Design, synthesis and biological activity of new CDK4-specific inhibitors, based on fascaplysin

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We present the design, synthesis, and biological activity of three classes of tryptamine derivatives, which are non-planar analogues of the toxic anti-cancer agent fascaplysin. We show these compounds to be selective inhibitors of CDK4 over CDK2, the most active compound **9q** has an IC_{50} for the inhibition of CDK4 of 6 μM.

Introduction

Fascaplysin **1** (Fig. 1), is a pentacyclic quaternary salt originally isolated from the Fijian sponge *Fascaplysinopsis* Bergquist sp.,[1] which inhibits the growth of several microbes, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Saccharomyces cerevisiae*, and suppresses the proliferation of mouse leukemia cells L-1210 with $ED_{50} = 0.2$ μm mL^{-1}. Fascaplysin has also been reported to specifically inhibit CDK4, causing G_1 arrest of tumour (U2-OS, HCT-116) and normal (MRC-5) cells.[2]

The inhibition of cyclin-dependent kinases, CDKs, by small molecules is an area of major current interest in the anti-cancer field.[3] CDKs are a vital component of the check-points in the various phases of the cell division cycle,[4] they are required for healthy cell growth and proliferation. CDK4 has a very specific function in the G_0–G_1 phase of the cell division cycle—the CDK4–cyclin D1 complex phosphorylates the protein retinoblastoma (pRB), an active repressor of the E2F family of transcription factors. CDK4-mediated hyperphosphorylation of pRB facilitates liberation of E2F proteins and allows them to carry out their transcriptional activation roles. This enables the cell to pass through the restriction point, an early G_1 checkpoint, where the cell commits itself to complete one cell division cycle.[5] Inhibition of CDK4 is therefore a vital factor in controlling the rate of cell proliferation. In normal cells this is carried out by CDK4-specific cyclin-dependent kinase inhibitors (CKIs) such as p16; in tumour cells, inactivating mutations which result in the underproduction of p16 are common.[6] Moreover, the activating partner cyclin D1 and the catalytic subunit CDK4 are often either overproduced or hyper-activated in many tumour cells. A small-molecule inhibitor of CDK4 would result in early G_1 arrest of the cell cycle and thus prevent uncontrolled cell growth, the hallmark of all tumour cells. Given that CDK4 is a kinase, the most obvious structures to act as inhibitors of CDK4 are analogues of ATP.[7] Additionally, it is known that structures totally unrelated to ATP, such as staurosporine and flavopiridol, are also effective inhibitors of CDK4.[3]

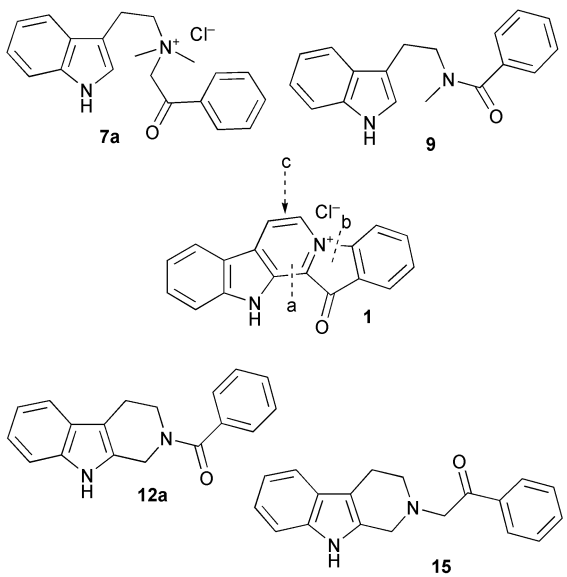

Fig. 1 Strategy used to produce the non-planar tryptamine derivatives **7a**, **9**, **12a** and **15** from fascaplysin **1**.

Fascaplysin **1** cannot be used as an anti-cancer drug because it is highly toxic—the potential for its planar structure to intercalate with DNA has been suggested as a possible explanation.[8] The aim of the current study is therefore to devise a potent, non-toxic (non-planar) CDK4 inhibitor based on the structure of fascaplysin.

Results and discussion

The general approach we adopt for generating non-toxic inhibitors of CDK4 involves the synthesis of non-planar analogues of

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fascaplysin, thus avoiding their interchelation with DNA. To enhance the chances of success, these compounds are designed to maintain most of the key interactions thought to occur between fascaplysin and CDK4. Since the 3-dimensional structure of CDK4 has not been determined, structural information is obtained by molecular modelling. Thus, prior to embarking on the synthesis of potential inhibitors, we first carried out *in silico* studies based on our homology model of CDK4, produced using the known crystal structures of CDK2 and CDK6 as templates (Fig. 3). Our dockings of ATP and fascaplysin suggest that inhibition of CDK4 activity by fascaplysin arises from binding to the same site as ATP (Fig. 2a). This suggests that a key feature of fascaplysin binding is the double hydrogen bond to Val 96[7] (Fig. 2b).

In this study, the general strategy we adopt for removing toxicity[10] (Fig. 1) comprises releasing bonds a and b in fascaplysin **1** and changing double bond c into a single bond, leading to the tryptamine derivative **7a**. This compound contains the structural components of fascaplysin, but it is non-planar and is therefore not likely to intercalate with DNA. This was our first generation compound, which had a great deal of flexibility due to rotation around six bonds. Herein we also describe the second generation compounds **9a–q** which have a shorter chain between the indole and the benzene ring and an amide bond leading to fewer degrees of rotational freedom in the molecules. In third generation compounds **12a–q** and **16** we have reduced still further the rotational freedom of the structure by incorporating the tetrahydro β-carboline structure. Hence, compounds **5a–c**, **7a–c**, **9a–q**, **10**, **12a–q**, and **13–16** were synthesised (Schemes 1–3). These compounds are not planar and so intercalation in DNA is very unlikely.

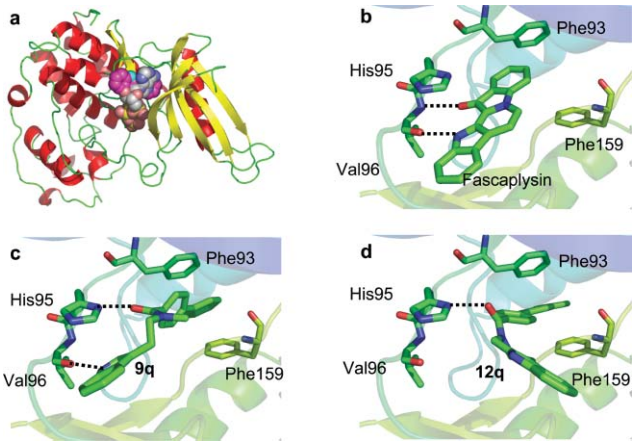
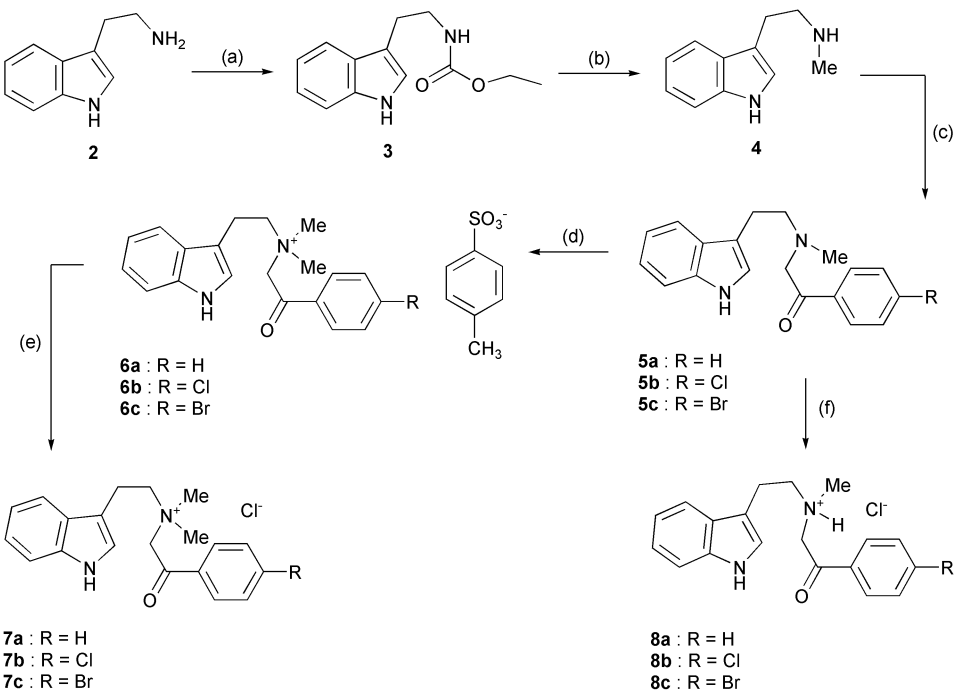


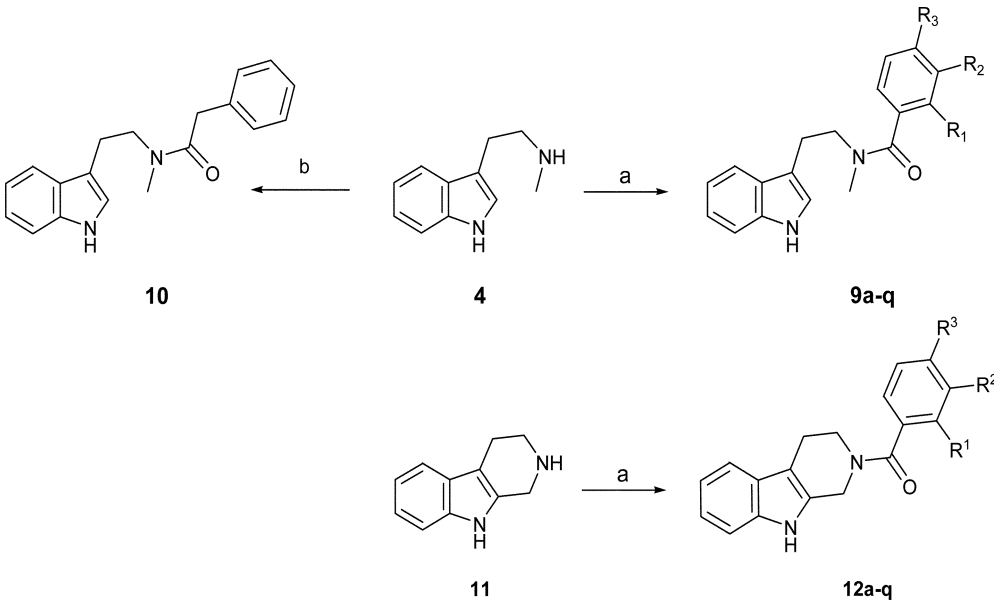
Fig. 2 The active site of our CDK4 model. (a) Cartoon representation of the overall structure of the CDK4, with the positions of ATP–Mg^{2+} (C in grey, N in slate, O in salmon, P in yellow) and fascaplysin (C in magenta, N in cyan, O in red) shown. (b) Predicted binding mode of fascaplysin. (c) Predicted binding mode of the most potent compound, **9q**; note the π–π interactions of the benzoid ring with Phe 93 and Phe 159. (d) Predicted binding mode of **12q**—this weaker inhibitor is structurally similar to, but more conformationally constrained than, **9q**. Hydrogen bonds are shown as dashed lines. Figures produced using PyMol.[9]

First generation compounds

The synthesis of **7a** is shown in Scheme 1. Tryptamine **2** was reacted with ethyl chloroformate to give the urethane **3** in 95% yield.[11] Reduction with lithium aluminium hydride produced



Scheme 1 *Reagents and conditions*. (a) Ethyl chloroformate, NaOH 4 M, $CHCl_3$, 3 h, 95%; (b) $LiAlH_4$, THF, N_2, reflux, 1 h, 89%; (c) $BrCH_2COC_6H_4R$, toluene, N_2, $NaHCO_3$, Na_2SO_4, H_2O, 4 h, 49–61%; (d) methyl-*p*-toluenesulfonate, acetonitrile, reflux, 4 h; (e) Dowex® Cl^- 1 × 8–400 ion exchange resin, overnight stirring and column, 46–53%; (f) HCl gas, Et_2O or CH_2Cl_2, <1 min, 46–88%.



	R^1	R^2	R^3			R^1	R^2	R^3
9a & 12a	H	H	H		**9j & 12j**	H	Br	H
9b & 12b	H	H	^{t}Bu		**9k & 12k**	H	H	Br
9c & 12c	F	H	H		**9l & 12l**	OMe	H	H
9d & 12d	H	F	H		**9m& 12m**	H	OMe	H
9e & 12e	H	H	F		**9n & 12n**	Me	H	H
9f & 12f	Cl	H	H		**9o & 12o**	H	Me	H
9g & 12g	H	Cl	H		**9p & 12p**	H	H	Me
9h & 12h	H	H	Cl		**9q & 12q**	H	H	Ph
9i & 12i	Br	H	H					

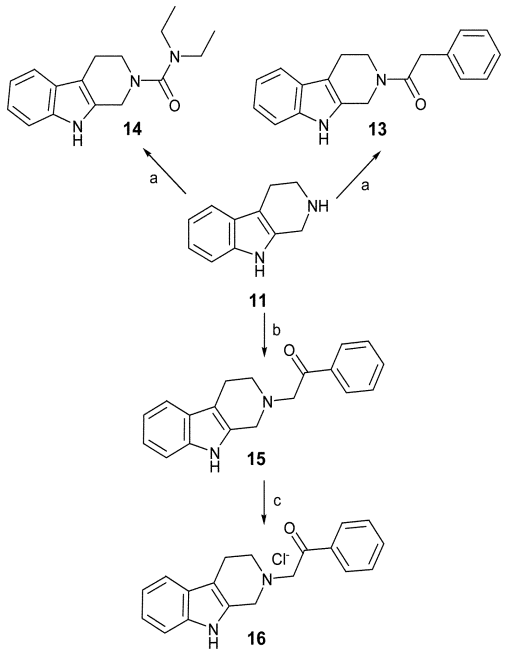
Scheme 2 *Reagents and conditions*. (a) $ClCOC_6H_4R$, $NaOH_{(aq)}$ 4 M, CH_2Cl_2, 0 °C, 15 min then RT, 3 h, 37–99%; (b) $ClCOCH_2C_6H_5$, $NaOH_{(aq)}$ 4 M, CH_2Cl_2, 0 °C, 15 min then RT, 3 h, 37–99%.

