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Synthesis of Indomethacin Analogues for Evaluation as Modulators of MRP Activity

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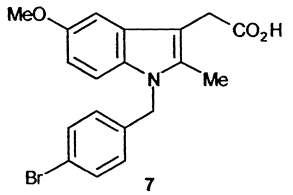
Abstract—Synthesis of a range of indomethacin analogues, required for investigation in combination toxicity assays, bearing both *N*-benzyl and *N*-benzoyl groups, is described.

Earlier work[1a] has established that a number of NSAIDs, including indomethacin and sulindac, have the ability to potentiate the toxicity of a range of anticancer drugs such as doxorubicin, vincristine and VP-16, especially in MRP-expressing cell lines such as DLKP and A549 while this effect was not evident in P-gp expressing cell lines such as DLKPA. Significantly, the activity in enhancing the toxicity of the anticancer drugs does not appear to be directly related to cyclooxygenase (COX) inhibition as a number of NSAIDs which are known to act as COX inhibitors do not display this effect. Two other groups have reported similar results with indomethacin in MRP expressing cell lines.[1b,c]

To explore this effect and, in particular, to determine SAR in potentiating the toxicity of anticancer drugs, a range of indomethacin analogues was synthesised and their activity tested in our screens (hereafter described as combination toxicity assays). Indomethacin **1** was a logical candidate for investigation as its structure is very amenable to modification to establish the influence of the various substituents, for example the role of the 5-methoxy, 2-methyl and chloro substituents, in addition to the importance of the *N*-benzoyl substituent, can be explored through synthesis and testing of appropriate analogues.

Indomethacin **1** was developed by Shen and co-workers in the Merck, Sharp and Dohme Research Laboratories in the early 1960's.[2,3] Significantly, the lead compound was 1-benzyl-5-methoxy-2-methylindole-3-acetamide **2**; when the side chain was modified to a carboxylic acid **3**, improved anti-inflammatory activity resulted. In an exhaustive study, Shen and co-workers prepared a further 350 analogues to determine the structure–activity relationship. The result of this study was four candidates that went forward for clinical evaluation (Fig. 1), and of these MK-615, later to receive the generic name indomethacin, proved to be the most effective anti-inflammatory agent in human subjects. Significantly, in terms of anti-inflammatory activity, both *benzyl* and *benzoyl* substituents on the indole nitrogen atom were tolerated.

The biological mechanisms of action of indomethacin and other NSAIDs have been extensively studied; cyclooxygenase (COX) inhibition is their principal mode of action.[4] Indomethacin, in common with most other NSAIDs, has been shown to inhibit both COX-1 and COX-2 isoforms; the gastrotoxicity associated with this class of compounds is believed to be due to COX-1 inhibition and accordingly extensive searching for selective COX-2 inhibitors has been undertaken in recent years.[5] Indeed, the indomethacin derivative in which the benzoyl group is replaced by a 4-bromobenzyl group **7** has been reported as a highly selective COX-2 inhibitor.[6]



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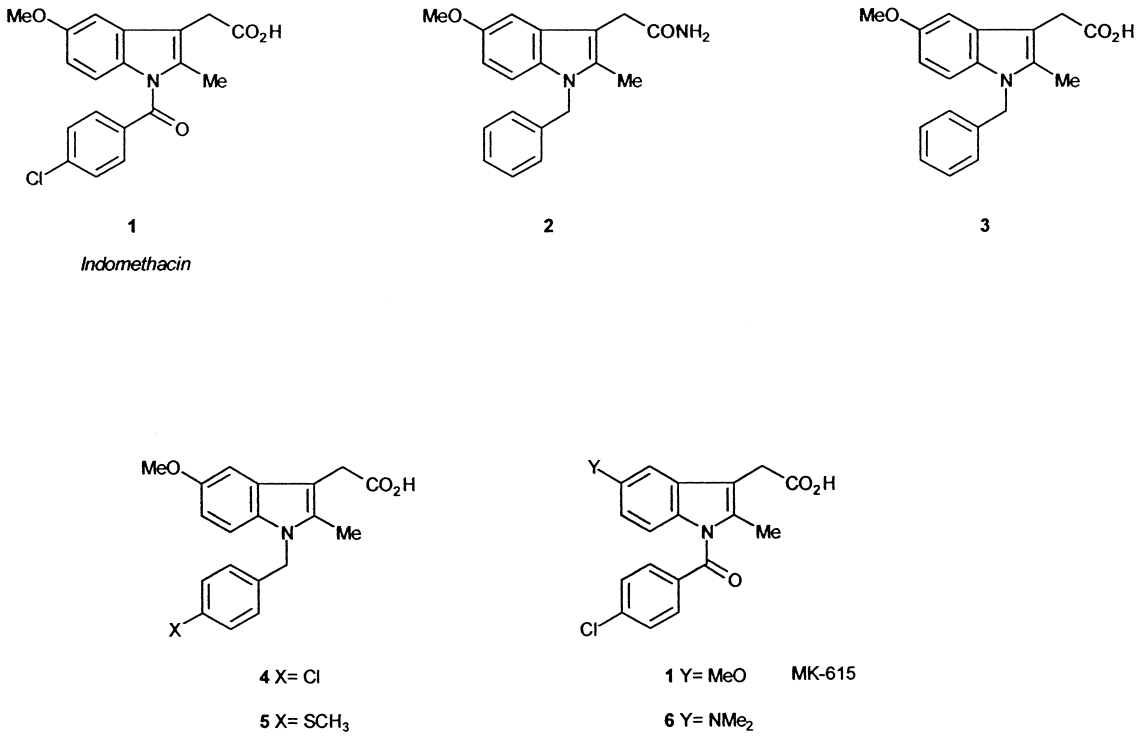


