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γ-Carboline AC190 analogues via palladium catalysed allene insertion stereo and regioselective 3- and 5- component cascades

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ABSTRACT

γ-Carbolines were prepared from pyrido[4,3-b]-5H-indoles via Pd(0)-catalysed, stereo and regioselective allene/uridine allene insertion 3- and 5- component cascades. This versatile reaction sequence gives a range of structurally diverse carboline derivatives and tolerates a broad range of substrates. The power of this approach has been harnessed to produce γ-carboline based HDAC inhibitors.

Keywords: γ-Carbolines, palladium catalysed, HDAC inhibitor, uridine allene, cascade chemistry

1. Introduction

Interest in β- and γ- carbolines (pyrido[4,3-b]-5H-indoles) and their analogues has increased considerably over the last decade primarily due to their wide ranging biological and pharmacological properties.[1-3] For instance, biologically active γ-tetrahydrocarboline derivatives include the antihistamines Mebhydrolin (Diazoline)[9] **1** and Dimebolin (Latrepirdine) **2**, the latter system showing potential in the treatment of Alzheimer's disease and other neurodegenerative diseases.[4,5] Additionally, Flutroline **3** has been used in the treatment of schizophrenia,[7a] and Tubastatin A **4** and its analogues have been shown to selectively inhibit histone deacetylase 6 (HDAC6),[8] and may hold promise in the treatment of certain cancers (Figure 1).

Furthermore, a series of putative HDAC inhibitors bearing α- and γ- carboline scaffolds has recently been patented for use as anti-cancer therapeutics by Grigg,[10] with the most promising candidates being AC148 (**5**) and AC190 (**6**). An important requirement for biological activity within these systems appears to be the presence of a benzamide moiety, which is thought to bind to zinc ion present in the active site of the HDAC enzyme.

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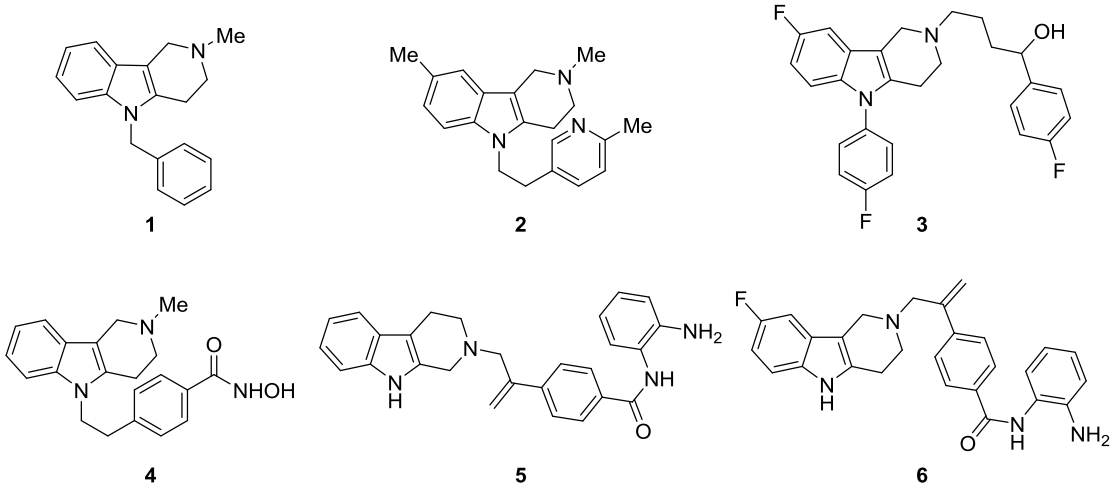


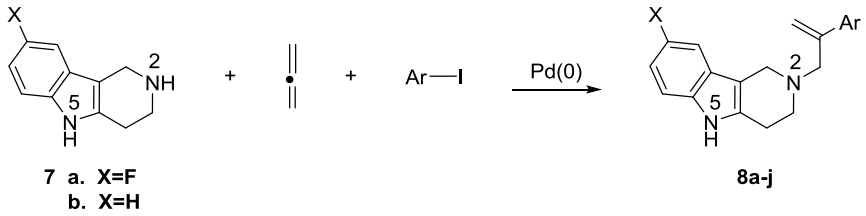
Figure 1. Biologically active carboline compounds.

We have previously described a powerful and versatile approach to a range of functionalised heterocycles based upon the use of a palladium-catalysed allene insertion multicomponent cascade.[11-15] As indicated above, we were able to utilise this chemistry to prepare novel carboline-based molecules, exemplified by AC190 **6** that are showing promise as anticancer drug leads. Encouraged by the ease with which these systems could be obtained, we wished to further explore the scope of this approach to such biologically active carboline systems with a view to identifying additional examples of HDAC inhibitors of therapeutic potential. Herein, we describe the application of this methodology to the production of a range of γ-tetrahydrocarboline-based derivatives.

2. Results and discussion

The γ-tetrahydrocarboline **7** was used along with a series of aryl or heteroaryl iodides and allene or uridine allene to generate a wide range of structurally diverse compounds via 3- and 5-component cascades.

For the 3-component cascade (Scheme 1), reaction of 8-fluoro-γ-tetrahydrocarboline **7a** or unsubstituted γ-tetrahydrocarboline **7b** (1.0 mmol), with a series of aryl/heteroaryl iodides (0.98 mmol) and allene (0.5 atm), catalysed by $Pd_2(dba)_3$ (2.5 mol%) and tri-2-furylphosphine (TFP) (5 mol%) with caesium carbonate or potassium carbonate (2 mmol) as the base, gave the resulting adducts (**8a-j)** in 64–78 % yield (Table 1, entries 1-10). All the cascades were regioselective in terms of producing products resulting from coupling at the aliphatic amine nitrogen.

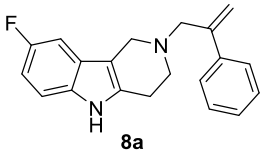
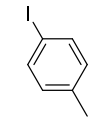
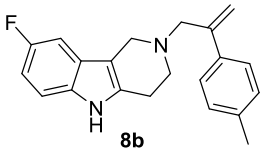
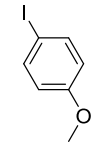
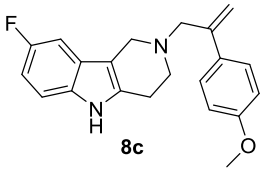
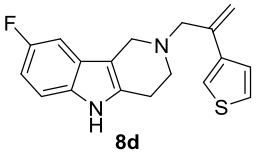
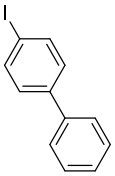
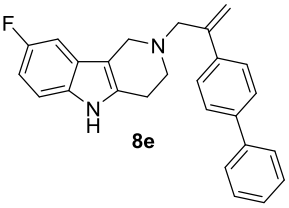
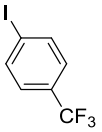
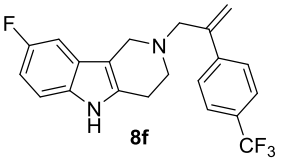
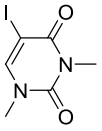
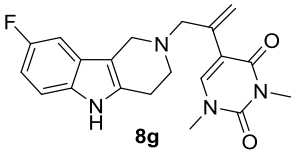
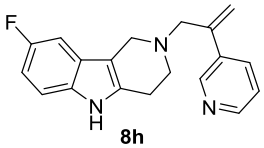


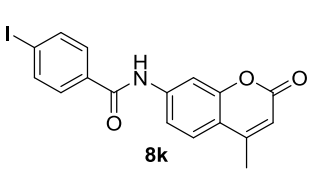
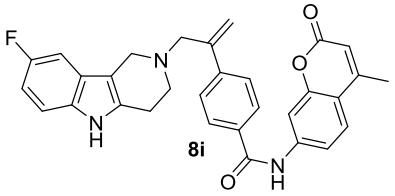
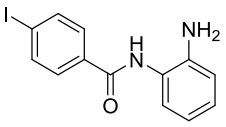
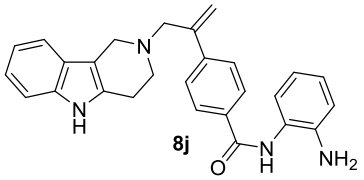
7 a. X=F
b. X=H

8a-j

Scheme 1: γ-Tetrahydrocarboline 3-component cascade reaction.

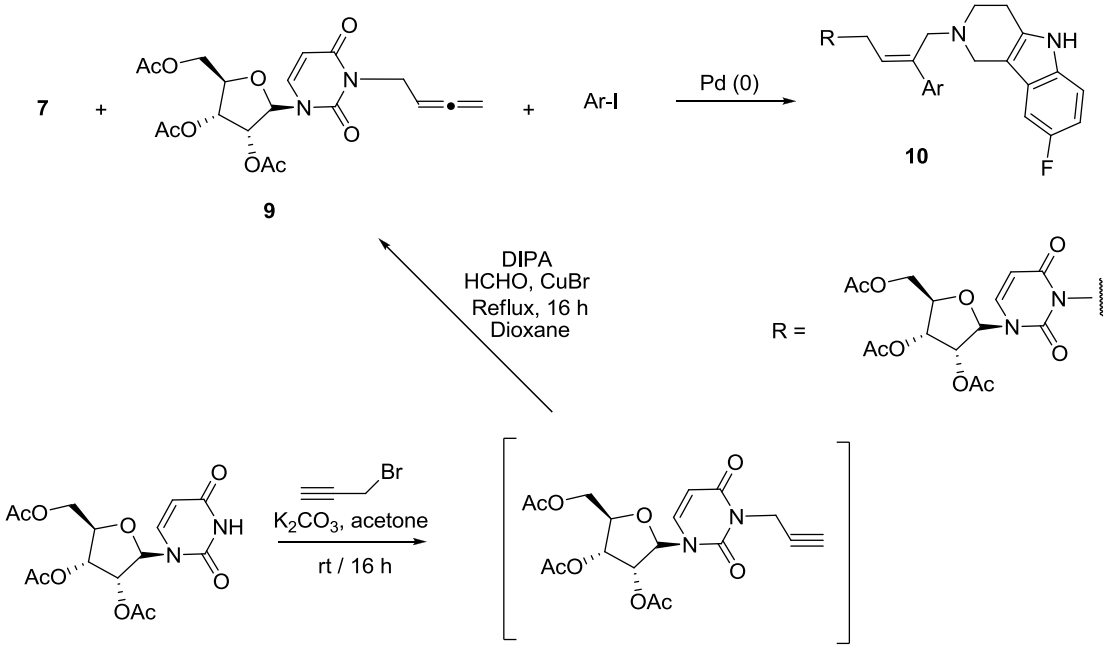
Table 1: 3-Component cascade synthesis of **8a-i**[a]

Entry	Ar	Compound	Yield (%)
1		 **8a**	72
2		 **8b**	69
3		 **8c**	70
4		 **8d**	78
5		 **8e**	65
6		 **8f**	67
7		 **8g**	74
8		 **8h**	77

9	 **8k**	 **8i**	64
10	 **8l**	 **8j**	72

a. **7a/7b** (1.0 mmol), Ar-I (0.98 mmol), Pd(0) (2.5 mol%)/ligand (5 mol%) base (2 mmol), MeCN (20 mL) at 80 °C for 18 h

Additionally, we wished to explore the feasibility of incorporating biologically important building blocks into this sequence. Thus, an analogous cascade process involving reaction of **7a** with aryl iodides and uridine-based allene (**9**)[15a] (Scheme 2) was also investigated, which would give access to interestingly functionalised nucleoside analogues such as **10,** (the predicted Z-stereochemistry within the alkene being based upon our previous observations[15b]), (Scheme 2).

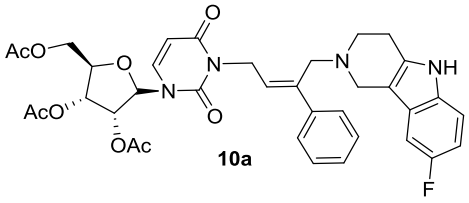
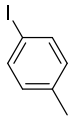
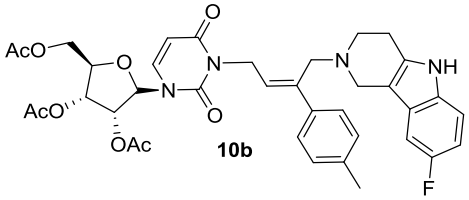
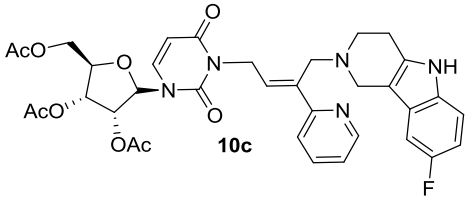
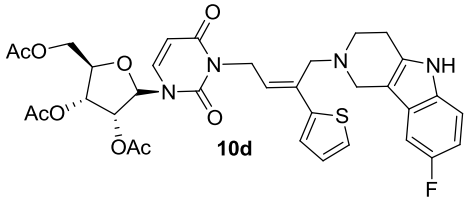
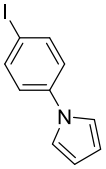
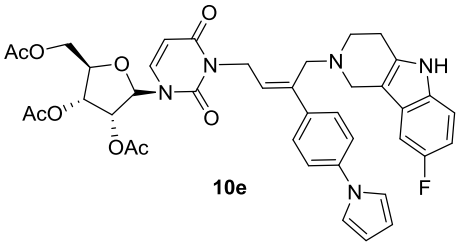


Scheme 2: γ-tetrahydrocarboline 3-component cascade reaction using uridine allene **9**.

The uridine allene **9** was readily prepared from uridine, 2',3',5'-triacetate via N-propargylation followed by homologation of the terminal alkyne using a cuprous bromide-catalysed reaction[16] with formaldehyde and diisopropylamine (DIPA) via a giving the uridine allene **9** in 55% yield (Scheme 2).

Compounds **10a-e** were readily prepared from γ-carboline (**7a**) and uridine allene (**9**)[15a] (Table 2, entry 1-5).

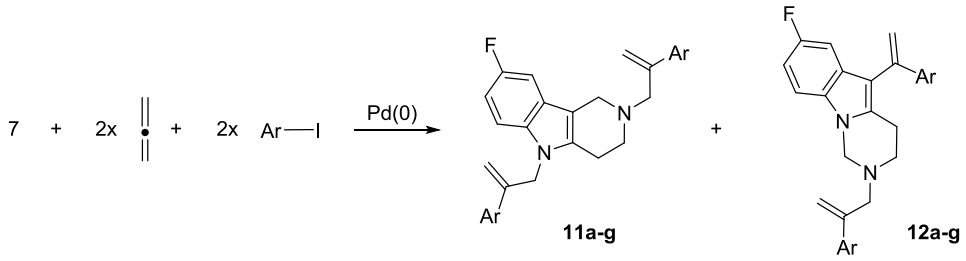
Table 2: 3 – Component cascade synthesis of **10a-e**[a]

Entry	Ar	Compound	Yield (%)
1		 **10a**	69
2		 **10b**	72
3		 **10c**	69
4		 **10d**	70
5		 **10e**	81

a. **7a** (1.0 mmol), Ar-I (0.98 mmol), $Pd_2(dba)_3$ (2.5 mol%)/ligand (5 mol%) base (2 mmol), MeCN (20 mL) at 80 °C for 3-7 h.

