A rapid, efficient and versatile green synthesis of 3,3'-diindolylmethanes

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Abstract

The natural product 3,3'-diindolylmethane (DIM) exhibits anti-cancer and immunostimulatory properties. We report an operationally simple, efficient and versatile synthesis of DIM derivatives by reaction of indoles with aldehydes in the presence of sulfuric acid in water. Short reaction times of only 5 min, simple work-up procedure, avoidance of hazardous organic solvents, and excellent yields are apparent advantages of this method. The synthetic protocol tolerates a broad range of functional groups allowing fast and straightforward access to a large variety of DIM derivatives, including 20 new compounds not previously described in literature, which have potential as anti-cancer drugs.

R^1 = H, CH$_3$, OCH$_3$, F, Cl
R^2 = (hetero)aromatic, aliphatic

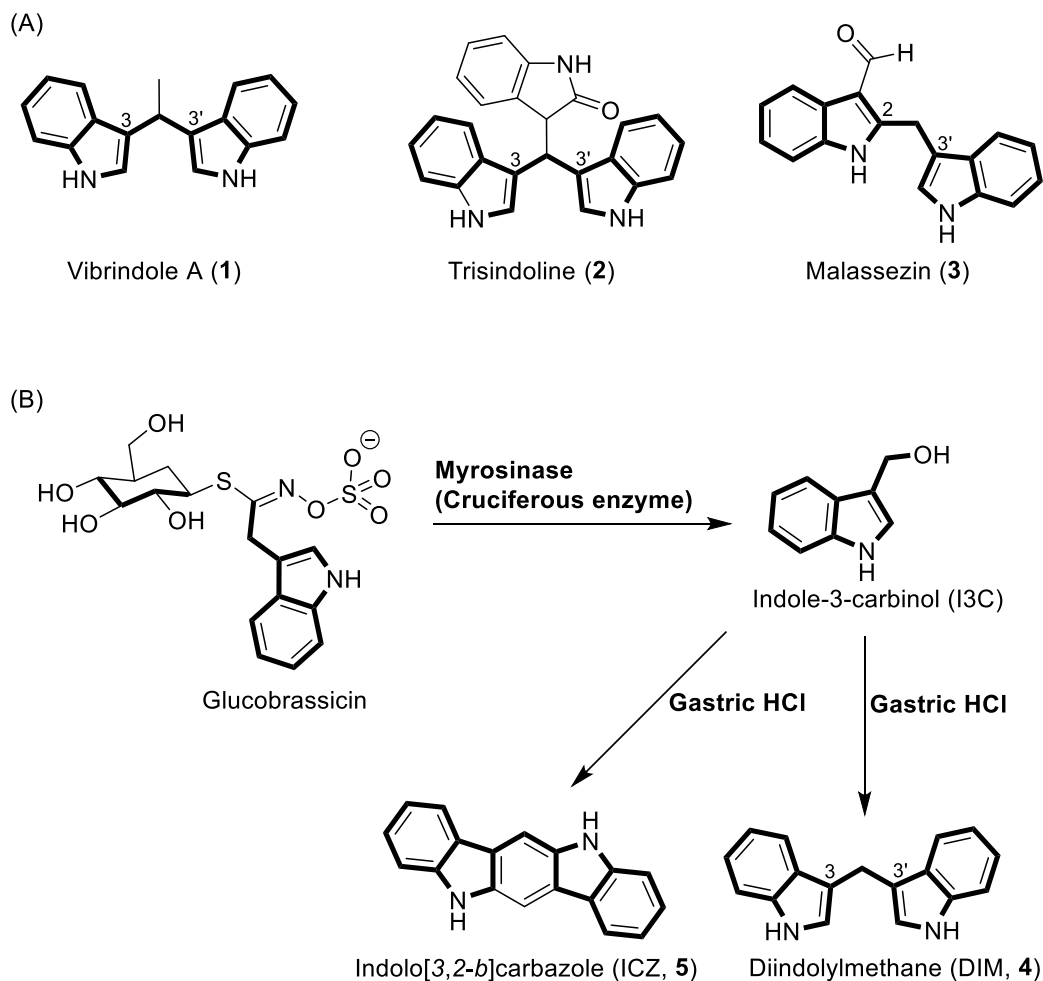**25 examples**
Yields from 56 to 97%
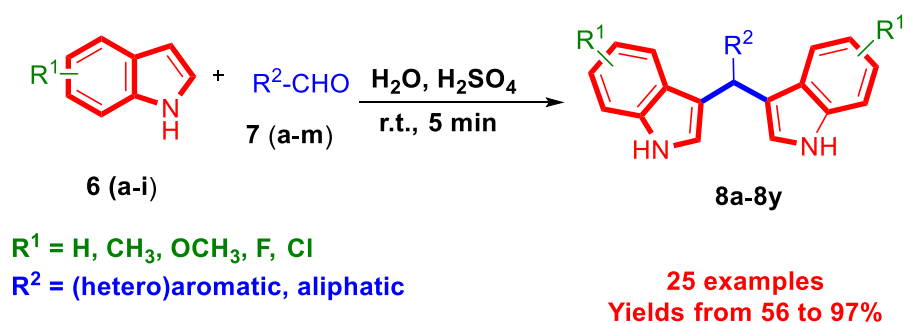
Keywords: Anti-cancer drugs, diindolylmethanes, indole, sulfuric acid, green synthesis

Introduction

The indole core is a privileged structure found in biologically active natural products as well as in synthetic drugs.[1-3] Specifically, diindolylmethanes[4] and diindolylethanes[5] are known to possess a wide variety of biological activities including anti-bacterial,[6] anti-microbial,[7] anti-fungal[8] and anti-tumor effects.[9] For example, vibrindole A (Figure 1A, **1**),[6] isolated from the culture medium of the marine bacterium *Vibrio parahemolyticus*, and trisindoline (Figure 1A, **2**), obtained from the culture of a bacterium *Vibrio sp.* exhibit anti-biotic activity.[10] Malassezin (Figure 1A, **3**) isolated from the yeast *Malassezia furfur*[11] is an agonist of the aryl hydrocarbon receptor (AhR),[12] a ligand-activated transcription factor associated with gastric carcinogenesis. 3,3'-Diindolylmethane (DIM, **4**), which has a skeleton consisting of two indole groups bridged by a single carbon atom at the 3- and 3'- positions, is a metabolite produced from glucobrassicin, which is found in large amounts in cruciferous vegetables such as broccoli, burssel sprouts and cauliflower. After hydrolysis of glucobrassicin by myrosinase, indole-3-carbinol (I3C) are formed, which then dimerizes to **4**, indolo[*3,2-b*]carbazole (ICZ, **5**) and further products, in the presence of gastric hydrochloric acid (Figure 1B).[13] It is estimated that approximately 10-20% of I3C is metabolized to **4**, and in addition, more than 15 different oligomeric compounds are formed.[14] Thus, **4** is a major product of I3C formed *in vivo*[15] and therefore the compound has been more extensively investigated than any other I3C metabolite.[16] Numerous studies have reported that **4** can affect mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt and nuclear factor-κB (NF-κB) signaling pathways.[17-20] It displays anti-inflammatory,[19] anti-angiogenic,[17] anti-cancer,[18,20] and anti-oxidant activities.[21] DIM was previously reported to act as an AhR agonist[22] and to inhibit histone deacetylase-1 (HDAC-1).[23] Recently DIM and its analogues have been identified and characterized as potent agonists of the immunostimulatory orphan G protein-coupled receptor GPR84.[24,25]

The goal of the present study was to develop a straightforward access to a broad range of synthetic derivatives and analogues of DIM for subsequent biological studies.

The majority of synthetic methods available for the preparation of DIM derivatives utilizes the Friedel-Crafts acylation reaction of indoles with various aldehydes or ketones in the presence of either a Lewis acid (e.g. $AlCl_3$, $BF_3 \cdot Et_2O$),[26] protic acids (e.g. HCl, TFA),[26] metal salts, such as $In(OTf)_3$,[26] $Dy(Otf)_3$,[26] $Ln(Otf)_3$,[26] $CeCl_3 \cdot 7H_2O$,[26] $RuCl_3 \cdot 3H_2O$,[26,27] or iodine.[26,27] The use of solid acidic catalysts[28,29] such as Amberlyst-15,[26] montmorillonite clay K-10[26] and zeolites[26] has also been reported. Moreover, benzoic acid,[30] sodium dodecylsulfate (SDS),[31] oxalic acid or *N*-acetyl-*N,N,N*-trimethylammonium bromide (CTAB) in water[32] were employed for the transformation of indoles to DIMs. Recently, the reaction of indoles, with *in situ* generated aldehydes from the corresponding alcohols has been reported to obtain DIMs. Examples include an iodine-catalyzed one-pot reaction of benzylic alcohols with indoles, ruthenium(III) chloride trihydrate-catalyzed aerobic oxidation reaction of benzylic alcohols with indoles and $RuCl_2(PPh_3)_3$/*bis*-[(2-diphenylphosphanyl)-phenyl]ether-catalyzed reaction of benzylic alcohols with indole in the presence of large amount of *tri*-potassium phosphate.[33,34] Although the reported methodologies are useful, there are still certain drawbacks such as the requirement of expensive catalysts[26,35] long reaction times[36,37] formation of hazardous by-products, harsh reaction conditions[38] and complex workup procedures to isolate the products of interest.[39] In this context, the development of a facile and efficient procedure for the synthesis of diindolylmethanes (DIMs) is highly desirable.

