating to remove all possible moisture. After the tube reached room temperature indole (30 mg, 1 equiv.) and *t*BuOK (1 equiv.) were added under nitrogen stream and then the solids remained under vacuum. After that, 3 cycles of vacuum/nitrogen were done to ensure the nitrogen atmosphere. Dry toluene (1 mL) was added to the solids, followed by benzyl alcohol (2 equiv.). The mixture was allowed to reach 110 °C and stirred for 6 h. The reaction was followed by TLC until consumption of starting material. After the reaction completion, the mixture was filtered over a celite pad and the solvent removed. The desired product was isolated after purification by chromatography.

An alternative work-up procedure was also tested that consisted on addition of ethyl acetate to the crude residue and washing two times with HCl (1 M). The combined aqueous layers were extracted with ethyl acetate to remove all the remaining product. The combined organic layers were dried with anhydrous sodium sulphate, filtered and concentrated. Both work-up protocols afforded the product with same yields.

3,3′-(Phenylmethylene)bis(1H-indole) (3 a)[42]

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 77% (31.7 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 2H), 7.42 (s, 1H), 7.40–7.36 (m, 5H), 7.33–7.28 (m, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.67 (s, 2H), 5.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.14, 136.79, 128.85, 128.34, 127.19, 126.25, 123.75, 122.03, 120.05, 119.79, 119.34, 111.16, 40.31.

3,3′-(Phenylmethylene)bis(5-fluoro-1H-indole) (3 b)[43]

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 52% (20.5 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 2H), 7.37–7.23 (m, 7H), 7.01 (d, *J* = 9.7 Hz, 2H), 6.93 (t, *J* = 9.0 Hz, 2H), 6.74 (s, 2H), 5.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.68 (d, *J* = 234.5 Hz), 143.41, 133.35, 128.62 (d, *J* = 20.8 Hz), 127.51 (d, *J* = 9.8 Hz), 126.56, 125.39, 119.62 (d, *J* = 4.7 Hz), 111.79 (d, *J* = 9.6 Hz), 110.54 (d, *J* = 26.4 Hz), 105.04, 104.80.

3,3′-(Phenylmethylene)bis(5-iodo-1H-indole) (3 c)[44]

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 40% (14.1 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 2H), 7.70 (s, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35–7.25 (m, 5H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.61 (s, 2H), 5.77 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.22, 135.94, 130.60, 129.63, 128.68, 128.67, 128.56, 126.66, 124.52, 118.96, 113.26, 83.07, 39.94.

3-((1H-Indol-3-yl)(phenyl)methyl)-1H-pyrrolo[2,3-b]pyridine (3 d)

Purification: silica gel, Hexane/AcOEt (6:1) with gradient; PTLC, Hexane/AcOEt (6:1) with gradient; Yield: 41% (8.43 mg); red oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 3.8 Hz, 1H), 8.04 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.41–7.27 (m, 6H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.94 (dd, *J* = 7.8, 4.6 Hz, 1H), 6.84 (s, 1H), 6.66 (s, 1H), 5.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.32, 143.65, 142.83, 136.84, 128.80, 128.70, 128.46, 128.39, 127.10, 126.49, 124.06, 123.63, 122.21, 119.94, 119.89, 119.51, 119.39, 118.22, 115.55, 111.23, 40.50. MS (EI) calcd. for $C_{22}H_{18}N_3$ (M + 1): 324.149 Found: 324.148.

*3,3′-((4-Methoxyphenyl)methylene)bis(1*H*-indole) (3 e)*[45]

Purification: silica gel, Hexane/AcOEt (6 : 1) with gradient; PTLC, Hexane/AcOEt (6 : 1) with gradient; Yield: 29% (12.97 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.24 (s, 1H), 7.16 (s, 2H), 7.14 (s, 1H), 7.06 (t, *J* = 7.6 Hz, 2H), 6.90 (t, *J* = 7.5 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 6.55 (s, 2H), 5.74 (s, 1H), 3.68 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.06, 136.87, 136.37, 129.74, 127.22, 123.65, 122.03, 120.22, 120.13, 119.33, 113.71, 111.14, 55.35, 39.48.

