Bioorganic & Medicinal Chemistry 16 (2008) 7728–7739

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis and biological evaluation of new tryptamine and tetrahydro-β-carboline-based selective inhibitors of CDK4

Paul R. Jenkins [a,*,§], James Wilson [a,§], Daniel Emmerson [a,†,§], Marcos D. Garcia [a,‡,§], Matthew R. Smith [a,§], Stephen J. Gray [a,§], Robert G. Britton [a,§], Sachin Mahale [b,¶], Bhabatosh Chaudhuri [b,¶]

[a] Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK
[b] School of Pharmacy, De Montfort University, Leicester LE1 9BH, UK

ARTICLE INFO

Article history:
Received 16 April 2008
Revised 24 June 2008
Accepted 2 July 2008
Available online 8 July 2008

This paper is dedicated to the memory of Prof. Yoshihiko Ito of Kyoto University, Japan.

Keywords:
CDK4 inhibitors
Suzuki–Miyaura reaction
Anti-cancer
Fascaplysin

ABSTRACT

We present the design, synthesis and biological activity of a library of substituted (biphenylcarbonyl)-tryptamine and (biphenylcarbonyl)-tetrahydro-β-carboline compounds related to the natural product fascaplysin, as novel inhibitors of CDK4/cyclin D1. We show all these molecules, prepared using the Suzuki–Miyaura reaction, being selective inhibitors of CDK4 over CDK2. The most active compounds have a CDK4 IC_{50} in the range 9–11 μM, three of them containing the *para*-biphenyl plus *para*-substituents supporting the existence of a π-stacking pocket within the active site of CDK4.

1. Introduction

The development of new inhibitors of the cyclin-dependent kinases is an ongoing area of research in the anti-cancer field.[1] The importance of the development of new inhibitors could be exemplified by the recent validation of CDK4/cyclinD1 as an anti-cancer drug target in MCF-7 breast cancer cells.[2]

The natural pigment fascaplysin (**1**, Fig. 1) was first isolated from the marine sponge *Fascaplysinopsis* Bergquist sp.[3] in 1988 and has a range of interesting properties.[4–6] It inhibits the growth of several organisms including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Saccharomyces cerevisiae*, it is capable of suppressing the proliferation of mouse leukaemia cells and is a potent inhibitor of cyclin-dependant kinase 4 (CDK4), causing cell cycle arrest at the G1 phase of the cell cycle in both normal and tumour cell lines.[7] Fascaplysin (**1**) itself has limited potential as an anti-cancer drug due to its toxic side effects, these are thought to arise largely from the ability of its planar structure to intercalate into the structure of DNA.[8]

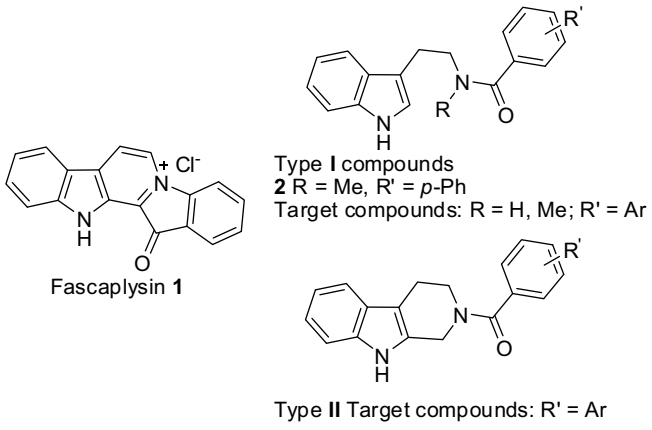


Figure. 1. Fascaplysin **1** and type **I**/**II** target compounds.

We have previously reported a systematic study on the synthesis and biological activity of non-planar analogues of fascaplysin.[9] To devise a potent, non-toxic (non-planar) CDK4 inhibitor based

* Corresponding author.
E-mail addresses: kin@leicester.ac.uk (P.R. Jenkins), mdgarcia@udc.es (M.D. Garcia), bchaudhuri@dmu.ac.uk (B. Chaudhuri).
† Present address: Department of Chemistry, Imperial College, London, UK.
‡ Present address: Departamento de Química Fundamental, Universidade da Coruña, campus da Zapateira, A Coruña, 15071, Spain (M.D.G.).
§ Tel.: +44 (0) 116 252 2124; fax: +44 (0) 116 252 3789.
¶ Tel.: +44 (0) 116 250 7280; fax: +44 (0) 116 257 7284.

0968-0896/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2008.07.002

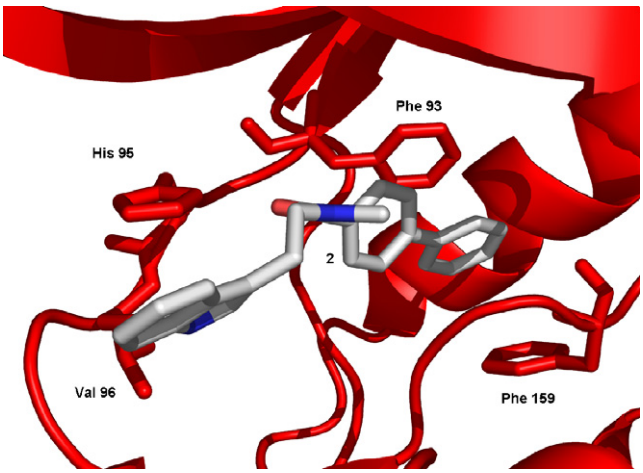


Figure. 2. Compound **2** docked with the CDK4 homology model.[9b]

on fascaplysin (**1**), we designed a series of tryptamine-based analogues of type **I** (Fig. 1).[9a,9b] Moreover, a series of related tetrahydro-β-carbolines of type **II** (Fig. 1), that have less conformational freedom, were synthesised.[9b] The most active compound reported in these series was biphenyl-4-carboxylic acid [2-(1*H*-indol-3-yl)-ethyl]-methyl-amide (**2**, Fig. 1), which has an IC_{50} of 6 μM for the inhibition of CDK4/cyclin D1 and 521 μM for the inhibition of CDK2/cyclin A.[10]

These results, coupled with in silico studies using our homology model of CDK4 postulated the existence of a strong π-stacking interaction between the terminal phenyl ring of compound **2** and two phenylalanine residues (Phe 93 and Phe 159) within the active site of CDK4 (Fig. 2),[9b] possibly analogous to the 'Phe 80 pocket' of CDK2,[11] where the amino acid residue Phe 93 of CDK4 would be equivalent to Phe 80 in CDK2.

In this paper, taking compound **2** as a lead, a series of bi- and tri-phenyl derivatives of type **I** and **II** (Fig. 1) were synthesised using the Suzuki–Miyaura reaction in an effort to investigate the nature and scope of the π-stacking interaction in the proposed 'Phe 93 pocket' of CDK4 as a possible target for the development of future inhibitors of this enzyme.

2. Results and discussion

2.1. Synthesis

Compound **2** was originally synthesised from *N*-ω-methyl tryptamine and biphenyl carbonyl chloride;[9a,9b] however, this synthetic route does not lend itself to the synthesis of the target compounds of type **I**/**II**, so a new strategy was designed using the Suzuki–Miyaura coupling reaction as the key step as exemplified in Scheme 1 in the retro-synthetic analysis of compound **2**. Hence, a library of analogues of type **I**/**II** bearing substitution on the terminal phenyl ring of the biphenyl system, differing groups on the chain nitrogen and alterations to the tryptamine backbone structure, were efficiently synthesised using this strategy (Schemes 2, 3 and Fig. 3).

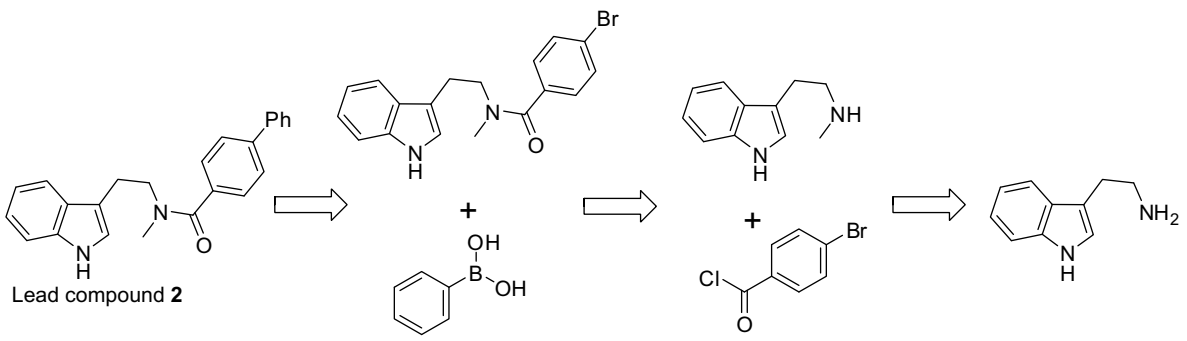
The Suzuki–Miyaura reaction is now a well-established procedure for the coupling of sp2 centres.[12–14] An aromatic halide, often an aromatic bromide, is coupled to an aromatic boronic acid using Pd^0 as a catalyst. The reaction is easily applicable to a wide range of substrates and generally proceeds in high yield, side products, and starting materials being easily separated by flash column chromatography. Even though the Suzuki–Miyaura reaction on indole substrates has been reported,[15] the closest example to the chemistry described in this paper is the conversion of a tryptamine sulfonamide to a biphenyl structure.[16] The results shown below further illustrate the versatility of this cross-coupling methodology for the synthesis of unsubstituted indole compounds.

Tryptamine (**3**) and *N*-ω-methyl tryptamine (**4**) (Scheme 2) were reacted with the corresponding *o*/*m*/*p*-benzoyl chlorides to produce key intermediates **5a–f** in moderate to good yields. Two series of type **I** *para*-biphenyl derivatives (**6a–k**) in which the terminal aromatic ring contained different substituents in the 4-position were prepared by Suzuki–Miyaura coupling of **5a** and **5d** with a range of 4-substituted boronic acids in yields of 42–65% (Scheme 1).

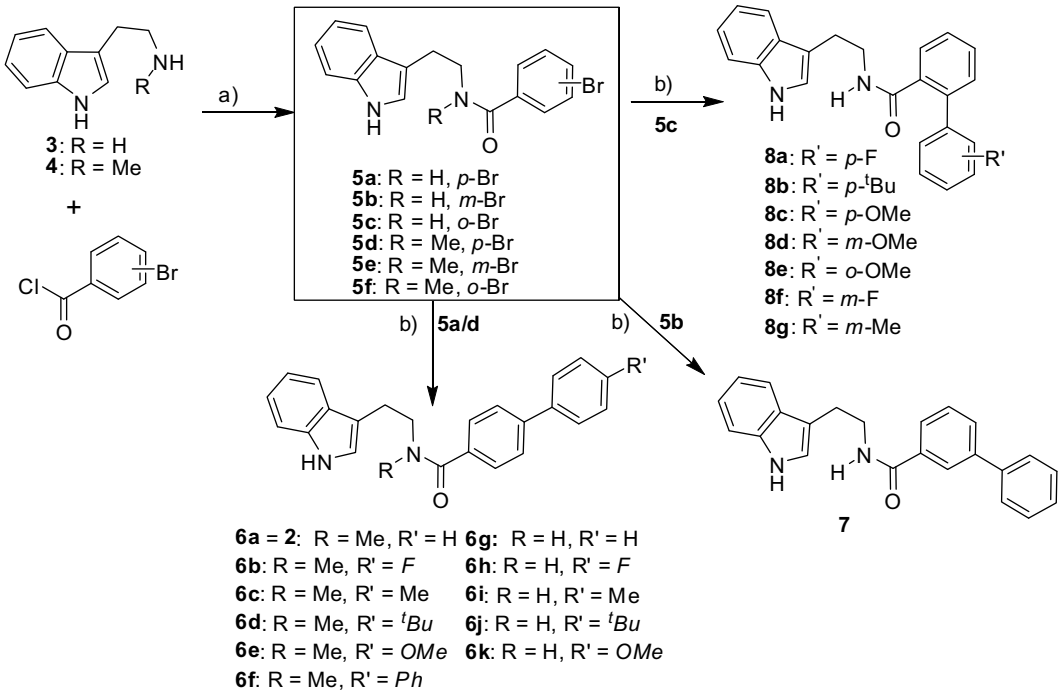
The biphenyl derivatives were also synthesised in the 1,2 form (*ortho*-biphenyl) by reaction of key intermediate **5c** with the appropriate phenylboronic acid to provide the series **8a–e** (Scheme 1). One example of 1,3-derivative (*meta*-biphenyl) was produced from the intermediate **5b** to give **7** (Scheme 1). As compound **7** was found to have a significantly lower IC_{50} value than compounds in the *ortho*/*para*-biphenyl type **I** series in an initial screen, no more compounds with the *meta*-biphenyl moiety were prepared for this study.

A small library of 1,2- 1,3- and 1,4-biphenyl inhibitors of type **II** was produced from the three tetrahydro-β-carboline derivatives **10a–c** (Scheme 3). The *ortho*-biphenyls **11a–d** (in 56–82% yields), *meta*-biphenyls **12a–h** (in 61–88% yields) and the *para*-biphenyl derivatives **13a–h** (in 66–91% yields).

