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Article

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General synthesis of unsymmetrical 3,3'-(aza)diindolylmethane derivatives

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Abstract

Diindolylmethane (DIM) and its derivatives have recently been in the focus of interest due to their significant biological activities, specifically in cancer prevention and therapy. Molecular targets of DIM have been identified, e.g., the immuno-stimulatory G protein-coupled receptor GPR84. However, most of the reported and investigated DIM derivatives are symmetrical because general methods for obtaining unsymmetrical DIMs have been lacking. To optimize the interaction of DIM derivatives with their protein targets, unsymmetrical substitution is required. In the present study we developed a new, mild and efficient access to unsymmetrically substituted 3,3'-DIMs by reaction of (3-indolylmethyl)trimethylammonium iodides with a wide range of substituted indole derivatives. 7-Azaindole also led to the 3,3'-connected DIM analog while 4- and 5-azaindoles reacted at the *N*1-nitrogen atom as confirmed by X-ray crystallography. The reactions were performed in water without the requirement of a catalyst or other additives. Wide substrate scope, operational simplicity, environmentally benign workup, and high yields are further advantages of the new method. The synthetic protocol proved to be suitable for upscaling to yield gram amounts for pharmacological studies. This procedure will

allow the preparation of a broad range of novel, unsymmetrical DIM derivatives to exploit their potential as novel drugs.

Keywords: Anti-cancer activity, azaindole, diindolylmethane, GPR84, environmentally benign synthesis, indole, natural product

Introduction

Diindolylmethane (DIM, **1**) and its derivatives and analogs constitute an important class of indole alkaloids. They consist of two indole rings connected by a single carbon atom at the 3- and 3'-positions (see Figure 1). DIM itself is a major metabolite of indole-3-carbinol produced from the glycoside glucobrassicin, which is found in cruciferous vegetables such as broccoli, brussel sprouts and cauliflower.[1] DIM was reported to exhibit anti-oxidant,[2] anti-inflammatory,[3] anti-angiogenic,[4] and anti-cancer activities.[5,6] It is used to treat recurrent respiratory papillomatosis,[7] a rare respiratory disease with tumors in the upper respiratory tract caused by the human papilloma virus. The compound was also evaluated in a Phase III clinical study for the treatment of cervical dysplasia,[8] and recently a Phase II clinical trial has been completed for stage I/II prostate cancer.[9] DIM was found to act synergistically when combined with the anti-cancer drug paclitaxel, an inhibitor of mitosis, to induce apoptosis in human breast cancer cells.[10]

Several molecular targets of DIM have been identified by *in vitro* studies: DIM was reported to activate the arylhydrocarbon receptor (at a concentration of 30 μM),[11] a ligand-activated transcription factor that regulates cell growth and differentiation. The compound was also reported to inhibit histone deacetylase-1 (HDAC-1) (at a concentration of 100 μM).[12] Recently, DIM and several fluorine-substituted derivatives were discovered to be potent agonists of the immune-stimulatory orphan G protein-coupled receptor GPR84 (at concentrations below 1 μM).[13,14] Several natural derivatives of DIM were identified and reported to possess biological activities. Bell et al. described the isolation of vibrindole A (**2**) from a culture of the marine bacterium *Vibrio parahemolyticus,*[15] and trisindoline (**3**) obtained from the culture of the bacterium *Vibrio sp*., both of which exhibited antibiotic activity.[16] Gu et al. isolated arsindoline A (**4**) and B (**5**) from the Xiamen sea bacterium strain CB101. Arsindoline B (**5**) exhibited activity against the A-549 cancer cell line (IC_{50} = 22.6 μM). Sterptindole (**6**) is a metabolite of the

common human intestinal bacterium *Streptococcus faecium* IB 37, and was reported to display DNA damaging and genotoxic properties.[17]

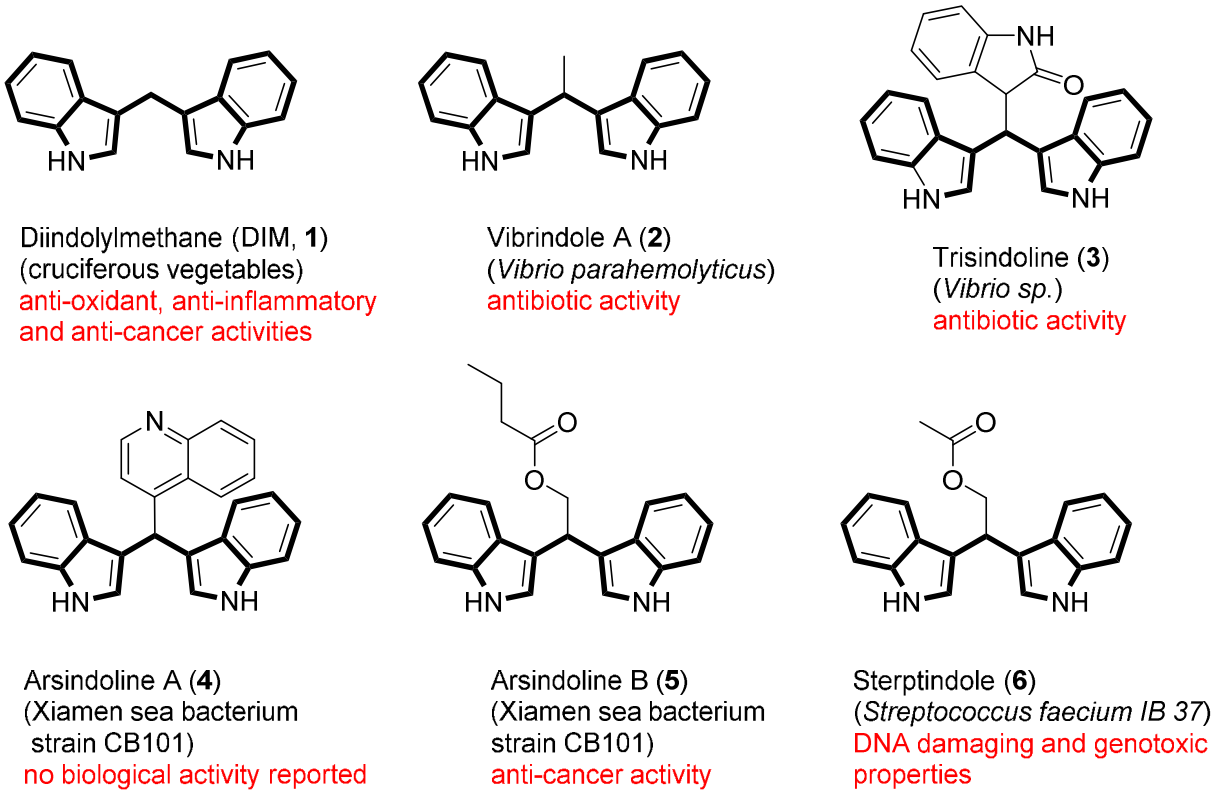


Figure 1 Structures of naturally occurring diindolylmethane derivatives; isolation sources are indicated in brackets and biological activities are highlighted in red color.

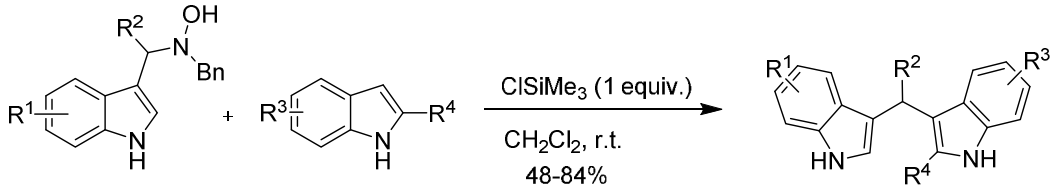
Due to the observed biological activities of DIM and its derivatives, a number of methods have been reported for their synthesis, in particular those yielding symmetrically substituted DIMs.[18] However, the preparation of unsymmetrically substituted DIM derivatives has remained challenging, and there are only few reports, all of which are suffering from serious limitations (see Figure 2). In 2000, Chalaye-Mauger et al. developed the first synthesis of unsymmetrically substituted DIMs by reaction of nitrones with indoles in the presence of trimethylsilyl chloride ($ClSiMe_3$) in dichloromethane.[19] In 2007, de la Herra´n et al. reported on a rhodium or iridium complex-catalyzed benzylic substitution of 3-(dimethylaminomethyl)indoles by indoles in the

presence of potassium phosphate as a base.[20] Pathak and co-workers described the reaction of vinylindoles with a large excess of indole derivatives (10 equiv.) in the presence of *para*-toluenesulfonic acid (*p*-TsOH) in *N*,*N*-dimethylacetamide (DMA).[21] A one-pot synthesis has been developed by performing an intermolecular Pummerer reaction using indole as a nucleophile in the presence of trifluoroacetic anhydride (TFAA) and copper(II) acetate in dimethyl sulfoxide (DMSO).[22] Recently, Xiao et al. reported on the dehydrative[23] S_N1-type reaction of 3-α-hydroxybenzylindoles with indoles yielding unsymmetrical phenyl-substituted DIMs. Although the described methods are useful for the synthesis of certain unsymmetrical DIMs, they have severe limitations and drawbacks, such as the use of expensive and highly toxic catalysts (example 2), substrate limitations (only substrates with an aromatic group at the benzylic position of indole, example 5), low yields (example 4), formation of hazardous by-products, harsh reaction conditions or tedious workup to isolate the products (examples 3 and 4), requirement of stoichiometric amounts of protic acids or Lewis acids/bases (examples 1, 3 and 4) and/or large amounts of reagents (example 3), and the use of organic solvents (examples 1-4).

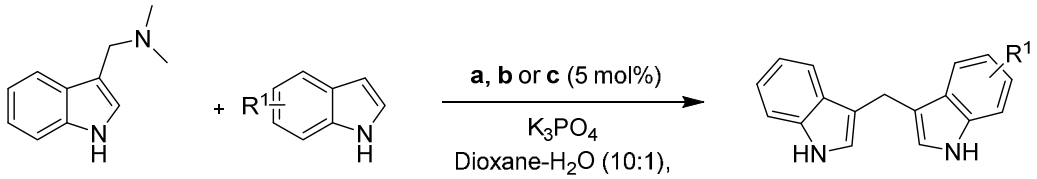
Therefore, the development of a new, general, mild and efficient procedure with broad functional group tolerance is urgently required to provide a broad range of unsymmetrical DIMs for biological studies. We have previously developed a new procedure for the synthesis of symmetrical DIMs, and established their structure-activity relationships (SARs) as agonists of the immunostimulatory G protein-coupled receptor GPR84.[14] Subsequently, we succeeded in improving the synthetic procedure to access a large variety of symmetrical DIM derivatives by reaction of indoles with various aromatic and aliphatic aldehydes in the presence of sulfuric acid in water.[24] However, we soon realized the current limitations, since unsymmetrical DIMs would be required for optimizing the compounds' interactions with their target.