Figure 1.

However, some NSAIDs also inhibit other enzymes, including phospholipase A_2 (PLA_2). In 1978, Kaplan and co-workers found that indomethacin **1** inhibits PLA_2 from rabbit polymorphonuclear leukocytes,[7] while more recent reports have studied the inhibitory abilities of other NSAIDs.[8] Development of selective inhibitors of human PLA_2, based on *N*-benzyl derivatives of indomethacin, has attracted considerable attention recently, including work by Kreft and co-workers[9] at Wyeth-Ayerst and Shevitz, Bach and co-workers[10–12] at Lilly.

A number of studies have considered the lipoxygenase and cycloxygenase-inhibitory properties of NSAIDs, including indomethacin, aspirin and sulindac, and their effects on tumour growth and promotion.[13] While this work was underway, a report by Levy and co-workers of indomethacin-mediated reversal of MDR in cell lines expressing MRP appeared.[1b]

In this paper, the synthesis of a range of indomethacin derivatives is described; the results of their biological evaluation in the enhancement of cytotoxicity of anti-cancer agents in MRP-expressing cell lines will be described elsewhere.[14]

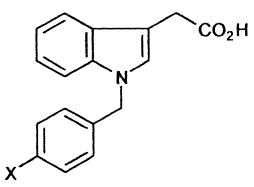
Results and Discussion

The indomethacin derivatives synthesised during this work are summarised in Figure 2 and can be considered in three distinct groups; compounds **4**, **5** and **7**–**11** and **13**–**20** are *N*-benzyl indole acetic acid derivatives, compounds **21**–**25** are *N*-benzoyl derivatives closely related in structure to indomethacin and compounds **26**–**29** are examples of the selective PLA_2 inhibitors developed by Bach and co-workers.[10–12] These compounds were selected to allow systematic investigation of the influence of each of the structural components of indomethacin on the enhancement of cytotoxicity of doxorubicin and other anticancer agents in the combination toxicity assays. SAR in this study were not necessarily expected to be identical to SAR in indomethacin analogues for anti-inflammatory effects, COX and PLA_2 inhibition. Therefore, inclusion of compounds which are known COX inhibitors (both COX-1 and COX-2 inhibitors including the selective COX-2 inhibitor **7**), and selective PLA_2 inhibitors with very little COX inhibition **26**–**29**, allowed us to investigate if there was any correlation between the results obtained in this study, and previously studied bioactivity profiles of indomethacin analogues, thereby providing information on the mode of action of MRP inhibition.

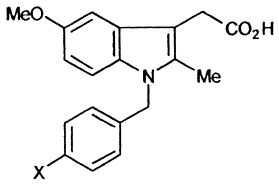
Synthesis of *N*-benzyl indomethacin analogues

The first class of compounds selected for investigation were *N*-benzyl derivatives of indomethacin; based on the precedent for COX and PLA_2 inhibition with *N*-benzyl derivatives of indomethacin outlined above, it was of interest to determine whether these derivatives would result in enhancement of the cytotoxicity of doxorubicin and other anti-cancer agents in the combination toxicity assays.

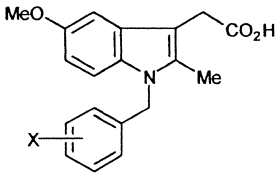
The first compounds investigated were simple *N*-benzyl indole-3-acetic acid derivatives **8**–**11** to establish if this substructure of indomethacin were sufficient for activity. These were prepared by benzylation of indole-3-acetic acid in the presence of sodium hydride in DMF as illustrated in Scheme 1.[15] Given the extensive structural



