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ScienceDirect
Tetrahedron 64 (2008) 901–914
Tetrahedron
www.elsevier.com/locate/tet

High throughput synthesis of diverse 2,5-disubstituted indoles using titanium carbenoids bearing boronate functionality

Calver A. Main [a], Hanna M. Petersson [a], Shahzad S. Rahman [b], Richard C. Hartley [a,*]

[a] WestCHEM, Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK
[b] GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

Received 25 June 2007; accepted 30 August 2007
Available online 24 October 2007

Abstract

A titanium benzylidene complex bearing a boronate group converted resin-bound esters into enol ethers. Suzuki cross-coupling with aryl iodides followed by cleavage with acid completed the solid-phase synthesis of 2,5-disubstituted *N*-Boc-indoles. Also reported is the use of *tert*-butyllithium and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to convert an aryl bromide into an arylboronate in the presence of a dithiane, with simultaneous reduction of an aryl azide to an amine.
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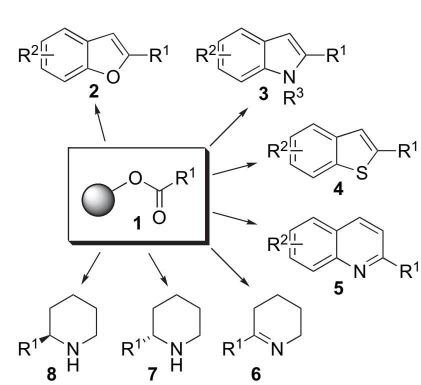
1. Introduction

The discovery of new lead compounds can be achieved through the synthesis of a large numbers of compounds in parallel, constituting a compound library, followed by high throughput screening.[1] The members of the library should be diverse in structure so as to effectively probe chemical space, but because chemical space is so large, the inclusion of structural features that are often associated with biological activity, known as 'privileged structures',[2,3] improves the chances of obtaining a useful lead compound. Once a lead is established, focussed libraries can then be prepared, which may well contain a range of privileged structures. The use of solid-phase synthesis facilitates the preparation of the libraries as it allows automation.[4]

Recently, we have developed functionalised titanium carbenoids[5] to prepare benzofurans **2**,[6,7] indoles **3**,[7] benzothiophenes **4**,[8] quinolines **5**,[9] cyclic imines[10,11] **6** and enantiomerically enriched piperidines[11] **7** and **8** from resin-bound esters **1**, so that each ester acts as a precursor to a range of privileged structures (Scheme 1). The general strategy involves using titanium carbenoids **9** containing a masked nucleophile to convert acid-stable, resin-bound esters **1** into acid-sensitive enol ethers **10** (Scheme 2). Treatment with mild acid leads to cleavage from resin with concomitant cyclisation to generate bicyclic heteroaromatic compounds **11** with no trace of the site of attachment to resin. The switch to a linker cleaved under orthogonal conditions ensures that any unreacted ester **1** remains attached to the resin and so the products **11** are released in high purity. Barrett and co-workers introduced the term 'chameleon catch' to describe this switch in the nature of a linker.[12,13] In theory, it allows greater diversity to arise from each resin-bound ester **1** as other products would be available from cleaving at the ester stage (e.g., carboxylic acids, alcohols, etc.).



Scheme 1.

* Corresponding author. Fax: +44 141 3304888.
E-mail address: richh@chem.gla.ac.uk (R.C. Hartley).

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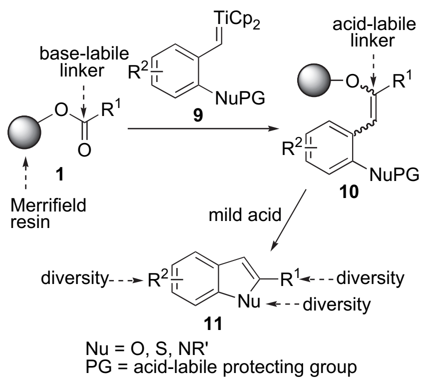
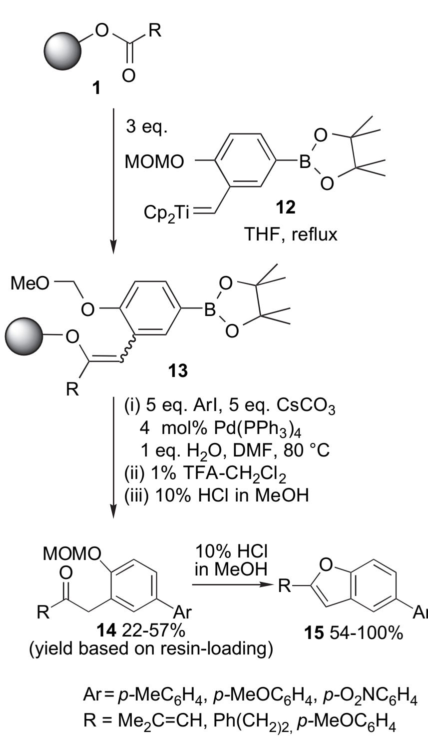
doi:10.1016/j.tet.2007.08.119



Scheme 2.

One limitation of our original strategy was that no additional diversity was added after the switch of the linker, and we overcame this in the benzofuran series by including a boronate group in the titanium reagent **12**.[14] Suzuki cross-coupling between boronate **13** and a variety of aryl iodides then allowed access to a range of ketones **14** that cyclised upon deprotection in strong acid to give 2,5-disubstituted benzofurans **15**. Aryl bromides react under the conditions used to generate our titanium benzylidene reagents **9**, precluding the introduction of aryl bromide or iodide functionality to the resin by our method.[7] However, immobilisation of the arylboronate component is advantageous as aryl halides are more widely and cheaply available than arylboronates. Therefore, it is surprising that the aryl halide is almost always the immobilised coupling partner for cross-couplings in SPS (Scheme 3).[15]



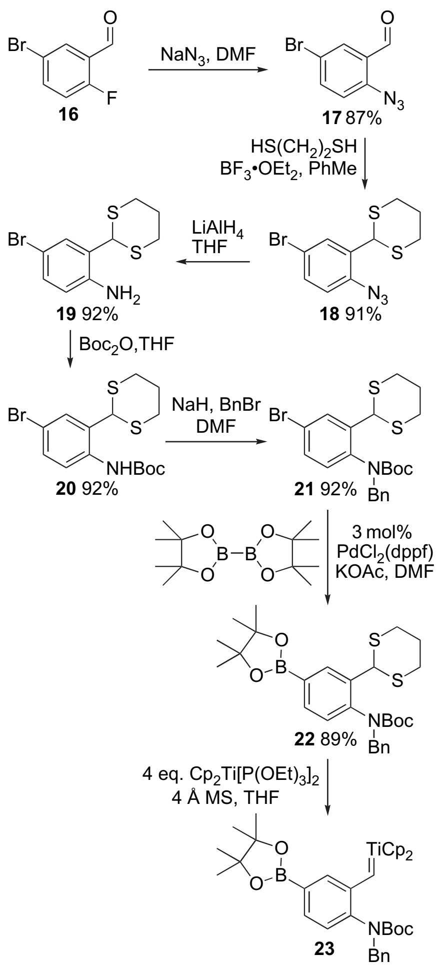
Scheme 3.

We here report a similar strategy for introducing diversity in the indole series. The indole moiety is the archetypal privileged structure, and alkaloids derived from the indole-containing amino acid, tryptophan, are found widely in nature.[16] These include the human 5-hydroxytryptamine (5-HT) hormones, serotonin, which is involved in regulation of the nervous system including neurotransmission, and melatonin, which regulates circadian rhythms and sleep processes. Although natural indoles are almost invariably 3-substituted, 2-substituted analogues of these hormones are also being investigated as potential therapeutic agents.[17] Other bioactive 2-substituted indoles recently reported include inhibitors of the proteases involved in coagulation, e.g., factor VIIa inhibitors,[18] antagonists of G-protein-coupled receptors,[19] anti-angiogenic compounds[20] and inhibitors of endothelin-converting-enzyme.[21] Naturally, new methods for the construction and modification of indole moieties during SPS are continually being reported.[22,23] However, the combination of intermolecular alkylidenation of an ester group followed by cyclisation to give an indole is unique to us.

2. Results and discussion

We chose 5-bromo-2-fluorobenzaldehyde **16** as the starting material for the synthesis of titanium benzylidene complexes, as we reasoned that an amino group could be introduced through SNAr displacement of the fluoride by a suitable nucleophile, the bromide could be replaced by boron through cross-coupling and the aldehyde would easily be converted into a dithiane (Scheme 4). Displacement of fluoride by azide proceeded smoothly to give aldehyde **17**, which was then converted into dithiane **18**. Reduction of the azide gave aniline derivative **19**. This was converted into carbamate **20**, which was benzylated to give aryl bromide **21**. Miyaura cross-coupling then introduced the boronate in high yield, completing the synthesis of a dithiane **22**.[24] Treating the dithiane **22** with freshly prepared Takeda reagent,[25] $Cp_2Ti[P(OEt)_3]_2$, gave a titanium carbenoid, presumed to be titanium benzylidene **23**. This was used immediately, without isolation, to benzylidenate resin-bound ester **24** (Scheme 5), prepared from Merrifield resin and contained within MacroKans™, which are small porous polypropylene reactors (0.315 mequiv of resin per reactor, using of resin with a loading of 1.97 mequiv g^{-1}) that allow easy handling of the resin in normal glassware. Cleavage of the resulting resin-bound enol ether **25** with acid and cyclisation under our published conditions then gave boronate **26**.[26] Alternatively, Suzuki cross-coupling between the resin-bound arylboronate **25** and aryl iodides to give enol ethers **27**, under conditions optimised previously,[14] followed by release and cyclisation gave *N*-benzyl indoles **28**, **29** and **30**. Yields are based on the original loading of the Merrifield resin and so are over five steps. The products were isolated in high purity without the need for chromatography.

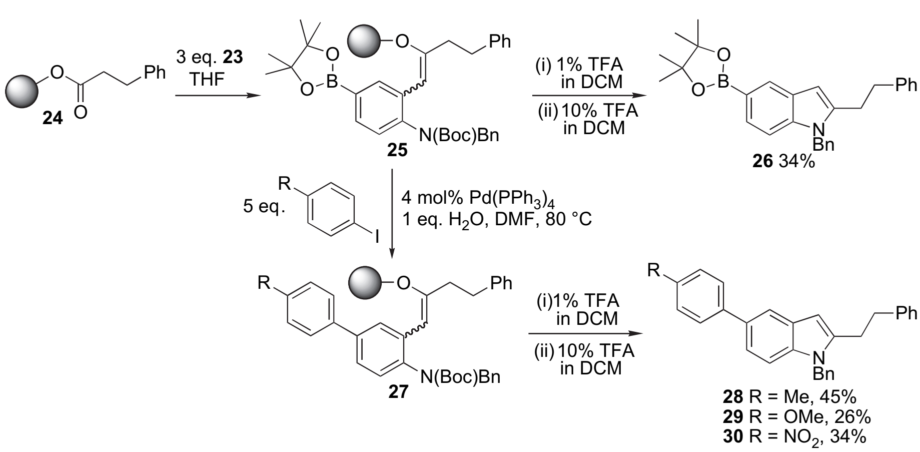
Although *N*-benzyl indoles can be deprotected to give indoles,[27] *N*-Boc protecting groups are more easily removed.[28]



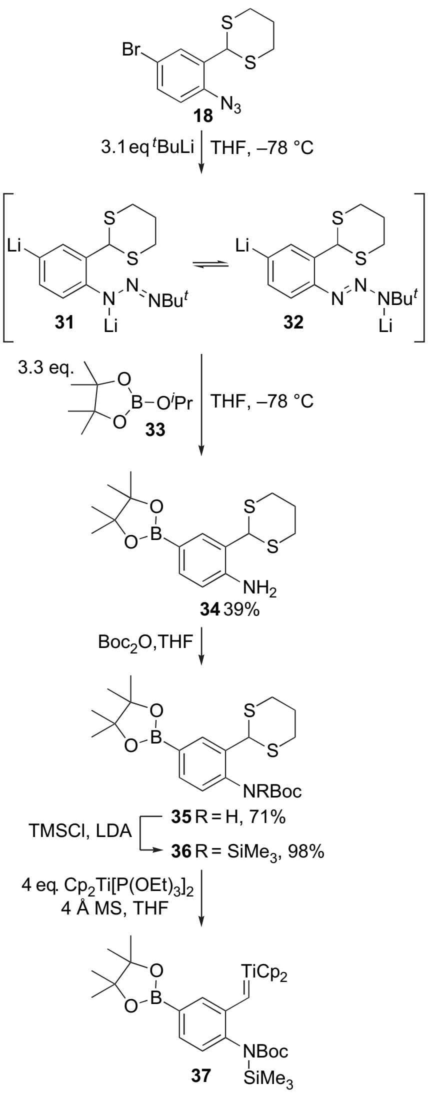
Scheme 4.