Previous work

1. Chalaye-Mauger et al. (2000)[19]

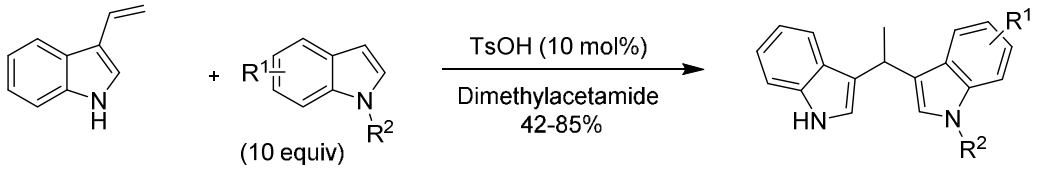


2. de la Herra´n et al. (2007)[20]

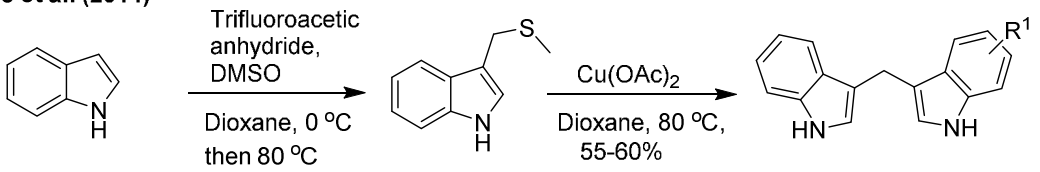


a: $[(cod)RhCl]_2$; **b**: $[(cod)_2Rh]BF_4$; **c**: $[(cod)IrCl]_2$

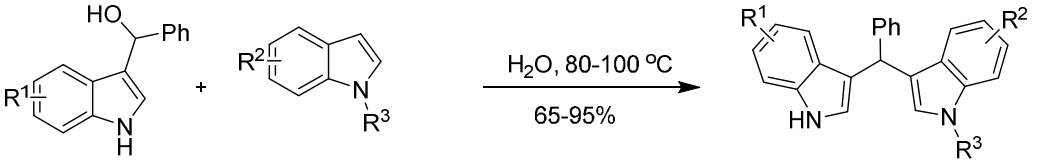
3. Pathak et al. (2012)[21]



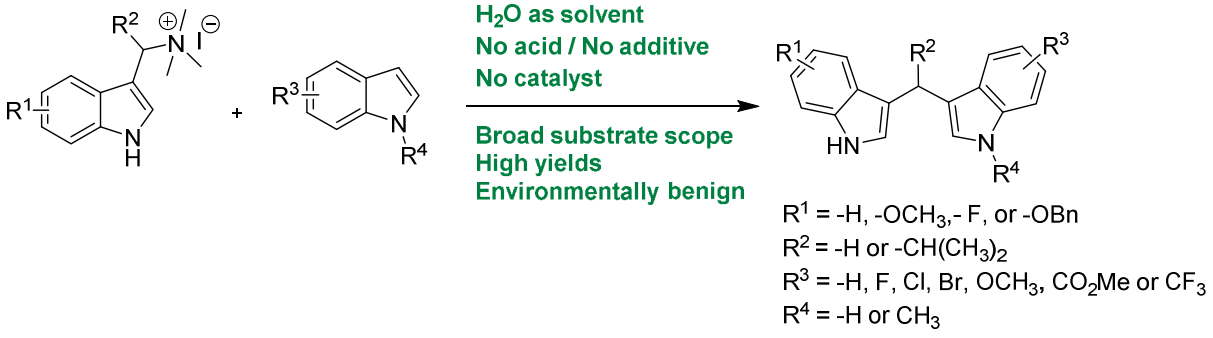
4. Abe et al. (2014)[22]



5. Xiao et al. (2016)[23]



Present study



R^1 = -H, $-OCH_3$,- F, or -OBn
R^2 = -H or $-CH(CH_3)_2$
R^3 = -H, F, Cl, Br, OCH_3, CO_2Me or CF_3
R^4 = -H or CH_3

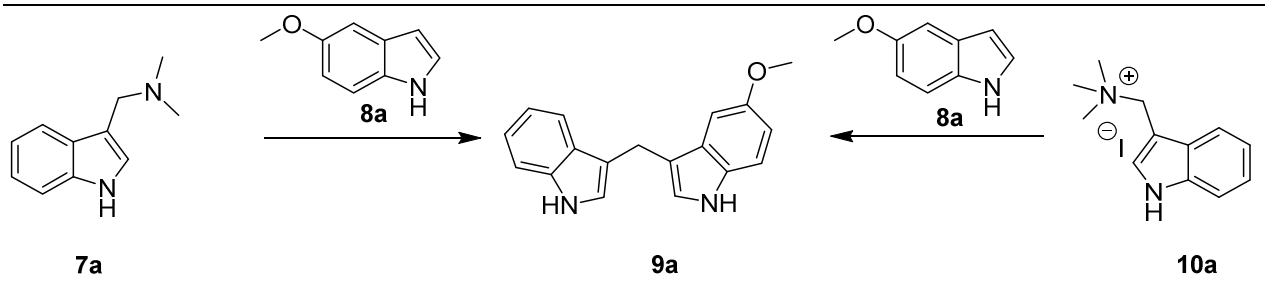
Figure 2 Synthetic approaches towards unsymmetrical DIMs.

In the present study, we report on a catalyst-free, mild and efficient, environmental friendly synthesis of unsymmetrical DIMs from readily accessible (3-indolylmethyl)trimethylammonium iodides as precursors. To the best of our knowledge, this is the first reported procedure for the preparation of unsymmetrical DIMs that proceeds in water without catalyst or any other additives. The present protocol provides an attractive and environmentally benign approach to a diverse range of functionalized unsymmetrical DIMs in a simple one-pot procedure. The new synthetic procedure will allow optimization of DIMs and full exploitation of their potential as novel drugs.

Results and discussion

The reaction of 3-(dimethylaminomethyl)indoles with indoles published by de la Herra´n was selected as a starting point with the aim to substantially modify it by omitting rhodium or iridium complexes as catalysts in order to develop an environmentally benign procedure for the preparation of unsymmetrically substituted DIMs. Initially, we studied the reaction of 3-(dimethylaminomethyl)indole (**7a**), with 5-methoxy-1*H*-indole (**8a**), leading to the formation of 3-((5-methoxy-1*H*-indol-3-yl)methyl)-1*H*-indole (**9a**), as a model for optimizing the reaction conditions (Table 1).

Table 1. Optimization of reaction conditions for the synthesis of 3-((1*H*-indol-3-yl)methyl)-5-methoxy-1*H*-indole[a]



7a **9a** **10a**

Entry	Solvent	Time (h)	Temp (^oC)	Yield (%)[b]	
				7a as starting compound	**10a** as starting compound
1	H_2O	12-48	r.t.	0[c]	15
2	CH_3OH	12-48	r.t.	0[c]	20
3	CH_2Cl_2	12-48	r.t.	0[c]	5
4	Dioxane	12-48	r.t.	0[c]	trace
5	THF	12-48	r.t.	0[c]	0[c]
6	CH_3CN	12-48	r.t.	0[c]	0[c]
7	DMF	12-48	r.t.	0[c]	0[c]
8	DMSO	12-48	r.t.	0[c]	0[c]
9	H_2O	12-48	50	trace	43
10	CH_3OH	12-48	50	0[c]	37
11	H_2O	48	80	5	85
12	H_2O	48	100	20	89
13	DMF	12-48	120	trace	77
14	DMSO	12-48	120	trace	71
15	Benzene	48	100	5	0[d]
16	Toluene	48	115	12	0[d]
17	*m*-Xylene	48	130	15	0[d]

18	--	48	100	--	--
19	CH_3COOH	48	r.t.	0[c]	0[c]
20	CH_3COOH/H_2O (1:1)	48	r.t.	0[c]	0[c]
21	CH_3COOH	12	100	10[e]	0[e]
22	CH_3COOH/H_2O (1:1)	48	100	22[e]	0[e]

[a]Reactions were performed with **7a** or **10a** (0.2 mmol) and **8a** (0.4 mmol) in 5 mL of solvent. [b]Isolated yield after column chromatography. [c]No reaction. [d]Desired product was not obtained although many spots appeared on TLC. [e]Several spots appeared on TLC along with the desired product.

Different solvent systems including water, methanol, dichloromethane, dioxane, tetrahydrofuran, acetonitrile, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetic acid, benzene, toluene, xylene as well as neat conditions at various temperatures for different reaction times were studied. When the reaction was performed at room temperature, no product was formed, even after 48 h (entry 1-8, 19 and 20). Upon gradually increasing the temperature from rt to 130 ^oC (entry 9-17, 21 and 22), the desired product was obtained, however with a maximum yield of only 22% in acetic acid : water (1:1) at 100 ^oC (entry 22). The reaction did not take place in methanol at 50 ^oC even after 48 h (entry 10), while in water, at 50 ^oC traces of product were observed (entry 9). Increasing the reaction temperature in water from 50 to 80 ^oC and further to 100 ^oC led to an increase in the formation of product resulting in a maximum yield of only 20% (entry 11, 12). The use of solvents such as DMF (entry 13, trace), DMSO (entry 14, trace), benzene (entry 15, yield 5%), toluene (entry 16, yield 12%), *m*-xylene (entry 17, yield 15%) or acetic acid (entry 21, yield 10%) did not improve the yield as compared to water, even at higher temperatures. These studies suggested that the amine functionality of 3-(dimethylaminomethyl)indole (**7a**) was not a good

leaving group, and a stabilized benzylic-type cation (indolenium ion) that could be trapped by the indole (**8a**) reacting as a nucleophile, was not easily formed under these conditions.

Therefore, we improved the leaving group ability of the tertiary amine of 3-(dimethylaminomethyl)indole (**7a**) by reacting it with methyl iodide yielding the quaternary ammonium salt **10a**, which would easily allow expulsion of the leaving group. Subsequently, the test reaction was studied using (3-indolylmethyl)trimethylammonium iodide (**10a**) instead of 3-(dimethylaminomethyl)indole (**7a**), with 5-methoxyindole (**8a**) under the same conditions as previously applied to the indole **7a** to yield product **9a**. Even at room temperature, this reaction led to the following yields: 15% in water, 20% in methanol, and 5% in CH_2Cl_2, while only traces were observed in dioxane (entries 1-4, 7 and 8). No product was obtained in THF, CH_3CN, DMF, DMSO, acetic acid or acetic acid/water (1:1) as solvents (entries 5-8, 19 and 20). Bingul et al. reported the synthesis of 4,6'- and 4,7'-unsymmetrical DIMs from hydroxymethyl indoles in acetic acid.[25] Using the same solvent for the reaction of **10a** did not yield any product. Elevating the reaction temperature led to a significant increase in the formation of the product (entry 9-12). To our delight, the desired product **9a** could be obtained in a high yield of 89% by reaction at 100 ^{o}C in water (entry 12). Screening of solvents demonstrated that water was a highly suitable solvent, while in apolar organic solvents like benzene, toluene or *m*-xylene (entries 15-17) the desired product was not formed. The reaction in polar aprotic solvents such as DMF or DMSO also led to very good results with 71% and 77% yield, respectively (entry 13 and 14), but water was the best solvent. The reaction in acetic acid or acetic acid/water (1:1) did not lead to the product. In the absence of solvent, no product was obtained either **(**entry 18).

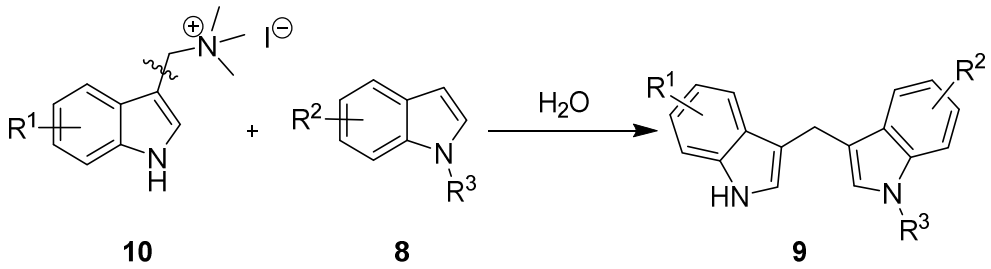
The isolation of product **9a** and its analogs was straightforward when compared to other methods. After completion of the reaction, water was decanted from the mixture and the product that settled on the wall of the flask was dissolved in ethyl acetate. The resulting solution was dried

over anhydrous sodium sulfate and, after filtration, evaporated under reduced pressure yielding the desired crude product, which was purified by recrystallization, or column chromatography, using non-chlorinated solvents.