N-methyltryptamine **4** in 89% yield.[11] This intermediate **4** was then reacted with different 4-substituted bromoacetophenone derivatives to afford the compounds **5a–c** in yields between 49% and 61% after column chromatography.[12] The tertiary amines **5a–c** were unstable after a week when stored at −25 °C, as indicated by NMR. These materials were reacted separately with methyl-*p*-toluene sulfonate to furnish the tosylate salts **7a–c**. Ion exchange using Dowex® Cl^- 1 × 8–400 ion exchange resin produced the chloride salts **7a–c** in yields between 46% and 53%.[13]

The CDK4 activities of compounds **7a–c** and **5a–c** have been tested for some of the biochemical features that would identify a CDK4 inhibitor. In accord with our predictions, the IC_{50} values (Table 1) show that all compounds are CDK4 active. Furthermore, the CDK2 activities of compounds **7a–c** and **5a–c**, measured in terms of IC_{50} values, reveal that all twelve tryptamine derivatives are CDK4 selective compared to CDK2 (Table 1). Representative compounds (**7a–c**), like fascaplysin, block growth of cancer cells in the G_1 phase of the cell division cycle and they also maintain the G_1 block of serum-starved cells. However, unlike fascaplysin, the compounds do not intercalate DNA or inhibit topoisomerase I which we believe contributes to the general toxicity of fascaplysin (manuscript in preparation).

Second generation compounds

As mentioned above the second generation compounds **9a–q** and **10** are amide derivatives of *N*-methyl tryptamine. The series of compounds were readily synthesised as shown in Scheme 2 and the results for the inhibition of CDK4 and CDK2 are shown in Table 1. The first clear trend from the results is the selectivity for inhibition of CDK4 compared to CDK2. The parent compound **9a** shows a modest IC_{50} of 88 μM; this activity changes when



Scheme 3 *Reagents and conditions*. (a) $ClCOC_6H_4R$, $NaOH_{(aq)}$ 4 M, CH_2Cl_2, 0 °C, 15 min then RT, 3 h, 63–91%; (b) $BrCH_2COC_6H_5$, toluene, N_2, $NaHCO_3$, Na_2SO_4, H_2O, 4 h, 61%; (c) HCl gas, CH_2Cl_2, 3 min, 95%.

halogen substituents are present on the benzenoid ring and shows a consistent improvement for *para* substituted derivatives (**9e**, *p*-F, IC_{50} 59; **9h**, *p*-Cl, IC_{50} 38 and **9k**, *p*-Br, IC_{50} 37 μM). The trend of improved activity, lower IC_{50}, for *para* substituted compounds is continued with **9p**, *p*-Me, IC_{50} 63; **9b**, *p*-^{t}Bu, IC_{50} 49 μM and the best result **9q**, *p*-Ph, IC_{50} 6 μM. The phenyl substitution in the *para* position appears responsible for enhanced inhibition of the series **9** compounds.

Third generation compounds

In the third generation compounds **12a–q** and **13–16** we have investigated the effect of a tetrahydro β-carboline structure, which further reduced the degree of conformational flexibility of the inhibitor. The series of compounds **12a–q**, **13** and **14** were readily synthesised by the same method used for **9a–q** as shown in Schemes 2 and 3. The β-carboline **11** was reacted with 2-bromoacetophenone in the presence of sodium hydrogen carbonate and sodium sulfate to produce **15** in 61% yield. The HCl salt **16** was then formed by bubbling HCl gas into a solution of **15** in dichloromethane. Surprisingly the resultant salt was soluble in dichloromethane, as no precipitate was formed, so the mixture was evaporated off to give the HCl salt **16** with 95% yield which was then characterized by NMR and mass spectroscopy. NMR clearly showed two NH signals (10.98 and 11.23 ppm) and the expected mass was recorded in a FAB experiment.

The results for the inhibition of CDK4 and CDK2 are shown in Table 1. Again we see that all compounds tested are selective inhibitors of CDK4 compared to CDK2. The parent structure **12a** has a modest IC_{50} of 92 μM, which is improved by halogen substituents of which **12e**, *p*-F, IC_{50} 55; **12g**, *m*-Cl, IC_{50} 56 and **12j**, *m*-Br, IC_{50} 32 μM are the most active. It is not clear at this stage why the *m*-Cl, **12g**, and *m*-Br, **12j**, compounds are better inhibitors in this series compared with *p*-Cl, **9h**, and *p*-Br, **9k**. The *meta* methyl

Table 1 CDK4 activity *versus* CDK2 activity

Compound	[a]CDK4 measured IC_{50}/μM	[b]CDK2 measured IC_{50}/μM
Fascaplysin **1**	0.55[10]	500
7a	68 ± 8	720 ± 16
7b	50 ± 7	605 ± 10
7c	50 ± 6	665 ± 18
5a	212 ± 16 (91 ± 7)[c]	1310 ± 21 (860 ± 14)[c]
5b	90 ± 11 (110 ± 9)[c]	910 ± 7 (911 ± 24)[c]
5c	80 ± 11.5 (84 ± 9)[c]	921 ± 16 (932 ± 20)[c]
9a	88 ± 6	1523 ± 38
9b	49 ± 7	658 ± 23
9c	103 ± 9	1230 ± 29
9d	88 ± 9	765 ± 27
9e	59 ± 7	850 ± 34
9f	46 ± 4	784 ± 20
9g	109 ± 8	1120 ± 38
9h	38 ± 6	731 ± 26
9i	74 ± 7	635 ± 40
9j	95 ± 7	584 ± 24
9k	37 ± 5	580 ± 38
9l	79 ± 9	849 ± 30
9m	81 ± 4	938 ± 47
9n	113 ± 8	1125 ± 40
9o	78 ± 8	830 ± 31
9p	63 ± 6	790 ± 27
9q	6 ± 1	521 ± 12
10	28 ± 4	959 ± 18
12a	92 ± 10	490 ± 40
12b	44 ± 9	720 ± 24
12c	61 ± 7	800 ± 22
12d	72 ± 5	680 ± 20
12e	55 ± 6	851 ± 22
12f	98 ± 10	1197 ± 30
12g	56 ± 6	873 ± 38
12h	76 ± 10	674 ± 25
12i	44 ± 5	679 ± 31
12j	32 ± 6	675 ± 30
12k	51 ± 4	875 ± 37
12l	26 ± 6	861 ± 42
12m	24 ± 4	766 ± 33
12n	68 ± 8	750 ± 31
12o	27 ± 5	818 ± 35
12p	45 ± 6	751 ± 34
12q	64 ± 9	829 ± 28
13	95 ± 11	1450 ± 42
14	54 ± 5	926 ± 35
15	62 ± 7	1301 ± 21
16	34 ± 4	1467 ± 39

[a] CDK4–cyclin D1 assay, using GST-RB152 fusion protein as the substrate. [b] CDK2–cyclin A assay using histone H1 as the substrate. [c] The values in parentheses () indicate the results of the HCl salts of **5a–c**, *e.g.* **8a–c**.

derivative **12o** has an IC_{50} of 27 μM making it the best of the three methyl derivatives, while *p*-^{t}Bu, **12b**, IC_{50} 44 and *p*-phenyl, **12q**, IC_{50} 64 μM are better inhibitors than the parent compound **12a**. The *meta*-methoxy compound **12m**, IC_{50} 24 μM, is the best result of this series and follows the trend of *meta* compounds being most active.

Biphenyl-4-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-methylamide 9q, the most potent inhibitor

The interactions of the most potent inhibitor, **9q**, were rationalised by *in silico* modelling. When docking our full set of compounds into the CDK4 model, only **9q** and **12q** (Chemscore values of the respective best solutions 32.8 kJ mol^{-1} and 32.2 kJ mol^{-1}) show similar Chemscore values to that observed for fascaplysin

1 (Chemscore 30.0 kJ mol^{-1}). All the other compounds are predicted to be weaker binders with Chemscore values in the range of 20 to 25 kJ mol^{-1}. The binding mode of **9q** with the best Chemscore value (Fig. 2c) clearly overlaps with the best binding mode of fascaplysin (Fig. 2b). In both complexes, the indole group occupies a similar position and the interaction between the quinole nitrogen and the backbone of Val 96 is maintained. With fascaplysin **1**, an additional hydrogen bond is predicted between the carbonyl of the ligand and the backbone amide of His 95; in **9q** this is predicted to be replaced by an interaction with the side chain N of His 95. The protein–ligand interactions elsewhere on the ligand differ more substantially. The larger aromatic moiety of **9q** is predicted to form a new π–π interaction with the side chain phenyl rings of both Phe 93 and Phe 159.

The binding mode of **12q** is noteworthy for different reasons. This structurally similar, but more conformationally constrained, compound is a much weaker inhibitor. Analysis of the docking solutions for **12q** with the best Chemscore values predicts two main clusters. In the cluster with the best Chemscore, **12q** is predicted not to bind in the ATP binding site of CDK4 but instead in a distinctly different part of the binding site that would not necessarily inhibit ATP binding. In the second cluster of solutions **12q** is located in the ATP binding site in a similar orientation to that predicted for fascaplysin and **9q** (Fig. 2d). This mode, like that predicted for **9q**, has a strong lipophylic component and the π–π interaction with Phe 93 and Phe 159 is maintained. In contrast, the position predicted to be occupied by the indole moiety is substantially different to that observed for both fascaplysin and **9q**. In particular, the position of the ring is incompatible with the double interaction with the backbone of His 95/Val 96. We therefore suggest that the good binding affinity of **9q** is facilitated both by retaining a double hydrogen bond with the backbone of His 95/Val 96 and introducing a new π interaction[14] from sandwiching the phenyl moiety of the ligand between the side chains of Phe 93 and Phe 159.

In conclusion, we have used a homology model of CDK4 to design specific inhibitors based on fascaplysin. The most potent compound, **9q**, has an IC_{50} value for the inhibition of CDK4 of 6 μM. Three additional compounds—**12l**, **12m** and **12o**—have IC_{50} values below 30 μM. The molecular basis of the affinity of **9q** is suggested to be due to the presence of a double hydrogen bond of the ligand with the backbone of His 95/Val 96 coupled with a π–π interaction—not present with fascaplysin—with the side chains of Phe 93 and Phe 159. This predicted new stabilising interaction will be studied elsewhere and will serve as a basis for the development of further potential inhibitors of CDK4.

Experimental

Modelling

Our homology model of CDK4 was produced using Modeller[15] with CDK2 (PDB[16] accession code 1HCK[14]; containing ATP–Mg^{2+} and sharing 40% sequence identity with CDK4) and CDK6 (1BLX[17]; sharing 70% sequence identity with CDK4) as templates (Fig. 3; sequence alignment produced using ClustalX[18] combined with structural alignment). Docking studies were then performed to generate 10 solutions for each of the compounds **7a–c**, **5a–c**, **9a–q**, **10**, **12a–q** and **13–16**, using GOLD v3.0[19] with the Chemscore fitness function.[20]

Bio assays

Expression and purification of CDK4–GST–cyclin D1, CDK2–GST–cyclin A 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.[22–24]

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 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

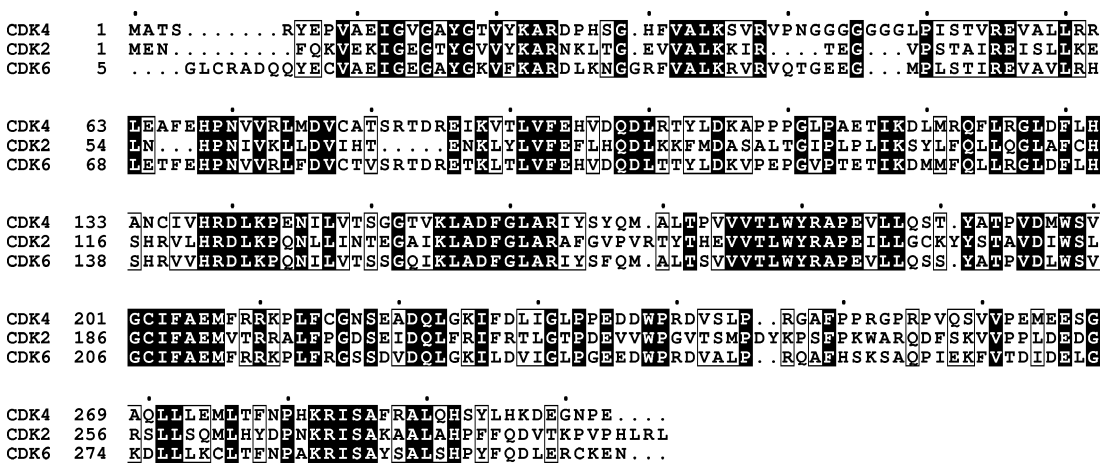


Fig. 3 Sequence alignment used to generate the homology model of CDK4 based on the structures of CDK2 and CDK6. Residues that are identical in all three sequences are shown on a black background, and residues that are similar are boxed. (Figure produced using ESPRIPT.[21])

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^{-1} 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 the addition of an 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 the case of the 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.

Chemistry

General

NMR spectra were recorded on a Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz) spectrometer. Chemicals shifts were measured relative to chloroform (^{13}C δ 77.0) or dimethylsulfoxide (^{13}C δ 39.5) and are expressed in ppm. Coupling constants *J* are expressed in Hertz and the measured 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 measured on a Kratos Concept 1H spectrometer using peak matching to a stable reference peak. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Dry solvents were provided by the system PURE SOLV™, Innovative Technology Inc.

[2-(1*H*-Indol-3-yl)-ethyl]-carbamic acid ethyl ester 3[13]. To a solution of tryptamine **2** (10.00 g, 62.4 mmol) in chloroform (156 mL) at 0 °C was added ethylchloroformate (5.97 mL, 62.4 mmol) and an aqueous solution of NaOH 4 M (15.60 mL, 62.4 mmol). After addition, the mixture was stirred for 3 h at room temperature, and then washed with water (150 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (2 × 150 mL). The chloroform and dichloromethane layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure to give an orange oil. No purification was needed. The oil was dried *in vacuo* to give the title compound **3** (13.78 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, *J* 7.0), 3.05 (2H, t, *J* 6.5), 3.60 (2H, q, *J* 6.5), 4.24 (2H, q, *J* 7.0), 5.12 (1H, br s), 6.99 (1H, s), 7.23 (1H, t, *J* 6.0), 7.30 (1H, td, *J* 6.0 and 1.2), 7.42 (1H, d, *J* 7.7), 7.71 (1H, d, *J* 7.7), 8.75 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.57 (CH_3), 25.64 (CH_2), 41.21 (CH_2), 60.72 (CH_2), 111.33 (CH), 112.33 (Cq), 118.54 (CH), 119.11 (CH), 121.83 (CH), 122.26 (CH), 127.18 (Cq), 136.39 (Cq), 156.93 (Cq). *R*f (ethyl acetate–$NH_{3(aq)}$ 100 : 5) 0.76. *m*/*z* (FAB^+) 232 (M^+), 233 $(M + H)^+$, 465 $(2M + H)^+$ (found: M^+, 232.12126. $C_{13}H_{16}N_2O_2$ requires M, 232.12118).