Figure 1. (A) Representative examples of biologically active natural diindolylmethanes (DIMs); (B) Conversion of glucobrassicin to produce DIM (**4**) and ICZ (**5**).

Results and Discussion

Optimization of the reaction conditions. Organic reactions in water as a reaction medium offer many advantages, including low cost, safe handling and environment compatibility. Recently we developed a new procedure for the synthesis of DIMs in aqueous media under microwave irradiation at 100 °C.[25] No catalyst was used for the reaction of indoles with formaldehyde, while sodium dodecylsulfate (SDS) was employed as an emulsifier for the reaction of indoles with aliphatic and aromatic aldehydes.[25]

In continuation of our research program, we have now further improved the synthetic access to a large variety of target compounds by developing an operationally simple, fast and efficient green procedure for the synthesis of DIMs.

The reaction of 4-methoxyindole with benzaldehyde (Scheme 1) was tried under a variety of conditions (see Table 1), and considerable variation in yields was observed.
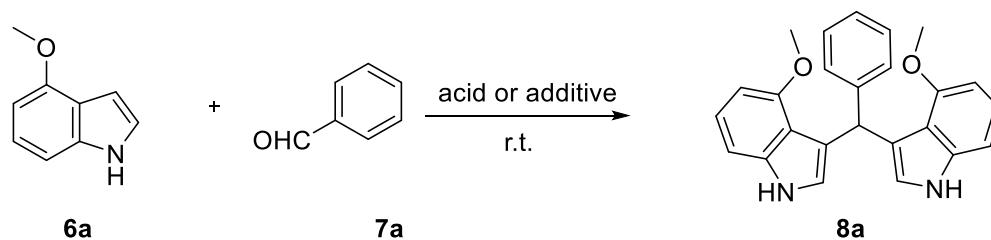
Scheme 1

Table 1. Optimization of the reaction conditions[a]

Entry	Acid or additive (mmol)	Solvent	Reaction time	Yield (%) [b]
1	concd.H_2SO_4 (2.0)	H_2O	2 h	40
2	concd.H_2SO_4 (5.0)	H_2O	30 min	87
3	concd.H_2SO_4 (10)	H_2O	5 min	95
4	concd.H_2SO_4 (20)	H_2O	5 min	93
5	concd.H_2SO_4 (10)	DCM	5 min	30
6	SDS (10% w/w)	H_2O	12 h	30
7	none	H_2O	5 h	0
8	$BF_3 \cdot Et_2O$ (5.0)	DCM	5 min	50
9	Trifluoroacetic acid (TFA) (5)	DCM	24 h	25

[a] All the reactions were conducted with 4-methoxyindole (**6a**, 10 mmol), and benzaldehyde (**7a**, 5 mmol) in the presence of acid or additive at room temperature. [b] Isolated yield.

In order to test this idea, we decided to synthesize DIMs from indoles and aldehydes in the presence of sulfuric acid, which has not been explored well. To the best of our knowledge, only one previous method for the preparation of 3,3'-DIMs in the presence of sulfuric acid in water has been described.[15] However, the published procedure was carried out under harsh conditions (reaction at 100 °C for 2.5 to 5 h) and suffered in several cases from low yields of less than 20%. Moreover, no efforts to optimize the reaction conditions had been undertaken and the scope of the reaction had not been explored. We therefore systematically studied the reaction conditions by exploring the transformation of 4-methoxyindole (**6a**, 10 mmol) with benzaldehyde (**7a**, 5 mmol) yielding 4,4'-dimethoxy-DIM (**8a**). The reaction was optimized by variation of type and amount of acid and solvent system. In Table 1, entries 1- 4, various stoichiometries of sulfuric acid in water as a reaction medium were employed. In the presence of 2 mmol of sulfuric acid the reaction was slow and only 40% of product was isolated after 2 h, while increasing the amount to 5 or 10 mmol raised product formation to 87% and 95%, respectively. Reaction in dichloromethane (DCM) was rapid but only 30% of the desired product was obtained (entry 5). This study suggested that water as a reaction medium increased the yield. Reaction in the presence of SDS (entry 6) was very slow and only 30% of product was isolated after 12 h. The reaction was not initiated without adding any acid or additive (entry 7). Sulfuric acid was clearly superior to other acids, namely the Lewis acid $BF_3 \cdot Et_2O$ (entry 8) or TFA (entry 9). We found sulfuric acid (10 mmol) in water to provide the optimal conditions for the synthesis of **8a** from 4-methoxyindole (**6a**, 10 mmol) and benzaldehyde (**7a**, 5 mmol), which gave **8a** in 95% yield.
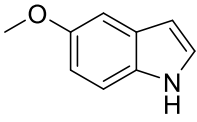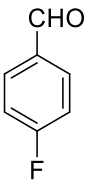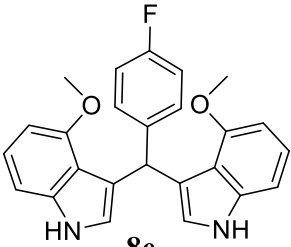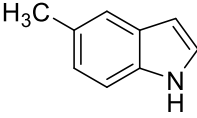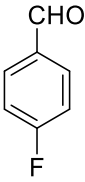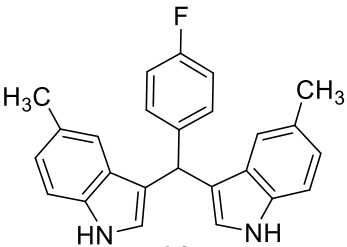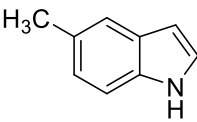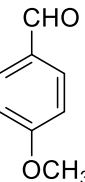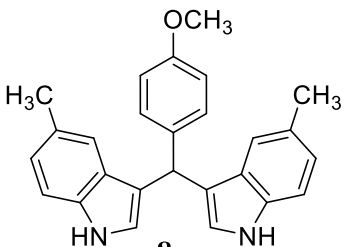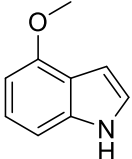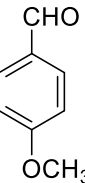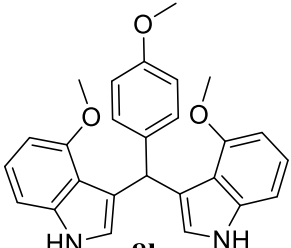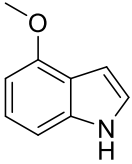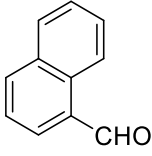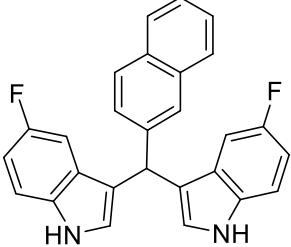
Substrate scope of the reaction and discussion. We then examined the substrate scope of these optimized reaction conditions with a variety of substituted indoles and aldehydes (see Table 2). It was observed that
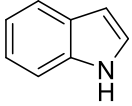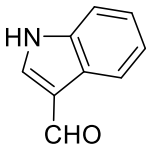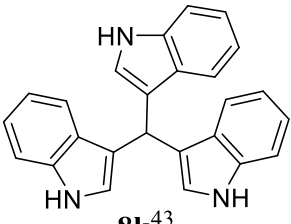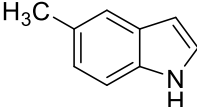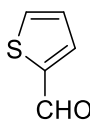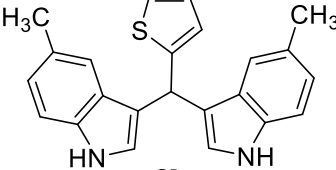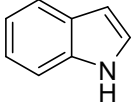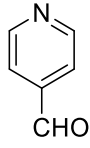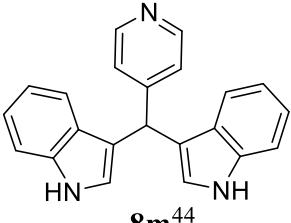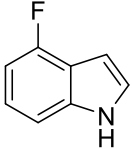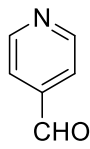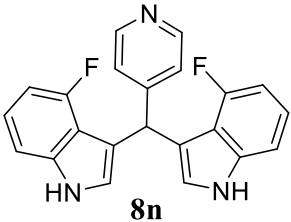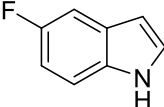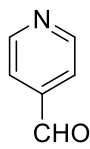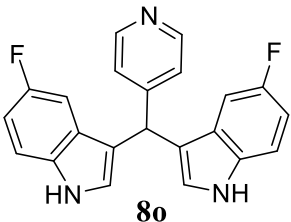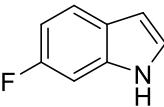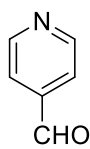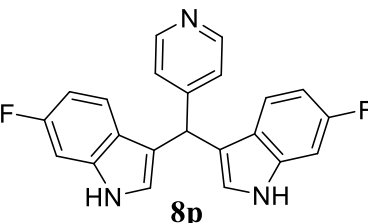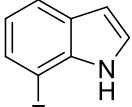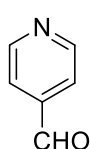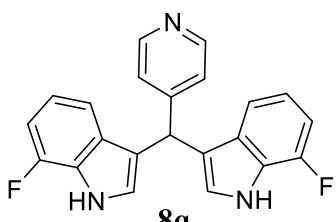
electron-donating substituents or electron-withdrawing substituents on the indole or on the aromatic aldehydes did not significantly impact on the reaction. For example the reaction of 4-methoxybenzaldehyde (**7b**) or 4-fluorobenzaldehyde (**7c**) with various substituted indoles afforded the corresponding DIMs in excellent yields of 82 to 96% (Table 2, compounds **8a**-**8h**). We observed that reactions of condensed aromatic aldehydes like naphthalene-1-carboxaldehyde (**7d**) or naphthalene-2-caboxaldehyde (**7e**) also proceeded smoothly and resulted in excellent yields of 83 and 89%, respectively (Table 2, compounds **8i** and **8j**).
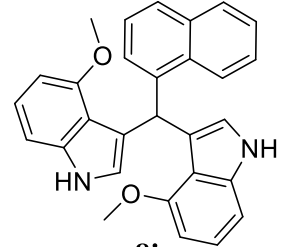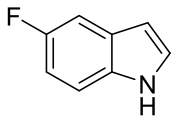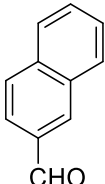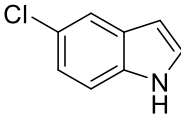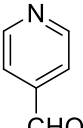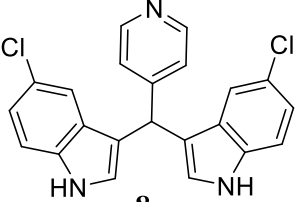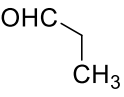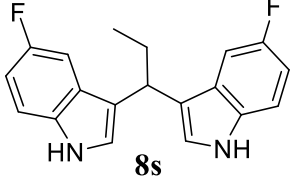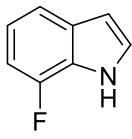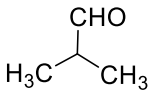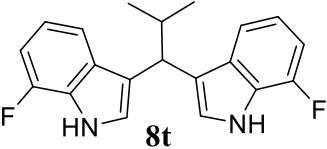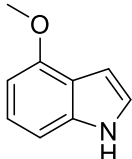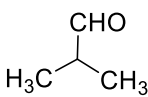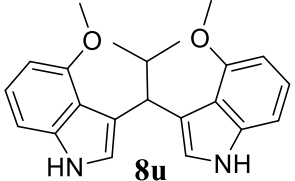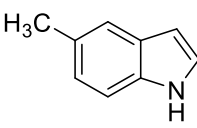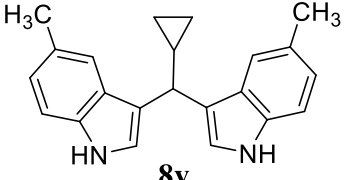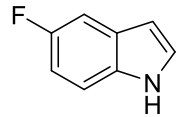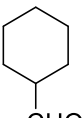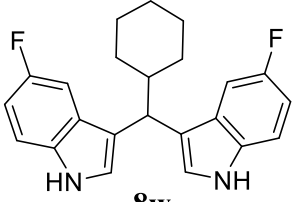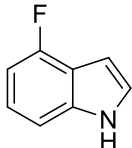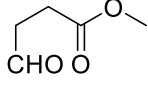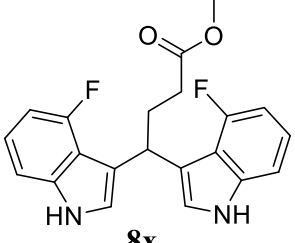
Table 2. Reaction of indole derivatives with aliphatic or aromatic aldehydes
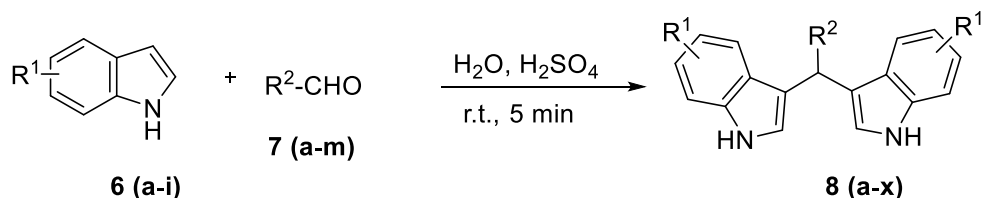
Entry	Indole	Aldehyde	Product	Yield (%)[a]	Purity (%)[b]
1	**6a**	**7a**	**8a**	95	99.9
2	**6b**	**7a**	**8b**[40]	92	99.2
3	**6b**	**7b**	**8c**[41]	82	96.3
4	**6c**	**7a**	**8d**[46]	87	97.0