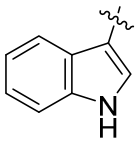
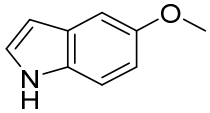
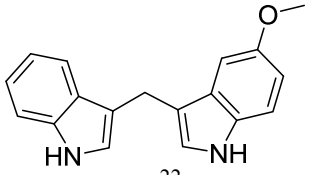
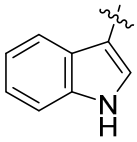
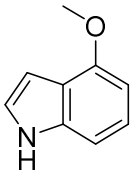
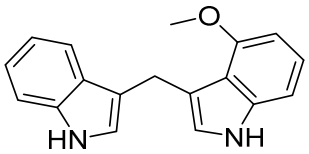
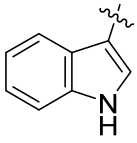
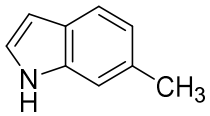
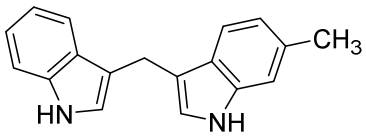
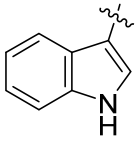
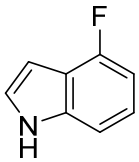
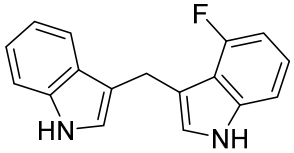
Figure S3 shows the ^{1}H NMR spectrum of product **9a (**DMSO-d_6, 303K**)**. The two NH protons for the indole moieties appeared at δ 10.70 and 10.53 ppm, respectively. The bridging methylene protons appeared as a singlet at δ 4.08 ppm. The nine aromatic protons were observed from δ 6.66-7.52 ppm. The two C2 protons of the indole moieties appeared at δ 7.12 and 7.05 ppm. These data confirmed that the indole residues were connected in the 3,3'-positions.

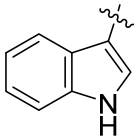
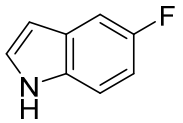
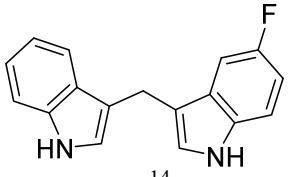
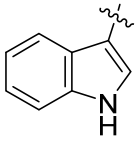
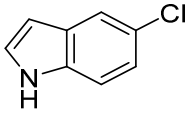
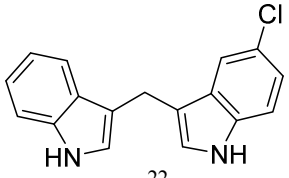
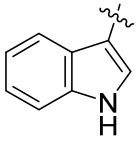
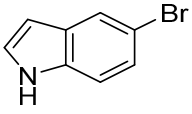
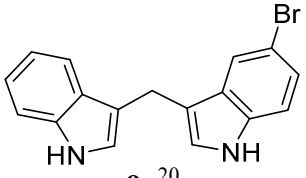
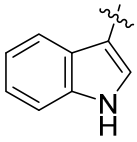
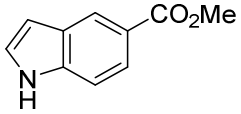
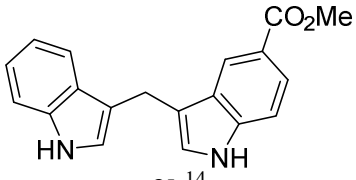
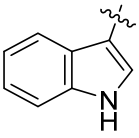
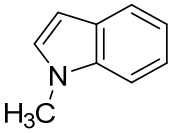
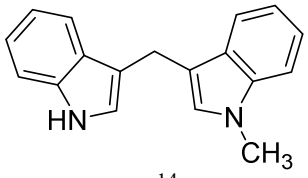
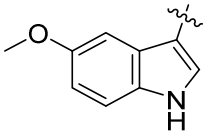
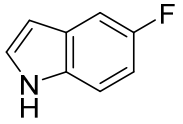
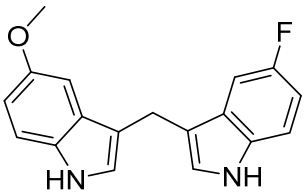
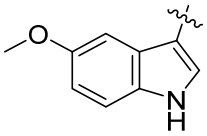
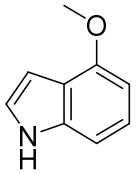
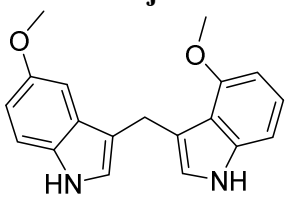
The optimized conditions were subsequently employed for synthesizing a wide range of both, symmetrical and unsymmetrical DIMs to examine the scope of the reaction. In general, the reactions of **10a-10e** with various indoles proceeded smoothly producing the desired DIM derivatives in good to excellent yields (**9b-9z**, and **9aa**). The electronic properties of the substituents at the indole that reacted as a nucleophile had a significant effect on the yields of the product, electron-donating substituents resulting in higher yields. For example, the reaction of (3-indolylmethyl)trimethylammonium iodides **10a-10e** with 5-methoxyindole (**8a**), 4-methoxylindole (**8b**), 6-methylindole (**8c**), and 5-methylindole (**8k**), respectively, afforded the corresponding DIMs in yields of 76 - 93% (Table 2, products **9b-9c**, **9k**, **9n**, **9r**, **9t**, **9u**, and **9y**). Electron-withdrawing substituents mostly led to a moderate decrease in yields. For example, halogen (F, Cl or Br), carboxylic acid ester, or trifluoromethyl substitution at the indole (**8d**, **8e**, **8f-8h**, **8j** and **8p**) resulted in yields of 64 - 79% (Table 2, compounds **9d-9h**, **9j**, **9l**, **9m**, **9o**, **9s**, **9v-9x)**. In case of two fluorine substituents, yields were significantly reduced to 53-57% (Table 2, compounds **9p**, and **9q**). The reaction proceeded well with *N1*-substituted indole **8i**, which provided **9i** in 78% yield, significantly higher as compared to the previously reported yield (40%) obtained by the Pummerer reaction.[14]

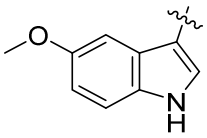
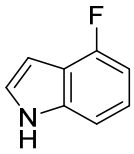
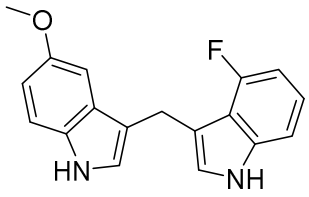
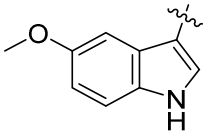
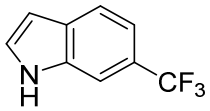
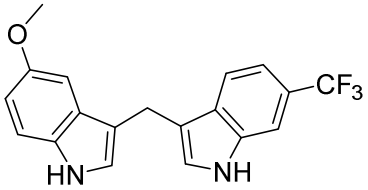
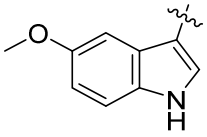
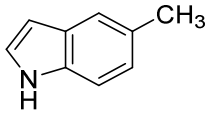
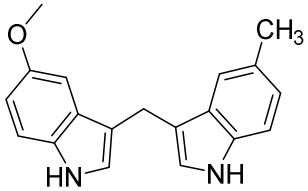
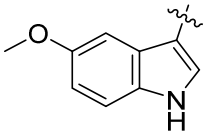
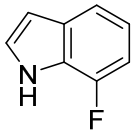
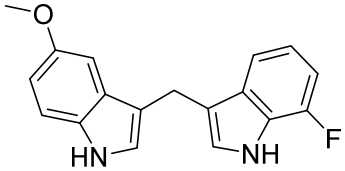
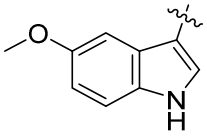
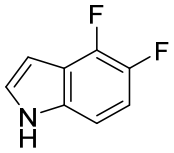
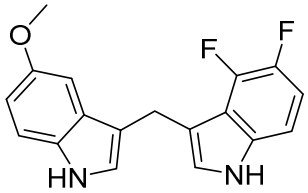
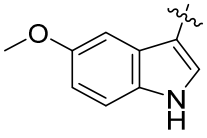
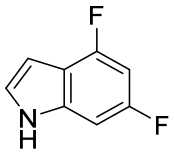
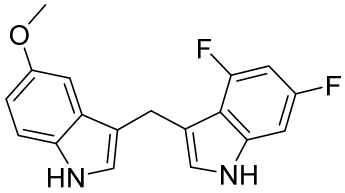
Table 2. Reaction of (3-indolylmethyl)trimethylammonium iodides with indoles

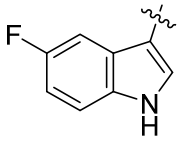
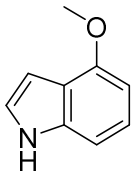
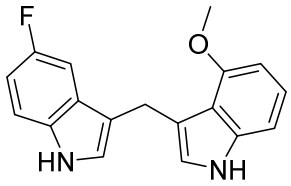
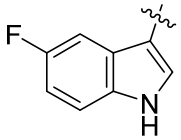
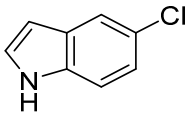
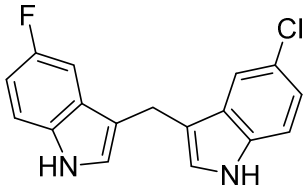
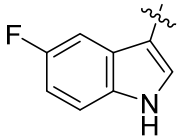
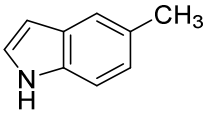
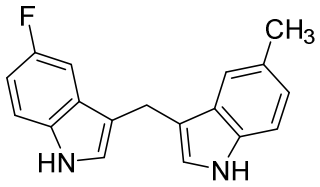
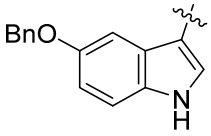
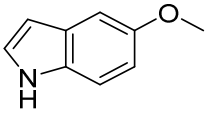
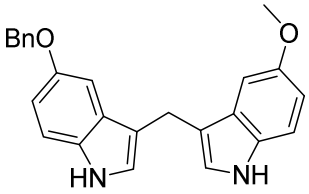
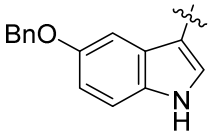
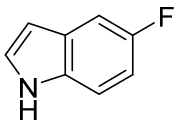
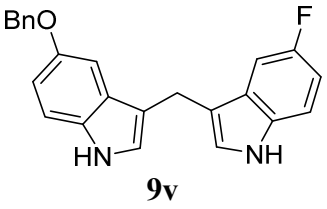
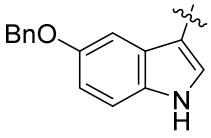
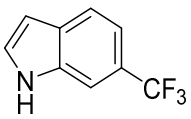
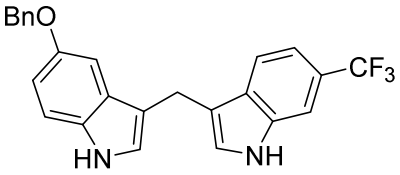
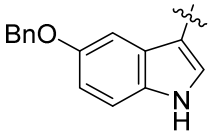
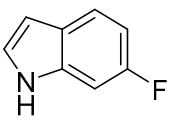
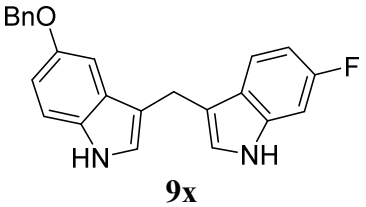


