Synthesis, crystal structure and biological activity of β-carboline based selective CDK4-cyclin D1 inhibitors†

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The design, synthesis and biological activity of a series of non-planar dihydro-β-carboline and β-carboline-based derivatives of the toxic anticancer agent fascaplysin is presented. We show these compounds to be selective inhibitors of CDK4 over CDK2 with an IC_{50} (CDK4-cyclin D1) = 11 μmol for the best compound in the series **4d**. The crystallographic analysis of some of the compounds synthesised (**3b/d** and **4a**–**d**) was carried out, in an effort to estimate the structural similarities between the designed inhibitors and the model compound fascaplysin.

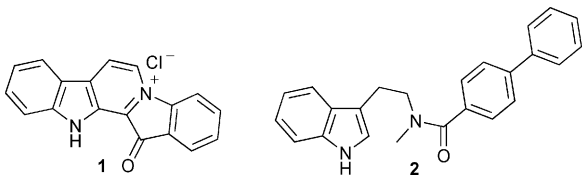
Introduction

The cyclin-dependent kinases (CDKs) are a set of proteins that play a vital role in the regulation of the cell cycle checkpoints, controlling the transition between the different phases of the process.[1] As a wide variety of diseases (cancer in particular) are characterised by a deregulation in the cell cycle causing uncontrolled cell proliferation, the inhibition of CDKs by small molecules is one of the most active fields in current anti-cancer research.[2]

In this context, the specific inhibition of the CDK4-cyclin D1 complex has arisen as an interesting anticancer target.[3] CDK4 is one of the key players in the transition between G_1 and S phases of the cell cycle and is constitutively activated in many human cancers. Similarly, cyclin D1 is often over expressed, whereas the CDK4 inhibitor (p16) is deleted in a variety of human tumours.

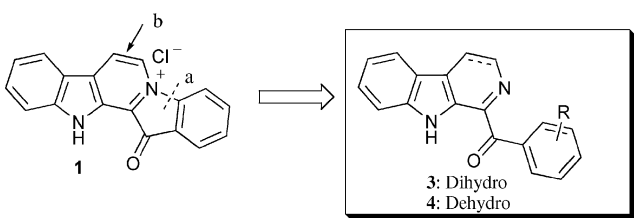
In recent times our group has been interested in the design, modelling, synthesis and biological evaluation of novel, specific CDK4-cyclin D1 inhibitors based on the structure of the pentacyclic quaternary salt fascaplysin **1**.[4–6] This natural product, originally isolated from the Fijian sponge *Fascaplynosis* Bergquist sp,[7] 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 $ED_{50} = 0.2\ \mu g\ mL^{-1}$. Fascaplysin has been also reported to specifically inhibit CDK4-cyclin D1 ($IC_{50} = 0.55\ \mu M$), causing G_1 arrest of both tumour (U2-OS, HCT-116) and normal (MRC-5) cells.[8] The use of fascaplysin **1** as an anticancer drug is limited due to its high toxicity; because of its planar structure it can act as a DNA intercalator.[9] The aim of the present study consists of the design of non-toxic (non-planar) analogues of the natural product with increased activity as CDK4-cyclin D1 inhibitors.

It has been shown, using a computational approach, that one of the most important features of the predicted binding mode of fascaplysin **1** in the ATP binding site of a CDK4 homology model is a double hydrogen bonding to Val 96.[6,10] It is also noteworthy that our most active compound so far, the tryptamine based compound **2** (IC_{50} = 6 μm), was predicted to be located in the ATP binding site of the CDK4 homology model in a similar fashion to fascaplysin **1** but with the double hydrogen-bonding interaction being with the backbone of His 95/Val 96 and an extra stabilization arising from a π–π stacking interaction between the biphenyl moiety of the ligand with the side chains of Phe 93 and Phe 159 (Scheme 1).[6]



Scheme 1 Structures of fascaplysin **1** and the tryptamine based analogue **2**.

Taking these facts into account we designed a series of non-planar β-carboline-based analogues of the natural product fascaplysin **1** of general type **3** and **4** with different substituents in the benzenoid ring by removing bond *a* in the original structure (Scheme 2) and in some cases converting double bond *b* into a single bond. As four of the five rings of fascaplysin **1**, and the relative disposition of the H-bond acceptors/donors needed for the double interaction with Val 96 (*i.e.* the carbonyl and the



Scheme 2 Strategy used to produce the non-planar β-carboline derivatives **3** and **4** from fascaplysin **1**.

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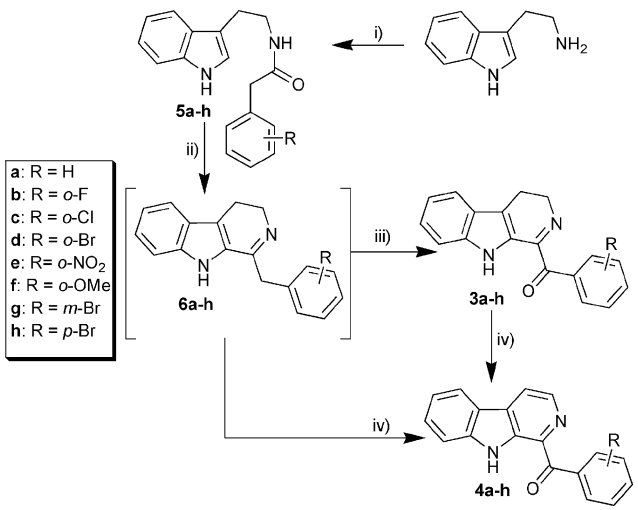
indolyl NH group in **3/4**), is nearly the same as in fascaplysin **1**, by inference, the binding mode and hence the CDK4 inhibition activity was expected to be retained.

Moreover, the introduction of different aromatic substituents in the benzenoid ring into the parent compounds of type **3** and **4**, was also planned in an attempt to explore the presence or not of stabilizing π–π interactions as for compound **2** leading to increased activities as CDK4-cyclin D1 specific inhibitors.

Results and discussion

β-Carboline and dihydro β-carboline compounds

In a previous communication,[11] the investigation of the spontaneous photo-oxidation of the 1-(2-bromo-benzyl)-4,9-dihydro-3*H*-β-carboline, led us to the development of a mild, green, regioselective and practical protocol for the preparation of a series of dihydro-β-carbolines of type-**3** and β-carbolines of type-**4** from tryptamine derivatives **5** by a sequential Bischler–Napieralski cyclisation followed by induced photo-oxidation of the non-isolated 1-benzyl-4,9-dihydro-3*H*-β-carboline derivatives **6** (Scheme 3).