[2-(1*H*-Indol-3-yl)-ethyl]-methylamine 4[25]. To a solution of **3** (13.78 g, 59.4 mmol) in dry THF (110 mL) under N_2 flux at 0 °C was added portionwise LAH (6.76 g, 178 mmol). After the addition was complete the mixture was heated under reflux for 1 h. The reaction was then cooled to 0 °C and the excess of LAH was hydrolysed by adding successively and very carefully: water (13.25 mL), 15% aqueous solution of NaOH (13.25 mL) and water (3 × 13.25 mL). During these steps it was necessary to add THF (100 mL) to avoid the mixture becoming very thick. The suspension was filtered and the white solid, made up of LiOH and $Al(OH)_3$, was washed with THF (30 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the title compound **4** (9.24 g, 89%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (1H, s), 2.35 (3H, s), 2.81–2.86 (2H, m), 2.89–2.94 (2H, m), 6.80 (1H, s), 7.03 (1H, td, *J* 7.4 and 1.2), 7.10 (1H, td, *J* 7.4 and 1.2), 7.19 (1H, d, *J* 7.6), 7.54 (1H, d, *J* 7.6), 9.52 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.42 (CH_2), 35.99 (CH_3), 51.82 (CH_2), 111.32 (CH), 112.91 (Cq), 118.65 (CH), 118.85 (CH), 121.59 (CH), 122.45 (CH), 127.30 (Cq), 136.53 (Cq). *R*f (ethyl acetate–MeOH–$NH_{3(aq)}$ 9 : 0.5 : 0.5) 0.4. Mp 82 °C. *m*/*z* (FAB^+) 175 $(M + H)^+$ (found: C, 75.74; H, 8.04; N, 16.00; MH^+, 175.12354. $C_{11}H_{15}N_2$ requires C, 75.82; H, 8.10; N, 16.08%; MH, 175.12352).

General procedure for the preparation of {[2-(1*H*-indol-3-yl)-ethyl]-methylamino}-ethanone derivatives

1-(4-Bromophenyl)-2-{[2-(1*H*-indol-3-yl)-ethyl]-methylamino}-ethanone 5c. To a solution of **4** (1.00 g, 5.74 mmol) in toluene (28 mL) was added a solution of $NaHCO_3$ (1.12 g, 13.3 mmol) and Na_2SO_3 (0.56 g, 4.48 mmol) in water (11.2 mL). The mixture was stirred under a N_2 atmosphere and 2,4′-dibromoacetophenone (1.59 g, 5.74 mmol) was added. The stirring was maintained for 4 h at room temperature, and the reaction mixture was washed with a saturated aqueous solution of Na_2HPO_4 (28 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel. Elution was made successively with: ethyl acetate–cyclohexane 7 : 3; ethyl acetate; ethyl acetate–methanol 1 : 1, to give the title compound **6c** as a hard and sticky paste (1.09 g, 51%). The identical procedure using as starting material 2-bromo-4′-chloroacetophenone and 2-bromoacetophenone was

used toward the synthesis of **5b** and **5a** in yields of 61% and 49%, respectively. Note: these compounds can be kept for up to one week at −23 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (3H, s), 2.89–2.94 (2H, m), 2.98–3.03 (2H, m), 3.87 (2H, s), 6.94 (1H, d, *J* 2.0), 7.08 (1H, td, *J* 7.4 and 1.1), 7.16 (1H, td, *J* 7.4 and 1.1), 7.31 (1H, br d, *J* 7.9), 7.47 (2H, dt, *J* 8.6 and 2.0, *para* benzene), 7.56 (1H, d, *J* 7.6), 7.75 (2H, dt, *J* 8.6 and 2.0, *para* benzene), 8.35 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.12 (CH_2), 42.42 (CH_3), 58.07 (CH_2), 63.60 (CH_2), 111.69 (CH), 113.91 (Cq), 119.09 (CH), 119.64 (CH), 122.34 (2CH), 127.76 (Cq), 128.82 (Cq), 130.20 (2CH), 132.17 (2CH), 134.84 (Cq), 136.98 (Cq), 196.38 (Cq). *R*f (ethyl acetate–cyclohexane 7 : 3) 0.58. *m*/*z* (FAB$^+$) 371 (M^+) (found: M^+, 371.07600. $C_{19}H_{19}BrN_2O$ requires M, 371.07590).

1-(4-Chlorophenyl)-2-{[2-(1*H*-indol-3-yl)-ethyl]-methylamino}-ethanone 5b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.84–2.90 (2H, m), 2.95–3.00 (2H, m), 3.81 (2H, s), 6.93 (1H, d, *J* 2.3), 7.08 (1H, td, *J* 7.8 and 1.2), 7.15 (1H, td, *J* 7.8 and 1.2), 7.30 (3H, 2 br d, *J* 7.8 and 7.8), 7.56 (1H, br d, *J* 7.8), 7.83 (2H, dt, *J* 7.8 and 2.3), 8.40 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.25 (CH_2), 42.58 (CH_3), 58.34 (CH_2), 64.08 (CH_2), 111.32 (CH), 113.64 (Cq), 118.71 (CH), 119.17 (CH), 121.87 (CH), 121.97 (CH), 127.42 (Cq), 128.74 (2CH), 129.77 (2CH), 134.15 (Cq), 136.30 (Cq), 139.52 (Cq), 196.58 (Cq). *R*f (ethyl acetate–cyclohexane 7 : 3) 0.68. *m*/*z* (FAB$^+$) 327 $(M + H)^+$ (found MH^+, 327.12635. $C_{19}H_{20}ClN_2O$ requires MH, 327.12642).

2-{[2-(1*H*-Indol-3-yl)-ethyl]-methylamino}-1-phenylethanone 5a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.75–2.81 (2H, m), 2.86–2.92 (2H, m), 3.78 (2H, s), 6.82 (1H, d, *J* 2.1), 6.94–7.06 (2H, m), 7.18 (1H, d, *J* 7.8), 7.26 (2H, apparent t, *J* 7.5), 7.39 (1H, tt, *J* 7.8 and 1.8), 7.47 (1H, d, *J* 7.5), 7.82 (2H, d, *J* 7.2), 8.51 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.34 (CH_2), 42.75 (CH_3), 58.49 (CH_2), 63.79 (CH_2), 111.44 (CH), 113.63 (Cq), 118.77 (CH), 119.15 (CH), 121.84 (CH), 122.13 (CH), 127.54 (Cq), 128.23 (2CH), 128.63 (2CH), 133.33 (CH), 136.07 (Cq), 136.42 (Cq), 197.65 (Cq). *R*f (ethyl acetate–cyclohexane 7 : 3) 0.37. *m*/*z* (FAB$^+$) 293 $(M + H)^+$ (found: MH^+, 293.16544. $C_{19}H_{21}N_2O$ requires MH, 293.16539).

General procedure for the formation of 2-(1*H*-indol-3-yl)-ethyl hydrochloride salts

[2-(4-Bromophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-methyl-ammonium chloride 8c. To a solution of **5c** in a minimum of diethyl ether (also for compound **5b**), or dichloromethane (for compound **5a**) was flushed HCl gas. After a few seconds a precipitate was formed, the colour generally white at the beginning and changing to tan afterwards. The mixture was filtered and the solid dried under vacuum to give the title compound **8c** (0.61 g, 77%). The identical procedure using as starting material **5b** and **5a** was used toward the synthesis of **8b** and **8a** in yields of 46% and 88%, respectively. ^{1}H NMR showed traces of ether in these products which could not be removed by treatment at high vacuum for several days.

^{1}H NMR (300 MHz, DMSO) δ 3.00 (3H, s), 3.23 (2H, t, *J* 7.8), 3.40 (2H, signal obscured by the water in solvent), 5.09 (1H, d, *J* 16.5), 5.18 (1H, d, *J* 16.5), 7.02 (1H, td, *J* 7.7 and 0.9), 7.10 (1H, td, *J* 7.7 and 0.9), 7.24 (1H, d, *J* 2.1), 7.37 (1H, d, *J* 7.7), 7.65 (1H, d, *J* 7.7), 7.85 (2H, dt, *J* 8.7 and 1.8), 7.94 (2H, dt, *J* 8.7 and 1.8), 10.34 (1H, s), 11.02 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 20.31 (CH_2), 41.68 (CH_3), 57.09 (CH_2), 60.87 (CH_2), 109.32 (CH), 112.05 (Cq), 118.75 (CH), 118.95 (CH), 121.72 (CH), 123.76 (CH), 127.14 (Cq), 129.34 (Cq), 130.61 (2CH), 132.57 (2CH), 133.32 (Cq), 136.71 (Cq), 191.66 (Cq). *m*/*z* (FAB$^+$) 371 $(M - Cl^-)^+$ (found: C, 55.88; H, 4.87; N, 6.76; $(M - Cl^-)^+$, 371.07600. $C_{19}H_{20}BrN_2O$ requires C, 55.97; H, 4.94; N, 6.87%; $(M - Cl^-)$, 371.07590).

[2-(4-Chlorophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-methyl-ammonium chloride 8b. ^{1}H NMR (300 MHz, DMSO) δ 3.00 (3H, d, *J* 3.9), 3.23 (2H, t, *J* 7.8), 3.50 (2H, signal obscured by the water in the solvent), 5.09 (1H, dd, *J* 18 and 4.8), 5.19 (1H, dd, *J* 18 and 2.7), 7.02 (1H, td, *J* 7.3 and 0.9), 7.10 (1H, td, *J* 7.3 and 0.9), 7.24 (1H, d, *J* 2.4), 7.37 (1H, d, *J* 7.3), 7.65 (1H, d, *J* 7.3), 7.71 (2H, br d, *J* 8.7), 8.03 (2H, br d, *J* 8.7), 10.35 (1H, s), 11.02 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 20.31 (CH_2), 41.68 (CH_3), 57.10 (CH_2), 60.88 (CH_2), 109.32 (CH), 112.05 (Cq), 118.76 (CH), 118.94 (CH), 121.72 (CH), 123.76 (CH), 127.14 (Cq), 129.62 (2CH), 130.58 (2CH), 133.02 (Cq), 136.72 (Cq), 140.05 (Cq), 191.44 (Cq). *m*/*z* (FAB$^+$) 327 $(M - Cl^-)^+$ (found: C, 62.84; H, 5.47; N, 7.63; $(M - Cl^-)^+$, 327.12649. $C_{19}H_{20}Cl_2N_2O$ requires C, 62.82; H, 5.55; N, 7.71%; $(M - Cl^-)$, 327.12642).

[2-(1*H*-Indol-3-yl)-ethyl]-methyl-(2-oxo-2-phenylethyl)-ammonium chloride 8a. ^{1}H NMR (300 MHz, DMSO) δ 3.02 (3H, d, *J* 4.5), 3.21–3.29 (2H, m), 3.42–3.47 (1H, m), 3.49–3.54 (1H, m), 5.16 (1H, dd, *J* 18.3 and 5.4), 5.24 (1H, dd, *J* 18.3 and 4.2), 7.25 (1H, d, *J* 2.1), 7.38 (1H, d, *J* 6.9), 7.60 (1H, t, *J* 7.6), 7.62 (1H, d, *J* 7.8), 7.68 (1H, d, *J* 7.8), 7.75 (1H, tt, *J* 7.2 and 1.5), 8.02 (2H, d, *J* 7.2), 10.66 (1H, s), 11.14 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 20.38 (CH_2), 41.51 (CH_3), 57.00 (CH_2), 60.74 (CH_2), 109.40 (CH), 112.06 (Cq), 118.80 (CH), 118.90 (CH), 121.66 (CH), 123.75 (CH), 127.18 (Cq), 128.67 (2CH), 129.45 (2CH), 134.36 (Cq), 135.10 (CH), 136.73 (Cq), 192.30 (Cq). *m*/*z* (FAB$^+$) 293 $(M - Cl^-)^+$, 621 $(2M - Cl^-)^+$ (found: $(M - Cl^-)^+$, 293.16534. $C_{19}H_{21}ClN_2O$ requires $(M - Cl^-)$, 293.16539).

General procedure for the formation of 2-(1*H*-indol-3-yl)-ethyl ammonium tosylate salts

[2-(4-Bromophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-dimethylammonium toluene-4-sulfonate 6c. To a solution of the **5c** (1.07 g, 2.89 mmol) in acetonitrile (14.5 mL) was added methyl-*p*-toluenesulfonate (0.54 g, 2.89 mmol). The mixture was heated under reflux for 4 h. After cooling at room temperature, the solvent was removed to give the title compound as a crude yellow powder **6c** (1.62 g, >100%). Further purification was not attempted according to the nature of the compound. NMR showed the presence of the starting material methyl-*p*-toluenesulfonate which was conveniently removed in the subsequent ion exchange step, this explains why the yield is more than 100%. The identical procedure using as starting material **5b** and **5a** was used toward the synthesis of **6b** and **6a** in quantitative yields for both.

^{1}H NMR (300 MHz, DMSO) of the expected compound **6c** δ 2.29 (3H, s), 3.23–3.26 (2H, m), 3.39 (6H, s), 3.83–3.88 (2H, m), 5.35 (2H, s), 7.03–7.13 (4H, m), 7.27 (1H, d, *J* 2.3), 7.37 (1H, d, *J* 8.0), 7.48 (2H, d, *J* 8.0), 7.59 (1H, d, *J* 7.7), 7.85 (2H, d, *J* 8.7), 7.93 (2H, d, *J* 8.7), 10.98 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 19.04 (CH_2), 21.24 (CH_3), 51.86 ($2CH_3$), 65.23 (CH_2), 65.38 (CH_2),

108.52 (CH), 112.10 (Cq), 118.63 (CH), 119.05 (CH), 121.81 (CH), 124.13 (CH), 125.96 (2CH), 127.02 (Cq), 128.50 (2CH), 129.39 (Cq), 130.47 (2CH), 132.52 (2CH), 133.90 (Cq), 136.73 (Cq), 138.06 (Cq), 146.22 (Cq), 191.24 (Cq). *m/z* (FAB^+) 386 ($M - CH_3C_6H_4SO_3^-)^+$, 943 ($2(M - CH_3C_6H_4SO_3^-)^+ + CH_3C_6H_4SO_3^-)^+$ (found: $(M - CH_3C_6H_4SO_3^-)^+$, 385.09152. $C_{20}H_{22}BrN_2O$ requires $(M - CH_3C_6H_4SO_3^-)$, 385.09155).