5	**6d**	**7c**	**8e**	96	99.7
6	**6c**	**7c**	**8f**	93	98.6
7	**6c**	**7b**	**8g**	89	99.5
8	**6a**	**7b**	**8h**	92	98.2
9	**6a**	**7d**	**8i**	83	97.7
10	**6e**	**7e**	**8j**	89	99.6

11	6b	7f	8k[43]	90	95.5
12	6c	7g	8l	81	96.8
13	6b	7h	8m[44]	94	98.2
14	6f	7h	8n	79	97.3
15	6e	7h	8o	87	98.2
16	6g	7h	8p	80	98.5
17	6h	7h	8q	77	96.1

18	**6i**	**7h**	**8r**	86	98.2
19	**6e**	**7i**	**8s**	61	98.2
20	**6h**	**7j**	**8t**	76	95.7
21	**6a**	**7j**	**8u**	72	95.2
22	**6c**	**7k**	**8v**	83	95.2
23	**6e**	**7l**	**8w**	87	95.5
24	**6f**	**7m**	**8x**	56	96.2
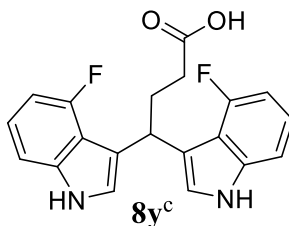
25	8x		97	96.3

[a] Isolated yields; all isolated products were characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS spectra. In addition, HPLC analysis coupled to electrospray ionization mass spectrometry (LC/ESI-MS) was performed, which was also used to determine the purity of the compounds; *[b]* Purity was determined using LC–MS coupled to a UV detector; *[c]* Compound **8y** was synthesized by the hydrolysis of **8x**.

The synthesis of trisindolylmethane (TIM, **8k**) a natural product isolated from the North Sea bacterium *Vibrio parahaemolyticus* Bio249 was explored.[45] As indicated in Table 2, **8k** was synthesized from 1*H*-indole (**6b**) by reaction with indol-3-carbaldehyde (**7f**) in a high yield of 90%. The efficiency of the new synthetic protocol was further examined by reacting heteroaromatic aldehydes. For example, the reaction of 2-thiophenecarbaldehyde (**7g**) or 4-pyridinecarbaldehyde (**7h**) with indoles resulted in high yields of 77 to 94% (Table 2, compounds **8l**-**8r**). In order to test the suitability of the procedure for large-scale synthesis, the reaction of 1*H*-indole (**6b**, 42 mmol) with 4-pyridinecarbaldehyde (**7g**, 21 mmol) was investigated. The reaction afforded 6.5 g of **8m** in 94% yield without any significant loss in efficiency. Thus, this synthetic protocol can be used as a practical method to prepare DIM derivatives on a larger scale.

The scope of the reaction was further examined by reacting a variety of aliphatic aldehydes including cyclic aldehydes. The reaction of indoles with non-cyclic aldehydes, for example, propionaldehyde (**7i**) or isobutyraldehyde (**7j**), resulted in moderate to good yields of 61 to 72% (Table 2, compounds **8s**-**8u**). On the other hand, the reaction of cyclic aldehydes, for example, the reaction of cyclopropanecarbaldehyde (**7k**) or cyclohexanecarbaldehyde (**7l**) with indoles gave excellent yields of 83 and 87%, respectively (Table 2, compounds **8v** and **8w**). The reaction of an aliphatic aldehyde containing a carboxylic acid ester group was also explored. As indicated in Table 2, produ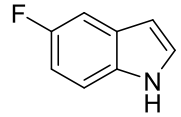ct **8x** was synthesized by reacting methyl 4-oxobutanoate (**7m**) with 4-fluoroindole (**6f**). Methyl ester **8x** was subsequently hydrolyzed by treatment with 2 N sodium hydroxide yielding the corresponding carboxylic acid derivative **8y**. In order to compare the efficiency of the new synthetic procedure with that of previously reported reaction conditions, times and yields for the preparation of 3,3'-di-(1*H*-indolyl)phenylmethane (**8b**) were compared (Table 3). Moreover the present method used water as a reaction medium which made work-up easy compared to other published procedures (see entry 3, 4, 6, 9 10, 13, 14, and 15). The reaction mixture was washed with ethyl acetate, dried and evaporated to obtain the desired compounds, which were in most cases purified by recrystallization or by washing with non-polar solvents. Thus, the present method clearly affords superior results with respect to the employed reagents, solvent, reaction time and eco-friendliness.