Unfortunately, Miyaura cross-coupling had failed when amine **19** or primary carbamate **20** was the substrate.[29] Presumably, coordination of palladium by the dithiane poisons the catalyst, and this coordination is prevented by the bulky *N*-benzylcarbamate. In addition to this limitation, we considered that the Miyaura cross-coupling was expensive, even if a cheaper catalysts is used,[30] due to the cost of bis(pinacolato)diboron. Consequently, it seemed better to introduce the boron by lithiation and trapping with a borate ester. Under optimised conditions, treatment of aryl bromide **18** with 3.1 equiv of *tert*-butyllithium and quenching with borate **33** gave amine **34** after crystallisation (Scheme 6). In spite of the modest yield, the ^{1}H NMR spectrum of the crude mixture following work up appeared to contain no other aromatic compounds. Two of the three equivalents of *tert*-butyllithium are required to convert the aryl bromide moiety into an aryllithium and to destroy the resulting *tert*-butyl bromide.[31] Organolithiums are known to attack the terminal nitrogen of aryl azides and alkyl azides to give 1-aryl-3-alkyltriazenes and 1,3-dialkyltriazenes, respectively,[32] so dilithiated triazenes **31** and **32** are likely to be intermediates. 1-Aryl-3-alkyltriazenes decompose in acid to the corresponding anilines with loss of nitrogen and generation of an alkyl carbocation, and the reaction is particularly fast when the carbocation is stabilised.[33] A similar decomposition appears to be induced by the borate **33**. Interestingly, 1,3-disubstituted triazenes have been used as electrophile-cleavable linkers in solid-phase synthesis, but trisubstituted triazenes are much more versatile and popular.[34] Although the reaction of allyl azide with aryllithiums, followed by acid-induced decomposition, is a known method for preparing anilines,[35] the generation of anilines from aryl azides using *tert*-butyllithium is new.

Boc protection of amine **34** gave carbamate **35**, which was then silylated to give a suitable substrate **36** for the generation of a titanium benzylidene **37** under Takeda conditions. Again, once generated, the titanium reagent was used immediately to benzylidenate resin-bound ester **24**, and cleavage with concomitant cyclisation was achieved under mild conditions[7,36] to give the *N*-Boc indole **39** (Scheme 7). Suzuki cross-couplings between the intermediate boronate **38** and a variety of aryl and heteroaryl iodides gave enol ethers and led to the production of 2,5-substituted indoles **40**–**43** in good purity without the need for chromatography. However, cross-coupling with 1-iodo-4-nitrobenzene gave a 5:1 mixture of the expected product **44** and a compound **45**, presumably arising from Buchwald coupling,[37,38] which could not be avoided.



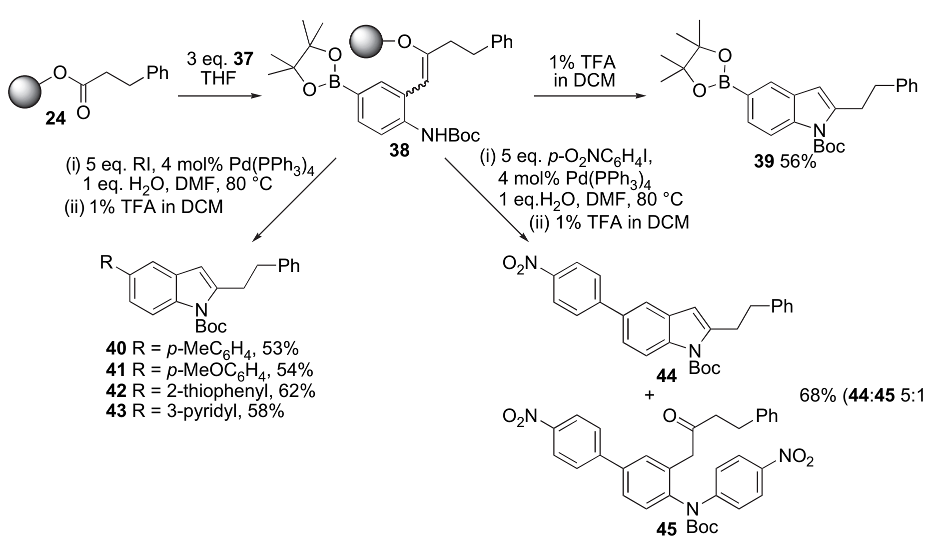
Scheme 5. Yields based on original loading of Merrifield resin.



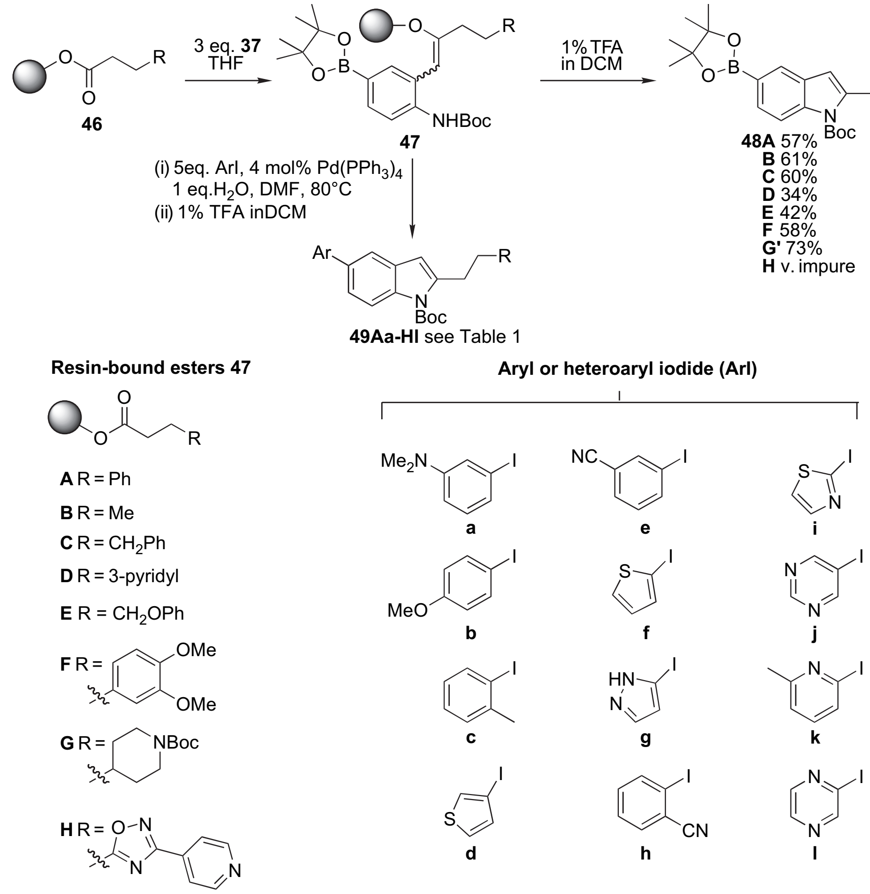
Scheme 6.

With good conditions in hand for the alkylidenation, cross-coupling, cleavage sequence, we decided to prepare a library of 96 indoles **49** (Scheme 8), using smaller amounts of resin in MiniKans™, which are smaller porous polypropylene reactors (93 μequiv of resin per MiniKan™, using Merrifield resin with a loading of 2.0 mequiv g^{-1}). Eight resin-bound esters **46** were prepared and for each ester 13 MiniKans™ containing the same resin-bound ester were alkylidenated together to give enol ethers **47**. One MiniKan™ from each batch was subjected to the cleavage conditions to give the boronates **48** in good yield and purity, with the exception of **48H**, which was very impure. The identity of the boronate products **48** was confirmed by ^{1}H NMR spectroscopy of the crude material from cleavage following evaporation of solvent. Enol ether **47G**, which has two *N*-Boc groups, yielded a mono-Boc compound **48G′**. It is believed that the *N*-Boc on the indole is retained, based on the chemical shift of the *tert*-butyl group and the obvious stability of the other *N*-Boc indoles **48A–F**. It is noteworthy that indoles containing Lewis basic sites (**48D–G′**) could be made using reagent **37**, but it would appear that the 1,2,4-oxadiazole unit has limited stability to the reaction conditions.

Twelve batches of the eight resin-bound enol ethers **47A–H** contained in MiniKans™ were each subjected to Suzuki cross-coupling with a different aryl or heteroaryl iodide, followed by cleavage from resin in separate vessels to give indoles **49**. The crude yields and purities are presented in Table 1. The library members were identified using reversed phase HPLC, with diode array UV detection (DAD-UV), evaporative light scattering detection (ELSD) and MS analysis. The purity values for the library members were determined using summed diode array UV detection (DAD-UV) between the wavelengths of 210 and 350 nm. In 13 examples (in bold), the identity of the library members were further confirmed by ^{1}H NMR spectroscopy following purification by reversed phase HPLC. It is noteworthy that even when the yield and purity were low, as was the case for indole **49Fh**, sufficient material



Scheme 7.



Scheme 8.

could be obtained for identification in this way, giving confidence that other compounds in the library were correctly identified by reversed phase HPLC/DAD-UV/ELSD/MS. Thus, in 79 cases the desired indole was produced (82% success). Surprisingly, di-Boc compounds **49G** were produced, and deprotection of the aliphatic amino group did not dominate. As would be expected from the poor quality of boronate **48H**, there were few products arising from enol ether **47H**. The enol ethers **47** had efficiently cross-coupled with a wide range of aryl and heteroaryl iodides including both electron-rich substrates **a**–**c** and electron-poor substrates **i**–**l**. It is not clear why some derivatives of 3-iodothiophene **d** were not formed, but 3-iodopyrazole[39] **g** appears to be a poor substrate for Suzuki cross-coupling. Indeed, there are no reports of palladium-catalysed cross-couplings with this substrate in the literature.

Table 1
Yields of indoles **49** synthesised (unpurified material, purities in parenthesis)

	A	B	C	D	E	F	G	H
a	66 (89)	72 (97)	78 (81)	53 (70)	64 (88)	72 (94)	68 (71)	[a]
b	**62 (69)**	55 (77)	**35 (78)**	61 (84)	**67 (47)**	**74 (70)**	**59 (60)**	[a]
c	**53 (79)**	48 (80)	37 (83)	56 (69)	**57 (77)**	**37 (43)**	46 (16)	[a]
d	[a]	[a]	56 (54)	63 (44)	65 (50)	80 (46)	[a]	[a]
e	**60 (66)**	62 (91)	30 (73)	72 (87)	**64 (29)**	35 (32)	39 (24)	[a]
f	65 (41)	76 (8)	65 (39)	60 (64)	43 (27)	30 (35)	39 (18)	[a]
g	57 (36)	[a]	[a]	[a]	92 (33)	89 (21)	71 (20)	[a]
h	50 (70)	73 (64)	41 (59)	65 (100)	**52 (48)**	**41 (13)**	57 (43)	39 (84)
i	58 (21)	49 (55)	48 (15)	62 (41)	59 (18)	40 (35)	[a]	18 (12)
j	85 (64)	69 (57)	41 (61)	57 (55)	60 (51)	38 (67)	34 (63)	[a]
k	81 (86)	62 (91)	78 (71)	90 (75)	89 (78)	68 (77)	67 (84)	[a]
l	45 (91)	74 (91)	51 (94)	76 (86)	**64 (64)**	48 (70)	42 (13)	[a]

[a] MW of product not detected.

