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Fascaplysin-inspired diindolyls as selective inhibitors of CDK4/cyclin D1

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ABSTRACT

We present the design, synthesis and biological activity of a new series of substituted 3-(2-(1*H*-indol-1-yl)ethyl)-1*H*-indoles and 1,2-di(1*H*-indol-1-yl)alkanes as selective inhibitors of CDK4/cyclin D1. The compounds were designed to explore the relationship between the connection mode of the indolyl moieties and their CDK inhibitory activities. We found all the above-mentioned designed compounds to be selective inhibitors of CDK4/cyclin D1 compared to the closely related CDK2/cyclin A, with IC_{50} for the best compounds **10m** and **13a** being 39 and 37 μm, respectively.

1. Introduction

The cyclin dependent kinases (CDKs) are a family of enzymes playing a key role as regulators of the eukaryotic cell division cycle,[1] the inhibition of these enzymes by small molecules is an area of major current interest in the anti-cancer field.[2] In particular, recent studies have shown that misregulation of CDK4 activity can lead to cancer, suggesting that inhibition of CDK4 could be of therapeutic benefice in cancer therapy.[2f,3] Conversely, inhibition of CDK2 which is often postulated as a cancer target, may not be as useful as initially proposed.[4] Consequently, the development of small molecule inhibitors of CDK4 which are specific compared to CDK2, is a very promising area of research.

The oxidised diindolyl derivative Indirubin **1,** is the active component from the traditional Chinese medicine 'Danggui Longhui Wan'.[5] Compound **1** is a selective inhibitor of a range of CDKs compared to other protein kinases.[6] Anticancer activity is not only a property of the oxidised indole rings of **1** as shown by the fact that 3,3′-diindolylmethane (DIM) **2**, a metabolic product of indole-3-carbinol, induces cell cycle arrest in the G_1 phase in human breast cancer cells by activation of the protein p21 (an endogenous inhibitor of CDKs).[7] The more complex diindolyl compound staurosporine **3**,[8] is an excellent unspecific inhibitor of many protein kinases, the lack of specificity is attributed to the binding mode of staurosporine closely mimicking that of ATP.[9]

In contrast with the examples mentioned above of diindolyl containing compounds **1**–**3**, molecules displaying a potent but non-specific CDK inhibitory activity, the marine natural product fascaplysin **4**[10] is one of the few CDK4/cyclin D1-specific inhibitors known,[11] with an IC_{50} = 0.55 μM.[12] Fascaplysin **4** has been considered for therapeutic trials,[13] although ultimately its use as anticancer drug is limited by its toxicity to normal cells, which is a result of its planar structure acting as a DNA intercalating agent.[14]

In terms of chemical structure, fascaplysin **4** is a combination of an indole and an oxindole ring connected through a covalent link between, respectively, the 2 and 3 positions of one indole ring and 1 and 2 positions of the second modified indole moiety (a '2,2-linkage' plus a '1,3-linkage', Fig. 2). In contrast, compounds **1**–**3** show different connection modes ('linkages') between the diindolyl (or modified diindolyl) subunits (Fig. 1).

In recent times our research group has been interested in the design, synthesis and biological evaluation of non-planar (non-toxic) analogues of fascaplysin **4** as CDK4/ cyclin D1-specific inhibitors.[15] In our previous work, the structure of **4** was simplified and/or modified in an effort to establish the key points in the mode of interaction between the designed fascaplysin-based compounds and the CDK4/cyclin D1 complex. Furthermore, the lack of toxicity of some of those fascaplysin-inspired derivatives (with tryptamine and tetrahydro-β-carboline derivatives was also reported, showing the potential of the designed strategy to obtain non-toxic and selective inhibitors of CDK4/cyclin D1.[15f,g]

Establishing the hypothesis that the mode of connection of the indolyl subunits in fascaplysin **4** (and other diindolyl compounds)

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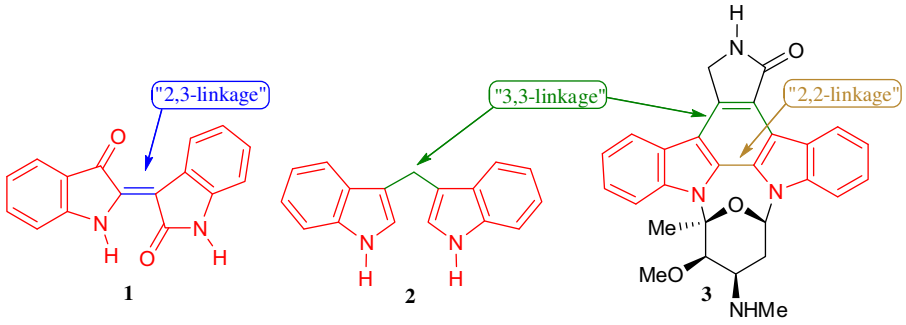


Figure 1. Selected diindolyl-based non-specific inhibitors of CDKs. The diindolyl or dioxindolyl moieties, and their connection modes ('linkages'), are highlighted in colours for clarity.

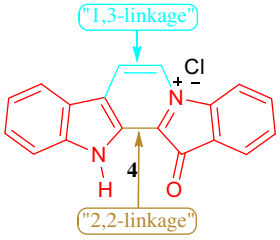


Figure 2. The natural pigment fascaplysin **4**. The modified diindolyl moiety, and its connection mode ('linkage'), is highlighted in colours for clarity.

is correlated with its specificity among the different CDKs, we describe in full our results on an investigation of this premise and its application to the discovery of selective CDK4/cyclin D1 inhibitors structurally inspired in the model compound fascaplysin **4**. Hence, two series of type **I**/**II** '1,3 or 1,1-linked' diindolyl compounds (Fig. 3) were designed, synthesised and evaluated for their CDK4/cyclin D1 and CDK2/cyclin A activities in order to corroborate our hypothesis.

2. Results and discussion

2.1. Design

In the preliminary publication on this work,[16] we reported the design and synthesis of non-planar fascaplysin analogues which might have good activity without the toxic side effects of the model compound. For that purpose, we considered the cleavage of bond *a* in structure **4**, the removal of the ketone at *b* and changing the double bond at *c* into a single bond leading to type **I** target compounds (Fig. 3). A further modification in the connection mode between the diindolyl moieties could lead us to the type **II** '1,1-linked' diindolyl target compounds.

In addition, concerning type **I** compounds, those were designed to explore the effect of a different pattern of substitution on position 5 and/or 5′ of the diindole scaffold; whilst type **II** compounds were intended to explore the influence of the size of the carbon chain linker on the CDK4/cyclin D1 inhibitory activity.

Before embarking on the synthesis of potential inhibitors we carried out in silico docking of the proposed type **I**/**II** compounds **10e–n** (Scheme 1) and **13a–e** (Scheme 2) in the active site of our homology model of CDK4[15a,b] using the program Gold.[17] All the compounds were predicted to exhibit CDK4 activity binding in the active site of the enzyme in a mode overlapping fascaplysin **4**. The predicted binding 'energies' (Goldscores) were in all the cases >40, demonstrating that the project could be, *a priori*, viable.[18]

2.2. Synthesis of substituted 3-(2-(1*H*-indol-1-yl)ethyl)-1*H*-indoles: type I target compounds

Type **I** target compounds **10e–n** (Scheme 1) were synthesised using the methodology optimised in our previous work.[16] In this manner, the corresponding indole derivative **5a–d** was reacted with oxalyl chloride affording the consequent indolyl-oxo-acetyl

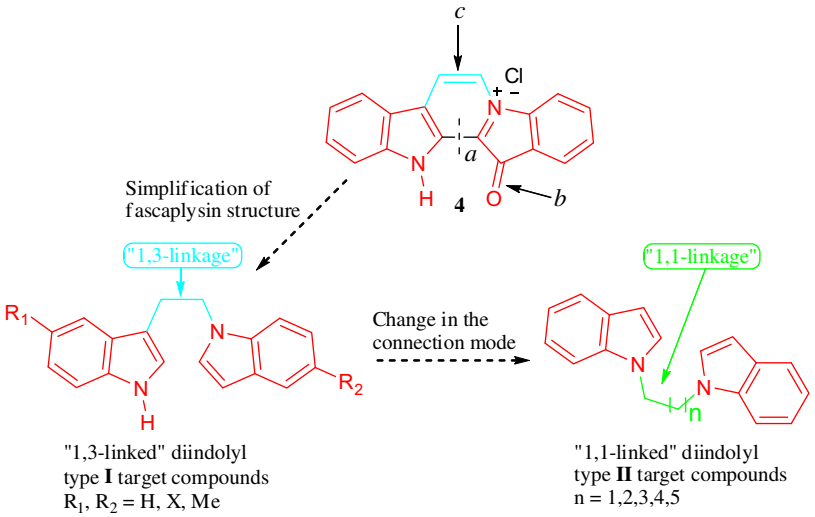
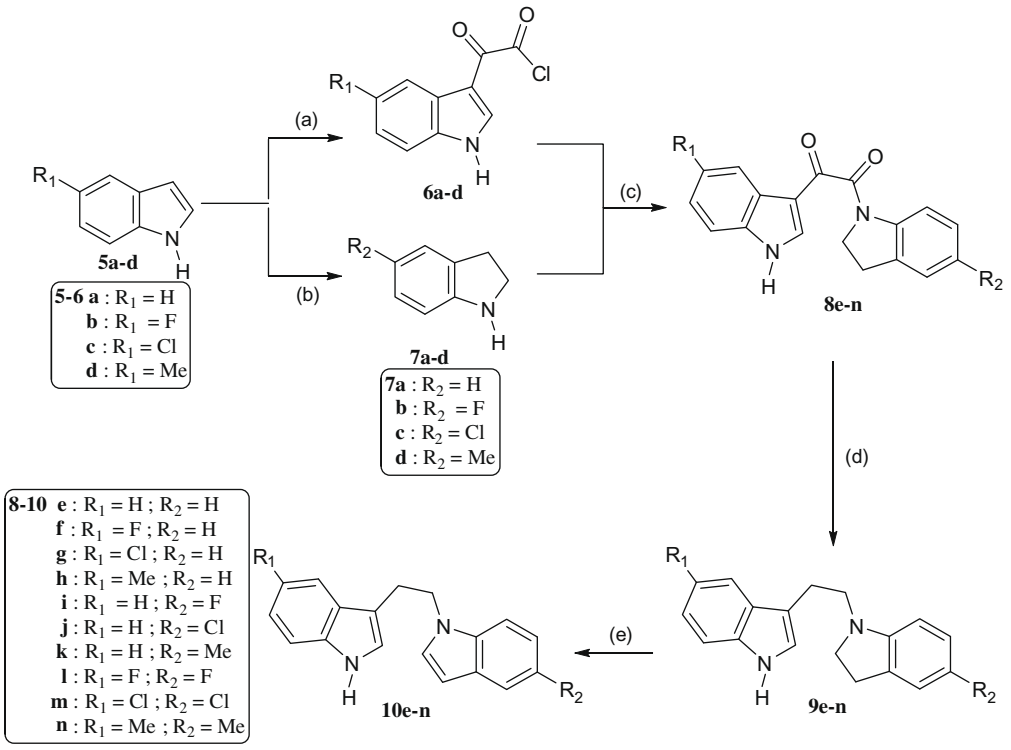
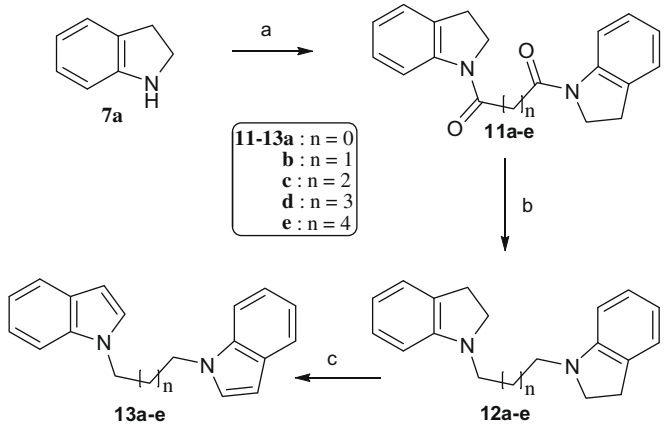


Figure 3. Strategy planned to convert fascaplysin **4** into type **I**/**II** '1,3 or 1,1-linked' diindolyl target compounds.



Scheme 1. Synthesis of type **I** target compounds **10e**–**n**: Reagents and conditions. (a) $(COCl)_2$, anhydrous ether, N_2, 0–5 °C, 1.5 h, 80–91%; (b) $NaBH_3CN$ 95%, glacial acetic acid, N_2, 15–17 °C, 2 h, 85–90%; (c) **6** in anhydrous THF, K_2CO_3, N_2, **7** was added at 0 °C, stir 2 h at rt, 78–90%; (d) $LiAlH_4$, anhydrous THF, anhydrous ether, N_2, reflux, 6 h, 57–99%; (e) activated MnO_2, $CHCl_3$, reflux, 60 h, 41–84%.