In order to further probe the range of structural diversity possible within this approach, a 5-component variant (defined in terms of utilising amine **7**, plus two molecules each of allene and aryl iodide respectively), of the cascade reaction was investigated and a third series of analogues (Table 3, entry 1-7) were prepared via 5-component cascades by using two equivalents of both aryl iodide and allene, with Cs_2CO_3 as base under similar reaction conditions to that used for the 3-component

cascades already described (Scheme 3). This cascade produced the anticipated products **11a-g** along with the rearrangement products, pyrimidino[1,6-a]indoles **12a-g,** as an approximately 1:1 mixture of **11**:**12** type compounds (Table 3, entries 1-7) in 48-66% yield. The ratio of products within in each case was determined using ^{1}H-NMR analysis of the crude reaction mixtures, prior to isolation of the isomers using column chromatography .



Scheme 3: 5-Component cascade reaction.

The structures of the two reaction products were confirmed in the case of **11b** and **12a** via single crystal x-ray crystallography (Figure 2).

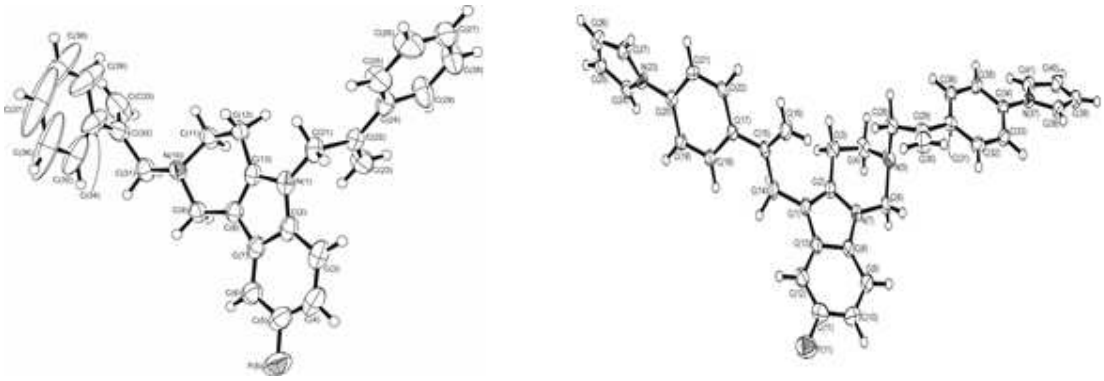
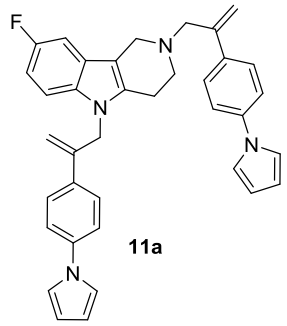
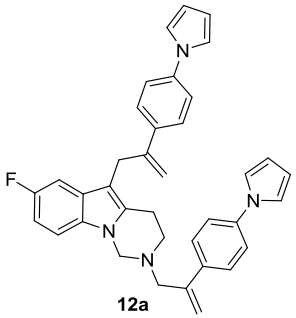
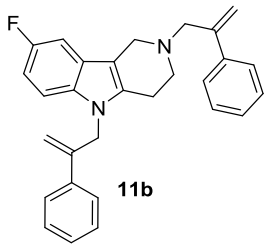
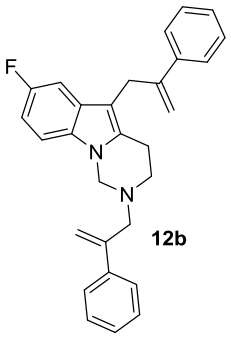
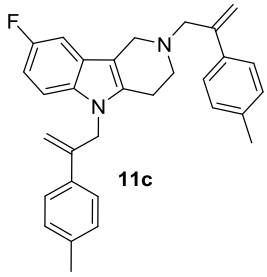
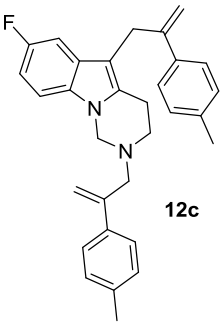
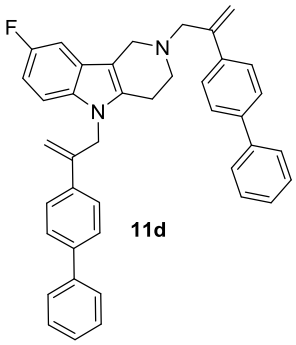
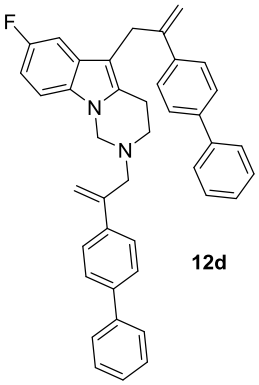
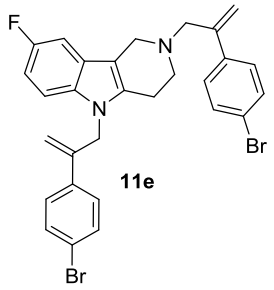
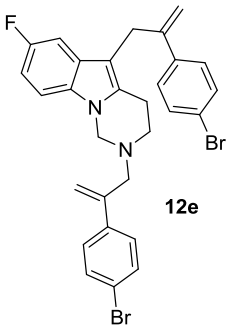
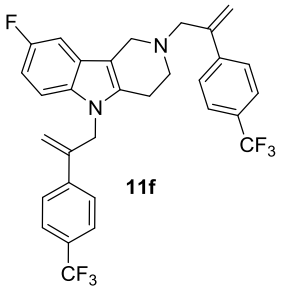
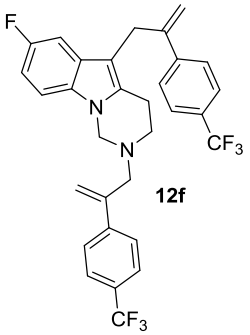
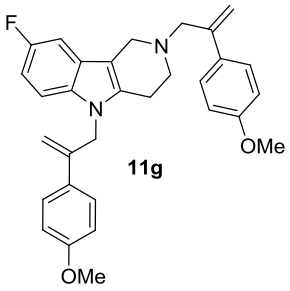
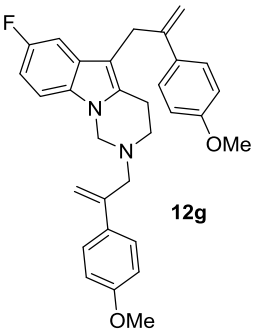


Figure 2. X-ray crystal structures of **11b** (left) and **12a** (right).

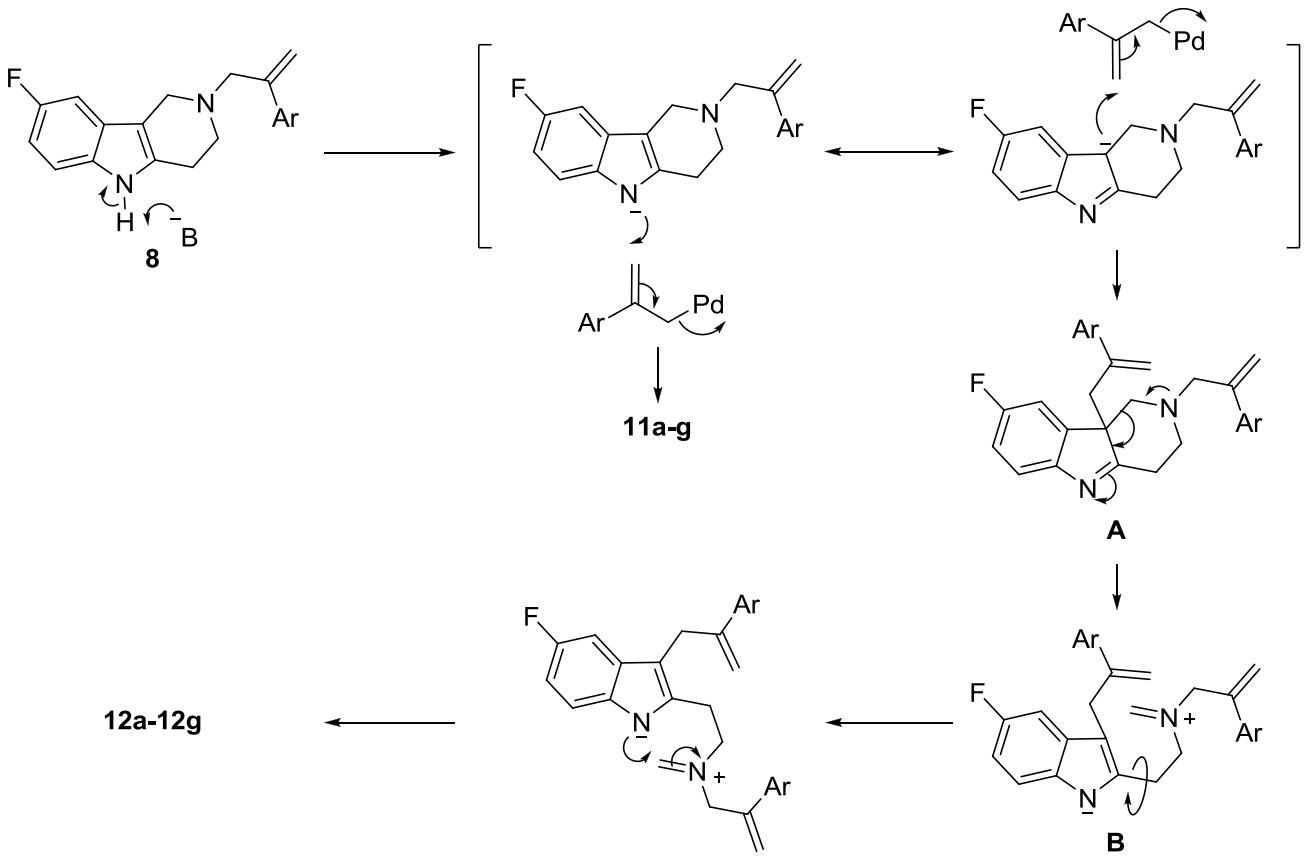
Table 3: 5-Component cascades products.[a]

Entry	Compounds		Yield (%)	Ratio of Products (%)
				95 : 96
1	 **11a**	 **12a**	62	47 : 53
2	 **11b**	 **12b**	65	50 : 50
3	 **11c**	 **12c**	62	50 : 50
4	 **11d**	 **12d**	48	45 : 55

5	 **11e**	 **12e**	55	50 : 50
6	 **11f**	 **12f**	54	46 : 54
7	 **11g**	 **12g**	66	50 : 50

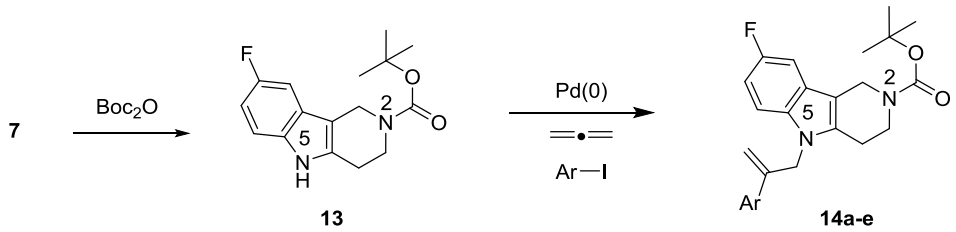
a. **7** (1.0 mmol), Ar-I (1.98 mmol), Pd(0) (5 mol%)/ligand (10 mol%), Cs_2CO_3 (4 mmol), MeCN (10 mL), 80 °C for 30 h.

A mechanism is proposed (Scheme 4) for formation of **12**. A palladium π–allyl coordinates to the indole double bond of the carboline and the indole lone pair triggers transfer of the allyl group to the 3–position of the indole to give intermediate **A** which initiates cleavage of the aliphatic ring to give **B**. Rotation of the iminium moiety facilitates ring closure with the indole nitrogen to give **12**.



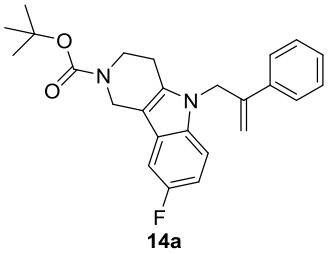
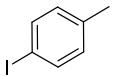
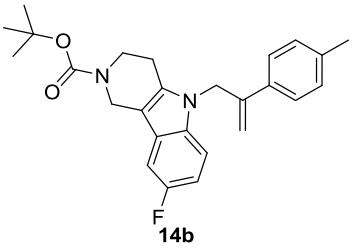
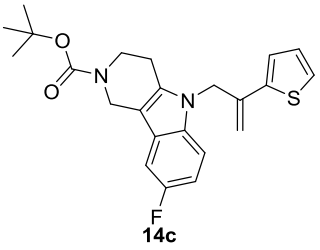
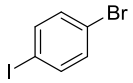
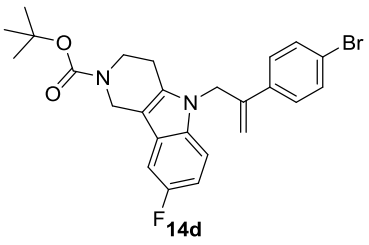
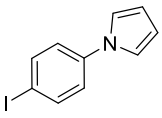
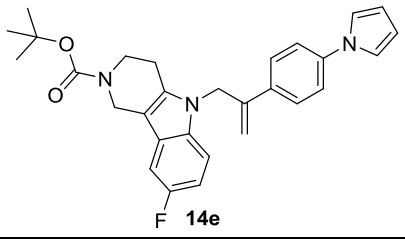
Scheme 4: Proposed mechanism of formation of **11a-g** and **12a-g.**

Protection of the aliphatic amine of **7** as the t-butyl carbamate derivative was investigated as a route to produce the γ-carboline product as opposed to the pyrimidino[1,6-a]indole rearrangement product. The BOC protected γ-carboline **13** was generated and successfully allylated at the 5-position giving **14a-e** in 69–81% yield (Table 5, entry 1-5) under similar reaction conditions to those previously described (Scheme 5) without formation of rearrangement product.



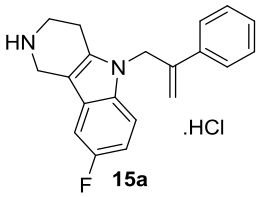
Scheme 5: Boc protection strategy for synthesis of substituted carbolines without formation of rearrangement products

Table 4: Boc protected 3 component cascade products[a]

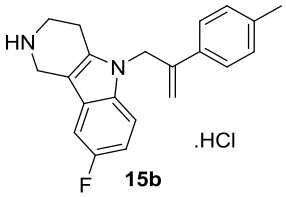
Entry	Ar	Compound	Yield (%)
1		 **14a**	72
2		 **14b**	69
3		 **14c**	81
4		 **14d**	78
5		 **14e**	74

a. **13** (1.0 mmol), Ar-I (0.98 mmol), Pd(0) (2.5 mol%)/ligand (5 mol%), Cs_2CO_3 (2 mmol), MeCN (10 mL), 80 °C for 16 h.

Deprotection of compounds **14a** and **14b** by addition of 10% HCl solution and heating to 60°C in methanol for 2 h and removal of methanol gave **15a** and **15b** as the hydrochloride salts in 85% and 90% yield respectively.