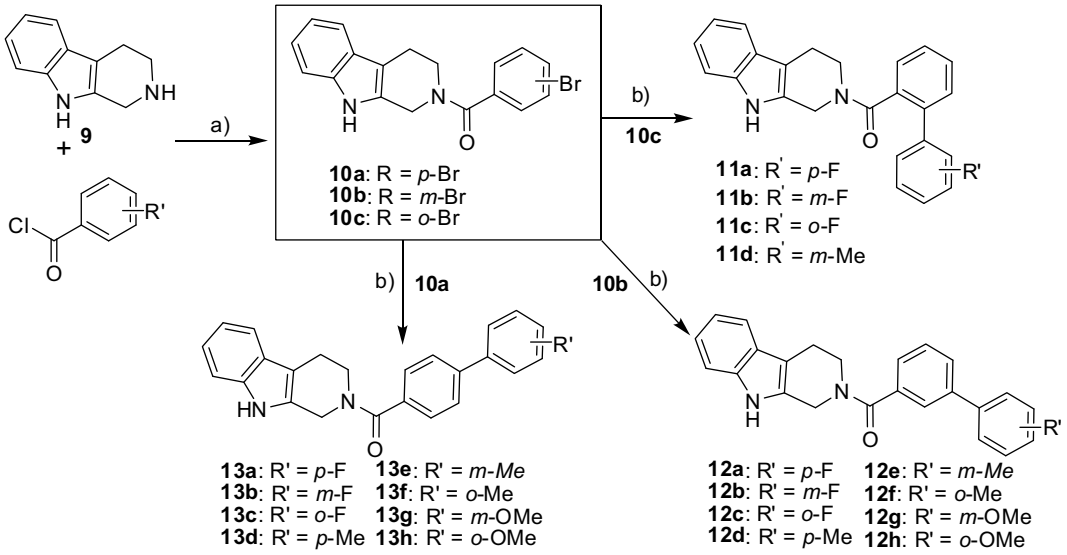
In some cases, the terminal phenyl ring of the biphenyl unit in type **I** and **II** compounds was replaced by a pyridine ring. Pyridine boronic acids have been used extensively in the Suzuki–Miyaura reaction; however, only very few examples involving indole and tryptamine substrates[17,16] have been reported. The compounds shown in Figure 3 further illustrate the range of structures that can be prepared using the highly versatile Suzuki–Miyaura reaction. For this purpose, key intermediates **5b**, **5d** and **10c** were



Scheme 1. Retrosynthetic analysis for lead compound **2**.



Scheme 2. Synthetic route to type **I** target compounds. Reagents and conditions: (a) CH_2Cl_2, NaOH (4 M, aq, 1 equiv), 0 °C 15 min then rt. 3 h; (b) $Pd(PPh_3)_4$, toluene, EtOH, $(HO)_2BC_6H_4R'$, K_2CO_3 (2 M, aq), 90 C, 24 h.



Scheme 3. Synthetic route to type **II** target compounds (for reagents and conditions see Scheme 2).

reacted with 3- and 4-pyridineboronic acids to produce compounds **14**, **15** and **16a–b** (54–80% yields).

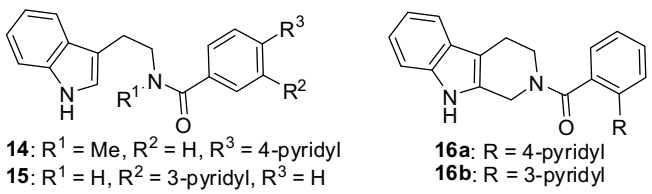


Figure. 3. Type **I**/**II** pyridinyl substituted inhibitors.

2.2. Biological evaluation

The *para*-biphenyl compound **6g**, Table 1 has an IC_{50} for CDK4 inhibition of 16 μM. The addition of a *para*-methyl group in **6i** leads to a small increase in the IC_{50} to 18 μM. However, with a *tert*-butyl group in **6j** the IC_{50} falls to 9.2 μM. One possible explanation for this is the existence of a synergy between the proposed π-stacking interaction and a strong lipophilic component in the binding mode of the inhibitors in the proposed 'Phe 93 pocket' of CDK4. A *para*-fluoro substituent in **6h** gives an IC_{50} of 15 μM, which is the same as the parent compound **6g**, within experimental error. A *para*-electron donating group such as OMe in **6k** leads to a substantially higher IC_{50} of 48 μM.

Table 1
CDK4 activity versus CDK2 activity

Compound	CDK4 inhibition[a] IC_{50}/μM	CDK2 inhibition[b] (IC_{50}/μM)
1 Fascaplysin	0.55	500
2 (6a)	6 ± 1	521 ± 12
6b	21 ± 3	875 ± 9
6c	24 ± 1.5	70 ± 4
6d	11.2 ± 1.3	745 ± 20
6e	49 ± 2	289 ± 10
6f	35 ± 2.5	91 ± 6
6g	16 ± 2.1	855 ± 7.5
6h	15 ± 1.5	764 ± 14
6i	18 ± 1.9	816 ± 12
6j	9.2 ± 0.8	790 ± 18
6k	48 ± 3.1	1085 ± 17
7	86 ± 4	1002 ± 13
8a	38 ± 2.6	1216 ± 19
8b	38 ± 2.5	262 ± 9
8c	79 ± 4	921 ± 12
8d	53 ± 1.8	926 ± 17
8e	26 ± 2	375 ± 10
8f	20 ± 1.5	417 ± 9
8g	15 ± 2	406 ± 12
11a	23 ± 1.5	357 ± 10
11b	35 ± 3	480 ± 10
11c	19 ± 2	434 ± 13
11e	26 ± 2	386 ± 11
12a	25 ± 1	318 ± 11
12b	27 ± 1	611 ± 12
12c	18 ± 2.5	335 ± 12
12d	24 ± 2	466 ± 10
12e	11 ± 1	465 ± 16
12f	75 ± 3	665 ± 13
12g	33 ± 3	362 ± 9
12h	79 ± 2.4	1109 ± 9
13a	12 ± 1.2	438 ± 12
13b	21 ± 1.5	296 ± 9
13c	17 ± 2	310 ± 15
13d	9 ± 0.8	736 ± 14
13e	25 ± 3	405 ± 12
13f	32 ± 2	340 ± 18
13g	28 ± 2	424 ± 12
13h	22 ± 1	321 ± 13
14	26 ± 2.5	92 ± 3
15	30 ± 2.5	150 ± 3.5
16a	39 ± 3	354 ± 5
16b	36 ± 4	312 ± 7

[a] CDK4-cyclin D1 assay, using GST-RB152 fusion protein as the substrate.
[b] CDK2-cyclin A assay using histone H1 as the substrate.

The trend described above for structures **6g–k** is also exhibited by derivatives of **2** (**6a**), **6b–f**. Compound **2** (**6a**) shows an IC_{50} for inhibition of CDK4 of 6 μM. The *para*-methyl group in compound **6c** leads to a higher IC_{50} of 24 μM, the figure then falls in the case of the *para*(*tert*-butyl) group in **6d** IC_{50} 11.2 μM and the *para*-phenyl of **6f** leads to an IC_{50} of 35 μM. In this series, the *para*-fluoro compound **6b** has a higher IC_{50} of 21 μM compared to the parent compound **2** (**6a**). Compound **6e** with a *para*-OMe group is a weaker inhibitor, IC_{50} 49 μM, a similar figure to **6k**.

Conversion to an *ortho*-biphenyl structure leads to compounds **8a–g**, where the IC_{50} values are in general higher than parent compounds **6g–k**. The most active compounds in the *ortho*-biphenyl series are **8e** *ortho*-OMe IC_{50} 26 μM, *meta*-fluoro **8f** 20 μM and finally the best compound is **8g** *meta*-Me IC_{50} 15 μM.

The overall conclusion of the results of type **I** compounds is that the best IC_{50} is obtained for the *para*-biphenyl compounds **6d** and **6j** (both with a *tert*-butyl group in the *para*-position of the outer phenyl ring) with IC_{50} values in the same range as for the lead compound **2** (**6a**).

Type **II** tetrahydro-β-carboline inhibitors **11a–d**, **12a–h** and **13a–h** show a range of IC_{50} values from 70 to 9 μM. In the *para*-biphenyl series, **13a–h,** three have IC_{50} less than 20 μM, the best compound **13d**, with a *para*-Me group, has an IC_{50} of 9 μM, *ortho*- and *para*-fluoro derivatives **13c** and **13a** show IC_{50} of 17 and 12 μM, respectively. The best *meta*-biphenyl substituent is the *meta*-methyl compound **12e** (IC_{50} 11 μM) and the best *ortho*-biphenyl compound is the *ortho*-fluoro compound **11c** (IC_{50} 19 μM). Following the trend of the type **I** compounds, the *para*-biphenyl molecules showed, in general, higher IC_{50} values than the *ortho*/*meta*-biphenyl series.

Inclusion of a pyridine moiety in the outer phenyl ring of type **I** and **II** target compounds (Fig. 3) leads to decreased CDK4 inhibition activities with respect to the lead compound **2**.

3. Conclusions

We have synthesised a library of biphenyl derivatives of tryptamine and tetra-hydro-β-carboline of type **I**/**II** using the Suzuki–Miyaura reaction, clearly showing the versatility of this important process.

Most of the compounds exhibit a clear CDK4/cyclin D1 selectivity (compared with CDK2/cyclin A). Additionally, *para*-biphenyl tryptamine and tetrahydro-β-carboline based compounds showed, in general, better biological results than the *ortho*- and *meta*-biphenyl analogues, pointing out the preferred orientation of the biphenyl moiety of the inhibitor within the proposed 'Phe 93 pocket' of the enzyme.

Three of the most active compounds **6d**, **6j** and **13d** (IC_{50} = 9.2, 11.2 and 9 μM, respectively) are *para*-substituted biphenyls with *tert*-butyl or Me in the *para*-position. This suggests that a strong lipophylic component in the binding mode of these compounds, as well as the proposed π-stacking interaction of the inhibitors within the 'Phe 93 pocket', could be responsible for the observed CDK4/cyclin D1 inhibition results.

4. Experimental

4.1. Bio assays

Expression and purification of CDK4/GST-cyclinD1, CDK2/GST-cyclinA and GST-RB152. Fusion proteins of human cyclins A and D1, covalently linked to glutathione *S*-transferase (GST), were co-expressed with the catalytic subunits CDK2 and CDK4 in Sf-9 insect cells as described previously.[18–21]

Active enzyme complexes, containing a catalytic subunit bound to GST-Cyclin, were bound to glutathione–agarose columns (Sigma, Catalogue 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, Catalogue No. 66830) with two buffer changes.

The GST-RB152 fusion construct was transformed into the *Escherichia coli* strain BL21(DE3)pLysS (Novagen Catalogue 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 Catalogue No. 15529-091) and were allowed to grow for 4 h in a shaking incubator at 37 °C and 220 rpm. Purification of the GST-RB152 protein was carried out as described previously.[21] 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 Catalogue 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 $MgCl_2$ and 0.1 mg/mL BSA) in order to obtain the desired concentrations. The kinase assay was performed in 50 μl of kinase buffer containing 2 μg of purified GST-RB152 (in case of Cdk4/GST-cyclin D1) or 3 μg of Histone H1 (in case of Cdk2/GST-cyclin A) and 6 μM ATP. The phosphatase and protease inhibitor cocktail containing β-glycerophosphate, sodium fluoride and sodium orthovanadate in the presence of reducing agent dithiothreitol was added at the final concentrations of 10, 0.1, 0.1 and 1, respectively. The assay was initiated by adding 200 ng of active enzyme complexes, and the plate was incubated for 30 min at 30 °C in a humidified incubator. The reaction was stopped by addition of equal volume of the Kinase Glow Reagent™ (Promega Catalogue No. V6711). The luminescence was measured using the Packard Luminometer (Fusion 3.50) and the rate of ATP depletion (rate of reaction) in the control blank reactions (i.e., without substrate or enzyme) was calculated and used to determine the IC_{50} concentrations of compounds. In case of CDK4/cyclin D1 assay, the two compounds fascaplysin and flavopiridol with known IC_{50} values were used to validate the assay. For the CDK2/cyclin A assay, roscovitine and flavopiridol were used as standards for the assay.

4.2. Chemistry

NMR spectra were recorded on Bruker DPX 300 (^{1}H, 300.13 MHz ; ^{13}C, 75.47 MHz; ^{19}F 282.39 MHz) or DPX 400 (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) spectrometers as indicated. Chemical shifts were measured relative to chloroform (^{1}H δ 7.26, ^{13}C δ 77.0) or dimethylsulfoxide (^{1}H δ 2.50, ^{13}C δ 39.43) and are expressed in ppm. Coupling constants *J* are expressed in Hertz and the 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 stable reference peak. Flash column chromatography was carried out using Merck Kiesegel 60 (230–400 mesh). Dry solvents were provided by a PURE SOLV™ system from Innovative Technology Inc.

4.2.1. [2-(1*H*-Indol-3-yl)-ethyl]-carbamic acid ethyl ester[9b,22]

To a solution of tryptamine **5** (10.00 g, 62.4 mmol) in $CHCl_3$ (156 mL) at 0 °C was added ethylchloroformate (5.97 mL, 62.4 mmol) and an aqueous solution of NaOH (15.60 mL, 4 M, 62.4 mmol). After addition, the mixture was stirred for 3 h at room temperature and then washed with water (150 mL), the aqueous phase was extracted with dichloromethane (2× 150 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give an orange oil, no purification was necessary. The oil was dried in vacuo to give the title compound **3** (13.78 g, 95%); δ_H (300 MHz, $CDCl_3$) 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), 7.30 (1H, td, *J* 6 and 1.2), 7.42 (1H, d, *J* 7.7), 7.71 (1H, d, *J* 7.7), 8.75 (1H, s); δ_C (75 MHz, $CDCl_3$) 14.57 (CH_3), 25.64 (CH_2), 41.21 (CH_2), 60.72 (CH_2), 111.33 (CH), 112.33, 118.54 (CH), 119.11 (CH), 121.83 (CH), 122.26 (CH), 127.18, 136.39, 156.93; *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.