3. Conclusion

In summary, we have synthesised new titanium carbenoid reagents bearing a boronate functionality, using a sequence that involved a novel reduction of an aryl azide with *tert*-butyllithium. We have demonstrated that this organotitanium reagent can be used for the SPS synthesis of 2,5-disubstituted indoles, and we have exemplified the benzylidenation, Suzuki cross-coupling, cleavage-cyclisation sequence for introducing diversity by successfully preparing 79 of the members of a potential 96-member library of indoles.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz, respectively. All coupling constants are measured in hertz and are uncorrected. DEPT was used to assign the signals in the ^{13}C NMR spectra as C, CH, CH_2 or CH_3. Mass spectra (MS) were recorded on a Jeol JMS700 (MStation) spectrometer. Infrared (IR) spectra were obtained on a Perkin–Elmer 983 spectrophotometer. A Golden Gate™ attachment that uses a type IIa diamond as a single reflection element was used so that the IR spectrum of each compound (solid or liquid) could be directly detected without any sample preparation. Column chromatography was carried out on silica gel, 70–230 mesh, or neutral alumina (Brockmann grade III). Tetrahydrofuran and diethyl ether were dried over sodium and benzophenone, and dichloromethane was dried over calcium hydride. The solid-phase syntheses were carried out using resin derived from commercially available Merrifield resin with the loadings described in the text below and contained in IRORI MacroKans™ (porous polypropylene reactors with an internal volume 2.4 mL, and a pore size of 74 μm) and IRORI MiniKans™ (porous polypropylene reactors with an internal volume 660 μL and a pore size of 74 μm).

*4.1.1. 2-Azido-5-bromobenzaldehyde **17***

Sodium azide (6.71 g, 103 mmol, 2 equiv) was added to a stirring solution of 5-bromo-2-flourobenzaldehyde **16** (10.5 g, 51.6 mmol, 1 equiv) in DMSO (100 mL) under argon. Reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was then poured into ice water and acidified with concentrated HCl. It was then extracted with DCM (2×), washed with water (2×), dried ($MgSO_4$) and concentrated to give 2-azido-5-bromobenzaldehyde **17** as a yellow solid (10.1 g, 44.8 mmol, 87%); mp 87–90 °C (yellow needles from ^{i}PrOH). R_f 0.58 [SiO_2, hexane–DCM (2:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1670 (CHO), 2129 (N_3), 2759 (CH stretch), 2877 (CH stretch). δ_H (400 MHz, $CDCl_3$): 7.17 (1H, d, *J* 8.6 Hz, H-3), 7.71 (1H, dd, *J* 2.4 and 8.6 Hz, H-4), 7.98 (1H, d, *J* 2.4 Hz, H-6), 10.28 (1H, s, CHO). δ_C (100 MHz, $CDCl_3$): 118.25 (C), 120.75 (CH), 127.94 (C), 131.62 (CH), 137.98 (CH), 141.85 (C), 187.07 (CH). *m*/*z* (EI): 227 [$M^{+\bullet}$ (^{81}Br), 6%], 225 [$M^{+\bullet}$ (^{79}Br), 6], 199 [$M^{+\bullet}$ (^{81}Br)−N_2, 27], 197 [$M^{+\bullet}$ (^{79}Br)−N_2, 27], 83 (100). HRMS: 226.9513 and 224.9541. $C_7H_4O^{81}BrN_3$ requires 226.9518, [$M^{+\bullet}$ (^{79}Br)] and $C_7H_4O^{79}BrN_3$ requires 224.9538.

*4.1.2. 2-(2′-Azido-5′-bromophenyl)-1,3-dithiane **18***

1,3-Propanedithiol (6.0 mL, 51 mmol, 1.2 equiv) was added to a solution of 2-azido-5-bromo-benzaldehyde **17** (10.0 g, 44.5 mmol, 1 equiv) and $BF_3\cdot OEt_2$ (7.0 mL, 55 mmol, 1.2 equiv) in dry toluene (100 mL) under an atmosphere of argon. The reaction mixture was stirred for 2 h. The reaction was then quenched by adding water and was extracted into DCM (2×). Combined organics were washed with 1 M NaOH (2×), water (2×), dried ($MgSO_4$) and concentrated to give 2-(2′-azido-5′-bromoophenyl)-1,3-dithiane **18** (12.8 g, 40.3 mmol, 91%). A small sample was recrystallised from isopropanol to give dithiane **18** as yellow needles; mp 162–164 °C. R_f 0.74 [SiO_2, hexane–DCM (2:1)]. ν_{max} (Golden Gate)/cm^{-1}: 2093 cm^{-1} (N_3), 2135 (N_3), 2898 (CH stretch). δ_H (400 MHz, $CDCl_3$): 1.86–1.97 (1H, m, H_{ax}-5), 2.14–2.21 (1H, m, H_{eq}-5), 2.91 (2H, dt, *J* 4.1 and 13.7 Hz, H_{eq}-4 and H_{eq}-6), 3.09 (2H, dt, *J* 2.4 and 13.5 Hz, H_{ax}-4 and H_{ax}-6), 5.43 (1H, s, H-2), 7.00 (1H, d, *J* 8.5 Hz, H-3′), 7.43 (1H, dd, *J* 2.3 and 8.5 Hz, H-4′), 7.74 (1H, d, *J* 2.3 Hz, H-6′). δ_C (100 MHz, $CDCl_3$): 24.95 (CH_2), 32.13 (CH_2), 44.29 (CH), 118.18 (C), 119.25 (CH), 132.08 (C), 132.48 (CH), 132.63 (CH), 135.99 (C). *m*/*z* (EI): 317 [$M^{+\bullet}$ (^{81}Br), 20%], 315 [$M^{+\bullet}$ (^{79}Br), 20], 215 [$M^{+\bullet}$ (^{81}Br)−N_2 and CH_2CHCH_2SH, 30], 213 [$M^{+\bullet}$ (^{79}Br)−N_2 and CH_2CHCH_2SH, 30], 83 (100). HRMS: 316.9484 and 314.9503. $C_{10}H_{10}{}^{81}BrN_3S_2$ requires 316.9478 and $C_{10}H_{10}^{79}BrN_3S_2$ requires 314.9500. Microanalysis: C, 38.05; H, 3.13; N, 13.08%. $C_{10}H_{10}BrN_3S_2$ requires C, 37.98; H, 3.19; N, 13.29%.

*4.1.3. 2-(2′-Amino-5′-bromophenyl)-1,3-dithiane **19***

2-(2′-Azido-5′-bromophenyl)-1,3-dithiane **18** (9.46 g, 29.9 mmol, 1 equiv) dissolved into dry THF (150 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.70 g, 44.9 mmol, 1.5 equiv) in dry THF (100 mL) under argon and the mixture was then stirred at rt for 2.5 h. Saturated aqueous NH_4Cl was added carefully under argon to quench the excess $LiAlH_4$. The reaction mixture was then extracted into Et_2O (2×), washed with water (2×), dried ($MgSO_4$) and concentrated to give amine **459** as a yellow oil (7.99 g, 27.5 mmol, 92%); R_f 0.32 [SiO_2, hexane–DCM (2:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1618 (NH_2 bend), 2898 (CH stretch), 2931 (CH stretch), 3353 (NH stretch), 3443 (NH stretch). δ_H (400 MHz, $CDCl_3$): 1.72–1.84 (1H, m, H_{ax}-5), 2.01–2.08 (1H, m, H_{eq}-5), 2.80 (2H, dt, *J* 4.0 and 13.7 Hz, H_{eq}-4 and H_{eq}-6), 2.94 (2H, dt, *J* 2.4 and 13.5 Hz, H_{ax}-4 and H_{ax}-6), 4.09 (2H, s, NH_2), 5.11 (1H, s, H-2), 6.45 (1H, d, *J* 8.5 Hz, H-3′), 7.09 (1H, dd, *J* 2.3 and 8.5 Hz, H-4′), 7.34 (1H, d, *J* 2.3 Hz, H-6′). δ_C (100 MHz, $CDCl_3$): 24.60 (CH_2), 31.05 (CH_2), 46.81 (CH), 109.34 (C), 117.48 (CH), 123.91 (C), 130.06 (CH), 130.87 (CH), 142.54 (C). *m*/*z* (EI): 291 [$M^{+\bullet}$ (^{81}Br), 45%], 289 [$M^{+\bullet}$ (^{79}Br), 45], 216 [$M^{+\bullet}$ (^{81}Br)−$^{\bullet}CH_2CH_2CH_2SH$, 57], 214 [$M^{+\bullet}$ (^{79}Br)−$^{\bullet}CH_2CH_2CH_2SH$, 57], 83 (100). HRMS: 290.9570 and 288.9598. $C_{10}H_{12}^{81}BrNS_2$

requires 290.9573 and $C_{10}H_{12}^{79}BrNS_2$ requires 288.9595. Microanalysis: C, 41.32; H, 4.11; N, 4.70%. $C_{10}H_{12}BrNS_2$ requires C, 41.38; H, 4.17; N, 4.83%.

4.1.4. 2-[2′-(N-Boc-amino)-5′-bromophenyl)]-1,3-dithiane **20**

A solution of 2-(2′-amino-5′-bromophenyl)-1,3-dithiane **19** (7.73 g, 26.6 mmol, 1 equiv) and di-*tert*-butyldicarbonate (6.39 g, 29.3 mmol, 1.1 equiv) in THF (50 mL) was heated under reflux, under argon, for 15 h. After this time, the reaction mixture was poured into water and extracted into DCM (2×). The combined organics were then washed with water (2×), dried ($MgSO_4$) and concentrated. Recrystallisation from DCM–hexane (1:6) gave carbamate **20** as a solid (7.26 g, 18.6 mmol, 70%); mp 127–128 °C. R_f 0.51 [SiO_2, hexane–DCM (2:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1687 cm^{-1} (C=O), 2929 (CH stretch), 2976 (CH stretch), 3241 (NH stretch), 3323 (NH stretch). δ_H (100 MHz, $CDCl_3$): 1.54 (9H, s, ^{t}Bu), 1.86–1.99 (1H, m, H_{ax}-5), 2.17–2.24 (1H, m, H_{eq}-5), 2.94 (2H, dt, *J* 3.9 and 13.8 Hz, H_{eq}-4 and H_{eq}-6), 3.09 (2H, dt, *J* 2.3 and 13.5 Hz, H_{ax}-4 and H_{ax}-6), 5.23 (1H, s, H-2), 7.26 (1H, s, NH), 7.39 (1H, dd, *J* 2.3 and 8.8 Hz, H-4′), 7.54 (1H, d, *J* 2.3 Hz, H-6′), 7.75 (1H, bd, *J* 8.1 Hz, H-3′). δ_C (400 MHz, $CDCl_3$): 25.39 (CH_2), 28.74 (CH_3), 32.22 (CH_2), 48.08 (CH), 81.31 (C), 116.98 (C), 124.65 (CH), 130 (C), 131.60 (CH), 132.38 (CH), 135.83 (C), 153.27 (C=O). *m/z* (EI): 391 [$M^{+\bullet}$ (^{81}Br), 11%], 389 [$M^{+\bullet}$ (^{79}Br), 10], 335 [$M^{+\bullet}$ (^{81}Br)–CH_2=$C(CH_3)_2$, 71], 333 [$M^{+\bullet}$ (^{79}Br)–CH_2=$C(CH_3)_2$, 65], 229 [$M^{+\bullet}$ (^{81}Br)–CH_2=$C(CH_3)_2$ and HSCH=$CHCH_2SH$, 74], 227 [$M^{+\bullet}$ (^{79}Br)–CH_2=$C(CH_3)_2$ and HSCH=$CHCH_2SH$, 72], 57.1 (100). HRMS: 391.0096. $C_{15}H_{20}^{81}BrNO_2S_2$ requires 391.0098. Microanalysis: C, 46.34; H, 5.26; N, 3.57; S, 16.53%. $C_{15}H_{20}BrNO_2S_2$ requires C, 46.15; H, 5.16; N, 3.59; S, 16.43%.