Scheme 2. Synthesis of type **II** target compounds **13a**–**e**. Reagents and conditions: (a) $ClCO(CH_2)_nCOCl$, K_2CO_3, anhydrous THF, N_2, 0 °C, 1.5 h, 69–87%; (b) $LiAlH_4$, anhydrous THF, anhydrous ether, N_2, reflux, over night, 36–76%; (c) activated MnO_2, $CHCl_3$, reflux, 60 h, 30–75%.

derivative **6a**–**d** in 80–91%.[19] Conversely, reduction of **5a**–**d** with cyanoborohydride in glacial acetic acid produced indolines **7a**–**d** in good yield,[20] Coupling of **6a**–**d** with **7a**–**d** under basic conditions afforded the indolyl-dihydro-indolyl-ethane diones **8e**–**n** with excellent yields.[21] Reduction of the carbonyl groups,[22] and further aromatization of the corresponding indoline subunit produced the desired target compounds **10e**–**n** in 41–84% yields.[21]

2.3. Synthesis of 1,2-di(1*H*-indol-1-yl)alkanes: type II target compounds

Synthesis of the type **II** target compounds **13a–e** was achieved in a similar fashion than for type **I** molecules. Two equivalents of the indoline **7a** were reacted with the corresponding acyl chloride to give the bis-dihydro-indolyl-ethane-diones (**11a–e**) in 69–87% yield. In some cases the yield could be improved by adding 3 equiv of indoline instead of two. Reduction of **11a–e** with lithium aluminium hydride gave the respective bis-dihydro-indolyl-ethane **12a–e** in 36–76% yield.[22] Final oxidation was performed using activated manganese(IV) oxide.[21] Under these conditions, the desired bis-indolyl-alkanes **13a–e** were obtained in 67–75% yield.

2.4. Biological evaluation. Selective inhibition of CDK4 versus CDK2

The type **I**/**II** target compounds **10e**–**n** and **13a**–**e**, as well as the synthetic intermediates **8e**–**n** and **12a**–**e**, were assayed in vitro. IC_{50} values were measured for inhibition of CDK4/cyclin D1 and CDK2/cyclin A using previously reported methods (see Section 4 for further details), and the results are shown in Table 1.

The first striking observation is that, as we expected, we have indeed achieved selectivity for CDK4 over CDK2 in almost all the compounds tested. Unfortunately, none of the compounds designed achieved the nM CDK4 inhibition activity displayed by the model compound fascaplysin **4** (Table 1, entry 1).

For type **I** target compounds **10e**–**n** and their synthetic dicarbonyl intermediates **8e**–**n** (Scheme 2), an increased CDK4 activity comes out for the 5,5′-disubstituted compounds **8l**–**n**/**10l**–**n** (Table 1, entries 9–11 and 19–21) compared with the monosubstituted analogues **8e–k**/**10e–k** (Table 1, entries 2–8 and 12–18). Figure 4 shows the most active compound of the type **I** series, **10m** (IC_{50} = 39 μM, Table 1, entry 20), docked in the active site of our CDK4 homology model, this indicates a possible hydrogen bond between the indole NH and the carbonyl group of valine 96. The other indole ring is close to the phenylalanines 93 and 159, where there is the strong possibility of π-stacking interactions. This fact is supported by our previous findings postulating the existence of a

Table 1
CDK4 activity versus CDK2 activity

Entry	Compound	CDK4 inhibition[a] IC_{50}/μM	CDK2 inhibition[b] IC_{50}/μM
1	**4**	0.55[12]	500[12]
2	**8e**	122	760
3	**8f**	116	1160
4	**8g**	96	985
5	**8h**	41.5	951
6	**8i**	136	790
7	**8j**	69.5	1030
8	**8k**	54	910
9	**8l**	48	816
10	**8m**	43.5	915
11	**8n**	38	710
12	**10e**	>500	>500
13	**10f**	50	200
14	**10g**	>500	>500
15	**10h**	150	400
16	**10i**	95	>500
17	**10j**	140	430
18	**10k**	130	500
19	**10l**	73	895
20	**10m**	38	862
21	**10n**	44	960
22	**12a**	66	1230
23	**12b**	Insoluble	Insoluble
24	**12c**	Insoluble	Insoluble
25	**12d**	Insoluble	Insoluble
26	**12e**	Insoluble	Insoluble
27	**13a**	37	940
28	**13b**	38	1070
29	**13c**	45	1026
30	**13d**	52	950
31	**13e**	106	1210

[a] CDK4/cyclin D1 assay, using GST-RB152 fusion protein as substrate.
[b] CDK2/cyclin A assay using Histone H1 as substrate (see Section 4 for further details).

π-stacking pocket ('Phe 93 pocket') within the active site of CDK4.[15b,d,e] The parent diindolyl compound **10e** is essentially inactive, an IC_{50} of 44 μM is obtained in **10n** by the introduction of two methyl groups, the introduction of one fluorine in **10f** and two fluorines in **10l** leads to IC_{50} values of 50 and 73 μM, respectively, while the introduction of 2 chlorine substituents in **10m** gave an IC_{50} of 39 μM. The electronic effect of these halogens appears to be markedly improving the π-stacking,[23] and hence, IC_{50} for CDK4 inhibition. In the case of indole–indolinyl compound **9e** the IC_{50} is 122 μM, substitution by methyl, fluoro and chloro groups lead to IC_{50}'s in the range 38–48 μM. Both series of compounds have broadly similar substituent effects.

Concerning the '1,1-linked' type **II** target compounds **13a–e** (Scheme 2), those presented a clear trend in its CDK4 inhibitory activities. In essence, as the carbon chain increases in length, the inhibition decreases. For the synthetic dicarbonyl intermediates **12a–e**, due to the lack of solubility of those compounds in the conditions required for the inhibition tests, the inhibition activities could only be measured for compound **12a**, that displayed the same patron of strong CDK4 selectivity compared with CDK2 (IC_{50}'s of 66 and 1230 μM, respectively). The most active compound of the series, **13a** showed an IC_{50} of 37 μM and its conformation docked on the active site of the CDK4 is shown in Figure 5.

As for type **I** target compounds, a strong evidence of a π-stacking interaction into the 'Phe 93 pocket' was found.

3. Conclusions and further work

We have prepared a library of '1,1-linked' and '1,3-linked' diindolyl compounds of type **I**/**II** (**10e–n**/**13a–e**) using a straightforward synthetic approach. These compounds (as well as their synthetic dicarbonyl intermediates **8e–n**/**12a**), displaying a selectivity for CDK4/cyclin D1 over CDK2/cyclin A, corroborate our hypothesis that the connection mode between the indole subunits for these simplified non-planar fascaplysin **4** derivatives is important for the selectivity among the above-mentioned kinases.

Docking of the most active compounds of the series into the active site of the enzyme, **10m** (IC_{50} = 39 μM) and **13a** (IC_{50} = 37 μM), illustrate our previous findings of the existence of a π-stacking pocket (namely the 'Phe 93 pocket') within the active site of CDK4.[15b,d,e]

The above-mentioned results could be considered a good starting point for the optimisation of the observed biological activity as CDK4 selective inhibitors of these fascaplysin-related non-planar compounds. Further work is also planned with the aim of synthesise different kinds of analogues modifying the nature of the connection mode and/or the linker joining the indole subunits as well as the pattern of substitution on the indolyl subunits.

4. Experimental

4.1. Bio assays

Expression and purification of CDK4/GST-CyclinD1, CDK2/GST-CyclinA and GST-RB152. Fusion proteins of human cyclins A and D1, covalently linked to glutathione s-transferase (GST), were co-expressed with the catalytic subunits CDK2 and CDK4 in Sf-9 insect cells as described previously.[24–28]

Active enzyme complexes, containing a catalytic subunit bound to GST-Cyclin, were bound to glutathione–agarose columns (Sigma, Cat. No. G3907) and were eluted from the columns with reduced glutathione. The reduced glutathione was removed by

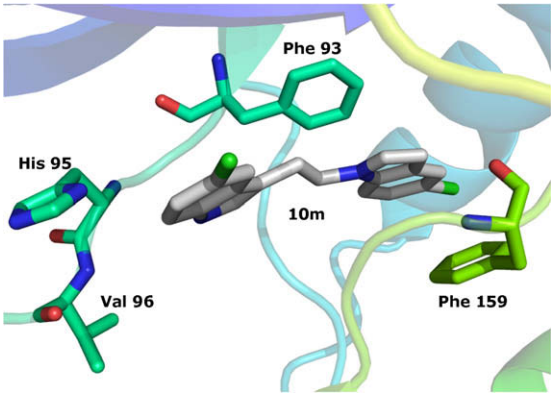


Figure 4. Compound **10m** docked into our CDK4 homology model.

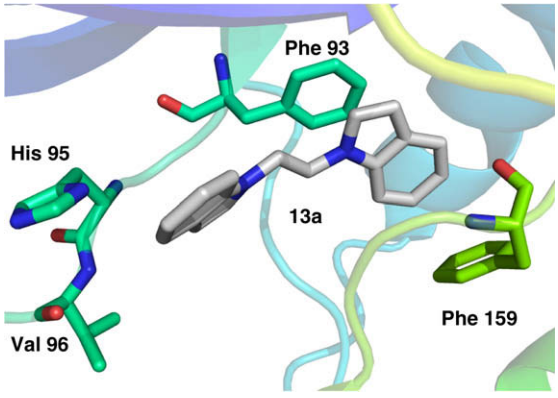


Figure 5. Compound **13a** docked into our CDK4 homology model.

dialysing the enzymes in 10,000 MCO dialysis cassettes (Pierce, Cat No. 66830) with two buffer changes.

The GST-RB152 fusion construct was transformed into the *Escherichia coli* strain BL21(DE3)pLysS (Novagen Cat. No 69451-4). For expression of GST-RB152, the cells were induced in the presence of a final concentration of 4 mM isopropyl-β-thiogalactopyranoside (IPTG, Invitrogen Cat. No. 15529-091) and were allowed to grow for 4 h in a shaking incubator at 37 °C and 220 rpm. Purification of the GST-RB152 protein was carried out as described previously.[24] Protein estimation was performed using the Bradford protein assay (Bio-Rad Laboratories) with bovine serum albumin (BSA) as the standard and the purity of the fusion protein was assessed by SDS–PAGE analysis. Proteins were stained with Coomassie blue for visualisation.

Kinase assays and IC_{50} determination. The assay measures the depletion in ATP concentration as a result of phosphorylation of retinoblastoma (GST-RB152) and Histone H1 (Upstate Biotech Cat. No. 14-155) by CDK4 and CDK2, respectively. The assay was run in a 96 well format and all steps in one assay were carried out in a single white polystyrene plate (Sarstedt, Catalogue No. DPS-134-050A). The compounds were dissolved in DMSO as 10 mM stock solutions. Compounds were further serially diluted in kinase buffer (40 mM Tris (pH 7.5), 20 mM $MgCl_2$, 0.1 mg/ml BSA) in order to obtain the desired concentrations. The kinase assay was performed in 50 μL of kinase buffer containing 2 μg of purified GST-RB152 (in case of Cdk4/GST-cyclin D1) or 3 μg of Histone H1 (in case of Cdk2/GST-cyclin A) and 6 μM ATP. The phosphatase and protease inhibitor cocktail containing β-glycerophosphate, sodium fluoride and sodium orthovanadate in the presence of reducing agent dithiothreitol was added at the final concentrations of 10 mM, 0.1 mM, 0.1 mM and 1 mM, respectively. The assay was initiated by adding 200 ng of active enzyme complexes and the plate was incubated for 30 min at 30 °C in a humidified incubator. The reaction was stopped by addition of equal volume of the Kinase Glow Reagent™ (Promega Cat. No. V6711). The luminescence was measured using the Packard Luminometer (Fusion 3.50) and the rate of ATP depletion (rate of reaction) in the control blank reactions (i.e., without substrate or enzyme) was calculated and used to determine the IC_{50} concentrations of compounds. In case of CDK4/cyclin D1 assay, the two compounds fascaplysin and flavopiridol with known IC_{50} values were used to validate the assay. For the CDK2/cyclin A assay, roscovitine and flavopiridol were used as standards for the assay.

4.2. Chemistry

NMR spectra were recorded on Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz; ^{19}F 282.39 MHz) or DPX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) spectrometers as indicated. Chemicals shifts were measured relative to chloroform (^{1}H δ 7.26, ^{13}C δ 77.0) or dimethylsulfoxide (^{1}H δ 2.50, ^{13}C δ 39.43) and are expressed in ppm. Coupling constants *J* are expressed in hertz and the measure values are corrected to one decimal place. Fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H using xenon and *m*-nitrobenzyl alcohol as the matrix. Electrospray (ES) mass spectra were recorded on a Micromass Quattro LC spectrometer. Accurate mass was measure on a Kratos Concept 1H spectrometer using peak matching to stable reference peak. Flash column chromatography was carried out using Merck Kiesegel 60 (230–400 mesh). Dry solvents were provided by a PURE SOLV™ system of Innovative Technology Inc.

In some cases the starting materials used were not completely soluble in the solvent specified; where this is the case the reaction was carried out in suspension. Amide compounds showed rotamers characteristics (broad singlets or double peaks) at room temperature, not all peaks were duplicated for the atoms of each molecule. The rotamer ratios were measured from a clear duplicated signal in the ^{1}H or ^{19}F NMR. For suitable stable compounds, high temperatures NMR were run. In these conditions the coalescent signals were described with the corresponding coalescence temperature.