4.2.2. [2-(1*H*-Indol-3-yl)-ethyl]-methyl-amine 4[9b,22]

To a solution of [2-(1*H*-indol-3-yl)-ethyl]-carbamic acid ethyl ester (13.78 g, 59.4 mmol) in dry THF (110 mL) under N_2 at 0 °C was added portionwise LiAlH (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 $LiAlH_4$ 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; mp 82 °C; δ_H (300 MHz, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 25.4 (CH_2), 36.0 (CH_3), 51.8 (CH_2), 111.3 (CH), 112.9, 118.7 (CH), 118.9 (CH), 121.6 (CH), 122.5 (CH), 127.3, 136.5; *m/z* (FAB) 175.12354 ($M+H^+$ $C_{11}H_{15}N_2$ requires 175.12352). Found: C, 75.74; H, 8.04; N, 16.00. $C_{11}H_{15}N_2$ requires C, 75.82; H, 8.10; N, 16.08.

4.3. General procedure for the synthesis of 5a–c

To a stirred solution of tryptamine **3** (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 was added dropwise the benzoyl chloride derivative (1.2 mmol). The mixture was stirred for 5 min at 0 °C and then for 3 h at room temperature. H_2O (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 flash column chromatography on silica gel. Elution was made successively with; ethyl acetate/petroleum ether 50:50 and ethyl acetate, to give the title compound.

4.3.1. 4-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-benzamide (5a)

Pale yellow solid; yield 67%; mp 148–149 °C; δ_H (300 MHz, $(CD_3)_2SO$) 3.0 (2H, t, 7.4) 3.6 (2H, q, 6.9), 7.0 (1H, t, 7.4), 7.1 (1H, t, 7.4), 7.2 (1H, d, 1.5), 7.4 (1H, d, 8.1), 7.6 (1H, d, 7.8), 7.7 (2H, d, 8.7), 7.8 (2H, d, 8.4), 8.7 (1H, t, 5.4), 10.8 (1H, s); δ_C (75 MHz; $(CD_3)_2SO$) 25.1 (CH_2), 40.3 (under solvent peak, CH_2), 111.4 (CH), 111.8, 118.2 (CH, d), 120.9 (CH), 122.7 (CH), 126.2, 127.2, 128.1 (CH, 2C), 129.0 (CH, 2C), 136.2, 136.5, 167.0; *m/z* (FAB) 343.04453 ($M+H^+$ $C_{17}H_{16}N_2OBr$ requires 343.04467). Found: C,59.38; N, 8.16; H,4.35. $C_{17}H_{15}N_2OBr$ requires C, 59.49; N, 8.16; H, 4.40.

4.3.2. 3-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-benzamide (5b)

Off white solid; yield 79%; mp 132–135 °C, δ_H (300 MHz; $(CD_3)_2SO$) 3.0 (2H, t, 7.6,), 3.6 (1H, aq, 7.0), 7.0 (1H, t, 7.0), 7.1 (1H, t, 7.0), 7.2 (1H, d, 2.1), 7.4 (1H, t, 7.9), 7.6 (1H, d, 8.9), 7.7 (1H, d, 8.9), 7.9 (1H, d, 7.9), 8.1 (1H, s), 10.8 (1H, s), δ_C (75 MHz; $(CD_3)_2SO$) 25.0 (CH_2), 40.3 (CH_2), 111.4, 111.8, 118.2, 120.9, 121.6, 122.6, 126.3, 127.3, 129.9, 130.5, 133.8, 136.2, 136.9, 164.6. *m/z* (FAB) 343.04427 ($M+H^+$ $C_{17}H_{16}BrN_2O$ requires 343.04460).

4.3.3. 2-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-benzamide (5c)

Off white solid; yield 86%; mp 144–145 °C; δ_H (300 MHz; $(CD_3)_2SO$) 3.0 (2H, t, 7.7), 3.5 (2H, aq, 6.9), 7.0 (1H, dt, 1.2, 7.9), 7.1 (1H, dt, 1.2, 6.9), 7.2 (1H, d, 2.2), 7.3–7.5 (4H, br m), 7.6 (1H, d, 7.7), 8.6 (1H, t, 5.7), 10.9 (1H, s); δ_C (75 MHz; $(CD_3)_2SO$) 25.5 (CH_2), 40.4 (CH_2), 111.9 (CH), 112.1, 118.7 (CH) (2C), 119.5, 121.4

(CH), 123.3 (CH), 127.7, 128.0 (CH), 129.2 (CH), 131.2 (CH), 133.1 (CH), 136.7, 139.8, 167.7. *m/z* (FAB) 343.04417 ($M+H^+$ $C_{17}H_{16}BrN_2O$ requires 343.04460).

4.4. General procedure for the synthesis of 5d/e

To a stirred solution of 2-(1*H*-indol-3-yl)-ethyl]-methyl-amine **4** (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 was added dropwise the appropriate benzoyl chloride derivative (1.2 mmol). The mixture was stirred for 5 min at 0 °C and for 3 h at room temperature. Water (20 mL) was added and the two layers were separated, the aqueous phase was extracted with dichloromethane (3× 20 mL). The organic layers were then dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel. Elution was made successively with; ethyl acetate/petroleum ether 50:50 and ethyl acetate, to give the expected compound.

4.4.1. 4-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-benzamide (5d)[9b]

White solid; yield 73%; mp 160 °C; rotamers 1/1.5 (from the duplicated triplet signal (^1H) at 3.45 and 3.77 ppm); δ_H (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); δ_C (75 MHz, $CDCl_3$) δ (*major rotamer*) 24.2 (CH_2), 33.0 (CH_3), 51.7 (CH_2), 111.4 (CH), 112.7, 118.0 (CH), 119.4 (CH), 122.1 (CH), 122.4 (CH), 123.3, 127.0, 128.1 (2CH), 131.3 (2× CH), 135.0, 136.3, 171.4; δ (distinct peaks for *minor rotamer*) 22.9 (CH_2), 38.2 (CH_3), 48.6 (CH_2), 118.7 (CH), 123.7, 127.5, 128.7 (CH), 131.6 (CH), 135.5, 170.4; *m/z* (ES^+) 358 $MH^{+;}$ (ES^-) 356 $(M-H)^-$; *m/z* (FAB) M^+, 357.06027 (M^+ $C_{18}H_{17}BrN_2O$ requires 357.06025). Found: C, 60.58; H, 4.96; N, 7.76. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84.

4.4.2. 3-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-benzamide (5e)[9b]

White solid; yield 76%; mp 166 °C; rotamers 1/1.4 (from the duplicated triplet signal (^1H) at 3.46 and 3.78 ppm); δ_H (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); δ_C (75 MHz, $CDCl_3$) δ (*major rotamer*) 24.2 (CH_2), 33.1 (CH_3), 51.9 (CH_2), 111.4 (CH), 112.7, 118.0 (CH), 119.4 (CH), 122.1 (CH), 122.3 (CH), 125.0 (CH), 127.0, 129.8 (CH), 129.9 (CH), 132.1 (CH), 133.0, 136.2, 138.2, 170.7; δ (distinct peaks for *minor rotamer*) 22.9 (CH_2), 38.2 (CH_3), 48.6 (CH_2), 118.7 (CH), 125.5 (CH), 127.5, 129.5 (CH), 130.1 (CH), 132.5 (CH), 136.0, 138.6, 169.7; *m/z* (ES^+) 357 M^+, 358 $MH^{+;}$ (ES^-) 356 $(M-H)^{-;}$ *m/z* (FAB) 357.06030 (M^+ $C_{18}H_{17}BrN_2O$ requires 357.06025). Found: C, 60.38; H, 4.80; N, 7.73. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84.

4.4.3. 2-Bromo-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-benzamide (5f)[9b]

Tan solid; yield 48%; mp 205 °C; rotamers 1/1.2 (from the duplicated triplet signal (^1H) at 3.34 and 3.79 ppm); δ_H (400 MHz, 363 K, $(CD_3)_2SO$) 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); δ_C (75 MHz, $(CD_3)_2SO$) δ (*major rotamer*) 24.3 (CH_2), 32.4 (CH_3), 51.3 (CH_2), 110.7, 111.9 (CH), 118.1 (CH), 118.7 (CH), 118.8, 121.4 (CH), 123.5 (CH), 127.7, 128.2 (CH), 128.5 (CH), 130.7 (CH), 132.7 (CH), 136.6, 138.8, 168.3; δ (distinct peaks for *minor rotamer*) 22.9 (CH_2), 36.5 (CH_3), 47.7 (CH_2), 111.6, 118.7 (CH), 118.9, 121.4 (CH), 123.4 (CH), 127.3, 130.9 (CH), 132.9 (CH), 136.8, 139.2, 168.2; *m/z* (ES^+) 358; (ES^-) 356 $(M-H)^-$; *m/z* (FAB^+) 357.06015 (M^+ $C_{18}H_{17}BrN_2O$ requires 357.06025). Found: C, 60.38; H, 4.81; N, 7.81. $C_{18}H_{17}BrN_2O$ requires C, 60.52; H, 4.80; N, 7.84.

4.5. General procedure for the preparation of compounds 2 (6a), 6b–k, 7, 8a–g, 11a–d, 12a–h, 13a–h, 14, 15 and 16a–b: The Suzuki coupling reaction

To a stirred solution of the corresponding brominated intermediate (**5a–f**, **10a–c**, 1 mmol) in toluene (10 mL), under nitrogen, were added K_2CO_3 (1 mmol, 2 M aqueous) and $Pd(PPh_3)_4$ (5 mol%, 0.05 mmol). The solution was stirred for 20 min at room temperature before the addition of a solution of the appropriately substituted boronic acid, (1.2 mmol) in EtOH (10 mL). The reaction mixture was heated to 90 °C for 24 h, then 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 1 h. The desired product was 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 product was then purified by flash column chromatography on silica from ethyl acetate–petroleum ether (40–60 °C).

4.5.1. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-fluoro-*N*-methylbiphenyl-4-carboxamide (6b)

Pale yellow solid; yield 65%; mp 181–183 °C; δ_H (300 MHz; $(CD_3)_2SO$) rotamers 1/1.25 (from the duplicated triplet signal (^1H) at 3.47 and 3.74 ppm); 2.91 (3H, br), 3.08 (2H, br), 3.47 (2H, br), 6.72 (distorted t), 6.93–7.06 (4H, m), 7.19–7.34 (7H, m), 7.45 (1H, br d, 7.2), 7.54 (2H, br d, 7.6), 7.70 (5H, m), 10.83 (1H, br s); δ (*distinct peaks for minor rotamer*) 3.74 (2H, br), 2.91 (3H, br), 3.08 (2H, br), 10.87 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 24.4 (CH_2), 32.8 (CH_3), 51.9 (CH_2) 110.9, 111.9 (CH), 116.3 (d, $^2J_{CF}$, 21, CH), 118.3 (CH), 118.7 (CH), 121.4 (CH), 123.7 (CH), 126.8 (CH), 127.4 (CH), 128.0, 129.2 (d, $^3J_{CF}$ 8, CH), 136.2, 136.4, 136.7, 140.0, 162.5 (d, $^1J_{CF}$, 245), 171.0; (*distinct peaks for minor rotamer*) 23.1 (CH_2), 37.9 (CH_3), 48.4 (CH_2), 123.3 (CH), 128.0, 170.0. Found: C, 77.32; N, 7.42; H, 5.60. $C_{24}H_{21}N_2OF$ requires C, 77.40; N, 7.52; H, 5.68.

4.5.2. *N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*,4′-dimethylbiphenyl-4-carboxamide (6c)

Off white solid; yield 44%; mp 215–217 °C; δ_H (300 MHz; $(CD_3)_2SO$) Rotomers 1/2.1 (from the duplicated triplet signal (^1H) at 3.46 and 3.73 ppm), 2.91 (3H, br), 3.07 (2H, br), 3.46 (2H, br), 6.70 (1H, br), 6.91–7.05 (3H, m), 7.19–7.30 (4H, m), 7.42–7.44 (1H, m), 7.56–7.67 (4H, m), 10.8 (1H, br s); δ (*distinct peaks for minor rotamer*) 3.73 (2H, br), 10.83 (1H, br s); δ_H (400 MHz; $(CD_3)_2SO$; 353 K) 2.38 (3H, s), 2.99 (5H, m), 3.64 (2H, br s), 6.89 (1H, br s), 7.05 (1H, t, 7.5), 7.10 (1H, br s), 7.23–7.36 (3H, m), 7.56–7.58 (2H, m), 7.61 (5H, d, 8.0), 10.60 (1H, s); δ_C (75 MHz; $(CD_3)_2SO$) 20.6 (CH_3), 23.9 (CH_2), 32.3 (CH_3), 51.4 (CH_2), 110.3, 111.3 (CH), 117.8 (CH), 118.2 (CH), 120.8 (CH), 123.0 (CH), 126.1 (CH, 2C), 126.5 (CH, 2C), 129.5 (CH, 4C), 135.4, 136.1, 136.5, 137.1, 140.4, 140.7, 170.5; δ (*distinct peaks for minor rotamer*) 22.5 (CH_2), 37.3 (CH_3), 47.8 (CH_2), 126.9 (CH), 127.4 (CH).