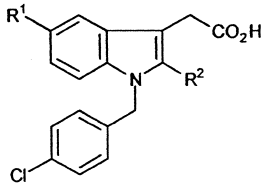
X	
H	8
Cl	9
Br	10
MeO	11



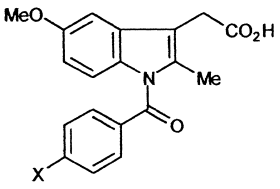
X	
H	13
Cl	4
Br	7
F	14
MeS	5
Me	15



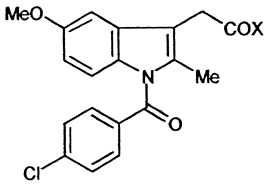
X	
3-Cl	16
2-Cl	17
3-F	18



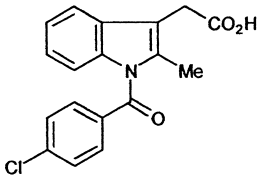
R^1	R^2	
MeO	H	19
H	Me	20



X	
H	21
Br	22



X	
OMe	23
NH*p*-Tol	24



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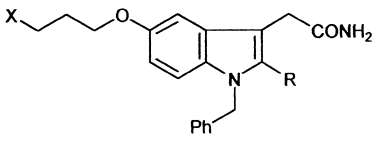
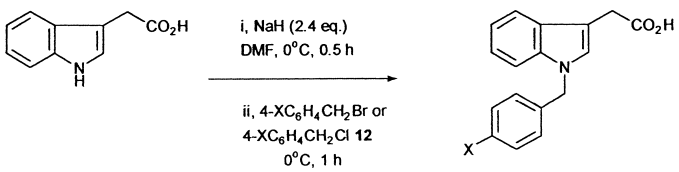


X	R	
CO_2H	Me	26
CO_2H	Et	27
$PO(OH)_2$	Me	28
$PO(OH)_2$	Et	29

Figure 2.



X		
H	8	30%
Cl	9	40%
Br	10	23%
MeO	11	47%

Scheme 1.

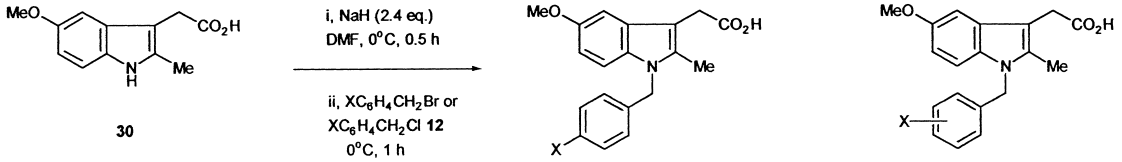
modification compared to indomethacin, it was not surprising that these compounds did not prove active in the combination toxicity assays.

A series of *N*-benzyl derivatives **4**, **5**, **7**, **13**–**18**, which were much more closely related structurally to indomethacin **1** than **8**–**11**, was prepared by benzylation of the commercially available 5-methoxy-2-methylindole-3-acetic acid **30** as illustrated in Scheme 2. Benzyl chlorides and benzyl bromides **12** were used as precursors, depending on which was more readily available, with no noticeable effect on the outcome of the benzylation. A pure sample of each of the *N*-benzyl derivatives was obtained by recrystallisation or chromatographic purification. This series allowed investigation of the influence, in the combination toxicity assay, of the nature of the 4-substituent (halo, methyl, methylthio or unsubstituted) on the benzyl group (**4**, **5**, **7**, **13**–**15**), and also the impact of moving the chloro substituent to the 2- or 3-position, or the fluoro substituent to the 3-position (**16**–**18**). The selective COX-2 inhibitor **7**[6] was included in this study.

To explore the influence of the 2-methyl and 5-methoxy substituents, the *N*-4-chlorobenzyl derivatives **19** and **20**, in which one of these groups is absent in each, were prepared by benzylation of 5-methoxyindole-3-acetic acid **31** and 2-methylindole-3-acetic acid **32**, respectively, with 4-chlorobenzyl chloride (Scheme 3).

Synthesis of *N*-benzoyl indomethacin analogues

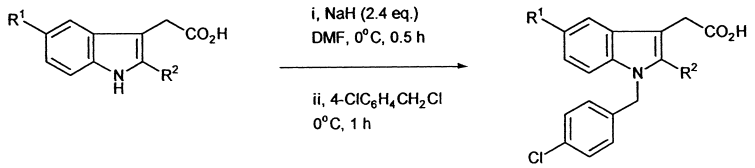
Whereas the syntheses of *N*-benzyl indomethacin analogues were achievable in a simple one-step process, this was not the case for the indomethacin analogues where the *N*-benzoyl unit is retained. Direct *N*-benzoylation of a commercially available indole nucleus is not feasible, and thus such compounds must be synthesised by an alternative route. The synthesis of indomethacin developed



X		
H	13	38%
Cl	4	41%
Br	7	20%
F	14	29%
MeS	5	17%
Me	15	12%

X		
3-Cl	16	46%
2-Cl	17	35%
3-F	18	43%

Scheme 2.