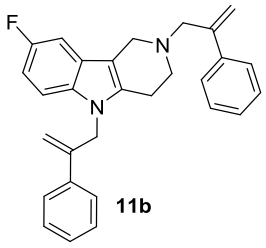
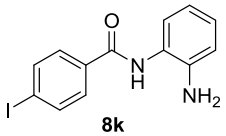
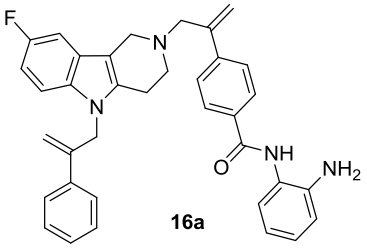
15a

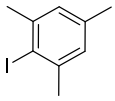
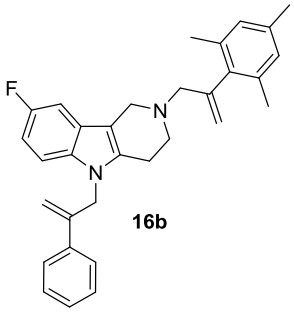
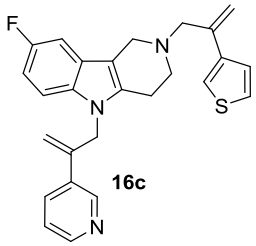


15b

Finally, a 3-component cascade was employed to generate γ-tetrahydrocarboline compounds with substituents at the 2- and 5-positions. The 3- component palladium catalysed cascade used **15a** (1 mmol) and aryl iodide (1.98 mmol), Pd(0) (2.5 mol%)/ligand (5 mol%), Cs_2CO_3 (2 mmol), MeCN (10 mL), 80 °C for 16 h to generate **11b**, **16a** and **16b)** in 51–79% yield (Table 5 entries 1-3). An example of modification of the 5-position was also reported under smilar reaction conditions starting from **8d** with 3-iodopyridine afforded **16c** in 69% yield (Table 5, entry 4). The reactions gave exclusively the desired products (**11b, 16a-c)** in high yield.

Table 5: 3-component cascades products substituted at the 3- and 5- positions.[a]

Entry	Ar	Compound	Yield (%)
1		 **11b**	75
2	 **8k**	 **16a**	51

3		 **16b**	79
4		 **16c**	69

a. **15a** (1.0 mmol), Ar-I (0.98 mmol), Pd(0) (2.5 mol%)/ligand (5 mol%), Cs_2CO_3 (2 mmol), MeCN (10 mL), 80 °C for 16 h.

Biological testing

Three of the previously described γ-carbolines (**8i**, **8j** and **16a**) were biologically assessed for their potential as HDAC inhibitors. HDAC selectivity profiling was carried out by Scottish Biomedical (Table 6) using a fluorimetric assay. The compounds were preincubated with enzyme for a period of 24 hours and the screen was run in duplicate.

Compounds **8j** and **16a**, which both have a benzamide moiety as their zinc binding group, both displayed inhibition of HDAC3 and HDAC2 respectively. Compound **8i** which possess a coumarin moiety in place of the benzamide group, showed no inhibitory effect on any of the HDACs tested. No inhibition of the HDAC1 isoform was observed. Compounds **8i** and **16a** were slightly more active against HDAC3 than HDAC2 and this, coupled with their lack of activity against HDAC1 indicates that it may be possible to develop these compounds into selective HDAC inhibitors.

Table 6: HDAC inhibition profiling.

Entry	Compound	**% Inhibition HDAC** 10μM		
		HDAC1	HDAC2	HDAC3
1	**8i**	0	0	0
2	**8j**	0	42.8 ± 0.1	97.1 ± 1.6
3	**16a**	0	10.1 ± 0.5	35.6 ± 1.1

3. Conclusion

A series of allylic γ-carbolines have been synthesised via efficient 3- and 5-component palladium catalysed cascade reactions leading to the creation of a range of substituted carboline-based compounds, some of which were designed to be analogues of known antitumor agents proposed to act as HDAC enzyme inhibitors.[10] These cascade reactions tolerate a broad range of substrates providing ready access to diversely substituted carboline scaffolds. Biological testing of a selected number of these systems showed inhibition of HDAC3 and HDAC2 for the most active compounds, indicating their potential as starting points for the development of future anticancer drugs.

4. Experimental

Column chromatography was performed on silica gel 60 (Merck, 230-400 mesh). ^{1}H NMR spectra were recorded at 500 MHz on a Bruker DPX500 instrument or at 300 MHz on a Bruker DPX300 instrument. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument. All spectra were obtained for $CDCl_3$ solutions unless stated otherwise. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (0.00 δ). Infra-red spectra were collected on a Perkin-Elmer Spectrum One FT-IR spectrometer. Samples were run as thin films on sodium chloride plates and were prepared by evaporation of a solution of compound in dichloromethane. Melting points were obtained on a Reichert hot-stage microscope and are uncorrected. Mass spectra were obtained on a Bruker, HCT-ultra (ES+). Accurate masses were obtained using a Bruker Daltonics micrOTOF spectrometer. Commercially available compounds were used as received. All compounds are named according to the IUPAC system; names were obtained using MDL Autonom.

General procedure A: 3-Component cascade.

Aryl iodide (1 mmol), nucleophile (0.8–1.2 mmol), tris-(2-furyl)-phosphine (TFP) (10 mol%), tris-dibenzylideneacetonedipalladium (0) (Pd_2dba_3) (2.5 mol%), base (2 mmol) and MeCN (20 mL) were combined in a Schlenk tube. After two freeze-pump-thaw cycles, allene gas (0.5 atm) was charged into the Schlenk tube, the mixture

thawed and then heated for 16-24 h at 70-80°C with magnetic stirring. After cooling to room temperature and venting excess allene, DCM (10 mL) was added, the mixture filtered, and the filtrate evaporated in vacuo. Column chromatography of the residue afforded the product.

General procedure B: 3-Component cascade - functionalized allene.

Aryl iodide (1 mmol), nucleophile (0.8–1.2 mmol), tris-(2-furyl)-phosphine (TFP) (10 mol%), functionalised allene (1–1.2 mmol), tris-dibenzylideneacetonedipalladium (0) (Pd_2dba_3) (2.5 mol%), base (2 mmol) and MeCN (20 mL) were combined in a RB flask and the mixture heated for 16–24 h at 70–80 °C with magnetic stirring. After cooling to room temperature and venting excess allene, DCM (10 mL) was added, the mixture filtered, and the filtrate evaporated in vacuo. Column chromatography of the residue afforded the pure product.

General procedure C: 5-Component cascade.

As for General Procedure A except that aryl iodide (2.0 mmol), nucleophile (0.8–1.2 mmol) and base (4 mmol) were employed.

8-Fluoro-2-(2-phenylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8a)

Prepared using General Procedure A from 4-iodobenzene (0.204 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.10 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / ether gave the product (R_f 0.20) as a pale yellow oil (0.221 g, 72%); δ_H (300 MHz, $CDCl_3$) 7.71 (br. s, 1H, NH), 7.55 (dd, 2H, J 8.1, 1.4, aryl CH), 7.26 (m, 3H, aryl CH), 7.07 (dd, 1H, J 8.9, 4.4, aryl CH), 7.01 (dd, 1H, J 9.6, 2.4, aryl CH), 6.80 (ddd, 1H, J 9.1, 8.9, 2.4, aryl CH), 5.52 (d, 1H, J 1.3, allyl CH), 5.33 (d, 1H, J 1.3, allyl CH), 3.68 (s, 2H, alkyl CH_2), 3.61 (s, 2H, alkyl CH_2), 2.86 (t, 2H, J 5.7, alkyl CH_2), 2.69 (t, 2H, J 5.7, alkyl CH_2); δ_C 157.5 (d, J 234), 144.6, 140.3, 134.4, 132.4, 128.9 (2C), 127.6, 126.3 (d, J 9.0), 125.9 (2C), 115.2, 111.0 (d, J 9.8), 109.1 (d, J 25.5), 109.0, 102.5 (d, J 24.5), 62.2, 49.9, 49.5, 23.7;

ν_{max}(film) 3423, 2900, 2092, 1634, 1484, 1458, 1324, 1264 cm^{-1}; m/z (ES^+) 307.2 (100%, MH^+); HRMS (ES^+): MH^+, found 307.1618. $C_{20}H_{20}FN_2$ requires 307.1605.

8-Fluoro-2-(2-p-tolylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8b)

Prepared using General Procedure A from 4-iodotoluene (0.218 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / ether gave the product (R_f 0.25) as a pale yellow oil (0.221 g, 69%). δ_H (300 MHz, $CDCl_3$) 7.73 (br. s, 1H, NH), 7.46 (d, 2H, J 8.2, aryl CH), 7.13 (d, 2H, J 8.2, aryl CH), 7.07 (dd, 1H, J 6.1, 9.3, aryl CH), 7.00 (dd, 1H, J 9.6, 2.5, aryl CH), 6.83 (ddd, 1H, J 9.3, 9.0, 2.5, aryl CH), 5.50 (d, 1H, J 1.4, allyl CH), 5.29 (d, 1H, J 1.4, allyl CH), 3.69 (s, 2H, alkyl CH_2), 3.61 (s, 2H, alkyl CH_2), 2.90 (t, 2H, J 5.6, alkyl CH_2), 2.77 (t, 2H, J 5.6, alkyl CH_2), 2.32 (s, 3H, alkyl CH_3); δ_C 158. 2 (d, J 234), 144.9, 137.8, 137.7, 134.8, 132.9, 129.3 (2C), 126.9 (d, J 9.7), 126.6 (2C), 115.1, 111.4 (d, J 9.8), 109.6, 109.4 (d, J 26.1), 103.1 (d, J 23.5), 62.7, 50.3, 49.9, 24.1, 21.5; ν_{max}(film) 3419, 3086, 3024, 2911, 2815, 2754, 1903, 1828, 1625, 1590, 1514, 1479 cm^{-1}; m/z (ES^+) 321.2 (100%, MH^+); HRMS (ES^+): MH^+, found 321.1753. $C_{21}H_{22}FN_2$ requires 321.1762.

8-Fluoro-2-(2-(4-methoxyphenyl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8c)

Prepared using General Procedure A from 4-iodoanisole (0.234 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.10 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Chromatography eluting with 2:1 v/v hexane / ether gave the product (R_f.0.45) as a pale yellow oil (0.235 g, 70%). δ_H (300 MHz, $CDCl_3$) 7.83 (br. s, 1H, NH), 7.52 (d, J 8.9, 2H, aryl CH), 7.12 (dd, J 8.7, 4.4, 1H, aryl CH), 7.01 (dd, J 9.6, 2.5, 1H, aryl CH), 6.84–6.79 (m, 3H, aryl CH), 5.45 (d, J 1.4, 1H, allyl CH), 5.24 (d, J 1.4, 1H, allyl CH), 3.77 (s, 3H, OCH_3), 3.68 (s, 2H, alkyl CH_2), 3.59 (s, 2H, alkyl CH_2), 2.88 (t, J 5.5, 2H, alkyl CH_2), 2.74 (t, J 5.5, 2H, alkyl CH_2); δ_C 159.7, 158.2 (d, J 233.8), 144.3, 134.8, 133.2, 132.9, 127.8 (s, 2C), 127.0 (d, J 9.8), 114.2, 114.0 (s, 2C), 111.4 (d, J 9.7), 109.7 (d, J 4.5), 109.4 (d, J 26.1), 103.1 (d, J 23.6), 62.8, 55.6, 50.2, 49.9, 24.2; ν_{max}(film) 3418,

3083, 3021, 2908, 1905, 1830, 1583 cm^{-1}; m/z (ES^+) 337.2 (100%, MH^+); HRMS (ES^+): MH^+, found 337.1706. $C_{21}H_{22}FN_2O$ requires 337.1711.

8-Fluoro-2-(2-(thiophen-3-yl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8d)

Prepared using General Procedure A from 3-iodothiophene (0.210 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / ether gave the product (R_f 0.33) as a pale yellow oil (0.272 g, 78%); δ_H (300 MHz, $CDCl_3$) 8.08 (br. s, 1H, NH) 7.55 (dd, 1H, J 3.0, 1.2, aryl CH), 7.30 (d, 1H, J 5.0, aryl CH), 7.20 (dd, 1H, J 5.0, 3.0, aryl CH), 7.09 (dd, 1H, J 8.7, 4.7, aryl CH), 7.00 (dd, 1H, J 9.6, 2.5, aryl CH), 6.80 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 5.54 (s, 1H, allyl CH), 5.26 (s, 1H, allyl CH), 3.66 (s, 2H, alkyl CH_2), 3.53 (s, 2H, alkyl CH_2), 2.85 (t, 2H, J 5.5, alkyl CH_2), 2.70 (t, 2H, J 5.5, alkyl CH_2); δ_C 157.5 (d, J 230), 141.8, 139.8, 134.9, 132.9, 126.8 (d, J 9.0), 126.5, 125.5, 122.0, 114.6, 111.5 (d, J 9.8), 109.5, 109.4 (d, J 24.0), 103.2 (d, J 24.5), 63.3, 50.3, 50.0, 24.3; ν_{max}(film) 3414, 3104, 2918, 2802, 1830, 1627, 1593, 1455, 1422, 1323, 1232 cm^{-1}; m/z (ES^+) 313.1 (100%, MH^+); HRMS (ES^+): MH^+, found 313.1089. $C_{18}H_{18}FN_2S$ requires 313.1096.

2-(2-(Biphenyl-4-yl)allyl)-8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8e)

Prepared using General Procedure A from 4-iodobiphenyl (0.280 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.10 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / ether gave the product (R_f 0.1) as a pale yellow solid. Crystallisation with hexane / DCM gave the product as colourless prisms (0.248 g, 65%), m.p. 101-103 °C; δ_H (300 MHz, $CDCl_3$) 7.74 (br. s, 1H, NH), 7.66 (d, 2H, J 8.5, aryl CH), 7.56-7.45 (m, 4H, aryl CH), 7.42-7.33 (m, 3H, aryl CH), 7.17 (dd, 1H, J 8.9, 4.4, aryl CH), 7.04 (dd, 1H, J 9.5, 2.4, aryl CH), 6.84 (ddd, 1H, J 9.1, 8.9, 2.5, aryl CH), 5.60 (d, 1H, J 1.4, allyl CH), 5.37 (d, 1H, J 1.4, allyl CH), 3.73 (s, 2H, alkyl CH_2), 3.67 (s, 2H, alkyl CH_2), 2.94 (t, 2H, J 5.6, alkyl CH_2), 2.81 (t, 2H, J 5.6, alkyl CH_2); δ_C 158.21 (d, J 234), 144.5, 141.2, 140.8, 139.6, 134.7, 132.9, 129.2 (2C), 127.7, 127.4 (2C), 127.3 (2C), 127.2 (2C), 127.0 (d, J 9.8), 116.0, 111.4 (d, J

9.8), 109.5 (d, J 4.6), 109.5 (d, J 26.2), 103.2 (d, J 23.5), 62.6, 50.2, 49.8, 24.1; ν_{max}(film) 3423, 2900, 2092, 1634, 1484, 1458, 1324, 1264 cm^{-1}; m/z (ES^+) 383.2 (100%, MH^+); HRMS (ES^+): MH^+, found 383.1924. $C_{26}H_{24}FN_2$ requires 383.1918.