Table 3. Comparison of reaction times and yields for the preparation of compound **8b** from indole and benzaldehyde using different reaction conditions

Entry	Reactions conditions	Reaction time	Yield (%)
1[a]	**H$_2$SO$_4$, H$_2$O, r.t.**	**5.0 min**	**92**
2[31]	Methanol, r.t.	18 h	78
3[26]	CH$_3$CN, TCT,[b] r.t.	2.0 h	90

4[26]	CH_3CN, $ZrCl_4$, r.t.	30 min	96
5[26]	Bentonitic clay	15 min	75
6[33]	H_2O, oxalic acid dihydrate [$(CO_2H)_2 \cdot 2H_2O$], CTAB,[c] r.t.	1.5 h	98
7[46]	CH_2Cl_2, $NaHSO_4 \cdot SiO_2$ or Amberlyst-15, r.t.	2.5 h	89
8[26]	$RuCl_3 \cdot 3H_2O/C_6H_6$, r.t.	30 min	92
9[47]	Trityl chloride, r.t. solvent-free	20 min	90
10[27]	CH_2Cl_2, PCl_5, r.t.	25 min	95
11[27]	$ZrOCl_2 \cdot 8H_2O$, solvent-free	40 min	84
12[26]	CH_3CN, $In(OTf)_3$	25 min	71
13[48]	$EtOH \cdot H_2O$, $Ln(OTf)_3$	12 h	95
14[26]	CH_3CN, Zeokarb-225	7.5 h	95
15[49]	CH_3CN, $LiClO_4$	2.0 h	80
16[26]	Ionic liquid, $Dy(OTf)_3$	1.0 h	98
17[50]	AgOTf,	24 h	41
18[30]	Benzoic acid, H_2O, 80 ºC	15 h	80

[a] Present method (in bold); [b] TCT, trichloro-1,3,5-triazine; [c] N-cetyl-N,N,N-trimethylammonium bromide (CTAB).

Conclusions

We have developed a simple, fast and efficient protocol for the synthesis of diversely substituted 3,3'-diindolylmethanes. A series of 25 derivatives was obtained, 20 of which have not been previously reported in literature. The new synthetic protocol offers several advantages including short reaction times, high yields of products, eco-friendliness and simple experimental settings as well as isolation procedures. In addition, this method is highly feasible and applicable to a broad range of aromatic, heteroaromatic and aliphatic aldehydes. It thus provides a convenient access to a large variety of DIM derivatives, which are of great interest due to their exciting biological activities.

Experimental Section

General. All materials were used as purchased (from Acros, Alfa Aesar, Grüssing, Merck, or Sigma-Aldrich, Germany). Thin-layer chromatography was performed using TLC aluminum silica gel 60 F254 sheets, or TLC aluminum RP silica gel 18 F_{254} sheets (Merck, Darmstadt, Germany). The purities of isolated products were determined by an LC-MS instrument coupled to electrospray ionization mass spectrometry (LC/ESI-MS) (Applied Biosystems API 2000 LCMS/MS, HPLC Agilent 1100) using the following procedure: the compounds were dissolved at a concentration of 1.0 mg/mL in acetonitrile, containing 2 mM CH_3COONH_4. 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 CH_3COONH_4) 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 254 nm and was ≥ 95% for all products.

^{1}H- and ^{13}C-NMR data were measured in DMSO-d_6 as a solvent. Chemical shifts are reported in parts per million (ppm) relative to the deuterated solvent (DMSO-d_6), δ ^{1}H: 2.49 ppm, ^{13}C: 39.7 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). The purities of isolated products were determined by ESI-mass spectra obtained on an HPLC-MS instrument (LC-MS) using the same procedure as previously published. Melting points were measured on a melting point apparatus (Büchi melting point B-545) and are uncorrected.

HRMS was recorded on a micrOTOF-Q mass spectrometer (Bruker) with ESI-source coupled with an HPLC Dionex Ultimate 3000 (Thermo Scientific) using an EC50/2 Nucleodur C18 Gravity 3 μm column (Macherey-Nagel). The column temperature was 425 °C. Ca. 1 μL of a 1 mg/mL solution of the sample in acetonitrile was injected and a flow rate of 0.3 mL/min was used. HPLC was started with a solution of acetonitrile in water (10:90), containing 2 mM CH$_3$COONH$_4$. The gradient was started after 1 min reaching 100% acetonitrile within 9 min and then flushed with this concentration for another 5 min. The infrared spectra were recorded as solid samples on an ALPHA-T (Bruker) with a Platinum ATR Module using Opus software. IR spectra were measured in the attenuated total reflection (ATR) mode in the region of 4000-385 cm^{-1}.

General procedure for the synthesis of 3,3'-diindolylmethanes 8a-8x

To the stirred mixture of the appropriate indole (3.1-6.7 mmol) and the appropriate aldehyde (1.5-3.3 mmol, 0.5 equiv.) dissolved in water (5 mL) concentrated sulfuric acid (1 equiv.) was added. The progress of the reaction was monitored immediately after the addition of H$_2$SO$_4$ by TLC using ethyl acetate: petroleum ether (20:80). After completion of the reaction as indicated by TLC, the aqueous mixture was dissolved in ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The resulting crude product was purified by recrystallization with an appropriate solvent system or by washing it with nonpolar solvents. Few compounds were purified by silica gel column chromatography using non-chlorinated solvent systems such as ethyl acetate: petroleum ether (b.p.42–62 °C) mixtures (10:90 to 20:80) as eluent to afford the pure diindolylmethane derivatives.

Di-(4-methoxy-1*H*-indol-3-yl)phenylmethane (8a). 4-Methoxyindole (**6a**, 0.5 g, 3.3 mmol) was treated with benzaldehyde (**7a**, 0.180 mL, 1.6 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.181 mL; 3.3 mol) in water. White solid; m.p. 284-286 °C; yield: 95%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (d, J = 2.5 Hz, 2H, 2 x NH), 7.31 – 7.13 (m, 4H, 12-H, 13-H, 15-H, 16-H), 7.13 – 7.00 (m, 1H, 14-H), 6.96 – 6.76 (m, 4H, 6-H, 6-'H, 7-H, 7'-H), 6.66 (s, 1H, 10-H), 6.53 (dd, J = 2.3, 0.8 Hz, 2H, 2-H, 2'-H), 6.34 (dd, J = 6.0, 2.6 Hz, 2H, 4-H, 4'-H), 3.59 (s, 6H, 2 x OCH$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.50 (4-C, 4'-C), 138.08 (9-C, 9'-C), 128.51 (12-C, 16-C), 127.64 (13-C, 15-C), 124.99 (14-C), 122.27 (6-C, 6'-C), 121.66 (2-C, 2'-C), 120.33 (8-C, 8'-C), 116.85 (3-C, 3'-C), 104.86 (7-C, 7'-C), 99.32 (5-C, 5'-C), 55.13 (10-C), 38.03 (2 x OCH$_3$); IR : 3400, 3343, 3009, 2929, 2839, 1734, 1575, 1433, 1216, 1117, 765 cm^{-1} ; LC-MS positive mode: 383 (M+H)$^+$; purity: 99.9%. HRMS (ESI-TOF) *m/z*: for (C$_{25}$H$_{23}$N$_2$O$_2$ [M + H]$^+$) calcd: 383.1760. Found 383.1754.

Di-(1*H*-indol-3-yl)phenylmethane (8b). Indole (**6b**, 0.5 g, 4.2 mmol) was treated with benzaldehyde (**7a**, 0.226 mL, 2.1 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.232 mL, 4.2 mmol) in water. The product was purified by column chromatography. Pale yellow solid; m.p. 145-147 (lit. m.p.: 146–148 °C);[40] Yield: 92%; LC-MS, negative mode: 321 (M-H)$^-$; purity: 99.2%.

Di-(1*H*-indol-3-yl)-4-methoxyphenylmethane (8c). Indole (**6b**, 0.5 g, 4.2 mmol) was treated with 4-methoxy-benzaldehyde (**7b**, 0.219 mL, 2.1 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.232 mL, 4.2 mmol) in water. The product was purified by column chromatography. Brown solid; m.p. 186-188°C (lit. m.p.: 188-190 °C);[41] Yield: 82%; LC-MS positive mode 353(M+H)$^+$; purity: 96.3%.

Di-(4-methyl-1*H*-indol-3-yl)phenylmethane (8d). 5-Methylindole (**6c**, 0.5 g, 3.8 mmol) was stirred with benzaldehyde (**7a**, 0.201 mL, 1.9 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.205 mL, 3.8

mmol) in water (5.0 mL). Brown solid; m.p. 192-194 (lit. m.p. 193–194 °C);[42] Yield: 87%; LC-MS, positive mode: 351 (M+H)$^+$; purity: 97.0%

Di-(4-methoxy-1*H*-indol-3-yl)-4-fluorophenylmethane (**8e**). 4-Methoxyindole (**6d**, 0.5 g, 3.3 mmol), was stirred with 4-fluorobenzaldehyde (**7c**, 0.214 mL, 1.6 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.232 mL, 4.2 mmol) in water. The crude compound was purified by recrystallization using CHCl$_3$; White solid; m.p. 174-176 °C; yield: 96%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.66 (d, *J* = 2.4 Hz, 2H, 2 x NH), 7.43 – 7.12 (m, 2H), 7.07 – 6.94 (m, 2H), 6.94 – 6.84 (m, 4H), 6.63 (s, 1H), 6.52 (dd, *J* = 2.4, 0.8 Hz, 2H, 2-H, 2'-H), 6.35 (dd, *J* = 6.3, 2.3 Hz, 2H, 6-H, 6'-H), 5.74 (s, 1H, 10-H), 3.59 (s, 6H, 2 x OCH$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.55 (5-C, 5'-C), 143.66 (11-C), 138.11 (12-C, 16-C), 130.02 (9-C, 9'-C), 129.95 (8-C, 8'-C), 122.25 (2-C, 2'-C), 121.75 (15-C), 120.17 (13-C), 116.75 (7-C, 7'-C), 114.28 (6-C, 6'-C), 114.12 (3-C, 3'-C), 104.89 (4-C, 4'-C), 99.35 (10-C), 55.13 (2 x OCH$_3$); IR : 3433, 3405, 3009, 2920, 2839, 1734, 1575, 1255, 1081, 765 cm^{-1}; LC-MS, positive mode 401 (M+H)$^+$; purity: 99.7 %. HRMS (ESI-TOF) *m/z*: for (C$_{25}$H$_{22}$FN$_2$O$_2$ [M + H]$^+$) calcd: 401.1665. Found 401.1660.