4.1.5. 2-[2′-(N-Boc-N-benzylamino)-5′-bromophenyl)]-1,3-dithiane **21**

NaH (0.38 g, 16 mmol, 1.2 equiv) was added portionwise to a solution of 2-[2′-(*N*-Boc-amino)-5′-bromophenyl)]-1,3-dithiane **20** (5.14 g, 13.2 mmol, 1 equiv) and benzyl bromide (1.90 mL, 1.4 mmol, 1.2 equiv) in DMF (60 mL) at 0 °C under argon. The reaction mixture was then allowed to warm to rt and stirred for 3 h. After this time, the reaction mixture was carefully poured into iced water and extracted into EtOAc (2×). The combined organics were washed with water (2×), dried ($MgSO_4$) and concentrated. Recrystallisation from DCM–hexane gave *N*-benzylcarbamate **21** as a yellow solid (3.37 g, 7.02 mmol, 54%); mp 155–157 °C. R_f 0.46 [SiO_2, hexane–DCM (2:1),]. ν_{max} (Golden Gate)/cm^{-1}: 1687 cm^{-1} (C=O), 2904 (CH stretch), 2966 (CH stretch). δ_H (400 MHz, $CDCl_3$): 1.40 (9H, s, ^{t}Bu), 1.85–1.98 (1H, m, H_{ax}-5), 2.13–2.18 (1H, m, H_{eq}-5), 2.80–3.02 (4H, m, H-4 and H-6), 4.30 (1H, d, *J* 14.4 Hz, $PhCH^AH^B$), 5.13 (1H, s, H-2), 5.25 (1H, d, *J* 14.1 Hz, $PhCH^AH^B$), 6.50 (1H, br s, H-3′), 7.20 (1H, dd, *J* 1.6 and 8.3 Hz, H-4′), 7.22–7.35 (5H, m, Ar-H), 7.70 (1H, d, *J* 2.3 Hz, H-6′). δ_C (100 MHz, $CDCl_3$): 25.39 (CH_2), 28.47 (CH_3), 32.49 (CH_2), 32.80(CH_2), 46.04 (CH), 53.75 (CH_2), 81.31 (C), 122.15 (C), 127.93 (CH), 128.84 (CH), 129.32 (CH), 131.43 (CH), 132.04 (CH), 132.82 (CH), 138.18 (C), 138.63 (C), 139.29 (C), 155.35 (C=O). *m/z* (EI): 481 [$M^{+\bullet}$ (^{81}Br), 5%], 479 [$M^{+\bullet}$ (^{79}Br), 4], 425 [$M^{+\bullet}$ (^{81}Br)–CH_2=$C(CH_3)_2$, 24], 423 [$M^{+\bullet}$ (^{79}Br)–CH_2=$C(CH_3)_2$, 22], 380 [$M^{+\bullet}$ (^{81}Br)–$^{\bullet}CO_2C(CH_3)_3$, 28], 378 [$M^{+\bullet}$ (^{79}Br)–$^{\bullet}CO_2C(CH_3)_3$, 26], 334 [$M^{+\bullet}$ (^{81}Br)–CH_2=$C(CH_3)_2$ and $^{\bullet}CH_2Ph$, 60], 332 [$M^{+\bullet}$ (^{79}Br)–CH_2=$C(CH_3)_2$ and $^{\bullet}CH_2Ph$, 55], 91.1 (100). HRMS: 481.0566 and 479.0591. $C_{22}H_{26}^{81}BrNO_2S_2$ requires 481.0569 and $C_{22}H_{26}^{79}BrNO_2S_2$ requires 479.0588. Microanalysis: C, 54.75; H, 5.40; N, 3.03; S, 13.42%. $C_{22}H_{26}BrNO_2S_2$ requires C, 54.99; H, 5.45; N, 2.92; S, 13.35%.

4.1.6. 2-[2′-(N-Boc-N-benzylamino)-5′-(4″,4″,5″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)-phenyl]-1,3-dithiane **22**

Following the general procedure for Miyaura cross-coupling, a flask charged with $PdCl_2$(dppf) (0.19 g, 0.26 mmol, 3 mol %), KOAc (2.49 g, 25.40 mmol, 3 equiv) and bis(pinacolato)diboron (2.37 g, 9.31 mmol, 1.1 equiv) was flushed with argon for 30 min. DMSO (45 mL) and aryl bromide **21** (4.07 g, 8.47 mmol, 1 equiv) were then added, the solution was degassed for 30 min and then stirred at 80 °C for 26 h. The reaction mixture was cooled to rt and water was added to the flask to induce precipitation. The grey solid was collected through filtration and washed several times with water. The grey solid was then dissolved in EtOAc and a black solid was removed by filtration through Celite. Removal of solvent under reduced pressure gave a solid, which was recrystallised from cyclohexane to give the arylboronate **22** as a pale brown powder (3.99 g, 89%). Mp 165–168 °C. R_f 0.33 [SiO_2, hexane–DCM (1:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1689 (C=O), 2928 (CH stretch), 2977 (CH stretch). δ_H (400 MHz, $CDCl_3$): 1.32 (12H, s, CH_3), 1.37 (9H, s, CH_3), 1.87–2.20 (2H, m, H-5_{ax+eq}), 2.80–3.05 (4H, m, H-4 and H-6), 4.32 (1H, d, *J* 14.5 Hz, $PhCH^AH^B$), 5.22 (1H, s, H-2), 5.23 (1H, d, *J* 14.8 Hz, $PhCH^AH^B$), 6.68 (1H, br s, H-3′), 7.21–7.23 (5H, m, Ar-H), 7.51 (1H, d, *J* 7.6 Hz, H-4′), 8.65 (1H, d, *J* 1.0 Hz, H-6′). δ_C (100 MHz, $CDCl_3$, 353 K): 24.98 (CH_3), 25.37 (CH_2), 28.25 (CH_3), 32.57 (CH_2), 46.93 (CH), 54.00 (CH_2), 80.58 (C), 83.99 (C), 127.33 (CH), 128.32 (CH), 128.85 (CH), 129.08 (CH), 134.94 (CH), 135.88 (CH), 136.28 (C), 138.48 (C), 142.35 (C), 155.23 (C=O). *m/z* (EI): 527 ($M^{+\bullet}$, 10%), 471 [$M^{+\bullet}$–CH_2=$C(CH_3)_2$, 25], 426 [$M^{+\bullet}$–$^{\bullet}CO_2C(CH_3)_3$, 55], 380 [$M^{+\bullet}$–CH_2=$C(CH_3)_2$ and $^{\bullet}CH_2Ph$], 91 ($^+CH_2Ph$, 100). HRMS: 527.2335. $C_{28}H_{38}NO_4S_2B$ requires 527.2335. Microanalysis: C, 63.28; H, 7.22; N, 2.77%. $C_{28}H_{38}BNO_4S_2$ requires C, 63.75; H, 7.26; N, 2.66%.

4.2. Resin-bound enol ether **25**

Cp_2TiCl_2 (0.94 g, 3.8 mmol, 12 equiv), magnesium turnings (0.10 g, 4.1 mmol, 13 equiv, predried at 250 °C overnight) and freshly activated 4 Å molecular sieves (0.25 g) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (1.3 mL, 7.6 mmol, 24 equiv). After stirring for 3 h at rt, a solution of the dithiane **22** (0.49 g, 0.95 mmol, 3 equiv) in dry THF (4 mL) was added to the mixture and stirring continued for 15 min. The solution was added to a flask containing resin-bound ester **24** contained in a MacroKan™ [0.315 mequiv prepared from 160 mg of Merrifield resin with a loading of 1.97 mequiv (chloride) g^{-1}] and preswollen in THF (6 mL) under argon. After 17 h the reactor was removed from the flask and washed with THF (5×) then alternately with MeOH and DCM (5×) and finally with MeOH and Et_2O. The reactor containing the resin-bound enol ether **25** was then dried under vacuum.

4.2.1. *N-Benzyl-2-phenethyl-5-(4′,4′,5′,5′-tetramethyl-1′,3′-dioxaborolan-2′-yl)indole* ***26***

A MacroKan™ containing the resin-bound enol ether **25** (0.315 mequiv) was shaken with trifluoroacetic acid (1%) in DCM (5 mL) for 1.5 h. The solution was removed and the MacroKan™ was washed with DCM (3×). Combined organics were concentrated under reduced pressure. The residue was placed under argon, dissolved in dry DCM (5 mL) and stirred at 0 °C under argon. Trifluoroacetic acid (0.5 mL, 6.5 mmol) was added dropwise and the mixture was allowed to warm to rt and then stirred for 2 h. After this time, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted into DCM (2×). The combined organics were washed with saturated aqueous sodium bicarbonate (2×), dried over magnesium sulfate and concentrated under reduced pressure to give indole **26** as a brown oil (46 mg, 34%). R_f 0.25 [SiO_2, hexane–DCM (1:1)]. ν_{max} (Golden Gate)/cm^{-1}: 2926 cm^{-1} (CH stretch), 1351 (B–O). δ_H (400 MHz, $CDCl_3$): 1.35 (12H, s, 4×CH_3), 2.96 (4H, s, CH_2CH_2Ph), 5.25 (2H, s, CH_2, NCH_2Ph), 6.40 (1H, s, H-3), 6.89 (2H, dd, *J* 1.8 and 8.0 Hz, Ar-H), 7.10–7.26 (9H, m, Ar-H), 7.58 (1H, dd, *J* 1.0 and 8.2 Hz, H-6), 8.12 (1H, s, H-4). δ_C (100 MHz, $CDCl_3$): 24.88 (CH_3), 28.63 (CH_2), 34.82 (CH_2), 46.28 (CH_2), 83.33 (C), 100.36 (CH), 108.73 (CH), 125.83 (CH), 126.13 (CH), 127.25 (CH), 127.78 (CH), 128.33 (CH), 128.40 (CH), 128.73 (CH), 137.65 (C), 139.20 (C), 140.56 (C). 141.13 (C). *m/z* (EI): 437 ($M^{+\bullet}$, 42%), 346 ($M^{+\bullet}$−$^{\bullet}CH_2Ph$, 100). HRMS: 437.2524 ($M^{+\bullet}$). $C_{29}H_{32}^{11}BNO_2$ requires 437.2526.

4.2.2. *N-Benzyl-5-(4′-methylphenyl)-2-phenethylindole* ***28***

$Pd(PPh_3)_4$ (15 mg, 4 mol %) was added to a stirring suspension of the resin-bound enol ether **25** (0.315 mequiv) contained in a MacroKan™, Cs_2CO_3 (0.54 g, 1.7 mmol, 5.3 equiv) and 4-iodotoluene (350 mg, 1.6 mmol, 5.1 equiv), in degassed DMF (15 mL) with H_2O (5.6 μL, 1 equiv) under argon. The suspension was stirred at 80 °C for 17 h. The mixture was allowed to cool and the MacroKan™ was separated from the reaction mixture and washed with 9:1 DMF–H_2O (3×), alternately with MeOH and DCM (3×) and finally with MeOH and Et_2O. The MacroKan™ containing resin-bound enol ether **27** was then dried under vacuum before being cleaved, in the same way as for the synthesis of boronate **26** to give indole **28** as a brown oil (55 mg, 45%). R_f 0.71 [SiO_2, hexane–DCM (1:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1452 (Ar), 1473 (Ar), 2919 (CH stretch). δ_H (400 MHz, $CDCl_3$): 2.37 (3H, s, CH_3), 2.93–3.02 (4H, m, CH_2CH_2Ph), 5.24 (2H, s, N-CH_2Ph), 6.42 (1H, s, H-3), 6.94 (2H, d, *J* 8.2 Hz, H-2′ and H-6′), 7.13 (2H, d, *J* 8.3 Hz, Ar-H), 7.17–7.28 (9H, m, Ar-H), 7.34 (1H, dd, *J* 1.7 and 8.5 Hz, H-6), 7.53 (2H, d, *J* 8.1 Hz, H-3′ and H-5′), 7.78 (1H, d, *J* 1.5 Hz, H-4). δ_C (100 MHz, $CDCl_3$): 21.04 (CH_3), 28.68 (CH_2), 34.91 (CH_2), 46.42 (CH_2), 100.03 (CH), 109.46 (CH), 118.27 (CH), 120.72 (CH), 125.90 (CH), 126.16 (CH), 127.14 (CH), 127.29 (CH), 128.33 (CH), 128.44 (CH), 128.52 (C), 128.77 (CH), 129.31 (CH), 133.03 (C), 135.74 (C), 136.61 (C), 137.77 (C), 139.75 (C), 141.10 (C), 141.15 (C). *m/z* (EI): 401 ($M^{+\bullet}$, 83), 310 ($M^{+\bullet}$−$^{\bullet}CH_2Ph$, 100). HRMS: 401.2148. $C_{30}H_{27}N$ requires 401.2144.