Scheme 3 *Reagents and conditions:* i) $RC_6H_4CH_2COCl$, CH_2Cl_2, $NaOH_{(aq)}$. ii) $POCl_3$, toluene, N_2, reflux, basic work-up. iii) hυ, O_2, toluene, 30 °C. iv) hυ, O_2, toluene, reflux.

To circumvent the intrinsic instability of type-**6** compounds, purification after cyclisation of the corresponding acetamide derivatives **5** was avoided, so the crude reaction product after basic work-up of the Bischler–Napieralski reaction was irradiated under the conditions detailed in Scheme 3.

Irradiation of **6a–h** in toluene with a 500 Watt halogen lamp (290–300 nm frequency cut-off) at 30 °C led, regioselectively in most cases, to the dihydro-β-carbolines (**3a–d**, **3g–h**) with satisfactory yields (44–59%) from the corresponding tryptamine derivative **5**. Irradiation under these conditions of crude **6e** led to decomposition of the starting material to a complex mixture, and irradiation of **6f** yielded a mixture of the dihydro-β-carboline **3f** (31% isolated yield) and the β-carboline **4f** (10% isolated yield). A slight modification of the irradiation method, inducing reflux of the toluene solution, produced the fully aromatic β-carbolines **4b–d**, **4f** and **4h** with modest to acceptable yields from **5a–h** (11–55%). On other occasions, the fully aromatic compounds **4a–e** were obtained in good yields (62–99%) by irradiation in refluxing toluene of the isolated ketoimines **3a–e**.

Solid state structure

As we wished to maintain the double H-bond to Val 96 as seen in fascaplysin **1**, X-ray structure analysis was carried out for some of the compounds **3/4** synthesised (**3b/d** and **4a–d**).

The conformation of type **4** compounds can be described by means of the torsion angles τ_1 (C11–C1–C12–O1) and τ_2 (C1–C12–C13–C14) (Fig. 1). Whilst τ_1 gives a qualitative idea of the deviation of the carbonyl group from the plane of the heterocyclic moiety, τ_2 is connected to the relative disposition of the β-carboline substructure and the benzenoid ring. For compounds of type **3** an extra degree of conformational freedom arises from the non-planar (non-aromatic) cyclic imine substructure in the β-carboline so a third torsion angle τ_3 (C4–C3–C2–N1) was included. In both cases, for type-**3** and type-**4** compounds, these defined torsion angles are interrelated because of the geometry of the molecules.

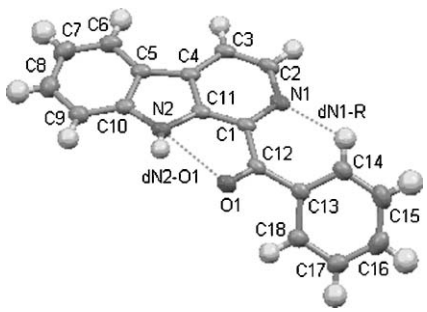


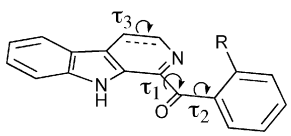
Fig. 1 MERCURY projection (displacement ellipsoids, 50% probability) of one of the two conformers of **4a** in the minimal asymmetric unit of the crystal, with the arbitrary labelling used in the study.†

As exemplified in Fig. 1 for compound **4a**, we found all the structures **3/4** displaying a strong N2–H · · · O1 intramolecular H-bond as in the model compound. The geometrical features of this interaction are shown in Table 1.

This intramolecular hydrogen bond is forced by the molecular geometry, with the carbonyl group located nearly in the same plane as the β-carboline moiety (the same situation occurs for fascaplysin), so the free rotation around the C1–C12 bond (characterized by the torsion angle τ_1) in compounds **4** is restricted. Once this geometry is constrained, the phenyl ring in **4** acquires a tilted-T shape relative to the planar heterocyclic substructure characterized by the torsion angle τ_2. For type-**3** molecules the non-planar configuration of the dihydro-β-carboline substructure (characterized by τ_3), causes the carbonyl group to be more out of the plane of the heterocyclic moiety than for type-**4** molecules, increasing τ_1 as exemplified in Fig. 2 for compounds **3d** and **4d**.

Moreover, this nearly planar configuration of the intramolecular donor/acceptors allows the molecule to form intermolecular cyclic dimers by a double hydrogen bonding as exemplified in Fig. 3 for **4a**. The β-carboline substructures of the two molecules are arranged in parallel planes separated by a perpendicular distance di (see Table 1 for geometrical details of the intermolecular hydrogen bonding).

Table 1 Geometrical data discussed in the text†



3b dihydro R = F
3d dihydro R = Br
4a dehydro R = H
4b dehydro R = F
4c dehydro R = Cl
4d dehydro R = Br

	Monomers						Dimers		
Structure	d(N2 ⋯ O1)/Å	∠N2HO1/°	τ_1/°	τ_2/°	τ_3/°	d(N1 ⋯ R)/Å	d(N2′ ⋯ O1)/Å	∠N2HO1/°	di/Å[c]
4a[b]	2.744	117.2	2.13	50.05	—	2.603	2.945	154.9	0.616
	2.767	115.7	11.78	−49.70	—	2.567	2.944	154.2	0.616
4b	2.889	113.4	−12.54	−63.18	—	3.099	3.056	144.4	1.095
4c	2.808	113.9	−5.70	−70.49	—	3.262	2.996	145.6	0.275
4d	2.813	114.2	−4.11	−68.10	—	3.351	3.013	145.0	0.000
3b	2.837	120.5	19.90	50.34	−45.53	2.939	—	—	—
3d	2.935	116.6	−24.94	−58.96	−17.30	3.361	3.088	153.8	0.770

[a] Data measured using the program Mercury. [b] Two different conformers are presented in the asymmetric unit cell for compound **4a**. [c] Perpendicular distance between the parallel planes containing the β-carboline (type **4** compounds) or indolyl (type **3**) moieties of the molecules involved in the double hydrogen bonding.