Di-(5-methyl-1*H*-indol-3-yl)-4-fluorophenylmethane (**8f**). 5-Methylindole (**6c**, 0.5 g, 3.8 mmol) was stirred with 4-fluorobenzaldehyde (**7c**, 0.214 mL, 1.6 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.205 mL, 3.3 mol) in water (5.0 mL). The crude compound was purified by recrystallization using CHCl$_3$; Pale yellow solid; m.p. 96-98 °C; yield: 93%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (d, *J* = 2.6 Hz, 2H, 2 x NH), 7.40 – 7.25 (m, 2H, 4-H, 4'-H), 7.22 (d, *J* = 8.2 Hz, 2H, 7-H, 7'-H), 7.12 – 6.92 (m, 4H, 12-H, 13-H, 15-H, 16-H), 6.85 (dd, *J* = 8.3, 1.6 Hz, 2H, 6-H, 6'-H), 6.69 (dd, *J* = 2.4, 0.8 Hz, 2H, 2-H, 2'-H), 5.76 (s, 1H, 10-H), 2.25 (s, 6H, 2 x CH$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.44 (14-C), 135.12 (11-C), 130.04 (9-C, 9'-C), 129.98 (12-C, 16-C), 126.64 (5-C, 5'-C), 123.76 (8-C, 8'-C), 122.66 (2-C, 2'-C), 118.62 (6-C, 6'-C), 117.67 (4-C, 4'-C), 114.81 (13-C, 15-C), 114.65 (3-C, 3'-C), 111.30 (7-C, 7'-C), 58.53 (10-C), 21.39 (2xCH$_3$); IR : 3396, 3015, 2919, 2854, 2839, 1716, 1503, 1418, 1216, 1039, 795 cm^{-1}; LC-MS negative mode 367 (M-H)$^-$; purity: 98.6%. HRMS (ESI-TOF) *m/z*: for (HRMS (ESI-TOF) *m/z* for (C$_{25}$H$_{22}$FN$_2$ [M + H]$^+$): calcd 369.1767. Found 369.1762.

Di-(5-methyl-1*H*-indol-3-yl)-4-methoxyphenylmethane (**8g**). 5-Methylindole (**6c**, 0.5 g, 3.8 mmol) was stirred with 4-methoxybenzaldehyde (**7b**, 0.219 mL, 1.9 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.202 mL, 3.7 mmol, 1 equiv.) in water (5.0 mL). The resulting pale brown solid was dissolved in THF and decolorized with charcoal; White solid; m.p. 92-94 °C; yield: 89%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.58 (d, *J* = 2.5 Hz, 2H, 2 x NH), 7.21 (dd, *J* = 8.5, 3.2 Hz, 4H, 7-H, 7'-H, 4-H, 4'-H), 7.05 (q, *J* = 1.0 Hz, 2H, 12-H, 16-H), 6.90 – 6.73 (m, 4H, 13-H, 15-H, 6-H, 6'-H), 6.67 (dd, *J* = 2.4, 0.9 Hz, 2H, 2-H, 2'-H), 5.68 (s, 1H, 10-H), 3.70 (s, 3H, OCH$_3$), 2.25 (s, 6H, 2 x CH$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.10 (14-C), 137.20 (9-C, 9'-C), 135.13 (3-C, 3'-C), 129.25 (12-C, 16-C), 126.98 (11-C), 126.51(5-C, 5'-C), 123.68 (8-C, 8'-C), 122.57 (6-C, 6'-C), 118.72 (4-C, 4'-C), 118.16 (13-C, 15-C), 113.49 (2-C, 2'-C), 111.25 (7-C, 7'-C), 55.05 (OCH$_3$), 21.42 (2 x CH$_3$) ; IR : 3392, 3252, 3055, 2921, 2895, 1716, 1634, 1455, 1418, 1174, 741 cm^{-1} ; LC-MS negative mode 379 (M-1H)$^{1-}$; purity: 99.5%. HRMS (ESI-TOF) *m/z*: for (HRMS (ESI-TOF) *m/z*: for (C$_{26}$H$_{24}$N$_2$O) calcd: 380.1889. Found 380.1883.

Di-(4-methoxy-1*H*-indol-3-yl)-4-methoxyphenylmethane (**8h**). 4-Methoxylindole (**6a**, 0.5 g, 3.3 mmol) was stirred with 4-methoxybenzaldehyde (**7b**, 0.224 mL, 1.6 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.235 mL, 3.3 mmol, 1 equiv.) in water (5.0 mL). White solid; m.p. 230-232 °C; yield: 92%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.60 (d, *J* = 2.5 Hz, 2H, 2xNH), 7.21 – 7.07 (m, 2H, 7-H, 7'-H), 6.91 – 6.85 (m, 4H, 6-H, 6'-H, 12-H, 16-H), 6.83 – 6.69 (m, 2H, 13-H, 15-H), 6.59 (s, 1H, 10-H), 6.49 (dd, *J* = 2.3, 0.8 Hz, 2H, 5-H, 5'-H), 6.33 (dd, *J* = 6.3, 2.2 Hz, 2H, 4-H, 4'-H), 3.68 (s, 3H, OCH$_3$), 3.59 (s, 6H, 2xOCH$_3$); ^{13}C NMR (126 MHz, DMSO) δ 156.88 (14-C), 154.64 (4-C, 4'-C), 139.54 (9-C, 9'-C), 138.11 (11-C, 12-C, 16-C), 129.36 (6-C, 6'-C), 122.08 (6-C, 6'-C), 121.62 (2-C, 2'-C), 120.84 (8-C, 8'-C), 116.85 (13-C, 15-C), 113.08 (3-C, 3'-C), 104.84 (7-C, 7'-C), 99.28 (5-C, 5'-C), 55.01 (OCH$_3$), 55.16 (2 x OCH$_3$); IR : 3440, 3393, 3019, 2927, 2833, 1748, 1609, 1577,1356, 1257, 1115,

773 cm^{-1}; LC-MS positive mode: 413 (M+H)$^+$; purity: 98.2%. HRMS (ESI-TOF) *m/z*: for (C$_{26}$H$_{25}$N$_2$O$_3$ [M + H]$^+$) calcd: 413.1865. Found 413.1860.

Di-(4-methoxy-1*H*-indol-3-yl)-1-naphthylmethane (8i). 4-Methoxyindole (**6a**, 0.5 g, 3.3 mmol) was treated with naphthalene-1-carboxaldehyde (**7d**, 0.265 g, 1.6 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.186 mL, 3.3 mmol) in water (5.0 mL). White solid; m.p. 256-258 °C; yield: 83%; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 10.65 (d, *J* = 2.5 Hz, 2H, 2 x NH), 8.54 – 8.10 (m, 1H, 18-H), 8.02 – 7.71 (m, 1H, 15-H), 7.67 (d, *J* = 8.1 Hz, 1H, 14-H), 7.52 (s, 1H, 10-H), 7.50 – 7.37 (m, 2H, 17-H, 16-H), 7.32 (dd, *J* = 8.2, 7.2 Hz, 1H, 13-H), 7.14 (dd, *J* = 7.2, 1.1 Hz, 1H, 12-H), 6.96 – 6.79 (m, 4H, 7-H, 7'-H, 6-H, 6'-H), 6.49 (d, *J* = 2.3 Hz, 2H, 2-H, 2'-H), 6.41 – 6.25 (m, 2H, 5-H, 5'-H), 3.48 (s, 6H, 2 x OCH$_3$); ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 154.70 (4-C, 4'-C), 144.04 (9-C, 9'-C) 138.24 (11-C), 133.69 (19-C, 20-C), 131.58 (6-C, 6'-C), 128.31 (15-C), 125.72 (14-C),125.61 (18-C), 125.38 (16-C), 125.04 (17-C), 124.84 (13-C), 124.44 (12-C), 122.96 (2-C, 2'-C), 121.72 (8-C, 8'-C), 119.71 (3-C, 3'-C), 116.79 (7-C, 7-C), 105.01 (5-C, 5'-C), 99.52 (10-C), 55.25 (2 x OCH$_3$); IR : 3386, 3057, 2928, 2836, 1613, 1504, 1433, 1332, 1115, 1070, 784 cm^{-1}; LC-MS positive mode: 407 (M+H)+; purity: 97.7%. (HRMS (ESI-TOF) m/z: for (C$_{29}$H$_{25}$N$_2$O$_2$ [M + H]+) calcd: 433.1916. Found 433.1911.