4.2.1. General procedure for the preparation of indolyl-oxo-acetyl chlorides 6a–d

To a solution of indole derivatives (17.10 mmol) in dry ether (34 mL) at 0 °C, under nitrogen flux, was added oxalyl chloride (19.80 mmol) over a period of 30 minutes. After addition, the mixture was stirred for 1 h at 0–5 °C. A yellow precipitate was formed and the mixture was filtered. The solid product was washed with dry ether and dried in vaccuo to give the expected compound.

4.2.1.1. (1*H*-indol-3-yl)-Oxo-acetyl chloride 6a. Yellow powder. Yield 84%. Decomposition point 116–117 °C. ^{1}H NMR (300 MHz, DMSO) δ 7.21–7.29 (2H, m), 7.52–7.58 (1H, m), 8.15–8.19 (1H, m), 8.41 (1H, d, *J* 3.3), 12.54 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 112.74 (Cq), 113.16 (CH), 121.56 (CH), 123.10 (CH), 124.08 (CH), 126.03 (Cq), 137.12 (Cq), 138.34 (CH), 165.63 (Cq), 181.16 (Cq). Anal. Calcd for $C_{10}H_6ClNO_2$: C, 57.85; H, 2.91; N, 6.75. Found: C, 57.69; H, 2.86; N, 6.70.

4.2.1.2. (5-Fluoro-1*H*-indol-3-yl)-oxo-acetyl chloride 6b. Yellow powder. Yield 80%. Decomposition point 145–146 °C. ^{1}H NMR (300 MHz, DMSO) δ 7.14 (1H, td, *J* 9.2 and 2.6), 7.57 (1H, dd, *J* 9.2 and 4.5), 7.84 (1H, dd, *J* 9.2 and 2.6), 8.48 (1H, d, *J* 3.3), 12.55 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 106.54 (CH, d, *J* 24.8), 112.25 (CH, d, *J* 25.5), 112.86 (Cq, d, *J* 4.2), 114.55 (CH, d, *J* 9.7), 126.78 (Cq, d, *J* 11.0), 133.71 (Cq), 139.69 (CH), 159.48 (Cq, d, *J* 235.7), 165.38 (Cq), 181.05 (Cq). ^{19}F NMR (282 MHz, DMSO) δ −120.41. Anal. Calcd for $C_{10}H_5ClFNO_2$: C, 53.24; H, 2.23; N, 6.21. Found: C, 53.32; H, 2.18; N, 6.11.

4.2.1.3. (5-Chloro-1*H*-indol-3-yl)-oxo-acetyl chloride 6c. Yellow powder. Yield 82%. Decomposition point 155 °C. ^{1}H NMR (300 MHz, DMSO) δ 7.31 (1H, dd, *J* 8.7 and 2.3), 7.58 (1H, d, *J* 8.7), 8.14 (1H, d, *J* 2.3), 8.49 (1H, d, *J* 3.3), 12.59 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 112.38 (Cq), 114.87 (CH), 120.65 (CH), 124.17 (CH), 127.27 (Cq), 127.81 (Cq), 135.64 (Cq), 139.57 (CH), 165.27 (Cq), 181.09 (Cq). Anal. Calcd for $C_{10}H_5Cl_2NO_2$: C, 49.62; H, 2.08; N, 5.79. Found: C, 49.65; H, 2.00; N, 5.76.

4.2.1.4. (5-Methyl-1*H*-indol-3-yl)-oxo-acetyl chloride 6d. Yellow powder. Yield 91%. Decomposition point 155 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.42 (3H, s), 7.10 (1H, dd, *J* 8.3 and 1.5), 7.42 (1H, d, *J* 8.3), 7.98 (1H, br s), 8.34 (1H, d, *J* 3.0), 12.28 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 21.77 (CH_3), 112.41 (Cq), 112.78 (CH), 121.32 (CH), 125.54 (CH), 126.30 (Cq), 132.12 (Cq), 135.43 (Cq), 138.27 (CH), 165.83 (Cq), 181.19 (Cq). Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.51; H, 3.59; N, 6.19.

4.2.2. General procedure for the preparation of dihydro indoles 7b–d (7a commercially available)

To a solution of 5-substituted indole (3.71 mmol) in glacial acetic acid (9.7 mL) under N_2 flux at 15–17 °C was added in one portion sodium cyanoborohydride 95% (11.50 mmol). After the addition, the mixture was stirred for 2 h at 15–17 °C. Water (48.9 mL) was added. The mixture was cooled in an ice bath and NaOH in pellets were added slowly until a strongly basic pH was obtained. The mixture was extracted with ether (3 × 25 mL). The combined ethered layers were washed with water (3 × 30 mL), brine (2 × 30 mL), dried over anhydrous potassium carbonate, and evaporated under reduced pressure to give the corresponding 5-substituted dihydro indoles.

4.2.2.1. 2,3-Dihydro-1*H*-indole 7a. Commercially available.

4.2.2.2. 5-Fluoro-2,3-dihydro-1*H*-indole 7b. Slightly pink oil. Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (2H, t, *J* 8.4), 3.39 (2H, t, *J* 8.4), 3.49 (1H, s), 6.37 (1H, dd, *J* 8.7 and 4.3), 6.57 (1H, m containing *J* 8.7), 6.70 (1H, m containing *J* 8.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.20 (CH_2), 47.90 (CH_2), 109.53 (CH, d, *J* 8.3), 111.99 (CH, d, *J* 23.8), 113.05 (CH, d, *J* 23.0), 131.23 (Cq, d, *J* 8.3), 147.70 (Cq), 156.99 (Cq, d, *J* 234.6). ^{19}F NMR (282 MHz, $CDCl_3$) δ −126.72. *m/z* (FAB^+) 137 M^+ found: M^+ 137.06412. C_8H_8FN requires M 137.06408.

4.2.2.3. 5-Chloro-2,3-dihydro-1*H*-indole 7c. Colourless oil. Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (2H, t, *J* 8.4), 3.45 (2H, t, *J* 8.4), 3.56 (1H, br s), 6.42 (1H, d, *J* 8.4), 6.85 (1H, m containing *J* 8.4), 6.94–6.95 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.80 (CH_2), 47.65 (CH_2), 109.95 (CH), 122.99 (Cq), 124.79 (CH), 126.93 (CH), 131.31 (Cq), 150.30 (Cq). *m/z* (FAB^+) 153 M^+ found; M^+ 153.03449. C_8H_8ClN requires M 153.03453.

4.2.2.4. 5-Methyl-2,3-dihydro-1*H*-indole 7d. Dark yellow oil. Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (3H, s), 2.88 (2H, t, *J* 8.4), 3.40 (2H, t, *J* 8.4), 3.45 (1H, br s), 6.45 (1H, d, *J* 7.8), 6.72 (1H, m containing *J* 7.8), 6.85 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.86 (CH_3), 30.04 (CH_2), 47.63 (CH_2), 109.48 (CH), 125.49 (CH), 127.56 (CH), 128.05 (Cq), 129.77 (Cq), 149.34 (Cq). *m/z* (FAB^+) 133 M^+ found: M^+ 133.08919. $C_9H_{11}N$ requires M 133.08915.

4.2.3. General procedure for the preparation of dihydro-indolyl indolyl ethane diones 8e–n

To a solution of the dihydro indole derivative (**7a–d**) (2.95 mmol) in dry THF (6 mL) under N_2 atmosphere, cooled in an ice bath, was added K_2CO_3 (5.89 mmol). The mixture was stirred under N_2 atmosphere and the indolyl-oxo-acetyl chloride derivative (**7a**–**d**) (2.95 mmol) in solution in dry THF (9 mL) under N_2 atmosphere was added slowly. The stirring was maintained 2 h at room temperature, and water (59 mL) was added. After 15 min supplementary stirring the expected compound (**9e**–**n**) was filtered, washed with water and dried under vacuum many days.

4.2.3.1. 1-(2,3-Dihydro-indol-1-yl)-2-(1*H*-indol-3-yl)-ethane-1,2-dione 8e. Prepared from **6a** and **7a**. Pale beige powder. Yield 87%. Rotamers observed in ratio 4:1 (from the duplicated triplet signal (^{1}H) at 4.13 and 4.26 ppm). Melting point 237–238 °C. ^{1}H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.20 (2H, t, *J* 8.3), 4.13 (2H, t, *J* 8.3), 7.18 (1H, td, *J* 7.5 and 0.9), 7.31–7.39 (4H, m), 7.58–7.64 (1H, m), 8.20–8.24 (2H, m), 8.31 (1H, s), 12.42 (1H, br s). δ (distinct peaks for *minor rotamer*) 4.26 (2H, t, *J* 8.6), 6.78–6.81 (1H, m), 7.00–7.03 (2H, m), 8.28 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.22 (CH_2), 48.49 (CH_2), 112.78 (Cq), 113.20 (CH), 117.06 (CH), 121.43 (CH), 123.11 (CH), 124.11 (CH), 125.04 (CH), 125.60 (CH), 125.71 (Cq), 127.61 (CH), 133.13 (Cq), 137.45 (Cq), 138.34 (CH), 142.38 (Cq), 165.15 (Cq), 185.16 (Cq). δ (distinct peaks for *minor rotamer*) 26.68 (CH_2), 47.26 (CH_2), 113.38 (CH), 123.24 (CH), 124.25 (CH), 126.32 (CH). *m/z* (FAB^+) 291 $(M+H)^+$ (found: C, 74.35; H, 4.69; N, 9.58; MH^+ 291.11331. $C_{18}H_{14}N_2O_2$ requires C, 74.47; H, 4.86; N, 9.65; MH 291.11335).

4.2.3.2. 1-(2,3-Dihydro-indol-1-yl)-2-(5-fluoro-1*H*-indol-3-yl)-ethane-1,2-dione 8f. Prepared from **6b** and **7a**. Pale pink solid. Yield 90%. Rotamers observed in ratio 4:1 (from the duplicated singlet signal (^{1}H) at 8.28 and 8.33 ppm). Melting point 242–246 °C. ^{1}H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.15 (2H, t, *J* 8.3), 4.08 (2H, t, *J* 8.3), 7.10–7.17 (2H, m), 7.19–7.34 (2H, m), 7.57 (1H, dd, *J* 9.0 and 4.5), 7.84 (1H, dd, *J* 9.6 and 2.4), 8.15 (1H, d, 7.8), 8.33 (1H, s), 12.41 (1H, br s). δ (distinct peaks for *minor rotamer*) 4.20 (2H, t, *J* 8.4), 6.71–6.74 (1H, m), 6.95–6.99 (2H, m), 8.28 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.23 (CH_2), 48.52 (CH_2), 106.42 (CH, d, *J* 24.2), 112.21 (CH, d, *J* 26.0), 112.89 (Cq, d, *J* 4.5), 114.63 (CH, d, *J* 9.8), 117.10 (CH), 125.10 (CH), 125.60 (CH), 126.37 (Cq, d, *J* 8.2), 127.60 (CH), 133.17 (Cq), 134.18 (Cq), 139.82 (CH), 142.35 (Cq), 159.45 (Cq, d, *J* 235.8), 164.87 (Cq), 184.93 (Cq). δ (distinct peaks for *minor rotamer*) 26.68 (CH_2), 47.29 (CH_2), 124.31 (CH), 126.32 (CH), 127.62 (CH), 133.82 (Cq), 140.08 (CH). ^{19}F NMR (282 MHz, DMSO) δ (*major rotamer*) −120.42. δ (*minor rotamer*) −120.21. *m/z* (FAB^+) 309 $(M+H)^+$ (found: C, 70.27; H, 4.16; N, 8.94; MH^+ 309.10399. $C_{18}H_{13}FN_2O_2$ requires C, 70.12; H, 4.25; N, 9.09; MH 309.10393).

4.2.3.3. 1-(5-Chloro-1*H*-indol-3-yl)-2-(2,3-dihydro-indol-1-yl)-ethane-1,2-dione 8g. Prepared from **6c** and **7a**. Pale pink powder. Yield 80%. Rotamers observed in ratio 4:1 (from the duplicated triplet signal (^{1}H) at 4.13 and 4.24 ppm). Melting point 270–271 °C. ^{1}H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.19 (2H, t, *J* 8.3), 4.13 (2H, t, *J* 8.3), 7.17 (1H, t, 7.5), 7.29–7.40 (3H, m), 7.62 (1H, d, *J* 8.7), 8.19 (1H, apparent d, estimated *J* 7.5), 8.20 (1H, br s), 8.39 (1H, s), 12.56 (1H, br s). δ (distinct peaks for *minor rotamer*) 4.24 (2H, t, *J* 8.4), 6.75–6.78 (1H, m), 6.99–7.03 (2H, m), 8.35 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.24 (CH_2), 48.52 (CH_2), 112.41 (Cq), 114.90 (CH), 117.11 (CH), 120.59 (CH), 124.16 (CH), 125.13 (CH), 125.60 (CH), 126.98 (Cq), 127.60 (CH), 127.79 (Cq), 133.18 (Cq), 135.98 (Cq), 139.59 (CH), 142.33 (Cq), 164.70 (Cq), 185.01 (Cq). δ (distinct peaks for *minor rotamer*) 26.69 (CH_2), 47.33 (CH_2), 112.78 (Cq), 113.20 (CH), 115.07 (CH), 124.35 (CH), 126.33 (CH), 127.70 (CH), 127.91 (Cq). *m/z* (FAB^+) 325 $(M+H)^+$ (found: C, 66.61; H, 3.92; N, 8.54; MH^+ 325.07443. $C_{18}H^{13}ClN_2O_2$ requires C, 66.57; H, 4.03; N, 8.63; MH 325.07438).