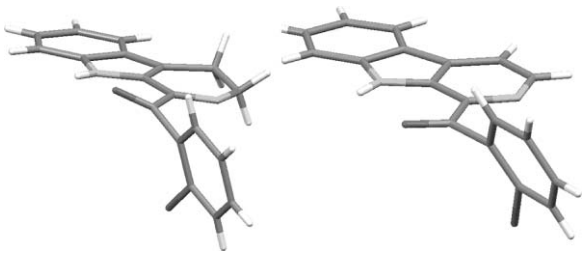


Fig. 2 MERCURY capped sticks representation of the minimal asymmetric unit in the crystalline structure for compound **3d** (left) and **4d** (right).†

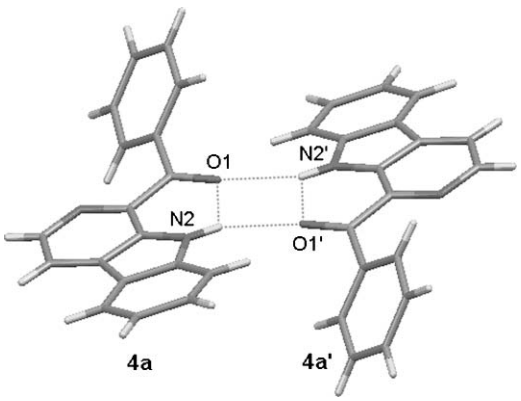


Fig. 3 MERCURY capped sticks representation of the cyclic symmetric dimer formed by two molecules of **4a** (symmetry codes x,y,z and $-x+1, -y, -z$). Intramolecular (N2H1 ⋯ O1, N2′H2′ ⋯ O1) and intermolecular (N2H ⋯ O1′, N2′H′ ⋯ O1). Hydrogen bonds shown as dashed blue lines.†

This finding modifies one of Etters rules for hydrogen bond priorities[12] which asserts that: "six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds", showing that the two situations can coexist for the same pair of donor/acceptors.

One interesting consequence of the rigidity of the molecules studied is the presence in most of the cases of short contacts between the pyridine-type nitrogen in **3**/**4** and the *ortho*-R group linked to C14 in the benzenoid ring. These non-covalent interactions are characterized by a d(N1–R) slightly lower (see Table 1 for details) than the corresponding sum of the van der Waals radii of the atoms r (r_F 1.47 Å, r_{Cl} 1.75 Å, r_{Br} 1.85 Å, r_N 1.55 Å[13] and r_H 1.09 Å).[14] Although these could be considered as halogen bonding for the compounds **4c/d** and **3b/d**, and non-classic hydrogen bonding for the two conformers found in the unit cell for **4a**, these interactions could be artefacts imposed by the constrained molecular geometry.‡

It is also probable that in solution, as in the solid state, these compounds could present a preferred rigid conformation arising from the inter/intramolecular H-bonding. For instance, in the ^{1}H-NMR spectra ($CDCl_3$, 300 MHz) of compounds **6d**, **3d** and **4d** the δNH_{indol} signal is respectively 8.00, 9.48 and 10.43 ppm; depending on the environment of the NH group as well as its ability to form intra and intermolecular hydrogen bondings.

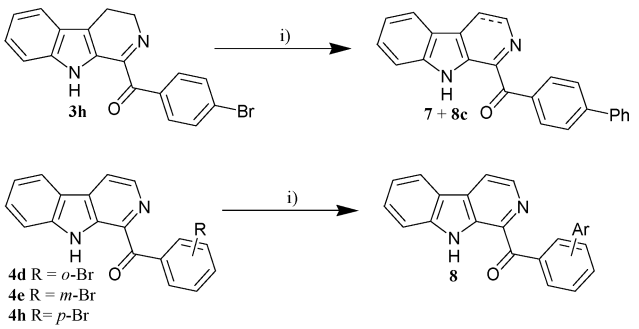
Bi/triphenyl compounds

Based on the good biological activity of compound **2**, our group has explored the design, synthesis and biological activity of a wide range of biphenyl derivatives of **2** demonstrating the existence of a π-stacking region in the active site of CDK4,[17] that could be analogous to the "Phe 80 pocket" of CDK2.[18]

In an effort to evaluate the importance of this π-stacking interaction compared to the double hydrogen bonding presented for fascaplysin, we planned a further functionalization of the parent dehydro and dihydro-β-carboline derivatives using the Suzuki–Miyaura cross-coupling reaction to prepare a library of bis/triphenyl compounds related to **3** and **4** (Scheme 4).

In a first attempt to use this approach, the *para*-brominated dihydro-β-carboline **3h** was used as starting material for the coupling reaction. This compound was reacted with phenylboronic

‡ The expected priority order for the halogen bond interactions C–X ⋯ B is B = S < N < O for the Lewis base and X = Cl < Br < I for the halogen,[15] the contact with X = F being rarely reported and quite controversial.[16] In our case, with the carbonyl group involved in two hydrogen bonds, the pyridine-like nitrogen is the only available acceptor for the intramolecular interaction.



Compound	Ar	Compound	Ar	Compound	Ar
8a	*o*-Ph	**8b**	*m*-Ph	**8c**	*p*-Ph
8d	*o*-4-Me-Ph	**8e**	*m*-4-Me-Ph	**8f**	*p*-4-Me-Ph
8g	*o*-4-F-Ph	**8h**	*m*-4-F-Ph	**8i**	*p*-4-F-Ph
8j	*o*-4-^{t}Bu-Ph	**8k**	*m*-4-^{t}Bu-Ph	**8l**	*p*-4-^{t}Bu-Ph
8m	*o*-4-Ph-Ph	**8n**	*m*-4-Ph-Ph	**8o**	*p*-4-Ph-Ph

Scheme 4 *Reagents and conditions:* i) $Pd(PPh_3)_{4(cat)}$, $K_2CO_{3(aq)}$, $ArB(OH)_2$, toluene–EtOH, 90 °C.

acid in a 1 : 1 mixture of toluene–EtOH at 90 °C using $Pd(PPh_3)_4$ as catalyst and aqueous K_2CO_3 as base. This produced an unresolved mixture of the desired dihydro-β-carboline **7** and the fully aromatic β-carboline **8d** in a 10 : 1 ratio.

Using the same reaction conditions with the corresponding *ortho*/*meta*/*para* brominated β-carbolines **4d**, **4e** and **4h** as starting materials, the synthesis of the target compounds **8a–o** was achieved in a straightforward fashion with high yields (82–99%, see experimental part for further details).