[2-(4-Chlorophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-dimethylammonium toluene-4-sulfonate 6b. ^{1}H NMR (300 MHz, DMSO) of the expected compound **6b** δ 2.28 (3H, s), 3.21–3.26 (2H, m), 3.40 (6H, s), 3.83–3.89 (2H, m), 5.37 (2H, s), 7.00–7.13 (4H, m), 7.28 (1H, d, *J* 2.2), 7.37 (1H, d, *J* 8.0), 7.48 (2H, d, *J* 8.0), 7.60 (1H, d, *J* 7.7), 7.71 (2H, d, *J* 8.6), 8.02 (2H, d, *J* 8.6), 10.99 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 19.04 (CH_2), 21.24 (CH_3), 51.85 ($2CH_3$), 65.25 (CH_2), 65.41 (CH_2), 108.52 (CH), 112.11 (Cq), 118.64 (CH), 119.04 (CH), 121.80 (CH), 124.14 (CH), 125.96 (2CH), 127.03 (Cq), 128.50 (2CH), 129.57 (2CH), 130.45 (2CH), 133.60 (Cq), 136.73 (Cq), 138.03 (Cq), 140.09 (Cq), 146.27 (Cq), 191.04 (Cq). *m/z* (FAB^+) 341 ($M - CH_3C_6H_4SO_3^-)^+$, 854 ($2(M - CH_3C_6H_4SO_3^-)^+ + CH_3C_6H_4SO_3^-)^+$ (found: $(M - CH_3C_6H_4SO_3^-)^+$, 341.14202. $C_{20}H_{22}ClN_2O$ requires $(M - CH_3C_6H_4SO_3^-)$, 341.14207).

[2-(1*H*-Indol-3-yl)-ethyl]-dimethyl-(2-oxo-2-phenylethyl)-ammonium toluene-4-sulfonate 6a. ^{1}H NMR (300 MHz, DMSO) of the expected compound **6a** δ 2.28 (3H, s), 3.21–3.36 (2H, m), 3.41 (6H, s), 3.84–3.90 (2H, m), 5.39 (2H, s), 7.03–7.14 (4H, m), 7.28 (1H, d, *J* 2.3), 7.38 (1H, d, *J* 8.0), 7.48 (2H, d, *J* 8.0), 7.60 (1H, d, *J* 6.9), 7.63 (2H, t, *J* 7.6), 7.78 (1H, t, *J* 7.6), 8.02 (2H, d, *J* 7.2), 10.99 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 19.06 (CH_2), 21.24 (CH_3), 51.82 ($2CH_3$), 65.22 (CH_2), 65.47 (CH_2), 108.52 (CH), 112.11 (Cq), 118.62 (CH), 119.05 (CH), 121.81 (CH), 124.12 (CH), 125.96 (2CH), 127.03 (Cq), 128.49 (2CH), 128.53 (2CH), 129.47 (2CH), 134.89 (Cq), 135.21 (CH), 136.73 (Cq), 138.00 (Cq), 146.30 (Cq), 192.00 (Cq). *m/z* (FAB^+) 307 ($M - CH_3C_6H_4SO_3^-)^+$, 786 ($2(M - CH_3C_6H_4SO_3^-)^+ + CH_3C_6H_4SO_3^-)^+$ (found: $(M - CH_3C_6H_4SO_3^-)^+$ 307.18104. $C_{20}H_{23}N_2O$ requires $(M - CH_3C_6H_4SO_3^-)$, 307.18104).

General procedure for the ion exchange of tosylate salts to chloride salts

[2-(4-Bromophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-dimethylammonium chloride 7c. To a solution of the crude tosylate salt **6c** (0.96 g, 1.73 mmol) in acetonitrile–water 2.3 : 5 (19.7 mL), was added Dowex® Cl^- 1 × 8–400 ion exchange resin (3.60 g). The suspension was stirred overnight at room temperature. A column was packed with Dowex® Cl^- 1 × 8–400 ion exchange resin (10 g) with the same solvent mixture. The suspension was poured onto the column and eluted with acetonitrile–water 2.3 : 5 (150 mL) and acetonitrile (100 mL). The combined eluate was evaporated under reduced pressure, an aqueous solution of HCl 2 N (3.2 mL) was added, and removed after a few minutes to give the title compound **7c** as a tan solid (0.33 g, 46%). The identical procedure using as starting material **6b** and **6a** was used toward the synthesis of **7b** and **7a** in yields of 50% and 53%, respectively.

^{1}H NMR (300 MHz, DMSO) of the expected compound **2c** δ 3.25–3.32 (2H, m), 3.51 (6H, s), 3.92–3.97 (2H, m), 5.54 (2H, s), 7.09 (1H, td, *J* 7.4 and 1.0), 7.17 (1H, td, *J* 7.4 and 1.0), 7.34 (1H, d, *J* 2.3), 7.43 (1H, d, *J* 7.8), 7.66 (1H, d, *J* 7.8), 7.91 (2H, d, *J* 8.6), 8.02 (2H, d, *J* 8.6), 11.13 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 19.09 (CH_2), 51.74 ($2CH_3$), 65.04 (CH_2), 65.49 (CH_2), 108.53 (CH), 112.11 (Cq), 118.66 (CH), 118.99 (CH), 121.73 (CH), 124.13 (CH), 127.03 (Cq), 129.35 (Cq), 130.55 (2CH), 132.50 (2CH), 133.96 (Cq), 136.72 (Cq), 191.50 (Cq). *m/z* (FAB^+) 385 $(M - Cl^-)^+$, 807 $(2(M - Cl^-)^+ + Cl^-)^+$ (found: C, 57.00; H, 5.27; N, 6.62; $(M - Cl^-)^+$, 385.09152. $C_{20}H_{22}BrN_2O$ requires C, 56.96; H, 5.26; N, 6.64%; $(M - Cl^-)$, 385.09155).

[2-(4-Chlorophenyl)-2-oxoethyl]-[2-(1*H*-indol-3-yl)-ethyl]-dimethylammonium chloride 7b. ^{1}H NMR (300 MHz, DMSO) of the expected compound **7b** δ 3.20–3.27 (2H, m), 3.50 (6H, s), 3.87–3.93 (2H, m), 5.53 (2H, s), 7.02 (1H, td, *J* 6.8 and 1.0), 7.11 (1H, td, *J* 6.8 and 1.0), 7.29 (1H, d, *J* 2.3), 7.37 (1H, d, *J* 7.8), 7.60 (1H, d, *J* 7.8), 7.70 (2H, d, *J* 8.6), 8.05 (2H, d, *J* 8.6), 11.10 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 19.08 (CH_2), 51.76 ($2CH_3$), 65.08 (CH_2), 65.49 (CH_2), 108.53 (CH), 112.10 (Cq), 118.65 (CH), 118.99 (CH), 121.74 (CH), 124.13 (CH), 127.03 (Cq), 129.55 (2CH), 130.50 (2CH), 133.65 (Cq), 136.70 (Cq), 140.05 (Cq), 191.23 (Cq). *m/z* (FAB^+) 341 $(M - Cl^-)^+$, 717 $(2(M - Cl^-) + Cl^-)^+$ (found: C, 63.57; H, 5.67; N, 7.32; $(M - Cl^-)^+$, 341.14209. $C_{20}H_{22}ClN_2O$ requires C, 63.67; H, 5.88; N, 7.42%; $(M - Cl^-)$, 341.14207).

[2-(1*H*-Indol-3-yl)-ethyl]-dimethyl-(2-oxo-2-phenylethyl)-ammonium chloride 7a. ^{1}H NMR (300 MHz, DMSO) δ 3.19–3.27 (2H, m), 3.48 (6H, s), 3.86–3.92 (2H, m), 5.48 (2H, s), 7.03 (1H, td, *J* 7.0 and 1.2), 7.11 (1H, td, *J* 8.2 and 1.2), 7.29 (1H, d, *J* 2.4), 7.38 (1H, dt, *J* 7.9 and 0.9), 7.58–7.65 (3H, m), 7.77 (1H, tt, *J* 7.4 and 1.3), 8.00–8.06 (2H, m), 11.06 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ 18.57 (CH_2), 51.25 ($2CH_3$), 64.61 (CH_2), 65.00 (CH_2), 108.01 (CH), 111.61 (Cq), 118.12 (CH), 118.52 (CH), 121.27 (CH), 123.60 (CH), 126.52 (Cq), 128.06 (2CH), 128.95 (2CH), 134.40 (Cq), 134.68 (CH), 136.21 (Cq), 191.61 (Cq). *m/z* (FAB^+) 307 $((M - Cl^-) + H)^+$, 649 $(2(M - Cl^-) + Cl^-)^+$ (found: $(M - Cl^-)^+$, 307.18103. $C_{20}H_{23}N_2O$ requires $(M - Cl^-)$, 307.18104).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methylbenzamide 9a**§. Yellow paste. Yield 37%. *R*f (ethyl acetate–petroleum ether 50 : 50) 0.15. Rotamers 1 : 1.4 (from the duplicated triplet signal (^{1}H) at 3.48 and 3.81 ppm). ^{1}H NMR (300 MHz, DMSO) δ (major rotamer) 2.89 (2H, t, *J* 7.2), 3.11 (3H, br s), 3.48 (2H, t, *J* 7.2), 6.81–7.29 (10H, m), 8.01 (1H, br s). δ (distinct peaks for minor rotamer) 2.80 (3H, s), 3.81 (2H, t, *J* 6.9), 7.65 (1H, d, *J* 6.9). ^{13}C NMR (75 MHz, DMSO) δ (major rotamer) 24.33 (CH_2), 32.78 (CH_3), 51.89 (CH_2), 110.91 (Cq), 111.82 (CH), 118.68 (CH), 121.39 (CH), 123.26 (CH), 123.43 (CH), 126.70 (CH), 127.38 (Cq), 128.67 (3CH), 129.26 (CH), 137.36 (2Cq), 171.17 (Cq). δ (distinct peaks for minor rotamer) 23.01 (CH_2), 37.83 (CH_3), 48.24 (CH_2), 118.32 (CH), 127.16 (CH), 127.76 (Cq), 129.66 (CH), 136.62 (Cq), 170.33 (Cq). *m/z* (ES^+) 279 (MH^+), 557 ($2M + H)^+$; (ES^-) 277 $(M - H)^-$, 555 $(2M - H)^-$; *m/z* (FAB^+) 279 MH^+ (found: MH^+, 279.14977. $C_{18}H_{18}N_2O$ requires MH, 279.14974).

4-*tert*-Butyl-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9b. White solid. Yield 57%. Mp 194 °C. Rotamers 1 : 1.6 (from

§ The general procedure for the synthesis of compounds **9a**–**q** and **10** is the same as the general procedure for the synthesis of compounds **12a**–**q**, except that methyltryptamine **4** was used as a starting material and not **11**.

the duplicated triplet signal (^{1}H) at 3.47 and 3.79 ppm). *R*f (ethyl acetate–petroleum ether, 50 : 50) 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 1.23 (9H, s), 2.86 (2H, distorted t, *J* 6.8), 3.09 (3H, s), 3.47 (2H, t, *J* 6.8), 6.75–7.31 (9H, m), 8.43 (1H, br s). δ (distinct peaks for minor rotamer) 2.81 (3H, s), 3.79 (2H, br t, *J* 7.1), 7.62 (1H, d, *J* 6.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.49 (CH_2), 31.27 ($3CH_3$), 33.06 (CH_3), 34.74 (Cq), 51.99 (CH_2), 111.32 (CH), 111.60 (Cq), 118.15 (CH), 119.21 (CH), 121.86 (2CH), 125.22 (3CH), 126.20 (CH), 127.10 (Cq), 133.52 (Cq), 136.34 (Cq), 152.23 (Cq), 172.76 (Cq). δ (distinct peaks for minor rotamer) 22.97 (CH_2), 38.29 (CH_3), 48.51 (CH_2), 112.86 (Cq), 118.70 (CH), 122.28 (2CH), 126.89 (CH), 127.57 (Cq), 133.72 (Cq), 152.55 (Cq), 171.62 (Cq). *m*/*z* (ES^+) 335 (MH^+); (ES^-) 333 ($M - H)^-$; *m*/*z* (FAB^+) 335 (MH^+), 670 ($2M + 2H)^+$ (found: C, 78.92; H, 7.88; N, 8.25; MH^+, 335.21232. $C_{22}H_{26}N_2O$ requires C, 79.01; H, 7.84; N, 8.38%; MH, 335.21234).

2-Fluoro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9c. Tan solid. Yield 59%. Mp 125 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^{1}H) at 3.40 and 3.79 ppm). *R*f (ethyl acetate–petroleum ether, 50 : 50) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.84 (2H, t, *J* 7.4), 3.10 (3H, s), 3.40 (2H, t, *J* 7.4), 6.73–7.29 (9H, m), 8.39 (1H, br s). δ (distinct peaks for minor rotamer) 2.73 (3H, s), 3.05 (2H, distorted t, *J* 7.4), 3.79 (2H, t, *J* 7.4), 7.62 (1H, d, *J* 7.5). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.29 (CH_2), 32.92 (CH_3), 48.42 (CH_2), 111.33 (CH), 111.43 (Cq), 112.62 (Cq), 115.83 (CH, d, *J* 15.5), 117.96 (CH), 118.66 (CH), 119.25 (CH), 121.90 (CH), 124.43 (CH, d, *J* 6.3), 127.24 (Cq, d, *J* 32.5), 128.64 (CH, d, *J* 4.6), 130.76 (CH, d, *J* 7.7), 136.35 (Cq), 158.00 (Cq, d, *J* 224.8), 166.78 (Cq). δ (distinct peaks for minor rotamer) 23.05 (CH_2), 37.01 (CH_3), 51.53 (CH_2), 115.55 (CH, d, *J* 15.6), 122.34 (CH), 124.66 (CH, d, *J* 7.4), 128.92 (CH, d, *J* 3.2), 131.13 (CH, d, *J* 8.0), 136.35 (Cq), 157.78 (Cq, d, *J* 302.2), 167.21 (Cq). ^{19}F NMR (282 MHz, $CDCl_3$) δ (major rotamer) −115.55. δ (minor rotamer) −115.15. *m*/*z* (ES^+) 297 (MH^+), 593 ($2M + H)^+$; (ES^-) 295 ($M - H)^-$, 591 ($2M - H)^-$; *m*/*z* (FAB^+) 297 (MH^+), 594 ($2M + 2H)^+$ (found: C, 72.89; H, 5.70; N, 9.39; MH^+, 297.14027. $C_{18}H_{17}FN_2O$ requires C, 72.96; H, 5.78; N, 9.45%; MH, 297.14032).