4.5.3. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-*tert*-butyl-*N*-methyl biphenyl-4-carboxamide (6d)

Off white solid; yield 51%; mp 178–180 °C, overlaping rotomers; δ_H (300 MHz; $(CD_3)_2SO$) 1.36 (9H, s, $C(CH_3)_3$), 2.86 (3H, br s), 3.04–3.14 (2H, br), 3.60–3.82 (2H, br), 7.08–7.62 (13H, br), 10.05 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 22.6 (CH_2), 23.9 (CH_2), 31.0

(CH_3), 32.3 (CH_3), 34.2 (C), 37.4 (CH_3), 47.9 (CH_2), 51.4 (CH_2), 110.4 (C), 111.4 (CH), 117.9 (CH), 120.9 (CH), 123.0 (CH), 125.7 (CH), 126.2 (CH), 126.4 (CH), 126.9 (CH), 127.5 (CH), 135.5 (C), 136.2 (C), 140.5 (C), 140.8 (C), 150.2 (C), 169.6 (C), 170.6 (C). Found: C, 81.81; N, 6.72; H, 7.27. $C_{28}H_{30}N_2O$ requires C, 81.91; N, 6.82; H, 7.36; *m/z* (ES^+) 411 [M+H^+], 433 [M+Na^+], (ES^-) 409 [M−H^-]; *m/z* (FAB) 411.24347 (M+H^+ $C_{28}H_{31}N_2O$ requires 411.24364).

4.5.4. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-methoxy-*N*-methylbiphenyl-4-carboxamide (6e)

Off white solid; yield 46%; mp 201–202 °C; δ_H (300 MHz; $(CD_3)_2SO$) Rotomers 1/1.8 (from the duplicated triplet signal (^1H) at 3.47 and 3.73 ppm), 2.91 (3H, br), 3.07 (2H, br), 3.46 (2H, br), 3.80 (3H, s), 6.71 (1H, m), 6.92–7.05 (4H, m), 7.18–7.20 (2H, m), 7.29–7.31 (1H, m), 7.41–7.53 (2H, m), 7.62 (3H, br m), 10.81 (1H, br s); δ (*distinct peaks for minor rotamer*) 3.07 (3H, br), 2.91 (2H, br), 3.73 (2H, br), δ_C (75 MHz; $(CD_3)_2SO$) 23.9 (CH_2), 32.3 (CH_3), 51.4 (CH_2), 55.1 (CH_3), 110.3, 111.3 (CH), 114.3 (CH, 4C), 117.8 (CH), 118.0 (CH) 120.8 (CH), 123.0 (CH), 125.8 (CH, 2C), 127.7 (CH, 2C), 131.7, 134.9, 136.1, 140.2, 140.5, 159.1, 170.5; δ (*distinct peaks for minor rotamer*) 22.5 (CH_2), 37.4 (CH_3), 47.8 (CH_2), 122.7 (CH), 126.8 (CH), 127.4 (CH); δ_C (100 MHz; $(CD_3)_2SO$, 353 K) 22.9 (CH2), 54.8 (CH3), 110.7, 110.8 (CH), 114.1 (CH), 117.5 (CH), 117.7 (CH), 120.4 (CH), 122.3 (CH), 125.3 (CH), 126.6 (CH), 126.8, 127.3 (CH), 131.5, 134.8, 135.9, 140.0, 158.9, 169.8.

4.5.5. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-phenyl-*N*-methylbiphenyl-4-carboxamide (6f)

Off white solid; yield 52%; mp 230–234 °C; δ_H (300 MHz; $(CD_3)_2SO$) rotamers 1/1.58 (from the duplicated triplet signal (^1H) at 3.49 and 3.75 ppm) 2.93 (3H, br), 3.09 (2H, br), 3.49 (2H, br), 6.74 (1H, br t, 7.0), 6.95–7.07 (2H, m), 7.23 (2H, br d, 7.4), 7.32 (1H, br d, 7.9), 7.37–7.42 (2H, m), 7.47–7.52 (3H, m), 7.63 (1H, d, 7.5), 7.74 (2H, br d, 7.4), 7.79 (4H, br s), 10.83 (1H, br s), δ (*distinct peaks for minor rotamer*) 3.75 (2H, br), 10.86 (1H, br s); δ_C (100 MHz; $(CD_3)_2SO$, 363 K) (*some peaks not observed due relaxation time*) 23.9, 111.9, 118.5, 118.7, 121.4, 123.3, 126.8, 127.0, 127.7, 128.0, 129.4, 136.6, 137.0, 139.0, 140.2, 140.2, 140.8, 170.7; *m/z* (FAB) 431.21230 (M+H^+ $C_{30}H_{27}N_2O$ requires 431.21234). Found: C, 3.56; N, 6.42; H, 5.94. $C_{30}H_{26}N_2O$ requires C, 83.69; N, 6.51; H, 6.09.

4.5.6. *N*-(2-(1*H*-Indol-3-yl)ethyl)biphenyl-4-carboxamide (6g)

Off white solid; yield 63%; mp 183–185 °C; δ_H (300 MHz; $(CD_3)_2SO$) 3.02 (2H, t, 7.5), 3.62 (2H, *ap*-q, 7.5, 5.6), 7.03 (1H, ddd, 7.5, 7.5, 1.1), 7.11 (1H, ddd, 7.5, 7.5, 1.1), 7.23 (1H, d, 2.2), 7.39 (1H, d, 7.5), 7.44 (1H, dd, 7.4, 1.1), 7.51 (2H, dd, 7.4, 7.4), 7.64 (1H, d, 7.4), 7.76 (2H, d, 7.4), 7.80 (2H, d, 8.4), 8.00 (2H, d, 8.4), 8.71 (1H, t, 5.6), 10.86 (1H, br s); δ_{13} (75 MHz; $(CD_3)_2SO$) 25.2, 40.3, 111.4, 111.9, 118.2, 118.3, 120.9, 122.6, 126.4, 126.8, 127.3, 127.8, 128.0, 129.0, 133.5, 136.2, 139.2, 142.5, 165.8; *m/z* (FAB) 341.16532 (M+H^+ $C_{23}H_{21}N_2O$ requires 341.16546). Found: C, 81.09; N, 8.18; H, 5.95. $C_{23}H_{20}N_2O$ requires C, 81.15; N, 8.23; H, 5.92.

4.5.7. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-fluorobiphenyl-4-carboxamide (6h)

Off white solid; yield 59%; mp 181–183 °C; δ_H (300 MHz; $(CD_3)_2SO$) 3.03 (2H, dd, 7.4, 7.4), 3.62 (2H, td, 7.4, 5.6), 7.04 (1H, td, 7.4, 1.1), 7.13 (1H, ddd, 7.4, 7.4, 1.1), 7.25 (1H, d, 2.2), 7.34–7.41 (3H, m), 7.65 (1H, d, 7.7), 7.79–7.86 (2H, m), 7.81 (2H, d, 8.4), 8.00 (2H, d, 8.4), 8.72 (1H, t, 5.6), 10.87 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 25.7 (CH_2), 40.7 (CH_2), 111.9 (CH), 112.4, 116.3 (d, $^2J_{CF}$, 21, CH), 118.7 (CH), 121.4 (CH), 123.1 (CH), 126.9 (CH, 2C), 127.8, 128.3 (CH, 2C), 129.4 (d, $^3J_{CF}$, 8, CH), 136.2 (d, $^4J_{CF}$, 3), 136.7 (CH), 142.0, 162.7 (d, $^1J_{CF}$, 245) 166.2; *m/z* (FAB) 359.15593 (M+H^+ $C_{23}H_{20}N_2OF$ requires 359.15597). Found: C, 76.97; N, 7.75; H, 5.51. $C_{23}H_{19}N_2OF$ requires C, 77.08; N, 7.82; H, 5.34.

4.5.8. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-methylbiphenyl-4-carboxamide (6i)

Off white solid; yield 42%; mp 204–206 °C; δ_H (300 MHz; $(CD_3)_2SO$) 2.39 (3H, s), 3.02 (2H, t, 7.5), 3.62 (2H, dt, 7.5, 5.6), 7.03 (1H, ddd, 7.4, 7.4, 1.1), 7.12 (1H, ddd, 7.4, 7.4, 1.1), 7.24 (1H, d, 2.2), 7.33 (2H, d, 8.1), 7.39 (1H, d, 8.1), 7.35 (1H, d, 8.1), 7.66 (2H, d, 8.1), 7.78 (2H, d, 8.4), 7.98 (2H, d, 8.4), 8.69 (1H, t, 5.6), 10.86 (1H, br); δ_C (75 MHz; $(CD_3)_2SO$) 21.2 (CH_2), 25.7 (CH_3), 40.7 (CH_2), 111.9 (CH), 112.4, 118.7 (CH), 118.8 (CH), 121.4 (CH), 123.1 (CH), 126.6 (CH, 2C), 127.1 (CH, 2C), 127.8, 128.3 (CH, 2C), 130.1 (CH, 2C), 133.7, 136.8 (2C), 137.9, 143.0, 166.3; *m/z* (FAB) 355.18110 (M+H^+ $C_{24}H_{23}N_2O$ requires 355.18104). Found: C, 79.20; N, 7.40; H, 5.84. $C_{24}H_{22}N_2O$ requires C, 81.33; N, 7.90; H, 6.26.

4.5.9. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-*tert*-butylbiphenyl-4-carboxamide (6j)

Off white solid; yield 61%; mp 201–203 °C; δ_H (300 MHz; $(CD_3)_2SO$) 1.37 (9H, s), 3.03 (2H, t, 7.3), 3.63 (2H, td, 7.3, 5.5), 7.04 (1H, br dd, 7.5, 7.5), 7.13 (1H, br dd, 7.5, 7.5), 7.25 (1H, d, 1.6), 7.40 (1H, d, 7.5), 7.55 (2H, d, 8.4), 7.66 (1H, d, 7.5), 7.71 (2H, d, 8.4), 7.80 (2H, d, 8.3), 7.99 (2H, d, 8.3), 8.70 (1H, dd, 5.5), 10.87 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 25.7 (CH_2), 31.6 (CH_3, 3C), 34.8, 40.7 (CH_2), 111.9, 112.4 (CH), 118.7 (CH), 118.8 (CH), 121.4 (CH), 123.1 (CH), 126.3 (CH, 2C), 126.7 (CH, 2C), 127.0 (CH, 2C), 127.8, 128.3 (CH, 2C), 133.7, 136.7, 136.8, 142.9, 151.0, 166.3; *m/z* (FAB) 397.22798 (M+H^+ $C_{27}H_{29}N_2O$ requires 397.22799). Found: C, 81.76; N, 6.97; H, 7.03. $C_{27}H_{28}N_2O$ requires C, 81.78; N, 7.06; H, 7.12.

4.5.10. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-methoxybiphenyl-4-carboxamide (6k)

Off white solid; yield 45%; mp 200–205 °C; δ_H (300 MHz; $(CD_3)_2SO$) 2.99 (2H, t, 7.4), 3.59 (2H, td, 7.4, 5.6), 3.81 (3H, s), 7.00 (1H, ddd, 7.4, 7.4, 1.1), 7.05 (2H, d, 8.8), 7.09 (1H, ddd, 7.4, 7.4, 1.1), 7.21 (1H, d, 2.2), 7.36 (1H, d, 7.4), 7.62 (2H, d, 7.4), 7.69 (2H, d, 8.8), 7.72 (2H, d, 8.5), 7.94 (2H, d, 8.5), 8.65 (1H, t, 5.6), 10.83 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 25.7 (CH_2), 40.7 (CH_2), 55.7 (CH_3),111.9 (CH), 112.4, 114.9 (CH), 118.7 (CH), 118.8 (CH), 121.4 (CH), 123.1 (CH), 126.3 (CH), 127.8, 128.3 (CH), 128.5 (CH), 129.2 (CH), 129.3 (CH), 131.9 (CH), 132.5 (CH), 133.2, 136.7, 159.8, 166.3. Found: C, 77.92; N, 7.41; H, 5.89. $C_{24}H_{22}N_2O_2$ requires C, 77.81; N, 7.56; H, 5.99.

4.5.11. *N*-(2-(1*H*-Indol-3-yl)ethyl)biphenyl-3-carboxamide (7)

Off white solid; yield 62%; mp 59–69 °C; δ_H (300 MHz; $(CD_3)_2SO$) 2.98 (2H, t, 7.5), 3.58 (2H, td, 7.5, 5.5), 6.98 (1H, ddd, 7.5, 7.5, 1.1), 7.07 (1H, ddd, 7.5, 7.5, 1.1), 7.20 (1H, d, 2.2), 7.35 (1H, br d, 8.0), 7.42 (1H, br d, 7.3), 7.50 (2H, dd, 7.9, 7.9), 7.57 (1H, d, 7.9, 7.9), 7.60 (1H, d, 7.9), 7.73 (2H, dd, 7.9, 1.4), 7.80–7.86 (2H, m), 8.12 (1H, dd, 1.5, 1.5), 8.74 (1H, dd, 5.5, 5.5), 10.82 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 25.1 (CH_2), 40.3 (CH_2), 111.3 (CH), 111.8, 118.2 (CH), 118.2 (CH), 120.8 (CH), 122.6 (CH), 125.2 (CH), 126.3 (CH), 126.8 (CH, 2C), 127.2, 127.7 (CH), 128.9 (CH, 2C), 129.1 (CH), 135.3, 136.2, 139.5, 140.1, 165.9; *m/z* (FAB) 341.16544 (M+H^+ $C_{23}H_{21}N_2O$ requires 341.16539). Found: C, 77.39; N, 7.89; H, 5.78. $C_{23}H_{20}N_2O$ requires C, 81.15; N, 8.23; H, 5.92.