Biological results

The CDK4 and CDK2 inhibitory activities of compounds **3a–d**, **3g–h**, **4a–d**, **4f–h**, **7**, and **8a–o** were measured in terms of IC_{50} using standard methods[6] and the results are shown in Table 2. As expected, all the compounds are active as CDK4 inhibitors showing a clear selectivity for this kinase compared to CDK2.

The first series of compounds discussed above, the dihydro-β-carboline derivatives, shows, in general, better activities compared to the corresponding fully aromatic compounds. In both series the introduction of a halogen in the *ortho*-position of the benzenoid ring increases the activity, the greater the electronegativity of the halogen the lesser the effect. Furthermore, taking the *ortho*-brominated derivatives **3d** and **4d** as reference, the activity of these compounds is decreased if the halogen is located in the *meta* or *para*-positions on the aromatic ring. For these two series the best hits correspond to the *ortho*-brominated compounds **3d** (IC_{50} = 11 μm) and **4d** (IC_{50} = 14 μm).

As the crystallographic analysis of compounds of type **3** and **4** has shown, these should exist in a rigid conformation, differing from fascaplysin only in the relative disposition of the outer phenyl group (characterised by τ_2), so a similar binding mode in the ATP site of the enzyme is expected.

Concerning the bi/triphenyl derivatives, the introduction of aromatic ring or rings in the initial structure decreases the activity with respect to the parent brominated compounds, the exception being **8f** (more active than **4h**) and **8k** (more active than **4g**).

For these series of compounds, instead of a synergic effect between the two interactions (*i.e.* the fascaplysin-like double hydrogen bonding and the π-stacking present in compound **2**), in our case, the decreased activities for the coupling products can be rationalized in terms of a competition between the two binding modes. Once the molecule is located in the ATP binding site in a similar fashion as for fascaplysin **1**, the bulky introduced bis/tris aromatic moieties are possibly not oriented properly in the direction of the π-stacking pocket.

Table 2 CDK4 activity *versus* CDK2 activity

Compound	CDK4 measured IC_{50}/μM[a]	CDK2 measured IC_{50}/μM[b]
Fascaplysin **1**	0.55	500
2	6 ± 1	521 ± 12
3a	45 ± 4	515 ± 11
3b	16 ± 2	812 ± 8
3c	12 ± 1.8	630 ± 15
3d	11 ± 2	818 ± 16
3g	78 ± 6	1209 ± 15
3h	34 ± 2	538 ± 9
4a	39 ± 3	913 ± 8
4b	24 ± 2.5	974 ± 11
4c	22 ± 2	855 ± 10
4d	14 ± 1	940 ± 12
4f	65 ± 3.5	512 ± 7
4g	32 ± 3	868 ± 10
4h	34 ± 2	538 ± 9
(**7**+**8a**)[c]	61 ± 4	712 ± 7
8a	72 ± 5	1216 ± 11
8b	67 ± 3	920 ± 20
8c	77 ± 4	1135 ± 18
8d	75 ± 4	496 ± 9
8e	59 ± 5	384 ± 15
8f	30 ± 1	983 ± 17
8g	65 ± 3	865 ± 13
8h	54 ± 5	367 ± 8
8i	42 ± 2	350 ± 8
8j	48 ± 2.5	423 ± 15
8k	25 ± 2	971 ± 11
8l	58 ± 3	800 ± 15
8m	77 ± 4	526 ± 14
8n	58 ± 2.5	437 ± 10
8o	61 ± 3.5	566 ± 12

[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] Tested as an unresolved mixture of **7** and **8a** in a 10 : 1 ratio.

Conclusions

A series of dehydro-β-carboline and β-carboline-based compounds related to the toxic anticancer agent fascaplysin **1** were synthesised and their biological activities as CDK4-cyclin D1 specific inhibitors measured.

Compounds **3a–d**, **3g–h**, **4a–d** and **4f–h** were designed to retain the double hydrogen bonding to Val 96 and prepared with acceptable yields by a novel synthetic methodology previously reported.

Compounds **7** and **8a–o** were produced using the well established Suzuki–Miyaura coupling methodology in an effort to increase the activities of the parent compounds by interaction with a proposed π-stacking pocket (Phe 93–159).

The structural similarity between compounds of type **3**/**4**, and fascaplysin **1** was estimated by means of the solid state structure analysis of some of the compounds synthesised (**3b**/**d** and **4a–d**).

This analysis showed the compounds have a rigid conformation, keeping the carbonyl group and the indolyl NH approximately in the same plane as for fascaplysin **1** caused by a strong intramolecular hydrogen bonding. As predicted, the compounds showed a good activity as CDK4-cyclin D1 inhibitors with an IC_{50} for the best compound of 11 μm.

The second series (compounds **7** and **8a–o**), showed in general a decreased activity compared to the parent compounds. This was attributed to a competition between the two proposed binding modes.

Experimental

General

All reactions were performed under an atmosphere of nitrogen (unless otherwise stated in the text) and solvent extractions dried with anhydrous sodium sulfate. NMR spectra were recorded on a Bruker DPX 300 (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz) spectrometer. Chemical 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 rounded 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). Melting points were recorded on a Reichert Kofler thermopan and are uncorrected.

Crystal structure determinations§

Single crystals of compounds **3b/d** and **4a-d** suitable for X-ray diffractometry were obtained by dissolving crystals of the corresponding pure compound in the minimum quantity of cold EtOH in an open vial that was then placed in a larger container with a little H_2O in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations, afforded the desired single crystals. These were mounted in inert oil and transferred to the cold gas stream of the diffractometer.

General method for the Suzuki coupling reaction

To a stirred solution of the corresponding brominated intermediate (**3h**, **4d/e/h**, 1 mmol) in toluene (10 mL), under nitrogen, was added K_2CO_3 (1 mmol, 2M aqueous solution) and $Pd(PPh_3)_4$ (5 mol%, 0.05 mmol). The solution was stirred for 20 minutes at room temperature before the addition of a solution of the appropriately substituted phenylboronic acid (1.2 mmol) in EtOH (10 mL), the reaction mixture was then heated to 90 °C for 24 h and allowed to cool to room temperature before the addition of H_2O_2 (30%, 1 mL). The reaction mixture was then stirred for a further hour, and extracted into $CHCl_3$, washed with saturated brine solution (2 × 25 mL) and H_2O (2 × 25 mL), aqueous washings being re-extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were then dried over anhydrous sodium or magnesium sulfate, filtered and isolated under reduced pressure. The crude products were then purified by flash column chromatography on silica from CH_2Cl_2.