3-Fluoro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9d. Tan solid. Yield 54%. Mp 144 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^{1}H) at 3.44 and 3.76 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.83 (2H, t, *J* 7.0), 3.07 (3H, s), 3.44 (2H, t, *J* 7.0), 6.63–7.22 (9H, m), 8.54 (1H, br s). δ (distinct peaks for minor rotamer) 2.73 (3H, s), 3.76 (2H, t, *J* 7.1), 7.60 (1H, d, *J* 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.20 (CH_2), 33.03 (CH_3), 51.81 (CH_2), 111.22 (Cq), 111.42 (CH), 112.52 (Cq), 113.75 (CH, d, *J* 22.8), 116.06 (CH, d, *J* 21.0), 117.88 (CH), 118.62 (CH), 119.28 (CH), 121.95 (CH), 122.19 (CH, d, *J* 10.6), 127.01 (Cq), 130.02 (CH, d, *J* 7.6), 136.33 (Cq), 138.26 (Cq, d, *J* 6.8), 162.28 (Cq, d, *J* 246.2), 170.96 (Cq). δ (distinct peaks for minor rotamer) 22.92 (CH_2), 30.95 (CH_3), 48.62 (CH_2), 114.16 (CH, d, *J* 23.7), 116.48 (CH, d, *J* 20.9), 122.41 (CH), 122.51 (CH, d, *J* 15.1), 127.51 (Cq), 130.28 (CH, d, *J* 11.3), 138.75 (Cq, d, *J* 10.4), 162.50 (Cq, d, *J* 225.0), 169.99 (Cq). ^{19}F NMR (282 MHz, $CDCl_3$) δ (major rotamer) −111.84. δ (minor rotamer) −111.87. *m*/*z* (ES^+) 297 (MH^+), 593 ($2M + H)^+$; (ES^-) 295 ($M - H)^-$, 591 ($2M - H)^-$; *m*/*z* (FAB^+) 297 (MH^+), 593 ($2M + H)^+$ (found: C, 72.85; H, 5.70; N, 9.35; MH^+, 297.14034. $C_{18}H_{17}FN_2O$ requires C, 72.96; H, 5.78; N, 9.45%; MH, 297.14032).

4-Fluoro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9e. White solid. Yield 58%. Mp 180 °C. Rotamers 1 : 1.5 (from the duplicated singlet signal (^{19}F) observed at room temperature at −112.22 and −111.49 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.14. ^{1}H NMR (400 MHz, DMSO, 363 K) δ 2.98 (2H, distorted t, *J* 5.7), 3.05 (3H, s), 3.61 (2H, t, *J* 5.7), 6.94 (1H, t, *J* 6.5), 7.05–7.14 (6H, m), 7.27 (1H, br t, *J* 7.0), 7.35 (1H, d, *J* 8.4), 10.54 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.15 (CH_2), 32.85 (CH_3), 51.88 (CH_2), 110.86 (Cq), 111.85 (CH), 115.41 (2CH, br d, *J* 20.0), 118.64 (2CH), 121.40 (CH), 123.57 (CH), 127.42 (Cq), 129.13 (2CH, d, *J* 11.0), 133.63 (Cq), 136.68 (Cq), 162.50 (Cq, d, *J* 259.6), 170.31 (Cq). δ (distinct peaks for minor rotamer) 23.01 (CH_2), 37.91 (CH_3), 48.40 (CH_2), 115.48 (CH, d, *J* 29.8), 115.68 (CH, d, *J* 19.9), 118.24 (CH), 123.29 (CH), 127.74 (Cq), 129.80 (CH, d, *J* 9.2), 169.43 (Cq). ^{13}C NMR (100 MHz, 363 K, DMSO) δ 23.75 (CH_2), 111.69 (Cq), 111.84 (CH), 115.29 (CH), 115.51 (CH), 118.45 (CH), 118.73 (CH), 121.40 (CH), 123.32 (CH), 127.77 (Cq), 129.34 (CH), 129.43 (CH), 133.93 (Cq), 136.96 (Cq), 162.77 (Cq, d, *J* 245.0), 170.06 (Cq). At this temperature, one CH_2 and one CH_3 were not observed. ^{19}F NMR (282 MHz, $CDCl_3$) δ (major rotamer) −112.22. δ (minor rotamer) −111.49. *m*/*z* (ES^+) 297 (MH^+), 593 ($2M + H)^+$; (ES^-) 295 ($M - H)^-$, 591 ($2M - H)^-$; *m*/*z* (FAB^+) 297 (MH^+), 593 ($2M + H)^+$ (found: C, 72.85; H, 5.93; N, 9.52; MH^+, 297.14035. $C_{18}H_{17}FN_2O$ requires C, 72.96; H, 5.78; N, 9.45%; MH, 297.14032).

2-Chloro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9f. Tan solid. Yield 55%. Mp 176 °C. Rotamers 1 : 1.2 (from the duplicated singlet signal (^{1}H) at 2.75 and 3.09 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.26. ^{1}H NMR (300 MHz, DMSO) δ (major rotamer) 2.85–2.93 (2H, m), 3.09 (3H, s), 3.26–3.33 (2H, m), 6.77–7.81 (9H, m), 10.82 (1H, br s). δ (distinct peaks for minor rotamer) 2.75 (3H, s), 3.01–3.07 (2H, m), 3.75 (2H, br s), 10.86 (1H, s). ^{13}C NMR (75 MHz, DMSO) δ (major rotamer) 24.26 (CH_2), 32.38 (CH_3), 51.25 (CH_2), 110.71 (Cq), 111.86 (CH), 118.09 (CH), 118.77 (CH), 121.39 (CH), 123.52 (CH), 127.33 (Cq), 127.69 (CH), 128.44 (CH), 129.43 (Cq), 129.63 (CH), 130.56 (CH), 131.08 (Cq), 136.63 (Cq), 167.48 (Cq). δ (distinct peaks for minor rotamer) 22.99 (CH_2), 36.39 (CH_3), 47.66 (CH_2), 111.64 (Cq), 118.68 (CH), 121.41 (CH), 123.40 (CH), 128.06 (CH), 128.16 (CH), 129.83 (CH), 130.76 (CH), 137.04 (Cq), 172.00 (Cq). *m*/*z* (ES^+) 313 (MH^+), 625 ($2M + H)^+$; (ES^-) 311 ($M - H)^-$, 623 ($2M - H)^-$; *m*/*z* (FAB^+) 313 (MH^+), (found: C, 68.95; H, 5.57; N, 8.83; MH^+, 313.11071. $C_{18}H_{17}ClN_2O$ requires C, 69.12; H, 5.48; N, 8.96%; MH, 313.11077).

3-Chloro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9g. Beige solid. Yield 52%. Mp 152 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^{1}H) at 3.55 and 3.86 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.96 (2H, t, *J* 7.1), 3.17 (3H, s), 3.55 (2H, t, *J* 7.1), 6.89–7.38 (9H, m), 8.11 (1H, br s). δ (distinct peaks for minor rotamer) 2.85 (3H, s), 3.86 (2H, t, *J* 7.1), 7.71 (1H, d, *J* 7.5). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.20 (CH_2), 33.04 (CH_3), 51.89 (CH_2), 111.35 (CH), 111.49 (Cq), 117.97 (CH), 119.44 (CH), 122.14 (2CH), 124.58 (CH), 126.64

(CH), 126.94 (Cq), 129.56 (2CH), 134.22 (Cq), 136.22 (Cq), 137.96 (Cq), 170.76 (Cq). δ (distinct peaks for minor rotamer) 22.89 (CH_2), 38.15 (CH_3), 48.57 (CH_2), 112.78 (Cq), 118.69 (CH), 122.26 (CH), 125.02 (CH), 127.11 (CH), 127.51 (Cq), 129.16 (CH), 129.79 (CH), 134.40 (Cq), 138.40 (Cq), 169.83 (Cq). *m/z* (ES^+) 313 (MH^+), 625 ($2M + H)^+$; (ES^-) 311 ($M - H)^-$, 623 ($2M - H)^-$; *m/z* (FAB^+) 313 (MH^+), 625 ($2M + H)^+$ (found: C, 69.00; H, 5.54; N, 8.88; MH^+, 313.11073. $C_{18}H_{17}ClN_2O$ requires C, 69.12; H, 5.48; N, 8.96%; MH, 313.11077).

4-Chloro-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9h. Beige solid. Yield 62%. Mp 160 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^1H) at 3.55 and 3.86 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.17. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.94 (2H, t, *J* 6.4), 3.17 (3H, s), 3.55 (2H, t, *J* 6.4), 6.87–7.42 (9H, m), 8.16 (1H, br s). δ (distinct peaks for minor rotamer) 2.86 (3H, s), 3.86 (2H, distorted t, *J* 5.4), 7.70 (1H, d, *J* 6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.17 (CH_2), 33.01 (CH_3), 51.74 (CH_2), 111.31 (CH), 112.77 (Cq), 118.01 (CH), 119.42 (CH), 122.12 (2CH), 127.03 (Cq), 127.89 (2CH), 128.38 (2CH), 135.02 (Cq), 136.27 (2Cq), 171.41 (Cq). δ (distinct peaks for minor rotamer) 22.88 (CH_2), 38.20 (CH_3), 48.59 (CH_2), 118.69 (CH), 122.31 (CH), 127.53 (Cq), 128.51 (CH), 128.64 (CH), 134.55 (Cq), 135.50 (Cq). *m/z* (ES^+) 313 (MH^+), 625 ($2M + H)^+$; (ES^-) 311 ($M - H)^-$, 623 ($2M - H)^-$; *m/z* (FAB^+) 313 (MH^+), 625 ($2M + H)^+$ (found: C, 68.99; H, 5.54; N, 8.87; MH^+, 313.11072. $C_{18}H_{17}ClN_2O$ requires C, 69.12; H, 5.48; N, 8.96%; MH, 313.11077).

2-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9i. Tan solid. Yield 48%. Mp 205 °C. Rotamers 1 : 1.2 (from the duplicated triplet signal (^1H) at 3.34 and 3.79 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.31. ^1H NMR (400 MHz, 363 K, DMSO) δ (major rotamer) 2.92 (2H, t, *J* 7.3), 3.10 (3H, s), 3.34 (2H, t, *J* 7.3), 6.90–7.10 (3H, m), 7.19–7.44 (5H, m), 7.63 (1H, br t, estimated *J* 9.4), 10.61 (1H, br s). δ (distinct peaks for minor rotamer) 2.77 (3H, s), 3.79 (2H, t, *J* 7.6), 6.84 (1H, t, *J* 7.4). ^{13}C NMR (75 MHz, DMSO) δ (major rotamer) 24.27 (CH_2), 32.37 (CH_3), 51.31 (CH_2), 110.69 (Cq), 111.89 (CH), 118.10 (CH), 118.74 (CH), 118.82 (Cq), 121.36 (CH), 123.54 (CH), 127.66 (Cq), 128.14 (CH), 128.49 (CH), 130.68 (CH), 132.72 (CH), 136.63 (Cq), 138.79 (Cq), 168.31 (Cq). δ (distinct peaks for minor rotamer) 22.94 (CH_2), 36.50 (CH_3), 47.67 (CH_2), 111.61 (Cq), 118.65 (CH), 118.94 (Cq), 121.42 (CH), 123.43 (CH), 127.32 (Cq), 130.87 (CH), 132.94 (CH), 136.77 (Cq), 139.16 (Cq), 168.15 (Cq). *m/z* (ES^+) 358; (ES^-) 356 ($M - H)^-$; *m/z* (FAB^+) 357 (M^+) (found: C, 60.38; H, 4.81; N, 7.81; M^+, 357.06015. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84%; M, 357.06025).

3-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9j. White solid. Yield 76%. Mp 166 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^1H) at 3.46 and 3.78 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.35. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.87 (2H, t, *J* 6.9), 3.09 (3H, s), 3.46 (2H, t, *J* 6.9), 6.76–7.61 (9H, m), 8.25 (1H, br s). δ (distinct peaks for minor rotamer) 2.76 (3H, s), 3.78 (2H, t, *J* 6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.20 (CH_2), 33.08 (CH_3), 51.94 (CH_2), 111.39 (CH), 112.72 (Cq), 117.97 (CH), 119.44 (CH), 122.13 (CH), 122.30 (CH), 125.04 (CH), 126.98 (Cq), 129.79 (CH), 129.94 (CH), 132.10 (CH), 132.99 (Cq), 136.22 (Cq), 138.15 (Cq), 170.65 (Cq). δ (distinct peaks for minor rotamer) 22.88 (CH_2), 38.18 (CH_3), 48.61 (CH_2), 118.66 (CH), 125.45 (CH), 127.52 (Cq), 129.45 (CH), 130.06 (CH), 132.51 (CH), 135.95 (Cq), 138.59 (Cq), 169.73 (Cq). *m/z* (ES^+) 357 (M^+), 358 (MH^+); (ES^-) 356 ($M - H)^-$; *m/z* (FAB^+) 357 (M^+) (found: C, 60.38; H, 4.80; N, 7.73; M^+, 357.06030. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84%; M, 357.06025).

4-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methylbenzamide 9k. White solid. Yield 73%. Mp 160 °C. Rotamers 1 : 1.5 (from the duplicated triplet signal (^1H) at 3.45 and 3.77 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.23. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.83 (2H, t, *J* 6.3), 3.07 (3H, s), 3.45 (2H, t, *J* 6.3), 6.71–7.62 (9H, m), 8.41 (1H, br s). δ (distinct peaks for minor rotamer) 2.76 (3H, s), 3.77 (2H, distorted t, *J* 7.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.17 (CH_2), 32.99 (CH_3), 51.72 (CH_2), 111.35 (CH), 112.65 (Cq), 117.98 (CH), 119.39 (CH), 122.05 (CH), 122.38 (CH), 123.27 (Cq), 127.04 (Cq), 128.09 (2CH), 131.33 (2CH), 135.02 (Cq), 136.31 (Cq), 171.44 (Cq). δ (distinct peaks for minor rotamer) 22.89 (CH_2), 38.18 (CH_3), 48.62 (CH_2), 118.65 (CH), 123.74 (Cq), 127.54 (Cq), 128.69 (CH), 131.60 (CH), 135.51 (Cq), 170.40 (Cq). *m/z* (ES^+) 358 (MH^+); (ES^-) 356 ($M - H)^-$; *m/z* (FAB^+) 357 (M^+) (found: C, 60.58; H, 4.96; N, 7.76; M^+, 357.06027. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84%; M, 357.06025).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-2-methoxy-*N*-methylbenzamide 9l.** Beige solid. Yield 57%. Mp 203 °C. Rotamers 1 : 1.3 (from the multiplet and triplet signals (^1H) at 3.38–3.46 and 3.88 ppm). *R*f (ethyl acetate–petroleum ether, 50 : 50) 0.09. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.81–2.95 (2H, m), 3.17 (3H, s), 3.38–3.46 (2H, m), 3.77 (3H, s), 7.11–7.38 (9H, m), 8.31 (1H, br s). δ (distinct peaks for minor rotamer) 2.77 (3H, s), 3.11–3.14 (2H, m), 2.78 (3H, s), 3.88 (2H, distorted t, *J* 7.5), 7.71 (1H, d, *J* 7.5), 8.34 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.51 (CH_2), 32.80 (CH_3), 51.57 (CH_2), 55.51 (CH_3), 110.96 (CH), 111.23 (CH), 112.05 (Cq), 118.24 (CH), 119.20 (CH), 120.83 (CH), 121.90 (CH), 122.04 (CH), 126.30 (Cq), 127.11 (Cq), 127.72 (CH), 130.06 (CH), 136.26 (Cq), 155.17 (Cq), 169.69 (Cq). δ (distinct peaks for minor rotamer) 23.00 (CH_2), 36.70 (CH_3), 47.94 (CH_2), 55.56 (CH_3), 112.98 (Cq), 118.74 (CH), 120.88 (CH), 121.84 (CH), 122.26 (CH), 126.72 (Cq), 127.56 (Cq), 127.78 (CH), 130.21 (CH), 136.32 (Cq), 155.27 (Cq). *m/z* (ES^+) 309 (MH^+), 617 ($2M + H)^+$; (ES^-) 307 ($M - H)^-$, 615 ($2M - H)^-$; *m/z* (FAB^+) 309 (MH^+), 618 ($2M + 2H)^+$ (found: C, 73.97; H, 6.49; N, 9.02; MH^+, 309.16027. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.08%; MH, 309.16030).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-3-methoxy-*N*-methylbenzamide 9m.** Tan solid. Yield 54%. Mp 175 °C. Rotamers 1 : 1.2 (from the duplicated triplet signal (^1H) at 3.48 and 3.78 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.17. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.89 (2H, br t, *J* 7.2), 3.10 (3H, br s), 3.48 (2H, t, *J* 7.2), 3.63 (3H, br s), 6.65–7.28 (9H, m), 8.20 (1H, br s). δ (distinct peaks for minor rotamer) 2.79 (3H, s), 3.70 (3H, s), 3.78 (2H, distorted t, *J* 7.1), 7.64 (1H, d, *J* 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.48 (CH_2), 33.03 (CH_3), 51.91 (CH_2), 55.25 (CH_3), 111.24 (CH), 111.85 (CH), 112.92 (Cq), 115.08 (CH), 118.63 (CH), 118.70 (CH), 119.33 (CH), 122.00 (CH), 122.12 (CH), 127.12 (Cq), 129.46 (CH), 136.26 (Cq), 137.78 (Cq), 159.50 (Cq), 172.02 (Cq). δ (distinct peaks for minor rotamer) 22.90