8-Fluoro-2-(2-(4-(trifluoromethyl)phenyl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8f)

Prepared using General Procedure A from 1-iodo-4-trifluorobenzene (0.272 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / DCM (R_f 0.3) crystallisation with hexane / DCM gave the product as pale yellow prisms (0.250 g, 67%). m.p. 181-183 °C; δ_H (300 MHz, $CDCl_3$) 7.77 (m, 1H, NH), 7.69 (d, 2H, J 8.2, aryl CH), 7.55 (d, 2H, J 8.2, aryl CH), 7.18 (dd, 1H, J 4.4, 8.9, aryl CH), 7.03 (dd, 1H, J 9.6, 2.5, aryl CH), 6.84 (ddd, 1H, J 9.1, 8.9, 2.4, aryl CH), 5.61 (s, 1H, allyl CH), 5.43 (s, 1H, allyl CH), 3.69 (s, 2H, alkyl CH_2), 3.64 (s, 2H, alkyl CH_2), 2.91 (t, 2H, J 5.6, alkyl CH_2), 2.79 (t, 2H, J 5.6, alkyl CH_2); δ_C (125 MHz) 158.2 (d, J 233.7), 144.1, 134.7, 132.9, 130.0, 129.6 (2C), 127.2 (2C), 126.8 (d, J 9.9), 125.8, 125.6, 125.6, 118.1, 111.5 (d, J 9.8), 109.5 (d, J 26.0), 109.3 (d, J 4.1), 103.1 (d, J 23.5), 62.6, 50.3, 49.8, 24.1; ν_{max}(Solid state) 2898, 1950, 1911, 1882,1734,1682 cm^{-1}; m/z (ES^+) 375.1 (100%, MH^+); HRMS (ES^+): MH^+, found 375.1470. $C_{21}H_{19}F_4N_2$ requires 375.1479.

5-(3-(8-Fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)prop-1-en-2-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (8g)

Prepared using General Procedure A from 5-iodo-1,3-dimethyluracil (0.266 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.10 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Chromatography, eluting with 95:5 v/v EtOAc / MeOH gave the product (R_f 0.10) as pale yellow prisms (0.274 g, 74%). m.p. 208-211 ^oC; δ_H (300 MHz, $CDCl_3$) 7.81 (br. s, 1H, NH) 7.60 (s, 1H, aryl CH), 7.22 (m, 1H, aryl CH), 7.05 (dd, 1H, J 4.4, 8.9, aryl CH), 6.82 (ddd, 1H, J 9.1, 8.9, 2.4, aryl CH), 5.80 (s, 1H, allyl CH), 5.32 (s, 1H, allyl CH), 3.65 (s, 2H, alkyl CH_2), 3.58 (s, 2H, alkyl CH_2), 3.33-3..30 (m, 6H, alkyl CH_3),

2.90 (br. s, 2H, alkyl CH_2), 2.85 (br. s, 2H, alkyl CH_2); δ_C (Acetone d_6) 162.9, 158.5 (d, J 236), 152.1, 142.9, 136.0, 139.9, 135.9, 126.4 (d, J 10.0), 117.7, 112.4 (d, J 10.0), 108.9 (d, J 25.0), 102.9 (d, J 24.0), 63.3, 50.6, 50.0, 37.2, 27.9, 24.5; ν_{max}(film) 3309, 2911, 2700, 1830, 1713, 1619, 1459 cm^{-1}; m/z (ES^+) 369.2 (100%, MH^+); HRMS (ES^+): MH^+, found 369.1711. $C_{20}H_{22}FN_4O_2$ requires 369.1721.

8-fluoro-2-(2-(pyridin-3-yl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (8h)

Prepared using General Procedure A from 3-iodopyridine (205 mg, 1.0 mmol), 8-fluoro- 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.10 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Chromatography eluting with 9:1 v/v EtOAc: Hexane gave the product as pale yellow prisms (0.224 g, 73%), m.p. 170-172 ^oC; δ_H (500 MHz, $CDCl_3$) 8.85 (s, 1H, aryl CH), 8.45(d, J 4.3, 1H, aryl CH), 8.15 (br, s, 1H, NH), 7.85 (d, J 7.1, 1H, aryl C17), 7.22 (m, 1H, aryl CH), 7.15(m, 1H, aryl CH), 7.05 (m, 1H, aryl CH), 6.82 (m, 1H, aryl CH), 5.57 (s, 1H, allyl CH), 5.40 (s, 1H, allyl CH), 3.69 (s, 2H, CH_2, alkyl CH_2), 3.60 (s, 2H, alkyl CH_2), 2.85 (t, J 5.6, 2H, alkyl CH_2), 2.75 (t, J 5.2, 2H, alkyl CH_2); δ_C 157.7 (d, J 234), 148.56, 147.83, 142,01, 135.58, 134.35, 133.84, 132.47, 126.4 (d, J 9.8), 123.11, 117.03, 111.0 (d, J 10.0), 109.2 (d, J 6.0), 109.3 (d J 25.0), 102.5 (d, J 25.0), 62.20, 49.77, 49.37, 23.84; ν_{max}(film) 3166, 2900**,** 1830, 1738, 1630, 1589, 1483, 1430, 1327, 1232 cm^{-1}; m/z (ES^+) 308.4 (100%, MH^+); HRMS (ES^+): MH^+, found 308.1543. $C_{19}H_{18}FN_3$ requires 308.1558; Found; C, 73.05 ; H, 5.9 ; N, 13.25 $C_{19}H_{18}N_3F$ 0.25 H_2O requires: C, 73.2 ; H,5.9 ; N, 13.45%.

4-iodo-N-(4-methyl-2-oxo-2H-chromen-7-yl) benzamide (8k)

A mixture of 4-iodobenzoic acid (1.00g, 4.03 mmol) and 7-amino-4-methyl coumarin (0.99 g, 5.64 mmol) in DMF (15 ml) was stirred at room temperature for 10 min. 4-(4,6-Dimethoxy-1,3,5-triazin-2yl)-4-methylmorpholin-4-ium chloride (1.12 g, 4.03 mmol) was added to the mixture and stirred at room temperature for 16.5 h. The mixture was quenched into water (50 ml) and extracted with ethyl acetate (3 x 15 ml), the combined organics were washed with aqueous sodium carbonate (1 x 10 ml), saturated ammonium chloride (1 x 10 ml) and brine (1 x 10 ml). The organics were dried ($MgSO_4$), filtered and concentrated in vacuo. Crystallisation from methanol

gave the product as pale yellow plates (1.13 g, 69%), m.p. 150–151 °C; δ_H (300 MHz, DMSO) 10.68 (s, 1H, NH), 7.98–7.90 (m, 3H, Ar-H), 7.79–7.72 (m, 4H, Ar-H), 6.29 (d, 1H, J 1.1, aryl CH), 2.41 (d, 3H, J 1.1, CH_3); δ_C 170.6, 165.2, 158.7, 158.3, 147.6, 142.6 (s, 2C), 138.9, 134.9 (s, 2C), 131.0, 121.4, 120.6, 117.7, 111.9, 105.2, 23.2; ν_{max}(film) 3370, 3055, 2305, 1915, 1787, 1694, 1681, 1618, 1525, 1483 cm^{-1}; m/z (ES^+) 406 (100%, MH^+), 428.(MNa^+); HRMS (ES^+): MH^+, found 405.9948. $C_{17}H_{13}INO_3$ requires 405.9935.

4-(3-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)prop-1-en-2-yl)-N-(4-methyl-2-oxo-2H-chromen-7-yl)benzamide (8i)

Prepared using General Procedure A from 4-iodo-N-(4-methyl-2-oxo-2H-chromen-7-yl) benzamide (0.405 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 16 h. Workup followed by chromatography, eluting with 2:1 v/v hexane / EtOAc (R_f 0.1) crystallisation with hexane/DCM gave the product as pale yellow prisms (0.325 g, 64%), m.p. 222–224 °C; δ_H (300 MHz, DMSO) 10.88 (s, 1H, NH), 10.59 (s, 1H, NH), 7.94–7.89 (m, 3H, Ar-H), 7.79–7.72 (m, 4H, Ar-H), 7.22 (dd, 1H, J 8.9, 4.6, aryl CH, 7.05 (dd, 1H, J 9.7, 2.5, aryl CH), 6.81 (ddd, 1H, J 9.7, 8.9, 2.5, aryl CH), 6.28 (d, 1H, J 1.2, aryl CH), 5.71 (s, 1H, allyl CH), 5.43 (s, 1H, allyl CH), 3.66 (s, 2H, alkyl CH_2), 3.57 (s, 2H, alkyl CH_2), 2.82 (t, 2H, J 5.1, alkyl CH_2), 2.72 (d, 2H, J 5.1, alkyl CH_2), 2.40 (d, 3H, J 1.1, alkyl CH_3); δ_C 171.1, 165.3, 161.8 (d, J 230.5), 158.7, 158.3, 149.0, 148.2, 147.8, 140.3, 138.5, 137.7, 132.9 (s, 2C), 131.6 (s, 2C), 131.0, 130.8 (s, J 10.1), 122.2, 121.2, 120.5, 117.6, 116.7 (d, J 8.6), 113.1 (d, J 27.8), 112.7 (d, J 4.6), 111.7, 107.2 (d, J 27.8), 66.7, 54.8, 54.2, 28.7, 23.2; ν_{max}(Solid state) 3485, 3253, 3042, 2250, 2124, 1996, 1827, 1766, 1717, 1670, 1618, 1581 cm^{-1}; m/z (ES^+) 508.2 (100%, MH^+); HRMS (ES^+): MH^+, found 508.2041. $C_{31}H_{27}F_4N_3O_3$ requires 508.1958.

N-(2-aminophenyl)-4-(3-(3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)prop-1-en-2-yl)benzamide (8j)

Prepared using General Procedure A from N-(2-aminophenyl)-4-iodobenzamide (0.338 g, 1.0 mmol), 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.172 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0

mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 16 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/EtOAc (R_f 0.15) crystallisation with hexane/DCM gave the product as pale yellow prisms (0.305 g, 72%). m.p. 157–159 °C; δ_H (500 MHz, DMSO) 10.75 (s, 1H, NH), 9.61 (s, 1H, NH), 7.94 (d, 2H, J 8.3, aryl CH), 7.74 (d, 2H, J 8.3, aryl CH), 7.30 (d, 1H, J 7.5, aryl CH), 7.26 (d, 1H, J 7.5, aryl CH), 7.18 (d, 1H, J 8.0, aryl CH), 7.03–6.89 (m, 3H, aryl CH), 6.78 (d, 1H, J 7.7, aryl CH), 6.60 (t, 1H, J 8.0, aryl CH), 5.70 (s, 1H, allyl CH), 5.45 (s, 1H, allyl CH), 4.90 (br. s, 2H, alkyl CH_2), 3.69 (s, 2H, alkyl CH_2), 3.63 (s, 2H, alkyl CH_2), 2.87 (br. s, 2H, alkyl CH_2), 2.74 (br. s, 2H, alkyl CH_2); δ_C 170.3, 149.2, 148.3, 147.6, 141.1, 138.7, 138.0, 132.8, 131.8, 131.6, 131.4, 130.7, 128.5, 125.4, 123.5, 122.1, 121.8, 121.4, 121.3, 116.0, 112.3, 66.9, 55.0, 54.4, 28.6; ν_{max}(film) 3370, 2988, 2305, 1915, 1787, 1694, 1681, 1618, 1588 cm^{-1}; m/z (ES^+) 423.2 (100%, MH^+); HRMS (ES^+): MH^+, found 423.2198. $C_{27}H_{27}N_4O$ requires 423.2179.

(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (9)[15a]

Propargyl bromide (1.1 ml, 10 mmol), (1.85 g, 5 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) were stirred at 20 °C in acetone for 16 h. The mixture was reduced in vacuo to afford the crude product and used in the next step without further purification. This material (2.04 g, 5 mmol), paraformaldehyde (0.37 g , 12.5 mmol), copper (I) bromide (0.36 g, 2.5 mmol) and diisopropylamine (1.4 ml, 10 mmol) in 1, 4-dioxane (8 ml), by stirring and heating at reflux for 16 h. Purification by flash chromatography eluting with 1:2 v/v hexane-EtOAc (R_f 0.3) afforded the product as a pale yellow gum (1g, 50%). δ_H (300 MHz, $CDCl_3$) 7.39 (d, 1H, J 8.1, aryl CH), 5.99 (d, 1H, J 4.5, alkyl CH), 5.82 (d, 1H, J 8.1, aryl CH), 5.38 (dd, 1H, J 5.8, 4.5, alkyl CH), 5.36 – 5.31 (m, 1H, alkyl CH), 5.25 (tt, 1H, J 12.8, 6.3, allyl CH), 4.83–4.78 (m, 2H, alkyl CH_2), 4.57–4.49 (m, 2H, allyl CH_2), 4.36 (br. s, 3H, alkyl CH_2 and CH), 2.14, 2.12 and 2.11 (3 x s, 3H, alkyl CH); δ_C 209.0, 170.5, 169.9, 169.8, 162.1, 150.7, 138.1, 102.8, 89.21, 86.0, 79.9, 77.5, 73.2, 70.2, 63.2, 39.4, 21.0, 20.8, 20.7; ν_{max}(film) 2107, 1960, 1749, 1668, 1455, 1372, 1228 cm^{-1}.

(2R,3R,4R,5S)-2-(acetoxymethyl)-5-(3-((Z)-4-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-3-phenylbut-2-enyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (10a)

Prepared using General Procedure B from 4-iodobenzene (0.204 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (422 mg, 1.0 mmol) in acetonitrile (10 mL), heated at 80 °C for 6 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/DCM (R_f 0.3) gave the product as a pale yellow oil (0.475 g, 69%). δ_H (300 MHz, $CDCl_3$) 7.99 (br. s, 1H, NH), 7.48 (d, 2H, J 6.9, aryl CH), 7.36 (d, 1H, J 8.1, aryl CH), 7.31–7.19 (m, 3H, aryl CH), 7.14 (dd, 1H, J 8.7, 4.3, aryl CH), 7.04 (dd, 1H, J 9.6, 2.3, aryl CH), 6.80 (ddd, 1H, J 9.1, 9.0, 2.3, aryl CH), 6.03 (d, 1H, J 4.3, alkyl CH), 5.89 (t, 1H, J 6.6, allyl CH), 5.82 (d, 1H, J 8.1, aryl CH), 5.39–5.29 (m, 2H, alkyl CH), 4.85 (d, 2H, J 6.6, alkyl CH_2), 4.34 (br. s, 3H, alkyl CH_2 and CH), 3.83 (s, 2H, alkyl CH_2), 3.72 (s, 2H, alkyl CH_2), 2.88 (t, 2H, J 5.5, alkyl CH_2), 2.73 (t, 2H, J 5.5, alkyl CH_2), 2.12, 2.12, and 2.07 (3 x s, 3H, alkyl CH_3); δ_C 170.2, 169.7, 162.1, 160.7, 159.7, 157.7 (d, J 234), 150.7, 142.1, 140.4, 137.4, 134.5, 132.4, 128.2, 127.3, 126.6, 126.4, 117.0 (d, J 8.5), 110.9 (d, J 9.7), 108.9 (d, J 25.9), 102.8 (d, J 23.8), 88. 6, 79.9, 79.7, 72.9, 70.0, 63.0, 56.2, 49.6, 49.4, 39.9, 23.8, 20.8, 20.5, 20.4; ν_{max}(film) 3360, 3057, 2922, 1749, 1711, 1668, 1484, 1455, 1372, 1228 cm^{-1}; m/z (ES^+) 689.3 (100%, MH^+); HRMS (ES^+): MH^+, found 689.2570. $C_{36}H_{38}FN_4O_9$ requires 689.2617.