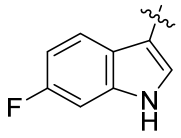
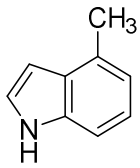
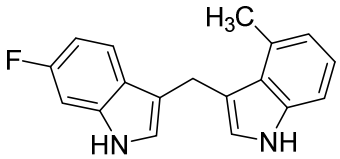
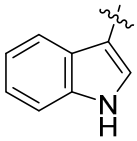
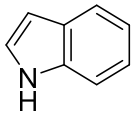
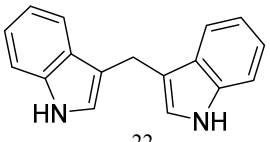
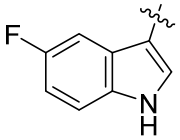
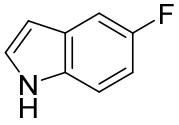
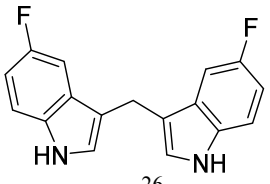
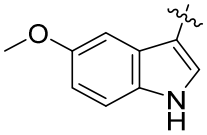
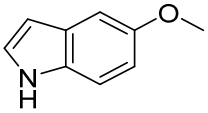
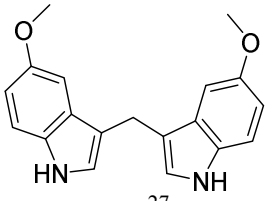
10 **8** **9**

Ammonium derivative (10)	Indole (8)	Product[a] (9)	Yield[b] (published yield)	Purity[c]
Unsymmetrically substituted DIMs				
 **10a**	 **8a**	 **9a**[22]	89% (64%)[22]	98%
 **10a**	 **8b**	 **9b**	85%	99%
 **10a**	 **8c**	 **9c**	76%	98%
 **10a**	 **8d**	 **9d**	74%	99%

 **10a**	 **8e**	 **9e**[14]	79% (48%)[14]	96%
 **10a**	 **8f**	 **9f**[22]	73% (55%)[22]	95%
 **10a**	 **8g**	 **9g**[20]	71% (81%)[20]	95%
 **10a**	 **8h**	 **9h**[14]	72% (35%)[14]	98%
 **10a**	 **8i**	 **9i**[14]	78% (40%)[14]	96%
 **10b**	 **8e**	 **9j**	75%	95%
 **10b**	 **8b**	 **9k**	93%	96%

 **10b**	 **8d**	 **9l**	71%	>99%
 **10b**	 **8j**	 **9m**	64%	96%
 **10b**	 **8k**	 **9n**	80%	96%
 **10b**	 **8l**	 **9o**	73%	98%
 **10b**	 **8m**	 **9p**	57%	96%
 **10b**	 **8n**	 **9q**	53%	97%

 **10c**	 **8b**	 **9r**	86%	98%
 **10c**	 **8f**	 **9s**	70%	95%
 **10c**	 **8k**	 **9t**	72%	98%
 **10d**	 **8a**	 **9u**	87%	95%
 **10d**	 **8e**	 **9v**	73%	95%
 **10d**	 **8j**	 **9w**	64%	>99%
 **10d**	 **8p**	 **9x**	68%	95%

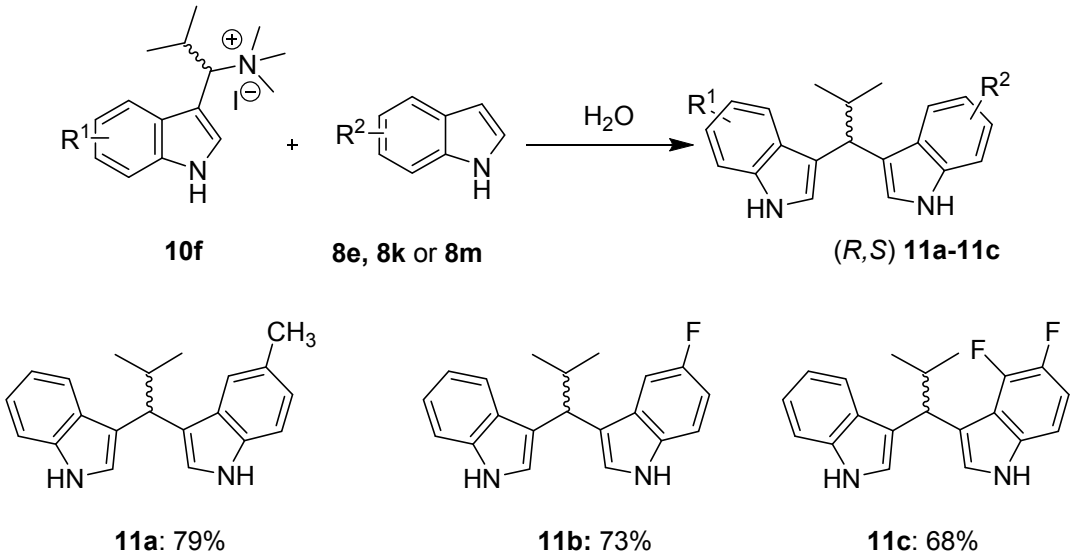
 **10e**	 **8q**	 **9y**	89%	96%
Symmetrically substituted DIMs				
 **10a**	 **8r**	 **1**[22]	92% (Gram scale, 94%) (80%)[22]	98%
 **10c**	 **8e**	 **9z**[26]	86% (37)[26]	98%
 **10b**	 **8a**	 **9aa**[27]	87% (68)[27]	97%

[a]All isolated products were characterized by ^{1}H and ^{13}C NMR spectra and their structures were confirmed. In addition, HPLC analysis coupled to electrospray ionization mass spectrometry (LC/ESI-MS) was performed. [b]Isolated yields. [c]Purity was determined by HPLC coupled to a UV diode array detector (DAD) at 220-400 nm.

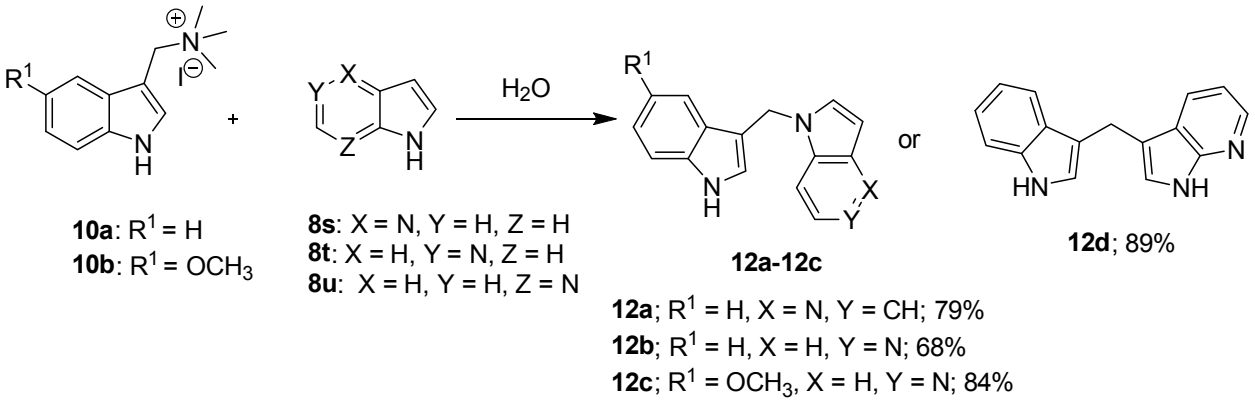
Next, this method was applied to the preparation of symmetrical diindolylmethane derivatives. As reported in Table 2, products **1**, **9z** and **9aa** were obtained in high yields of 86 - 92%, and these were in all cases higher than those reported for previously published methods (37 – 80%). In order to investigate whether the new method could be used on a larger scale, we performed gram-scale reactions of (3-indolylmethyl)trimethylammonium iodide (**10a**, 2.3 g, 7.3 mmol) with indole (**8r**, 1.74 g, 14.6 mmol), and with 5-fluoroindole (**8e**, 2.00 g, 14.8 mmol), respectively.

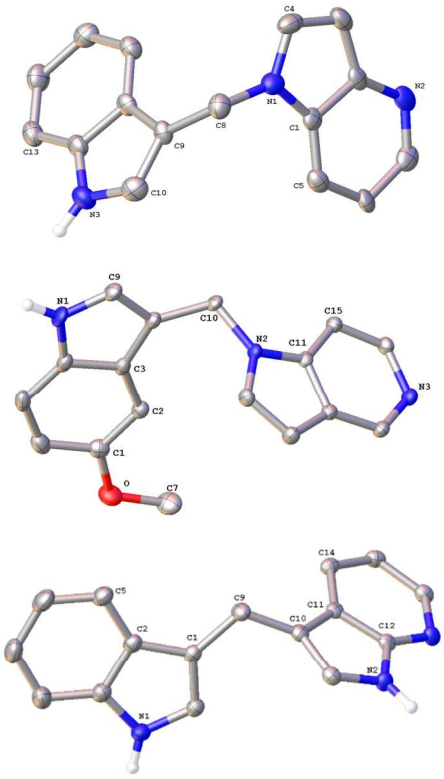
The reactions proceeded without any significant loss in efficiency affording 1.69 g of **1** (94% yield) and 1.65 g of **9e** (80% yield). Compounds **9z** and **9aa** had previously been identified as potent agonists of the immunostimulatory orphan G protein-coupled receptor GPR84,[14] which was proposed as a drug target for acute myeloid leukemia,[28] and might have potential for the treatment of other cancers as well.

We further studied whether the reaction could be employed for the preparation of DIM derivatives substituted at the bridging methylene group. For that purpose the sterically demanding *α*-isopropyl-substituted (3-indolylmethyl)trimethylammonium iodide **10f** was reacted with various substituted indole derivatives (**8e**, **8k** or **8m**, Scheme 1). All reactions proceeded smoothly yielding the desired DIM derivatives in good yields of 68 - 79% (see **11a-11c**, Scheme 1); an electron-withdrawing substituent at the indole only slightly reduced the yields (product **11c**; 68%). The products (**11a-c**) are chiral representing mixtures of enantiomers, which have not been separated.



Scheme 1. Synthesis of unsymmetrical DIM derivatives substituted at the methylene bridge **11a-11c** (racemates).





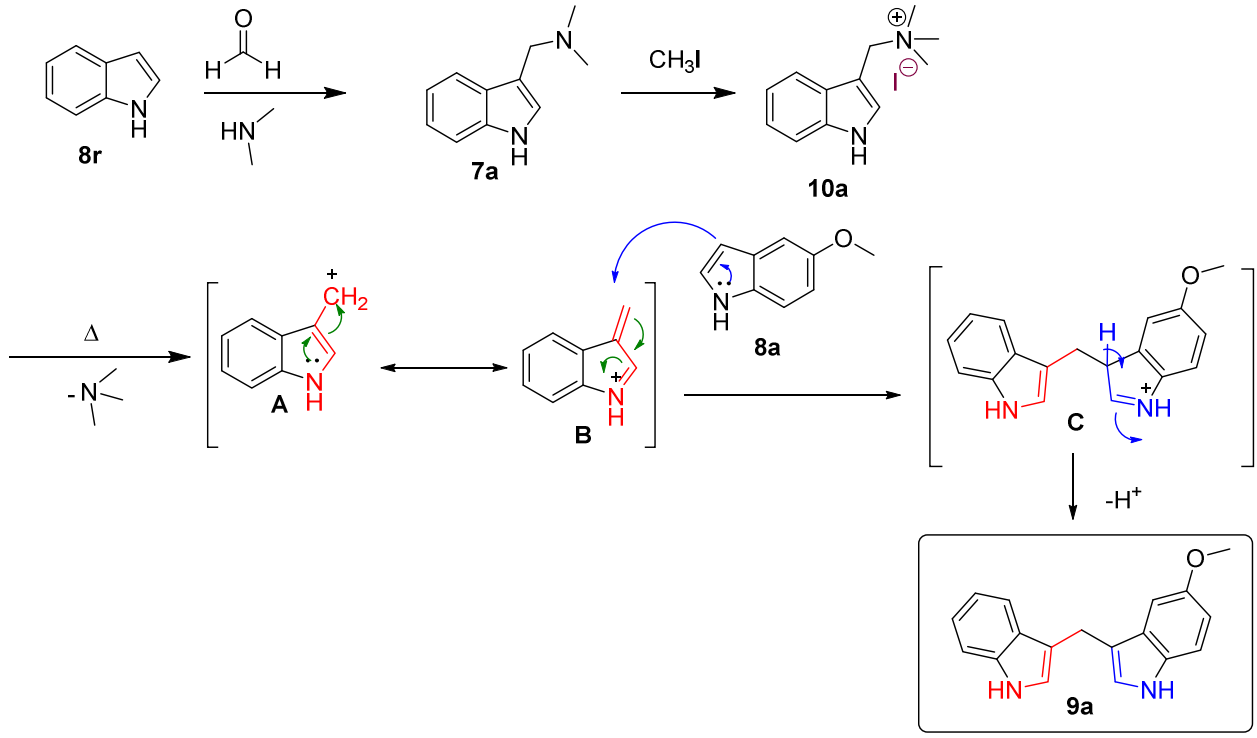
Scheme 2. Synthesis of azaindole derivatives **12a-12d** and X-ray structures of products **12a**, **12c** and **12d**.