(CH_2), 38.13 (CH_3), 48.41 (CH_2), 112.14 (CH), 115.39 (CH), 118.24 (CH), 119.03 (CH), 127.26 (Cq). *m/z* (ES^+) 309 (MH^+), 617 ($2M + H)^+$; (ES^-) 307 ($M - H)^-$, 615 ($2M - H)^-$; *m/z* (FAB^+) 309 MH^+ (found: C, 73.87; H, 6.44; N, 9.01; MH^+, 309.16031. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.08%; MH, 309.16030).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-2,*N*-dimethylbenzamide 9n.** Tan solid. Yield 63%. Mp 188 °C. Rotamers 1 : 1.4 (from the duplicated triplet signal (^1H) at 3.40 and 3.91 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.24. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.19 (3H, s), 2.90 (2H, t, *J* 7.7), 3.20 (3H, s), 3.40 (2H, t, *J* 7.7), 6.90–7.34 (9H, m), 8.33 (1H, br s). δ (distinct peaks for minor rotamer) 2.24 (3H, s), 2.75 (3H, s), 3.16 (2H, apparent t, estimated *J* 7.5), 3.91 (2H, td, *J* 7.5), 7.70 (1H, d, *J* 7.5), 8.35 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 18.91 (CH_3), 24.51 (CH_2), 32.52 (CH_3), 51.38 (CH_2), 111.24 (CH), 111.67 (Cq), 118.22 (CH), 119.28 (CH), 121.84 (CH), 121.98 (CH), 125.80 (CH), 125.92 (CH), 127.01 (Cq), 128.67 (CH), 130.30 (CH), 133.97 (Cq), 136.28 (Cq), 136.50 (Cq), 171.86 (Cq). δ (distinct peaks for minor rotamer) 18.81 (CH_3), 23.04 (CH_2), 36.80 (CH_3), 47.53 (CH_2), 111.28 (CH), 112.72 (Cq), 118.69 (CH), 122.09 (CH), 122.21 (CH), 125.71 (CH), 127.50 (Cq), 130.32 (CH), 133.88 (Cq), 136.36 (Cq), 137.00 (Cq), 171.40 (Cq). *m/z* (ES^+) 293 (MH^+), 585 ($2M + H)^+$; (ES^-) 291 ($M - H)^-$, 583 ($2M - H)^-$; *m/z* (FAB^+) 293 (MH^+) (found: C, 78.08; H, 6.73; N, 9.51; MH^+, 293.16541. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.89; N, 9.58%; MH, 293.16539).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-3,*N*-dimethylbenzamide 9o.** White solid. Yield 56%. Mp 140 °C. Rotamers 1 : 1.3 (from the duplicated triplet signal (^1H) at 3.47 and 3.80 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.20. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.15 (3H, s), 2.89 (2H, t, *J* 6.9), 3.10 (3H, br s), 3.47 (2H, t, *J* 6.9), 6.81–7.30 (9H, m), 8.07 (1H, br s). δ (distinct peaks for minor rotamer) 2.27 (3H, s), 2.80 (3H, s), 3.80 (2H, apparent t, estimated *J* 6.3), 7.65 (1H, d, *J* 7.2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.34 (CH_3), 24.39 (CH_2), 33.01 (CH_3), 51.93 (CH_2), 111.32 (CH), 111.61 (Cq), 118.15 (CH), 119.24 (CH), 121.92 (2CH), 122.06 (Cq), 123.42 (CH), 127.07 (CH), 128.19 (CH), 129.81 (CH), 136.30 (Cq), 136.47 (Cq), 138.22 (Cq), 172.64 (Cq). δ (distinct peaks for minor rotamer) 22.96 (CH_2), 38.18 (CH_3), 48.47 (CH_2), 112.83 (Cq), 118.71 (CH), 122.25 (2CH), 123.86 (CH), 127.53 (CH), 130.13 (CH), 136.71 (Cq), 171.54 (Cq). *m/z* (ES^+) 293 (MH^+), 585 ($2M + H)^+$; (ES^-) 291 ($M - H)^-$; *m/z* (FAB^+) 293 (MH^+) (found: C, 77.88; H, 6.81; N, 9.42; MH^+, 293.16542. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.89; N, 9.58%; MH, 293.16539).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-4,*N*-dimethylbenzamide 9p.** White solid. Yield 77%. Mp 178 °C. Rotamers 1 : 1.3 (from the duplicated broad singlet signals (^1H) at 3.46 and 3.77 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.24. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.24 (3H, br s), 2.84 (2H, br s), 3.07 (3H, br s), 3.46 (2H, br s), 6.70–7.15 (9H, m), 8.51 (1H, br s). δ (distinct peaks for minor rotamer) 2.79 (3H, br s), 3.77 (2H, br s), 7.60 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.35 (CH_3), 24.47 (CH_2), 33.14 (CH_2), 52.00 (CH_3), 111.36 (CH), 111.53 (Cq), 118.20 (CH), 119.11 (CH), 121.82 (2CH), 126.51 (CH), 127.08 (Cq), 128.94 (3CH), 133.56 (Cq), 136.36 (Cq), 139.15 (Cq), 172.65 (Cq). δ (distinct peaks for minor rotamer) 22.98 (CH_2), 38.26 (CH_2), 48.57 (CH_3), 112.74 (Cq), 118.67 (CH), 122.26 (2CH), 127.08 (CH), 127.55 (Cq), 133.71 (Cq), 139.54 (Cq), 171.63 (Cq). *m/z* (ES^+) 293 (MH^+), 585 ($2M + H)^+$; (ES^-) 291 ($M - H)^-$; *m/z* (FAB^+) 293 (MH^+) (found: C, 77.91; H, 6.81; N, 9.62; MH^+, 293.16543. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.89; N, 9.58%; MH, 293.16539).

Biphenyl-4-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-methylamide 9q. Beige solid. Yield 58%. Mp 178 °C. Rotamers 1 : 1.5 (from the duplicated triplet signal (^1H) at 3.59 and 3.89 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.16. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.95 (2H, distorted t, *J* 6.8), 3.18 (3H, s), 3.59 (2H, t, *J* 6.8), 6.84–7.55 (14H, m), 8.42 (1H, br s). δ (distinct peaks for minor rotamer) 2.91 (3H, br s), 3.89 (2H, apparent t, estimated *J* 6.9), 7.72 (1H, br d, *J* 6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.41 (CH_2), 33.06 (CH_3), 51.92 (CH_2), 111.33 (2CH), 111.57 (Cq), 118.15 (CH), 119.31 (2CH), 121.96 (2CH), 127.01 (2CH), 127.16 (2CH), 127.54 (Cq), 127.66 (CH), 128.87 (2CH), 135.21 (Cq), 136.34 (Cq), 140.45 (Cq), 141.95 (Cq), 172.35 (Cq). δ (distinct peaks for minor rotamer) 22.98 (CH_2), 38.28 (CH_3), 48.55 (CH_2), 112.86 (Cq), 118.73 (CH), 122.30 (CH), 135.47 (Cq), 142.34 (Cq), 171.27 (Cq). *m/z* (ES^+) 355 (MH^+); (ES^-) 353 ($M - H)^-$; *m/z* (FAB^+) 355 (MH^+) (found: C, 81.34; H, 6.07; N, 7.84; MH^+, 355.18103. $C_{24}H_{22}N_2O$ requires C, 81.26; H, 6.26; N, 7.90%; MH, 355.18104).

***N*-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-2-phenylacetamide 10§.** Yellow paste. Yield 55%. Rotamers 1 : 1.2 (from the duplicated doublet signal (^1H) at 7.58 and 7.69 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.27. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.98 (2H, t, *J* 7.1), 3.08 (3H, s), 3.62 (2H, t, *J* 7.1), 3.76 (2H, s), 6.84 (1H, d, *J* 2.4), 7.09–7.39 (8H, m), 7.58 (1H, d, *J* 7.8), 8.92 (1H, br s). δ (distinct peaks for minor rotamer) 2.94 (3H, s), 3.07 (2H, apparent t, estimated *J* 7.5), 3.44 (2H, s), 3.76 (2H, apparent t, estimated *J* 7.5), 6.91 (1H, d, *J* 2.4), 7.69 (1H, d, *J* 7.5), 8.70 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 24.19 (CH_2), 33.68 (CH_3), 40.33 (CH_2), 50.88 (CH_2), 111.76 (CH), 112.58 (Cq), 118.09 (CH), 118.64 (CH), 119.43 (CH), 122.05 (CH), 122.40 (CH), 122.78 (CH), 126.71 (CH), 127.49 (Cq), 128.60 (CH), 128.89 (CH), 135.39 (Cq), 136.52 (Cq), 171.59 (Cq). δ (distinct peaks for minor rotamer) 23.22 (CH_2), 36.50 (CH_3), 41.28 (CH_2), 49.25 (CH_2), 111.44 (CH + Cq), 119.16 (CH), 121.77 (CH), 126.80 (CH), 127.05 (Cq), 128.73 (CH), 128.94 (CH), 135.12 (Cq), 136.42 (Cq), 171.14 (Cq). *m/z* (FAB^+) 293 (MH^+) (found: MH^+, 293.16532. $C_{19}H_{20}N_2O$ requires MH, 293.16539).

General procedure for the synthesis of phenyl-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone and all derivatives 12a–q, 13 and 14. To a suspension of carboline (1.2 mmol) in dichloromethane (3 mL) at 0 °C was added slowly an aqueous solution of sodium hydroxide 4 M (1.2 mmol). After 5 min stirring at 0 °C, the benzoyl chloride derivative (1.2 mmol) was added dropwise. The mixture was stirred for 5 min at 0 °C and 3 h at room temperature. Water (20 mL) was added. The two layers were separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel. Elution was made successively with: ethyl acetate–petroleum ether 50 : 50 and ethyl acetate, to give the expected compound.

Phenyl-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12a. Yellow solid. Yield 82%. Mp 78 °C. Rotamers 1 : 3 (from the duplicated broad singlet signal (^{1}H) at 8.71 and 9.23 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.27. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.88 (2H, br s), 3.75 (2H, br s), 4.99 (2H, br s), 7.16–7.30 (4H, m), 7.54–7.56 (5H, m), 9.23 (1H, br s). δ (distinct peaks for minor rotamer) 2.97 (2H, br s), 4.16 (2H, br s), 4.54 (2H, br s), 8.71 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.21 (CH_2), 41.28 (CH_2), 46.18 (CH_2), 107.51 (Cq), 111.41 (CH), 117.86 (CH), 119.44 (CH), 121.68 (CH), 126.86 (Cq), 126.99 (CH), 128.81 (2CH), 130.15 (2CH), 130.28 (Cq), 136.14 (Cq), 136.53 (Cq), 171.80 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (FAB$^+$) 276 (M^+), 277 (MH^+) (found: M^+, 276.12624. $C_{18}H_{16}N_2O$ requires M, 276.12626).

(4-*tert*-Butylphenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12b. White solid. Yield 90%. Mp 217 °C. Rotamers 1 : 2 (from the duplicated broad singlet signal (^{1}H) at room temperature at 10.66 and 10.94 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.34. ^{1}H NMR (400 MHz, 373 K, DMSO) δ 1.36 (9H, s), 2.81 (2H, t, *J* 5.6), 3.83 (2H, t, *J* 5.6), 4.79 (2H, s), 7.01 (1H, td, *J* 7.4 and 1.1), 7.08 (1H, td, *J* 7.4 and 1.1), 7.34 (1H, d, *J* 8.0), 7.41–7.43 (3H, m), 7.51 (2H, d, *J* 8.0), 10.53 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.80 (CH_2), 31.48 ($3CH_3$), 34.95 (Cq), 43.15 (CH_2), 44.10 (CH_2), 107.53 (Cq), 111.51 (CH), 117.92 (CH), 119.04 (CH), 121.30 (CH), 125.55 (2CH), 127.17 (2CH), 127.35 (Cq), 131.42 (Cq), 134.20 (Cq), 136.90 (Cq), 152.96 (Cq), 170.64 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (FAB$^+$) 333 (MH^+) (found: C, 79.56; H, 7.28; N, 8.40; MH^+, 333.19665. $C_{22}H_{24}N_2O$ requires C, 79.48; H, 7.28; N, 8.43%; MH, 333.19669).

(2-Fluorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12c. Yellow solid. Yield 95%. Mp 79 °C. Rotamers 1 : 2.6 (from the duplicated broad singlet signal (^{1}H) at 4.35 and 4.82 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.29. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.66 (2H, br s), 3.51 (2H, t, *J* 5.4), 4.82 (2H, s), 6.92–7.37 (8H, 2m), 8.69 (1H, br s). δ (distinct peaks for minor rotamer) 2.77 (2H, br s), 4.35 (2H, br s), 8.19 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.96 (CH_2), 40.85 (CH_2), 45.65 (CH_2), 107.60 (Cq), 111.30 (CH), 116.10 (CH, d, *J* 21.1), 117.82 (CH), 119.42 (CH), 121.71 (CH), 124.30 (Cq, d, *J* 17.7), 124.83 (CH, d, *J* 3.0), 126.71 (Cq), 128.83 (CH, d, *J* 3.0), 129.80 (Cq), 131.56 (CH, d, *J* 8.0), 136.45 (Cq), 158.44 (Cq, d, *J* 246.5), 166.63 (Cq). δ (distinct peaks for minor rotamer) 21.04 (CH_2), 45.11 (CH_2), 109.03 (Cq), 111.09 (CH), 115.89 (CH, d, *J* 18.1), 118.13 (CH), 119.59 (CH), 121.89 (CH), 126.81 (Cq), 129.36 (Cq), 136.33 (Cq), 158.39 (Cq, d, *J* 241.1), 166.08 (Cq). ^{19}F NMR (282 MHz, $CDCl_3$) δ (major rotamer) −114.86. δ (minor rotamer) −114.47. *m/z* (ES$^+$) 295 (MH^+), 589 ($2M + H)^+$; (ES$^-$) 293 ($M - H)^-$. *m/z* (FAB$^+$) 294 (M^+), 295 (MH^+) (found: MH^+, 295.12473. $C_{18}H_{15}FN_2O$ requires MH, 295.12467).