(2R,3R,4R,5S)-2-(acetoxymethyl)-5-(3-((Z)-4-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-3-p-tolylbut-2-enyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (10b)

Prepared using General Procedure B from 4-iodotoluene (0.214 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (422 mg, 1.0 mmol) in acetonitrile (10 mL), heated at 80 °C for 6 h. Workup followed by chromatography, eluting with 19:1 v/v chloroform : MeOH (R_f 0.25) gave the product as a pale yellow foam (0.508 g, 72%). δ_H (300 MHz, $CDCl_3$) 8.03 (br. s, 1H, NH), 7.39–7.34 (m, 3H, aryl CH), 7.13–6.99 (m, 4H, aryl CH), 6.79 (ddd, 1H, J 9.2, 9.0, 2.4, aryl CH), 6.03 (d, 1H, J 4.3, alkyl CH), 5.86 (t, 1H, J 6.8, allyl CH), 5.82 (d, 1H, J 8.1, aryl CH),

5.38–5.31 (m, 2H, alkyl CH), 4.83 (d, 2H, J 6.8, alkyl CH_2), 4.34 (br. s, 3H, alkyl CH_2 and CH), 3.80 (s, 2H, alkyl CH_2), 3.70 (s, 2H, alkyl CH_2), 2.96 (t, 2H, J 5.2, alkyl CH_2), 2.85 (d, 2H, J 5.2, alkyl CH_2), 2.31 (s, 3H, alkyl CH_3), 2.12, 2.11 and 2.10 (3x s, 3H, alkyl CH_3); δ_C 170.2 (2C), 169.7, 162.1, 157.6 (d, J 233.3), 150.7, 140.3, 139.1, 137.4, 137.0, 134.5, 132.4, 129.6, 128.9, 126.5, 126.4 (d, J 9.8), 125.6, 111.0 (d, J 9.8), 108.7 (d, J 26.2), 102.9, 102.7 (d, J 23.5), 88.5, 79.8, 72.9, 70.0, 63.0, 56.1, 49.7, 49.3, 39.9, 23.8, 21.1, 20.8, 20.5, 20.4; ν_{max}(film) 3362, 3057, 2923, 1749, 1711, 1668, 1594, 1512, 1484, 1455, 1373, 1229 cm^{-1}; m/z (ES^+) 703.3 (100%, MH^+); HRMS (ES^+): MH^+, found 703.2790. $C_{37}H_{40}FN_4O_9$ requires 703.2774.

(2R,3R,4R,5S)-2-(acetoxymethyl)-5-(3-((Z)-4-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-3-(pyridin-3-yl)but-2-enyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (10c)

Prepared using General Procedure B from 3-iodopyridine (0.205 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (422 mg, 1.0 mmol) in acetonitrile (10 mL), heated at 80 °C for 3 h. Workup followed by chromatography, eluting with 19:1 v/v chloroform : MeOH (R_f 0.35) gave the product as a yellow foam (0.475 g, 69%). δ_H (300 MHz, $CDCl_3$) 8.77 (d, 1H, J 1.6, aryl CH), 8.47 (dd, 1H, J 4.8, 1.6, aryl CH), 8.44 (br. s, 1H, NH), 7.84 (dd, 1H, J 6.2, 1.6, aryl CH), 7.43 (d, 1H, J 8.1, aryl CH), 7.25–7.14 (m, 2H, aryl CH), 7.07 (dd, 1H, J 9.6, 2.3, aryl CH), 6.83 (ddd, 1H, J 9.2, 9.1, 2.4, aryl CH), 6.07 (d, 1H, J 4.6, alkyl CH), 5.96 (t, 1H, J 6.5, allyl CH), 5.88 (d, 1H, J 8.1, aryl CH), 5.45–5.32 (m, 2H, alkyl CH), 4.89 (d, 2H, J 6.6, alkyl CH_2), 4.38 (br. s, 3H, alkyl CH_2 and CH), 3.83 (s, 2H, alkyl CH_2), 3.74 (s, 2H, alkyl CH_2), 2.89 (t, 2H, J 5.4, alkyl CH_2), 2.75 (t, 2H, J 5.4, alkyl CH_2), 2.16, 2.15 and 2.11 (3 x s, 3H, alkyl CH_3); δ_C 170.6, 170.1 (2C), 162.4, 158.1 (d, J 233.5), 151.1, 148.7, 148.3, 138.0, 137.6, 134.8, 134.6, 132.9, 128.1, 126.8 (d, J 10.0), 123.4, 111.4 (d, J 9.6), 109.3 (d, J 25.9), 109.2 (d, J 4.5), 103.3, 103.1 (d, J 23.6), 89.1, 80.2, 73.4, 70.4, 63.4, 56.2, 50.1, 49.7, 40.0, 24.3, 21.2, 20.9, 20.8; ν_{max}(film) 3362, 3057, 2945, 1749, 1711, 1669, 1592, 1512, 1482, 1456, 1372, 1230 cm^{-1}; m/z (ES^+) 690.3 (100%, MH^+); HRMS (ES^+): MH^+, found 690.2567. $C_{35}H_{37}FN_5O_9$ requires 690.2570.

(2R,3R,4R,5S)-2-(acetoxymethyl)-5-(3-((E)-4-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)-3-(thiophen-2-yl)but-2-enyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (10d)

Prepared using General Procedure B from 2-iodothiophene (0.210 g, 1.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (422 mg, 1.0 mmol) in acetonitrile (10 mL), heated at 80 °C for 7 h. Workup followed by chromatography, eluting with 50:1 v/v chloroform/MeOH (R_f 0.3) gave the product as a pale yellow foam (0.485 g, 70%); δ_H (300 MHz, $CDCl_3$) 7.86 (br. s, 1H, NH), 7.37 (d, J 8.2, 1H, aryl CH), 7.23 (dd, 1H, J 3.6, 1.0, aryl CH), 7.17 (dd, 1H, J 8.8, 4.3, aryl CH), 7.12 (dd, 1H, J 5.1, 1.0, aryl CH), 7.06 (dd, 1H, J 9.6, 2.4, aryl CH), 6.92 (dd, 1H, J 5.1, 36, aryl CH), 6.83 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 6.11–6.00 (m, 2H, allyl and alkyl CH), 5.83 (d, 1H, J 8.1, aryl CH), 5.39–5.31 (m, 2H, alkyl CH), 4.82 (d, 2H, J 6.9, alkyl CH_2), 4.35 (br. s, 3H, alkyl CH_2 and CH), 3.77 (s, 4H, alkyl CH_2), 2.95 (t, 2H, J 5.3, alkyl CH_2), 2.82 (t, 2H, J 5.3, alkyl CH_2); δ_C 170.2, 169.7, 162.0, 157.7 (d, J 233.3), 150.7, 145.1, 137.4, 134.5, 134.3, 132.4, 127.0, 126.5 (d, J 9.8), 124.8, 124.2, 123.9, 111.0 (d, J 10.1), 109.0, 108.9 (d, J 25.1), 102.9, 102.8 (d, J 20.8), 88.5, 79.8, 76.7, 72.9, 70.0, 63.0, 56.4, 49.6, 49.3, 39.5, 23.9, 20.8, 20.5, 20.5; ν_{max}(film) 1750, 1668, 1456, 1233 cm^{-1}; m/z (ES^+) 695.2 (100%, MH^+); HRMS (ES^+): MH^+, found 695.2197. $C_{34}H_{36}FN_4O_9S$ requires 695.2187.

(2S,3R,4R,5R)-2-(3-((Z)-3-(4-(1H-pyrrol-1-yl)phenyl)-4-(8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)but-2-enyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-(acetoxymethyl)tetrahydrofuran-3,4-diyl diacetate (10e)

Prepared using General Procedure B from 1-(4-iodophenyl)-1H-pyrrole (0.268 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(3-(buta-2,3-dienyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (422 mg, 1.0 mmol) in acetonitrile (10 mL), heated at 80 °C for 6 h. Workup followed by chromatography, eluting with 19:1 v/v EtOAC /MeOH (R_f 0.5) the product as pale yellow foam (0.600

g, 81%); δ_H (300 MHz, $CDCl_3$) 7.94 (br. s, 1H, NH), 7.55 (d, 2H, J 8.8, aryl CH), 7.37 (d, 1H, J 8.2, aryl CH), 7.27 (d, 2H, J 8.8, aryl CH), 7.14 (dd, 1H, J 8.8, 4.3, aryl CH), 7.08–7.01 (m, 3H, aryl CH), 6.82 (ddd, 1H, J 9.2, 9.1, 2.5, aryl CH), 6.35–6.28 (m, 2H, aryl CH), 6.02 (d, 1H, J 4.5, alkyl CH), 5.92 (t, 1H, J 6.7, allyl CH), 5.83 (d, 1H, J 8.1, aryl CH), 5.36–5.30 (m, 2H, alkyl CH), 4.85 (d, 2H, J 6.7, alkyl CH_2), 4.35 (d, 3H, J 1.3, alkyl CH_2 and CH), 3.83 (s, 2H, alkyl CH_2), 3.74 (s, 2H, alkyl CH_2), 2.91 (t, 2H, J 5.3, alkyl CH_2), 2.75 (t, 2H, J 5.3, alkyl CH_2), 2.13, 2.12 and 2.08 (3 x s, 3H, alkyl CH_3); δ_C 170.2, 169.7, 162.1, 157.7 (d, J 233.4), 150.7, 149.1 (d, J 8.7), 139.7, 139.4, 139.1, 137.6, 134.4, 132.5, 127.8 (s, 2C), 126.3, 123.8 (d, J 22.3), 120.0 (s, 2C), 119.2 (s, 2C), 111.2 (d, J 9.3), 110.4 (s, 2C), 108.9 (d, J 25.9), 108.7 (d, J 5.2), 102.8, 102.7 (d, J 23.3), 88.8, 79.7, 73.0, 70.0, 63.0, 55.9, 49.7, 49.3, 39.8, 23.7, 20.8, 20.5, 20.5; ν_{max}(film) 3362, 2932, 1749, 1710, 1666, 1521, 1482, 1456 cm^{-1}; m/z (ES^+) 754.3 (100%, MH^+); HRMS (ES^+): MH^+, found 754.2879. $C_{40}H_{41}FN_5O_9$ requires 754.2888.

2,5-Bis(2-(4-(1H-pyrrol-1-yl)phenyl)allyl)-8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11a) and 2,5-Bis(2-(4-(1H-pyrrol-1-yl)phenyl)allyl)-7-fluoro-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12a)

Prepared using General Procedure C from 1-(4-iodophenyl)-1H-pyrrole (0.536 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 4.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 30 h. Chromatography (R_f 0.42, 4:1 hexanes: EtOAc) afforded the mixture of products **11a** and **12a** as a yellow oil. Chromatography eluting with chloroform afforded **11a** (R_f 0.1) as a pale yellow oil (0.160 g, 29%) and **12a** (R_f 0.3), crystallization from ether gave **12a** as colourless prisms (0.180 g, 33%). m.p. 222-224 °C.

11a. δ_H (300 MHz, $CDCl_3$) 7.63 (d, 2H, J 8.6, aryl CH), 7.44 (d, 2H, J 8.7, aryl CH), 7.36 (d, 2H, J 8.7, aryl CH), 7.31 (d, 2H, J 8.6, aryl CH), 7.08 (m, 6H, aryl CH), 6.86 (ddd, 1H, J 9.1, 9.0 2.4, aryl CH), 6.40–6.29 (m, 4H, aryl CH), 5.56 (s, 1H, allyl CH), 5.33 (br. s, 2H, allyl CH), 4.90 (s, 2H, alkyl CH_2), 4.42 (s, H, allyl CH), 3.75 (s, 2H, alkyl CH_2), 3.62 (s, 2H, alkyl CH_2), 2.92 (t, 2H, J 5.3, alkyl CH_2), 2.71 (t, 2H, J 5.3, alkyl CH_2); δ_C 157.8 (d, J 234.0), 143.6, 142.2, 140.5, 140.0, 137.4, 135.9, 135.9,

133.3, 127.6, 127.0, 126.4, 126.1 (d, J 9.8), 120.3, 120.1, 119.2, 119.2, 115.5, 112.7, 110.8, 110.5, 109.7 (d, J 9.7), 108.9 (d, J 26.0), 108.5 (d, J 4.5), 102.9 (d, J 23.5), 62.2, 49.8, 49.6, 46.4, 22.6; ν_{max}(film) 2780, 2253, 1713, 1521,1482; m/z (ES^+) 553.3 (100%, MH^+); HRMS (ES^+): MH^+, found 553.2768. $C_{37}H_{34}FN_4$ requires 553.2762.

12a. δ_H (500 MHz, $CDCl_3$) 7.59 (d, J 8.7, 2H, aryl CH), 7.51 (d, J 8.6, 2H, aryl CH), 7.32 (d, 2H, J 8.6, aryl CH), 7.33 (d, 2H, J 8.7, aryl CH), 7.15 (dd, 1H, J 9.9, 2.3, aryl CH), 7.09–7.06 (m, 5H, aryl CH), 6.86 (ddd, 1H, J 9.1, 8.9, 2.5, aryl CH), 6.35 (td, 4H, J 5.9, 2.2, aryl CH), 5.57 (d, 1H, J 0.8 allyl CH), 5.39 (d, 1H, J 1.2, allyl CH), 5.23 (d, 1H, J 0.8, allyl CH), 4.98 (d, 1H, J 1.2, allyl CH), 4.85 (s, 2H, alkyl CH_2), 3.79 (s, 2H, alkyl CH_2), 3.64 (s, 2H, alkyl CH_2), 3.14 (t, 2H, J 6.2, alkyl CH_2), 2.91 (t, 2H, J 6.2, alkyl CH_2); δ_C 158.3 (d, J 234), 145.6, 143.2, 140.6, 140.3, 139.2, 137.0, 133.9, 132.0, 129.4 (d, J 9.9), 127.9 (s, 2C), 127.6 (s, 2C), 120.6 (s, 2C), 120.5 (s, 2C), 119.6 (s, 4C), 116.7, 113.7, 111.0 (s, 2C), 110.9 (s, 2C), 109.2 (d, J 9.9), 108.9 (d, J 26.5), 108.0, 107.9, 104.0 (d, J 23.6), 63.7, 57.1, 47.7, 30.2, 19.8; ν_{max}(film) 2901, 2780, 2253, 1793, 1713, 1522, 1481 cm^{-1}; m/z (ES^+) 553. (100%, MH^+); HRMS (ES^+): MH^+, found 553.2751. $C_{37}H_{34}FN_4$ requires 553.2762.

8-fluoro-2,5-bis(2-phenylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11b) and 7-Fluoro-2,5-bis(2-phenylallyl)-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12b)

Prepared using General Procedure C from iodobenzene (0.404 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302, 4.0 mmol) and allene (0.5 bar) in acetonitrile (20 mL), heated at 80 °C for 30 h. Chromatography eluting 4:1 hexanes: EtOAc (R_f 0.5) afforded a mixture of products **11b** and **12b** as a yellow oil. Chromatography, eluting using chloroform, afforded **11b** (R_f 0.05) as a pale yellow oil (0.136 g, 32.5%) and **12b** (R_f 0.6) as pale yellow plates, crystallization from DCM: hexane gave **12b** as colourless prisms (0.136 g, 32.5%) m.p. 202-203 °C.