Next, we investigated the reaction of (3-indolylmethyl) trimethylammonium iodides **10a** and **10b** with 4-azaindole (**8s**) and 5-azaindole (**8t**), respectively. Interestingly, we noticed that in these cases, the *N*1 rather than the 3-position of 4-azaindole (**8s**) and 5-azaindole (**8t**) was alkylated

yielding products **12a** (79%), **12b** (68%) and **12c** (84%) in high yields (Scheme 2). The reason for this regioselectivity may be due to the different electronic properties of the azaindoles. The ^{1}H-NMR spectra indicated *N*1-alkylation: the shift of the bridging methylene protons appeared at 5.54 ppm compared to 4.08-4.15 ppm for DIM derivatives. X-ray crystallography unambiguously confirmed the structures of **12a** and **12c** (see Scheme 2).[29] In contrast, the reaction of **10a** with 7-azaindole (**8u**) yielded the desired product **12d**, in which the 3-position of **8u** is connected *via* the 3-position to the indole like in the DIM derivatives. Compound **12d** had previously been prepared by reaction of 7-azaindole with 3-hydroxymethylindole in the presence of metallic sodium at 100 ^{o}C for 9 h. The yield of **12d** obtained in that reaction was significantly lower (44%) when compared to the present method (89%).[30] We confirmed the structure of **12d** by X-ray crystallography (see Scheme 2).[29] Compound **12d** had previously been reported to exhibit anticancer activity against prostate cancer and leukemia in DU145 and HL60 cells.[30]

Next we studied reactions of benzofuran, and benzothiophene, respectively, with **10a** using the same conditions. However, no products were formed even after an extended reaction time of 72 h. This can be explained by the significantly lower nucleophilic character of benzofuran and benzothiophene as compared to indole.

The proposed reaction mechanism is outlined in Scheme 3 for **9a** as an example. The trimethylammonium iodide **10a**, formed by Mannich reaction of indole (**8r**), formaldehyde and dimethylamine, undergoes nucleophilic attack by indole derivative **8a**, forming the 3,3'-DIM derivative **9a** along with trimethylammonium iodide. As an intermediate, the elimination product **A** can be formed upon heating, which represents a strong electrophile (Scheme 3).



Scheme 3. Plausible mechanism for the developed synthesis of DIMs.

Taken together, the described environmentally benign synthetic protocol provides a convenient access to a wide range of unsymmetrical diindolylmethanes and some of their aza-analogs. The reaction tolerates a broad range of substrates and proceeds with notable regioselectivity. It is clean and performed under mild conditions in water and no catalyst or any other additive is required. The described reaction provides an economic, simple handling, alternative to copper-, iridium- or rhodium-catalyzed reactions for the synthesis of unsymmetrical DIMs. The protocol is suitable for upscaling to obtain gram amount of the target molecules, which represent an important new class of immunostimulatory anti-cancer drug molecules.

EXPERIMENTAL SECTION

General Experimental Methods. All materials were purchased from commercial suppliers and used without further purification. Thin-layer chromatography was performed using TLC aluminum silica gel 60 F254 sheets, or TLC aluminum RP silica gel 18 F254 sheets. An LCMS instrument coupled to electrospray ionization mass spectrometry (LC/ESI-MS) determined the purities of isolated products using the following procedure: the compounds were dissolved at a concentration of 1.0 mg/mL in acetonitrile, containing 2 mM NH_4CH_3COO. Then, 10 µL of the sample was injected into an HPLC column (Phenomenex Luna 3µ C18, 50 × 2.00 mm). Elution was performed with a gradient of water : methanol (containing 2 mM NH_4CH_3COO) from 90:10 to 0:100 starting the gradient immediately at a flow rate of 250 µL/min for 15 min followed by washing with 100 % methanol for another 15 min. UV absorption was detected from 200 to 600 nm using a diode array detector. The purity of the compounds was determined at 220-400 nm and was ≥ 95% for all products. ^{1}H- and ^{13}C-NMR or ^{13}C-NMR Attached proton test (^{13}Capt-NMR) data were measured in $CDCl_3$ or DMSO-d_6 as a solvent. Chemical shifts are reported in parts per million (ppm) relative to the deuterated solvents (DMSO-d_6), ^{1}H: 2.49 ppm, ^{13}C: 39.70 ppm;

($CDCl_3$) ^{1}H: 7.25 ppm, ^{13}C: 77.17 ppm; coupling constants J are given in Hertz and spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet), br (broad). Melting points were measured on a melting point apparatus (BÜCHI melting point B-545) and are uncorrected.

Compounds **1**,[22] **9a**,[22] **9e**,[14] **9f**,[22] **9g**,[20] **9h**,[14] **9z**,[26] **9aa**,[27] and **12d**,[30] have previously been reported but were now obtained by new methods.

General Procedure for the Synthesis of Indole Derivatives 7. To a solution of 17.0 ml of dimethylamine (2 M in THF, 34.1 mmol) in a 100 mL round bottom flask at 0 ^{o}C, 2.6 ml (34.1 mmol) of formaldehyde (37 % w/v in H_2O) and glacial acetic acid (3.0 ml, 78.5 mmol, 2.3 equiv.) were added and the solution was stirred for 10 min. To this mixture, 34.1 mmol of the appropriate indole dissolved in glacial acetic acid (4 ml) was added dropwise. After the addition was completed, the reaction mixture was slowly brought to room temperature and stirred overnight. Completion of the reaction was monitored by TLC. The reaction mixture was poured into water and brought to an alkaline pH by the addition of 2 N aq. NaOH solution. The resulting precipitate was filtered off, washed with water and dried under vacuum.

*3-(Dimethylaminomethyl)indole (**7a**)*.[31] Yield 70% (4.20 g); Colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.86 (s, 1H, NH), 7.58 (d, J = 8.0 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 8.2, 7.0 Hz, 1H), 6.95 (dd, J = 8.1, 7.0, 1.1 Hz, 1H), 3.51 (s, 2H), 2.13 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 136.5, 127.7, 124.4, 121.0, 119.2, 118.4, 111.8, 111.2, 54.6, 45.0.

*5-Methoxy-3-(dimethylaminomethyl)indole (**7b**).*[32] Yield 56% (3.89 g); Colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.69 (s, 1H, NH), 7.22 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 8.7, 2.5 Hz, 1H), 3.73 (s, 3H), 3.47 (s, 2H), 2.13 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 153.1, 131.6, 128.0, 125.2, 112.0, 111.6, 111.1, 101.1, 55.5, 54.6, 45.7.

*5-Fluoro-3-(dimethylaminomethyl)indole (**7c**).*[33] Yield 59% (3.86 g); Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.85 (s, 1H, NH), 7.32 (dd, J = 8.2, 1.0 Hz, 1H), 7.17 (s, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.92 (dd, J = 8.1, 7.0, Hz, 1H), 3.44 (s, 2H), 2.17 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.7, 132.5, 128.2, 123.5, 118.6, 115.5, 114.6, 111.1, 54.5, 45.0.

*5-Benzyloxy-3-(dimethylaminomethyl)indole (**7d**).*[31] Yield 60% (5.7 g); Colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.71 (s, 1H, NH), 7.55 – 7.42 (m, 2H), 7.42 – 7.33 (m, 2H), 7.33 – 7.26 (m, 1H, 7.23 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 6.2, 2.5 Hz, 2H), 6.79 (dd, J = 8.8, 2.5 Hz, 1H), 5.06 (s, 2H), 3.46 (s, 2H), 2.12 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.1, 138.0, 131.8, 128.4, 128.1, 127.7, 127.7, 125.3, 112.0, 111.6, 111.5, 102.9, 70.1, 54.5, 45.0.

*6-Fluoro-3-(dimethylaminomethyl)indole (**7e**):*[34] Yield 53% (3.55 g), Colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.92 (s, 1H), 7.56 (dd, J = 8.7, 5.6 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.09 (dd, J = 10.1, 2.4 Hz, 1H), 6.81 (ddd, J = 9.8, 8.6, 2.4 Hz, 1H), 3.48 (s, 2H), 2.11 (s, 6H). ^{13}C (500 MHz, DMSO-d$_6$) δ (ppm) 159.7, 158.2, 136.4, 136.3, 125.0, 125.0, 124.5, 120.3, 120.2, 112.2, 107.0, 106.8, 97.5, 97.3, 54.6, 45.0.

*(R,S)-3-((1-N,N-Dimethylamino-2-methyl)propyl)-1H-indole (**7f**).* Compound **7f** was synthesized from **8r** (34.1 mmol) and isobutyraldehyde (34.1 mmol) using the same procedure as for the synthesis of **7a**-**7d**. After completion of the reaction, the mixture was poured into water and brought to an alkaline pH value by the addition of 2 N aq. NaOH solution. The product was extracted using 10% methanol in ethylacetate (2 x 100 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. Red solid, yield; 45% (3.32 g); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.92 (s, 1H, NH), 7.60 (dd, J = 7.9, 1.0 Hz, 1H), 7.32 (dt, J = 8.2, 0.9 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.1, 6.9, Hz, 1H), 6.93 (d, J = 8.0, 6.9, 1.0 Hz, 1H), 3.39 (d, J = 9.2 Hz, 1H), 2.25 (dp, J = 9.4, 6.5 Hz, 1H), 2.02 (s, 6H), 0.98 (d, J = 6.4 Hz, 3H, CH_3), 0.68 (d, J = 6.5 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 136.1, 128.9, 123.9, 120.5, 119.2, 118.4, 111.4, 110.4, 67.7, 41.9, 29.7, 21.3, 20.3. LC-MS (m/z): positive mode 217 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{14}H_{20}N_2$ $[M+H]^+$) calcd: 217.1705. Found 217.1699.

General Procedure for the Synthesis of Ammonium Iodide Derivatives 10. To a solution of **7** (40 mmol) in benzene (20 ml), methyl iodide (80 mmol) was added. After 24 h of stirring at room temperature, diethylether (50 ml) was added. The resulting precipitate was filtered off and washed with diethyl ether to yield **10**, which was used without further purification and characterizations.

General Procedures for the Synthesis of (Un)symmetrical Di(aza)indolylmethanes (1, 9a-9z, and **9aa)**. A 50 mL sealed tube was charged with (3-indolylmethyl)trimethylammonium iodide (**10**, 1.6 mmol) and indole derivative or azaindole (**8**, 3.2 mmol) in H_2O (5 mL). The slurry reaction mixture was stirred at 80 °C. TLC monitoring indicated the progress of the reaction; a

small amount of the mixture was taken from the reaction mixture, dissolved in ethyl acetate and checked. The elution was carried out with the suitable solvent system for each case, and the spots on the chromatograms were visualized under UV light. Once the reaction was completed, the mixture was allowed to cool to room temperature. Water was decanted from the mixture, and the product that settled on the wall of the tube was dissolved in ethyl acetate (10 mL). The resulting solution was dried over Na_2SO_4 and the product was purified by recrystallization or column chromatography as described below.