4.2.3. *N-Benzyl-5-(4′-methoxyphenyl)-2-phenethylindole* ***29***

In the same way, resin-bound enol ether **25** (0.315 mequiv) and 4-iodoanisole (370 mg, 1.6 mmol) yielded indole **29** as a brown oil (34 mg, 26%). R_f 0.50 [SiO_2, hexane–DCM (1:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1453 cm^{-1} (Ar), 1474 (Ar), 2936 (CH stretch). δ_H (400 MHz, $CDCl_3$): 2.85–2.95 (4H, m, CH_2CH_2Ph), 3.74 (3H, s, OCH_3), 5.17 (2H, s, N–CH_2Ph), 6.34 (1H, s, H-3), 6.85–6.89 (4H, m, Ar-H), 7.04–7.20 (9H, m, Ar-H), 7.23 (1H, dd, *J* 1.7 and 8.5 Hz, H-6), 7.48 (2H, m, Ar-H), 7.66 (1H, d, *J* 1.5 Hz, H-4). δ_C (100 MHz, $CDCl_3$): 28.68 (CH_2), 34.88 (CH_2), 46.40 (CH_2), 55.29 (CH_3), 99.94 (CH), 109.46 (CH), 114.02 (CH), 118.00 (CH), 120.57 (CH), 125.88 (CH), 126.16 (CH), 127.28 (CH), 128.22 (CH), 128.33 (CH), 128.43 (CH), 128.52 (C), 128.77 (CH), 132.75 (C), 135.26 (C), 136.41 (C), 137.76 (C), 141.09 (C), 141.14 (C), 158.34 (C). *m/z* (EI): 417 ($M^{+\bullet}$, 61), 326 ($M^{+\bullet}$−$^{\bullet}CH_2Ph$, 100), 91 ($^{+}CH_2Ph$, 31). HRMS: 417.2093. $C_{30}H_{27}NO$ required 417.2095.

4.2.4. *N-Benzyl-5-(4′-nitrophenyl)-2-phenethylindole* ***30***

In the same way, resin-bound enol ether **25** (0.315 mequiv) and 4-iodonitrobenzene (0.45 g, 1.6 mmol) yielded indole **30** as a brown oil (45 mg, 34%). R_f 0.47 [SiO_2, hexane–DCM (1:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1338 cm^{-1} (NO_2), 1453 (Ar), 1512 (NO_2), 3024 (CH stretch). δ_H (400 MHz, $CDCl_3$): 2.98–3.05 (4H, m, CH_2CH_2Ph), 5.29 (2H, s, N–CH_2Ph), 6.40 (1H, s, H-3), 6.95 (2H, d, *J* 6.6 Hz, Ar-H), 7.15 (2H, d, *J* 6.9 Hz, Ar-H), 7.16–7.31 (7H, m, Ar-H), 7.37 (1H, dd, *J* 1.7 and 8.5 Hz, H-6), 7.74 (2H, d, *J* 8.8 Hz, Ar-H), 7.84 (1H, d, *J* 1.6 Hz, H-4), 8.24 (2H, d, *J* 8.8 Hz, H-3′ and H-5′). δ_C (100 MHz, $CDCl_3$): 28.60 (CH_2), 34.73 (CH_2), 46.47 (CH_2), 100.39 (CH), 109.96 (CH), 119.12 (CH), 120.59 (CH), 123.97 (CH), 125.80 (CH), 126.24 (CH), 127.43 (CH), 128.29 (CH), 128.46 (CH), 128.65 (C), 128.83 (CH), 130.31 (C), 137.34 (C), 137.47 (C), 140.88 (C), 141.98 (C), 146.13 (C), 149.11 (C). *m/z* (EI): 432 ($M^{+\bullet}$, 44%), 341 ($M^{+\bullet}$−$^{\bullet}CH_2Ph$, 100), 295 ($M^{+\bullet}$−$^{\bullet}CH_2Ph$ and NO_2, 13), 91 ($^{+}CH_2Ph$, 51). HRMS: 433.1917. $C_{29}H_{24}N_2O_2$ requires 433.1916.

*4.2.5. 2-[2′-Amino-5′-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)]-1,3-dithiane **34***

tert-Butyllithium (69.5 mL, 1.7 M, 118 mmol) was added dropwise over a period of 1 h 45 min to a cooled (−80 to −89 °C) stirred solution of aryl azide **18** (12.1 g, 38.1 mmol) in dry THF (120 mL) under argon ensuring the temperature did not exceed −80 °C. The reaction mixture was stirred for 15 min at −80 °C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25.6 mL, 126 mmol) was added dropwise over 45 min and the resulting mixture was stirred for 1 h 30 min before being allowed to warm to rt and stirred overnight. Water buffered to pH 7 was added and the mixture extracted with DCM (3×). The combined organics were washed with water and then with brine (3×) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a dark brown oil. Crystallisation from pentane and ethyl acetate gave the boronate **34** as a brown solid (4.97 g, 39%). Mp 190–193 °C. R_f 0.70 [SiO_2, DCM–hexane]. ν_{max} (Golden Gate)/cm^{-1}: 1607 (Ar), 3402 (NH_2). δ_H (400 MHz, $CDCl_3$): 1.23 (12H, s, CH_3), 1.82–1.99 (1H, m, H_{ax}-5), 2.09–2.21 (1H, m, H_{eq}-5), 2.83 (2H, td, *J* 4.0 and 13.0 Hz, H_{eq}-4 and H_{eq}-6), 3.01 (2H, dt, *J* 2.0 and 13.0 Hz, H_{ax}-4 and H_{ax}-6), 4.40 (2H, br s, NH_2), 5.26 (1H, s, H-2), 6.57 (1H, d, *J* 8.1 Hz, H-3′), 7.48 (1H, dd, *J* 1.4 and 8.1 Hz, H-4′), 7.63 (1H, d, *J* 1.3 Hz, H-6′). δ_C (100 MHz, $CDCl_3$): 24.89 (CH_3), 25.29 (CH_2), 32.00 (CH_2), 49.97 (CH), 83.40 (C), 116.16 (CH), 121.50 (C), 136.21 (CH), 136.29 (CH), 147.82 (C). *m/z* (EI): 337 ($M^{+\bullet}$, 79%), 262 (100). HRMS: 337.1338. $C_{16}H_{24}O_2NS_2B$ requires 337.1341. Microanalysis: C, 57.02; H, 7.17; N, 4.22%. $C_{16}H_{24}O_2NS_2B$ requires C, 56.97; H, 7.17; N, 4.15%.

*4.2.6. 2-[2′-tert-Butoxycarboxyamino-5′-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)]-1,3-dithiane **35***

A solution of amine **34** (5.81 g, 17.2 mmol) in dry THF (150 mL) and $(Boc)_2O$ (7.89 g, 36.2 mmol) was heated under reflux for 12 h under argon. After this time an additional equivalent of $(Boc)_2O$ (3.75 g) was added and the reaction mixture stirred at reflux for a further 24 h. The reaction mixture was then allowed to cool to rt and quenched with water. The mixture was extracted with DCM (2×) and the combined organics were washed with water (2×) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow solid. Column chromatography eluting with hexane–EtOAc (4:1) gave carbamate **35** as a pale yellow solid (5.41 g, 71%). Mp 99–101 °C. R_f 0.45 [SiO_2, hexane–EtOAc (4:1)]. ν_{max} (Golden Gate)/cm^{-1}: 1366 (B–O), 1478 (Ar), 1682 (C=O). δ_H (400 MHz, $CDCl_3$): 1.32 (12H, s, CH_3), 1.54 (9H, s, ^{t}Bu), 1.91 (1H, ttd, *J* 3.0, 12.5 and 14.1 Hz, H_{ax}-5), 2.17 (1H, ttd, *J* 2.3, 3.9 and 14.2 Hz, H_{eq}-5), 2.93 (2H, ddd, *J* 3.3, 3.9 and 14.4, H_{eq}-4 and H_{eq}-6), 3.06 (2H, ddd, *J* 2.3, 12.5 and 14.4 Hz, H_{ax}-4 and H_{ax}-6), 5.34 (1H, s, H-2), 7.69 (1H, br s, NH), 7.71 (1H, dd, *J* 1.4 and 8.3 Hz, H-4′), 7.78 (1H, d, *J* 1.4 Hz, H-6′), 7.96 (1H, d, *J* 8.3 Hz, H-3′). δ_C (100 MHz, $CDCl_3$): 24.86 (CH_3), 25.17 (CH_2), 28.40 (CH_3), 31.93 (CH_2), 49.52 (CH), 80.59 (C), 83.73 (C), 85.17 (CH), 135.61 (CH), 135.91 (CH), 139.62 (C), 146.75 (C), 152.75 (C). *m/z* (EI): 437 ($M^{+\bullet}$, 6%), 380 (71), 274 ($M^{+\bullet}$, $-{}^\bullet C(CH_3)_3$ and HSCH=CHCH$_2$SH, 100). HRMS: 437.1866. $C_{21}H_{32}O_4NS_2B$ requires 437.1867.

*4.2.7. 2-[2′-Aminosilylcarbamate-5′-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)]-1,3-dithiane **36***

A solution of lithium diisopropylamide (1.80 mL, 2.0 M, 3.4 mmol) was added dropwise to a cooled stirred solution of carbamate **35** (1.22 g, 2.8 mmol) and TMSCl (0.42 mL, 3.4 mmol) in THF (30 mL) at −78 °C under an inert atmosphere of argon. The reaction mixture was then allowed to warm to rt over 45 min and was allowed to stir for a further 1 h at rt. After this time, the solvent was removed in vacuo and ether (30 mL) was added. The resulting white solid was filtered off and the ethereal solution concentrated to furnish target *N*-silylcarbamate **36** as an off-white solid (1.40 g, 98%). δ_H (400 MHz, $CDCl_3$): 0.24 (9H, s, Si–CH_3), 1.33 (12H, s, CH_3), 1.54 (9H, s, ^{t}Bu), 1.92–2.05 (1H, m, H_{ax}-5), 2.14–2.22 (1H, m, H_{eq}-5), 2.88–3.07 (4H, m, H_{eq}-4, H_{eq}-6, H_{ax}-4 and H_{ax}-6), 5.21 (1H, s, H-2), 6.94 (1H, d, *J* 7.7 Hz, H-3′), 7.65 (1H, dd, *J* 1.3 and 7.7 Hz, H-4′), 8.06 (1H, d, *J* 1.3 Hz, H-6′). δ_C (100 MHz, $CDCl_3$): 0.60 (CH_3), 23.52 (CH_3), 23.82 (CH_2), 27.05 (CH_3), 30.59 (CH_2), 48.18 (CH), 79.26 (C), 82.39 (C), 119.35 (C), 126.95 (C), 134.27 (CH), 134.58 (CH), 138.28 (C), 151.41 (C). *m/z* (EI): 509 ($M^{+\bullet}$, 3%), 452 [($M^{+\bullet}-{}^\bullet C(CH_3)_3$, 55)], 408 [($M^{+\bullet}-{}^\bullet C(CH_3)_3$ and CO_2, 60)], 346 ($M^{+\bullet}$, $-{}^\bullet C(CH_3)_3$ and HSCH=CHCH$_2$SH, 100). HRMS: 509.2263. $C_{24}H_{40}O_4NS_2BSi$ requires 509.2261.

*4.3. Resin-bound enol ether **38***

Resin-bound enol ether was prepared in the same way as resin-bound enol ether **25**, but using dithiane **36** instead of dithiane **22** with resin-bound ester **24** contained in a MacroKan™ [0.325 mequiv prepared from 170 mg of Merrifield resin with a loading of 1.91 mequiv (chloride) g^{-1}].