R^1	R^2		
MeO	H	31	
H	Me	32	

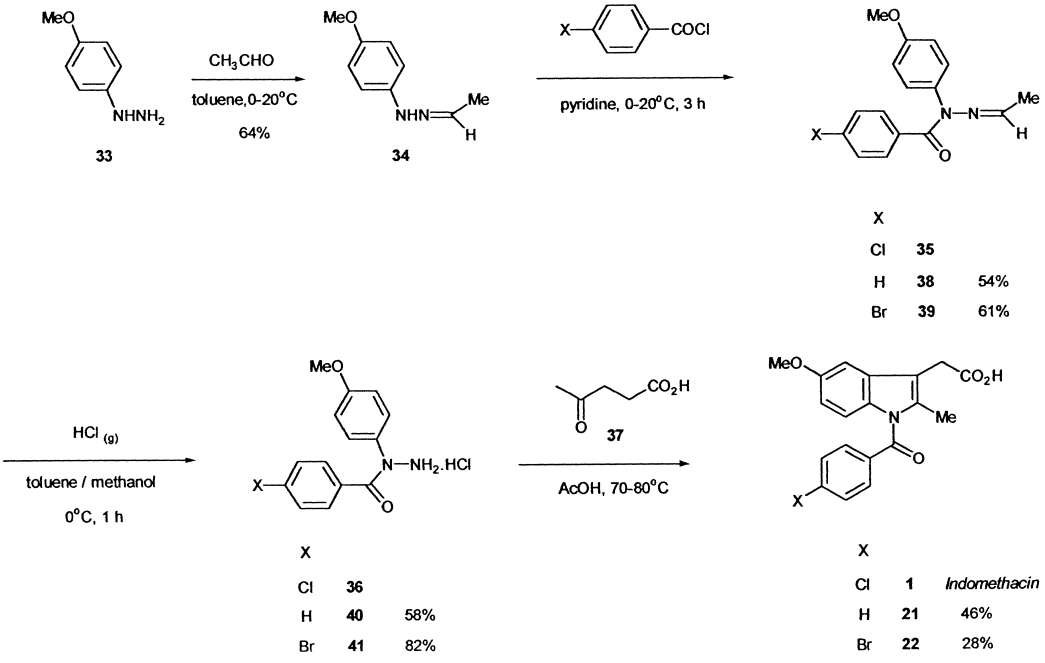
R^1	R^2		
MeO	H	19	28%
H	Me	20	36%

Scheme 3.

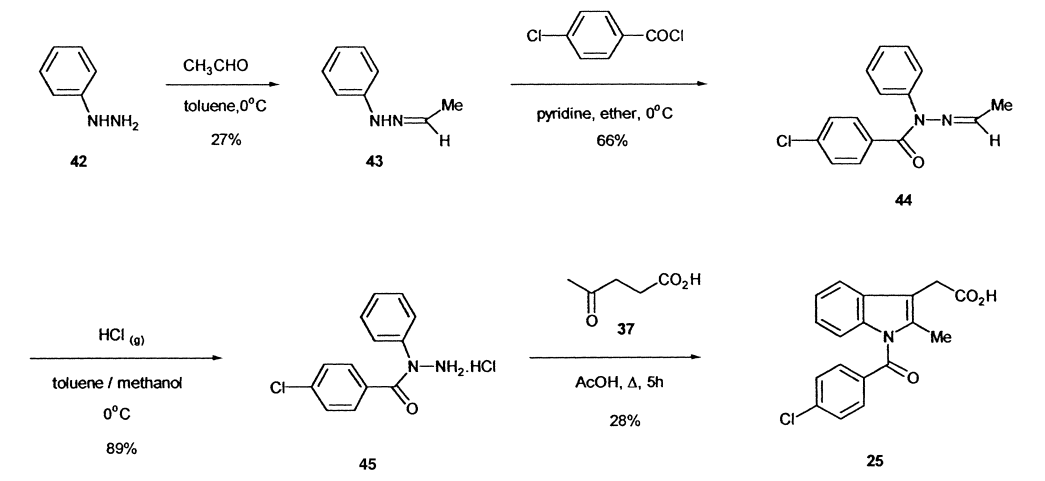
by Yamamoto offers an elegant entry to these compounds as outlined in Scheme 4.[16] *para*-Methoxyphenylhydrazine **33** is treated with acetaldehyde in toluene at 0 °C to give the hydrazone **34**. This may then be benzoylated at the N^1-position to give the N^1,N^1-disubstituted hydrazone **35**, which upon treatment with gaseous hydrogen chloride affords the hydrazine hydrochloride **36**. Subsequent cyclisation with levulinic acid **37** in the classic Fischer indole synthesis provides indomethacin **1**.

Based on this synthetic route the indomethacin analogues **21**, **22** and **25** were prepared (Schemes 4 and 5) to allow investigation of the significance of the chloro and methoxy substituents on the activity in the combination toxicity assay. Both 4-methoxyphenylhydrazine **33** and phenylhydrazine **42** were easily protected as their acetaldehyde hydrazones **34** and **43**, respectively. Hydrazone **34** was benzoylated with benzoyl chloride and 4-bromobenzoyl chloride to produce **38** and **39** respectively. Benzoylation of the hydrazone **43** with 4-chlorobenzoyl chloride was conducted in ether forming **44** in good yield. Despite Yamamoto's report[16] that the benzoylated hydrazone **35** precipitated out from the reaction medium and was separable by simple filtration, this never proved to be the case with **38**, **39** and **44**. Instead, it was necessary to quench the reactions and obtain these products by flash column chromatography. Each of the benzoylated hydrazones were obtained as a single isomer.