4.2.3.4. 1-(2,3-Dihydro-indol-1-yl)-2-(5-methyl-1*H*-indol-3-yl)-ethane-1,2-dione 8h. Prepared from **6d** and **7a**. White solid. Yield 78%. Rotamers observed in ratio 4:1 (from the duplicated triplet signal (^{1}H) at 4.06 and 4.20 ppm). Melting point 255–260 °C. ^{1}H NMR (300 MHz, DMSO) δ (*major rotamer*) 2.44 (3H, s), 3.14 (2H, t, *J* 8.3), 4.06 (2H, t, *J* 8.3), 7.09–7.14 (2H, m), 7.25–7.33 (2H, m), 7.43 (1H, d, *J* 8.4), 7.99 (1H, s), 8.14–8.18 (2H, m), 12.27 (1H, br s). δ (distinct peaks for *minor rotamer*) 2.46 (3H, s), 4.20 (2H, t, *J* 8.4), 6.72–6.76 (1H, m), 6.93–6.99 (2H, m). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 21.75 (CH_3), 28.21 (CH_2), 48.48 (CH_2), 112.42 (Cq), 112.81 (CH), 117.04 (CH), 121.26 (CH), 125.00 (CH), 125.57 (CH), 126.01 (Cq), 127.59 (CH), 132.12 (Cq), 133.11 (Cq), 135.74 (Cq), 138.24 (CH), 142.40 (Cq), 165.22 (Cq), 185.10 (Cq), one CH signal is not observed. δ (distinct peaks for *minor rotamer*) 26.66 (CH_2), 47.24 (CH_2), 113.20 (CH), 124.21 (CH), 135.88 (Cq). *m/z* (FAB^+) 305 $(M+H)^+$ (found: C, 74.91; H, 5.19; N, 9.12; MH^+ 305.12908. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20; MH 305.12900).

4.2.3.5. 1-(5-Fluoro-2,3-dihydro-indol-1-yl)-2-(1*H*-indol-3-yl)-ethane-1,2-dione 8i. Prepared from **7a** and **7b**. White powder. Yield 84%. Rotamers observed in ratio 4:1 (from the duplicated triplet signal (^{1}H) at 4.11 and 4.23 ppm). Melting point 205–206 °C. ^{1}H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.16 (2H, t, *J* 8.3), 4.11 (2H, t, *J* 8.3), 7.07–7.32 (4H, m), 7.54–7.57 (1H, m), 8.12–8.26 (3H, m), NH signal is not observed. δ (distinct peaks for *minor rotamer*) 4.26 (2H, t, *J* 8.4), 6.71–6.75 (1H, m), 6.85–6.91 (2H, m). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 27.81 (CH_2), 48.39 (CH_2), 112.77 (Cq), 112.93 (CH, d, *J* 23.5), 113.26 (CH), 113.85 (CH, d, *J* 23.0), 117.87 (CH, d, *J* 8.3), 121.42 (CH), 123.09 (CH), 124.08 (CH), 125.77 (Cq), 135.82 (Cq, d, *J* 8.9), 137.61 (Cq), 138.58 (CH), 138.86 (Cq), 159.60 (Cq, d, *J* 240.5), 164.88 (Cq), 184.95 (Cq). δ (distinct peaks for *minor rotamer*)

26.87 (CH_2), 47.79 (CH_2), 113.41 (CH), 123.26 (CH), 125.56 (CH), 137.96 (Cq), 138.77 (CH). ^{19}F NMR (282 MHz, DMSO) δ (*major rotamer*) –118.07. δ (*minor rotamer*) –119.58. *m/z* (FAB^+) 309 $(M+H)^+$ (found: C, 70.07; H, 4.27; N, 8.89; MH^+ 309.10388. $C_{18}H_{13}FN_2O_2$ requires C, 70.12; H, 4.25; N, 9.09; MH 309.10393).

4.2.3.6. 1-(5-Chloro-2,3-dihydro-indol-1-yl)-2-(1*H*-indol-3-yl)-ethane-1,2-dione 8j. Prepared from **6a** and **7c**. White solid. Yield 87%. Rotamers observed in ratio 5:1 (from the duplicated singlet signal (^1H) at 8.25 and 8.28 ppm). Melting point 245–246 °C. ^1H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.15 (2H, t, *J* 8.4), 4.11 (2H, t, *J* 8.4), 7.25–7.38 (4H, m), 7.53–7.57 (1H, m), 8.14 (1H, d, *J* 8.7), 8.18–8.20 (1H, m), 8.28 (1H, s), 12.36 (br s, 1H). δ (distinct peaks for *minor rotamer*) 4.23 (2H, t, *J* 8.3), 6.70 (1H, d, *J* 8.7), 7.05 (1H, dd, *J* 8.6 and 2.0), 8.25 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.13 (CH_2), 48.81 (CH_2), 112.76 (Cq), 113.20 (CH), 118.09 (CH), 121.46 (CH), 123.16 (CH), 124.16 (CH), 125.62 (CH), 125.71 (Cq), 127.42 (CH), 128.59 (Cq), 135.77 (Cq), 137.44 (Cq), 138.44 (CH), 141.44 (Cq), 165.12 (Cq), 184.82 (Cq). δ (distinct peaks for *minor rotamer*) 26.63 (CH_2), 47.69 (CH_2), 113.32 (CH), 123.37 (CH), 124.32 (CH), 125.45 (Cq), 126.27 (CH), 128.10 (Cq), 136.45 (Cq), 137.63 (Cq), 139.33 (Cq). *m/z* (FAB^+) 325 $(M+H)^+$ (found: C, 66.61; H, 4.07; N, 8.50; MH^+ 325.07439. $C_{18}H^{13}ClN_2O_2$ requires C, 66.57; H, 4.03; N, 8.63; MH 325.07438).

4.2.3.7. 1-(1*H*-Indol-3-yl)-2-(5-methyl-2,3-dihydro-indol-1-yl)-ethane-1,2-dione 8k. Prepared from **6a** and **7d**. White solid. Yield 86%. Rotamers observed in ratio 4:1 (from the duplicated singlet signal (^1H) at 2.16 and 2.30 ppm). Melting point 225–226 °C. ^1H NMR (300 MHz, DMSO) δ (*major rotamer*) 2.30 (3H, s), 3.10 (2H, t, *J* 8.3), 4.05 (2H, t, *J* 8.3), 7.06–7.13 (2H, m), 7.24–7.32 (2H, m), 7.52–7.56 (1H, m), 8.03 (1H, d, *J* 8.1), 8.15–8.18 (1H, m), 8.24 (1H, s), 12.26 (1H, br s). δ (distinct peaks for *minor rotamer*) 2.16 (3H, s), 4.19 (2H, t, *J* 8.4), 6.62 (1H, d, *J* 8.1), 6.75 (1H, d, *J* 8.4), 8.19 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 21.16 (CH_3), 28.17 (CH_2), 48.58 (CH_2), 112.85 (Cq), 113.21 (CH), 116.77 (CH), 121.42 (CH), 123.07 (CH), 124.06 (CH), 125.75 (Cq), 126.09 (CH), 127.93 (CH), 133.21 (Cq), 134.23 (Cq), 137.50 (Cq), 138.30 (CH), 140.11 (Cq), 164.83 (Cq), 185.25 (Cq). δ (distinct peaks for *minor rotamer*) 20.78 (CH_3), 26.66 (CH_2), 47.33 (CH_2), 113.32 (CH), 123.24 (CH), 124.19 (CH), 126.76 (CH), 133.47 (Cq), 133.90 (Cq), 137.70 (Cq). *m/z* (FAB^+) 305 $(M+H)^+$, 609 $(2\,M+H)^+$ (found: C, 75.12; H, 5.29; N, 9.13; MH^+ 305.12907. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20; MH 305.12900).

4.2.3.8. 1-(5-Fluoro-2,3-dihydro-indol-1-yl)-2-(5-fluoro-1*H*-indol-3-yl)-ethane-1,2-dione 8l. Prepared from **6b** and **7b**. White powder. Yield 89%. R_f (EtOAc/petroleum ether, 1:2) 0.10. Rotamers observed in ratio 6.7:1 (from duplicated triplet signal (^1H) at 4.13 and 4.23 ppm). Melting point 266–267 °C. ^1H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.11 (2H, t, *J* 8.2), 4.13 (2H, t, *J* 8.2), 7.06 (1H, tt, *J* 9.0 and 2.7), 7.12–7.18 (2H, m), 7.58 (1H, dd, *J* 8.7 and 4.8), 7.88 (1H, dd, *J* 9.5 and 2.6), 8.14 (1H, dd, *J* 8.6 and 5.1), 8.36 (1H, s), NH signal is not observed. δ (distinct peaks for *minor rotamer*) 4.23 (2H, t, *J* 8.3), 6.70 (1H, dd, *J* 8.6 and 4.8), 6.82 (1H, td, *J* 8.6 and 2.7), 8.32 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.28 (CH_2), 48.90 (CH_2), 106.51 (CH, d, *J* 24.7), 112.22 (CH, d, *J* 24.6), 112.80 (CH, d, *J* 22.6), 113.02 (Cq), 113.78 (CH, d, *J* 22.8), 114.51 (CH, d, *J* 10.4), 117.93 (CH, d, *J* 8.5), 126.50 (Cq, d, *J* 11.6), 134.00 (Cq), 135.77 (Cq, d, *J* 9.5), 138.75 (Cq), 139.68 (CH), 159.50 (Cq, d, *J* 233.9), 159.64 (Cq, d, *J* 239.1), 164.47 (Cq), 184.82 (Cq). δ (distinct peaks for *minor rotamer*) 26.85 (CH_2), 47.82 (CH_2), 112.98 (Cq), 134.26 (Cq), 136.50 (Cq). ^{19}F NMR (282 MHz, DMSO) δ (*major rotamer*) –120.34, –117.97. δ (*minor rotamer*) –120.08, –119.51. *m/z* (ES^+) 327 MH^+, (ES^-) 325 $(M-H)^-$; *m/z* (FAB^+) 327 $(M+H)^+$ (found MH^+ 327.09442. $C_{18}H_{12}F_2N_2O_2$ requires MH 327.09451).

4.2.3.9. 1-(5-Chloro-2,3-dihydro-indol-1-yl)-2-(5-chloro-1*H*-indol-3-yl)-ethane-1,2-dione 8m. Prepared from **6c** and **7c**. White powder. Yield 86%. R_f (EtOAc/petroleum ether, 1:2) 0.10. Rotamers observed in ratio 6.7:1 (from duplicated triplet signal (^1H) at 4.12 and 4.22 ppm). Melting point 291–293 °C. ^1H NMR (300 MHz, DMSO) δ (*major rotamer*) 3.15 (2H, t, *J* 8.2), 4.12 (2H, t, *J* 8.2), 7.34 – 7.37 (3H, m), 7.58 (1H, dd, *J* 8.7 and 0.6), 8.12 (1H, d, *J* 8.4), 8.16 (1H, d, *J* 1.8), 8.36 (1H, s), 12.59 (1H, br s). δ (distinct peaks for *minor rotamer*) 4.22 (2H, t, *J* 8.6), 6.69 (1H, d, *J* 8.7), 7.06 (1H, dd, *J* 8.6 and 2.3), 7.59 (1H, broad d, *J* 8.5), 8.33 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 28.14 (CH_2), 48.83 (CH_2), 112.39 (Cq), 114.85 (CH), 118.13 (CH), 120.62 (CH), 124.21 (CH), 125.60 (CH), 126.97 (Cq), 127.39 (CH), 127.87 (Cq), 128.70 (Cq), 135.80 (Cq), 135.90 (Cq), 139.65 (CH), 141.37 (Cq), 164.63 (Cq), 184.67 (Cq). δ (distinct peaks for *minor rotamer*) 26.73 (CH_2), 47.76 (CH_2), 114.39 (CH), 123.93 (CH). *m/z* (ES^+) 359 M^+, (ES^-) 359 M^-; *m/z* (FAB^+) 359 M^+ (found: C, 60.05; H, 3.23; N, 7.72; M^+ 359.03551. $C_{18}H_{12}Cl_2N_2O_2$ requires C, 60.19; H, 3.37; N, 7.80; M 359.03541).

4.2.3.10. 1-(5-Methyl-2,3-dihydro-indol-1-yl)-2-(5-methyl-1*H*-indol-3-yl)-ethane-1,2-dione 8n. Prepared from **6d** and **7d**. White powder. Yield 92%. R_f (EtOAc/petroleum ether, 1:2) 0.14. Rotamers observed in ratio 4:1 (from duplicated triplet signal (^1H) at 4.05 and 4.18 ppm). Melting point 275–277 °C. ^1H NMR (300 MHz, DMSO) δ (*major rotamer*) 2.29 (3H, s), 2.43 (3H, s), 3.06 (2H, t, *J* 8.2), 4.05 (2H, t, *J* 8.2), 7.05–7.10 (4H, m), 7.43 (1H, d, *J* 8.7), 8.02 (1H, br s), 8.18 (1H, br s), 12.27 (1H, s very weak signal). δ (*distinct peaks for minor rotamer*) 2.15 (3H, s), 2.46 (3H, s), 4.18 (2H, t, *J* 8.6), 6.63 (1H, d, *J* 8.7), 6.74 (1H, broad, *J* 8.1), 8.05 (1H, s), 8.13 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (*major rotamer*) 21.13 (CH_3), 21.73 (CH_3), 28.16 (CH_2), 48.58 (CH_2), 112.52 (Cq), 112.79 (CH), 116.75 (CH), 121.27 (CH), 125.54 (CH), 126.03 (CH), 126.08 (Cq), 127.92 (CH), 132.11 (Cq), 133.17 (Cq), 134.20 (Cq), 135.71 (Cq), 138.13 (CH), 140.11 (Cq), 164.87 (Cq), 185.23 (Cq). δ (*distinct peaks for minor rotamer*) 20.77 (CH_3), 26.65 (CH_2), 47.33 (CH_2), 112.97 (CH), 125.68 (CH), 126.73 (CH), 127.95 (CH), 132.33 (Cq), 137.94 (CH), 165.06 (Cq). *m/z* (ES^+) 319 MH^+, 637 $(2\,M+H)^+$, (ES^-) 317 $(M-H)^-$, 635 $(2\,M-H)^-$; *m/z* (FAB^+) 319 $(M+H)^+$ (found: MH^+ 319.14476. $C_{20}H_{18}N_2O_2$ requires MH 319.14465).