11b. δ_H (300 MHz, $CDCl_3$) 7.65–7.48 (m, 2H, aryl CH), 7.47–7.21 (m, 8H, aryl CH), 7.14–7.05 (m, 2H, aryl CH), 6.85 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 5.54 (d, 1H, J 1.5, allyl CH), 5.34 (d, 1H, J 1.1, allyl CH), 5.32 (s, 1H, allyl CH), 4.92 (s, 2H, alkyl CH_2), 4.39 (s, 1H, allyl CH), 3.75 (s, 2H, alkyl CH_2), 3.63 (s, 2H, alkyl CH_2), 2.92 (t, 2H, J 5.6, alkyl CH_2), 2.70 (t, 2H, J 5.6, alkyl CH_2); δ_C 157.8 (d, J 233.8), 144.4, 143.2, 140.3, 138.8, 135.9, 133.2, 128.6, 128.3, 128.2, 127.6, 126.4, 126.1 (d, J 9.8),

125.9, 115.6, 112.7, 109.7 (d, J 9.8), 108.8 (d, J 26.1), 108.3 (d, J 4.2), 102.8 (d, J 23.5), 61.9, 49.8, 49.6, 46.4, 22.5; ν_{max}(film) 3055, 2803, 1472, 1422, 1266, 1201, 1154 cm^{-1}; m/z (ES^+) 423.2 (100%, MH^+); HRMS (ES^+): MH^+, found 423.22247. $C_{29}H_{28}FN_2$ requires 423.2231.

12b. δ_H (C_6D_6, 300 MHz) 7.49–7.37 (m, 4H, Ar-H), 7.14–7.04 (m, 7H, aryl CH), 6.95 (ddd, 1H, J 9.1, 8.9, 2.4, aryl CH), 6.69 (dd, 1H, J 4.3, 8.8, aryl CH), 5.43 (d, 1H, J 1.3, allyl CH), 5.33 (d, 1H, J 0.7, allyl CH), 5.05 (s, 1H, allyl CH), 5.00 (d, 1H, J 1.3, allyl CH), 4.32 (s, 2H, alkyl CH_2), 3.72 (s, 2H, alkyl CH_2), 3.28 (s, 2H, alkyl CH_2), 2.61 (t, 2H, J 6.1, alkyl CH_2), 2.47 (t, 2H, J 6.1, alkyl CH_2); δ_C 157.6 (d, J 234), 144.5, 143.1, 140.7, 138.3, 135.6, 133.1, 128.8, 128.4 (2C,), 128.2 (s, 2C), 127.2, 126.7 (s, 2C), 126.4 (d, J 9.0), 126.1 (s, 2C), 115.7, 112.3, 109.4 (d, J 10), 108.2 (d, J 24.5), 108.1, 102.6 (d, J 24.5), 72.3, 57.9, 49.6, 46.4, 22.5; ν_{max}(film) 3199, 2799, 1472, 1423, 1266, 1153 cm^{-1}; m/z (ES^+) 423.2 (100%, MH^+); HRMS (ES^+): MH^+, found 423.2231. $C_{29}H_{28}FN_2$ requires 423.2246.

8-Fluoro-2,5-bis(2-p-tolylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11c) and 7-Fluoro-2,5-bis(2-p-tolylallyl)-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12c)

Prepared using General Procedure C from iodotoluene (0.432 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 4.0 mmol) and allene (0.5 bar) in acetonitrile (20 mL), heated at 80 °C for 30 h. Chromatography (R_f 0.30, 3:1 hexanes: EtOAc) afforded the mixture of products as a pale yellow oil. Chromatography, eluting with chloroform, afforded **11c** (R_f 0.05) as a pale yellow oil (0.136 g, 32.5%) and **12c** (R_f 0.5) as pale yellow plates (0.136 g, 31%), crystallization from DCM: Hexane gave **12c** as colourless prisms (0.135 g, 31%), m.p. 194–196 °C.

11c. δ_H (300 MHz, C_6D_6) 7.69 (d, 2H, J 8.2, aryl CH), 7.33–7.27 (dd, 1H, J 9.64, 2.60, aryl CH), 7.23 (d, 2H, J 8.2, aryl CH), 7.15 (d, 2H, J 8.0, aryl CH), 7.12–7.04 (m, 3H, aryl CH), 6.94 (dd, 1H, J 8.8, 4.3, aryl CH), 5.67 (d, 1H, J 1.8, allyl CH), 5.44 (s, 1H, allyl CH), 5.21 (s, 1H, allyl CH), 4.51 (s, 2H, alkyl CH_2), 4.35 (s, 1H, allyl CH), 3.76 (s, 2H, alkyl CH_2), 3.60 (s, 2H, alkyl CH_2), 2.79 (t, 2H, J 5.6, alkyl CH_2), 2.44 (t, 2H, J 5.6, alkyl CH_2), 2.23 and 2.22 (2 x s, 3H, alkyl CH_3); δ_C (C_6D_6) 158.5 (d, J 233.5), 145.3, 143.3, 138.0, 137.8, 137.4, 136.3, 136.2, 133.8, 129.4 (s, 2C), 129.2 (s, 2C), 129.1 (d, J 10.2),126.8 (s, 2C), 126.0 (s, 2C), 114.3, 111.6, 110.1 (d, J 9.6), 109.1 (d, J 25.9), 109 (d, J 4.6), 103.4 (d, J 23.4), 62.7, 50.0, 49.9, 46.3,

22.9, 21.1, 21.1; ν_{max}(film) 3084, 2914, 1938, 1816, 1630, 1581, 1473 cm^{-1}; m/z (ES^+) 451.3(100%, MH^+), 489.2 (MK^+); HRMS (ES^+): MH^+, found 451.2535. $C_{31}H_{32}FN_2$ requires 451.2544.

12c. δ_H (300 MHz, $CDCl_3$) 7.43 and 7.38 (d, J 8.2, 2H, aryl CH), 7.18–7.10 (m, 5H, aryl CH), 7.06 (dd, J 8.8, 4.3, aryl CH), 6.84 (ddd, J 9.1, 9.0, 2.5, 1H, aryl CH), 5.50 (s, 1H, allyl CH), 5.32 (s, 1H, allyl CH), 5.17 (s, 1H, allyl CH), 4.88 (s, 1H, allyl CH), 4.82 (s, 2H, alkyl CH_2), 3.78 (s, 2H, alkyl CH_2), 3.64 (s, alkyl CH_2), 3.11 (t, J 6.2, alkyl CH_2), 2.88 (t, J 6.2, alkyl CH_2), 2.35 and 2.33 (2 x s, 3H, alkyl CH_3); δ_C 158.3 (d, J 234.1), 146.3, 144.1, 139.1, 138.1, 137.6, 137.0, 133.9, 132.0, 129.5 (s, 2C), 129.3 (s, 2C), 129.1 (d, J 10.2), 126.6(s, 2C), 126.4(s, 2C), 115.8, 112.8, 109.1 (d, J 10.0), 108.7 (d, J 26.2), 108.2 (d, J 4.7), 103.9 (d, J 23.4), 63.8, 57.0, 47.6, 30.2, 21.6, 21.5, 19.7; ν_{max}(film) 3084, 2914, 1816, 1630, 1581 cm^{-1}; m/z (ES^+) 451.3 (100%, MH^+); HRMS (ES^+): MH^+, found 451.2539. $C_{31}H_{32}FN_2$ requires 451.2544.

2,5-Bis(2-(biphenyl-4-yl)allyl)-8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11d) and 2,5-Bis(2-(biphenyl-4-yl)allyl)-7-fluoro-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12d)

Prepared using General Procedure C from 4-iodobiphenyl (0.560 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 4.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 30 h. Chromatography (R_f 0.35, 3:1 hexanes: EtOAc) afforded the mixture of products as a yellow oil. Chromatography eluting chloroform afforded **11d** (R_f 0.45) as a pale yellow oil (0.124 g, 21.5%) and **12d** (R_f 0.55) as colourless prisms (0.152 g, 26.5%), m.p. 209-211 °C.

11d. δ_H (300 MHz, $CDCl_3$) 7.73–7.30 (m, 18H, aryl CH), 7.13 (dd, 1H, J 8.7, 4.1, aryl CH), 7.09 (dd, J 9.4, 2.1, 1H, aryl CH), 6.87 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 5.61 (s, 1H, allyl CH), 5.39 (s, 1H, allyl CH), 5.37 (s, 1H, allyl CH), 4.97 (s, 2H, allyl CH), 4.42 (s, 1H, allyl CH), 3.78 (s, 1H, alkyl CH_2), 3.67 (s, 2H, alkyl CH_2), 2.96 (t, 2H, J 5.4, alkyl CH_2), 2.76 (d, 2H, J 5.4, alkyl CH_2); δ_C 157.5 (d, J 236.4), 144.1, 142.7, 141.1, 140.82, 140.4, 140.4, 139.1, 137.6, 136.0, 133.3, 128.9, 128.8, 127.6, 127.3, 127.3, 127.1, 127.0, 126.9, 126.8, 126.2, 115.5, 112.6, 109.7 (d, J 9.8), 108.8 (d, J 25.6), 108.5 (d, J 4.6), 102.9 (d, J 23.2), 62.0, 49.8, 49.6, 46.3, 22.6; ν_{max}(film) 3262, 3031, 2806, 1637, 1487, 1421, 1266, 1153 cm^{-1}; m/z (ES^+) 575.3 (100%, MH^+); HRMS (ES^+): MH^+, found 575.2831. $C_{41}H_{36}FN_2$ requires 575.2857.

12d. δ_H (500 MHz, $CDCl_3$) 7.68–7.53 (m, 12H, aryl CH), 7.43–7.38 (m, 4H, aryl CH), 7.36–7.28 (m, 2H, aryl CH), 7.20 (dd, J 9.6, 2.6, 1H, aryl CH) 7.06 (dd, J 8.9, 4.3, 1H, aryl CH), 6.85 (ddd, J 8.9, 9.0, 2.5, 1H, aryl CH), 5.59 (d, J 0.96, 1H, allyl CH), 5.42 (d, J 1.01, 1H, allyl CH), 5.23 (d, J 0.63, 1H, allyl CH), 4.98 (d, J 1.35, 1H, allyl CH), 4.83 (s, 2H, alkyl CH_2), 3.84 (s, 2H, alkyl CH_2), 3.67 (s, 2H, alkyl CH_2), 3.12 (t, J 6.2, 2H, alkyl CH_2), 2.90 (t, J 6.2, 2H, alkyl CH_2); δ_C 157.9 (d, J 233.8), 145.7, 143.36, 140.7, 140.5, 140.2, 138.3, 134.8, 133.5, 131.6, 130.5, 129.0, 128.8, 128.6, 128.4, 127.4, 127.3, 127.1 (d, J 6.0), 127.0, 126.9, 126.7, 126.5, 125.4, 116.3, 113.3, 108.8 (d, J 9.8), 108.4 (d, J 26.2), 107.7 (d, J 4.6), 103.6 (d, J 23.4), 63.4, 56.5, 47.3, 29.8, 19.3; ν_{max}(film) 3262, 3021, 2796, 2621, 1671, 1615, 1528, 1391, 1264 cm^{-1}; m/z (ES^+) 575.3 (100%, MH^+); HRMS (ES^+): MH^+, found 575.2840. $C_{41}H_{36}FN_2$ requires 575.2857.

2,5-Bis(2-(4-bromophenyl)allyl)-8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11e) and 7-Fluoro-2,5-bis(2-(4-(trifluoromethyl)phenyl)allyl)-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12e)

Prepared using General Procedure C from 1-iodo-4-bromobenzene (0.562 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 4.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 30 h. Chromatography (R_f 0.30, 3:1 hexanes: EtOAc) afforded the mixture of product as a yellow oil. Chromatography eluting chloroform afforded **11e** (R_f 0.05) as a pale orange foam (0.164 g, 27.5%) and **12e** (R_f 0.6) as orange prisms (0.164 g, 27.5%) m.p. 199-202 °C.

11e. δ_H (300 MHz, $CDCl_3$) 7.49–7.39 (m, 6H, aryl CH), 7.26 (d, 2H, J 8.6, aryl CH), 7.10 (dd, 1H, J 8.7, 3.7, aryl CH), 7.05 (dd, 1H, J 9.4, 2.0, aryl CH), 6.86 (ddd, 1H, J 9.1, 9.0, 2.4, aryl CH), 5.53 (s, 1H, allyl CH), 5.33 (s, 2H, allyl CH), 4.89 (s, 2H, alkyl CH_2), 4.46 (s, 1H, allyl CH), 3.71 (s, 2H, alkyl CH_2), 3.59 (s, 2H, alkyl CH_2), 2.89 (t, 2H, J 5.5, alkyl CH_2), 2.68 (t, 2H, J 5.5, alkyl CH_2); δ_C 158.2 (d, J 234.8), 144.0, 142.7, 139.4, 138.0, 136.2, 133.5, 132.1 (s, 2C), 131.7 (s, 2C), 128.5 (s, 2C), 127.9 (s, 2C), 126.5 (d, J 10.1), 122.6, 122.0, 116.5, 113.9, 110.0 (d, J 9.8), 109.3 (d, J 26.1), 108.9 (d, J 4.7), 103.3 (d, J 23.4), 62.4, 50.1, 49.9, 46.72, 22.97; ν_{max}(film) 3053, 1628, 1588, 1488, 1422, 1266 cm^{-1}; m/z (ES^+) 579 (50%, M-2), 581 (100%, MH^+), 583 (50%, M+2); HRMS (ES^+): MH^+, found 581.0445. $C_{29}H_{26}Br_2FN_2$ requires

581.0445; (Found: C, 59.95, H, 4.30, N, 4.70, Br, 27.65. $C_{29}H_{25}Br_2FN_2$ requires: C, 60.02, H, 4.34, N, 4.83, Br, 27.54).

12e. δ_H (300 MHz, $CDCl_3$) 7.49–7.36 (m, 6H, aryl CH), 7.31 (d, 2H, J 8.6, aryl CH), 7.14 (dd, 1H, J 9.8, 2.4, aryl CH), 7.06 (dd, 1H, J 8.8, 4.3, aryl CH), 6.85 (ddd, 1H, J 9.1, 9.0, 2.4, aryl CH), 5.54 (s, 1H, allyl CH), 5.34 (d, 1H, J 0.7, allyl CH), 5.22 (s, 1H, allyl CH), 4.98 (s, 1H, J 0.7, allyl CH), 4.79 (s, 2H, alkyl CH_2), 3.76 (s, 2H, alkyl CH_2), 3.61 (s, 2H, alkyl CH_2), 3.08 (t, 2H, J 6.2, alkyl CH_2), 2.85 (t, 2H, J 6.2, alkyl CH_2); δ_C 157.9 (d, J 234.0), 145.2, 142.9, 140.4, 138.3, 133.4, 131.57, 131.5, 131.3, 128.6 (d, J 9.8), 128.0 (s, 2C), 127.8 (s, 2C), 121.9, 121.4, 116.8, 113.9, 108.8 (d, 10.2), 108.5 (d, J 26.6), 107.4 (d, J 4.7), 103.4 (d, J 23.6), 63.3, 56.6, 47.1, 29.8, 19.3; νmax(film) 3392, 3022, 2900, 2651, 2351, 1624, 1579, 1488 cm^{-1}; m/z (ES+) 579 (50%, M-2), 581 (100%, MH^+), 583 (50%, M+2); HRMS (ES^+): MH^+, found 581.0442. $C_{29}H_{26}Br_2FN_2$ requires 579.0441; (Found: C, 59.80, H, 4.30, N, 4.75, Br, 27.75. $C_{29}H_{25}Br_2FN_2$ requires: C, 60.02, H, 4.34, N, 4.83, Br, 27.54).