*4.3.1. N-Boc-2-phenylethyl-5-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)]-indole **39***

A MacroKan™ containing the resin-bound enol ether **25** (0.325 mequiv) was shaken with trifluoroacetic acid (1%) in DCM (5 mL) for 1.5 h. The solution was removed and the reactor was washed with DCM (3×). Combined organics were concentrated under reduced pressure to give indole **39** as a purple solid (81 mg, 56%). Mp 101–104 °C. R_f 0.76 [SiO_2, DCM]. ν_{max} (Golden Gate)/cm^{-1}: 1734 (C=O), 2976 (CH). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.68 (9H, s, ^{t}Bu), 3.01 (2H, t, *J* 8.4 Hz, H-2′), 3.32 (2H, t, *J* 8.4 Hz, H-1′), 6.33 (1H, s, H-3), 7.18–7.29 (5H, m, Ar-H), 7.69 (1H, dd, *J* 0.9 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 0.9 Hz, H-4), 8.04 (1H, d, *J* 8.4 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 24.93 (CH_3), 28.27 (CH_3), 31.76 (CH_2), 35.20 (CH_2), 83.65 (C), 83.95 (C), 107.64 (CH), 114.94 (CH), 126.00 (CH), 127.06 (CH), 128.38 (CH), 128.43 (CH), 128.90 (C), 129.74 (CH), 138.69 (C), 141.47 (C), 141.59 (C), 150.52 (C). *m/z* (EI): 447 ($M^{+\bullet}$, 19%), 391 ($M^{+\bullet}-CH_2=C(CH_3)_2$, 44), 300 (82), 83 (100). HRMS: 447.2577. $C_{27}H_{34}O_4NB$ requires 447.2571.

4.3.2. *N-Boc-5-(4′-methylphenyl)-2-(2″-phenylethyl)indole* ***40***

$Pd(PPh_3)_4$ (14.4 mg, 4 mol %) was added to a stirring suspension of resin-bound enol ether **25** (0.325 mequiv) contained in a MacroKan™, Cs_2CO_3 (511 mg, 1.5 mmol, 4.6 equiv) and 4-iodotoluene (338 mg, 1.55 mmol, 4.8 equiv), in degassed DMF (15 mL) with H_2O (5.6 μL, 0.31 mmol, 0.96 equiv) under argon. The mixture was stirred at 80 °C for 5 h. Cleavage in the same way as for indole **39** gave indole **40** as a brown solid (74.1 mg, 53%). Mp 75–78 °C. R_f 0.76 [SiO_2, DCM]. ν_{max} (Golden Gate)/cm^{-1}: 1468 (Ar), 1731 (C=O), 2929 (CH), 2077 (CH), 3025 (Ar-H). δ_H (400 MHz, $CDCl_3$): 1.63 (9H, s, ^{t}Bu), 2.33 (3H, s, CH_3), 2.97 (2H, t, *J* 8.4 Hz, CH_2Ph), 3.28 (2H, t, *J* 8.4 Hz, CH_2CH_2Ph), 6.32 (1H, s, H-3), 7.14–7.27 (5H, m, Ar-H), 7.22 (2H, d, *J* 8.8 Hz, Ar-H), 7.40 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.47 (2H, d, *J* 8.8 Hz, Ar-H), 7.56 (1H, d, *J* 2.0 Hz, H-4), 8.03 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 21.12 (CH_3), 28.32 (CH_3), 32.52 (CH_2), 35.25 (CH_2), 83.93 (C), 107.57 (CH), 115.80 (CH), 118.06 (CH), 122.71 (CH), 126.07 (CH), 127.14 (CH), 128.45 (CH), 128.47 (CH), 129.78 (CH), 129.87 (C), 135.85 (C), 135.91 (C), 136.49 (C), 138.84 (C), 141.52 (C), 142.31 (C), 150.62 (C). *m/z* (EI): 411 ($M^{+\bullet}$, 34%), 355 ($M^{+\bullet}$–CH_2=$C(CH_3)_2$, 56), 264 (95), 290 (100). HRMS: 411.2199. $C_{28}H_{29}O_2N$ requires 411.2198.

4.3.3. *N-Boc-5-(4′-methoxyphenyl)-2-(2″-phenylethyl)indole* ***41***

In the same way, but using 4-iodoanisole (365 mg) as the aryl iodide in the Suzuki cross-coupling gave indole **41** as a dark brown solid (74.3 mg, 54%). Mp 80–83 °C. ν_{max} (Golden Gate)/cm^{-1}: 1468 (Ar), 1731 (C=O), 2929 (CH). δ_H (400 MHz, $CDCl_3$): 1.61 (9H, s, ^{t}Bu), 2.95 (2H, t, *J* 7.8 Hz, CH_2Ph), 3.26 (2H, t, *J* 7.8 Hz, CH_2CH_2Ph), 3.76 (3H, s, OCH_3), 6.29 (1H, s, H-3), 6.89 (2H, d, *J* 2.0 Hz, H-3′ and H-5′), 7.09–7.25 (5H, m, Ph), 7.34 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.48 (2H, d, *J* 2.0 Hz, H-2′ and H-6′), 7.52 (1H, d, *J* 2.0 Hz, H-4), 8.03 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 28.31 (CH_3), 31.83 (CH_2), 35.24 (CH_2), 55.40 (CH_3), 82.87 (C), 107.43 (CH), 114.20 (CH), 115.79 (CH), 117.79 (CH), 122.66 (CH), 126.05 (CH), 128.26 (CH), 128.43 (CH), 128.64 (CH), 128.79 (C), 133.27 (C), 134.51 (C), 134.58 (C), 140.43 (C), 141.22 (C), 149.51 (C), 157.70 (C). Mass (*m/z*) LRMS (EI$^+$): 427 ($M^{+\bullet}$, 52%), 371 ($M^{+\bullet}$–CH_2=$C(CH_3)_2$, 87), 280 (100). HRMS: 427.2148. $C_{28}H_{29}O_3N$ requires 427.2147.

4.3.4. *N-Boc-2-(2′-phenylethyl)-5-(2″-thiophenyl)indole* ***42***

In the same way, but using 2-iodothiophene (322 mg) as the aryl iodide in the Suzuki cross-coupling gave indole **42** as a dark brown solid (81 mg, 62%). Mp 108–110 °C. ν_{max} (Golden Gate)/cm^{-1}: 1470 (Ar), 1726 (C=O), 2854 (CH), 2925 (CH). δ_H (400 MHz, $CDCl_3$): 1.68 (9H, s, ^{t}Bu), 3.03 (2H, t, *J* 8.0 Hz, CH_2Ph), 3.33 (2H, t, *J* 8.0 Hz, CH_2CH_2Ph), 6.35 (1H, s, H-3), 7.02–7.08 (1H, m, H-4″), 7.18–7.31 (7H, m, H-5″, H-3″ and Ph), 7.51 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.66 (1H, d, *J* 2.0 Hz, H-4), 8.07 (1H, d, *J* 8.8 Hz, H-7). δ_C (100 MHz, $CDCl_3$): 28.25 (CH_3), 31.76 (CH_2), 35.12 (CH_2), 84.05 (C), 107.45 (CH), 115.90 (CH), 117.08 (CH), 121.76 (CH), 122.61 (CH), 124.08 (CH), 126.03 (CH), 127.94 (CH), 128.40 (CH), 128.42 (CH), 129.30 (C), 129.80 (C), 135.99 (C), 141.39 (C), 142.56 (C), 145.16 (C), 150.41 (C). *m/z* (EI): 403 ($M^{+\bullet}$, 43%), 347 ($M^{+\bullet}$–CH_2=$C(CH_3)_2$, 67], 212 (100). HRMS: 403.1607. $C_{25}H_{25}O_3NS$ requires 403.1606.

4.3.5. *N-Boc-2-(2′-phenylethyl)-5-(3″-pyridyl)indole* ***43***

In the same way, but using 3-iodopyridine (312 mg) as the aryl iodide in the Suzuki cross-coupling gave indole **43** as its TFA salt (105 mg) as a dark brown solid. A portion of the salt (40.0 mg) was treated with $NaHCO_3$ and extracted into DCM. The combined organics were concentrated under reduced pressure to give the indole **43** (27.6 mg, 58%) as a brown oil. ν_{max} (KBr)/cm^{-1}: 1496 (Ar), 1733 (C=O), 2854 (CH), 2974 (CH). δ_H (400 MHz, $CDCl_3$): 1.64 (9H, s, ^{t}Bu), 2.98 (2H, t, *J* 7.8 Hz, C*H*$_2$Ph), 3.30 (2H, t, *J* 7.8 Hz, C*H*$_2$CH$_2$Ph), 6.35 (1H, s, H-3), 7.12–7.23 (5H, m, Ph), 7.40 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.58 (1H, d, *J* 2.0 Hz, H-4), 7.84–7.87 (1H, m, H-5″), 8.12 (1H, d, *J* 8.8 Hz, H-7), 8.52 (1H, d, *J* 8.6 Hz, H-4″), 8.68 (1H, d, *J* 2.2 and 8.6 Hz, H-6″), 9.04 (1H, d, *J* 2.2 Hz, H-2″). δ_C (100 MHz, $CDCl_3$): 27.25 (CH_3), 30.74 (CH_2), 34.12 (CH_2), 83.15 (C), 106.41 (CH), 115.13 (CH), 117.30 (CH), 121.51 (CH), 125.03 (CH), 126.74 (CH), 127.39 (C), 128.14 (CH), 128.31 (CH), 130.21 (C), 137.14 (C), 139.21 (CH), 140.31 (CH), 141.72 (C), 140.07 (C), 142.73 (CH), 143.42 (C), 149.93 (C). *m/z* (EI): 398 ($M^{+\bullet}$, 21%), 342 [$M^{+\bullet}$–CH_2=$C(CH_3)_2$, 48], 251 (65), 207 (100). HRMS: 398.1996. $C_{26}H_{26}O_2N_2$ requires 398.1994.

4.3.6. *N-Boc-5-(4″-nitrophenyl)-2-(2′-phenylethyl)indole* ***44*** *and 1-[2′-(N-Boc- 4″-nitrophenylamino)-5′-(4‴-nitrophenyl)phenyl]-4-phenylbutan-2-one* ***45***

In the same way, but using 1-iodo-4-nitrobenzene (391 mg) and heating at 80 °C for only 2 h in the Suzuki cross-coupling, gave a 5:1 mixture of indole **44** and ketone **45** (97 mg, 68%) after cleavage. Pure samples of each compound were obtained by chromatography (DCM). Indole **44** was isolated as a yellow solid. R_f 0.85 [SiO_2, DCM]. ν_{max} (Golden Gate)/cm^{-1}: 1341 (NO_2), 1516 (NO_2), 1595 (Ar), 1734 (C=O), 2926 (CH), 2968 (CH). δ_H (400 MHz, $CDCl_3$): 1.63 (9H, s, CH_3), 2.97 (2H, t, *J* 7.9 Hz, C*H*$_2$Ph), 3.28 (2H, t, *J* 7.9 Hz, C*H*$_2$CH$_2$Ph), 6.33 (1H, s, H-3), 7.13–7.22 (5H, m, Ar-H), 7.41 (1H, dd, *J* 1.9 and 8.7 Hz, H-6), 7.61 (1H, d, *J* 1.7 Hz, H-4), 7.67 (2H, d, *J* 8.8 Hz, H-2″ and H-6″), 8.09 (1H, d, *J* 8.7 Hz, H-7), 8.19 (2H, d, *J* 8.8 Hz, H-3″ and 5″). δ_C (100 MHz, $CDCl_3$): 28.30 (CH_3), 31.77 (CH_2), 35.16 (CH_2), 84.39 (C), 107.50 (CH), 116.57 (CH), 119.43 (CH), 122.73 (CH), 124.10 (CH), 126.14 (CH), 128.38 (CH), 127.71 (CH), 128.42 (CH), 130.03 (C), 133.26 (C), 136.93 (C), 141.29 (C), 143.04 (C), 146.67 (C), 148.24 (C), 150.34 (C). *m/z* (EI): 442 ($M^{+\bullet}$, 16%), 386 ($M^{+\bullet}$–CH_2=$C(CH_3)_2$, 63), 295 (86), 57 (100). HRMS: 442.1893. $C_{27}H_{26}O_4N_2$ requires 442.1893. Ketone **45** was isolated as an orange solid. R_f 0.48 [SiO_2, DCM]. ν_{max} (Golden Gate)/cm^{-1}: 1342 (NO_2), 1517 (NO_2), 1592 (Ar), 1717 (C=O), 2924 (CH). δ_H (400 MHz, $CDCl_3$): 1.38 (9H, s, CH_3), 2.71 (4H, m, CH_2CH_2Ph), 3.46 (1H, d, *J* 15.7 Hz), 3.54 (1H, d, *J* 15.7 Hz), 7.03–7.21 (5H, m, Ar-H), 7.25 (1H, d, *J* 8.2 Hz, H-3′), 7.29 (2H, d, *J* 9.3 Hz, H-2″ and H-6″), 7.41 (1H, d, *J* 2.2 Hz, H-6′), 7.55 (1H, dd, *J* 2.2 and 8.2 Hz, H-4′), 7.67 (2H, d, *J* 8.8 Hz, H-2‴ and H-6‴), 8.04 (2H, d, *J* 9.3 Hz, H-3″ and H-5″), 8.25 (2H, d, *J* 8.8 Hz, H-3‴ and H-5‴). δ_C (100 MHz, $CDCl_3$): 28.09 (CH_3), 29.60 (CH_2), 45.18 (CH_2), 83.28 (C), 123.48 (CH), 124.21 (CH), 124.31 (CH), 126.31 (CH), 127.54 (CH), 127.99 (CH), 128.28 (CH), 128.56 (CH), 130.59 (CH), 131.27 (CH), 133.50 (C), 138.96 (C), 140.48 (C), 140.59 (C), 143.70 (C), 146.03 (C), 147.45 (C), 147.64 (C), 152.65 (C), 205.36 (C). *m/z* (FAB^+): 582 ($M+H^+$, 22%), 526 [$(M+H)^+-CH_2=C(CH_3)_2$, 40], 482 (58), 481 (32), 59 (100). HRMS: 582.2240. $C_{33}H_{32}O_7N_3$ requires $M+H^+$, 582.2240.