Di-(5-fluoro-1*H*-indol-3-yl)-2-naphthylmethane (8j). 5-Fluoroindole (**6e**, 0.5 g, 3.6 mmol) was treated with naphthalene-2-carboxaldehyde (**7e**, 0.288 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.197 mL, 3.6 mmol) in water (5.0 mL). The resulting orange viscous oil was dissolved in THF and decolorized with charcoal. Pale yellow oil; yield: 89%; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 10.96 (d, *J* = 2.5 Hz, 2H, 2 x NH), 7.92 – 7.66 (m, 4H, 13-H, 14-H, 16-H, 17-H), 7.53 (dd, *J* = 8.5, 1.8 Hz, 1H, 15-H), 7.50 – 7.40 (m, 2H, 12-H, 14'-H), 7.35 (dd, *J* = 8.8, 4.6 Hz, 2H, 7-H, 7'-H), 6.98 (dd, *J* = 10.1, 2.5 Hz, 4H, 4-H, 4'-H, 2-H, 2'-H), 6.87 (td, *J* = 9.2, 2.6 Hz, 2H, 6-H, 6'-H), 5.95 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 157.47 (5-C, 5'-C), 142.24 (11-C), 133.38 (20-C), 133.19 (19-C),131.89 (9-C, 9'C), 127.74 (8-C, 8'-C), 127.70 (12-C), 127.57 (18-C), 127.52 (17-C), 126.97 (13-C), 126.89 (16-C), 126.08 (14-C), 126.00 (15-C), 125.93 (2-C, 2'C), 117.96 (6-C, 6'C), 112.66 (4-C, 4'C), 109.31 (7-C, 7'C), 108.78 (3-C, 3'C), 103.59 (10-C); IR : 3412, 3057, 2923, 2849, 1625, 1579, 1481, 1449, 1116, 1089, 935, 774 cm^{-1}; LC-MS, positive mode: 407 (M+H)$^+$; purity: 99.6%. (HRMS (ESI-TOF) m/z for (C$_{27}$H$_{18}$F$_2$N$_2$; + NH$_4$ = C$_{27}$H$_{22}$F$_2$N$_3$) calcd: 426.1782. Found 426.1776.

Tris-(1*H*-indol-3-yl)methane (8k). Indole (**6b**, 0.5 g, 3.1 mmol) was treated with indole-3-carboxaldehyde (**7f**, 0.170 g, 1.5 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.356 mL, 3.1 mmol) in water (5.0 mL). The resulting yellow solid was dissolved in THF and decolorized with charcoal; White solid; m.p. 245-247 °C (lit. m.p.: 245-249 °C);[43] yield: 90%; LC-MS, positive mode 362 (M+H)$^+$; purity: 95.5%.

Di-(5-methyl-1*H*-indol-3-yl)-2-thienylmethane (8l). 5-Methylindole (**6c**, 0.5 g, 3.8 mmol) was treated with 2-thiophenecarboxaldehyde (**7g**, 0.213 mL, 1.9 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.202 mL, 3.8 mmol, 1 equiv.) in water (5.0 mL). Brown solid; m.p. 85-87 °C; yield: 81%; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 10.65 (d, *J* = 2.6 Hz, 2H, 2 x NH), 7.27 (dd, *J* = 5.1, 1.3 Hz, 1H, 14-H), 7.22 (d, *J* = 8.2 Hz, 2H, 4-H, 4'-H), 7.15 (dd, *J* = 1.7, 0.9 Hz, 2H, 6-H, 6'-H), 6.93 – 6.88 (m, 3H, 7-H, 7'-H, 13-H), 6.86 (ddd, *J* = 6.5, 2.6, 1.4 Hz, 3H, 2-H, 2'-H, 12-H), 6.03 (d, *J* = 1.0 Hz, 1H, 10-H), 2.27 (s, 6H, 2 x CH$_3$);^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 150.70 (9-C, 9'-C), 135.75 (11-C), 128.35 (5-C, 5'-C), 127.43 (8-C, 8'-C), 127.20 (12-C), 125.38 (13-C), 124.54 (14-C), 124.21 (2-C, 2'-C), 123.42 (6-C, 6'-C), 119.41 (4-C, 4'-C), 118.56 (3-C, 3'-C), 112.08 (7-C, 7'-C), 60.61 (10-C), 22.18 (2 x CH$_3$); IR : 3410, 3084, 3010, 2915, 2854, 1541, 1480, 1457, 1219, 1090, 859, 720 cm^{-1}; LC-MS, positive mode: 357 (M+H)$^+$; purity: 96.8%. HRMS (ESI-TOF) *m/z*: for (C$_{23}$H$_{21}$N$_2$S [M + H]$^+$) calcd: 357.1425. Found 357.1420.

Di-(1*H*-indol-3-yl)-4-pyridylmethane (8m). Indole (**6b**, 5 g, 4.2 mmol) was treated with 4-pyridine-carboxaldehyde (**7h**, 1.96 mL, 2.1 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (2.27 mL, 4.2 mmol, 1 equiv.) in water (5.0 mL). The resulting pink solid was dissolved in ethanol and decolorized with

charcoal; White solid; m.p. 157-159 °C (lit. m.p.: 158-161 °C);[44] yield: 94%; LC-MS, positive mode: 324(M+H)$^+$; purity: 98.2%.

Di-(4-fluoro-1*H*-indol-3-yl)-4-pyridylmethane (**8n**). 4-Fluoroindole (**6f**, 0.5 g, 3.6 mmol) was treated with 4-pyridinecarboxaldehyde (**7h**, 0.170 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol, 1 equiv.) in water (5.0 mL). Orange solid; m.p. >300 °C; yield: 79%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 2H, 2 x NH), 8.66 – 7.92 (m, 2H, 13-H, 15-H), 7.28 (d, *J* = 5.8 Hz, 2H, 12-H, 16-H), 7.19 (d, *J* = 8.2 Hz, 2H, 7-H, 7'-H), 7.01 (td, *J* = 8.0, 5.0 Hz, 2H, 6-H, 6'-H), 6.72 (d, *J* = 2.4 Hz, 2H, 5-H, 5'-H), 6.63 (dd, *J* = 11.4, 7.8 Hz, 2H, 2-H, 2'-H), 6.16 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.21 (4-C,), 155.40 (4'-C), 148.65 (11-C), 139.64 (13-C, 15-C), 139.54 (9-C, 9'-C), 124.57 (12-C, 16-C), 124.01 (2-C, 2'-C), 121.91(6-C, 6'-C), 115.54 (7-C, 7'-C), 115.51 (5-C, 5'-C), 108.27 (3-C, 3'-C), 103.71 (10-C); IR : 3207, 3085, 2999, 1748, 1698, 1634, 1577, 1347, 1224, 1090, 780 cm^{-1}; LC-MS, positive mode: 360 (M+H)$^+$; purity: 97.3%. HRMS (ESI-TOF) *m/z*: for (C$_{22}$H$_{16}$F$_2$N$_3$ [M + H]$^+$) calcd: 360.1312. Found 360.1307.

Di-(5-fluoro-1*H*-indol-3-yl)-4-pyridylmethane (**8o**). 5-Fluoroindole (**6e**, 0.5g, 3.6 mmol) was treated with 4-pyridinecarboxaldehyde (**7h**, 0.170 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol, 1 equiv.) in water (5.0 mL). The resulting pink solid was dissolved in ethanol and decolorized with charcoal; Brown solid; m.p. 192-194 °C; yield: 87%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (d, *J* = 3.0 Hz, 2H, 2 x NH), 8.78 – 8.72 (m, 2H, 13-H, 15-H), 7.94 – 7.89 (m, 2H, 12-H, 16-H), 7.38 (dd, *J* = 8.9, 4.6 Hz, 2H, 7-H, 7'-H), 7.17 (d, *J* = 2.8 Hz, 2H, 2-H, 2'-H), 7.07 (dd, *J* = 9.9, 2.7 Hz, 2H, 6-H, 6'-H), 6.92 (td, *J* = 9.2, 2.7 Hz, 2H, 4-H, 4'-H), 6.18 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.51 (5-C), 157.74 (5'-C), 155.90 (11-C), 142.45 (13-C, 15-C), 133.30 (9-C, 9'-C), 126.55 (12-C, 16-C), 126.22 (8-C, 8'-C), 124.32 (2-C, 2'-C), 114.99 (6-C, 6'-C), 113.54 (7-C, 7'-C), 112.98 (3-C, 3'-C), 109.40 (4-C, 4'-C), 103.56 (10-C); IR : 3365, 3239, 3064, 1716, 1634, 1486, 1456, 1163, 936, 800 cm^{-1}; LC-MS positive mode: 360 (M+H)$^+$; purity: 98.2%. HRMS (ESI-TOF) *m/z*: for (C$_{22}$H$_{16}$F$_2$N$_3$ [M + H]$^+$) calcd: 360.1312. Found 360.1307.