*3,3′-(Phenylmethylene)bis(5-bromo-1*H*-indole) (3 f)*[46]

Purification: silica gel, Hexane:AcOEt (6 : 1) with gradient; PTLC, Hexane/AcOEt (6 : 1) with gradient; Yield: 54% (20 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 2H), 7.39 (s, 2H), 7.25–7.07 (m, 10H), 6.55 (s, 2H), 5.67 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.20, 135.50, 128.82, 128.68, 128.57, 126.67, 125.11, 124.91, 122.43, 119.21, 112.82, 112.72, 40.04.

*3,3′-(Phenylmethylene)bis(1*H*-pyrrolo[2,3-b]pyridine) (3 g)*[47]

Purification: silica gel, Hexane/AcOEt (6 : 1) with gradient; PTLC, Hexane/AcOEt (6 : 1) with gradient; Yield: 76% (31.2 mg); Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.43 (s, 2H), 8.16 (d, *J* = 3.9 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 6.97 (s, 2H), 6.92 (dd, *J* = 7.6, 4.7 Hz, 2H), 5.86 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): 148.83, 144.06, 142.47, 128.23, 127.14, 126.11, 123.82, 118.79, 116.42, 114.88.

*3-((1H-Indol-3-yl)(phenyl)methyl)-5-bromo-1*H*-indole (3 h)*[48]

Purification: silica gel, Hexane/AcOEt (6 : 1) with gradient; PTLC, Hexane/AcOEt (6 : 1) with gradient; Yield: 46% (10.43 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 2H), 7.43 (s, 1H), 7.28 (d, *J* = 4.1 Hz, 1H), 7.24 (s, 1H), 7.22–7.21 (m, 2H), 7.19 (s, 1H), 7.16 (s, 3H), 7.15–7.13 (m, 2H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.59–6.52 (m, 2H), 5.73 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.67, 136.90, 135.46, 128.78, 128.47, 127.15, 127.10, 126.48, 126.48, 125.02, 124.97, 123.70, 122.52, 122.19, 120.01, 119.65, 119.53, 119.47, 112.77, 112.64, 111.22, 40.20.

*3,3′-(Pyridin-2-ylmethylene)bis(1*H*-indole) (3 i)*[49]

Purification: silica gel, Hexane/AcOEt (4 : 1) with gradient; PTLC, Hexane/AcOEt (4 : 1); Yield: 57% (23.6 mg); grey solid; ^{1}H NMR (400 MHz, Acetone-d_6): δ = 10.00 (s, 2H), 8.48 (d, *J* = 4.5 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.36 (t, J = 8.8 Hz, 5H), 7.17–7.07 (m, 1H), 7.02 (t, J = 7.6 Hz, 2H), 6.90 (s, 2H), 6.87 (t, *J* = 7.5 Hz, 2H), 6.02 (s, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ = 168.39, 152.84, 141.03, 139.98, 131.23, 127.54, 126.57, 125.11, 125.03, 123.22, 122.41, 121.79, 115.20, 47.24.

*3,3′-(Furan-2-ylmethylene)bis(1*H*-indole) (3 j)*[50]