Each of the N^1,N^1-disubstituted hydrazones **38**, **39** and **44** was easily converted to the corresponding hydrazine hydrochlorides **40**, **41** and **45** with gaseous hydrogen chloride. Here, the hydrazone was dissolved in toluene/methanol and when an excess of hydrogen chloride was bubbled through the solution for 1 h at 0 °C the desired hydrazine hydrochloride could be obtained in good yield and used without further purification. To effect the



Scheme 4.



Scheme 5.

Fischer Indole synthesis, each of the three disubstituted hydrazine hydrochlorides **40**, **41** and **45** was, in turn, reacted with levulinic acid **37** in acetic acid to give the desired indomethacin analogues **21, 22** and **25** (Schemes 4 and 5). While the reaction proceeded efficiently at 70–80°C with the methoxy substituted derivatives **40** and **41**, reflux in acetic acid was necessary to form **25** reflecting the decreased activity in the absence of the methoxy substituent. The dechloro derivative of indomethacin **21** and the bromo derivative of indomethacin **22** were obtained by recrystallisation; the demethoxy derivative of indomethacin **25** was purified by flash column chromatography. The compounds were fully characterised and displayed spectroscopic characteristics very similar to those of indomethacin **1** as expected.

To determine the significance of the carboxylic acid moiety, the indomethacin derivatives **23** and **24** were prepared as outlined in Scheme 6. While these compounds may hydrolyse in vivo to release indomethacin, their solubility and transport properties would be expected to be very different to those of the free acid **1**. The methyl ester **23** and the *p*-tolyl amide **24** were prepared via coupling with methanol and *p*-toluidine, respectively, in the presence of DCC and DMAP.

Synthesis of the *N*-benzyl indoleacetamide derivatives

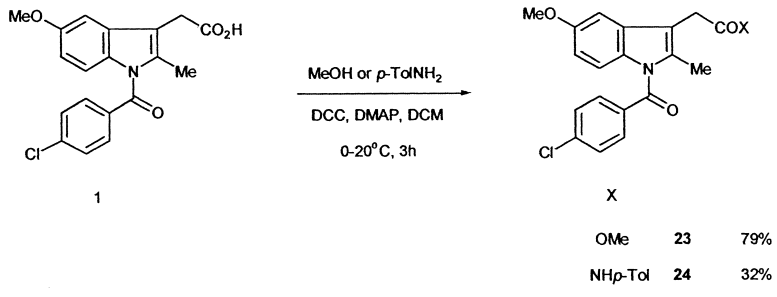
The *N*-benzyl indoleacetamide derivatives **26–29** were the next targets selected on the basis of the recent interest in these compounds as selective PLA_2 inhibitors with very low COX inhibition.[12b] Determination of the activity of these compounds in the combination toxicity assays would be of interest, to establish if there is any correlation between this study, PLA_2 inhibition and COX inhibition. Martinelli and co-workers[21] have reported a practical synthetic route to **29** employing a Nenitzescu reaction as the key step, and this approach was employed in this work for the synthesis of each of the compounds **26–29** as summarised in Scheme 7.

The enamino esters **46** and **47** were easily prepared in quantitative yields by condensing benzylamine with methyl acetoacetate and methyl propionylacetate in the presence of a catalytic amount of *p*-toluenesulphonic acid and could be used without further purification. The Nenitzescu cyclisation of the enamino esters with *p*-benzoquinone is the key step in this synthetic strategy forming the indole nucleus with the desired 1,2,3,5-substituent pattern. Thus the enamino esters **46** and **47** when reacted with *p*-benzoquinone in nitromethane gave the 3-(carbomethoxy)-2-methyl-1-(phenylmethyl)-5-hydroxyindole **48** in 47% yield and its 2-ethyl homologue **49** in 53% yield. The products in both cases were separable by simple filtration and could be used without further purification.

Before the 3-methyl ester can be reduced, the 5-hydroxy function must be first protected. Treatment of indoles **48** and **49** with methyl iodide under phase transfer conditions resulted in the alkylated products **50** and **51**. These 5-methoxyindoles were recrystallised from *iso*-propanol to give **50** (57%) and **51** (61%). Reduction of the 3-methyl ester side chain could now proceed. This was achieved with lithium aluminium hydride in THF at room temperature following the procedure described by Martinelli and co-workers,[21] the reactions proceeding cleanly to afford alcohols **52** and **53** without further need for purification.