*Di-(1H-indole-3-yl)methane (**1**).*[22] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and an indole (**8r**, 3.2 mmol) were used for this reaction. Yield 92% (362 mg). White solid; ^{1}H NMR (600 MHz, $CDCl_3$-*d*) δ (ppm) 7.90 (s, 2H, 2 x NH), 7.61 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.19 – 7.12 (m, 2H, 6-H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 1.2 Hz, 2H), 4.23 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$-*d*) δ (ppm) 136.4, 127.5, 122.1, 121.9, 119.1, 115.7, 111.0, 21.2. LC-MS (m/z): positive mode 247 [M+H]1+. Purity by HPLC-UV (254 nm)-ESI-MS: 98%.

*3-((5-Methoxy-1H-indol-3-yl)methyl)-1H-indole (**9a**).*[22] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 5-methoxyindole (**8a**, 3.2 mmol) were used for this reaction. Yield 89% (393 mg). Brown solid; m.p. 103−105 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.69 (s, 1H, NH), 10.53 (d, *J* = 2.4 Hz, 1H, NH), 7.51 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.94 – 6.83 (m, 1H), 6.67 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.08 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 152.9, 136.5, 131.7, 127.6, 127.4, 123.6, 122.9, 120.9, 118.8, 118.1, 112.0, 100.9, 55.5, 21.0. LC-MS (m/z): positive mode 277 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%.

*3-((4-Methoxy-1H-indol-3-yl)methyl)-1H-indole (**9b**).* (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 4-methoxyindole (**8b**, 3.2 mmol) were used for this reaction. Yield 85% (375 mg); Pale orange oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.70 (s, 1H, NH), 10.61 (s, 1H, NH), 7.51 (dd, J = 7.9, 1.1 Hz, 1H), 7.31 (dd, J = 8.3, 1.0 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.02 (dd, J = 8.1, 7.0 Hz, 1H), 6.98 – 6.85 (m, 3H, 2-H), 6.76 (d, J = 2.3 Hz, 1H), 6.45 – 6.37 (m, 1H), 4.25 (d, J = 1.1 Hz, 2H), 3.84 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 154.6, 138.0, 136.4, 127.4, 122.9, 121.8, 121.6, 120.7, 118.1 115.3, 111.4, 105.0, 98.8, 55.1, 22.4. LC-MS (m/z): positive mode 277 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 99%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{17}N_2O$ $[M+H]^+$) calcd: 277.1341. Found 277.1331.

*3-((6-Methyl-1H-indol-3-yl)methyl)-1H-indole (**9c**).* (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 6-methylindole (**8c**, 3.2 mmol) were used for this reaction. Yield 76% (316 mg); Brown solid; m.p. 121−123 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.87 (s, 1H, NH), 10.51 (s, 1H, NH), 7.49 (dd, J = 7.8, 1.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.30 (dd, J = 8.1, 1.0 Hz, 1H), 7.09 (d, J = 1.9 Hz, 2H, 2-H), 7.04 – 6.99 (m, 2H), 6.90 (dd, J = 8.0, 6.9 Hz, 1H), 6.77 – 6.65 (m, 1H), 4.08 (d, J = 0.9 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 137.0, 136.5, 129.8, 127.3, 125.3, 122.8, 122.1, 120.8, 119.9, 118.8, 118.5, 118.1, 114.4, 114.1, 111.4, 111.2, 21.5, 21.1. LC-MS (m/z): positive mode 261$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{17}N_2$ $[M+H]^+$) calcd: 261.1392. Found 261.1374.

*3-((4-Fluoro-1H-indol-3-yl)methyl)-1H-indole (**9d**).* (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 4-fluoroindole (**8d**, 3.2 mmol) were used for this reaction. Yield 74%

(312 mg); Pale orange solid; m.p. 137−139 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.99 (s, 1H, NH), 10.78 (s, 1H, NH), 7.55 – 7.48 (m, 1H), 7.32 (dd, J = 8.2, 1.0 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.08 – 7.02 (m, 2H), 7.02 – 6.94 (m, 2H), 6.92 (dd, J = 8.1, 7.0, Hz, 1H), 6.70 – 6.59 (m, 1H), 4.20 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.7, 139.5, 139.4, 136.5, 127.2, 123.5, 123.3, 122.7, 121.5, 121.4, 120.9, 118.6, 115.5, 114.6, 113.1, 108.1, 103.4, 22.0. LC-MS (m/z): positive mode 265$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 99%. HRMS (ESI-TOF) m/z: for ($C_{17}H_{14}ClN_2$ $[M+H]^{+}$) calcd: 281.0846. Found 281.0838.

3-((5-Fluoro-1H-indol-3-yl)methyl)-1H-indole ***(9e).***[14] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 5-fluoroindole (**8e**, 3.2 mmol) were used for this reaction. Yield 79% (333 mg); Brown solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.96 (s, 1H, NH), 0.63 (s, 1H, NH), 7.50 (d, J = 7.8 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.21 (td, J = 5.2, 2.6 Hz, 2H), 7.16 (d, J = 2.3 Hz, 1H), 7.02 (dd, J = 8.1, 6.9, Hz, 1H), 6.91 (dd, J = 7.9, 6.9, Hz, 1H), 6.85 (td, J = 9.2, 2.6 Hz, 1H), 4.09 (s, 2H). ^{13}Capt NMR (126 MHz, DMSO-d_6) δ (ppm) 157.5, 136.5, 133.2, 127.3, 125.0, 122.9, 122.8, 120.9, 120.8, 118.1, 114.7, 114.0, 112.2, 111.4, 108.1, 103.4, 20.9. LC-MS (m/z): positive mode 263 $[M-H]^{1-}$. Purity by HPLC UV (254 nm) ESI-MS: 96%.

3-((5-Chloro-1H-indol-3-yl)methyl)-1H-indole ***(9f).***[22] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 5-chloroindole (**8f**, 3.2 mmol) were used for this reaction. Yield 73% (327 mg); Brown solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)10.91 (s, 1H), 10.70 (s, 1H), 7.55 – 7.39 (m, 2H), 7.38 – 7.27 (m, 2H), 7.22 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.96 – 6.83 (m, 1H), 4.10 (d, J = 1.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 136.5, 135.0, 128.4, 127.2, 124.8, 122.9, 122.8, 120.9, 120.8, 118.7, 118.2, 118.0, 114.3, 113.9, 113.0, 111.4, 20.9. LC-MS (m/z): positive mode 281 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%.

*3-((5-Bromo-1H-indol-3-yl)methyl)-1H-indole (**9g**).*[20] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 5-bromoindole (**8g**, 3.2 mmol) were used for this reaction. Yield 71% (370 mg); Slightly red powder; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.13 (s, 1H, NH), 10.62 (s, 1H, NH), 7.64 (d, J = 2.0 Hz, 1H), 7.49 (dd, J = 7.9, 1.1 Hz, 1H), 7.35 – 7.24 (m, 2H), 7.21 (d, J = 2.3 Hz, 1H), 7.18 – 7.08 (m, 2H), 7.02 (dd, J = 8.2, 6.9, Hz, 1H, 6.91 (dd, J = 7.9, 6.9 Hz, 1H), 4.10 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 135.2, 129.2, 127.2, 124.7, 123.3, 123.0, 121.0, 120.9, 118.8, 118.2, 114.2, 113.9, 113.5, 111.5, 20.9. LC-MS (m/z): positive mode 326 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%.

*Methyl 3-((1H-Indol-3-yl)methyl)-1H-indole-5-carboxylate (**9h**).*[14] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and methyl 4-1*H*-indole-5-carboxylate (**8h**, 3.2 mmol) were used for this reaction. Yield 72% (350 mg); Brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.32 (s, 1H), 10.72 (s, 1H), 8.20 (s, 1H), 7.68 (dd, J = 8.6, 1.7 Hz, 1H), 7.50 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.31 (dt, J = 8.1, 0.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.03 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 6.91 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.17 (d, J = 1.1 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 167.4, 139.2, 136.6, 127.2, 126.9, 124.9, 122.9, 122.0, 121.4, 121.0, 119.8, 118.7, 118.2, 115.9, 113.9, 111.5, 51.7, 20.9. LC-MS (m/z): positive mode 305 $[M-H]^{1+}$. Purity by HPLC UV (254 nm) ESI-MS: 98%.

*3-(1H-Indol-3-ylmethyl)-1-methyl-1H-indole (**9i**).*[14] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 1-methyl-1H-indole (**8i**, 3.2 mmol) were used for this reaction. Yield 78% (324 mg); Brown solid;. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.71 (s, 1H), 7.52 (dd, J = 18.0, 7.9 Hz, 2H), 7.32 (dd, J = 11.6, 8.2 Hz, 2H), 7.13 (d, J = 2.3 Hz, 1H), 7.12 – 7.05 (m, 2H),

7.05 – 6.98 (m, 1H), 6.93 (dt, *J* = 20.4, 7.4 Hz, 2H), 4.11 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 136.9, 136.5, 127.6, 127.2, 122.9, 121.0, 120.9, 118.9, 118.7, 118.22, 118.16, 114.1, 113.8, 111.4, 109.5, 33.0, 20.8. LC-MS (m/z): positive mode 261 $[M-H]^{1+}$. Purity by HPLC UV (254 nm) ESI-MS: 96%.

5-Methoxy-3-((5-fluoro-1H-indol-3-yl)methyl)-1H-indole ***(9j)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 5-fluoroindole (**8e**, 3.2 mmol) were used for this reaction. Yield 75% (353 mg); Brown solid; m.p. 112−114 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.80 (s, 1H, NH), 10.53 (s, 1H, NH), 7.29 (dd, *J* = 8.8, 4.6 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.85 (td, *J* = 9.2, 2.6 Hz, 1H), 6.68 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.05 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ (ppm) 157.5, 155.7, 133.2, 131.7, 127.6, 125.0, 123.6, 113.8, 112.33, 112.25, 112.0, 110.8, 109.0, 108.8, 103.5, 103.3, 55.5, 20.9. LC-MS (m/z): positive mode 295 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{16}FN_2O$ $[M+H]^{+}$) calcd: 295.1247. Found 295.1240.

5-Methoxy-3-((4-methoxy-1H-indol-3-yl)methyl)-1H-indole ***(9k)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 4-methoxyindole (**8b**, 3.2 mmol) were used for this reaction. Yield 76% (372 mg); Orange viscous oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.62 (s, 1H, NH), 10.49 (s, 1H, NH), 7.20 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.97 – 6.85 (m, 2H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.67 (dt, *J* = 8.7, 2.5 Hz, 1H), 6.45 – 6.40 (m, 1H), 4.22 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 154.6, 152.9, 138.0, 131.6, 127.7, 123.6, 121.7, 121.6, 117.0, 115.14, 115.06, 111.9, 110.7, 105.0, 100.1, 98.8, 55.4, 55.0, 22.4. LC-MS (m/z): positive mode 307

$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{19}H_{19}N_2O_2$ $[M+H]^+$) calcd: 307.1447. Found 307.1441.

4-Fluoro-3-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole ***(9l)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 4-fluoroindole (**8d**, 3.2 mmol) were used for this reaction. Yield 71% (334 mg); Pale orange solid; m.p. 89-91°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.98 (s, 1H), 10.67 (s, 1H, 7.20 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 8.1, 0.9 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 7.00 (d, J = 3.3 Hz, 2H), 6.99 (m, 1H), 6.71 (m, 2H), 4.16 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) 157.7, 155.8, 153.0, 139.5, 131.7, 127.5, 123.56, 123.48, 121.5, 115.7, 115.6, 114.4, 113.0, 112.0, 110.9, 108.1, 55.5, 22.1. LC-MS (m/z): positive mode 295 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: >99%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{16}FN_2O$ $[M+H]^+$) calcd: 295.1247. Found 295.1238.