Purification: silica gel, Hexane/AcOEt (4 : 1) with gradient; PTLC, Hexane/AcOEt (4 : 1); Yield: 31% (12.3 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 3H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 1.2 Hz, 2H), 6.31 (s, 1H), 6.06 (d, *J* = 2.9 Hz, 1H), 5.95 (s, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.24, 141.33, 136.66, 126.90, 123.20, 122.05, 119.79, 119.45, 117.26, 117.26, 111.26, 110.26, 106.72, 34.23.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[2] K. Kaur, V. Jaitak, *Anti-Cancer Agents Med. Chem.* **2019**, *19*, 962–983.
[3] M. S. Estevão, L. C. Carvalho, D. Ribeiro, D. Couto, M. Freitas, A. Gomes, L. M. Ferreira, E. Fernandes, M. M. B. Marques, *Eur. J. Med. Chem.* **2010**, *45*, 4869–4878.
[4] Nisha, S. Singh, N. Sharma, R. Chandra, *Org. Chem. Front.* **2022**, *9*, 3624–3639.
[5] A. Nasreen, R. Varala, K. S. Rao, *Org. Commun.* **2017**, *10*, 104–113.
[6] H. Veisi, R. Gholbedaghi, J. Malakootikhah, A. Sedrpoushan, B. Maleki, D. Kordestani, *J. Heterocycl. Chem.* **2010**, *47*, 1398–1405.
[7] Z. Zheng, D. Zha, P. Cui, H. Zhang, C. Li, J. Shi, B. Han, *Results Chem.* **2021**, *3*, 100247.
[8] A. Mondal, R. Sharma, B. Dutta, D. Pal, D. Srimani, *J. Org. Chem.* **2022**, *87*, 3989–4000.
[9] A. E. Putra, K. Takigawa, H. Tanaka, Y. Ito, Y. Oe, T. Ohta, *Eur. J. Org. Chem.* **2013**, 6344–6354.
[10] D. Konwar, U. Bora, *ChemistrySelect* **2020**, *5*, 7460–7466.
[11] J.-B. Peng, X. Qi, X.-F. Wu, *Synlett* **2016**, *28*, 175–194.
[12] J.-B. Peng, X. Qi, X.-F. Wu, *ChemSusChem* **2016**, *9*, 2279–2283.
[13] Y. Bai, D. C. Davis, M. Dai, *J. Org. Chem.* **2017**, *82*, 2319–2328.
[14] C. Mukhopadhyay, P. K. Tapaswi, R. J. Butcher, *Tetrahedron Lett.* **2010**, *51*, 1797–1802.
[15] J. Jin, Y. Li, S. Xiang, W. Fan, S. Guo, D. Huang, *Org. Biomol. Chem.* **2021**, *19*, 4076–4081.