Suzuki coupling of compound 3h. The reaction between the brominated derivative **3h** and phenylboronic acid in the conditions explained above yielded, after column chromatography (CH_2Cl_2), an unresolved mixture of **7** + **8a** in a 10 : 1 ratio (isolated overall yield 67%). The spectroscopic data for the major compound is described below.

Biphenyl-4-yl(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)-methanone 7. 67% (Mixture), yellow sticky solid, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.05 (2H, t, *J* 8.8), 4.21 (2H, t, *J* 8.8), 7.18 (1H, ddd, *J* 8.0, 7.0, 1.0), 7.33 (1H, ddd, *J* 8.3, 7.0, 1.2), 7.42–7.52 (4H, m), 7.63–7.66 (3H, m), 7.71 (2H, d, *J* 8.6), 8.28 (2H, d, *J* 8.6) and 9.51 (1H, br s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.1 (CH_2), 49.3 (CH_2), 112.3 (CH), 118.0 (Cq), 119.9 (CH), 120.3 (CH), 124.8 (Cq), 125.1 (CH), 126.6 (Cq), 126.9 (CH), 127.3 (CH), 128.2 (CH), 128.9 (CH), 131.6 (CH), 134.0 (Cq), 136.9 (Cq), 140.0 (Cq), 146.2 (Cq), 155.9 (Cq) and 192.8 (Cq); *m/z* (ES^+) 351 (MH^+).

Biphenyl-2-yl-(9*H*-β-carbolin-1-yl)-methanone 8a. 99% Yield, yellow solid; mp 194–195 °C (from EtOH); Found: C, 82.83; H, 4.70; N 7.84%; $C_{24}H_{16}N_2O$ requires: C, 82.74; H, 4.63; N, 8.04%; ν_{max}/cm^{-1} 3366, 3058, 1635, 1425, 1315, 1210, 1117, 969, 748, 737, 701; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.06–7.17 (3H, m), 7.30–7.35 (3H, m), 7.48–7.64 (5H, m), 7.72 (1H, dd, *J* 1.2 and 7.4), 8.00 (1H, d, *J* 4.9), 8.11 (1H, d, *J* 8.0 Hz), 8.42 (1H, d, *J* 4.9) and 10.28 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 115.4 (CH), 118.5 (CH), 120.1 (CH), 120.7 (Cq), 120.8 (CH), 121.8 (CH), 126.8 (CH), 126.9 (CH), 128.1 (CH), 128.9 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 130.6 (CH), 131.4 (Cq), 136.4 (Cq), 136.6 (Cq), 138.5 (CH), 138.6 (Cq), 141.1 (Cq), 142.01 (Cq) and 200.6 (CO) ppm; *m/z* (ES^+) 349 (MH^+); *m/z* (FAB^+) 351 (MH^+) (found: MH^+, 349.13407; $C_{24}H_{17}N_2O$ requires 349.13409).

Biphenyl-3-yl-(9*H*-β-carbolin-1-yl)-methanone 8b. 93% Yield, yellow solid; mp 151–152 °C (from EtOH); Found: C, 82.83; H, 4.56; N 7.99%; $C_{24}H_{16}N_2O$ requires: C, 82.74; H, 4.63; N, 8.04%; ν_{max}/cm^{-1} 3436, 3057, 1614, 1425, 1316, 1203, 748, 722, 693; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34–7.41 (2H, m), 7.48 (2H, t, *J* 7.4), 7.59–7.70 (5H, m), 7.85 (1H, dt, *J* 1.4 and 7.8), 8.18–8.21 (2H, m), 8.29 (1H, dt, *J* 7.7 and 1.3), 8.52 (1H, t, *J* 1.7), 8.62 (1H, d, *J* 4.9) and 10.46 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 110.9 (CH), 117.5 (CH), 119.7 (CH), 119.7 (Cq), 120.7 (CH), 126.2 (CH), 126.5 (CH), 127.3 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 129.1 (CH), 129.9 (Cq), 129.9 (CH), 130.6 (Cq), 135.1 (Cq), 136.2 (Cq), 137.0 (CH), 139.5 (Cq), 140.0 (2 × Cq) and 194.5 (CO) ppm; *m/z* (ES^+) 349 (MH^+); *m/z* (FAB^+) 351 (MH^+) (found: MH^+, 349.13404; $C_{24}H_{17}N_2O$ requires 349.13409).

Biphenyl-4-yl-(9*H*-β-carbolin-1-yl)-methanone 8c. 99% Yield, yellow solid; mp 183–184 °C (from EtOH); Found: C, 82.63; H, 4.59; N 7.91%; $C_{24}H_{16}N_2O$ requires: C, 82.74; H, 4.63; N, 8.04%; ν_{max}/cm^{-1} 3377, 3055, 1641, 1425, 1318, 1205, 742, 728, 709, 688; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33–7.43 (2H, m), 7.49 (2H, t, *J* 7.3), 7.62–7.64 (2H, m), 7.66–7.60 (2H, m), 7.76 (2H, dt, *J* 1.8

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and 8.4), 8.18–8.21 (2H, m), 8.43 (2H, dt, *J* 1.7 and 8.4), 8.63 (1H, d, 4.9 Hz) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 118.5 (CH), 120.7 (CH), 120.8 (Cq), 121.8 (CH), 126.7 (CH), 127.3 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 131.6 (Cq), 131.8 (CH), 136.3 (Cq), 136.4 (Cq), 137.3 (Cq), 138.0 (CH), 140.3 (Cq), 141.0 (Cq), 145.0 (Cq) and 194.8 (CO) ppm; *m/z* (ES^+) 349 (MH^+); *m/z* (FAB^+) 351 (MH^+) (found: MH^+, 349.13416; $C_{24}H_{17}N_2O$ requires 349.13409).