4.4. Library synthesis

4.4.1. Resin-bound enol ether *47*

Cp_2TiCl_2 (3.623 g, 14.5 mmol, 12 equiv), magnesium turnings (0.391 g, 15.9 mmol, 13 equiv, predried at 250 °C overnight) and freshly activated 4 Å molecular sieves (703 mg) were heated, gently, under reduced pressure (0.3 mmHg) for about 1 min and then placed under argon. Dry THF (20 mL) was added followed by dry $P(OEt)_3$ (5.2 mL, 29 mmol, 24 equiv). After stirring for 3 h at rt, a solution of the dithiane **36** (1.85 g, 3.6 mmol, 3 equiv) in dry THF (20 mL) was added to the mixture and stirring continued for 15 min. After this time, 13 MiniKans™, each containing one of the resin-bound esters **46A–H** [93 μequiv/MiniKan™ prepared from 46.5 mg of Merrifield resin with a loading of 2.0 mequiv (chloride) g^{-1}], that had been purged with argon were added. After 17 h the MiniKans™ were removed from the flask and washed with THF (5×) then alternately with MeOH and DCM (5×) and finally with MeOH and Et_2O. The 13 MiniKans™ containing one of the resin-bound enol ethers **47A–H** were then dried under vacuum. The same procedure was employed for all eight resin-bound esters **46A–H**, using 104 MiniKans™ in total.

4.4.2. N-Boc-2-(2′-phenylethyl)-5-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)indole *48A*

One MiniKan™ containing resin-bound enol ether **47A** (93 μequiv) was shaken with trifluoroacetic acid (1%) in DCM (5 mL) for 1.5 h. The solution was removed and the reactor was washed with DCM (3×). Combined organics were concentrated under reduced pressure to give indole **47A** (23.7 mg, 57%). ^1H NMR data as reported for indole **39** above.

4.4.3. N-Boc-2-propyl-5-(4′,5′-tetramethyl-1′,3′,2′-dioxaborolan-2′-yl)indole *48B*

In the same way, one MiniKan™ containing resin-bound enol ether **47B** (93 μequiv) gave indole **48B** (21.8 mg, 61%). δ_H (400 MHz, $CDCl_3$): 1.03 (2H, t, *J* 7.2 Hz, CH_3CH_2), 1.37 (12H, s, CH_3), 1.67 (9H, s, ^{t}Bu), 2.93–2.98 (4H, m, CH_2CH_2), 6.34 (1H, s, H-3), 7.65 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 8.06 (1H, d, *J* 1.2 Hz, H-4), 8.21 (1H, d, *J* 8.4 Hz, H-7).

4.4.4. N-Boc-2-(3′-phenylpropyl)-5-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)indole *48C*

In the same way, one MiniKan™ containing resin-bound enol ether **47C** (93 μequiv) gave indole **48C** (25.7 mg, 60%). δ_H (400 MHz, $CDCl_3$): 1.33 (12H, s, CH_3), 1.66 (9H, s, ^{t}Bu), 2.04 (2H, qn, *J* 7.4 Hz, $CH_2CH_2CH_2$), 2.73 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2Ph$), 3.03 (2H, t, *J* 7.4 Hz, CH_2Ph), 7.19–7.29 (5H, m, Ar-H), 6.34 (1H, s, H-3), 7.67 (1H, dd, *J* 1.6 and 8.4 Hz, H-6), 7.93 (1H, d, *J* 1.6 Hz, H-4), 8.08 (1H, d, *J* 8.4 Hz, H-7).

4.4.5. N-Boc-2-[2′-(3″-pyridyl)]-5-(4‴,5‴-tetramethyl-1‴,3‴,2‴-dioxaborolan-2‴-yl)indole *48D*

In the same way, one MiniKan™ containing resin-bound enol ether **47D** (93 μequiv) gave indole **48D** (24.2 mg, 58%). δ_H (400 MHz, DMSO-d_6): 1.21 (9H, s, ^{t}Bu), 1.24 (12H, s, CH_3), 2.76 (2H, t, *J* 7.2 Hz, CH_2CH_2), 3.17 (2H, t, *J* 7.2 Hz, CH_2CH_2), 6.32 (1H, s, H-3), 7.12 (1H, dd, *J* 1.6 and 8.4 Hz, H-6), 7.22 (1H, d, *J* 1.6 Hz, H-4), 7.25 (1H, br dd, *J* 4.8 and 7.7 Hz, H-5″), 7.62 (1H, d, *J* 8.4 Hz, H-7), 7.67 (1H, br d, *J* 7.8 Hz, H-4″), 8.41 (1H, br s, H-2″), 8.43 (1H, br d, *J* 4.7 Hz, H-6″).

4.4.6. N-Boc-2-(3′-phenoxypropyl)-5-(4″,5″-tetramethyl-1″,3″,2″-dioxaborolan-2″-yl)indole *48E*

In the same way, one MiniKan™ containing resin-bound enol ether **47E** (93 μequiv) gave indole **48E** (17.5 mg, 42%). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.68 (9H, s, ^{t}Bu), 2.19 (2H, qn, *J* 7.4 Hz, $CH_2CH_2CH_2$), 3.20 (2H, t, *J* 7.2 Hz, $CH_2CH_2CH_2OPh$), 4.04 (2H, t, *J* 7.4 Hz, CH_2OPh), 6.37 (1H, s, H-3), 6.88–6.95 (3H, m, Ar-H), 7.27–7.29 (2H, m, Ar-H), 7.67 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 1.2 Hz, H-4), 8.07 (1H, d, *J* 8.4 Hz, H-7).

4.4.7. N-Boc-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-5-(4‴,5‴-tetramethyl-1‴,3‴,2‴-dioxaborolan-2‴-yl)indole *48F*

In the same way, one MiniKan™ containing resin-bound enol ether **47F** (93 μequiv) gave indole **48F** (27.1 mg, 58%). δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, CH_3), 1.67 (9H, s, ^{t}Bu), 2.96 (2H, t, *J* 7.2 Hz, H-2′), 3.30 (2H, t, *J* 7.4 Hz, H-1′), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.32 (1H, s, H-3), 6.71 (1H, d, *J* 1.6 Hz, H-2″), 6.77–6.78 (2H, m, H-5″ and H-6″), 7.68 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 7.92 (1H, d, *J* 1.2 Hz, H-4), 8.06 (1H, d, *J* 8.4 Hz, H-7).

4.4.8. N-Boc-2-[2′-(piperidin-4″-yl)ethyl]-5-(4‴,5″-tetramethyl-1‴,3‴,2‴-dioxaborolan-2‴-yl)indole, trifluoroacetate salt *48G′*

In the same way, one MiniKan™ containing resin-bound enol ether **47E** (93 μequiv) gave indole **48G′** (36.6 mg, 73%). δ_H (400 MHz, $CDCl_3$): 1.37 (12H, s, CH_3), 1.53–1.56 (5H, m, H-pip), 1.69 (9H, s, ^{t}Bu), 2.00–2.10 (2H, m, piperidine), 2.90–3.10 (4H, m, CH_2CH_2), 3.45–3.60 (2H, m, 2× CH^AH^BN), 6.34 (1H, s, H-3), 7.68 (1H, dd, *J* 1.2 and 8.4 Hz, H-6), 7.93 (1H, s, H-4), 8.01 (1H, d, *J* 8.4 Hz, H-7), 9.11 (2H, br s, NH_2).

4.5. Indoles *49Aa–Hl*

$Pd(PPh_3)_4$ (15 mg, 4 mol %) was added to a flask containing eight MiniKans™ each containing a different resin-bound enol ether **47A–H** (93 μequiv/MiniKan™), stirring with Cs_2CO_3 (1.21 g, 3.7 mmol), one of the aryl iodides **a–h** (3.7 mmol) and water (13.3 μL, 0.74 mmol) in degassed DMF (30 mL) under argon. The suspension was shaken at 80 °C for 6 h. The mixture was allowed to cool and the MiniKans™ were separated from the reaction mixture and washed with 9:1 DMF–H_2O (3×), alternately with MeOH and DCM (3×) and finally with MeOH and Et_2O. The MiniKans™ containing resin were then dried under vacuum. This procedure was used for each of the 12 different aryl iodides **a–h** and the resulting 96 MiniKans™, each containing a different resin-bound enol ether, were placed in an IRORI Clevap™ (automatic cleavage and evaporation) station, so that each MiniKan™ was treated separately with trifluoroacetic acid (1%) in DCM for 1.5 h, then with DCM–MeOH (4:1) for 0.5 h and the combined organics from each MiniKan™ were collected separately and evaporated to give indoles **49Aa–Hl** in the yields and purities shown in Table 1. Analysis of the library was by reversed phase HPLC/DAD-UV/ELSD/MS using a Waters Analytical 4-way MUX QC System with an Agilent Zorbax SB C8, 21.2×250 mm column and eluting with 0.1% trifluoroacetic acid in MeCN–H_2O (4:1), flow=25 mL min^{-1}. HPLC MS data is displayed in Table 2 (library members in bold also have ^1H NMR data for the reversed phase HPLC-purified indoles as listed below).

4.5.1. N-Boc-5-(4′-methoxyphenyl)-2-(2″-phenylethyl)indole *49Ab*

Data are as reported under indole **41** above.

4.5.2. N-Boc-5-(2′-methylphenyl)-2-(2″-phenylethyl)indole *49Ac*

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.28 (3H, s, CH_3), 3.04 (2H, t, *J* 7.6 Hz, CH_2Ph), 3.36 (2H, t, *J* 7.6 Hz, CH_2CH_2Ph), 6.39 (1H, s, H-3), 7.20 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.22–7.32 (9H, m, Ph, H-3′ to H-6′), 7.38 (1H, d, *J* 2.0 Hz, H-4), 8.09 (1H, d, *J* 8.8 Hz, H-7).

4.5.3. N-Boc-5-(3′-cyanophenyl)-2-(2″-phenylethyl)indole *49Ae*

δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 3.05 (2H, t, *J* 7.8 Hz, CH_2Ph), 3.37 (2H, t, *J* 7.8 Hz, CH_2CH_2Ph), 6.41 (1H, s, H-3), 7.18–7.32 (5H, m, Ph), 7.44 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.53 (1H, dt, *J* 0.4 and 7.6 Hz, H-5′), 7.59–7.63 (2H, m, H-4 and H-6′), 7.86 (1H, ddd, *J* 1.2, 2.0 and 8.0 Hz, H-4′), 7.91–7.92 (1H, m, H-2′), 8.16 (1H, d, *J* 8.8 Hz, H-7).