[16] V. D. Kadu, S. N. Chandrudu, M. G. Hublikar, D. G. Raut, R. B. Bhosale, *RSC Adv.* **2020**, *10*, 23254–23262.
[17] F. Stanek, R. Pawlowski, P. Morawska, R. Bujok, M. Stodulski, *Org. Biomol. Chem.* **2020**, *18*, 2103–2112.
[18] J. V. Alegre-Requena, A. Valero-Tena, I. G. Sonsona, S. Uriel, R. P. Herrera, *Org. Biomol. Chem.* **2020**, *18*, 1594–1601.
[19] M. Hajibabaei, M. A. Senejani, F. Shafiei, *Appl. Organomet. Chem.* **2020**, *34*, e5641.
[20] W. J. Patterson, K. Lucas, V. A. Jones, Z. Chen, K. Bardelski, M. Guarino-Hotz, C. S. Brindle, *Eur. J. Org. Chem.* **2021**, 6737–6742.
[21] Y. Quan, G. Lan, W. Shi, Z. Xu, Y. Fan, E. You, X. Jiang, C. Wang, W. Lin, *Angew. Chem. Int. Ed.* **2021**, *60*, 3115–3120; *Angew. Chem.* **2021**, *133*, 3152–3157.
[22] B. Deb, S. Debnath, A. Chakraborty, S. Majumdar, *RSC Adv.* **2021**, *11*, 30827–30839.
[23] G. Kalita, N. Deka, D. Paul, L. Thapa, G. K. Dutta, P. N. Chatterjee, *Synlett* **2021**, *32*, 304–308.
[24] S. O. Lee, J. Choi, S. Kook, S. Y. Lee, *Org. Biomol. Chem.* **2020**, *18*, 9060–9064.
[25] P. Saini, P. Kumari, S. Hazra, A. J. Elias, *Chem. Asian J.* **2019**, *14*, 4154–4159.
[26] N. Biswas, R. Sharma, D. Srimani, *Adv. Synth. Catal.* **2020**, *362*, 2902–2910.
[27] N.-K. Nguyen, M.-T. Ha, H. Y. Bui, Q. T. Trinh, B. N. Tran, V. T. Nguyen, T. Q. Hung, T. T. Dang, X. H. Vu, *Catal. Commun.* **2021**, *149*, 106240.
[28] N.-K. Nguyen, D. L. Tran, T. Q. Hung, T. M. Le, N. T. Son, Q. T. Trinh, T. T. Dang, P. Langer, *Tetrahedron Lett.* **2021**, *68*, 152936.
[29] P. Praveen, P. Parameswaran, M. Majik, *Synthesis* **2015**, *47*, 1827–1837.
[30] J. Madasu, S. Shinde, R. Das, S. Patel, A. Shard, *Org. Biomol. Chem.* **2020**, *18*, 8346–8365.
[31] T. Liu, K. Wu, L. Wang, Z. Yu, *Adv. Synth. Catal.* **2019**, *361*, 3958–3964.
[32] Q.-L. Luo, W.-H. Nan, Y. Li, X. Chen, *Arkivoc* **2014**, *2014*, 350–361.
[33] J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2016**, *138*, 7402–7410.
[34] K. Azizi, R. Madsen, *Chem. Sci.* **2020**, *11*, 7800–7806.
[35] T. Ghosh, S. Jana, J. Dash, *Org. Lett.* **2019**, *21*, 6690–6694.
[36] M. S. Estevão, L. C. R. Carvalho, M. Freitas, A. Gomes, A. Viegas, J. Manso, S. Erhardt, E. Fernandes, E. J. Cabrita, M. M. B. Marques, *Eur. J. Med. Chem.* **2012**, *54*, 823–833.
[37] M. J. D. Pires, D. L. Poeira, S. I. Purificação, M. M. B. Marques, *Org. Lett.* **2016**, *18*, 3250–3253.
[38] S. I. Purificação, M. J. D. Pires, R. Rippel, A. S. Santos, M. M. B. Marques, *Org. Lett.* **2017**, *19*, 5118–5121.
[39] I. Rodriguez-Oliva, N. Losada-Garcia, A. S. Santos, M. M. B. Marques, J. M. Palomo, *Asian J. Org. Chem.* **2021**, *10*, 872–878.
[40] A. S. Santos, M. M. Martins, A. C. Mortinho, A. M. S. Silva, M. M. B. Marques, *Tetrahedron Lett.* **2020**, *61*, 152303.
[41] A. Palmieri, M. Petrini, *Synthesis* **2019**, *51*, 829–841.
[42] S. Badigenchala, D. Ganapathy, A. Das, R. Singh, G. Sekar, *Synthesis* **2013**, *46*, 101–109.
[43] N.-K. Nguyen, D. L. Tran, T. Q. Hung, T. M. Le, N. T. Son, Q. T. Trinh, T. T. Dang, P. Langer, *Tetrahedron Lett.* **2021**, *68*, 152936.
[44] X. Liu, S. Ma, P. H. Toy, *Org. Lett.* **2019**, *21*, 9212–9216.
[45] D. Sun, G. Jiang, Z. Xie, Z. Le, *Chin. J. Chem.* **2015**, *33*, 409–412.
[46] R. M. N. Kalla, J. V. John, H. Park, I. Kim, *Catal. Commun.* **2014**, *57*, 55–59.
[47] V. Yadav, E. Balaraman, S. B. Mhaske, *Adv. Synth. Catal.* **2021**, *363*, 4430–4439.
[48] Y. Zou, C. Chen, X. Chen, X. Zhang, W. Rao, *Eur. J. Org. Chem.* **2017**, 2266–2271.
[49] S. S. Mohapatra, Z. E. Wilson, S. Roy, S. V. Ley, *Tetrahedron* **2017**, *73*, 1812–1819.
[50] J. Beltrá, M. C. Gimeno, R. P. Herrera, *Beilstein J. Org. Chem.* **2014**, *10*, 2206–2214.

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