(9*H*-β-Carbolin-1-yl)-(4′-methyl-biphenyl-2-yl)-methanone 8d. 99% Yield, yellow solid; mp 185–186 °C (from EtOH); Found: C, 82.95; H, 4.98; N 7.65%; $C_{25}H_{18}N_2O$ requires: C, 82.85; H, 5.01; N, 7.73%; ν_{max}/cm^{-1} 3407, 3045, 1641, 1463, 1315, 1207, 1114, 972, 766, 750, 728, 711; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.20 (3H, s), 6.96 (2H, d, *J* 7.9), 7.20 (2H, d, *J* 8.0), 7.34 (1H, t, *J* 7.3), 7.45–7.63 (5H, m), 7.69 (1H, dd, *J* 1.0 and 7.6), 8.05 (1H, d, *J* 4.9), 8.13 (1H, d, *J* 7.8), 8.45 (1H, d, *J* 4.9) and 10.31 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.01 (CH_3), 111.9 (CH), 118.5 (CH), 120.7 (CH), 120.7 (Cq), 121.7 (CH), 126.4 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 130.4 (CH), 131.4 (Cq), 131.6 (Cq), 136.3 (Cq), 136.6 (2 × Cq), 138.1 (Cq), 138.4 (CH), 141.0 (Cq), 141.9 (Cq) and 200.6 (CO) ppm; *m/z* (ES^+) 363 (MH^+); *m/z* (FAB^+) 363 (MH^+) (found: MH^+, 363.14973; $C_{25}H_{18}N_2O$ requires 363.14975).

(9*H*-β-Carbolin-1-yl)-(4′-methyl-biphenyl-3-yl)-methanone 8e. 94% Yield, yellow solid; mp 159–160 °C (from EtOH); Found: C, 82.75; H, 5.11; N 7.63%; $C_{25}H_{18}N_2O$ requires: C, 82.85; H, 5.01; N, 7.73%; ν_{max}/cm^{-1} 3437, 3060, 1615, 1425, 1316, 1249, 1204, 978, 785, 750, 734, 723; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s), 7.27 (2H, d, *J* 8.0), 7.36 (1H, quintet, *J* 4.0), 7.57–7.64 (5H, m), 7.81 (1H, dt, *J* 1.7 and 7.7), 8.18–8.21 (2H, m), 8.28 (1H, dt, *J* 1.3 and 7.7), 8.50 (1H, t, *J* 1.6), 8.62 (1H, d, *J* 4.9) and 10.46 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 112.0 (CH), 118.6 (CH), 120.8 (CH), 120.9 (Cq), 121.8 (CH), 127.1 (CH), 128.4 (CH), 129.3 (CH), 129.6 (CH), 130.0 (CH), 130.9 (CH), 131.70 (Cq), 136.3 (Cq), 137.3 (Cq), 137.4 (2xCq), 137.8 (Cq), 138.1 (Cq), 138.2 (CH), 141.0 (Cq) and 195.7 (CO) ppm; *m/z* (ES^+) 363 (MH^+); *m/z* (FAB^+) 363 (MH^+) (found: MH^+, 363.14976; $C_{25}H_{18}N_2O$ requires 363.14975).

(9*H*-β-Carbolin-1-yl)-(4′-methyl-biphenyl-4-yl)-methanone 8f. 97% Yield, yellow solid; mp 209–210 °C (from EtOH); Found: C, 82.77; H, 4.96; N 7.61%; $C_{25}H_{18}N_2O$ requires: C, 82.85; H, 5.01; N, 7.73%; ν_{max}/cm^{-1} 3398, 3056, 1640, 1424, 1317, 1214, 1204, 970, 793, 737, 727, 707; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.42 (3H, s), 7.31 (2H, d, *J* 8.0 Hz), 7.36 (1H, quintet, *J* 4.0), 7.57–7.63 (4H, m), 7.74 (2H, dt, *J* 1.7 and 8.4), 8.17–8.20 (2H, m), 8.28 (2H, dt, *J* 1.3 and 7.7 Hz), 8.64 (1H, d, *J* 4.9 Hz) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75MHz, $CDCl_3$) δ 21.2 (CH_3), 112.0 (CH), 118.5 (CH), 120.7 (CH), 120.8 (Cq), 121.8 (CH), 126.5 (CH), 127.18 (CH), 129.3 (CH), 129.6 (CH), 131.7 (Cq), 131.8 (CH), 136.0 (Cq), 136.5 (Cq), 137.3 (Cq), 137.4 (Cq), 138.0 (Cq), 138.1 (CH), 141.0 (Cq), 141.0 (Cq) and 194.9 (CO) ppm; *m/z* (ES^+) 363 (MH^+); *m/z* (FAB^+) 363 (MH^+) (found: MH^+, 363.14979; $C_{25}H_{18}N_2O$ requires 363.14975).

(9*H*-β-Carbolin-1-yl)-(4′-fluoro-biphenyl-2-yl)-methanone 8g. 97% Yield, yellow solid; mp 245–246 °C (from EtOH); Found: C, 78.52; H, 4.07; N 7.58%; $C_{24}H_{15}FN_2O$ requires: C, 78.68; H, 4.13; N, 7.65%; ν_{max}/cm^{-1} 3390, 3059, 1634, 1624, 1426, 1316, 1209, 1117, 970, 859, 750, 734; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.84 (2H, t, *J* 8.6), 7.27–7.36 (3H, m), 7.48–7.62 (5H, m), 7.71 (1H, d, *J* 7.2), 8.03 (1H, d, *J* 4.9), 8.13 (1H, d, *J* 8.0), 8.41 (1H, d, *J* 4.9) and 10.28 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, DMSO) δ 113.0 (CH), 114.7 (CH, d, $^2J_{CF}$ 21.5), 119.0 (CH), 119.9 (Cq), 120.2 (CH), 121.8 (CH), 126.7 (CH), 128.9 (CH), 129.1 (CH), 129.6 (CH), 130.0 (CH), 130.2 (CH, d, $^3J_{CF}$ 8.1), 130.8 (Cq), 135.1 (Cq), 136.2 (Cq), 137.0 (Cq), 137.4 (CH), 139.3 (Cq), 139.6 (Cq), 141.8 (Cq), 161.2 (Cq, d, $^1J_{CF}$ 243.6) and 198.8 (CO) ppm; *m/z* (ES^+) 367 (MH^+); *m/z* (FAB^+) 367 (MH^+) (found: MH^+, 367.12476; $C_{24}H_{15}FN_2O$ requires 367.12468).