Elaboration of the 3-hydroxymethyl function to an acetamide was achieved in two steps. Conversion of **52** and **53** to the cyanoindoles **54** and **55** was achieved with cyanotrimethylsilane as nucleophile in the presence of boron trifluoride etherate. Purification was easily achieved by elution through a silica gel plug to give **54** in 72% yield and **55** in 71% yield. Hydrolysis of the cyano function was accomplished with powdered potassium hydroxide in refluxing *tert*-butanol. Chromatographic purification of the 2-ethylindoleacetamide **57** by chromatography gave the product in 66% yield, while its 2-methyl homologue **56**, which was prepared on a larger scale, was purified by two recrystallisations followed by chromatography of the concentrated mother liquor to give the product in an overall yield of 70%. Cleavage of the 5-methoxy protecting group was achieved cleanly by treatment with boron tribromide solution in dichloromethane at 0 °C to give the 5-hydroxyindoleacetamides **58** (88%) and **59** (98%) without further purification.

Elaboration at the 5-position could now commence. While Martinelli and co-workers[21] had conducted the alkylation of **59** to **63** under phase transfer conditions, in this work each of the alkylations to form **60–63** were conducted using sodium hydride in DMF following the conditions described by Bach and co-workers.[12b] Alkylation with ethyl 4-bromobutyrate proceeded in reasonable yield to give the chain-extended products **60** and **61** in 38 and 49% yields, respectively, after chromatographic purification. In both cases unreacted starting material



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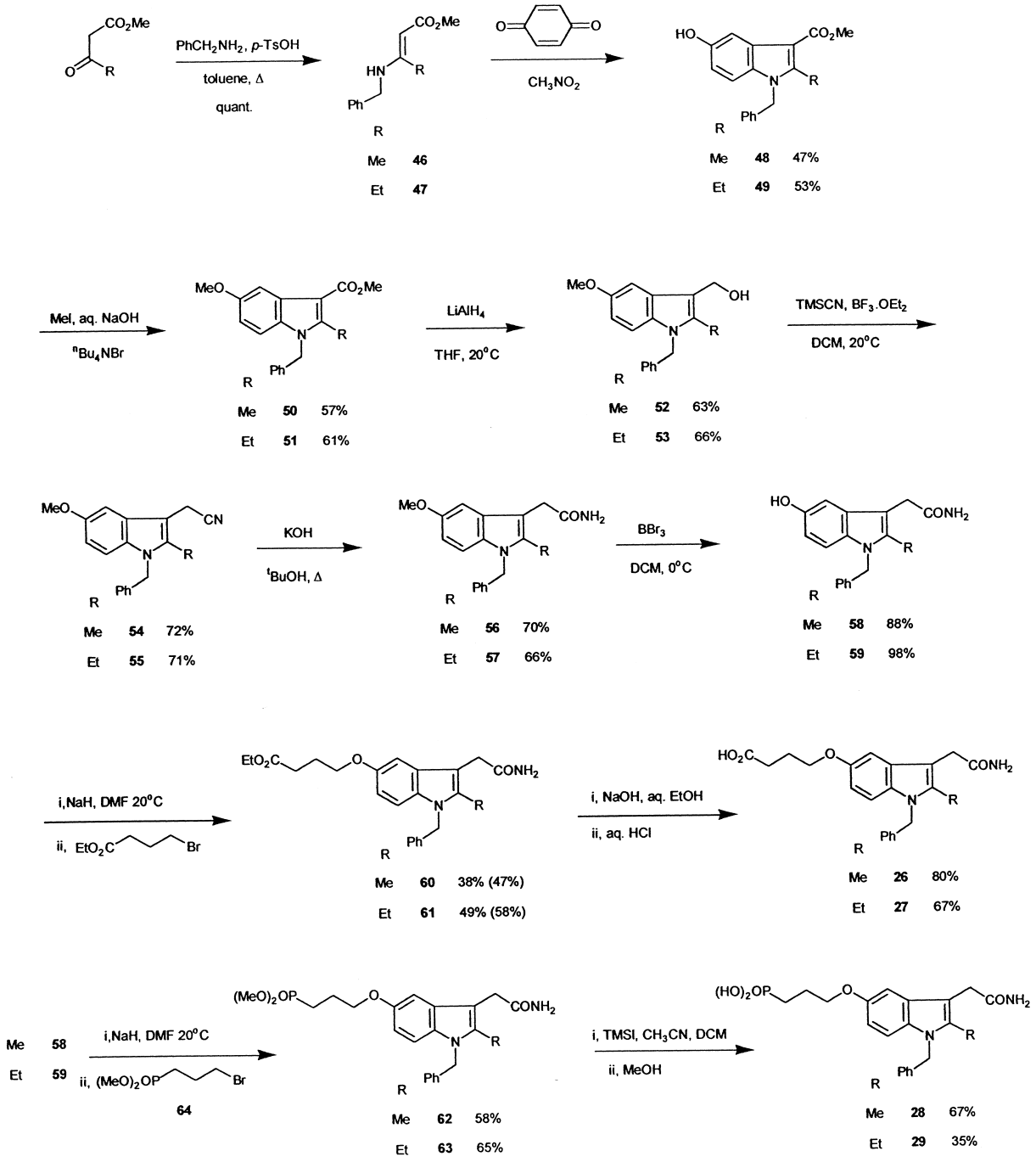
X

OMe	23	79%
NHp-Tol	24	32%

Scheme 6.