5-Methoxy-3-((6-(trifluoromethyl)-1H-indol-3-yl)methyl)-1H-indole ***(9m)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 6-trifluoromethylindole (**8j**, 3.2 mmol) were used for this reaction. Yield 64% (352 mg); Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.17 (s, 1H), 10.76 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.4, 2.1 Hz, 2H), 7.07 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.68 (dd, J = 8.8, 2.5 Hz, 1H), 4.12 (d, J = 1.0 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 153.0, 135.3, 131.7, 127.5, 126.5, 123.7, 119.6, 115.0, 113.7, 112.1, 110.9, 100.8, 55.5, 20.8. LC-MS (m/z): positive mode 345 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{19}H_{15}F_3N_2O$ $[M+H]^+$) calcd: 344.1136. Found 344.1131.

5-Methoxy-3-((5-methyl-1H-indol-3-yl)methyl)-1H-indole ***(9n)***. 5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 5-methylindole (**8k**, 3.2 mmol) were used for this reaction. Yield 80% (371 mg); Brown solid; m.p. 109−111 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.54 (s, 1H), 10.52 (s, 1H), 7.30 (dd, J = 1.5, 0.7 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.04 (dd, J = 17.5, 2.3 Hz, 2H), 6.99 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 8.2, 1.6 Hz, 1H), 6.67 (dd, J = 8.7, 2.4 Hz, 1H), 4.04 (d, J = 1.0 Hz, 2H), 3.70 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.9, 134.9, 131.7, 127.6, 127.6, 126.4, 123.5, 123.0, 122.4, 118.4, 114.20, 113.7, 112.0, 111.10, 55.5, 21.4, 21.0. LC-MS (m/z): positive mode 291$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{19}H_{18}N_2O$ $[M+H]^+$) calcd: 290.1419. Found 290.1407.

7-Fluoro-3-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole ***(9o)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 7-fluoroindole (**8l**, 3.2 mmol) were used for this reaction. Yield 73% (343 mg); Brown solid; m.p. 97−99 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.18 (s, 1H), 10.54 (s, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.25 – 7.12 (m, 2H, 2-H), 7.06 (d, J = 2.4 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.93 (m, 2H), 6.68 (dd, J = 8.7, 2.5 Hz, 1H), 4.08 (d, J = 0.9 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.9, 148.2, 131.7, 127.5, 124.1, 123.6, 118.5, 118.4, 113.7, 112.0, 110.9, 105.8, 105.6, 100.8, 55.5, 21.0. LC-MS (m/z): positive mode 295$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{16}FN_2O$ $[M+H]^+$) calcd: 295.1247. Found 295.1241.

5-Methoxy-3-((4,5-difluoro-1H-indol-3-yl)methyl)-1H-indole ***(9p)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 4,5-difluoroindole (**8m**, 3.2 mmol) were used for this reaction. Yield 57% (284 mg); Orange solid; m.p. 118−120 °C. ^{1}H

NMR (500 MHz, DMSO-d_6) δ (ppm) 10.75 (s, 1H), 10.69 (s, 1H), 7.43 (dd, J = 11.5, 8.1 Hz, 1H), 7.29 (dd, J = 11.3, 7.0 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.68 (dd, J = 8.7, 2.5 Hz, 1H), 4.04 (d, J = 0.9 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.9, 147.4, 145.5, 143.8, 131.7, 131.4, 127.5, 124.9, 123.7, 122.6, 114.9, 113.6, 112.1, 110.9, 105.3, 105.2, 55.5, 20.8. LC-MS (m/z): positive mode 313 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{15}F_2N_2O$ $[M+H]^+$) calcd: 313.1152. Found 313.1136.

4,6-Difluoro-3-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole ***(9q)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 4,6-difluoroindole (**8n**, 3.2 mmol) were used for this reaction. Yield 53% (264 mg); Brown solid; m.p. 78−80 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.06 (s, 1H), 10.64 (m, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 7.01 – 6.90 (m, 2H), 6.75 (m, 2H), 4.12 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 153.0, 138.1, 131.6, 127.4, 124.0, 123.5, 114.1, 113.3, 112.1, 110.9, 100.7, 94.2, 93.9, 55.5, 21.9. LC-MS (m/z): positive mode 313$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 97%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{15}F_2N_2O$ $[M+H]^+$) calcd: 313.1152. Found 313.1149.

*5-Fluoro-3-((4-methoxy-1H-indol-3-yl)methyl)-1H-indole-(****9r****)*. (5-Fluoro-3-indolylmethyl)trimethylammonium iodide (**10c**, 1.6 mmol) and 4-methoxyindole (**8b**, 3.2 mmol) were used for this reaction. Yield 86% (378 mg); Yellow solid; m.p. 146−148 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.76 (s, 1H), 10.68 (s, 1H), 7.33 (m, 1H), 7.23 (m, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.97 (m, 1H), 6.90 (m, 1H), 6.87 (m, 2H), 6.42 (dd, J = 7.4, 1.0 Hz, 1H), 4.21 (d, J = 0.9 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.5, 155.7, 138.0, 133.0,

125.01, 121.8, 121.6, 116.9, 115.8, 115.7, 114.7, 112.3, 108.8, 103.4, 98.9, 55.0, 22.3. LC-MS (m/z): positive mode 295$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{16}FN_2O$ $[M+H]^+$) calcd: 295.1247. Found 295.1240.

5-Chloro-3-((5-fluoro-1H-indol-3-yl)methyl)-1H-indole ***(9s)***. (5-Fluoro-3-indolylmethyl)trimethylammonium iodide (**10c**, 1.6 mmol) and 5-chloroindole (**8f**, 3.2 mmol) were used for this reaction. Yield 70% (334 mg); Brown solid; m.p. 173−175 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.00 (m, 1H), 10.91 (s, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.34 (m, 1H), 7.30 (m, 1H), 7.26 (dd, J = 9.3, 2.4 Hz, 2H), 7.20 (dd, J = 10.1, 2.5 Hz, 1H), 7.01 (dd, J = 8.6, 2.1 Hz, 1H), 6.85 (td, J = 9.2, 2.5 Hz, 1H), 4.06 (d, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.5, 155.7, 135.0, 133.2, 128.4, 127.4, 127.4, 125.1, 124.9, 122.9, 120.8, 118.0, 114.3, 113.0, 109.1, 103.3, 20.8. LC-MS (m/z): positive mode 298$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%. HRMS (ESI-TOF) m/z: for ($C_{17}H_{12}ClFN_2$ $[M+H]^+$) calcd: 298.0673. Found 298.0664.

5-Fluoro-3-((5-methyl-1H-indol-3-yl)methyl)-1H-indole ***(9t)***. (5-Fluoro-3-indolylmethyl)trimethylammonium iodide (**10c**, 1.6 mmol) and 5-methylindole (**8k**, 3.2 mmol) were used for this reaction. Yield 72% (320 mg); Brown solid; m.p. 163−166 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.98 (s, 1H), 10.68 (s, 1H), 7.31 (m, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.22 (m, 1H), 7.18 (d, J = 1.8 Hz, 2H), 7.08 (d, J = 2.3 Hz, 1H), 6.90 – 6.69 (m, 2H), 4.05 (d, J = 1.1 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.5, 155.7, 134.9, 133.2, 127.51, 126.5, 123.0, 122.5, 118.3, 113.4, 112.3, 111.2, 109.0, 108.8, 103.5, 21.4, 20.9. LC-MS (m/z): positive mode 279 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{16}FN_2$ $[M+H]^+$) calcd: 279.1298. Found 279.1283.

5-Benzyloxy-3-((5-methoxy-1H-indol-3-yl)methyl)-1H-indole ***(9u)***. (5-Benzyloxy-3-indolylmethyl)trimethylammonium iodide (**10d**, 1.6 mmol) and 5-methoxyindole (**8a**, 3.2 mmol) were used for this reaction. Yield 87% (531 mg); Brown solid; m.p. 140−142 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.80 (s, 2H), 7.45 – 7.39 (m, 2H,), 7.39 – 7.33 (m, 2H), 7.32 – 7.26 (m, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 6.76 (dd, J = 8.7, 2.4 Hz, 1H), 6.68 (dd, J = 8.7, 2.4 Hz, 1H), 5.02 (s, 2H), 4-02 (s,), 3.70 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.9, 151.9, 138.0, 131.9, 131.7, 128.4, 127.73, 127.68, 127.64, 123.7 (2-C), 123.6, 114.1, 114.0, 112.0, 111.5, 110.8, 102.5, 70.0, 55.5, 21.0. LC-MS (m/z): positive mode 383$[M+H]^{1+}$. Purity by HPLC UV (254 nm)-ESI-MS: 95%. HRMS (ESI-TOF) m/z: for ($C_{25}H_{23}N_2O_2$ $[M+NH_4]^+$) calcd: 383.1760. Found 383.1749.

5-Benzyloxy-3-((5-fluoro-1H-indol-3-yl)methyl)-1H-indole ***(9v)***. (5-Benzyloxy-3-indolylmethyl)trimethylammonium iodide (**10d**, 1.6 mmol) and 5-fluoroindole (**8e**, 3.2 mmol) were used for this reaction. Yield 73% (432 mg); Brown solid; m.p. 142−144 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.80 (s, 1H), 10.65 (s, 1H), 7.42 (dt, J = 7.1, 1.2 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.31 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 7.11 (dd, J = 14.0, 2.4 Hz, 2H), 6.85 (td, J = 9.2, 2.6 Hz, 1H), 6.75 (dd, J = 8.7, 2.4 Hz, 1H), 5.02 (s, 2H), 4.03 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 157.4, 155.9, 151.9, 138.0, 133.2, 131.89, 128.5, 127.8, 127.7, 127.6, 125.1, 123.8, 114.6, 113.8, 112.1, 111.6, 109.0, 108.8, 103.5, 103.3, 70.0, 20.9. LC-MS (m/z): positive mode 371 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%. HRMS (ESI-TOF) m/z: for ($C_{24}H_{20}FN_2O$ $[M+NH_4]^+$) calcd: 371.1560. Found 371.1549.

*5-(Benzyloxy)-3-((6-(trifluoromethyl)-1H-indol-3-yl)methyl)-1H-indole (**9w**).* (5-Benzyloxy-3-indolylmethyl)trimethylammonium iodide (**10d**, 1.6 mmol) and 6-trifluoromethylindole (**8j**, 3.2 mmol) were used for this reaction. Yield 64% (430 mg); Yellow solid; m.p. 147−149 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.16 (d, J = 2.4 Hz, 1H), 10.57 (d, J = 2.6 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.66 (q, J = 0.9 Hz, 1H), 7.40 (m, 3H), 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 1H), 7.20 (dd, J = 8.5, 2.7 Hz, 2H), 7.13 – 7.04 (m, 2H), 6.76 (dd, J = 8.7, 2.5 Hz, 1H), 5.02 (s, 2H, OCH_2), 4.11 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 151.9, 137.9, 135.3, 131.9, 129.7, 128.4, 127.7, 127.5, 126.5, 123.7, 119.6, 114.9, 114.4, 114.4, 112.1, 111.6, 108.8, 102.4, 70.0, 20.8. LC-MS (m/z): positive mode 421$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: >99%. HRMS (ESI-TOF) m/z: for ($C_{25}H_{20}F_3N_2O$ $[M+H]^+$) calcd: 421.1528. Found 421.1527.

*5-(Benzyloxy)-3-((6-fluoro-1H-indol-3-yl)methyl)-1H-indole (**9x**).* (5-Benzyloxy-3-indolylmethyl)trimethylammonium iodide (**10d**, 1.6 mmol) and 6-fluoroindole (**8p**, 3.2 mmol) were used for this reaction. Yield 68% (403 mg); Yellow solid; m.p. 122−124 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.76 (s, 1H), 10.67 (s, 1H), 7.47 (dd, J = 8.7, 5.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 (dd, J = 8.4, 6.6 Hz, 2H), 7.32 – 7.25 (m, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.14 – 7.02 (m, 4H), 6.76 (td, J = 8.9, 2.4 Hz, 2H), 5.02 (s, 2H), 3.98 (d, J = 52.2 Hz, 2H). ^{13}C NMR (126 MHz DMSO-d_6) δ (ppm) 159.8, 157.9, 138.0, 136.4, 136.3, 131.9, 128.4, 127.7, 127.7, 127.6, 124.2, 123.7, 123.4, 123.4, 119.7, 119.7, 113.9, 112.0, 111.6, 106.6, 102.50, 97.2, 70.0, 20.9. LC-MS (m/z): positive mode 371$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 95%. HRMS (ESI-TOF) m/z: for ($C_{24}H_{20}FN_2O$ $[M+H]^+$) calcd: 371.1560. Found 371.1563.