(9*H*-β-Carbolin-1-yl)-(4′-fluoro-biphenyl-3-yl)-methanone 8h. 97% Yield, yellow solid; mp 188–189 °C (from EtOH); Found: C, 78.59; H, 4.04; N 7.51%; $C_{24}H_{15}FN_2O$ requires: C, 78.68; H, 4.13; N, 7.65%; ν_{max}/cm^{-1} 3437, 3053, 1615, 1593, 1425, 1317, 1204, 1162, 979, 840, 751, 736; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, t, *J* 8.7), 7.37 (1H, quintet, *J* 4.0), 7.58–7.66 (5H, m), 7.78 (1H, dt, *J* 1.4 and 7.7), 8.18–8.21 (2H, m), 8.30 (1H, dt, *J* 1.3 and 7.7), 8.47 (1H, t, *J* 1.6), 8.3 (1H, d, 4.9) and 10.46 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.0 (CH), 115.8 (CH, d, $^2J_{CF}$ 21.4), 118.9 (CH), 120.0 (Cq), 120.2 (CH), 121.8 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 130.0 (CH), 129.6 (CH), 130.2 (CH), 131.1 (Cq), 135.9 (Cq), 136.0 (Cq), 136.1 (Cq), 137.2 (CH), 138.3 (Cq), 138.7 (Cq), 141.7 (Cq), 162.0 (Cq, d, $^1J_{CF}$ 244.6) and 193.9 (CO) ppm; *m/z* (ES^+) 367 (MH^+); *m/z* (FAB^+) 367 (MH^+) (found: MH^+, 367.12462; $C_{24}H_{15}FN_2O$ requires 367.12468).

(9*H*-β-Carbolin-1-yl)-(4′-fluoro-biphenyl-4-yl)-methanone 8i. 95% Yield, yellow solid; mp 221–222 °C (from EtOH); Found: C, 78.53; H, 4.05; N 7.54%; $C_{24}H_{15}FN_2O$ requires: C, 78.68; H, 4.13; N, 7.65%; ν_{max}/cm^{-1} 3431, 3041, 1601, 1426, 1317, 1215, 1164, 970, 837, 794, 736, 714; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, t, *J* 8.7), 7.36 (1H, quintet, *J* 4.0), 7.62–7.66 (4H, m), 7.71 (1H, d, *J* 8.4), 8.18–8.20 (2H, m), 8.42 (2H, d, *J* 8.4) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.0 (CH), 115.8 (CH, d, $^2J_{CF}$ 21.5), 118.8 (CH), 120.0 (Cq), 120.2 (CH), 121.8 (CH), 126.1 (CH), 128.1 (CH), 128.9 (CH), 131.0 (Cq), 131.5 (CH), 135.6 (Cq), 135.7 (Cq), 135.8 (Cq), 136.2 (Cq), 136.3 (Cq), 137.1 (CH), 141.7 (Cq), 142.6 (Cq), 162.3 (Cq, d, $^1J_{CF}$ 245.3) and 193.0 (CO) ppm; *m/z* (ES^+) 367 (MH^+); *m/z* (FAB^+) 367 (MH^+) (found: MH^+, 367.12471; $C_{24}H_{15}FN_2O$ requires 367.12468).

(4′-*tert*-Butyl-biphenyl-2-yl)-(9*H*-β-carbolin-1-yl)-methanone 8j. 96% Yield, yellow solid; mp 176–177 °C (from EtOH); Found: C, 83.02; H, 5.86; N 6.83%; $C_{28}H_{24}N_2O$ requires: C, 83.14; H, 5.98; N, 6.93%; ν_{max}/cm^{-1} 3421, 2921, 1651, 1429, 1315, 1245, 1206, 969, 835, 762, 752, 737, 725; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (9H, s), 7.11 (2H, d, *J* 8.4 Hz), 7.22 (2H, d, *J* 8.4 Hz), 7.32 (1H, t, *J* 6.5 Hz), 7.46–7.63 (5H, m), 7.71 (1H, dd, *J* 0.8 and 7.4 Hz), 7.98 (1H, d, *J* 5.0 Hz), 8.12 (1H, d, *J* 7.9 Hz), 8.40 (1H, d, *J* 5.0 Hz) and 10.23 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 31.1 (CH_3), 31.3 (Cq), 112.0 (CH), 118.3 (CH), 120.7 (CH), 120.7 (Cq), 121.8 (CH), 125.0 (CH), 126.5 (CH), 128.5 (CH), 129.2 (CH), 129.4 (CH), 130.2 (CH), 130.6 (CH), 131.3 (Cq), 136.5 (Cq), 136.7 (Cq), 138.0 (Cq), 138.4 (CH), 138.7 (Cq), 141.1 (Cq), 142.0 (Cq), 149.7 (Cq) and 194.9 (CO) ppm; *m/z* (ES^+) 405 (MH^+); *m/z*

(FAB$^+$) 405 (MH$^+$) (found: MH$^+$,405.19661; $C_{28}H_{24}N_2O$ requires 405.19670).

(4′-*tert*-Butyl-biphenyl-3-yl)-(9*H*-β-carbolin-1-yl)-methanone 8k. 99% Yield, yellow solid; mp 173–174 °C (from EtOH); Found: C, 83.06; H, 5.89; N 6.83%; $C_{28}H_{24}N_2O$ requires: C, 83.14; H, 5.98; N, 6.93%; ν_{max}/cm^{-1} 3423, 2962, 1621, 1427, 1317, 1248, 1207, 979, 841, 791, 754, 728; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (9H, s), 7.36 (1H, quintet, *J* 4.0 Hz), 7.50 (2H, d, *J* 8.4 Hz), 7.60–7.64 (5H, m), 7.83 (1H, d, *J* 7.8 Hz), 8.18–8.21 (2H, m), 8.28 (1H, d, *J* 7.7 Hz), 8.52 (1H, br t), 8.63 (1H, d, *J* 4.9 Hz) and 10.47 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 31.3 (CH_3), 34.5 (Cq), 112.0 (CH), 118.5 (CH), 120.7 (CH), 120.8 (Cq), 121.8 (CH), 125.8 (CH), 126.9 (CH), 128.3 (CH), 129.2 (CH), 129.7 (CH), 129.9 (CH), 130.9 (CH), 131.6 (Cq), 136.3 (Cq), 137.3 (Cq), 137.7 (Cq), 138.0 (Cq), 138.1 (CH), 140.9 (Cq), 141.0 (Cq), 150.6 (Cq) and 195.6 (CO) ppm; *m*/*z* (ES$^+$) 405 (MH$^+$); *m*/*z* (FAB$^+$) 405 (MH$^+$) (found: MH$^+$, 405.19660; $C_{28}H_{24}N_2O$ requires 405.19670).