4.5.12. *N*-(2-(1H-Indol-3-yl)ethyl)-4′-fluorobiphenyl-2-carboxamide (8a)

White solid; yield 28%; mp 157–159 °C; δ_H (300 MHz; $(CD_3)_2SO$) 2.78 (2H, t, 7.3), 7.04 (1H, t, 6.9), 7.12 (1H, t, 6.9), 7.16 (1H, d, 2.3), 7.19

(1H, t, 8.9), 7.43 (2H, d, 5.3), 7.44–7.47 δ (6H, m), 7.55 (1H, d, 7.4), 8.34 (1H, t, 5.7), 10.86 (1H, br s); δ_F (282 MHz, $CDCl_3$) −114.37 δ; δ_C (75 MHz; $(CD_3)_2SO$) 24.6 (CH2), 39.6 (CH2), 111.3 (CH), 111.6, 114.8 (d, $^2J_{CF}$, 21, CH, 2C), 118.1 (CH, 2C), 120.8 (CH), 122.3, 122.5 (CH), 127.0 (CH), 127.5 (CH), 129.2 (CH), 129.7 (CH), 130.2 (d, $^3J_{CF}$, 8, CH, 2C), 136.1, 136.5 (d, $^4J_{CF}$, 3), 137.3, 137.9, 161.5 (d, $^1J_{CF}$, 243), 168.8;); *m/z* (ES^-) 357 (100%, $M-H^-$) (ES^+) 359 (100% $M+H^+$); *m/z* (FAB) 359.1559 ($M+H^+$ $C_{23}H_{19}N_2OF$ requires 279.14981). Found: C, 74.99; N, 7.35; H, 4.62. $C_{23}H_{19}N_2OF$ requires C, 77.08; N, 7.82; H, 5.34.

4.5.13. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-*tert*-butylbiphenyl-2-carboxamide (8b)

White solid; yield 16%; mp 149–151 °C; δ_H (300 MHz; $CDCl_3$) 1.35 (9H, s) 2.62 (2H, t, 6.8) 3.50 (2H, td, 6.8, 5.4) 5.30 (1H, t, 5.4), 6.55 (1H, d, 2.0), 7.05 (1H, dd, 6.9, 6.9), 7.15 (1H, dd, 6.9, 6.9), 7.31 (1H, d, 8.1), 7.31–7.41 (4H, m), 7.37 (2H, d, 8.5), 7.45 (2H, d, 8.5), 7.64 (1H, d, 7.5), 7.87 (1H, br s); δ_C (75 MHz; $CDCl_3$) 24.5 (CH_2), 31.0 (CH_3, 3C), 34.1, 36.9 (CH_2), 111.3 (CH), 111.6, 118.0 (CH, 2C), 120.8 (CH), 122.4 (CH), 124.8 (CH, 2C), 126.7 (CH), 127.0, 127.5 (CH), 127.9 (CH, 2C), 129.1 (CH), 129.6 (CH), 136.1, 137.1, 137.3, 138.7, 149.4, 169.0; *m/z* (FAB) 397.2280 ($M+H^+$ $C_{27}N_2OH_{29}$ requires 397.22799).

4.5.14. *N*-(2-(1*H*-Indol-3-yl)ethyl)-4′-methoxybiphenyl-2-carboxamide (8c)

White solid; yield 34%; mp 155–157 °C; δ_H (300 MHz; $CDCl_3$) 2.72 (2H, t, 6.8), 3.55 (2H, dt, 6.8), 3.80 (3H, s), 5.34 (1H, t, 4.8), 6.66 (1H, d, 2.3), 6.89 (2H, d, 8.8), 7.07 (1H, t, 6.9), 7.16 (1H, t, 6.9), 7.28–7.32 (2H, m), 7.30 (2H, d, 8.7), 7.36 (1H, d, 7.4), 7.41 (1H, d, 7.4), 7.48 (1H, d, 7.8), 7.64 (1H, d, 7.6), 7.99 (1H, br s); δ_C (75 MHz; $CDCl_3$) 24.6 (CH_2), 39.6 (CH_2), 55.0 (CH_3), 111.2 (CH), 111.6, 113.5 (CH, 2C), 118.1 (CH, 2C), 120.8 (CH), 122.5 (CH), 126.4 (CH), 127.1, 127.5 (CH), 129.1 (CH), 129.4 (CH, 2C), 129.5 (CH), 132.4, 136.1, 137.2, 138.5, 158.5, 169.1; *m/z* (FAB) 371.1759 ($M+H^+$ $C_{24}N_2O_2H_{23}$ requires 371.17595).

4.5.15. *N*-(2-(1*H*-Indol-3-yl)ethyl)-3′-methoxybiphenyl-2-carboxamide (8d)

Pale orange solid; yield 38%; mp 156–158 °C; δ_H NMR (300 MHz, $(CD_3)_2SO$) 2.76 (2H, t, 7.3), 3.84 (3H, s), 6.99 (1H, d, 7.7), 7.04 (1H, t, 7.1), 7.07 (1H, s), 7.14 (1H, t, 7.1), 7.18 (1H, d, 1.6), 7.35 (1H, d, 7.9), 7.40–7.45 (2H, m), 7.42 (1H, d, 7.9), 7.50–7.55 (2H, m), 7.50 (1H, d, 6.9), 7.57 (2H, d, 7.2), 8.34 (1H, t, 5.7), 10.89 (1H, br s); δ_C (75 MHz; $CDCl_3$) 24.6 (CH_2), 39.7 (CH_2), 54.9 (CH_3), 111.3 (CH), 111.6, 112.6 (CH), 114.0 (CH), 118.1 (CH), 118.1 (CH), 120.7 (CH), 120.8 (CH), 122.4 (CH), 127.0 (CH), 127.1, 127.5 (CH), 129.1(CH, 2C), 129.6 (CH), 136.1, 137.4, 138.8, 141.5, 158.9, 169.0; *m/z* (FAB) 371.17598 ($M+H^+$ $C_{24}H_{23}N_2O_2$ requires 371.17595).

4.5.16. *N*-(2-(1*H*-Indol-3-yl)ethyl)-2′-methoxybiphenyl-2-carboxamide (8e)

Off white solid; yield 72%; mp 137–139 °C; δ_H NMR (300 MHz, $CDCl_3$) 2.57 (2H, t, 7.0), 3.42 (2H, q, 6.9), 3.51 (3H, s), 5.58 (1H, t, 4.2), 6.64 (1H, d, 2.0), 6.71 (1H, d, 8.1), 6.88 (1H, t, 7.4), 6.99 (1H, t, 7.0), 7.06–7.11 (m, 2H), 7.15–7.20 (m, 2H), 7.24 (1H, d, 8.2), 7.32 (1H, d, 7.5), 7.36 (1H, d, 7.3), 7.40 (1H, d, 7.4), 7.68 (1H, d, 7.4), 8.10 (br s); δ_C (75 MHz; $(CD_3)_2SO$) 24.8 (CH_2), 39.6 (CH_2), 54.9 (CH_3), 110.7 (CH), 111.3 (CH), 111.6, 118.1 (CH, 2C), 120.1 (CH), 120.8 (CH), 122.4 (CH), 126.7 (CH), 127.1, 127.1 (CH), 128.6 (CH), 129.0 (CH), 129.3, 130.2 (CH), 130.8 (CH), 136.1, 136.3, 137.7, 155.9, 168.5; *m/z* (FAB) 371.17602 ($M+H^+$ $C_{24}H_{23}N_2O_2$ requires 371.17595).

4.5.17. *N*-(2-(1*H*-Indol-3-yl)ethyl)-3′-fluorobiphenyl-2-carboxamide (8f)

Pale beige solid; yield 33%; mp 96–99 °C; δ_H NMR (300 MHz, $(CD_3)_2SO$) 2.67 (2H, t, 7.4), 6.96 (1H, t, 7.0), 7.05 (1H, t, 7.0), 7.10 (1H, d, 1.7), 7.14–7.24 (2H, m), 7.21 (1H, d, 5.5), 7.33 (1H, d, 7.9), 7.38–7.51 (4H, m), 7.43 (1H, d, 6.4), 7.50 (1H, d, 6.0), 8.36 (1H, t, 5.7), 10.81 (1H, br s); δ_C (75 MHz; $CDCl_3$) 24.6 (CH_2), 39.7 (CH_2), 111.3 (CH), 111.5, 113.8 (d, $^2J_{CF}$, 21, CH), 115.1 (d, $^2J_{CF}$, 22, CH), 118.0 (CH), 118.1 (CH), 120.8 (CH), 122.4 (CH), 124.5 (d, $^4J_{CF}$, 2, CH), 127.1, 127.5 (CH), 127.5 (CH), 129.3 (CH), 129.6 (CH), 130.0 (d, $^3J_{CF}$, 8, CH), 136.1, 137.4, 137.6 (d, $^4J_{CF}$, 2), 142.5 (d, $^3J_{CF}$, 8), 161.8 (d, $^1J_{CF}$, 243), 167.8; δ_F (282 MHz, $CDCl_3$) −112.66; *m/z* (FAB) 359.15607 ($M+H^+$ $C_{23}H_{20}FN_2O$ requires 359.15597).

4.5.18. *N*-(2-(1*H*-Indol-3-yl)ethyl)-3′-methylbiphenyl-2-carboxamide (8g)

Pale yellow solid; yield 52%; mp 121–122 °C; δ_H NMR (300 MHz, $(CD_3)_2SO$) 2.62 (2H, t, 7.2), 2.37 (3H, s), 6.96 (1H, t, 7.8), 7.03 (1H, t, 7.8), 7.07 (1H, d, 2.3), 7.13 (1H, d, 7.0), 7.18–7.25 (3H, m), 7.24 (1H, s), 7.34 (1H, d, 8.0), 7.37–7.42 (2H, m), 7.46 (1H, d, 7.3), 7.48 (1H, d, 7.3), 8.21 (1H, t, 5.7), 10.78 (1H, br s); δ_C (75 MHz; $(CD_3)_2SO$) 21.0 (CH_3), 24.7 (CH_2), 39.7 (CH_2), 111.3 (CH), 111.6, 118.0 (CH), 118.1 (CH), 120.8 (CH), 122.4 (CH), 125.4 (CH), 126.8 (CH), 127.1, 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.1 (CH), 129.6 (CH), 136.1, 137.0, 137.4, 139.0, 140.1, 169.0; *m/z* (FAB) 355.18098 ($M+H^+$ $C_{24}H_{23}N_2O$ requires 355.18103).

4.6. General procedure for the synthesis of phenyl-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone derivatives 10a–c

To a suspension of carboline **9** (1.2 mmol) in CH_2Cl_2 (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 appropriate benzoyl chloride derivative (1.2 mmol) was added dropwise. The mixture was stirred for 5 min at 0 °C and for a further 3 h at room temperature. H_2O (20 mL) was added. The two layers were separated and the aqueous phase was extracted with dichloromethane (3× 20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica. Elution was made successively with; ethyl acetate/petroleum ether (40–60 °C) 50:50 and ethyl acetate, to give the expected compound.

4.6.1. (4-Bromo-phenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone (10a)

White solid; yield 62%; mp 217 °C; rotamers 1/1.7 (from the duplicated singlet signal (^1H) at room temperature at 4.59 and 4.83 ppm); δ_H (400 MHz, $(CD_3)_2SO$, 363 K) 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); δ_C (75 MHz, $CDCl_3$) δ 22.0 (CH_2), 40.9 (CH_2), 45.9 (CH_2), 107.1, 111.6 (CH), 118.0 (CH), 119.1 (CH), 121.4 (CH), 123.5, 127.0, 129.5 (2CH), 131.0, 132.0 (2CH), 135.8, 136.5, 169.6; *m/z* (ES^+) 356 $(M+2H)^+$; (ES^-) 353 $(M-H)^-$. *m/z* (FAB) 354.03677 ($M+H^+$ $C_{18}H_{15}BrN_2O$ requires 354.03677). Found: C, 60.87; H, 4.20; N, 7.70. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89.

4.6.2. (3-Bromo-phenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone (10b)

White solid; yield 91%; mp 207 °C; rotamers 1/1.6 (from the duplicated broad singlet signal (^1H) at room temperature at 4.60 and 4.84 ppm); δ_H (400 MHz, $(CD_3)_2SO$), 373 K) 2.80 (2H, t, 5.8), 3.81 (2H, br s), 4.77 (2H, s), 7.00 (1H, td, 7.5, 1.2), 7.08 (1H, td, 7.5, 1.2), 7.34 (1H, d, 7.6), 7.41–7.48 (3H, m), 7.64–7.69 (2H, m), 10.52 (1H, br s); δ_C (100 MHz; $(CD_3)_2SO$); 373 K) 21.7 (CH_2), 43.1 (CH_2), 44.1 (CH_2), 107.5, 111.5 (CH), 118.0 (CH), 119.1 (CH), 121.4 (CH), 122.2, 126.1 (CH), 127.3, 129.9 (CH), 131.1 (CH), 131.1, 132.8 (CH), 136.9, 139.3, 168.8; *m/z* (ES^+) 355 MH^+; (ES^-)

353 $(M-H)^-$;. *m/z* (FAB) 355.04478 ($M+H^+$ $C_{18}H_{15}BrN_2O$ requires 355.04460). Found: C, 60.94; H, 4.17; N, 7.93. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.87.