8-Fluoro-2,5-bis(2-(4-(trifluoromethyl)phenyl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11f) and 7-Fluoro-2,5-bis(2-(4-(trifluoromethyl)phenyl)allyl) -1,2,3,4-tetrahydropyrimido[1,6-a]indole (12f)

Prepared using General Procedure C from 1-iodo-4-trifluorobenzene (0.544 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Chromatography (R_f 0.45, 2:1 hexanes: EtOAc) afforded the mixture of product as an orange oil. Further chromatography, eluting with chloroform, afforded **11f** (R_f 0.25) as a colourless oil (0.139g, 25%) and **12f** (R_f 0.50) as colourless prisms (0.161 g, 29%) m.p. >230 °C.

11f. δ_H (300 MHz, $CDCl_3$) 7.49–7.39 (m, 6H, aryl CH), 7.26 (d, 2H, J 8.6, aryl CH), 7.10 (dd, 1H, J 9.7, 2.4, aryl CH), 7.06 (dd, 1H, J 8.8, 4.3, aryl CH), 6.86 (ddd, 1H, J 9.1, 9.0, 2.4, aryl CH), 5.53 (s, 1H, allyl CH), 5.33 (s, 2H, allyl CH), 4.89 (s, 2H, alkyl CH_2), 4.46 (s, 1H, allyl CH), 3.71 (s, 2H, alkyl CH_2), 3.59 (s, 2H, alkyl CH_2), 2.89 (t, 2H, J 5.5, alkyl CH_2), 2.68 (t, 2H, J 5.5, alkyl CH_2); δ_C 157.7 (d, J 233.9), 145.7, 145.5, 143.3, 133.8, 132.0, 129.7 (2C) 128.3 (2C), 127.6 (2C), 127.1 (2C), 125.6 (d, J 9.0), 125.4, 124.3, 117.6, 116.1, 109.7, 109.2, 109.1 (d, J 10.0), 107.8 (d, J 24.5), 107.3 (d, J 4.5), 103.8 (d, J 24.5), 62.7, 57.3, 47.4, 31.2, 21.3; ν_{max}(film) 3081,

2920, 1948, 1818, 1630, 1583, 1471, 1318 cm^{-1}; m/z (ES^+) 559.2 (100%, MH^+); HRMS (ES^+): MH^+, found 559.1951. $C_{31}H_{26}F_7N_2$ requires 558.1979.

12f. δ_H (C_6D_6, 500 MHz) 7.62 (d, J 8.3, 2H, aryl CH), 7.54 (m, 4H, aryl CH), 7.48, (d, 2H, J 8.3, aryl CH), 7.15 (dd, 1H, J 9.7, 2.4, aryl CH), 7.07, 6.86 (ddd, 1H, J 9.1, 8.9, 2.5, aryl CH), (dd, 1H, J 8.8, 4.3, aryl CH), 5.61 (s, 1H, allyl CH), 5.40 (s, 1H, allyl CH), 5.30 (s, 1H, allyl CH), 5.10 (d, 1H, J 0. 9, allyl CH), 4.81 (s, 2H, alkyl CH_2), 3.80 (s, 2H, alkyl CH_2), 3.65 (s, 2H, alkyl CH_2), 3.10 (t, 2H, J 6.1, alkyl CH_2), 2.86 (t, 2H, J 6.1, alkyl CH_2); δ_C 157.5 (d, J 234), 145.7, 145.5, 143.3, 133.8, 132.0, 129.4 (2C) 128.8 (2C), 127.0 (2C), 126.9 (2C), 125.8 (d, J 9.0), 125.7, 125.6, 118.6, 115.6, 109.3, 109.2, 108.9 (d, J 10.0), 107.7 (d, J 24.5), 107.4 (d, J 4.5), 104.0 (d, J 24.5), 63.7, 57.0, 47.6, 32.0, 20.3; ν_{max}(film) 3083, 2920, 1948, 1818, 1630, 1583, 1471, 1318 cm^{-1}; m/z (ES^+) 559.2 (100%, MH^+); (Found: C, 66.60, H, 4.45, N, 4.95 $C_{31}H_{25}F_7N_2$ requires: C, 66.66, H, 4.51, N, 5.02).

8-Fluoro-2,5-bis(2-p-tolylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (11g) and 7-Fluoro-2,5-bis(2-p-tolylallyl)-1,2,3,4-tetrahydropyrimido[1,6-a]indole (12g)

Prepared using General Procedure C from 1-iodo-4-methoxybenzene (0.470 g, 2.0 mmol), 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.190 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), Cs_2CO_3 (1.302 g, 4.0 mmol) and allene (0.5 bar) in acetonitrile (20 mL), heated at 80 °C for 30 h. Chromatography (R_f 0.20, 3:1 hexanes: EtOAc) afforded the mixture of products as a pale yellow oil. Further chromatography, eluting with chloroform, afforded **11g** (R_f 0.05) as a pale yellow oil (0.130 g, 31%) and **12g** (R_f 0.3) as a colourless oil (0.130 g, 31%).

11g. δ_H (300 MHz, $CDCl_3$) 7.53 (d, 2H, J 8.8, aryl CH), 7.36 (d, 2H, J 8.8, aryl CH), 7.14–7.03 (m, 2H, aryl CH), 6.93–6.78 (m, 6H, aryl CH), 5.46 (s, 1H, allyl CH), 5.24 (s, 2H, allyl CH), 4.88 (s, 2H, alkyl CH_2), 4.30 (s, 1H, allyl CH), 3.82 (s, 3H, alkyl CH_3), 3.78 (s, 3H, alkyl CH_3), 3.73 (s, 2H, alkyl CH_2), 3.59 (s, 2H, alkyl CH_2), 2.90 (t, 2H, J 5.4, alkyl CH_2), 2.70 (t, 2H, J 5.4, alkyl CH_2); δ_C 159.6, 159.1, 157.7 (d, J 225.1), 143.8, 142.4, 136.0, 133.2, 132.7, 131.2, 127.5, 126.9, 126.1 (d, J 9.9), 114.0, 113.8, 113.6, 111.0, 109.7 (d, J 9.8), 108.7 (d, J 25.9), 108.4 (d, J 4.6), 102.8 (d, J 23.5), 62.2, 55.4, 55.3, 49.8, 49.6, 46.4, 22.6; ν_{max}(film) 3696, 3155, 2902, 2839, 2253, 1793, 1654, 1606, 1512, 1466 cm^{-1}; m/z (ES^+) 451.3 (100%, MH^+); HRMS (ES^+): MH^+, found 451.2539. $C_{31}H_{32}FN_2$ requires 451.2544.

12g. δ_H (300 MHz, $CDCl_3$) 7.49 (d, 2H, J 8.7, H-3' or H-3''), 7.42 (d, 2H, J 8.7, H-3' or H-3''), 7.16 (dd, 1H, J 9.8, 2.2, H-6), 7.06 (dd, 1H, J 8.8, 4.4, H-9), 6.92–6.79 (m, 5H, H-8, H-2' and H-2''), 5.46 (s, 1H, H-12_B), 5.29 (s, 1H, H-15_B), 5.12 (s, 1H, H-12_A), 4.86 (s, 1H, H-15_A), 4.82 (s, 1H, H-1), 3.81 and 3.80 (2x s, 3H, H4' and H-4''), 3.78 (s, 2H, H-11), 3.63 (s, 2H, H-13), 3.11 (t, 2H, J 6.1, H-3), 2.88 (t, 2H, J 6.1, H-4); δ_C 159.0, 157.8 (d, J 233.0), 145.4, 143.1, 134.0, 133.5, 131.7 (d, J 21.7), 127.4 (s, 2C), 127.1 (s, 2C), 114.5, 113.7 (s, 2C), 113.5 (s, 2C), 111.7, 108.7 (d, J 9.5), 108.3 (d, J 26.5), 107.8 (d, J 4.8), 103.5 (d, J 23.4), 63.3, 56.7, 55.3, 47.2, 29.8, 19.3; ν_{max}(film) 3689, 3054, 2986, 2305, 1623, 1513, 1481, 1421 cm^{-1}; m/z (ES^+) 451.3 (100%, MH^+); HRMS (ES^+): MH^+, found 451.2539. $C_{31}H_{32}FN_2$ requires 451.2544.

tert-Butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (13)

8-Fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole **7** (3.80 g, 20 mmol) and Boc_2O (8.72 g, 40 mmol) were stirred in a mixture of dioxane (100 mL) and water (66 mL). The mixture was adjusted to pH 9 by drop wise addition of sodium hydroxide solution (10%). The resulting colourless solution was stirred for 1 h, the organic solvent was removed in vacuo and the resulting colourless precipitate was collected by filtration to give the product as colourless plates (4.38 g, 87%), m.p. 146–147 °C; δ_H (300 MHz, $CDCl_3$) 8.13 (s, 1H, NH), 7.20 (dd, 1H, J 8.6, 4.2, aryl CH), 7.21–7.07 (m, 1H, aryl CH), 6.88 (ddd, 1H, J 9.1, 9.0, 2.3, aryl CH), 4.59 (s, 2H, alkyl CH_2), 3.81 (t, 2H, J 5.7, alkyl CH_2), 2.81 (t, 2H, J 5.7, alkyl CH_2), 1.51 (s, 9H, alkyl CH_3); δ_C 157.7 (d, J 234), 155.4, 134.2, 132.5, 125.8 (d, J 9.9), 111.4 (d, J 9.4), 109.4 (d, J 26.0), 107.3, 102.7 (d, J 23.5), 80.3, 41.4, 40.7, 28.6 (3C), 23.6; ν_{max}(film) 3337, 3233, 2992, 2492, 2214, 2072, 1944, 1733, 1407 cm^{-1}; HRMS (ES^+): MH^+, found 313.1328. $C_{16}H_{19}FN_2O_2Na$ requires 313.1323.

tert-Butyl 8-fluoro-5-(2-phenylallyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (14a)

Prepared using General Procedure A from iodobenzene (0.204 g, 1.0 mmol), tert-butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.290 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), Cs_2CO_3 (0.650 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/EtOAc (R_f 0.6) and crystallisation with methanol gave the product as colourless prisms (0.293 g,

72%), m.p. 98–100 °C; δ_H (300 MHz, $CDCl_3$) 7.46–7.30 (m, 5H, aryl CH), 7.14 (m, 2H, aryl CH), 6.89 (ddd, 1H, J 9.1, 9.0, 2.4, aryl CH), 5.33 (s, 1H, allyl CH), 4.96 (s, 2H, alkyl CH_2), 4.62 (s, 2H, alkyl CH_2), 4.36 (s, 1H, allyl CH), 3.81 (br. s, 2H, alkyl CH_2), 2.73 (br. s, 2H, alkyl CH_2), 1.51 (s, 9H, alkyl CH_3); δ_C 157.8 (d, J 234), 155.2, 143.2, 138.7, 135.8, 135.2, 133.3, 128.7 (2C), 128.3, 125.9 (2C), 125.5 (s, J 8.7), 112.7, 109.9 (d, J 10.1), 109.4 (d, J 26.1), 107.2, 103.0 (d, J 26.8), 80.0, 46.5, 41.3, 40.7, 28.5 (3C), 22.4; ν_{max}(Solid state): 3685, 3155, 2981, 2930, 2253, 1818, 1683, 1479, 1427 cm^{-1}; m/z (ES^+) 407.2 (80%, MH^+), 351.2 (100%, MH^+); HRMS (ES^+): MH^+, found 407.2150. $C_{25}H_{28}F N_2O_2$ requires 407.2129.

tert-Butyl 8-fluoro-5-(2-p-tolylallyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (14b)

Prepared using General Procedure A from 4-iodotoluene (0.218 g, 1.0 mmol), tert-butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.290 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), Cs_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 4:1 v/v hexane/EtOAc (R_f 0.4) gave the product as a colourless oil (0.280 g, 69%); δ_H (500 MHz, $CDCl_3$) 7.38 (d, 2H, J 8.1, aryl CH), 7.24 (d, 2H, J 8.1, aryl CH), 7.22–7.14 (m, 2H, aryl CH), 6.94 (ddd, 1H, J 9.1, 9.0, 2.3, aryl CH), 5.35 (s, 1H, allyl CH), 4.99 (s, 2H, alkyl CH_2), 4.67 (s, 2H, alkyl CH_2), 4.37 (s, 1H, allyl CH), 3.86 (br. s, 2H, alkyl CH_2), 2.78 (br. s, 2H, alkyl CH_2), 2.42 (s, 3H, alkyl CH_3), 1.57 (s, 9H, alkyl CH_3); δ_C (125 MHz) 157.8 (d, J 234.5), 155.2, 143.0, 138.2, 135.8, 133.3, 129.4 (s, 2C), 129.0, 128.4, 125.7 (s, 2C), 125.5 (s, J 8.7), 111.8, 109.9 (d, J 10.0), 109.4 (d, J 26.1), 102.9 (d, J 25.1), 80.0, 46.5, 41.4, 40.7, 28.5 (s, 3C), 22.5, 21.2; ν_{max}(film) 3391, 2530, 2194, 2064, 2011, 1897, 1674, 1461 cm^{-1}; m/z (ES^+) 443.2 (100%, MNa^+); 277.1 (100%, MH^+); HRMS (ES^+): MH^+, found 443.2112. $C_{26}H_{29}F N_2NaO_2$ requires 443.2105).

tert-Butyl 8-fluoro-5-(2-(thiophen-2-yl)allyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (14c)

Prepared using General Procedure A from 2-iodothiophene (0.210 g, 1.0 mmol), tert-butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.290 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), Cs_2CO_3 (0.650 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h.