4.2.4. General procedure for the preparation of dihydro-indolyl ethyl indoles 9e–n

To a suspension of the lithium aluminium hydride (5.51 mmol) in dry ether (12.5 mL) under N_2 atmosphere, was added dropwise a solution of the dihydro-indolyl indolyl ethane dione (**8e–n**) (0.69 mmol) in dry THF (4.5 mL). The mixture was heated under reflux 6 h, and cooled to room temperature then to 0 °C. A saturated solution of Na_2SO_4 was added slowly, until the mixture became milky white. After filtration the organic and aqueous layers were evaporated. The crude was redissolve in dichloromethane, washed with water (4 × 20 mL), dried (Na_2SO_4) and the organic layers concentrated to give the title compound. A purification was needed for **9g**,**i**,**j**,**l**,**m**,**n** using a column chromatography of silica gel with the following gradient of eluent: ethyl acetate/cyclohexane (1/9), ethyl acetate/cyclohexane (2/8) and ethyl acetate.

4.2.4.1. 3-[2-(2,3-Dihydro-indol-1-yl)-ethyl]-1*H*-indole 9e. Prepared from **8e**. Yellow solid. Yield 91%. Melting point 124–125 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.91 (2H, t, *J* 8.3), 2.99 (2H, t, *J* 8.3), 3.33–3.41 (4H, 2 overlapping triplets, estimated *J* 8), 6.44 (1H, d, *J* 7.8), 6.57 (1H, td, *J* 7.5 and 0.9), 6.97–7.17 (5H, m), 7.29 (1H, distorted

dt, estimated *J* 7.8 and 0.6), 7.58 (1H, dd, *J* 7.5 and 0.6), 7.88 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.10 (CH_2), 28.73 (CH_2), 49.85 (CH_2), 53.09 (CH_2), 107.05 (CH), 111.33 (CH), 113.93 (Cq), 117.52 (CH), 118.80 (CH), 119.37 (CH), 121.81 (CH), 122.05 (CH), 124.57 (CH), 127.47 (CH), 127.58 (Cq), 130.17 (Cq), 136.34 (Cq), 152.47 (Cq). *m*/*z* (FAB$^+$) 262 M$^+$ (found: C, 82.41; H, 6.90; N, 10.49; M$^+$ 262.14696. $C_{18}H_{18}N_2$ requires C, 82.24; H, 6.92; N, 10.68; M 262.14700).

4.2.4.2. 3-[2-(2,3-Dihydro-indol-1-yl)-ethyl]-5-fluoro-1*H*-indol 9f. Prepared from **8f**. Tan solid. Yield 94%. Melting point 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87–2.95 (4H, 2 distorted t, estimated *J* 8.0), 3.29–3.38 (4H, 2 distorted t, estimated *J* 8.0), 6.42 (1H, d, *J* 7.8), 6.57 (1H, t, *J* 7.2), 6.86 (1H, td, *J* 9.0 and 1.8), 6.96–7.01 (3H, m), 7.14–7.20 (2H, m), 7.86 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.05 (CH_2), 28.65 (CH_2), 49.62 (CH_2), 53.05 (CH_2), 103.67 (CH, d, *J* 23.5), 106.87 (CH), 110.42 (CH, d, *J* 26.3), 111.77 (CH, d, *J* 9.9), 114.31 (Cq, d, *J* 4.5), 117.47 (CH), 123.49 (CH), 124.49 (CH), 127.38 (CH), 127.93 (Cq, d, *J* 9.6), 130.04 (Cq), 132.73 (Cq), 152.32 (Cq), 157.80 (Cq, d, *J* 234.5). ^{19}F NMR (282 MHz, $CDCl_3$) δ −124.69. *m*/*z* (FAB$^+$) 280 M$^+$ (found: C, 77.30; H, 6.36; N, 9.59; M$^+$ 280.13751. $C_{18}H_{17}FN_2$ requires C, 77.12; H, 6.11; N, 9.99% ; M 280.13758).

4.2.4.3. 5-Chloro-3-[2-(2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9g. Prepared from **8g**. Beige solid. Yield 72%. R_f (EtOAc/cyclohexane, 20:80) 0.33. Melting point 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85–2.92 (4H, m), 3.29 (2H, t, *J* 7.8), 3.32 (2H, t, *J* 8.4), 6.43 (1H, d, *J* 7.8), 6.62 (1H, td, *J* 7.4 and 0.9), 6.86 (1H, d, *J* 2.4), 6.99–7.05 (4H, m), 7.52 (1H, s), 7.86 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.02 (CH_2), 28.75 (CH_2), 49.77 (CH_2), 53.15 (CH_2), 107.15 (CH), 112.38 (CH), 113.78 (Cq), 117.75 (CH), 118.32 (CH), 122.32 (CH), 123.34 (CH), 124.69 (CH), 125.09 (Cq), 127.54 (CH), 128.73 (Cq), 130.25 (Cq), 134.66 (Cq), 152.44 (Cq). *m*/*z* (FAB$^+$) 296 M$^+$ (found: C, 72.96; H, 5.80; N, 9.39; M$^+$ 296.10799. $C_{18}H_{17}ClN_2$ requires C, 72.84; H, 5.77; N, 9.44; M 296.10803).

4.2.4.4. 3-[2-(2,3-Dihydro-indol-1-yl)-ethyl]-5-methyl-1*H*-indole 9h. Prepared from **8h**. Dark yellow powder. Yield 92%. Melting point 100–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.91 (2H, t, *J* 8.4), 2.95 (2H, t, *J* 8.4), 3.31–3.40 (4H, m), 6.44 (1H, d, *J* 7.8), 6.57 (1H, td, *J* 7.5 and 0.9), 6.94–7.02 (4H, m), 7.15–7.18 (1H, m), 7.34 (1H, d, *J* 0.9), 7.77 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.57 (CH_3), 23.05 (CH_2), 28.65 (CH_2), 49.73 (CH_2), 53.01 (CH_2), 106.91 (CH), 110.84 (CH), 113.60 (Cq), 117.34 (CH), 118.43 (CH), 121.76 (CH), 123.66 (CH), 124.44 (CH), 127.35 (CH), 127.76 (Cq), 128.57 (Cq), 130.06 (Cq), 134.59 (Cq), 152.41 (Cq). *m*/*z* (FAB$^+$) 276 M$^+$ (found: C, 88.64; H, 7.79; N, 10.78; M$^+$ 276.16259. $C_{19}H_{20}N_2$ requires C, 88.72; H, 7.84; N, 10.89; M 276.16265).

4.2.4.5. 3-[2-(5-Fluoro-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9i. Prepared from **8i**. Brown solid. Yield 78%. R_f (EtOAc/cyclohexane, 20:80) 0.27. Melting point 134–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (2H, t, *J* 8.1), 2.97 (2H, t, *J* 8.3), 3.29 (2H, t, *J* 8.3), 3.35 (2H, t, *J* 8.1), 6.29 (1H, dd, *J* 8.4 and 4.2), 6.63–6.75 (2H, m), 6.97 (1H, s), 7.04–7.16 (2H, m), 7.28 (1H, d, *J* 7.8), 7.56 (1H, d, *J* 7.5), 7.89 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.06 (CH_2), 28.72 (CH_2), 50.53 (CH_2), 53.62 (CH_2), 106.95 (CH, d, *J* 8.2), 111.22 (CH), 112.14 (CH, d, *J* 23.9), 112.94 (CH, d, *J* 22.9), 113.98 (Cq), 118.73 (CH), 119.40 (CH), 121.62 (CH), 122.10 (CH), 127.49 (Cq), 131.64 (Cq, d, *J* 4.1), 136.27 (Cq), 148.70 (Cq), 157.03 (Cq, weak signal). ^{19}F NMR (282 MHz, $CDCl_3$) δ −127.98. *m*/*z* (FAB$^+$) 280 M$^+$ (found: C, 76.95; H, 6.22; N, 9.80; M$^+$ 280.13756. $C_{18}H_{17}FN_2$ requires C, 77.12; H, 6.11; N, 9.99; M 280.13758).

4.2.4.6. 3-[2-(5-Chloro-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9j. Prepared from **8j**. Beige solid. Yield 57%. R_f (EtOAc/cyclohexane, 20:80) 0.35. Melting point 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (2H, t, *J* 8.1), 3.12 (2H, t, *J* 8.4), 3.46 (2H, t, *J* 8.1), 3.52 (2H, t, *J* 8.4), 6.44 (1H, d, *J* 8.1), 7.06–7.10 (3H, m), 7.21–7.33 (2H, m), 7.40 (1H, d, *J* 8.1), 7.72 (1H, d, *J* 7.5), 7.95 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.98 (CH_2), 28.49 (CH_2), 49.73 (CH_2), 53.13 (CH_2), 107.42 (CH), 111.33 (CH), 113.81 (Cq), 118.75 (CH), 119.47 (CH), 121.77 (CH), 122.17 (CH), 124.71 (CH), 127.06 (CH), 127.50 (Cq), 131.99 (Cq), 136.31 (Cq), 151.11 (Cq), one quaternary ^{13}C is not observed. *m*/*z* (FAB$^+$) 296 M$^+$ (found: M$^+$ 296.10802. $C_{18}H_{17}ClN_2$ requires M 296.10803).

4.2.4.7. 3-[2-(5-Methyl-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9k. Prepared from **8k**. Yellow oil. Yield 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (3H, s), 2.84 (2H, t, *J* 8.1), 2.95 (2H, distorted t, estimated *J* 7), 3.29 (2H, t, *J* 8.1), 3.31 (2H, t, *J* 8.4), 6.36 (1H, d, *J* 7.8), 6.79 (1H, d, *J* 7.8), 6.84 (1H, s), 6.89 (1H, d, *J* 2.4), 7.04 (1H, td, *J* 6.9 and 1.2), 7.10 (1H, td, *J* 6.9 and 1.2), 7.20 (1H, dd, *J* 7.5 and 1.2), 7.55 (1H, dd, *J* 7.2 and 0.3), 7.80 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.80 (CH_3), 23.09 (CH_2), 28.79 (CH_2), 50.41 (CH_2), 53.48 (CH_2), 107.16 (CH), 111.26 (CH), 114.12 (Cq), 118.83 (CH), 119.37 (CH), 121.72 (CH), 122.06 (CH), 125.51 (CH), 126.97 (Cq), 127.60 (CH + Cq), 130.52 (Cq), 136.31 (Cq), 150.36 (Cq). *m*/*z* (FAB$^+$) 276 M$^+$ (found: M$^+$ 276.16269. $C_{19}H_{20}N_2$ requires M 276.16265).

4.2.4.8. 5-Fluoro-3-[2-(5-fluoro-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9l. Pale yellow powder. Yield 84%. R_f (EtOAc/petroleum ether, 1:2) 0.39. Melting point 117–118 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.86 (2H, t, *J* 8.3), 2.92 (2H, t, *J* 7.6), 3.29 (2H, t, *J* 7.6), 3.37 (2H, t, *J* 8.3), 6.45 (1H, dd, *J* 8.6 and 4.4), 6.77 (1H, td, *J* 9.0 and 2.9), 6.86–6.90 (1H, m), 6.94 (1H, dd, *J* 9.2 and 2.6), 7.31–7.33 (2H, m), 7.37 (1H, dd, *J* 8.9 and 4.4), 10.97 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 22.78 (CH_2), 28.52 (CH_2), 50.18 (CH_2), 53.30 (CH_2), 103.41 (CH, d, *J* 22.6),107.18 (CH, d, *J* 10.7), 109.45 (CH, d, *J* 24.8), 112.27 (CH, d, *J* 23.7), 112.63 (CH, d, *J* 10.7), 112.89 (Cq), 113.08 (CH, d, *J* 22.6), 125.35 (CH), 127.95 (Cq, d, *J* 9.5), 132.02 (Cq, d, *J* 8.3), 133.36 (Cq), 149.34 (Cq), 155.92 (Cq, d, *J* 230.8), 157.20 (Cq, d, *J* 229.6). ^{19}F NMR (282 MHz, DMSO) δ −128.22, −125.54. *m*/*z* (ES$^+$) 299 MH$^+$, (ES$^-$) 297 (M−H)$^-$; *m*/*z* (FAB$^+$) 298 M$^+$ (found: C, 72.55; H, 5.36; N, 9.38; M$^+$ 298.12816. $C_{18}H_{16}N_2F_2$ requires C, 72.47; H, 5.41; N, 9.39; M 298.12816).