4.6.3. (2-Bromo-phenyl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone (10c)

White solid; yield 64%; mp 190 °C; rotamers 1/3.3 (from the duplicated broad singlet signal (^1H) at 8.03 and 8.59 ppm); δ_H (300 MHz, $CDCl_3$) (*major rotamer*) 2.66 (1H, t, 6.5), 2.73 (1H, t, 5.0), 3.49 (2H, t, 5.7), 4.77 (1H, d, 16.8), 5.06 (1H, d, 16.8), 6.93–7.56 (8H, m), 8.59 (1H, br s); δ (distinct peaks for *minor rotamer*) 2.61 (1H, apparent t, *J* 6.3), 2.79 (1H, t, 5.0), 2.85 (2H, t, 5.7), 4.24 (1H, d, 16.1), 4.38 (1H, d, 16.1), 8.03 (1H, br s); δ_C (75 MHz, $CDCl_3$) δ (*major rotamer*) 21.9 (CH_2), 40.5 (CH_2), 45.2 (CH_2), 107.6, 111.3 (CH), 117.8 (CH), 119.3, 119.5 (CH), 121.8 (CH), 126.7, 127.6 (CH), 127.9 (CH), 129.7, 130.5 (CH), 133.0 (CH), 136.4, 138.2, 168.9; δ (distinct peaks for *minor rotamer*) 21.0 (CH_2), 44.9 (CH_2), 109.2, 111.0 (CH), 118.2 (CH), 119.1, 119.7 (CH), 121.9 (CH), 126.8, 129.2, 132.9, 136.3, 138.3, 168.4; *m/z* (ES^+) 355 MH^+; (ES^-) 354 $(M)^-$; *m/z* (FAB) 354.03678 (M^+ $C_{18}H_{15}BrN_2O$ requires 354.03677). Found: C, 60.75; H, 4.17; N, 7.92. $C_{18}H_{15}BrN_2O$ requires C, 60.86; H, 4.26; N, 7.89.

4.6.4. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(4′-fluorobiphenyl-2-yl)methanone (11a)

Off White amorphous solid; 63% yield; mp 136–139 °C; 2.2:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.14–2.21 (1H, m), 2.42–2.52 (1H, m), 2.89–2.96 (1H, m), 3.35–3.42 (1H, m), 4.23 (1H, d_{AB}, *J* 17.0), 5.03 (1H, d_{AB}, *J* 17.0), 6.62 (1H, at, *J* 8.7), 6.87–7.13 (5H, m), 7.20–7.43 (6H, m), 8.70 (1H, s), *distinct signals for minor rotamer*: 2.58–2.65 (1H, m), 3.64–3.73 (1H, m), 3.82 (1H, d_{AB}, *J* 16.0), 3.82–3.90 (1H, m), 4.03 (1H, d_{AB}, *J* 16.1), 7.94 (1H, s); δ_C (75.5 MHz, $CDCl_3$) 21.4 (CH_2), 40.2 (CH_2), 44.8 (CH_2), 107.4, 111.0 (CH), 115.4 (CH, d, $^2J_{CF}$ 21.5), 117.6 (CH), 119.2 (CH), 121.5 (CH), 126.4, 127.1 (CH), 127.8 (CH), 129.4, 129.6 (CH), 129.6 (CH), 130.1 (CH, d, $^3J_{CF}$ 8.4), 135.4, 135.7 (d, $^4J_{CF}$, 3.6), 136.2, 137.7, 162.4 (d, $^2J_{CF}$ 247), 170.1; (*distinct signals for minor rotamer*) 20.6 (CH_2), 40.2 (CH_2), 44.7 (CH_2), 108.7, 110.6 (CH), 115.0 (CH, d, $^2J_{CF}$ 21.5), 117.9 (CH), 119.4 (CH), 121.7 (CH), 126.7, 127.1 (CH), 127.7 (CH), 128.8, 129.4 (CH), 129.5 (CH), 129.8 (CH, d, $^3J_{CF}$ 8.4), 135.1 (d, $^4J_{CF}$, 3.6), 135.5, 136.0, 137.8, 162.2 (d, $^2J_{CF}$ 248), 170.9; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14821 (M^+ $C_{24}H_{19}N_2OF$ requires 370.14814).

4.6.5. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-fluorobiphenyl-2-yl)methanone (11b)

Off white amorphous solid; 56% yield; mp 203–207 °C; 2:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.55–2.76 (2H, m, CH_2), 3.09 (1H, ddd, *J* 13.2, 8.5, 4.7), 3.52 (1H, dat, 13.2, 4.8), 4.41 (1H, d_{AB}, *J* 17.0), 5.14 (1H, d_{AB}, *J* 17.0), 6.95–7.17 (12H, m, ArH), 8.59 (1H, s, ArH), (*distinct signals for minor rotamer*) 2.25–2.30 (2H, m, CH_2), 3.80 (1H, ddd, *J* 12.6, 7.4, 5.2, CH_2), 3.99 (1H, d_{AB}, *J* 16.3, CH_2), 4.07 (1H, m, CH_2), 4.19 (1H, d_{AB}, *J* 16.3, CH_2), 7.88 (1H, s, NH); δ_C (75.5 MHz, $CDCl_3$) 21.4 (CH_2), 40.2 (CH_2), 44.8 (CH_2), 107.5, 111.0 (CH), 114.6 (CH, d, $^2J_{CF}$ 21.0), 115.4 (CH, d, $^2J_{CF}$ 22.0), 117.7 (CH), 119.3 (CH), 121.6 (CH), 124.3 (CH, d, $^4J_{CF}$ 2.7), 126.5, 127.3 (CH), 128.2 (CH), 129.3 (CH), 129.4, 129.6 (CH, d, $^3J_{CF}$ 6.6), 129.6 (CH), 135.5, 136.2, 137.5, 141.8 (d, $^3J_{CF}$ 7.8), 162.9 (Cq, d, $^1J_{CF}$ 247), 170.7; (*distinct signals for minor rotamer*) 20.5 (CH_2), 40.3 (CH_2), 44.8 (CH_2), 108.9, 110.7 (CH), 114.4 (CH, d, $^2J_{CF}$ 20.9), 115.1 (CH, d, $^2J_{CF}$ 22.0), 117.9 (CH), 119.4 (CH), 121.7 (CH), 124.0 (CH, d, $^4J_{CF}$ 2.7), 126.8, 127.4 (CH), 128.2 (CH), 128.8, 129.7 (CH), 130.0 (CH, d, $^3J_{CF}$ 8.4), 135.5, 136.0, 137.5, 141.2 (Cq, d, $^3J_{CF}$ 7.8), 162.4 (Cq, d, $^1J_{CF}$ 247), 169.9; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14815 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.6. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-fluorobiphenyl-2-yl)methanone (11c)

Off white amorphous solid; 82% yield; mp 188–190 °C; 3:2 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.36 (1H, br s), 2.56 (1H, br s), 3.13 (1H, br s), 3.57 (1H, br s), 4.21 (1H, d_{AB}, *J* 16.7), 4.99 (1H, d_{AB} *J* 16.4), 6.40–7.40 (12H, m, ArH), 8.62 (1H, br s); (*distinct signals for minor rotamer*) 2.32 (1H, br s), 2.52 (1H, br s), 3.44 (1H, br s), 4.00–4.09 (3H, m), 7.82 (1H, br s, NH); δ_C(75.5 MHz, $CDCl_3$) 21.5 (CH_2), 40.4 (CH_2), 45.1 (CH_2), 107.5, 111.1 (CH), 115.6 (CH, d, $^2J_{CF}$ 22.3), 117.6 (CH), 119.2 (CH), 121.4 (CH), 124.1 (CH, d, $^3J_{CF}$ 3.7), 126.5, 126.9 (Cq, d, $^2J_{CF}$ 16.8) 127.0 (CH), 128.2 (CH), 129.2 (CH), 129.6, 129.7 (CH, d, $^3J_{CF}$ 8.2), 131.0 (CH, d, $^4J_{CF}$ 1.9), 131.4 (CH, d, $^4J_{CF}$ 3.0), 133.2, 136.2, 136.2, 159.4 (d, $^1J_{CF}$ 246), 170.6; (*distinct signals for minor rotamer*) 20.6 (CH_2), 40.3 (CH_2), 44.8 (CH_2), 108.7, 110.7 (CH), 115.0 (CH, d, $^2J_{CF}$ 22.3), 117.8 (CH), 119.3 (CH), 121.5 (CH), 123.7 (CH, d, $^3J_{CF}$ 3.6), 126.3 (Cq, d, $^2J_{CF}$ 14.8), 127.1 (CH), 127.3, 128.3 (CH), 128.9 (CH), 129.0, 129.5 (CH, d, $^3J_{CF}$ 8.2), 130.7 (CH, d, $^4J_{CF}$ 2.1), 131.2 (CH, d, $^4J_{CF}$ 2.8), 132.6 (136.1, 136.4, 159.0 (d, $^1J_{CF}$ 245), 169.6; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14821 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.7. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-methylbiphenyl-2-yl)methanone (11d)

Off white amorphous solid; yield 97%; mp 187–191 °C; 1.7:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.04–2.19 (1H, m, CH_2), 2.14 (3H, s, CH_3), 2.38–2.50 (1H, m, CH_2), 2.91 (1H, ddd, *J* 13.0, 8.5, 4.7, CH_2), 3.39 (1H, dat, *J* 13.3, 5.0, CH_2), 4.27 (1H, d_{AB}, pseudo *J* 17.0, CH_2), 5.01 (1H, $d_{AB,}$ pseudo *J* 17.0, CH_2), 6.84–7.40 (12H, m), 8.84 (1H, m, CH_2); (*distinct signals for minor rotamer*) 1.89 (3H, s, CH_3), 2.38–2.50 (1H, m, CH_2), 2.54–2.62 (1H, m, CH_2), 3.56 (1H, ddd, *J* 12.6, 7.8, 4.8, CH_2), 3.03 (1H, d_{AB}, pseudo *J* 16.4, CH_2), 3.97 (1H, d_{AB}, *J* 16.4, CH_2), 3.94–4.01 (1H, m, CH_2), 8.00 (1H, s, NH); δ_C(75.5 MHz, $CDCl_3$), 21.1 (CH_2), 21.3 (CH_3), 40.2 (CH_2), 44.7 (CH_2), 107.2, 111.0 (CH), 117.5 (CH), 119.0 (CH), 121.3 (CH), 125.4 (CH), 126.4, 127.2 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 129.4, 129.5 (CH), 129.5 (CH), 135.2, 136.2, 138.0, 138.9, 139.5, 171.1; (*distinct signals for minor rotamer*) 20.5 (CH_2), 21.0 (CH_3), 40.2 (CH_2), 44.7 (CH_2), 108.5, 110.7 (CH), 117.7 (CH), 119.1 (CH), 121.3 (CH), 125.3 (CH), 126.7, 127.0 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 129.0, 129.4 (CH), 129.4 (CH), 135.3, 136.0, 137.7, 138.9, 139.1, 170.3; *m/z* (ES+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17324 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.8. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(4′-fluorobiphenyl-3-yl)methanone (12a)

Off white amorphous solid; 83% yield; mp 132–135 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.81 (2H, br s), 2.72 (2H, br s), 4.93 (2H, br s), 7.05–7.64 (12H, m, Ar), 8.75 (1H, br s); (*distinct signals for minor rotamer*) 2.90 (2H, br s), 4.10 (2H, br s), 4.58 (2H, br s), 8.10 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 22.1 (CH_2), 44.1 (CH_2), 46.0 (CH_2), 107.6, 111.1 (CH), 115.8 (CH, d, $^2J_{CF}$ 21.4), 117.7 (CH), 119.4 (CH), 121.7 (CH), 125.4 (CH), 125.5 (CH), 126.7, 128.4 (CH), 128.7 (CH, d, $^3J_{CF}$ 8.1), 129.1 (CH), 129.9, 136.2 (d, $^5J_{CF}$ 1.3), 136.2 (d, $^4J_{CF}$ 4.8), 136.6, 140.7, 162.1 (Cq, d, $^1J_{CF}$, 247), 171.3; *m/z* (ES+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14822 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.9. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-fluorobiphenyl-3-yl)methanone (12b)

Off white amorphous solid; 72% yield; mp 134–138 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.85 (2H, br s, CH_2), 3.76 (2H, br s, CH_2), 4.97 (2H, br s, CH_2), 7.07–7.72 (12H, m, ArH), 8.90 (1H, br s); (*distinct signals for minor rotamer*) 2.95 (2H, br s, CH_2), 4.14 (2H, br s, CH_2), 4.62 (2H, br s, CH_2), 8.28 (1H, br s); δ_C

(75.5 MHz, $CDCl_3$), 22.0 (CH_2), 41.2 (CH_2), 4.60 (CH_2), 107.4, 111.1 (CH), 113.9 (CH, d, $^2J_{CF}$ 22.1), 114.5 (CH, d, $^2J_{CF}$ 20.9), 117.7 (CH), 119.4 (CH), 121.6 (CH), 122.7 (CH, d, $^4J_{CF}$ 2.7), 125.4 (CH), 126.1 (CH), 126.6, 128.5 (CH), 129.2 (CH), 129.9, 130.3 (CH, d, $^3J_{CF}$, 8.4), 136.2, 136.6, 140.3 (d, $^4J_{CF}$ 1.2), 142.2 (d, $^3J_{CF}$ 7.8), 163.1 (d, $^1J_{CF}$ 246), 171.2; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14806 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.10. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-fluorobiphenyl-3-yl)methanone (12c)

Off white amorphous solid; 83% yield; mp 125–127 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.71 (2H, br s), 3.52–3.63 (2H, m), 4.76-4.81 (2H, m), 6.96–7.56 (12H, m), 8.80 (1H, br s); (*distinct signals for minor rotame):* 2.76 (2H, br s), 3.96 (2H, br s), 4.36–4.47 (2H, m), 8.13 (1H, br s); δ_C (100 MHz, $CDCl_3$) 22.0 (CH_2), 41.1 (CH_2), 46.1 (CH_2), 107.5, 111.1 (CH), 116.1 (CH, d, $^2J_{CF}$ 22.7), 117.7 (CH), 119.3 (CH), 121.5 (CH), 124.5 (CH, d, $^3J_{CF}$ 3.6), 126.1 (CH), 126.6, 127.4 (CH), 127.8, 128.8 (CH), 129.4 (CH, d, $^3J_{CF}$ 8.4), 129.9, 130.4 (CH, d, $^4J_{CF}$ 3.0), 130.6 (CH, d, $^4J_{CF}$ 3.3), 136.1, 136.1 (d, $^2J_{CF}$ 13.5), 137.8, 159.6 (d, $^1J_{CF}$ 248), 171.2.