Di-(6-fluoro-1*H*-indol-3-yl)-4-pyridylmethane (**8p**). 6-Fluoroindole (**6g**, 0.5g, 3.6 mmol) was treated with 4-pyridinecarboxaldehyde (**7h**, 0.170 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol, 1 equiv.) in water (5.0 mL). The resulting pink solid was dissolved in ethanol and decolorized with charcoal ; White solid d; m.p. 219-221 °C; yield: 80%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.15 (d, *J* = 2.5 Hz, 2H, 2 x NH), 8.94 – 8.19 (m, 2H, 13-H, 15-H), 8.13 – 7.70 (m, 2H, 12-H, 16-H), 7.28 (dd, *J* = 8.7, 5.4 Hz, 2H, 4-H, 4'-H), 7.15 (dd, *J* = 10.1, 2.4 Hz, 2H, 7-H, 7'-H), 7.00 (d, *J* = 2.4 Hz, 2H, 2-H, 2'-H), 6.78 (ddd, *J* = 9.6, 8.7, 2.4 Hz, 2H, 5-H, 5'-H), 6.18 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.01 (6-C), 158.15 (6'-C), 142.92 (11-C), 136.51 (13-C, 15-C), 126.13 (9-C, 9'-C), 125.14 (12-C, 16-C), 123.13 (8-C, 8'-C), 119.90 (2-C, 2'-C), 117.33 (7-C, 7'-C), 115.18 (4-C, 4'-C), 107.28 (5-C, 5'-C), 97.89 (10-C); IR : 3734, 3648, 3208, 1716, 1625, 1541, 1456, 1252, 950, 803 cm^{-1}; LC-MS, positive mode: 360 (M+H)$^+$; purity: 98.5%. HRMS (ESI-TOF) *m/z*: for (C$_{22}$H$_{16}$F$_2$N$_3$ [M + H]$^+$) calcd: 360.1312. Found 360.1307.

Di-(7-fluoro-1*H*-indol-3-yl)-4-pyridylmethane (**8q**). 7-Fluoroindole (**6h**, 0.5g, 3.6 mmol) was treated with 4-pyridinecarboxaldehyde (**7h**, 0.170 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol, 1 equiv.) in water (5.0 mL). White solid; m.p. 242-244 °C; yield: 77%; δ ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.61 (d, *J* = 2.5 Hz, 2H, 2 x NH), 8.87 – 8.53 (m, 2H, 13-H, 15-H), 7.98 – 7.71 (m, 2H, 12-H, 16-H), 7.14 (dd, *J* = 7.3, 1.3 Hz, 2H, 4-H, 4'-H), 7.09 (d, *J* = 2.5 Hz, 2H, 5-H, 5'-H), 6.96 – 6.73 (m, 4H, 6-H, 6'-H, 2-H, 2'-H), 6.23 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.99 (7-C, 7'-C), 150.38 (13-C, 15-C), 148.44 (11-C), 142.64 (9-C, 9'-C), 126.28 (8-C, 8'-C), 125.71 (12-C, 16-C), 119.33 (2-C, 2'-C), 116.00 (4-C, 4'-C), 115.99 (5-C, 5'-C), 115.13 (3-C, 3'-C), 106.57 (6-C, 6'-C), 106.47 (10-C); IR : 3208, 3065, 3009, 1748, 1716, 1634, 1576, 1447, 1224, 975, 779 cm^{-1}; LC-MS, positive mode: 360 (M+H)$^+$; purity: 96.1%. HRMS (ESI-TOF) *m/z*: for (C$_{22}$H$_{16}$F$_2$N$_3$ [M + H]$^+$) calcd: 360.1312. Found 360.1307.

Di-(5-chloro-1*H*-indol-3-yl)-4-pyridylmethane (8r). 5-Chloroindole (**6i**, 0.5 g, 3.1 mmol) was treated with 4-pyridinecarboxaldehyde (**7g**, 0.168 mL, 1.5 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.356 mL, 3.1 mmol) in water (5.0 mL). The resulting pink solid was dissolved in ethanol and decolorized with charcoal; White solid; m.p. 292-294 °C; yield: 86%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.12 (d, *J* = 2.6 Hz, 2H, 2 x NH), 8.53 – 8.32 (m, 2H, 13-H, 15-H), 7.38 (d, *J* = 8.6 Hz, 2H, 12-H, 16-H), 7.34 – 7.31 (m, 2H, 6-H, 6'-H), 7.30 (d, *J* = 2.0 Hz, 2H, 4'-H, 4'-H), 7.04 (dd, *J* = 8.6, 2.1 Hz, 2H, 7-H, 7'-H), 6.99 (d, *J* = 2.5 Hz, 2H, 2'-H, 2'-H), 5.90 (s, 1H, 10-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.77 (13-C, 15-C), 142.19 (11-C), 135.12, (9-C, 9'-C), 127.42,(12-C, 16-C), 126.33 (5-C, 5'-C), 123.60 (8-C, 8'-C), 121.57 (2-C, 2'-C), 121.25 (4-C, 4'-C), 117.95 (6-C, 6'-C), 114.70 (7-C, 7'-C), 113.54 (3-C, 3'-C), 113.30 (10-C); IR : 3201, 3076, 2974, 2884, 1632, 1589, 1496, 1347, 1225, 1046, 895, 789 cm^{-1} ; LC-MS, positive mode: 393 (M+H)$^+$; purity: 98.2%. HRMS (ESI-TOF) *m/z*: for ($C_{22}H_{15}Cl_2N_3$ [M + H]$^+$) calcd: 392.0712. Found 392.0716.

1,1-Di-(5-fluoro-1*H*-indol-3-yl)propane (8s). 5-Fluoroindole (**6e**, 1.0 g, 6.7 mmol) was treated with propionaldehyde (**7i**, 0.197 mL, 3.3 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.356 mL, 6.7 mmol) in water (5.0 mL). The resulting green viscous oil was dissolved in THF and decolorized with charcoal ; Yellow viscous oil; yield: 61%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (d, *J* = 2.5 Hz, 2H, 2 x NH), 7.35 (d, *J* = 2.4 Hz, 2H, 2-H, 2'-H), 7.26 (dd, *J* = 8.8, 4.6 Hz, 2H, 7-H, 7'-H), 7.14 (dd, *J* = 10.3, 2.6 Hz, 2H, 4-H, 4'-H), 6.81 (td, *J* = 9.2, 2.6 Hz, 2H, 6-H, 6'-H), 4.16 (t, *J* = 7.6 Hz, 1H, 10-CH), 2.14 (p, *J* = 7.4 Hz, 2H, 11-CH$_2$), 0.88 (t, *J* = 7.3 Hz, 3H, 12-CH$_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.63 (5-C, 5'-C), 133.29 (9-C, 9'-C), 126.94 (8-C, 8'-C), 124.34 (2-C, 2'-C), 118.73 (3-C, 3'-C), 112.27 (6-C, 6'-C), 108.89 (7-C, 7'-C), 108.72 (4-C, 4'-C), 40.11 (10-C), 27.60 (11-C), 13.02 (12-C); IR : 3462, 2420, 2959, 2925, 2869, 1868, 1578, 1480, 1166, 935, 792 cm^{-1} ; LC-MS, positive mode: 328 (M+H$_2$O)$^+$; purity: 98.2%. HRMS (ESI-TOF) *m/z*: for ($C_{19}H_{17}F_2N_2$ [M + H]$^+$) calcd: 311. 1360 Found 311. 1354.

1,1-Di-(7-fluoro-1*H*-indol-3-yl)-2-methylpropane (8t). 7-Fluoroindole (**6h**, 0.5g, 3.6 mmol) was treated with isobutyraldehyde (**7j**, 0.150 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol) in water (5.0 mL). The resulting purple colored viscous oil was dissolved in THF and decolorized with charcoal ;Light Brown oil ; yield: 76%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (d, *J* = 2.2 Hz, 2H, 2 x NH), 7.40 (d, *J* = 7.8 Hz, 2H, 4-H, 4'-H), 7.37 (d, *J* = 2.5 Hz, 2H, 2-H, 2'-H), 6.90 –6.80 (m, 2H, 5-H, 5'-H), 6.81 – 6.73 (m, 2H, 6-H, 6'-H), 4.09 (d, *J* = 9.4 Hz, 1H, 10-H), 2.76 – 2.56 (m, 1H, 11-H), 0.91 (d, *J* = 6.5 Hz, 6H, 12- and 13-CH$_3$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.30 (7-C, 7'-C), 148.38 (9-C, 9'-C), 131.35 (2-C, 2'-C), 123.99 (8-C, 8'-C), 119.22 (5-C, 5'-C), 118.36 (4-C, 4'-C), 115.34 (3-C, 3'-C), 115.32 (6-C, 6'-C), 105.54 (10-C), 31.82(12-C), 20.21 (12-and 13-C); IR : 3472, 3419, 2957, 2927, 2868, 1705, 1638, 1497, 1221, 785 cm^{-1} ; LC-MS, positive mode: 325 (M+H)$^+$; purity: 95.2%. HRMS (ESI-TOF) *m/z*: for ($C_{20}H_{19}F_2N_2$; NH$_4$ = $C_{20}H_{22}F_2N_3^+$) calcd: 342. 1782 Found 342. 1776.