(3-Fluorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12d. Pale yellow solid. Yield 99%. Mp 65 °C. Rotamers 1 : 5 (from the duplicated triplet signal (^{1}H) at 2.81 and 3.42 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.35. ^{1}H NMR (400 MHz, 373 K, DMSO) δ (major rotamer) 2.81 (2H, t, *J* 5.6), 3.81 (2H, br s), 4.78 (2H, s), 7.00 (1H, td, *J* 7.5 and 1.0), 7.08 (1H, td, *J* 7.5 and 1.0), 7.27–7.35 (3H, m), 7.42 (1H, d, *J* 8.0), 7.50–7.55 (2H, m), 10.52 (1H, br s). δ (distinct peaks for minor rotamer) 3.42 (2H, t, *J* 7.0), 7.65 (1H, br d, *J* 8.8), 7.83 (1H, br d, *J* 8.2), 11.36 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.10 (CH_2), 41.22 (CH_2), 46.07 (CH_2), 107.57 (Cq), 111.26 (CH), 114.24 (CH, d, *J* 22.6), 117.11 (CH, d, *J* 20.9), 117.88 (CH), 119.56 (CH), 121.83 (CH), 122.60 (CH), 126.76 (Cq), 129.85 (Cq), 130.61 (CH, d, *J* 7.7), 136.40 (Cq), 138.05 (Cq, d, *J* 6.6), 162.99 (Cq, d, *J* 246.7), 170.16 (Cq). No rotamers observed in ^{13}C at RT. ^{19}F NMR (282 MHz, $CDCl_3$) δ (major rotamer) −111.15, δ (minor rotamer) −112.77. *m/z* (FAB$^+$) 294 (M^+), 295 (MH^+) (found: MH^+, 295.12470. $C_{18}H_{15}FN_2O$ requires MH, 295.12467).

(4-Fluorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12e. Yellow solid. Yield 97%. Mp 76 °C. Rotamers 1 : 4 (from the duplicated broad singlet signal (^{1}H) at 4.43 and 4.75 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.33. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.70 (2H, br s), 3.56 (2H, br s), 4.75 (2H, br s), 6.63–7.35 (8H, 2m), 8.75 (1H, br s). δ (distinct peaks for minor rotamer) 4.00 (2H, br s), 4.43 (2H, br s), 8.69 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.13 (CH_2), 41.41 (CH_2), 46.26 (CH_2), 107.57 (Cq), 111.24 (CH), 115.81 (2CH, d, *J* 21.7), 117.89 (CH), 119.55 (CH), 121.81 (CH), 126.78 (Cq), 129.31 (2CH, d, *J* 7.9), 130.00 (Cq), 132.00 (Cq, d, *J* 3.2), 136.41 (Cq), 163.63 (Cq, d, *J* 248.6), 170.80 (Cq). No rotamers observed in ^{13}C at RT. ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.52. *m/z* (FAB$^+$) 294 (M^+) (found: MH^+, 295.12470. $C_{18}H_{15}FN_2O$ requires MH, 295.12467).

(2-Chlorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12f. White solid. Yield 81%. Mp 97 °C. Rotamers 1 : 3 (from the duplicated doublet signal (^{1}H) at 4.56 and 5.18 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.39. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.75 (1H, t, *J* 6.3), 2.84 (1H, t, *J* 5.1), 3.63 (2H, t, *J* 5.7), 4.92 (1H, d, *J* 16.8), 5.18 (1H, d, *J* 16.8), 7.10–7.36 (8H, m), 8.27 (1H, br s). δ (distinct peaks for minor rotamer) 2.73 (1H, apparent t, estimated *J* 6.0), 2.90 (1H, t, *J* 6.0), 2.98 (2H, t, *J* 5.7), 4.40 (1H, d, *J* 16.5), 4.56 (1H, d, *J* 16.5), 7.78 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.88 (CH_2), 40.33 (CH_2), 45.13 (CH_2), 108.01 (Cq), 111.08 (CH), 117.88 (CH), 119.66 (CH), 121.94 (CH), 126.74 (Cq), 127.27 (CH), 127.65 (CH), 129.59 (Cq), 129.82 (CH), 130.34 (CH), 130.57 (Cq), 136.02 (Cq), 136.29 (Cq), 168.04 (Cq). δ (distinct peaks for minor rotamer) 21.00 (CH_2), 44.71 (CH_2), 110.88 (CH), 118.23 (CH), 119.83 (CH), 122.11 (CH), 127.39 (CH), 127.95 (CH), 129.71 (CH). *m/z* (ES$^+$) 311 (MH^+), 621 ($2M + H)^+$; (ES$^-$) 309 ($M - H)^-$. *m/z* (FAB$^+$) 311 (MH^+) (found: MH^+, 311.09503. $C_{18}H_{15}ClN_2O$ requires MH, 311.09512).

(3-Chlorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12g. Pale yellow solid. Yield 73%. Mp 72 °C. Rotamers 1 : 3.3 (from the duplicated broad singlet signal (^{1}H) at room temperature at 4.46 and 4.80 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.44. ^{1}H NMR (400 MHz, 373 K, DMSO) δ 2.81 (2H, t, *J* 5.9), 3.81 (2H, br s), 4.78 (2H, s), 7.00 (1H, td, *J* 7.5 and 1.2), 7.08 (1H, td, *J* 7.5 and 1.2), 7.34 (1H, d, *J* 8.0), 7.42 (2H, apparent dd, estimated *J* 7.2 and 1.6), 7.50–7.54 (3H, m), 10.52 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.10 (CH_2), 41.17 (CH_2), 46.08 (CH_2), 107.69 (Cq), 111.18 (CH), 117.88 (CH), 119.63 (CH), 121.92 (CH), 124.97 (CH), 126.74 (Cq), 127.12 (CH), 129.71 (Cq), 130.10 (2CH), 134.76 (Cq), 136.32 (Cq), 137.68 (Cq), 170.03 (Cq). No rotamers observed in ^{13}C at RT.

m/z (FAB$^+$) 311 (MH$^+$) (found: MH$^+$, 311.09512. $C_{18}H_{15}ClN_2O$ requires MH, 311.09512).

(4-Chlorophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12h. White solid. Yield 83%. Mp 196 °C. Rotamers 1 : 2 (from the duplicated broad singlet signal (^{1}H) at room temperature at 4.60 and 4.83 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.41. ^{1}H NMR (400 MHz, 373 K, DMSO) δ 2.81 (2H, t, *J* 5.5), 3.81 (2H, br t, *J* 5.5), 4.78 (2H, s), 7.01 (1H, td, *J* 7.5 and 0.9), 7.08 (1H, td, *J* 7.5 and 0.9), 7.35 (1H, d, *J* 8.0), 7.42 (2H, d, *J* 7.6), 7.48–7.53 (3H, m), 10.52 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.74 (CH_2), 43.09 (CH_2), 44.17 (CH_2), 107.50 (Cq), 111.54 (CH), 117.94 (CH), 119.10 (CH), 121.37 (CH), 127.31 (Cq), 129.01 (2CH), 129.15 (2CH), 131.18 (Cq), 134.96 (Cq), 135.81 (Cq), 136.91 (Cq), 169.50 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (ES$^+$) 311 (MH$^+$), 621 (2M + H)$^+$; (ES$^-$) 309 (M − H)$^-$. *m/z* (FAB$^+$) 311 (MH$^+$) (found: C, 69.58; H, 4.54; N, 8.94; MH$^+$, 311.09522. $C_{18}H_{15}ClN_2O$ requires C, 69.57; H, 4.86; N, 9.01%; MH, 311.09512).

(2-Bromophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12i. White solid. Yield 64%. Mp 190 °C. Rotamers 1 : 3.3 (from the duplicated broad singlet signal (^{1}H) at 8.03 and 8.59 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.66 (1H, t, *J* 6.5), 2.73 (1H, t, *J* 5.0), 3.49 (2H, t, *J* 5.7), 4.77 (1H, d, *J* 16.8), 5.06 (1H, d, *J* 16.8), 6.93–7.56 (8H, m), 8.59 (1H, br s). δ (distinct peaks for minor rotamer) 2.61 (1H, apparent t, estimated *J* 6.3), 2.79 (1H, t, *J* 5.0), 2.85 (2H, t, *J* 5.7), 4.24 (1H, d, *J* 16.1), 4.38 (1H, d, *J* 16.1), 8.03 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.87 (CH_2), 40.47 (CH_2), 45.24 (CH_2), 107.63 (Cq), 111.28 (CH), 117.81 (CH), 119.34 (Cq), 119.48 (CH), 121.77 (CH), 126.70 (Cq), 127.60 (CH), 127.86 (CH), 129.68 (Cq), 130.52 (CH), 133.00 (CH), 136.39 (Cq), 138.18 (Cq), 168.93 (Cq). δ (distinct peaks for minor rotamer) 21.01 (CH_2), 44.87 (CH_2), 109.18 (Cq), 111.03 (CH), 118.15 (CH), 119.10 (Cq), 119.66 (CH), 121.93 (CH), 126.81 (Cq), 129.15 (Cq), 132.87 (CH), 136.28 (Cq), 138.27 (Cq), 168.44 (Cq). *m/z* (ES$^+$) 355 (MH$^+$); (ES$^-$) 354 (M)$^-$. *m/z* (FAB$^+$) 355 (MH$^+$) (found: C, 60.75; H, 4.17; N, 7.92; M$^+$, 354.03678. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89%; M, 354.03677).

(3-Bromophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12j. White solid. Yield 91%. Mp 207 °C. Rotamers 1 : 1.6 (from the duplicated broad singlet signal (^{1}H) at room temperature at 4.60 and 4.84 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.41. ^{1}H NMR (400 MHz, 373 K, DMSO) δ 2.80 (2H, t, *J* 5.8), 3.81 (2H, br s), 4.77 (2H, s), 7.00 (1H, td, *J* 7.5 and 1.2), 7.08 (1H, td, *J* 7.5 and 1.2), 7.34 (1H, d, *J* 7.6), 7.41–7.48 (3H, m), 7.64–7.69 (2H, m), 10.52 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.70 (CH_2), 43.06 (CH_2), 44.09 (CH_2), 107.49 (Cq), 111.54 (CH), 117.96 (CH), 119.09 (CH), 121.37 (CH), 122.24 (Cq), 126.12 (CH), 127.29 (Cq), 129.93 (CH), 131.09 (CH + Cq), 132.84 (CH), 136.90 (Cq), 139.33 (Cq), 168.80 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (ES$^+$) 355 (MH$^+$); (ES$^-$) 353 (M − H)$^-$. *m/z* (FAB$^+$) 355 (MH$^+$) (found: C, 60.94; H, 4.17; N, 7.93; MH$^+$, 355.04478. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.87%; MH, 355.04460).

(4-Bromophenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12k. White solid. Yield 62%. Mp 217 °C. Rotamers 1 : 1.7 (from the duplicated broad singlet signal (^{1}H) at room temperature at 4.59 and 4.83 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.45. ^{1}H NMR (400 MHz, DMSO, 363 K) δ 2.79 (2H, t, *J* 5.8), 3.79 (2H, br s), 4.75 (2H, s), 6.99 (1H, td, *J* 7.4 and 0.8), 7.07 (1H, td, *J* 7.6 and 1.2), 7.32 (1H, d, *J* 8.0), 7.40–7.44 (4H, m), 7.67 (1H, dt, *J* 8.8 and 2.4), 10.55 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.03 (CH_2), 40.94 (CH_2), 45.94 (CH_2), 107.05 (Cq), 111.55 (CH), 118.02 (CH), 119.06 (CH), 121.38 (CH), 123.53 (Cq), 126.97 (Cq), 129.47 (2CH), 131.01 (Cq), 132.03 (2CH), 135.84 (Cq), 136.46 (Cq), 169.56 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (ES$^+$) 356 (M + 2H)$^+$; (ES$^-$) 353 (M − H)$^-$. *m/z* (FAB$^+$) 355 (MH$^+$) (found: C, 60.87; H, 4.20; N, 7.70; M$^+$, 354.03674. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89%; M, 354.03677).

(2-Methoxyphenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12l. White solid. Yield 83%. Mp 92–93 °C. Rotamers 1 : 3.2 (from the duplicated broad singlet signals (^{1}H) at 2.62 and 2.78 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.24. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.62 (2H, br s), 3.47 (2H, t, *J* 5.4), 3.69 (3H, s), 4.80 (1H, d, *J* 16.7), 4.92 (1H, d, *J* 16.7), 6.75–7.37 (8H, m), 8.89 (1H, br s). δ (distinct peaks for minor rotamer) 2.78 (2H, br s), 3.58 (3H, s), 4.25–4.31 (2H, m), 8.20 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (major rotamer) 21.95 (CH_2), 40.56 (CH_2), 45.38 (CH_2), 55.56 (CH_3), 107.62 (Cq), 111.14 (CH), 111.32 (CH), 117.69 (CH), 119.23 (CH), 121.02 (CH), 121.47 (CH), 125.94 (Cq), 126.75 (Cq), 127.83 (CH), 130.29 (Cq), 130.66 (CH), 136.47 (Cq), 155.56 (Cq), 169.20 (Cq). δ (distinct peaks for minor rotamer) 21.15 (CH_2), 44.85 (CH_2), 108.92 (Cq), 111.04 (CH), 111.14 (CH), 118.01 (CH), 119.44 (CH), 121.02 (CH), 121.63 (CH), 126.89 (Cq), 128.13 (CH), 129.98 (Cq), 130.74 (CH), 136.30 (Cq), 168.69 (Cq). *m/z* (ES$^+$) 307 (MH$^+$), 613 (2M + H)$^+$; (ES$^-$) 611 (2M − H)$^-$. *m/z* (FAB$^+$) 307 (MH$^+$) (found: C, 74.53; H, 5.91; N, 9.04; MH$^+$, 307.14463. $C_{19}H_{18}N_2O_2$ requires C, 74.49; H, 5.92; N, 9.14%; MH 307.14465).