4.6.11. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(4′-methylbiphenyl-3-yl)methanone (12d)

Off white amorphous solid; yield 61%; mp 166–168 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.27 (3H, br s), 2.67 (2H, br s), 3.58 (2H, br s), 4.80 (2H, br s), 6.93–7.57 (12H, m), 8.80 (1H, br s); (*distinct signals for the minor rotamer*) 2.78 (2H, br s), 3.96 (2H, br s), 4.43 (2H, br s), 8.20 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 21.0 (CH_3), 22.0 (CH_2), 41.0 (CH_2), 46.0 (CH_2), 107.4, 111.1 (CH), 117.6 (CH), 119.2 (CH), 121.5 (CH), 125.1 (CH), 125.2 (CH), 126.5, 126.8 (CH), 128.3 (CH), 129.0 (CH), 129.5 (CH), 129.9, 136.1, 136.3, 137.1, 137.5, 141.4, 171.5; *m/z* (ES^+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17309 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.12. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-methylbiphenyl-3-yl)methanone (12e)

Off white amorphous solid; yie;d 88%; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.29 (3H, br s), 2.69 (2H, br s), 3.60 (2H, br s), 4.38 (2H, br s), 6.94–7.59 (12H, m), 8.79 (1H, br s); (*distinct signals for the minor rotamer*) 2.79, (2H, br s), 3.98 (2H, br s), 4.45 (2H, br s), 8.17 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 21.4 (CH_3), 22.0 (CH_2), 41.1 (CH_2), 46.0 (CH_2), 107.4, 111.1 (CH), 117.6 (CH), 119.3 (CH), 121.5 (CH), 124.1 (CH), 125.4 (CH), 126.6, 127.8 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 129.0 (CH), 129.9, 136.2, 136.3, 138.5, 140.0, 141.7, 171.5.

4.6.13. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-methylbiphenyl-3-yl)methanone (12f)

Off white amorphous solid; yield 80%; mp 139–141 °C; 3:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.15 (3H, br s), 2.67 (2H, br s), 3.60 (2H, br s), 4.79 (2H, br s), 6.60–6.65 (1H, m), 6.80–7.58 (11H, m), 8.74 (1H, br s); δ (distinct signals for *minor rotamer*) 2.75 (2H, br s), 3.94 (2H, br s), 4.40 (2H, br s), 8.24 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 20.5 (CH_3), 22.1 (CH_2), 41.1 (CH_2), 46.1 (CH_2), 107.4, 111.0 (CH), 117.8 (CH), 119.6 (CH), 121.8 (CH), 125.4 (CH), 125.9 (CH), 126.8, 127.5 (CH), 127.6 (CH), 128.5 (CH), 129.8 (CH), 130.4 (CH), 130.4, 130.7 (CH), 135.2, 135.9, 136.2, 140.8, 142.2, 171.5; *m/z* (ES^+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17322 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.14. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-methoxybiphenyl-3-yl)methanone (12g)

Off white amorphous solid; yield 74%; 4:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.85 (2H, br s), 3.77 (2H, br s), 3.87 (3H, br s) 4.97 (2H, br s), 6.95–7.75 (12H, m), 8.88 (1H, br s); δ (distinct signals for *minor rotamer*) 2.95 (2H, br s), 4.13 (2H, br s), 4.61 (2H, br s), 8.30 (1H, br s); δ_H (75.5 MHz, $CDCl_3$) 22.0 (CH_2), 41.0 (CH_2), 46.0 (CH_2), 55.2 (CH_3), 107.5, 111.1 (CH), 112.7 (CH), 113.2 (CH), 117.7 (CH), 119.3 (CH), 119.5 (CH), 121.6 (CH), 125.5 (CH), 125.7 (CH), 126.6, 128.6 (CH), 129.0 (CH), 129.9 (CH), 136.2, 135.5, 141.5, 141.5, 159.9, 171.4 (C=O); *m/z* (ES+) 383 ($[M+H]^+$ 100%); *m/z* (FAB) 382.16820 (M^+ $C_{25}H_{22}N_2O_2$ requires 382.16813).

4.6.15. Biphenyl-3-yl(3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)methanone (12h)

Beige solid; 92% yield; mp 104–106 °C; 3.6:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.71 (2H, br s), 3.63 (2H, br s), 4.84 (2H, br s), 6.95–7.60 (13H, m, Ar), 8.67 (1H, br s); δ *(distinct signals for minor rotamer*) 2.80 (2H, br s), 3.99 (2H, br s), 4.47 (2H, br s), 8.04 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 22.1 (CH_2), 41.1 (CH_2), 46.1 (CH_2), 107.6, 111.1 (CH), 117.7 (CH), 119.4 (CH), 121.7 (CH), 125.5 (CH), 125.6 (CH), 126.7, 127.1 (CH), 127.7 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.9, 136.3, 136.5, 140.0, 143.6, 171.5; *m/z* (ES+) 353 ($[M+H]^+$, 100%).

4.6.16. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(4′-fluorobiphenyl-4-yl)methanone (13a)

Off white amorphous solid; 80% yield; mp 227−229 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.88 (2H, br s), 3.79 (2H, br s), 4.97 (2H, br s), 7.09 (12H, m, ArH), 8.34 (1H, br s, NH); δ *(distinct signals for minor rotamer*) 2.95 (2H, br s), 4.13 (2H, br s), 4.69 (2H, br s), 7.83 (1H br s); δ_C (100 MHz, $(CD_3)_2SO$) 21.5 (CH_2), 45.4 (CH_2), 54.8 (CH_2), 106.5, 111.0 (CH), 115.7 (CH, d, $^2J_{CF}$ 21.6), 117.4 (CH), 118.5 (CH), 120.8 (CH), 126.4, 126.6 (CH), 127.4 (CH), 128.7 (CH, d, $^3J_{CF}$ 8.4), 130.6, 135.0, 135.7 (d, $^5J_{CF}$ 2.4), 135.9 (Cq, d, $^4J_{CF}$ 2.8), 140.2, 162.0 (d, $^1J_{CF}$ 245), 169.7; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14821 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.17. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-fluorobiphenyl-4-yl)methanone (13b)

Pale yellow amorphous solid; 84% yield; mp 212–216 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.77 (2H, br s, CH_2), 3.67 (2H, br s, CH_2), 4.86 (2H, br s, CH_2), 6.97–7.56 (12H, m, Ar), 8.57 (1H, br s); δ *(distinct signals for minor rotamer*) 4.02 (2H, br s, CH_2), 4.56 (2H, br s, CH_2), 7.97 (1H, br s); δ_C (75.5 MHz, $CDCl_3$), 22.1 (CH_2), 41.2 (CH_2), 46.1 (CH_2), 107.7, 111.1 (CH), 114.0 (CH, d, $^2J_{CF}$ 22.1), 114.6 (CH, d, $^2J_{CF}$ 20.9), 117.8 (CH), 119.5 (CH), 121.8 (CH), 122.8 (CH, d, $^4J_{CF}$ 2.7), 126.7, 127.3 (CH), 127.6 (CH), 129.9, 130.4 (CH, d, $^3J_{CF}$ 8.4), 135.3, 136.3, 141.5 (d, $^4J_{CF}$ 1.5), 142.4 (d, $^3J_{CF}$ 7.5), 163.2 (d, $^1J_{CF}$ 246), 171.2; *m/z* (ES+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14819 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.18. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-fluorobiphenyl-4-yl)methanone (13c)

Pale yellow amorphous solid; 79% yield; mp 197–200 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.89 (2H, br s, CH_2), 3.81 (2H, m, CH_2), 4.96 (2H, br s, CH_2), 7.01–7.80 (12H, m, ArH), 8.36 (1H, br s, NH); δ *(distinct signal for minor rotamer*) 4.10 (2H, m, CH_2), 4.69 (2H, m, CH_2), 9.08 (1H, br s); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_2), 40.3 (CH_2), 45.5 (CH_2), 106.5, 111.0 (CH), 116.1 (CH, d, $^2J_{CF}$ 22.5), 117.4 (CH), 118.5 (CH), 120.8 (CH), 125.0 (CH, d, $^3J_{CF}$ 3.5), 126.4, 127.0 (CH), 127.4 (d, $^2J_{CF}$ 13.1), 128.8 (CH, d, $^4J_{CF}$ 3.0), 129.9 (CH, d, $^3J_{CF}$ 8.3), 130.6, 130.7 (CH, d, $^4J_{CF}$ 3.2), 135.5, 135.9, 136.2, 159.0 (d, $^1J_{CF}$ 246), 169.5; *m/z* (ES^+) 371 ($[M+H]^+$, 100%); *m/z* (FAB) 370.14821 (M^+ $C_{24}H_{19}FN_2O$ requires 370.14814).

4.6.19. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(4′-methylbiphenyl-4-yl)methanone (13d)

Off white amorphous solid; yield 66%; mp 223–226 °C; 4:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.32 (3H, br s), 2.78 (2H, br s), 3.68 (2H, br s), 4.84 (2H, br s), 6.99–7.61 (12H, m), 8.53 (1H, br s); δ *(distinct signals for minor rotamer*) 1.81 (3H, br s), 3.99 (2H, br

s), 4.57 (2H, br s), 8.11 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 21.1 (CH_3), 22.1 (CH_2), 41.1 (CH_2), 46.1 (CH_2), 107.8, 111.1 (CH), 117.8 (CH), 119.5 (CH), 121.7 (CH), 126.8, 126.9 (CH), 127.0 (CH), 127.5 (CH), 129.6 (CH), 134.4, 136.3, 137.2, 137.7, 142.7, 171.4 (C=O), *δ (distinct signals for minor rotamer*) 128.4 (CH), 128.6 (CH), 132.0 (CH), 132.0 (CH), 132.1 (CH); *m/z* (ES^+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17324 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.20. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-methylbiphenyl-4-yl)methanone (13e)

Pale beige amorphous solid; yield 91%; mp 158–161 °C; 5:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.31 (2H, br s, CH_3), 2.72 (2H, br s, CH_2), 3.62 (2H, br s, CH_2), 4.81 (2H, br s, CH_2), 6.96–7.54 (12H, m, Ar), 8.77 (1H, br s); *δ (distinct signals for minor rotamer*) 2.75 (2H, br s, CH_2), 3.96 (2H, br s, CH_2), 4.51 (2H, br s, CH_2), 8.24 (1H, br s); δ_C (300 MHz, $CDCl_3$) 21.5 (CH_3), 22.0 (CH_2), 41.1 (CH_2), 46.1 (CH_2), 107.4, 111.1 (CH), 117.7 (CH), 119.3 (CH), 121.5 (CH), 124.2 (CH), 126.6, 127.2 (CH), 127.4 (CH), 127.8 (CH), 128.5 (CH), 128.7 (CH), 130.0, 134.4, 136.2, 138.5, 140.0, 142.9, 171.5; *m/z* (ES+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17320 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.21. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-methylbiphenyl-4-yl)methanone (13f)

Off white amorphous solid; yield 69%; mp 185–188 °C; 6:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.19 (3H, br s), 2.77 (2H, br s), 4.85 (2H, br s), 6.96–7.54 (12H, m), 8.74 (1H, br s); *δ (distinct signals for minor rotamer*) 2.70 (2H, br s), 3.55 (2H, br s), 4.80 (2H, br s), 8.07 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 20.4 (CH_3), 22.1 (CH_2), 41.2 (CH_2), 46.1 (CH_2), 107.6, 111.1 (CH), 117.7 (CH), 119.4 (CH), 121.6 (CH), 125.8 (CH), 126.7, 126.8 (CH), 127.6 (CH), 129.4 (CH), 129.6 (CH), 130.0, 130.4 (CH), 134.3, 135.2, 136.3, 140.8, 143.7, 171.5; *m/z* (ES^+) 367 ($[M+H]^+$ 100%); *m/z* (FAB) 366.17316 (M^+ $C_{25}H_{22}N_2O$ requires 366.17321).

4.6.22. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(3′-methoxybiphenyl-4-yl)methanone (13g)

Pale yellow amorphous solid; yield 68%; mp 182–185 °C; 4:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.71 (2H, br s), 3.62 (2H, br s), 3.74 (3H, br s), 4.80 (2H, br s), 6.83–7.53 (12H, m), 8.78 (1H, br s); *δ (distinct signals for minor rotamer*) 3.97 (2H, br s), 4.49 (2H, br s), 8.25 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 22.0 (CH_2), 41.1 (CH_2), 46.0 (CH_2), 55.2 (CH_3), 107.8, 111.1 (CH), 112.8 (CH), 113.1 (CH), 117.7 (CH), 119.3 (CH), 119.5 (CH), 121.6 (CH), 126.7, 127.3 (CH), 127.4 (CH), 129.9 (CH), 130.0, 134.8, 136.2, 141.5, 142.6, 159.9, 171.3 (C=O); *m/z* (ES^+) 383 ($[M+H]^+$ 100%); *m/z* (FAB) 382.16821 (M^+ $C_{25}H_{22}N_2O_2$ requires 382.16813).