4.2.4.9. 5-Chloro-3-[2-(5-chloro-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9m. Yellow powder. Yield 69%. R_f (EtOAc/petroleum ether, 50:50) 0.52. Melting Point 79–81 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.84 (2H, t, *J* 8.3), 2.92 (2H, t, *J* 7.6), 3.29 (2H, t, *J* 7.6), 3.41 (2H, t, *J* 8.3), 6.45 (1H, d, *J* 8.4), 6.96 (1H, dd, *J* 8.4 and 2.1), 7.01 (1H, apparent d, estimated *J* 1.5), 7.07 (1H, dd, *J* 8.9 and 2.0), 7.31 (1H, s), 7.38 (1H, d, *J* 8.7), 7.61 (1H , d, *J* 1.5), 10.97 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 22.53 (CH_2), 28.24 (CH_2), 49.37 (CH_2), 52.78 (CH_2), 107.78 (Cq), 112.43 (CH), 113.34 (CH), 118.02 (Cq), 120.50 (Cq), 121.31 (CH), 123.54 (CH), 124.60 (Cq), 125.14 (CH), 127.06 (CH), 128.87 (CH), 132.41 (Cq), 135.12 (Cq), 151.59 (Cq). *m*/*z* (ES$^+$) 331 MH$^+$, (ES$^-$) 329 (M−H)$^-$; *m*/*z* (FAB$^+$) 330 M$^+$ (found: C, 65.26; H, 4.72; N, 8.58; M$^+$ 330.06904. $C_{18}H_{16}N_2F_2$ requires C, 65.27; H, 4.87; N, 8.46; M 330.06905).

4.2.4.10. 5-Methyl-3-[2-(5-methyl-2,3-dihydro-indol-1-yl)-ethyl]-1*H*-indole 9n. Yellow powder. Yield 82%. R_f (EtOAc/petroleum ether, 1:2) 0.58. Melting point 55–56 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.20 (3H, s), 2.44 (3H, s), 2.85 (2H, t, *J* 8.0), 2.96 (2H, t , *J* 7.7), 3.33 (2H, t, *J* 8.0) 3.36 (2H, t, *J* 7.7), 6.45 (1H, d, *J* 7.7), 6.82 (1H, d, *J* 7.8), 6.85 (1H, s), 6.95 (1H, dd, *J* 8.3 and 1.7), 7.19 (1H, d, *J* 2.4), 7.31 (1H, d, *J* 8.1), 7.40 (1H, s), 10.74 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 20.89 (CH_3), 21.81 (CH_3), 22.94 (CH_2), 28.62 (CH_2), 50.34 (CH_2), 53.18 (CH_2), 107.21 (CH), 111.61 (CH), 112.10 (Cq), 118.33 (CH), 123.00 (CH), 123.14 (CH), 125.52 (CH), 126.03

(Cq), 127.11 (Cq), 127.73 (CH), 128.03 (Cq), 130.39 (Cq), 135.18 (Cq), 150.72 (Cq). *m/z* (ES^+) 291 MH^+, (ES^-) 289 $(M-H)^-$; *m/z* (FAB^+) 290 M^+ (found: C, 82.82; H, 7.65; N, 9.57; M^+ 290.17835. $C_{20}H_{22}N_2$ requires C, 82.72; H, 7.64; N, 9.65; M 290.17830).

4.2.5. General procedure for the preparation of indolyl ethyl indoles 10e–n

To a solution of dihydro indolyl ethyl indole (**6e–n**) (2.05 mmol) in $CHCl_3$ (12 mL) was added activated manganese dioxide (14.3 mmol). The mixture was heated under reflux for 60 h. After cooling to room temperature, the crude suspension was filtered through Celite and the filtrate was concentrated under vacuum. The crude product was purified by column chromatography on silica gel with the following gradient of solvent ethyl acetate/cyclohexane (1/9), ethyl acetate/cyclohexane (2/8), then ethyl acetate to give the title compound (**10e–n**).

4.2.5.1. 3-[2-Indol-1-yl-ethyl]-1*H*-indole 10e. Prepared from **9e**. Yellow solid. Yield 55%. R_f (EtOAc/petroleum ether, 20:80) 0.33. Melting point 154–155 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.31 (2H, td, *J* 7.2 and 0.6), 4.46 (2H, t, *J* 7.2), 6.48 (1H, dd, *J* 3.3 and 0.6), 6.77 (1H, d, *J* 2.1), 6.99 (1H, d, *J* 3.3), 7.12–7.29 (4H, m), 7.38–7.42 (2H, m), 7.63–7.69 (2H, m), 7.92 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.33 (CH_2), 46.99 (CH_2), 100.83 (CH), 109.39 (CH), 111.30 (CH), 112.63 (Cq), 118.48 (CH), 119.26 (CH), 119.58 (CH), 120.99 (CH), 121.37 (CH), 122.20 (CH), 122.30 (CH), 127.17 (Cq), 128.02 (CH), 128.68 (Cq), 135.85 (Cq), 136.24 (Cq). *m/z* (FAB^+) 260 M^+, 261 $(M+H)^+$ (found: C, 82.97; H, 6.18; N, 10.72; M^+ 260.13122. $C_{18}H_{16}N_2$ requires C, 83.04; H, 6.19; N, 10.76; M 260.13135).

4.2.5.2. 5-Fluoro-3-(2-indol-1-yl-ethyl)-1*H*-indole 10f. Prepared from **9f**. Tan solid. Yield 56%. R_f (EtOAc/cyclohexane, 20:80) 0.30. Melting point 141–142 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.14 (2H, t, *J* 7.1), 4.32 (2H, t, *J* 7.1), 6.35 (1H, d, *J* 3.0), 6.64 (1H, d, *J* 2.1), 6.85 (1H, d, *J* 3), 6.88 (1H, td, *J* 9 and 2.4), 7.03 (1H, td, *J* 6.9 and 0.9), 7.09–7.19 (3H, m), 7.25 (1H, d, *J* 8.1), 7.56 (1H, d, *J* 7.8), 7.77 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.24 (CH_2), 46.82 (CH_2), 100.92 (CH), 103.41 (CH, d, *J* 23.4), 109.32 (CH), 110.56 (CH, d, *J* 26.4), 111.91 (CH, d, *J* 9.8), 112.77 (Cq), 119.29 (CH), 121.00 (CH), 121.42 (CH), 124.15 (CH), 127.51 (Cq, d, *J* 9.1), 127.96 (CH), 128.67 (Cq), 132.68 (Cq), 135.83 (Cq), 157.88 (Cq, d, *J* 235.3). ^{19}F NMR (282 MHz, $CDCl_3$) δ −124.41. *m/z* (FAB^+) 278 M^+ (found: C, 77.49; H, 5.33; N, 9.90; M^+ 278.12195. $C_{18}H_{15}FN_2$ requires C, 77.68; H, 5.43; N, 10.07; M 278.12193).

4.2.5.3. 5-Chloro-3-(2-indol-1-yl-ethyl)-1*H*-indole 10g. Prepared from **9g**. Tan solid. Yield 62%. R_f (EtOAc/petroleum ether, 20:80) 0.27. Melting point 93–94 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (2H, t, *J* 6.9), 4.22 (2H, t, *J* 6.9), 6.32 (1H, dd, *J* 3.0 and 0.6), 6.42 (1H, d, *J* 2.4), 6.77 (1H, d, *J* 3.3), 6.98–7.03 (3H, m), 7.08 (1H, td, *J* 6.9 and 1.2), 7.18 (1H, d, *J* 7.5), 7.37 (1H, s), 7.53 (1H, d, *J* 7.5), 7.57 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.09 (CH_2), 46.83 (CH_2), 100.98 (CH), 109.45 (CH), 112.36 (CH + Cq), 118.03 (CH), 119.41 (CH), 121.09 (CH), 121.51 (CH), 122.45 (CH), 123.87 (CH), 125.32 (Cq), 128.10 (CH), 128.25 (Cq), 128.73 (Cq), 134.53 (Cq), 135.89 (Cq). *m/z* (FAB^+) 294 M^+ (found: C, 73.46; H, 4.92; N, 9.38; M^+ 294.09231. $C_{18}H_{15}ClN_2$ requires C, 73.34; H, 5.13; N, 9.50; M 294.09238).

4.2.5.4. 3-(2-Indol-1-yl-ethyl)-5-methyl-1*H*-indole 10h. Prepared from **9h**. Tan powder. Yield 41%. R_f (EtOAc/cyclohexane, 20:80) 0.38. Melting point 102–103 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (3H, s), 3.38 (2H, t, *J* 7.2), 4.54 (2H, t, *J* 7.2), 6.59 (1H, dd, *J* 3.3 and 0.8), 6.67 (1H, d, *J* 3.1), 7.08 (1H, d, *J* 3.3), 7.18 (1H, dd, *J* 8.1 and 1.2), 7.26–7.31 (2H, m), 7.37 (1H, td, *J* 7.7 and 1.2), 7.48–7.52 (2H, m), 7.63 (1H, br s), 7.81 (1H, dd, *J* 7.8 and 0.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.78 (CH_3), 26.40 (CH_2), 47.12 (CH_2), 100.95 (CH), 109.68 (CH), 111.16 (CH), 112.06 (Cq), 118.31 (CH), 119.49 (CH), 121.18 (CH), 121.57 (CH), 122.65 (CH), 123.88 (CH), 127.48 (Cq), 128.32 (CH), 128.83 (2Cq), 134.67 (Cq), 136.67 (Cq). *m/z* (FAB^+) 274 M^+ (found: MH^+ 274.14703. $C_{19}H_{18}N_2$ requires M 274.14700).

4.2.5.5. 5-Fluoro-1-[2-(1*H*-indol-3-yl)-ethyl]-1*H*-indole 10i. Prepared from **9i**. Yellow solid. Yield 65%. R_f (EtOAc/petroleum ether, 20:80) 0.27. Melting point 144–145 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (2H, t, *J* 7.1), 4.47 (2H, t, *J* 7.1), 6.45 (1H, dd, *J* 3.3 and 0.9), 6.78 (1H, d, *J* 2.4), 6.99 (1H, td, *J* 9.3 and 2.7), 7.05 (1H, d, *J* 3.0), 7.20–7.36 (4H, m), 7.44 (1H, dd, *J* 8.1 and 0.9), 7.65 (1H, d, *J* 8.1), 7.97 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.36 (CH_2), 47.27 (CH_2), 100.77 (CH, d, *J* 4.7), 105.58 (CH, d, *J* 23.2), 109.73 (CH, d, *J* 9.5), 109.91 (CH, d, *J* 26.0), 111.32 (CH), 112.46 (Cq), 118.40 (CH), 119.62 (CH), 122.27 (CH, d, *J* 5.1), 127.05 (Cq), 128.79 (Cq, d, *J* 10.6), 129.56 (CH), 132.34 (Cq), 136.24 (Cq), 157.77 (Cq, d, *J* 233.7), one CH is not observed. ^{19}F NMR (282 MHz, $CDCl_3$) δ −125.72. *m/z* (FAB^+) 278 M^+ (found: C, 77.51; H, 5.42; N, 9.96; M^+ 278.12197. $C_{18}H_{15}FN_2$ requires C, 77.68; H, 5.43; N, 10.07; M 278.12193).

4.2.5.6. 5-Chloro-1-[2-(1*H*-indol-3-yl)-ethyl]-1*H*-indole 10j. Prepared from **9j**. Pale yellow solid. Yield 63%. R_f (EtOAc/petroleum ether, 20:80) 0.33. Melting point 117–118 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (2H, t, *J* 7.2), 4.22 (2H, t, *J* 7.2), 6.23 (1H, br s), 6.47 (1H, br s), 6.80 (1H, d, *J* 3.0), 6.99–7.20 (5H, m), 7.44 (1H, d, *J* 7.5), 7.48 (1H, br s), 7.60 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.37 (CH_2), 47.19 (CH_2), 100.60 (CH), 110.50 (CH), 111.44 (CH), 112.30 (Cq), 118.44 (CH), 119.69 (CH), 120.34 (CH), 121.70 (CH), 122.29 (CH), 122.44 (CH), 125.03 (Cq), 127.07 (Cq), 129.45 (CH), 129.66 (Cq), 134.40 (Cq), 136.27 (Cq). *m/z* (FAB^+) 294 M^+ (found: C, 73.23; H, 4.99; N, 9.50; M^+ 294.09240. $C_{18}H_{15}ClN_2$ requires C, 73.34; H, 5.13; N, 9.50; M 294.09238).

4.2.5.7. 1-[2-(1*H*-Indol-3-yl)-ethyl]-5-methyl-1*H*-indole 10k. Prepared from **9k**. Yellow oil. Yield 51%. R_f (EtOAc/petroleum ether, 20:80)0.36. ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.14 (2H, t, *J* 7.2), 4.27 (2H, t, *J* 7.2), 6.25 (1H, d, *J* 2.7), 6.55 (1H, d, *J* 1.8), 6.80 (1H, d, *J* 3.0), 6.94 (1H, d, *J* 8.1), 7.03–7.22 (4H, m), 7.33 (1H, s), 7.50 (1H, d, *J* 7.5), 7.64 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.48 (CH_3), 26.33 (CH_2), 47.05 (CH_2), 100.27 (CH), 109.16 (CH), 111.35 (CH), 112.64 (Cq), 118.53 (CH), 119.58 (CH), 120.69 (CH), 122.18 (CH), 122.37 (CH), 123.07 (CH), 127.17 (Cq), 128.15 (CH), 128.49 (Cq), 129.00 (Cq), 134.31 (Cq), 136.26 (Cq). *m/z* (FAB^+) 274 M^+ (found: C, 83.00; H, 6.60; N, 10.20; M^+ 274.14698. $C_{19}H_{18}N_2$ requires C, 83.18; H, 6.61; N, 10.21; M 274.14700).