4.5.4. N-Boc-5-(4′-methoxyphenyl)-2-(3″-phenylpropyl)indole *49Cb*

δ_H (400 MHz, $CDCl_3$): 1.68 (9H, s, ^{t}Bu), 2.00–2.10 (2H, m, $CH_2CH_2CH_2$), 2.75 (2H, t, *J* 7.6 Hz, CH_2Ph), 3.06 (2H, t, *J* 7.6 Hz, $CH_2CH_2CH_2$Ph), 3.85 (3H, s, OCH_3), 6.39 (1H, s, H-3), 6.98 (2H, d, *J* 8.8 Hz, H-3′ and H-5′), 7.17–7.32 (5H, m, Ph), 7.42 (1H, dd, *J* 2.0 and 8.4 Hz, H-6), 7.56 (2H, d, *J* 8.8 Hz, H-2′ and H-6′), 7.60 (1H, d, *J* 1.6 Hz, H-4), 8.11 (1H, d, *J* 8.4 Hz, H-7).

4.5.5. N-Boc-5-(4′-methoxyphenyl)-2-(3″-phenoxypropyl)indole *49Eb*

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.21 (2H, tt, *J* 6.4 and 7.4 Hz, $CH_2CH_2CH_2$), 3.23 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$OPh), 3.85 (3H, s, OCH_3), 4.06 (2H, t, *J* 6.4 Hz, CH_2OPh), 6.42 (1H, s, H-3), 6.89–6.98 (3H, m, Ph), 7.00 (2H, d, *J* 2.8 Hz, H-3′ and H-5′), 7.26–7.30 (2H, m, Ph), 7.43 (1H, dd, *J* 2.0 and 8.4 Hz, H-6), 7.54 (2H, d, *J* 8.8 Hz, H-2′ and H-6′), 7.60 (1H, d, *J* 2.0 Hz, H-4), 8.10 (1H, d, *J* 8.4 Hz, H-7).

4.5.6. N-Boc-5-(2′-methylphenyl)-2-(3″-phenoxypropyl)indole *49Ec*

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 2.28 (3H, s, CH_3), 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$OPh), 4.07 (2H, t, *J* 6.2 Hz, CH_2OPh), 6.41 (1H, s, H-3), 6.90–6.96 (3H, m, Ph), 7.20 (1H, dd, *J* 2.0 and 8.4 Hz, H-6), 7.22–7.26 (6H, m, H-3′ to H-6′ and Ph), 7.37 (1H, d, *J* 2.0 Hz, H-4), 8.10 (1H, d, *J* 8.4 Hz, H-7).

Table 2
HPLC retention times (min) for indoles **49** (detected $M+H^+$ in parenthesis)

	A	B	C	D	E	F	G	H
a	1.73 (440.2)	1.61 (378.2)	1.88 (454.2)	1.44 (441.2)	1.73 (470.2)	1.49 (550.3)	2.00 (547.3)	[a]
b	**5.30 (427.2)**	4.75 (365.2)	**6.32 (441.2)**	1.42 (428.2)	**5.33 (457.3)**	**3.93 (487.2)**	**7.46 (534.3)**	[a]
c	**7.22 (411.2)**	6.41 (349.2)	8.72 (425.2)	1.58 (412.2)	**7.23 (441.2)**	**5.17 (471.2)**	5.24 (518.3)	[a]
d	[a]	[a]	6.03 (417.2)	1.40 (404.2)	5.14 (433.2)	3.79 (463.2)	[a]	[a]
e	**4.90 (422.2)**	4.43 (360.2)	5.87 (436.2)	1.35 (423.2)	**4.92 (452.2)**	3.66 (482.2)	6.86 (529.3)	[a]
f	5.64 (403.1)	1.44 (341.1)	6.78 (417.1)	1.45 (404.2)	5.99 (443.2)	4.19 (463.2)	8.02 (510.3)	[a]
g	1.26 (387.1)	[a]	[a]	[a]	3.83 (417.2)	1.52 (447.2)	2.06 (494.3)	[a]
h	4.34 (422.1)	3.93 (360.1)	5.15 (436.2)	1.33 (423.2)	**4.40 (452.2)**	**3.35 (482.2)**	5.92 (529.3)	1.45 (491.2)
i	3.89 (404.1)	3.46 (342.1)	4.59 (418.2)	1.26 (405.1)	3.92 (434.2)	2.98 (464.1)	[a]	1.48 (473.2)
j	8.57 (399.2)	7.55 (337.2)	11.52 (413.2)	1.49 (400.1)	9.12 (429.2)	6.17 (459.2)	5.33 (506.3)	[a]
k	1.51 (412.2)	1.44 (350.2)	4.97 (426.2)	1.28 (413.2)	1.53 (442.2)	1.37 (472.2)	1.72 (519.3)	[a]
l	5.10 (399.2)	4.50 (337.2)	6.36 (413.2)	1.30 (400.2)	**5.22 (429.2)**	3.84 (459.2)	7.81 (506.3)	[a]

[a] MW of product not detected.

4.5.7. *N-Boc-5-(3′-cyanophenyl)-2-(3″-phenoxypropyl)indole **49Ee***

δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.23 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2OPh$), 4.06 (2H, t, *J* 6.2 Hz, CH_2OPh), 6.44 (1H, s, H-3), 6.89–6.96 (3H, m, Ph), 7.26–7.31 (2H, m, Ph), 7.43 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.53 (1H, t, *J* 7.6 Hz, H-5′), 7.59–7.63 (2H, m, H-4 and H-6′), 7.86 (1H, td, *J* 1.4 and 7.6 Hz, H-4′), 7.91 (1H, t, *J* 1.6 Hz, H-2′), 8.17 (1H, d, *J* 8.8 Hz, H-7).

4.5.8. *N-Boc-5-(2′-cyanophenyl)-2-(3″-phenoxypropyl)indole **49Eh***

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$), 4.06 (2H, t, *J* 6.2 Hz, CH_2CH_2OPh), 6.45 (1H, s, H-3), 6.88–6.96 (3H, m, Ph), 7.26–7.31 (2H, m, Ph), 7.40–7.44 (2H, m, H-4′ and H-6), 7.55 (1H, dd, *J* 0.8 and 7.6 Hz, H-6′), 7.61–7.66 (2H, m, H-4 and H-5′), 7.77 (1H, dd, *J* 2.0 and 8.0 Hz, H-3′), 8.18 (1H, d, *J* 8.8 Hz, H-7).

4.5.9. *N-Boc-2-(3′-phenoxypropyl)-5-(pyrazin-2″-yl)indole **49El***

δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.22 (2H, tt, *J* 6.2 and 7.4 Hz, $CH_2CH_2CH_2$), 3.24 (2H, t, *J* 7.4 Hz, $CH_2CH_2CH_2$), 4.07 (2H, t, *J* 6.2 Hz, CH_2CH_2OPh), 6.48 (1H, s, H-3), 6.89–6.97 (3H, m, Ph), 7.26–7.30 (2H, m, Ph), 7.90 (1H, dd, *J* 1.6 and 8.8 Hz, H-6), 8.12 (1H, d, *J* 1.6 Hz, H-4), 8.21 (1H, d, *J* 8.8 Hz, H-7), 8.47 (1H, d, *J* 2.4 Hz, H-6″), 8.62 (1H, dd, *J* 1.6 and 2.4 Hz, H-5″), 9.08 (1H, d, *J* 1.6 Hz, H-3″).

4.5.10. *N-Boc-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-5-(4‴-methoxyphenyl)indole **49Fb***

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.97 (2H, t, *J* 7.8 Hz, CH_2Ph), 3.33 (2H, t, *J* 7.8 Hz, CH_2CH_2Ph), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.37 (1H, s, H-3), 6.73 (1H, d, *J* 1.6 Hz, H-2″), 6.77–6.80 (2H, m, H-5″ and H-6″), 6.98 (2H, d, *J* 8.8 Hz, H-3‴ and H-5‴), 7.44 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.55–7.60 (3H, m, H-4, H-2‴ and H-6‴), 8.10 (1H, d, *J* 8.8 Hz, H-7).

4.5.11. *N-Boc-2-[2′-(3″,4″-dimethoxyphenyl)ethyl]-5-(2‴-methylphenyl)indole **49Fc***

δ_H (400 MHz, $CDCl_3$): 1.70 (9H, s, ^{t}Bu), 2.29 (3H, s, $ArCH_3$), 2.98 (2H, t, *J* 7.8 Hz, H-2′), 3.33 (2H, t, *J* 7.8 Hz, H-1′), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.37 (1H, s, H-3), 6.73 (1H, s, H-2″), 6.81 (2H, s, H-5″ and H-6″, coincident), 7.20 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.23–7.28 (4H, m, H-3‴ to H-6‴), 7.37 (1H, d, *J* 2.0 Hz, H-4), 8.09 (1H, d, *J* 8.8 Hz, H-7).

4.5.12. *N-Boc-5-(3′-cyanophenyl)-2-[2″-(3‴,4‴-dimethoxyphenyl)ethyl]indole **49Fe***

δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.98 (2H, t, *J* 7.6 Hz, H-2″), 3.34 (2H, t, *J* 7.6 Hz, H-1″), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.33 (1H, s, H-3), 6.73 (1H, d, *J* 1.6 Hz, H-2‴), 6.74–6.82 (2H, m, H-5‴ and H-6‴), 7.45 (1H, dd, *J* 2.0 and 8.4 Hz, H-6), 7.52 (1H, dt, *J* 0.4 and 7.8 Hz, H-5′), 7.59–7.63 (2H, m, H-4 and H-6′), 7.86 (1H, td, *J* 1.6 and 8.0 Hz, H-4′), 7.91 (t, *J* 1.4 Hz, H-2′), 8.17 (1H, d, *J* 8.8 Hz, H-7).

4.5.13. *N-Boc-5-(2′-cyanophenyl)-2-[2″-(3‴,4‴-dimethoxyphenyl)ethyl]indole **49Fh***

δ_H (400 MHz, $CDCl_3$): 1.71 (9H, s, ^{t}Bu), 2.98 (2H, t, *J* 7.8 Hz, H-2″), 3.34 (2H, t, *J* 7.8 Hz, H-1″), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.42 (1H, s, H-3), 6.72–6.82 (3H, m, H-2‴, H-5‴ and H-6‴), 7.40–7.45 (2H, m, H-4′ and H-6), 7.55 (1H, dd, *J* 0.8 and 7.6 Hz, H-6′), 7.62–7.66 (2H, m, H-4 and H-5′), 7.77 (1H, dd, *J* 0.8 and 7.6 Hz, H-3′), 8.18 (1H, d, *J* 8.4 Hz, H-7).

4.5.14. *N-Boc-2-[2′-(N-Boc-piperidin-4″-yl)ethyl]-5-(4‴-methoxyphenyl)indole **49Gb***

δ_H (400 MHz, $CDCl_3$): 1.06–1.25 (2H, m, piperidine), 1.46 (9H, s, ^{t}Bu), 1.49–1.78 (5H, m, piperidine), 1.70 (9H, s, ^{t}Bu), 2.60–2.70 (2H, m, CH_2CH_2CH), 3.05 (2H, t, *J* 7.6 Hz, H-1′), 3.86 (3H, s, OCH_3), 4.05–4.20 (2H, m, $2\times CH^AH^BN$), 6.37 (1H, s, H-3), 6.99 (2H, d, *J* 8.8 Hz, H-3‴ and H-5‴), 7.43 (1H, dd, *J* 2.0 and 8.8 Hz, H-6), 7.55 (2H, d, *J* 8.8 Hz, H-2‴ and H-6‴), 7.58 (1H, d, *J* 2.0 Hz, H-4), 8.08 (1H, d, *J* 8.8 Hz, H-7).

Acknowledgements

GSK and University of Glasgow for funding. Thanks to Ian Davidson for HPLC-UV/MS.

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