4.6.23. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2′-methoxybiphenyl-4-yl)methanone (13h)

Off white amorphous solid; yield 96%; mp 167–171 °C; 3:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.89 (2H, br s, CH_2), 3.81–3.85 (2H, m, CH_2), 5.01 (2H, br s, CH_2), 7.05–7.71 (12H, m, ArH), 9.14 (1H, br s); *δ (distinct signals for minor rotamer*) 2.96 (2H, br s, CH_2), 4.15 (2H, br s, CH_2), 4.60 (2H, br s CH_2), 8.42 (1H, br s); δ_C (75.5 MHz, $CDCl_3$), 22.0 (CH_2), 41.1 (CH_2), 46.0 (CH_2), 55.3 (OCH_3), 107.3, 111.1 (CH), 117.6 (CH), 119.1 (CH), 120.8 (CH), 121.4 (CH), 126.5 (CH), 126.6, 126.7 (CH), 129.1 (CH), 129.3, 129.6 (CH), 130.0, 130.7 (CH), 134.1, 136.2, 140.2, 156.2, 171.5; *m/z* (ES^+) 383 ($[M+H]^+$ 100%); *m/z* (FAB) 382.16814 (M^+ $C_{25}H_{22}N_2O_2$ requires 382.16813).

4.6.24. *N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*-methyl-4-(pyridin-4-yl)benzamide (14)

White solid; yield 68%; mp 195 °C; rotomers 1.6/1 (from the duplicated triplet signal at 3.47 and 3.75 ppm); δ_H (400 MHz, 363 K, $(CD_3)_2SO$) 2.97 (3H, s), 3.00 (2H, t, 6.7), 3.64 (2H, dd, 6.7, 6.7), 6.88 (1H, t, 7.4), 7.05 (1H, t, 7.4), 7.09 (1H, s), 7.35 (2H, d, 8.0), 7.37 (2H, d, 6.0), 7.67 (2H, d, 6.0), 7.73 (2H, d, 8.0), 8.66 (2H, d, 6.0), 10.55 (1H, br s); δ_C (75 MHz, CD_2Cl_2) *δ* (*major rotamer*) 24.5 (CH_2), 33.0 (CH_3), 52.1 (CH_2), 111.7 (CH), 111.9, 113.2, 118.4 (CH), 119.4 (CH), 122.2 (CH, 2C), 122.9 (CH), 127.1 (CH, 2C), 127.5 (CH, 2C), 128.1 (CH), 136.8, 137.7, 138.7, 147.9, 150.4 (CH, 2C), 171.8; *δ* (distinct peaks for *minor rotamer*) 23.3 (CH_2), 38.2 (CH_3), 48.8 (CH_2), 119.0 (CH), 122.8 (CH, 2C), 127.4 (CH, 2C); *m/z* (ES^+) 356 ($M+H^+$), (ES^-) 354 ($M-H^-$); *m/z* (FAB) 356.17627 ($M+H^+$ $C_{23}H_{22}N_3O$ requires 356.17629). Found: C, 77.80; H, 5.86; N, 11.90. $C_{23}H_{21}N_3O$ requires C, 77.72; H, 5.96; N, 11.82%.

4.6.25. *N*-(2-(1*H*-Indol-3-yl)ethyl)-3-(pyridin-3-yl)benzamide (15)

White solid; yield 80%; mp 59 °C; δ_H (300 MHz, $(CD_3)_2SO$) 3.04 (2H, t, 7.2), 3.64 (2H, t, 7.2), 7.04 (1H, td, 7.9, 1.2), 7.13 (1H, td, 7.0, 1.2), 7.25 (1H, s), 7.41 (1H, d, 7.9), 7.57–7.72 (3H, m), 7.94 (2H, dd, 7.9, 2.0), 8.17 (2H, dd, 7.9, 2.0), 8.66 (1H, s), 8.87 (1H, t, 6.0), 8.99 (1H, br s), 10.87 (1H, br s); δ_C (75 MHz, 363K, $CDCl_3$) 25.2 (CH2), 40.7 (CH2), 111.5 (CH), 112.7, 118.7, 119.4 (CH), 122.1 (CH), 125.9 (CH), 126.5 (CH), 127.4, 128.5 (CH), 129.3 (CH), 129.8 (CH), 132.0 (CH), 134.5 (CH), 135.7, 136.6, 138.0, 148.0 (CH), 148.6 (CH), 167.3; *m/z* (ES^+) 342 ($M+H^+$), (ES^-) 340 ($M-H^-$); *m/z* (FAB) 342.16061 ($M+H^+$ $C_{22}H_{20}N_3O$ requires 342.16064). Found: C, 74.33; H, 5.28; N, 11.70. $C_{22}H_{19}N_3O$ requires C, 77.40; H, 5.61; N, 12.31%.

4.6.26. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2-(pyridin-4-yl)phenyl)methanone (16a)

Off white amorphous solid; 73% yield; mp 135–138 °C; 2.0:1.0 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.14–2.21 (1H, m), 2.61–2.64 (1H, m) 3.11 (1H, br s), 3.51 (1H, br s), 4.35 (1H, d_{AB}, *J* 15.8), 5.12 (1H, d_{AB}, *J* 16.2), 7.02–7.70 (10 H, m), 8.59 (2H, br s), *δ (distinct signals for minor rotamer*) 2.68 (1H, br s), 2.76 (1H, br s), 3.90–3.93 (2H, m), 3.98–4.04 (1H, m), 4.20–4.25 (1H, m), 8.33 (2H, br s); δ_C (75.5 MHz, $CDCl_3$) 21.5 (CH_2), 40.2 (CH_2), 44.9 (CH_2), 107.1, 111.0 (CH), 117.6 (CH), 119.2 (CH), 121.5 (CH), 123.3 (CH), 126.4, 127.2 (CH), 128.4 (CH), 129.1 (CH), 129.3, 129.4 (CH), 129.7 (CH), 132.0 (CH), 135.5, 135.9, 136.3, 147.6, 149.6 (CH), 170.0; *δ (distinct signals for minor rotamer*) 20.5 (CH), 40.4 (CH), 45.0 (CH), 108.8, 110.7 (CH), 118.0 (CH), 119.5 (CH), 121.8 (CH), 123.0 (CH), 126.6, 127.2 (CH), 128.6 (CH), 128.6, 129.0 (CH), 129.2 (CH), 129.7 (CH), 131.9 (CH), 135.5, 136.0, 136.1, 147.2, 149.1 (CH), 169.4; *m/z* (ES+) 354 ($[M+H]^+$, 100%); *m/z* (FAB) 354.16054 ($M+H^+$ $C_{23}H_{20}N_3O$ requires 354.16064).

4.6.27. (3,4-Dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(2-(pyridin-3-yl)phenyl)methanone (16b)

Off white amorphous solid; 54% yield; 2:1 mixture of rotamers; δ_H (300 MHz, $CDCl_3$) 2.15–2.20 (1H, m), 2.50–2.55 (1H, m), 3.04–3.10 (1H, m), 3.40–3.45 (1H, m), 4.36 (1H, d_{AB}, *J* 16.8), 5.02 (1H, d_{AB}, *J* 16.8), 6.88–7.61 (10 H, m), 8.42–8.44 (2H, m), 8.66–8,67 (1H, m), 9.08 (1H, br s), *δ (distinct signals for minor rotamer*) 2.62–2.66 (1H, m), 2.53–2.54 (1H, m), 3.69–3.76 (1H, m), 3.86–3.97 (2H, m), 4.09–4.14 (1H, m), 8.07–8.08 (1H, m, Ar), 8.46 (1H, br s), 8.53 (1H, br s); δ_C (75.5 MHz, $CDCl_3$) 21.4 (CH_2), 40.3 (CH_2), 44.9 (CH_2), 107.3, 108.6, 111.0 (CH), 117.7 (CH), 119.2 (CH), 121.5 (CH), 123.3 (CH), 126.5, 127.3 (CH), 128.6 (CH), 129.4, 129.7 (CH), 131.9 (CH), 135.1, 135.5, 135.7, 136.0 (CH), 148.7 (CH), 148.9 (CH), 170.2; *δ (distinct signals for minor rotamer*) 20.6 (CH_2), 40.4 (CH_2), 44.8 (CH_2), 107.3, 108.6, 110.9 (CH), 117.8 (CH), 119.3 (CH), 121.7 (CH), 122.9 (CH), 126.7, 127.5 (CH), 128.4 (CH), 129.4 (CH), 129.7 (CH), 129.4, 132.0 (CH), 134.8, 136.1, 136.3, 148.0 (CH), 148.9 (CH), 169.5; *m/z* (ES+) 354 ($[M+H]^+$, 100%); *m/z* (FAB) 354.16066 ($M+H^+$ $C_{23}H_{20}N_3O$ requires 354.16064).

Acknowledgments

This work was made possible by financial support from Cancer Research UK. We are also grateful to Johnson Matthey PLC ("JM") for the kind loan of palladium chloride; M.D.G. thanks the Xunta de Galicia (Programa Isidro Parga Pondal) for financial support.

References

1. (a) Huwe, A.; Mazitschek, R.; Giannis, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2122; (b) DePinto, W. et al *Mol. Cancer Ther.* **2006**, *5*, 2644; (c) Vander Wel, S. N. et al *J. Med. Chem.* **2005**, *48*, 2371; (d) Honma, T. et al *J. Med. Chem.* **2001**, *44*, 4628; (e) Toogood, P. L. et al *J. Med. Chem.* **2005**, *48*, 2388.
2. Grillo, M.; Bott, M. J.; Khandke, N.; McGinnis, J. P.; Miranda, M.; Meyyappan, M.; Rosfjord, E. C.; Rabindran, S. K. *Breast Cancer Res. Treat.* **2005**, *95*, 185.
3. Roll, D. M.; Ireland, C. M.; Lu, H. S. M.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 3276–3278.
4. Segraves, N. L.; Lopez, S.; Johnson, T. A.; Said, S. A.; Fu, F.; Schmitz, F. J.; Pietraszkiewich, H.; Valeriote, F. A.; Crews, P. *Tetrahedron Lett.* **2003**, *44*, 3471.
5. Fretz, H.; Ucci-Stoll, K.; Hug, P.; Schoepfer, J.; Lang, M. *HeIv. Chim. Acta* **2000**, *83*, 3064.
6. Fretz, H.; Ucci-Stoll, K.; Hug, P.; Schoepfer, J.; Lang, M. *HeIv. Chim. Acta* **2001**, *84*, 867.
7. Soni, R.; Muller, L.; Ferut, P.; Schoepfer, J.; Stephan, C.; Zumstein-Mecker, S.; Fretz, H.; Chaudhuri, B. *Biochem. Biophys. Res.* **2007**, *275*, 877.
8. Hormann, A.; Chaudhuri, B.; Fretz, H. *Bioorg. Med. Chem.* **2001**, *9*, 917.
9. (a) Aubry, C. A.; Jenkins, P. R.; Mahale, S.; Chaudhuri, B.; Marechal, J.-D. ; Sutcliffe, M. J. *Chem. Commun.* **2004**, *15*, 1696; (b) Aubry, C. A.; Wilson, A. J.; Jenkins, P. R.; Mahale, S.; Chaudhuri, B.; Maréchal, J.-D.; Sutcliffe, M. J. *Org. Biomol. Chem.* **2006**, *4*, 787; (c) Garcia, M. D.; Wilson, A. J.; Emmerson, D. P. G.; Jenkins, P. R. *Chem. Commun.* **2006**, *24*, 2586; (d) Garcia, M. D.; Wilson, A. J.; Emmerson, D. P. G.; Jenkins, P. R.; Mahale, S.; Chaudhuri, B. *Org. Biomol. Chem.* **2006**, *424*, 4478.
10. Mahale, S.; Wilson, A. J.; Aubry, C.; Maréchal, J.-D.; Sutcliffe, M. J.; Chaudhuri, B.; Jenkins, P. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4272.
11. Davies, T. G.; Pratt, D. J.; Endicott, J. A.; Johnson, L. N.; Noble, M. E. M. *Pharmacol. Ther.* **2002**, *93*, 125.
12. Suzuki, A. *Chem. Commun.* **2005**, 4759.
13. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
14. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
15. Schultz, P. G.; Wu, T. Y. H. *Org. Lett.* **2002**, *4*, 4033.
16. Weinstein, D. S.; Liu, W.; Gu, Z.; Langevine, C.; Ngu, K.; Fadnis, L.; Combs, D. W.; Sitkoff, D.; Ahmad, S.; Zhuang, S.; Chen, X.; Wang, F.-L.; Loughney, D. A.; Atwal, K. S.; Zahler, R.; Macor, J. E.; Madsen, C. S.; Murugesan, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1435.
17. Jiang, W.; Sui, Z.; Macielag, M. J.; Walsh, S. P.; Fiordeliso, J. J.; Lanter, J. C.; Guan, J.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; Craig, E.; Haynes-Johnson, D.; John, T. M.; Clancy, J. *J. Med. Chem.* **2003**, *46*, 441.
18. Phelps, D.; Xiong, Y. *Methods Enzymol.* **1996**, *283*, 194.
19. Meijer, L.; Borgne, A.; Mulner, O.; Chong, J. P. J.; Blow, J. J.; Inagaki, N.; Inagaki, M.; Delcros, J. G.; Moulinoux, J. P. *Eur. J. Biochem.* **1997**, *243*, 527.
20. Boris, S.; Richard, L.; Robert, L. S. *J. Biol. Chem.* **1997**, *272*, 33327.
21. Grisar, . M.; Petty, M. A.; Bolkenius, F. N.; Dow, J.; Wagner, J.; Wagner, E. R.; Haegele, K. D.; Dejong, W. *J. Med. Chem.* **1991**, *34*, 257.