(4′-*tert*-Butyl-biphenyl-4-yl)-(9*H*-β-carbolin-1-yl)-methanone 8l. 99% Yield, yellow solid; mp 245–246 °C (from EtOH); Found: C, 83.21; H, 5.88; N 6.82%; $C_{28}H_{24}N_2O$ requires: C, 83.14; H, 5.98; N, 6.93%; ν_{max}/cm^{-1} 3420, 2964, 1649, 1604, 1424, 1309, 1242, 1203, 1182, 1118, 964, 827, 796, 747, 732; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (9H, s), 7.36 (1H, quintet, *J* 4.0 Hz), 7.52 (2H, d, *J* 7.5 Hz), 7.62–7.65 (4H, m), 7.77 (2H, d, *J* 8.3 Hz), 8.18–8.21 (2H, m), 8.28 (1H, d, *J* 7.7 Hz), 8.43 (2H, d, *J* 8.3 Hz), 8.64 (1H, d, *J* 4.9 Hz) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 31.4 (CH_3), 34.6 (Cq), 112.0 (CH), 118.5 (CH), 120.8 (CH), 120.9 (Cq), 121.8 (CH), 125.9 (CH), 126.6 (CH), 127.0 (CH), 129.3 (CH), 131.7 (Cq), 131.9 (CH), 136.0 (Cq), 136.5 (Cq), 137.3 (Cq), 137.4 (Cq), 138.1 (CH), 141.0 (Cq), 145.0 (Cq), 151.2 (Cq) and 194.9 (CO) ppm; *m*/*z* (ES$^+$) 405 (MH$^+$); *m*/*z* (FAB$^+$) 405 (MH$^+$) (found: MH$^+$, 405.19663; $C_{28}H_{24}N_2O$ requires 405.19670).

(9*H*-β-Carbolin-1-yl)-[1,1′;4′,1″]terphenyl-2-yl-methanone 8m. 98% Yield, yellow solid; mp 216–217 °C (from EtOH); Found: C, 84.93; H, 4.56; N 6.55%; $C_{30}H_{20}N_2O$ requires: C, 84.88; H, 4.75; N, 6.60%; ν_{max}/cm^{-1} 3324, 3027, 1644, 1425, 1313, 1205, 966, 755, 721; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22–7.42 (10H, m), 7.48–7.64 (5H, m), 7.73 (1H, dd, *J* 0.7 and 7.5), 7.98 (1H, d, *J* 4.9), 8.07 (1H, d, *J* 7.9), 8.42 (1H, d, *J* 4.9) and 10.32 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 118.5 (CH), 120.7 (Cq), 120.8 (CH), 121.8 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 128.6 (CH), 129.2 (CH), 129.6 (CH), 130.2 (CH), 130.6 (CH), 131.4 (Cq), 136.3 (Cq), 136.6 (Cq), 138.5 (CH), 138.5 (Cq), 139.6 (Cq), 140.1 (Cq), 140.5 (Cq), 141.1 (Cq), 141.5 (Cq) and 200.4 (CO) ppm; *m*/*z* (ES$^+$) 425 (MH$^+$); *m*/*z* (FAB$^+$) 425 (MH$^+$) (found: MH$^+$, 425.16543; $C_{30}H_{20}N_2O$ requires 425.16540).

(9*H*-β-Carbolin-1-yl)-[1,1′;4′,1″]terphenyl-3-yl-methanone 8n. 97% Yield, yellow solid; mp 216–217 °C (from EtOH); Found: C, 84.80; H, 4.80; N 6.58%; $C_{30}H_{20}N_2O$ requires: C, 84.88; H, 4.75; N, 6.60%; ν_{max}/cm^{-1} 3424, 3034, 1619, 1425, 1315, 1203, 977, 757, 733, 717; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, quintet, *J* 3.8), 7.47 (2H, t, *J* 7.5), 7.61–7.67 (5H, m), 7.73 (4H, q, *J* 8.3 and 17.5), 7.89 (1H, d, *J* 7.8), 8.19–8.22 (2H, m), 8.30 (1H, d, *J* 7.7), 8.57 (1H, br t), 8.65 (1H, d, *J* 4.9) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.0 (CH), 118.6 (CH), 120.8 (Cq), 120.8 (CH), 121.8 (CH), 127.1 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 128.8 (CH), 129.3 (CH), 129.7 (CH), 130.3 (CH), 130.9 (CH), 131.7 (Cq), 136.3 (Cq), 137.2 (Cq), 137.4 (Cq), 138.2 (CH), 139.5 (Cq), 140.4 (Cq), 140.5 (Cq), 140.6 (Cq), 140.5 (Cq), 141.1 (Cq) and 195.6 (CO) ppm; *m*/*z* (ES$^+$) 425 (MH$^+$); *m*/*z* (FAB$^+$) 425 (MH$^+$) (found: MH$^+$, 425.16536; $C_{30}H_{20}N_2O$ requires 425.16540).

(9*H*-β-Carbolin-1-yl)-[1,1′;4′,1″]terphenyl-4-yl-methanone 8o. 82% Yield, yellow solid; mp 255–256 °C (from EtOH); ν_{max}/cm^{-1} 3387, 3053, 3034, 1640, 1426, 1316, 1247, 1206, 1117, 970, 758, 735; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34–7.40 (2H, m), 7.48 (2H, t, *J* 7.6), 7.63–7.84 (10H, m), 8.19–8.21 (2H, m), 8.44 (2H, d, *J* 8.2), 8.66 (1H, d, *J* 4.9) and 10.48 (1H, br s, D_2O exch, NH) ppm; ^{13}C-NMR (75 MHz, DMSO) δ 113.5 (CH), 116.2 (CH), 119.4 (CH), 120.6 (CH), 120.7 (Cq), 122.3 (CH), 126.4 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 129.2 (CH), 129.5 (Cq), 131.6 (CH), 136.3 (Cq), 136.8 (Cq), 136.9 (Cq), 137.7 (CH), 138.6 (Cq), 139.9 (Cq), 140.5 (Cq), 142.2 (Cq), 143.6 (Cq) and 193.6 (CO) ppm; *m*/*z* (ES$^+$) 425 (MH$^+$); *m*/*z* (FAB$^+$) 425 (MH$^+$) (found: MH$^+$, 425.16538; $C_{30}H_{20}N_2O$ requires 425.16540).

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