(3-Methoxyphenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12m. Yellow solid. Yield 98%. Mp 75–78 °C. Rotamers 1: 2.7 (from the duplicated broad singlet signal (^{1}H) at 4.48 and 4.81 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.73 (2H, br s), 3.68 (2H, br s), 3.73 (3H, s), 4.81 (2H, br s), 6.80–7.43 (8H, m), 8.60 (1H, br s). δ (distinct peaks for minor rotamer) 4.48 (2H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.15 (CH_2), 41.13 (CH_2), 46.06 (CH_2), 55.42 (CH_3), 107.72 (Cq), 111.19 (CH), 112.21 (CH), 115.94 (CH), 117.83 (CH), 118.97 (CH), 119.52 (CH), 121.77 (CH), 126.79 (Cq), 129.84 (CH), 130.07 (Cq), 136.34 (Cq), 137.32 (Cq), 159.73 (Cq), 171.40 (Cq). No rotamers observed in ^{13}C at RT. *m/z* (ES$^+$) 307 (MH$^+$), 613 (2M + H)$^+$. *m/z* (FAB$^+$) 307 (MH$^+$) (found: MH$^+$, 307.14460. $C_{19}H_{18}N_2O_2$ requires MH 307.14465).

(1,3,4,9-Tetrahydro-β-carbolin-2-yl)-*o*-tolylmethanone 12n. White solid. Yield 83%. Mp 186 °C. Rotamers 1 : 2.8 (from the duplicated singlet signal (^{1}H) at 2.24 and 2.39 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.32. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.39 (3H, s), 2.78 (2H, apparent d, *J* 4.8), 3.62 (2H, apparent q, *J* 5.7), 4.93 (1H, d, *J* 16.2), 5.18 (1H, d, *J* 16.2), 7.10–7.57 (8H, m), 8.98 (1H, br s). δ (distinct peaks for minor rotamer) 2.24 (3H, s), 2.97 (2H, apparent t, estimated *J* 5.1), 4.35 (2H, br s), 8.24 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$)

δ (major rotamer) 19.13 (CH_3), 22.01 (CH_2), 40.38 (CH_2), 45.22 (CH_2), 107.52 (Cq), 111.27 (CH), 117.77 (CH), 119.42 (CH), 121.70 (CH), 125.72 (CH), 126.11 (CH), 126.74 (Cq), 129.16 (CH), 130.08 (Cq), 130.65 (CH), 134.39 (Cq), 136.34 (Cq), 136.42 (Cq), 171.33 (Cq). δ (distinct peaks for minor rotamer) 18.87 (CH_3), 21.14 (CH_2), 45.10 (CH_2), 109.05 (Cq), 111.06 (CH), 118.15 (CH), 119.62 (CH), 121.90 (CH), 126.86 (Cq), 129.52 (Cq), 130.56 (CH), 134.31 (Cq), 136.51 (Cq), 170.72 (Cq). *m/z* (FAB^+) 291 (MH^+) (found: C, 78.48; H, 6.35; N, 9.77; MH^+, 291.14969. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65%; MH, 291.14974).

(1,3,4,9-Tetrahydro-β-carbolin-2-yl)-*m*-tolylmethanone 12o. White solid. Yield 76%. Mp 170 °C. Rotamers 1 : 3.5 (from the duplicated broad singlet signal (^1H) at room temperature at 4.44 and 4.82 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.40. ^1H NMR (400 MHz, 373 K, DMSO) δ 2.39 (3H, s), 2.79 (2H, t, *J* 5.5), 3.81 (2H, t, *J* 5.5), 4.77 (2H, s), 7.00 (1H, td, *J* 7.5 and 1.1), 7.08 (1H, td, *J* 7.5 and 1.1), 7.24–7.38 (5H, m), 7.42 (1H, d, *J* 8.0), 10.52 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.23 (CH_2), 21.76 (CH_3), 43.04 (CH_2), 44.13 (CH_2), 107.51 (Cq), 111.51 (CH), 117.93 (CH), 119.05 (CH), 121.31 (CH), 124.18 (CH), 127.34 (Cq), 127.64 (CH), 128.73 (CH), 130.50 (CH), 131.38 (Cq), 136.89 (Cq), 137.15 (Cq), 138.37 (Cq), 170.66 (Cq). *m/z* (ES^+) 291 (MH^+), 581 $(2M + H)^+$; (ES^-) 289 $(M - H)^-$. *m/z* (FAB^+) 291 (MH^+) (found: C, 78.78; H, 6.06; N, 9.42; MH^+, 291.14968. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65%; MH, 291.14974).

(1,3,4,9-Tetrahydro-β-carbolin-2-yl)-*p*-tolylmethanone 12p. White solid. Yield 90%. Mp 186 °C. *R*f (ethyl acetate–petroleum ether 50 : 50) 0.57. ^1H NMR (400 MHz, 373 K, DMSO) δ 2.39 (3H, s), 2.80 (2H, br t, *J* 5.6), 3.82 (2H, t, *J* 5.6), 4.78 (2H, s), 7.01 (1H, td, *J* 7.3 and 0.8), 7.08 (1H, td, *J* 7.3 and 1.1), 7.28 (2H, br d, *J* 7.6), 7.34 (1H, br d, *J* 8.0), 7.37 (2H, br d, *J* 8.0), 7.42 (1H, br d, *J* 7.6), 10.52 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.23 (CH_2), 21.78 (CH_3), 43.12 (CH_2), 44.17 (CH_2), 107.53 (Cq), 111.52 (CH), 117.93 (CH), 119.05 (CH), 121.31 (CH), 127.28 (2CH), 127.36 (Cq), 129.36 (2CH), 131.44 (Cq), 134.24 (Cq), 136.90 (Cq), 139.70 (Cq), 170.69 (Cq). No rotamers observed at RT neither from the ^1H nor from the ^{13}C NMR. *m/z* (FAB^+) 291 (MH^+) (found: C, 78.76; H, 6.12; N, 9.63; MH^+, 291.14978. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65%; MH, 291.14974).

Biphenyl-4-yl-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone 12q. White solid. Yield 47%. Mp 239 °C. *R*f (ethyl acetate–petroleum ether 50 : 50) 0.63. ^1H NMR (400 MHz, 373 K, DMSO) δ 2.83 (2H, t, *J* 5.6), 3.86 (2H, t, *J* 5.6), 4.80 (2H, s), 6.99 (1H, td, *J* 7.6 and 0.7), 7.07 (1H, td, *J* 7.6 and 1.1), 7.33 (1H, br d, *J* 8.0), 7.42 (2H, br d, *J* 7.2), 7.50 (2H, br t, *J* 6.8), 7.56 (2H, dt, *J* 5.2 and 1.6), 7.72 (2H, dt, *J* 8.0 and 2.0), 7.77 (2H, dt, *J* 6.0 and 2.1), 10.54 (1H, br s). ^{13}C NMR (100 MHz, 373 K, DMSO) δ 21.79 (CH_2), 107.51 (Cq), 111.52 (CH), 117.93 (CH), 119.05 (CH), 121.32 (CH), 127.17 (2CH), 127.21 (2CH), 127.32 (Cq), 127.90 (2CH), 128.23 (CH), 129.38 (2CH), 131.35 (Cq), 135.97 (Cq), 136.88 (Cq), 140.03 (Cq), 142.02 (Cq), 170.35 (Cq). Two CH_2 are missing from the ^{13}C NMR at 373 K. The two signals were observed at 75 MHz, at RT, in DMSO at 41.11 and 45.49 ppm. No rotamers observed at RT neither from the ^1H nor from the ^{13}C NMR. *m/z* (ES^+) 353 (MH^+); (ES^-) 351 $(M - H)^-$. *m/z* (FAB^+) 353 (MH^+) (found: C, 81.86; H, 5.62; N, 7.98; MH^+, 353.16532. $C_{24}H_{20}N_2O$ requires C, 81.79; H, 5.72; N, 7.95%; MH, 353.16539).

2-Phenyl-1-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone 13. White solid. Yield 63%. Mp 188–190 °C. Rotamers 1 : 4 (from the duplicated singlet signal (^1H) at 4.52 and 4.77 ppm). *R*f (ethyl acetate–petroleum ether 50 : 50) 0.36. ^1H NMR (300 MHz, $CDCl_3$) δ (major rotamer) 2.56 (2H, t, *J* 5.7), 3.70 (2H, t, *J* 5.7), 3.81 (2H, s), 4.77 (2H, s), 6.99 (1H, td, *J* 7.3 and 1.2), 7.06 (1H, td, *J* 7.3 and 1.3), 7.13–7.29 (6H, m), 7.33 (1H, d, *J* 7.5), 8.32 (1H, br s). δ (distinct peaks for minor rotamer) 2.75 (2H, t, *J* 5.7), 3.75 (2H, s), 3.92 (2H, t, *J* 5.7), 4.52 (2H, s), 7.41 (1H, d, *J* 7.8), 7.80 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.78 (CH_2), 40.74 (CH_2), 41.36 (CH_2), 44.52 (CH_2), 107.76 (Cq), 111.07 (CH), 117.77 (CH), 119.48 (CH), 121.71 (CH), 126.94 (CH), 128.71 (2CH), 128.83 (2CH), 130.27 (Cq), 134.96 (Cq), 136.22 (Cq), 170.59 (Cq). One ^{13}C quaternary is not observed. No rotamers observed in ^{13}C at RT. *m/z* (ES^+) 291 (MH^+), 581 $(2M + H)^+$. *m/z* (ES^-) 289 $(M - H)^-$, 579 $(2M - H)^-$. *m/z* (FAB^+) 290 (M^+), 291 (MH^+) (found: M^+, 290.14192. $C_{19}H_{18}N_2O$ requires M, 290.14191).

1,3,4,9-Tetrahydro-β-carboline-2-carboxylic acid diethylamide 14. White solid. Yield 91%. Mp 102 °C. *R*f (ethyl acetate–petroleum ether 50 : 50) 0.22. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (6H, t, *J* 7.1), 2.77 (2H, t, *J* 5.4), 3.22 (4H, q, *J* 7.1), 3.45 (2H, t, *J* 5.4), 4.37 (2H, s), 7.00 (2H, apparent quintet, estimated *J* 7.3), 7.20 (1H, d, *J* 7.5), 7.37 (1H, d, *J* 7.2), 9.11 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.35 ($2CH_3$), 21.78 (CH_2), 42.18 ($2CH_2$), 44.69 (CH_2), 47.06 (CH_2), 107.94 (Cq), 111.13 (CH), 117.78 (CH), 119.17 (CH), 121.31 (CH), 126.99 (Cq), 131.79 (Cq), 136.42 (Cq), 165.03 (Cq). No rotamers observed at RT neither from the ^1H nor from the ^{13}C NMR. *m/z* (FAB^+) 271 (M^+), 272 (MH^+) (found: C, 70.93; H, 7.50; N, 15.36; M^+, 271.16850. $C_{16}H_{21}N_3O$ requires C, 70.82; H, 7.80; N, 15.49%; M, 271.16846).

1-Phenyl-2-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone 15. To a solution of 1,2,3,4-tetrahydro-β-carboline (0.40 g, 2.32 mmol) in toluene (26 mL) was added a solution of $NaHCO_3$ (0.45 g, 5.39 mmol) and Na_2SO_3 (0.23 g, 1.81 mmol) in water (8.0 mL). The mixture was stirred under N_2 atmosphere and 2-bromoacetophenone (0.23 g, 1.16 mmol) was added. The stirring was maintained for 4 h at room temperature. The crude mixture was evaporated under reduced pressure and the resulting crude product was purified directly by column chromatography on silica gel. Elution was made successively with: ethyl acetate–cyclohexane 50 : 50 and ethyl acetate to give the title compound **19** as an orange solid (0.21 g, 61%). Mp 152–153 °C. *R*f (ethyl acetate–petroleum ether 50 : 50) 0.37. ^1H NMR (300 MHz, $CDCl_3$) 2.78 (2H, t, *J* 5.7), 2.98 (2H, t, *J* 5.7), 3.78 (2H, s), 3.97 (2H, s), 7.01 (1H, t, *J* 3.2), 7.01 (1H, ddd, *J* 10.5 and 6.9 and 1.8), 7.15–7.19 (1H, m), 7.34–7.40 (3H, m), 7.48 (1H, tt, *J* 7.4 and 1.7), 7.90–7.93 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) 20.64 (CH_2), 50.08 (CH_2), 51.13 (CH_2), 62.70 (CH_2), 107.95 (Cq), 110.87 (CH), 117.92 (CH), 119.34 (CH), 121.41 (CH), 127.17 (Cq), 128.19 (2CH), 128.63 (2CH), 131.25 (Cq), 133.39 (CH), 135.91 (Cq), 136.06 (Cq), 196.80 (Cq). *m/z* (ES^+) 291 (MH^+), 581 $(2M + H)^+$. *m/z* (ES^-) 289 $(M - H)^-$, 579 $(2M - H)^-$. *m/z* (FAB^+) 291 (MH^+) (found: C, 78.67; H, 6.30; N, 9.71; M^+, 291.14975. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65%; M, 291.14974).

2-(2-Oxo-2-phenylethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-2-ium chloride 16. To a solution of **15** (0.20 g, 0.07 mmol) in a minimum of dichloromethane was flushed HCl gas. After around 3 min the mixture was evaporated under reduced pressure to give the title compound **16** (0.21 g, 95%) as a yellow solid, which was dried under vacuum for a few days. Mp 158–159 °C. ^{1}H NMR (300 MHz, DMSO) 3.17 (2H, t, *J* 5.3), 3.74 (2H, br s), 4.70 (2H, br s), 5.31 (2H, s), 7.10 (1H, td, *J* 7.6 and 1.0), 7.18 (1H, td, *J* 7.6 and 1.0), 7.44 (1H, d, *J* 7.8), 7.55 (1H, d, *J* 7.5), 7.67 (2H, apparent t, estimated *J* 7.7), 7.82 (1H, t, *J* 7.4), 8.10 (2H, apparent d, estimated *J* 7.2), 10.98 (1H, br s), 11.23 (1H, br s). ^{13}C NMR (75 MHz, DMSO) 18.29 (CH_2), 49.79 (CH_2), 51.67 (CH_2), 60.00 (CH_2), 105.43 (Cq), 111.87 (CH), 118.47 (CH), 119.47 (CH), 122.18 (CH), 126.21 (Cq), 126.32 (Cq), 128.70 (2CH), 129.49 (2CH), 134.26 (Cq), 135.20 (CH), 136.74 (Cq), 192.19 (Cq). *m/z* (ES^+) 291 $(M - Cl)^+$, 582 $(2(M - Cl))^+$. *m/z* (ES^-) 325 $(M - H)^-$, 615 $(2(M - H) - Cl)^-$. *m/z* (FAB^+) 291 $(M - Cl)^+$ (found: $(M - Cl)^+$, 291.14970. $C_{19}H_{19}ClN_2O$ requires $(M - Cl)$, 291.14974).

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