*6-Fluoro-3-((4-methyl-1H-indol-3-yl)methyl)-1H-indole (**9y**).* (6-Fluoro-3-indolylmethyl)trimethylammonium iodide (**10e**, 1.6 mmol) and 4-methylindole (**8q**, 3.2 mmol)

were used for this reaction. Yield 89% (393 mg); red solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.77 (s, 1H), 10.69 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 8.7, 5.5 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.10 (dd, J = 10.3, 2.4 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 8.2, 7.0 Hz, 1H), 6.83 – 6.73 (m, 2H), 6.64 (dt, J = 7.1, 1.1 Hz, 1H), 4.24 (s, 2H), 2.49 (s, 3H merged with DMSO-d_6). ^{13}C NMR (151 MHz, DMSO) δ 159.7, 158.2, 137.1, 136.4, 129.9, 125.9, 124.0, 123.6, 121.0, 119.8, 115.9, 115.9, 114.4, 109.5, 106.6, 97.5, 23.0, 19.9. LC-MS (m/z): positive mode 279 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{18}H_{15}FN_2$ $[M+H]^{+}$) calcd: 279. 1298 Found 279. 1292.

Di-(5-fluoro-1H-indole-3-yl)methane ***(9z)***.[27] (5-Fluoro-3-indolylmethyl)trimethylammonium iodide (**10c**, 1.6 mmol) and 5-fluoroindole (**8e**, 3.2 mmol) were used for this reaction. Yield 86% (390 mg); Light brown solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.14 (m, 2H), 7.29 (dd, J = 8.8, 4.6 Hz, 2H), 7.26 (d, J = 2.4 Hz, 2H), 7.21 (dd, J = 10.1, 2.6 Hz, 2H), 6.85 (td, J = 9.2, 2.6 Hz, 2H), 4.32 – 3.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.4, 155.8, 133.2, 127.5, 127.4, 125.1, 114.4, 112.4, 112.3, 109.0, 108.9, 103.5, 103.3. LC-MS (m/z): positive mode 283 $[M+1]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%.

Di-(5-methoxy-1H-indole-3-yl)methane ***(9aa)***.[27] (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 5-methoxyindole (**8a**, 3.2 mmol) were used for this reaction. Yield 87% (425 mg); Yellow solid; Spectral data is consistent with previous reports.[27] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.52 (d, J = 2.1 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 2.3 Hz, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.68 (dd, J = 8.7, 2.5 Hz, 2H), 4.05 (s, 2H), 3.70 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 152.9, 131.7, 127.7, 123.6,

114.1, 112.0, 110.8, 100.9, 55.5 21.0. LC-MS (m/z): positive mode 307 $[M+18]^{18+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 97%.

3-(1-(1H-Indol-3-yl)-2-methylpropyl)-5-methyl-1H-indole ***(11a)***. (3-Indolyl(2-methyl)propyl)trimethylammonium iodide (**10f**, 1.6 mmol) and 5-methylindole (**8k**, 3.2 mmol) were used for this reaction. Yield 79% (376 mg); Brown solid; m.p. 126−128 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.78 (s, 1H), 10.53 (s, 1H), 7.57 (dd, J = 8.1, 1.0 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.28 – 7.23 (m, 2H), 7.20 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 8.1, 7.0, Hz, 1H), 6.87 (dd J = 8.0, 7.0 Hz, 1H), 6.80 (dd, J = 8.3, 1.5 Hz, 1H), 4.06 (d, J = 9.2 Hz, 1H), 2.62 (dp, J = 9.1, 6.5 Hz, 1H), 2.32 (s, 3H), 0.91 (d, J = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 136.3, 134.6, 127.6, 127.3, 126.3, 122.3, 122.2, 122.2, 120.6, 119.1, 118.6, 118.4, 117.9, 111.3 111.0, 32.1, 22.0, 21.5. LC-MS (m/z): positive mode 320$[M+18]^{18+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{21}H_{23}N_2$ $[M+H]^+$) calcd: 303.1861. Found 303.1858.

3-(1-(1H-indol-3-yl)-2-methylpropyl)-5-fluoro-1H-indole ***(11b)***. (3-Indolyl(2-methyl)propyl)trimethylammonium iodide (**10f**, 1.6 mmol) and 5-fluoroindole (**8e**, 3.2 mmol) were used for this reaction. Yield 73% (357 mg); Brown solid; m.p. 130−132 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 10.95 (s, 1H), 10.70 (s, 1H), 7.56 (dd, J = 8.0, 1.0 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.31 (d, J = 2.3 Hz, 1H), 7.29 – 7.20 (m, 3H), 6.97 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.87 (ddd, J = 8.1, 6.9, 1.0 Hz, 1H), 6.80 (td, J = 9.1, 2.6 Hz, 1H), 4.05 (d, J = 9.2 Hz, 1H), 2.63 (dp, J = 9.0, 6.5 Hz, 1H), 0.91 (dd, J = 6.5, 1.2 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 157.4, 136.3, 132.9, 127.5, 127.4, 127.2, 124.5, 122.3, 120.6, 119.1, 118.6, 118.5, 118.0, 112.2, 111.3, 31.7, 22.0, 22.0. LC-MS (m/z): positive mode 306 $[M+1]^{1+}$. Purity by HPLC-UV (254

nm)-ESI-MS: 97%. HRMS (ESI-TOF) m/z: for ($C_{20}H_{20}FN_2$ $[M+H]^+$) calcd: 307.1611. Found: 307.1609.

3-(1-(1H-indol-3-yl)-2-methylpropyl)-4,5-difluoro-1H-indole ***(11c)***. (3-Indolyl(2-methyl)propyl)trimethylammonium iodide (**10f**, 1.6 mmol) and 5,6,-difluoroindole (**8m**, 3.2 mmol) were used for this reaction. Yield 68% (352 mg); Brown solid; m.p. 133−135 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.06 (s, 1H), 10.76 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.48 (dd, J = 8.8, 8.0 Hz, 1H), 7.35 (dd, J = 8.6, 2.4 Hz, 2H), 7.29 – 7.19 (m, 2H), 7.01 – 6.90 (m, 1H), 6.89 – 6.81 (m, 1H), 4.05 (d, J = 9.1 Hz, 1H), 2.62 (dp, J = 9.4, 6.5 Hz, 1H), 0.90 (dd, J = 6.6, 3.4 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 147.2, 145.2, 136.3, 131.2, 127.2, 124.3, 124.2, 122.3, 120.7, 119.1, 118.8, 118.0, 117.8, 111.3, 105.6, 105.4, 31.7, 22.0, 21.9. LC-MS (m/z): positive mode 325 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{20}H_{19}F_2N_2$ $[M+H]^+$) calcd: 325.1516. Found 325.1503.

1-((1H-Indol-3-yl)methyl)-1H-pyrrolo[3,2-b]pyridine ***(12a)***. (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 4-azaindole (**8s**, 3.2 mmol) were used for this reaction. Yield 79% (312 mg); White solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.41 (s, 1H), 8.28 (dd, J = 4.6, 1.4 Hz, 1H), 8.03 (dt, J = 8.3, 1.2 Hz, 1H), 7.78 (d, J = 3.3 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 8.0, 1.0 Hz, 1H), 7.41 – 7.26 (m, 1H), 7.19 – 6.99 (m, 2H), 6.98 – 6.79 (m, 1H), 6.50 (dd, J = 3.3, 1.0 Hz, 1H), 5.54 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 146.6, 142.4, 136.5, 132.2, 128.6, 126.3, 125.1, 121.5, 119.0, 118.5, 117.4, 116.0, 111.7, 110.6, 101.1, 41.7 LC-MS (m/z): positive mode 248$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 98%. HRMS (ESI-TOF) m/z: for ($C_{16}H_{14}N_3$ $[M+H]^+$) calcd: 248.1188. Found 248.1180.

1-((1H-Indol-3-yl)methyl)-1H-pyrrolo[3,2-c]pyridine ***(12b)***. (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 5-azaindole (**8t**, 3.2 mmol) were used for this reaction. Yield 68% (268 mg); Yellow solid; m.p. 210−212 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.05 (s, 1H), 8.79 (s, 1H), 8.18 (d, J = 5.9 Hz, 1H), 7.70 (d, J = 5.8 Hz, 1H), 7.60 (s, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.04 (dd, J = 8.1, 7.0 Hz, 1H), 6.97 – 6.84 (m, 1H), 6.57 (d, J = 3.4 Hz, 1H), 5.54 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 142.9, 139.4, 139.2, 136.5, 130.4, 126.3, 125.2, 121.5, 119.0, 118.5, 111.8, 110.5, 105.9, 100.3, 41.7. LC-MS (m/z): positive mode 248 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: >99%. HRMS (ESI-TOF) m/z: for ($C_{16}H_{14}N_3$ $[M+H]^+$) calcd: 248.1188. Found 248.1182.

1-((5-methoxy-1H-indol-3-yl)methyl)-1H-pyrrolo[3,2-c]pyridine ***(12c)***. (5-Methoxy-3-indolylmethyl)trimethylammonium iodide (**10b**, 1.6 mmol) and 5-azaindole (**8t**, 3.2 mmol) were used for this reaction. Yield 84% (595 mg); Brown solid; m.p. 188−190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.15 (s, 1H), 8.77 (s, 1H), 8.16 (d, J = 5.8 Hz, 1H), 7.67 (dt, J = 5.9, 1.1 Hz, 1H), 7.59 (d, J = 3.2 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 8.8, 2.4 Hz, 1H), 6.55 (dd, J = 3.0, 0.8 Hz, 1H), 5.50 (s, 2H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 153.4, 143.2, 139.9, 139.1, 131.6, 130.2, 126.7, 125.7, 125.3, 112.4, 111.4, 110.4, 105.8, 100.7, 100.1, 55.4, 41.3. LC-MS (m/z): positive mode 278$[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 96%. HRMS (ESI-TOF) m/z: for ($C_{17}H_{16}N_3O$ $[M + H]^+$) calcd: 278.1293. Found 278.1291.

3-((1H-indol-3-yl)methyl)-1H-pyrrolo[2,3-b]pyridine ***(12d)***.[30] (3-Indolylmethyl)trimethylammonium iodide (**10a**, 1.6 mmol) and 7-azaindole (**8u**, 3.2 mmol) were used for this reaction. Yield 89 % (352 mg); Light brown solid; Spectral data is consistent with previous reports.[31] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 11.23 (s, 1H), 10.74 – 10.70 (m, 1H), 8.13 (dd, J = 4.7, 1.8 Hz, 1H), 7.87 (dd, J = 7.9, 1.7 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.02 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 6.98 – 6.87 (m, 2H), 4.12 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 148.9, 142.3, 136.5, 128.1, 127.2, 126.9, 123.2, 122.9, 120.9, 119.5, 118.7, 118.2, 114.8, 113.9, 113.3, 111.5, 21.1. LC-MS (m/z): positive mode 248 $[M+H]^{1+}$. Purity by HPLC-UV (254 nm)-ESI-MS: 97%.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website:

^{1}H and ^{13}C- or $^{13}C_{apt}$-NMR spectra for all products, X-ray crystal structure determination and X-ray crystallographic data for **12a**, **12c** and **12d** (PDF and CIF).

AUTHOR INFORMATION

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