4.2.5.8. 5-Fluoro-3-[2-(5-fluoro-3a,7a–dihydro-indol-1-yl)-ethyl]-1*H*-indole 10l. Yellow powder. Yield 84%. R_f (EtOAc/petroleum ether, 20:80) 0.12. Melting point 134–135 °C. ^1H NMR (300 MHz, DMSO) δ 3.18 (2H, t, *J* 7.4), 4.44 (2H, t, *J* 7.4), 6.40 (1H, d, *J* 2.7), 6.96 (2H, qd, *J* 2.4 and 9.0), 7.15 (1H, d, *J* 2.4), 7.30 (1H, t, *J* 2.7), 7.34 (1H, t, *J* 2.9), 7.36 (1H, d, *J* 4.5), 7.39 (1H, d, *J* 3.3), 7.46 (1H, dd, *J* 4.4 and 8.9), 10.99 (1H, br s). ^{13}C NMR (75 MHz, DMSO) δ 26.25 (CH_2), 46.98 (CH_2), 100.91 (CH, d, *J* 4.8), 103.51 (CH, d, *J* 22.7), 105.38 (CH, d, *J* 22.6), 109.34 (CH, d, *J* 8.5), 109.68 (CH, d, *J* 9.8), 111.17 (CH, d, *J* 9.6), 111.74 (Cq, d, *J* 4.8), 112.74 (CH, d, *J* 9.5), 125.78 (CH), 127.82 (Cq, d, *J* 9.5), 128.79 (Cq, d, *J* 10.1), 130.90 (CH), 132.90 (Cq), 133.31 (Cq), 157.28 (Cq, d, *J* 229.61), 157.49 (Cq, d, *J* 229.60). ^{19}F NMR (282 MHz, DMSO) (H decoupled) δ −125.44, −125.26. ^{19}F NMR (282 MHz, DMSO) (Non H decoupled) δ −125.43 (1F, td, *J* 4.3 and 9.8), −125.26 (1F, td, *J* 4.8 and 9.3). *m/z* (ES^+) 297 MH^+, (ES^-) 295 $(M-H)^-$; *m/z* (FAB^+) 296 M^+ (found: C, 72.99; H, 4.86; N, 9.53; M^+ 296.11256. $C_{18}H_{14}N_2F_2$ requires C, 72.96; H, 4.76; N, 9.45; M 296.11251).

4.2.5.9. 5-Chloro-3-[2-(5-chloro-3a,7a–dihydro-indol-1-yl)-ethyl]-1*H*-indole 10m. Yellow powder. Yield 68%. R_f (EtOAc/petroleum ether, 20:80) 0.16. Melting point 79–81 °C. ^{1}H NMR (300 MHz, DMSO) δ 3.15 (2H, t, *J* 7.5), 4.43 (2H, t, *J* 7.5), 6.37 (1H, d, *J* 3.0), 7.05 (1H, dd, *J* 8.7 and 2.1), 7.09 (1H, dd, *J* 9.0 and 2.1), 7.11 (1H, d, *J* 2.7), 7.34 (1H, d, *J* 8.4), 7.40 (1H, d, *J* 3.0), 7.48 (1H, d, *J* 9.0), 7.55 (1H, d, *J* 2.1), 7.57 (1H, d, *J* 2.1), 11.04, (1H, br s). ^{13}C NMR (75 MHz, DMSO) δ 26.05 (CH_2), 46.93 (CH_2), 100.61 (CH), 111.33 (Cq), 111.82 (CH), 113.30 (CH), 118.09 (CH), 119.93 (CH), 121.21 (CH), 121.35 (CH), 123.57 (Cq), 123.96 (Cq), 125.56 (CH), 128.65 (Cq), 129.62 (Cq), 130.84 (CH),134.58 (Cq), 134.96 (Cq). *m*/*z* (ES^-) 327 $(M-H)^-$; *m*/*z* (FAB^+) 328 M^+ (found: C, 65.59; H, 4.23; N, 8.46; M^+ 328.05345. $C_{18}H_{14}N_2Cl_2$ requires C, 65.67; H, 4.29; N, 8.51; M 328.05340).

4.2.5.10. 5-Methyl-3-[2-(5-methyl-3a,7a–dihydro-indol-1-yl)-ethyl]-1*H*-indole 10n. Tan powder. Yield 76%. R_f (EtOAc/petroleum ether, 20:80) 0.29. Melting point 109–110 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.44 (3H, s), 2.46 (3H, s), 3.20 (2H, t, *J* 7.5), 4.43 (2H, t, *J* 7.5), 6.35 (1H, d, *J* 3.6), 6.99 (2H, td, *J* 8.3 and 1.4), 7.04 (1H, d, *J* 2.4), 7.26 (1H, d, *J* 3.0), 7.33 (1H, d, *J* 8.7), 7.37–7.41 (3H, m), 10.77 (1H, br s). ^{13}C NMR (75 MHz, DMSO) δ 21.62 (CH_3), 21.81 (CH_3), 26.44 (CH_2), 46.88 (CH_2), 100.28 (CH), 109.87 (CH), 111.00 (Cq), 111.63 (CH), 118.37 (CH), 120.59 (CH), 123.05 (CH), 123.14 (CH), 123.60 (CH), 127.30 (Cq), 127.78 (Cq), 127.86 (Cq), 129.00 (CH + Cq), 134.61 (Cq),135.14 (Cq). *m*/*z* (ES^+) 289 MH^+, (ES^-) 287 $(M-H)^-$; *m*/*z* (FAB^+) 288 M^+ (found: C, 83.35; H, 6.92; N, 9.68; M^+ 288.16271. $C_{20}H_{20}N_2$ requires C, 83.30; H, 6.99; N, 9.71; M 288.16265).

4.2.6. General procedure for the preparation of 1,2-bis-(2,3-dihydro-indol-1-yl)-1,2-dione derivatives 11a–e

To a solution of indoline (22.93 mmol) in dry THF (15 mL) under N_2 atmosphere, cooled in an ice bath, was added K_2CO_3 (45.85 mmol). The mixture was stirred under N_2 atmosphere and the corresponding acyl chloride (11.46 mmol) in solution in dry THF (16 mL) under N_2 atmosphere was added slowly. The stirring was maintained 2 hours at room temperature, and water (230 mL) was added. After 15 min. supplementary stirring the expected compound (**1a–e**) was filtered, washed with water and dried with a freeze drier over night.

4.2.6.1. 1,2-Bis-(2,3-dihydro-indol-1-yl)-ethane-1,2-dione 11a. Pink powder. Yield 87%. Three rotamers designated A, B, C were observed in ratio 15:4:1 (from the triplet signals (^{1}H) at 3.97, 4.14 and 4.21 ppm). Melting point 191–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (*major rotamer* A) 3.13 (4H, t, *J* 8.4), 4.14 (4H, t, *J* 8.4), 6.84–7.24 (6H, m), 8.15 (2H, d, *J* 7.5). δ (distinct peaks for the *minor rotamer* B) 3.97 (4H, t, *J* 8.4), 8.23 (2H, d, *J* 8.1). δ (distinct peaks for the *minor rotamer* C) 4.21 (4H, t, *J* 8.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ (*major rotamer* A) 28.23 ($2CH_2$), 48.39 ($2CH_2$), 117.52 (2CH), 124.90 (2CH), 125.11 (2CH), 127.69 (2CH), 132.15 (2Cq), 141.69 (2Cq), 161.08 (2Cq). δ (distinct peaks for the *minor rotamer* B) 28.06 ($2CH_2$), 46.87 ($2CH_2$), 112.61 (2CH), 124.64 (2CH), 125.91 (2CH), 128.09 (2CH), 133.01 (2Cq), 141.45 (2Cq), 161.78 (2Cq). δ (distinct peaks for the *minor rotamer* C) 26.71 ($2CH_2$), 47.74 ($2CH_2$), 112.51 (2CH), 124.74 (2CH), 125.25 (2CH), 127.84 (2CH), 132.08 (2Cq), 139.40 (2Cq). *m*/*z* (ES^+) 293 MH^+, 585 (2 M+H)$^+$; (ES^-) 291 $(M-H)^-$; (FAB^+) 293 $(M+H)^+$ (found: C, 74.08; H, 5.46; N, 9.47; MH^+ 293.12898. $C_{18}H_{16}N_2O_2$ requires C, 73.96; H, 5.52; N, 9.58; MH 293.12900).

4.2.6.2. 1,3-Bis-(2,3-dihydro-indol-1-yl)-propane-1,3-dione 11b. Very poor solubility in $CDCl_3$. Not soluble in all other D-solvents. Tan powder. Yield 86%. Melting point 246–248 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (4H, t, *J* 8.2); 3.74 (2H, br s); 4.28 (4H, t, *J* 8.2); 7.04 (2H, t, *J* 7.5); 7.20 (4H, apparent t, *J* 5.7); 8.22 (2H, d, *J* 7.8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.05 ($2CH_2$); 46.09 (CH_2 weak signal); 48.77 ($2CH_2$); 117.30 (2CH); 124.21 (2CH); 124.60 (2CH); 127.55 (2CH); 131.50 (2Cq); 142.67 (2Cq); 164.43 (2Cq). *m*/*z* (ES^+) 307 MH^+; *m*/*z* (FAB^+) 307 MH^+, (found: C, 74.48; H, 6.00; N, 9.07; MH^+ 307.14467. $C_{19}H_{18}N_2O_2$ requires C, 74.48; H, 5.93; N, 9.15; MH^+ 307.14465).

4.2.6.3. 1,4-Bis-(2,3-dihydro-indol-1-yl)-butane-1,4-dione 11c. Brown powder. Yield 69%. Melting point 242–243 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (4H, s), 3.14 (4H, t, *J* 8.4), 4.09 (4H, t, *J* 8.4), 6.92 (2H, distorted triplet, estimated *J* 7.1), 7.09 (4H, distorted t, estimated *J* 6.9), 8.12 (2H, d, *J* 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.03 ($2CH_2$), 30.44 ($2CH_2$), 47.92 ($2CH_2$), 116.93 (2CH), 123.59 (2CH), 124.54 (2CH), 127.47 (2CH), 131.15 (2Cq), 143.02 (2Cq), 170.10 (2Cq). *m*/*z* (ES^+) 321 MH^+, 641 (2 M+H)$^+$; (FAB^+) 321 M^+ (found: C, 75.09; H, 6.20; N, 8.73; MH^+ 321.16037. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74; MH 321.16030).

4.2.6.4. 1,5-Bis-(2,3-dihydro-indol-1-yl)-pentane-1,5-dione 11d. Beige fine powder. Yield 83%. Melting point 214–215 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (2H, quintet, *J* 6.7, weak signal); 2.62 (4H, t, *J* 6.7); 3.18 (4H, t, *J* 8.4); 4.07 (4H, t, *J* 8.4); 7.00 (2H, t, *J* 7.4); 7.17 (2H, d, *J* 7.5); 7.19 (2H, t, *J* 7.5); 8.23 (2H, d, *J* 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.40 (CH_2, weak signal); 28.04 ($2CH_2$); 34.69 ($2CH_2$); 47.98 ($2CH_2$); 116.89 (2CH); 123.56(2CH); 124.55 (2CH); 127.49 (2CH); 131.15 (2Cq); 143.03 (2Cq); 170.93 (2Cq). *m*/*z* (ES^+) 335 MH^+; *m*/*z* (FAB^+) 335 MH^+, (found: C, 75.54; H, 6.63; N, 8.28; MH^+ 335.17599. $C_{21}H_{22}N_2O_2$ requires C, 75.41; H, 6.64; N, 8.38; MH^+ 335.17595).

4.2.6.5. 1,6-Bis-(2,3-dihydro-indol-1-yl)-hexane-1,6-dione 11e. Very poor solubility in $CDCl_3$. Not soluble in all other D-solvents. Slightly pink powder. Yield 76%. Melting point 245–247 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (4H, m), 2.53 (4H, br s), 3.21 (4H, t, *J* 8.3), 4.09 (4H, t, *J* 8.3), 7.02 (2H, t, *J* 7.8), 7.20 (4H, distorted t, estimated *J* 7.8), 8.25 (2H, d, *J* 8.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.29 ($2CH_2$), 28.04 ($2CH_2$), 35.79 ($2CH_2$), 48.01 ($2CH_2$), 116.98 (2CH), 123.52 (2CH), 124.50 (2CH), 127.51 (2CH), 131.06 (2Cq), 143.07 (2Cq), 171.03 (2Cq). *m*/*z* (ES^+) 349 MH^+; (FAB^+) 349 MH^+ (found: C, 75.93; H, 6.84; N, 7.92; MH^+ 349.19165. $C_{22}H_{24}N_2O_2$ requires C, 75.83; H, 6.94; N, 8.04; MH 349.19160).