Scheme 7.

was recovered and could be reused resulting in corrected yields of 47 and 58%, respectively. Saponification with aqueous sodium hydroxide and subsequent acidification with hydrochloric acid gave the PLA_2 inhibitors **26** in 80% yield and **27** in 67% yield.

In order to obtain the phosphonic acid analogues **28** and **29**, the bromo phosphonate **64** was synthesised by an Arbuzov reaction of trimethylphosphite with an excess of dibromopropane.[22] The phosphonate side-chain was then attached to the 5-hydroxyindoleacetamides **58** and **59** in a similar fashion to before: treatment first with sodium hydride, then with the (bromopropyl)phosphonate **64** affords **62** and **63** in reasonable yield (Scheme 7). In both cases, the starting material was completely consumed. The 2-methylindoleacetamide **62** was obtained in 58% yield after chromatographic purification. When the crude product from the reaction leading to the 2-ethylindoleacetamide **63** was analysed by ^1H and ^{13}C NMR spectroscopy, it was found to be essentially pure, being contaminated only with DMF, and thus it was used in the next step without further purification. However, a 100 mg sample was reserved and purified by chromatography to give an analytically pure sample, with an overall yield of 65%.

Cleavage of the phosphonate ester function was achieved with iodotrimethylsilane in dichloromethane/

acetonitrile at room temperature. The intermediate trimethylsilyl phosphonate esters give, upon methanol work-up, the desired phosphonic acids **28** and **29**. The 2-methyl derivative **28** was obtained in 67% yield after recrystallisation (ethyl acetate:acetonitrile:acetic acid: water 21/7/7/9), while the 2-ethyl derivative **29** was obtained in 35% yield after recrystallisation from the same solvent mixture.

In summary, a series of indomethacin analogues has been prepared to allow investigation of SAR in combination toxicity assays. All of the compounds were tested for their ability to inhibit MRP-1-mediated drug efflux, as measured by the enhancement of adriamycin toxicity in a miniaturised 96-well acid-phosphatase-based assay in a human lung carcinoma cell line, DLKP.[23] Indomethacin, which we have shown to be a potent MRP-1 inhibitor was used as a positive control.[1a] The derivatives **4**, **7**, **14**, **18**, **21**, **22**, **25**, **26** and **27** all displayed MRP-1 inhibitory activity. It was found that the use of *N*-benzyl in place of the *N*-benzoyl group did not abolish MRP-1 inhibitory activity but the stringency of the requirements for substituents in the phenyl ring was much greater in the absence of the carbonyl group. The compounds were also assayed for COX-1, COX-2 and GST inhibitory activity as indomethacin is a potent inhibitor of all three enzymes. The results indicated that there were different structural requirements for inhibition of each of the different molecular targets. These results will be discussed in more detail in a future paper outlining the full biological properties of the agents.[14]

Experimental

High field ^{1}H and ^{13}C NMR spectra were recorded on a Jeol GSX FT spectrometer at 270.05 and 67.80 MHz, respectively. Low field ^{1}H NMR spectra were recorded on a Jeol PMX60SI (60 MHz) spectrometer. Spectra recorded in $CDCl_3$ are reported in parts per million from internal tetramethylsilane. Spectra recorded in DMSO-d_6 are reported in parts per million from internal 3-(trimethylsilyl)propionic-*2,2,3,3*-d_4 acid, sodium salt. Coupling constants are reported in Hertz. The ^{31}P and ^{31}C NMR spectra of **28** were recorded on a Jeol Eclipse + 400 spectrometer. Mass spectra were recorded on a Kratos Profile HV-4 double focusing high resolution mass spectrometer. Elemental analyses were recorded on a Perkin-Elmer 240 elemental analyser. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer as liquid films, chloroform ($CHCl_3$) solutions or potassium bromide (KBr) discs. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Thin layer chromatography was performed on DC-Alufoilen Kieselgel $60F_{254}$ 0.2 mm plates (Merck) and visualised under UV light and with a vanillin stain. Flash column chromatography was performed using Kieselgel 60 (Merck) 230–400 mesh.

All solvents were distilled before use: hexane from calcium chloride, dichloromethane and ethyl acetate from phosphorus pentoxide. Dry solvents were prepared by refluxing over a drying agent under an inert atmosphere: THF was dried over sodium/ benzophenone, ether and toluene were dried over calcium hydride. Dimethylformamide was distilled from calcium hydride under reduced pressure (ca 15 mm Hg) and stored over activated molecular sieves.

1-Benzylindole-3-acetic acid 8. To a slurry of sodium hydride (60% dispersion in mineral oil; 0.55 g, 13.8 mmol, 2.4 equiv) in dry DMF (10 mL) under nitrogen at 0 °C was added indole-3-acetic acid (1.00 g, 5.71 mmol) in one portion. Stirring at 0 °C was continued for 30 min. Benzyl bromide (0.82 mL, 6.84 mmol, 1.2 equiv) was added in one portion and stirring continued for 1 h. The reaction was quenched by pouring into ice–water (ca 100 mL), the resultant mixture acidified with 10% hydrochloric acid and the crude product obtained by filtration. Recrystallisation (ether/ethanol) afforded the title compound as a white solid (0.4459 g, 29.5%).