1,1-Di-(4-methoxy-1*H*-indol-3-yl)-2-methylpropane (8u). 4-Methoxyindole (**6a**, 1.0 g, 6.7 mmol) was treated with isobutyraldehyde (**7j**, 0.197 mL, 3.3 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.356 mL, 6.7 mmol) in water (10.0 mL). The crude compound purified by recrystallization using CHCl$_3$; White solid; m.p. 189-191°C; yield: 72%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.62 (d, *J* = 2.1 Hz, 2H, 2 x NH), 6.99 (d, *J* = 2.4 Hz, 2H, 2-H, 2'-H), 6.91 – 6.80 (m, 4H, , 6-H, 6'-H, 7-H, 7'-H), 6.37 (dd, *J* = 6.8, 1.7 Hz, 2H, 5-H, 5'-H), 5.23 (s, 1H, 10-CH), 3.81 (s, 5H, 2 x OCH$_3$), 2.33 (s, 1H, 11-CH), 0.86 (d, *J* = 6.6 Hz, 6H, 12-CH$_3$ and 13-CH$_3$); ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.65 (4-C, 4'-C), 137.57 (9-C, 9'-C), 122.20 (6-C, 6'-C), 121.17 (2-C, 2'-C), 120.20 (8-C, 8'-C), 117.62 (3-C, 3'-C), 104.73 (7-C, 7'-C), 98.81(5-C, 5'-C), 54.86 (10-C), 40.11 (2 x OCH$_3$), 21.70 (11-C), 14.30 (12-C, 13-C). IR : 3388, 3300, 2923, 2853, 1717, 1614, 1575, 1507, 1349, 1252, 1069, 968, 774 cm^{-1}; LC-MS, positive mode 328 (M+H$_2$O)$^+$; purity: 95.2%. HRMS (ESI-TOF) *m/z*: for ($C_{22}H_{25}N_2O_2$ [M + H]$^+$) calcd: 349.1916 Found 349.1911.

(Cyclopropyl)di-(5-methyl-1*H*-indol-3-yl)methane (8v). 5-Methylindole (**6c**, 0.5 g, 3.8 mmol) was stirred with cyclopropanecarboxaldehyde (**7k**, 0.143 mL, 1.9 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.202 mL, 3.8 mmol, 1 equiv.) in water (5.0 mL). Brown solid; m.p. 164-166 °C; yield: 83%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.85 (br s, 2H, 2 x NH), 7.29 − 6.98 (m, 6H, 4-H, 4'-H, 6-H, 6'-H, 7-H, 7'-H), 6.79 (dd, J = 8.2, 1.6 Hz, 2H, 2-H, 2'-H), 3.71 (d, J = 8.6 Hz, 1H, 10-H), 2.25 (s, 6H, 2 x CH$_3$), 1.59 (qt, J = 8.1, 4.9 Hz, 1H, 11-H), 0.64 − 0.38 (m, 2H, 12-CH$_2$), 0.33 − 0.16 (m, 2H, 13-CH$_2$). ^{13}C NMR (126 MHz, DMSO-d_6) δ 135.00 (9-C,9'-C), 127.22 (5-C, 5'-C), 126.15 (8-C, 8'-C), 122.45 (2-C, 2'-C), 122.24 (6-C, 6'-C), 118.86 (4-C, 4'-C), 118.20 (3-C, 3'-C), 111.10 (7-C, 7'-C), 37.91 (10-C), 21.46 (2 x CH$_3$), 16.92 (11-C), 4.98 (12- and 13-CH$_2$); IR : 3401, 3074, 2994, 2917, 2855, 1719, 1577, 1542, 1419, 1240, 1089, 791 cm^{-1} ; LC-MS, positive mode: 315 (M+H)$^+$; purity: 95.2%. HRMS (ESI-TOF) *m/z*: for (C$_{22}$H$_{23}$N$_2$; Na = C$_{22}$H$_{22}$N$_2$Na$^+$) calcd: 337.1681 Found 337.1675.

(Cyclohexyl)di-(5-fluoro-1*H*-indol-3-yl)methane (8w). 5-Fluoroindole (**6e**, 0.5g, 3.6 mmol) was treated with cyclohexanecarboxaldehyde (**7l**, 0.219 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol) in water (5.0 mL). Brown viscous oil; yield: 87%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (d, J = 2.5 Hz, 2H, 2 x NH), 7.41 (d, J = 2.5 Hz, 2H, 2-H, 2'-H), 7.29 (dd, J = 10.4, 2.6 Hz, 2H, 7-H, 7'-H), 7.24 (dd, J = 8.8, 4.6 Hz, 2H, 4-H, 4'-H), 6.80 (td, J = 9.1, 2.6 Hz, 2H, 6-H, 6'-H), 4.04 − 3.98 (m, 1H, 10-H), 2.24 (td, J = 11.0, 7.6 Hz, 1H, 11-H), 1.77 − 1.52 (m, 2H, cychex-CH$_2$), 1.53 − 1.34 (m, 1H, cychex-CH), 1.33 − 1.18 (m, 2H, cychex-CH$_2$ &-CH), 0.97 − 0.68 (m, 4H, 2 x cychex-CH$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.44 (5-C, 5'-C), 132.93 (9-C, 9'-C), 132.93 (8-C, 8'-C), 127.46, (2-C, 2'-C), 124.51 (6-C, 6'-C), 112.10 (3-C, 3'-C), 108.57 (7-C, 7'-C), 103.58 (4-C, 4'-C), 59.07 (10-C), 31.91 (11-C), 26.01 (2 x cychex-C), 14.21 (3 x cychex-C); IR : 3467, 3421, 2922, 2849, 1716, 1626, 1578, 1482, 1374, 1168, 936, 794 cm^{-1} ; LC-MS, positive mode 360 (M+H)$^+$; purity: 95.5%. HRMS (ESI-TOF) *m/z*: for (C$_{23}$H$_{23}$F$_2$N$_2$ [M +H]$^+$) calcd: 365.1829 Found 365.1824.

Methyl 5,5-di-(4-fluoro-1*H*-indol-3-yl)butanoate (8x). 4-Fluoroindole (**6f**, 0.5g, 3.6 mmol) was treated with 4-oxobutanoic acid methyl ester (**7m**, 0.209 mL, 1.8 mmol, 0.5 equiv.) in the presence of concentrated sulfuric acid (0.196 mL, 3.6 mmol) in water (5.0 mL). White solid; m.p. 147-149 °C; yield: 56%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 2H, 2 x NH), 7.14 (d, J = 8.1 Hz, 2H, 6-H, 6'-H), 7.04 (d, J = 2.4 Hz, 2H, 2-H, 2'-H), 6.97 (td, J = 7.9, 4.9 Hz, 2H, 5-H, 5'-H), 6.68 − 6.60 (m, 2H, 7-H, 7'-H), 4.70 (t, J = 6.8 Hz, 1H, 10-H), 3.50 (s, 3H, COOCH$_3$), 2.39 − 2.28 (m, 4H, 12-CH$_2$ and 11-CH$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.34 (COOH), 157.45 (4-C, 4'-C), 155.51 (9-C, 9'-C), 139.37 (2-C, 2'-C), 122.85 (6-C, 6'-C), 121.41 (8-C, 8'-C), 121.35 (5-C, 5'-C), 117.45 (7-C, 7'-C), 108.07 (3-C, 3'-C), 103.62 (10-C), 51.21 (COOCH$_3$), 34.17 (11-C), 32.69 (121-C); IR : 3395, 3331, 2959, 2923, 2851, 2310, 1748, 1695, 1503, 1435, 1253, 1031, 777 cm^{-1} ; LC-MS, positive mode: 386 (M+H$_2$O)$^{18+}$; purity: 96.2%. HRMS (ESI-TOF) *m/z*: for (C$_{21}$H$_{18}$F$_2$N$_2$O$_2$; NH$_4$ = C$_{21}$H$_{2''}$F$_2$N$_3$O$_2$$^+$) calcd: 386.1680 Found calcd: 386.1675.

Synthesis of 5,5-di-(4-fluoro-1*H*-indol-3-yl)butanoic acid (8y)
To a solution of methyl 5,5-di-(4-fluoro-1*H*-indol-3-yl)pentanoate (**8x**, 50 mg) in ethanol (10 mL) 2 *N* NaOH (5 mL) was added and the mixture was refluxed for 1 h. After cooling the mixture, the ethanol was evaporated under reduced pressure. The resulting residue was dissolved in water and acidified with 6 *N* HCl to pH ≤ 1. The precipitated solid was filtered off, washed with water and dried at room temperature for 24 h. White solid; m.p. 169-171 °C; yield: 97%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H, COOH), 11.05 (s, 2H, 2 x NH), 7.14 (d, J = 8.2 Hz, 2H, 6-H, 6'-H), 7.04 (d, J = 2.4 Hz, 2H, 2-H, 2'-H), 6.97 (td, J = 8.0, 4.9 Hz, 2H, 5-H, 5'-H), 6.64 (dd, J = 11.6, 7.7 Hz, 2H, 7-H, 7'-H), 4.69 (t, J = 7.4 Hz, 1H, 10-H), 2.31 (q, J = 7.5 Hz, 2H, 12-CH$_2$), 2.23 (dd, J = 8.5, 6.0 Hz, 2H, 11-CH$_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.51 (COOH), 157.46 (4-C, 4'-C), 155.52, (9-C, 9'-C), 139.47 (2-C, 2'-C), 122.79 (6-C, 6'-C), 121.38 (8-C, 8'-C), 121.32, (5-C, 5'-C) 117.67 (7-C, 7'-C), 108.06 (3-C, 3'-C), 103.60 (10-C), 34.22 (11-C), 33.00 (12-C); IR : 3440, 3340, 2994, 2922, 2853, 1685, 1578, 1507, 1348, 1221, 1031, 908, 730 cm^{-1} ; LC-MS, positive mode: 355 (M+H)$^+$; purity: 96.3%. HRMS (ESI-TOF) *m/z*: for (C$_{20}$H$_{16}$F$_2$N$_2$O$_2$; NH$_4$ = C$_{20}$H$_{20}$F$_2$N$_3$O$_2$$^+$) calcd: 372.1518 Found calcd: 372.1518.

Acknowledgements

Supplementary Material

Characterization data (for all new products), copies of ^{1}H and ^{13}C NMR, HRMS and IR spectra associated with this paper.

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