Workup followed by chromatography, eluting with 2:1 v/v hexane / EtOAc (R_f 0.6) and crystallisation with methanol gave the product as colourless prisms (0.333 g, 81%), m.p. 136–138 °C; δ_H (300 MHz, $CDCl_3$) 7.35 (dd, 1H, J 4.9, 3.0, aryl CH), 7.29–7.24 (m, 2H, aryl CH), 7.14 (m, 2H, aryl CH), 6.89 (ddd, 1H, J 9.1, 9.0, 2.4, aryl CH), 5.38 (s, 1H, allyl CH), 4.95 (s, 2H, alkyl CH_2), 4.63 (s, 2H, alkyl CH_2), 4.28 (s, 1H, allyl CH), 3.82 (s, 2H, alkyl CH_2), 2.74 (s, 2H, alkyl CH_2), 1.51 (s, 9H, alkyl CH_3); δ_C 157.9 (d, J 234.8), 155.2, 141.8, 136.7, 135.7, 133.3, 127.6, 125.5 (d, J 10.6), 125.0, 123.3, 110.9, 109.9 (d, J 10.2), 109.5 (d, J 26.0), 107.4 (s, J 13.1), 103.0 (d, J 23.1), 80.0, 45.9, 41.3, 40.7, 28.5, 22.4; ν_{max}(film) 3054, 2986, 2305, 2126, 2054, 1686, 1626, 1604, 1551, 1479, 1421 cm^{-1}; HRMS (ES^+): MH^+, found 413.1638. $C_{23}H_{26}N_2O_2FS$ requires 413.1621.

tert-Butyl 5-(2-(4-bromophenyl)allyl)-8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (14d)

Prepared using General Procedure A from 4-iodo-1-bromobenzene (0.282 g, 1.0 mmol), tert-butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.290 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), Cs_2CO_3 (0.650 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 4:1 v/v hexane/EtOAc (R_f 0.45) and crystallisation with methanol gave the product as colourless prisms (0.395 g, 78%). m.p. 121–122 °C; δ_H (300 MHz, $CDCl_3$) 7.50 (d, 2H, J 8.5, aryl CH), 7.27 (d, 2H, J 8.7, aryl CH), 7.18–7.08 (m, 2H, aryl CH), 6.90 (ddd, 1H, J 9.1, 9.0, 2.3, aryl CH), 5.34 (s, 1H, allyl CH), 4.93 (s, 2H, alkyl CH_2), 4.61 (s, 2H, alkyl CH_2), 4.43 (s, 1H, allyl CH), 3.81 (s, 2H, alkyl CH_2), 2.72 (s, 2H, alkyl CH_2), 1.51 (s, 9H, alkyl CH_3); δ_C 157.8 (d, J 234.7), 142.2, 137.5, 133.2, 131.8 (s, 2C), 127.5 (s, 2C), 122.3, 113.5, 109.8 (d, J 9.5), 109.5 (d, J 25.9), 103.3 (d, J 23.5), 46.3, 28.5 (s, 3C), 22.5, 22.4; ν_{max}(film) 3337, 3233, 2992, 2492, 2214, 2072, 1944, 1733, 1407, 1123 cm^{-1}; m/z (ES^+) 507.1(50%, MNa^+), 509.1(50%, MNa^+); HRMS (ES^+): MNa^+, found 507.1059. $C_{25}H_{26}BrFN_2O_2Na$ requires 507.1054.

tert- Butyl 5-(2-(4-(1H-pyrrol-1-yl)phenyl)allyl)-8-fluoro-3,4-dihydro-1H-pyrido [4,3-b]indole-2(5H)-carboxylate (14e)

Prepared using General Procedure A from 1-(4-iodophenyl)-1H-pyrrole (0.268 g, 1.0 mmol), tert-butyl 8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate

(0.290 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/EtOAc (R_f 0.6) gave the product as a colourless foam (0.365 g, 74%); δ_H (300 MHz, $CDCl_3$) 7.48 (d, 2H, J 8.8, aryl CH), 7.40 (d, 2H, J 8.8, aryl CH), 7.20–7.13 (m, 2H, aryl CH), 7.11 (t, 2H, J 2.2, aryl CH), 6.91 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 6.37 (t, 2H, J 2.2, aryl CH), 5.37 (s, 1H, allyl CH), 4.98 (s, 2H, alkyl CH_2), 4.62 (s, 2H, alkyl CH_2), 4.40 (s, 1H, allyl CH), 3.82 (s, 2H, alkyl CH_2), 2.76 (s, 2H, alkyl CH_2), 1.51 (s, 9H, alkyl CH_2); δ_C 157.8 (d, J 234.8), 142.2, 140.5, 135.7, 133.2, 129.0, 127.0 (2C), 125.5(d, J 9.5), 120.3 (2C), 119.1 (2C), 112.7 (2C), 110.8, 109.8 (d, J 7.5), 109.4 (d, J 26.1), 107.3 (d, J 8.4) 103.0 (d, J 24.3), 80.0, 50.9, 46.4, 41.3, 40.6, 28.5 (3C), 22.5; ν_{max}(film) 3689, 3155, 2981, 2929, 2253, 1793, 1685, 1628, 1594, 1479, 1426 cm^{-1}; m/z (ES^+) 494.2 (100%, MNa^+); HRMS (ES^+): MNa^+, found 494.2224. $C_{29}H_{30}FN_3O_2Na$ requires 494.2214.

8-Fluoro-5-(2-phenylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole hydrochloride (15a)

A mixture of tert-butyl-8-fluoro-5-(2-phenylallyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.41 g, 1 mmol) and 10% HCl (5 ml) in methanol (10 ml) was stirred at 60°C for 1 hour. The organic solvent was removed in vacuo and the resulting colourless precipitate was collected by filtration to give the product as colourless prisms (0.261 g, 85%), m.p. 202-203 °C; δ_H (300 MHz, CD_3OD) 7.55–7.47 (m, 2H, aryl CH), 7.42–7.29 (m, 4H, aryl CH), 7.21 (dd, 1H, J 9.3, 2.5, aryl CH), 6.97 (ddd, 1H, J 9.3, 9.0, 2.5, aryl CH), 5.36 (s, 1H, allyl CH), 5.17 (s, 2H, alkyl CH_2), 4.45 (s, 1H, allyl CH), 4.43 (s, 2H, alkyl CH_2), 3.62 (t, 2H, J 6.1, alkyl CH_2), 3.12 (t, 2H, J 6.1 alkyl CH_2); δ_C (75 MHz, CD_3OD) 159.4 (d, J 234.3), 145.6, 140.0, 135.0, 134.5, 129.7 (s, 2C), 129.4, 127.2 (s, 2C), 126.4 (d, J 10.5), 113.1, 112.0 (d, J 9.6), 111.2 (d, J 26.3), 103.8 (d, J 24.6), 103.4, 47.7, 42.9, 42.0, 20.7; ν_{max}(film) 3485, 3270, 3006, 2250, 2124, 1667, 1626, 1476, 1364, 1151 cm^{-1}; m/z (ES^+) 307.2 (65%, MH^+); 277.1 (100%, MH^+); HRMS (ES^+): MH^+, found 307.1597. $C_{20}H_{20}FN_2$ requires 307.1605.

8-Fluoro-5-(2-p-tolylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole hydrochloride (15b)

A mixture of tert-butyl 8-fluoro-5-(2-p-tolylallyl)-3,4-dihydro-1H-pyrido[4,3-b]indole-2(5H)-carboxylate (0.42 g, 1.0 mmol) and 10% HCl (5 ml) in methanol (10 ml) was stirred at 60 °C for 1 hour. The organic solvent was removed in vacuo and the resulting colourless precipitate was collected by filtration to give the product as colourless prisms (0.288 g, 90%). m.p. 178–179 °C; δ_H (500 MHz, DMSO) 9.40 (s, 2H, NH), 7.54–7.47 (m, 3H, aryl CH), 7.36 (dd, 1H, J 9.8, 2.5, aryl CH), 7.21 (d, 2H, J 8.0, aryl CH), 7.00 (ddd, 1H, J 9.1, 9.0, 2.5, aryl CH), 5.33 (s, 1H, allyl CH), 5.22 (s, 2H, alkyl CH_2), 4.31 (s, 2H, alkyl CH_2), 4.27 (s, 1H, allyl CH), 3.49 (br. s, 2H, alkyl CH_2), 3.02 (br. s, 2H, alkyl CH_2), 2.32 (s, 3H, alkyl CH_3); δ_C 158. 2 (d, J 234), 144.9, 137.8, 137.7, 134.8, 132.9, 129.3, 126.9 (d, J 9.7), 126.6, 115.1, 111.4 (d, J 9.8), 109.6, 109.4 (d, J 26.1), 103.1 (d, J 23.5), 62.7, 50.3, 49.9, 24.1, 21.5; ν_{max}(film) 3445, 3071, 3007, 2597, 2205, 2140, 1666, 1470 cm^{-1}; m/z (ES^+) 321.2 (100%, MH^+); HRMS (ES^+): MH^+, found 321.1697. $C_{21}H_{22}N_2F$ requires 321.1689.

N-(2-aminophenyl)-4-(3-(8-fluoro-5-(2-phenylallyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl)prop-1-en-2-yl)benzamide (16a)

Prepared using General Procedure A from N-(2-aminophenyl)-4-iodobenzamide (0.388 g, 1.0 mmol), 8-fluoro-5-(2-phenylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole **15a** (0.306 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/EtOAc (R_f 0.1) gave the product as a pale yellow foam (0.284 g, 51%); δ_H (500 MHz, DMSO) 9.62 (s, 1H, NH), 7.95 (d, 2H, J 7.6, aryl CH), 7.72 (d, 2H, J 8.3, aryl CH), 7.55 (d, 2H, J 7.6, aryl CH), 7.45–7.30 (m, 4H, aryl CH), 7.20–7.10 (m, 2H, aryl CH), 6.97 (t, 1H, J 7.7, aryl CH), 6.89 (ddd, 1H, J 9.3, 9.0, 2.6, aryl CH), 6.79 (d, 1H, J 8.1, aryl CH), 6.60 (t, 1H, J 7.7, aryl CH), 5.69 (s, 1H, allyl CH), 5.43 (s, 1H, allyl CH), 5.33 (s, 1H, allyl CH), 5.14 (s, 2H, alkyl CH_2), 4.90 (br. s, 2H, NH_2), 4.30 (s, 1H, allyl CH), 3.67 (s, 2H, alkyl CH_2), 3.64 (s, 2H, alkyl CH_2), 2.86 (t, 2H, J 5.7, alkyl CH_2), 2.69 (t, 2H, J 5.7, alkyl CH_2); δ_C (75 MHz, DMSO) 164.98, 156.85 (d, J 231.4), 144.1, 143.8, 143.1, 142.5, 142.3, 138.3, 136.4, 133.5, 133.0, 128.4, 128.1, 127.6, 126.6, 126.4, 126.1, 126.0, 125.3 (d, J 10.1), 123.3, 116.7, 116.4 (s, J 14.9), 116.1 (d, J 9.8), 111.8, 110.5 (d, J 9.8), 108.3 (s, J 25.4), 107.7 (s, J 17.3), 107.6, 102.0 (d, J 22.9), 61.2, 49.4, 48.9, 45.9, 22.2; ν_{max}(film) 3435, 2252, 2126, 1661, 1226

cm^{-1}; m/z (ES^+) 557.3 (100%, MH^+); HRMS (ES^+): MH^+, found 557.2722. $C_{36}H_{34}FN_4O$ requires 557.2711.

8-Fluoro-5-(2-p-tolylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (16b)

Prepared using General Procedure A from 2-iodo-1,3,5-trimethylbenzene (0.246 g, 1.0 mmol), 8-fluoro-5-(2-phenylallyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.307 g, 1.0 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), TFP (0.023 g, 0.1 mmol), K_2CO_3 (0.276 g, 2.0 mmol) and allene (0.5 bar) in acetonitrile (10 mL), heated at 80 °C for 24 h. Workup followed by chromatography, eluting with 2:1 v/v hexane/EtOAc (R_f 0.6) gave the product as pale yellow oil (0.367 g, 79%); δ_H (300 MHz, $CDCl_3$) 7.47–7.32 (m, 5H, aryl CH), 7.13 (dd, 1H, J 8.9, 4.3, aryl CH), 7.08 (dd, 1H, J 9.7, 2.3, aryl CH), 6.92–6.82 (m, 3H, aryl CH), 5.65 (d, 1H, J 1.8, allyl CH), 5.34 (s, 1H, allyl CH), 5.03 (d, 1H, J 1.8, allyl CH), 4.97 (s, 2H, alkyl CH_2), 4.40 (s, 1H, allyl CH), 3.83 (s, 2H, alkyl CH_2), 3.25 (s, 2H, alkyl CH_2), 3.04 (t, 2H, J 5.5, alkyl CH_2), 2.81 (t, 2H, J 5.5, alkyl CH_2), 2.28 (s, 3H, alkyl CH_3), 2.25 (s, 6H, alkyl CH_3); δ_C 156.9 (d, J 233.7), 144.2, 142.4, 138.1, 137.5, 135.6, 135.1, 134.7, 132.5, 127.9 (s, 2C), 127.7, 127.5 (s, 2C), 127.4, 125.3 (d, J 9.9), 125.1 (s, 2C), 113.2, 111.9, 108.9 (d, J 9.8), 108.0 (d, J 26.3), 107.8, 102.1 (d, J 23.5), 61.0, 49.7, 49.5, 45.7, 22.0, 20.2, 18.9 (s, 2C); ν_{max}(film) 3054, 2987, 2685, 2305, 1671, 1482, 1422, 1265; m/z (ES^+) 465.3 (100%, MH^+); HRMS (ES^+): MH^+, found 465.2719. $C_{32}H_{34}FN_2$ requires 465.2701.

8-fluoro-5-(2-(pyridin-3-yl)allyl)-2-(2-(thiophen-3-yl)allyl)-2,3,4,5-tetrahydro-1H-indeno[1,2-c]pyridine (16c)

Prepared using General Procedure A from 3-iodopyridine (1 mmol), 8-fluoro-2-(2-(thiophen-3-yl)allyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (**8d**) (1 mmol, 190 mg) and $Pd(OAc)_2$ (5 mol%), triphenylphosphine (10 mol%), Cs_2CO_3 (2 mmol) in acetonitrile (15 ml) at 80 ^oC for 24 h. Purification by flash column chromatography, eluting with 9:1 v/v EtOAc: hexane, afforded the product (69%) as pale yellow, amorphous solid, m. p. 110–112 ^oC; δ_H (500 MHz, $CDCI_3$) 8.66 (d, 1H, J 2.0, aryl CH), 8.55 (dd, 1H, J 1.6 and 4.8, aryl CH), 7.60–7.57 (m, 2H, aryl CH), 7.32–7.21 (m, 3H, aryl CH), 7.11–7,06 (m, 2H, aryl CH), 6.85 (m, 1H, aryl CH), 5.54 (s, 1H, allyl CH), 5.37 (s, 1H, allyl CH), 5.27 (s, 1H, allyl CH), 4.90 (s, 2H, alkyl CH_2), 4.61

(s, 1H, allyl CH), 3.71 (s, 2H, alkyl CH_2), 3.55 (s, 2H, alkyl CH_2), 2.90 (t, 2H, J 5.6, alkyl CH_2), 2.70 (t, 2H, J 5.5, alkyl CH_2); δc 158.2 (d, J 235.0), 149.79, 147.72, 141.72, 141.25, 139.85, 136.19, 133.69, 133.57, 126.67, 126.65, 126.44, 125.33, 123.72, 121.94, 115.33, 114.44, 110.04 (d, J 10.0), 109.45 (d, J 23.5), 109.25 (d, J 4.7), 102.8 (d, J 24.0), 63.10, 50.21, 50.0, 46.88, 23.20. ν_{max}(film) 3418, 2920, 2800, 1627, 1587, 1473, 1424, 1357, 1201, 1154, 905, 791 cm^{-1}; m/z (ES^+) 430.4 (M+1, 38), 236(100); HRMS (ES^+): HRMS (ES^+): MH^+, found 430.1749. $C_{26}H_{24}N_3SF$ requires 430.1748.

Crystalographic data

CCDC 721640 (**11b**. Archive Code: 08_07_08, identification code: AD2008_19, Formula $C_{29}H_{27}FN_2$, FW: 422.53) and 721641 (**12a**.: Archive Code: 08_11_16, identification code: mc1002, Formula $C_{37}H_{33}FN_4$, FW: 552.67) contain the supplementary crystallographic data for compounds **11b and 12a** respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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