4.2.7. General procedure for the preparation of 1,2-bis-(2,3-dihydro-indol-1-yl) derivatives 12a–e

To a suspension of the lithium aluminium hydride (37.45 mmol) in dry ether (85 mL) under N_2 atmosphere, was added slowly a suspension of the 1,2-Bis-(2,3-dihydro-indol-1-yl)-1,2-dione derivatives **11a–e** (4.68 mmol) in dry THF (30.5 mL). The mixture was heated under reflux at least over night with a calcium chloride exit, and cooled to room temperature then to 0 °C. A saturated solution of Na_2SO_4 was added slowly, until the mixture became milky white. After filtration, the organic and aqueous layers were evaporated. The crude was redissolve in dichloromethane, washed with water (4 × 100 mL), dried (Na_2SO_4) and the organic layer concentrated to give crude product. A purification done using a column chromatography of silica gel with the following gradient of eluent: ethyl acetate/petroleum ether (2.5:97.5), ethyl acetate/petroleum ether (5:95), ethyl acetate/petroleum ether (10:90), ethyl acetate/petroleum ether (20:80), and ethyl acetate gave the title compound **12a–e**.

4.2.7.1. 1,2-Bis-(2,3-dihydro-indol-1-yl)-ethane 12a. Pale pink powder. Yield 36%. Melting point 75–76 °C. R_f (EtOAc/petroleum ether, 10: 90) 0.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (4H, t, *J* 8.4), 3.23 (4H, s), 3.35 (4H, t, *J* 8.4), 6.41 (2H, d, *J* 8.1), 6.56 (2H, t, *J*

7.1), 6.97 (4H, apparent t, estimated *J* 6.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.80 ($2CH_2$), 47.60 ($2CH_2$), 53.70 ($2CH_2$), 106.73 (2CH), 117.66 (2CH), 124.58 (2CH), 127.46 (2CH), 129.86 (2Cq), 152.41 (2Cq). *m*/*z* (ES$^+$) 265 MH$^+$; (FAB$^+$) 264 M$^+$ (found: C, 81.81; H, 7.58; N, 10.67; M$^+$ 264.16262. $C_{18}H_{20}N_2$ requires C, 81.78; H, 7.62; N, 10.60; M 264.16265).

4.2.7.2. 1,3-Bis-(2,3-dihydro-indol-1-yl)-propane 12b. Yellow oil. Yield 39%. R_f (petroleum ether/ethyl acetate: 95/5) 0.22. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (2H, quintet, *J* 7.1, weak signal), 2.97 (4H, t, *J* 8.3), 3.17 (4H, t, *J* 7.1), 3.35 (4H, t, *J* 8.3), 6.48 (2H, d, *J* 8.1), 6.64 (2H, t, *J* 7.5), 7.02–7.09 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.65 (CH_2), 26.70 ($2CH_2$), 47.22 ($2CH_2$), 53.43 ($2CH_2$), 107.07 (2CH), 117.58 (2CH), 124.48 (2CH), 127.40 (2CH), 130.06 (2Cq), 132.78 (2Cq). *m*/*z* (ES$^+$) 279 MH$^+$; *m*/*z* (FAB$^+$) 278 M$^+$ (found: C, 82.12 ; H, 7.91 ; N, 9.92 ; M$^+$ 278.17821. $C_{19}H_{22}N_2$ requires C, 82.06; H, 7.95; N, 10.06; M$^+$ 278.17830).

4.2.7.3. 1,4-Bis-(2,3-dihydro-indol-1-yl)-butane 12c. White solid. Yield 76%. Melting point 96–97 °C. R_f (EtOAc/petroleum ether, 10:90) 0.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (4H, quintet, *J* 3.2), 2.88 (4H, t, *J* 8.3), 3.03 (4H, distorted t, estimated *J* 6.4), 3.27 (4H, t, *J* 8.3), 6.39 (2H, d, *J* 8.1), 6.56 (2H, t, *J* 7.5), 6.98 (2H, t, *J* 7.5), 6.99 (2H, d, *J* 7.5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.20 ($2CH_2$), 28.60 ($2CH_2$), 49.20 ($2CH_2$), 53.16 ($2CH_2$), 106.86 (2CH), 117.41 (2CH), 124.41 (2CH), 127.30 (2CH), 130.01 (2Cq), 152.69 (2Cq). *m*/*z* (FAB$^+$) 292 M$^+$ (found: C, 82.12; H, 8.26; N, 9.63; M$^+$ 292.19399. $C_{20}H_{24}N_2$ requires C, 82.15; H, 8.27; N, 9.58; M 292.19395).

4.2.7.4. 1,5-Bis-(2,3-dihydro-indol-1-yl)-pentane 12d. Yellow oil. Yield 66%. R_f (petroleum ether–ethyl acetate, 95:5) 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43–1.53 (2H, m, weak signal); 1.66 (4H, quintet, *J* 7.5); 2.94 (4H, t, *J* 8.4); 3.05 (4H, t, *J* 7.5); 3.33 (4H, t, *J* 8.4); 6.45 (2H, d, *J* 8.1); 6.62 (2H, td, *J* 7.4 and 0.9); 7.05 (4H, apparent t, estimated *J* 7.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.99 (CH_2); 27.35 ($2CH_2$); 28.65 ($2CH_2$); 49.33 ($2CH_2$); 53.18 ($2CH_2$); 106.87 (2CH); 117.35 (2CH); 124.43 (2CH); 127.35 (2CH); 130.03 (2Cq); 152.77 (2Cq). *m*/*z* (ES$^+$) 307 MH$^+$; *m*/*z* (FAB$^+$) 306 M$^+$, (found: C, 82.35; H, 8.67; N, 8.98; M$^+$ 306.20969. $C_{21}H_{26}N_2$ requires C, 82.29; H, 8.57; N, 9.14; M$^+$ 306.20960).

4.2.7.5. 1,6-Bis-(2,3-dihydro-indol-1-yl)-hexane 12e. White powder. Yield 50%. Melting point 77–78 °C. R_f (EtOAc/petroleum ether, 10:90) 0.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (4H, br s), 1.54 (4H, distorted broad t, estimated *J* 5.7), 2.86 (4H, t, *J* 8.4), 2.96 (4H, t, *J* 7.4), 3.24 (4H, t, *J* 8.4), 6.37 (2H, d, *J* 8.1), 6.54 (2H, t, *J* 7.2), 6.96 (2H, t, *J* 6.9), 6.98 (2H, d, *J* 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.23 ($2CH_2$), 27.44 ($2CH_2$), 28.65 ($2CH_2$), 49.31 ($2CH_2$), 53.15 ($2CH_2$), 106.89 (2CH), 117.33 (2CH), 124.43 (2CH), 127.35 (2CH), 130.04 (2Cq), 152.81 (2Cq). *m*/*z* (ES$^+$) 321 MH$^+$; (FAB$^+$) 320 M$^+$ (found: C, 82.39; H, 8.82; N, 8.68; M$^+$ 320.22521. $C_{22}H_{28}N_2$ requires C, 82.45; H, 8.81; N, 8.74; M 320.22525).

4.2.8. General procedure for the preparation of 1,2-bis-(indol-1-yl) derivatives 13a–e

To a solution of 1,2-Bis-(2,3-dihydro-indol-1-yl) derivatives (**12a–e**) (1.71 mmol) in $CHCl_3$ (9.7 mL) was added activated manganese dioxide (23.94 mmol). The mixture was heated under reflux for 60 h. After cooling to room temperature, the crude suspension was filtered through Celite and the filtrate was concentrated under vacuum. The crude product was purified by column chromatography on silica gel with the following gradient of solvent ethyl acetate/petroleum ether (10:90) and ethyl acetate to give the title compound **14a–e**.

4.2.8.1. 1,2-Bis-(indol-1-yl)-ethane 13a. Beige solid. Yield 67%. Melting point 62–63 °C. R_f (EtOAc/petroleum ether, 10:90) 0.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (4H, s), 6.30 (2H, d, *J* 3.0), 6.48 (2H, d, *J* 3.3), 7.01–7.15 (6H, m), 7.54 (2H, d, *J* 7.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.23 ($2CH_2$), 101.88 (2CH), 108.79 (2CH), 119.72 (2CH), 121.27 (2CH), 121.83 (2CH), 128.02 (2CH), 128.92 (2Cq), 135.60 (2Cq). *m*/*z* (ES$^+$) 261 MH$^+$; (FAB$^+$) 260 M$^+$ (found: C, 83.07; H, 6.18; N, 10.66; M$^+$ 260.13140. $C_{18}H_{16}N_2$ requires C, 83.04; H, 6.19; N, 10.76; M 260.13135).

4.2.8.2. 1,3-Bis-(indol-1-yl)-propane 13b. Yellow oil. Yield 30%. R_f (petroleum ether/ethyl acetate: 80:20) 0.64. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (2H, quintet, *J* 6.9), 4.08 (4H, t, *J* 6.9), 6.52 (2H, dd, *J* 3.2 and 0.5), 7.04 (2H, d, *J* 3.3), 7.08–7.21 (6H, m), 7.64 (2H, td, *J* 7.8 and 1.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.20 (CH_2), 43.43 ($2CH_2$), 101.66 (2CH), 109.30 (2CH), 119.55 (2CH), 121.16 (2CH), 121.70 (2CH), 127.63 (2CH), 128.78 (2Cq), 135.89 (2Cq). (ES$^+$) 275 MH$^+$ (FAB$^+$) 274 M$^+$. EA (found: C, 83.17; H, 6.58; N, 10.27; M$^+$ 274.14693. $C_{19}H_{18}N_2$ requires C, 83.16; H, 6.63; N, 10.21; M 274.14700).

4.2.8.3. 1,4-Bis-(indol-1-yl)-butane 13C. Beige solid. Yield 75%. Melting point 78–79 °C. R_f (EtOAc/petroleum ether, 10: 90) 0.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (4H, quintet, *J* 3.2), 3.90 (4H, distorted t, estimated *J* 6.3), 6.37 (2H, d, *J* 3.3), 6.86 (2H, d, *J* 3.0), 7.00 (2H, distorted td, estimated *J* 8.6 and 1.2), 7.10 (2H, td, *J* 7.2 and 1.1), 7.16 (2H, distorted d, estimated *J* 8.1), 7.53 (2H, d, *J* 7.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.78 ($2CH_2$), 45.93 ($2CH_2$), 101.34 (2CH), 109.35 (2CH), 119.43 (2CH), 121.14 (2CH), 121.58 (2CH), 127.74 (2CH), 128.70 (2Cq), 135.94 (2Cq). *m*/*z* (ES$^+$) 289 MH$^+$; (FAB$^+$) 288 M$^+$ (found: C, 83.25; H, 6.83; N, 9.85; M$^+$ 288.16271. $C_{20}H_{20}N_2$ requires C, 83.30; H, 6.99; N, 9.71; M 288.16265).

4.2.8.4. 1,5-Bis-(indol-1-yl)-pentane 13d. Pale yellow powder. Yield 47%. Melting point 80–82 °C. R_f (petroleum ether–ethyl acetate, 80:20) 0.64. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (2H, m, weak signal); 1.71 (4H, quintet, *J* 7.3); 3.94 (4H, t, *J* 7.3); 6.38 (2H, d, *J* 3.2); 6.90 (2H, d, *J* 3.2); 7.01 (2H, td, *J* 7.3 and 0.8); 7.11 (2H, td, *J* 7.6 and 1.1); 7.19 (2H, d, *J* 8.1); 7.54 (2H, d, *J* 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.52 (CH_2 weak signal); 29.95 ($2CH_2$); 46.19 ($2CH_2$); 101.14 (2CH); 109.37 (2CH); 119.34 (2CH); 121.07 (2CH); 121.48 (2CH); 127.79 (2CH); 128.67 (2Cq); 135.94 (2Cq). *m*/*z* (ES$^+$) 303 MH$^+$; *m*/*z* (FAB$^+$) 302 M$^+$, (found: C, 83.42; H, 7.38; N, 9.32; M$^+$ 302.17824. $C_{21}H_{22}N_2$ requires C, 83.39; H, 7.35; N, 9.26; M$^+$ 302.17830).

4.2.8.5. 1,6-Bis-(indol-1-yl)-hexane 13e. White powder. Yield 70%. Melting point 83–84 °C. R_f (EtOAc/petroleum ether, 10: 90) 0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (4H, quintet, *J* 3.8), 1.69 (4H, quintet, *J* 6.9), 3.95 (4H, t, *J* 6.9), 6.38 (2H, d, *J* 3.3), 6.93 (2H, d, *J* 3.3), 7.00 (2H, t, *J* 7.4), 7.10 (2H, t, *J* 7.4), 7.20 (2H, d, *J* 8.1), 7.54 (2H, d, *J* 7.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.63 ($2CH_2$), 30.10 ($2CH_2$), 46.23 ($2CH_2$), 101.01 (2CH), 109.38 (2CH), 119.26 (2CH), 121.02 (2CH), 121.41 (2CH), 127.77 (2CH), 128.63 (2Cq), 135.97 (2Cq). *m*/*z* (ES$^+$) 317 MH$^+$; (FAB$^+$) 316 M$^+$ (found: C, 83.54; H, 7.53; N, 8.95; M$^+$ 316.19400. $C_{22}H_{24}N_2$ requires C, 83.50; H, 7.64; N, 8.85; M 316.19395).

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