Mp 153–154 °C (lit.[15] 148 °C); ν_{max} (KBr)/cm^{-1} 3000–2500 (OH), 1702 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.63 (m, 10H, indole-H and Ph), 5.27 (s, 2H, N-CH_2), 3.80 (s, 2H, CH_2CO_2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.8 (C=O), 137.3 (*i*-Ph), 136.6 (C7a), 128.8, 126.9 (*o*- and *m*-Ph), 127.9 (C3a), 127.6, 127.3 (C2 and *p*-Ph), 122.1 (C5), 119.6, 119.1 (C4 and C6), 109.8 (C7), 106.9 (C3), 50.0 (N-CH_2), 31.0 (CH_2CO_2H); *m*/*z* 265 (M^+, 8%), 149 (12), 91 (28), 84 (66), 49 (100); (found: C, 76.7; H, 6.0; N, 5.4. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%).

1-(4-Chlorobenzyl)indole-3-acetic acid 9. The procedure followed was as detailed above, using: *para*-chlorobenzyl chloride (1.10 g, 6.84 mmol, 1.2 equiv). Upon acidification, the crude product was extracted with dichloromethane (50 mL), the organic layer washed with water (3×50 mL) and brine (50 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo. Recrystallisation (ether/ethanol) afforded the title compound as a pale yellow solid (0.6925 g, 40.5%).

Mp 146–148 °C; ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1713 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.00–7.63 (m, 9H, indole-H and C_6H_4), 5.23 (s, 2H, CH_2), 3.80 (s, 2H, CH_2CO_2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.6 (C=O), 136.5 (*i*-Ph), 135.9 (C7a), 133.5 (*p*-Ph), 129.0, 128.4 (*o*- and *m*-Ph), 127.9 (C3a), 127.1 (C2), 122.3 (C5), 119.8, 119.2 (C4 and C6), 109.7 (C7), 107.2 (C3), 49.4 (N-CH_2), 31.0 (CH_2CO_2H); *m*/*z* 299, 301 ($M^+[^{35/37}Cl]$, 32%), 255 (31), 125 (100); (found: C, 67.8; H, 4.9; N, 4.65; Cl, 11.4. $C_{17}H_{14}NClO_2$ requires C, 68.1; H, 4.7; N, 4.7; Cl, 11.8%).

1-(4-Bromobenzyl)indole-3-acetic acid 10. The procedure followed was as detailed above, using: *para*-bromobenzyl bromide (1.71 g, 6.84 mmol, 1.2 equiv). Recrystallisation of the crude product (ether/ethanol) afforded the title compound as a pale yellow solid (0.4493 g, 22.9%).

Mp 147–149 °C; ν_{max} (KBr)/cm^{-1} 3000–2500 (OH), 1710 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.85–7.63

(m, 9H, indole-H and C_6H_4), 5.21 (s, 2H, CH_2), 3.78 (s, 2H, CH_2CO_2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.6 (C=O), 136.4 (C7a), 131.9 (*m*-Ph), 128.5 (*o*-Ph), (*i*-Ph not seen), 128.0 (C3a), 127.1 (C2), 122.3 (C5), 121.6 (*p*-Ph), 119.7, 119.2 (C4 and C6), 109.7 (C7), 107.2 (C3), 49.5 (N-CH_2), 30.9 (CH_2CO_2H); *m*/*z* 343, 345 (M^+ [$^{79/81}$Br], 30%), 299 (30), 224 (60), 125 (100); (found: C, 59.0; H, 4.3; N, 3.8; Br, 23.1. $C_{17}H_{14}NBrO_2$ requires C, 59.3; H, 4.1; N, 4.1; Br, 23.2%).

1-(4-Methoxybenzyl)indole-3-acetic acid 11. The procedure followed was as detailed above, using: *para*-methoxybenzyl bromide (0.93 mL, 6.84 mmol, 1.2 equiv). Recrystallisation of the crude product (ether/ethanol) afforded the title compound as a pale yellow solid (0.7957 g, 47.2%).

Mp 133–135 °C; ν_{max} (KBr)/cm^{-1} 3300–2200 (OH), 1712 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 6.79–7.62 (m, 9H, indole-H and C_6H_4), 5.20 (s, 2H, N–CH_2), 3.78 (s, 2H, CH_2CO_2H), 3.76 (s, 3H, CH_3O); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.6 (C=O), 159.1 (*p*-Ph), 136.5 (C7a), 129.3 (*i*-Ph), 128.3 (*o*-Ph), 127.9 (C3a), 127.1 (C2), 122.0 (C5), 119.5, 119.0 (C4 and C6), 114.2 (*m*-Ph), 109.8 (C7), 106.7 (C3), 55.3 (CH_3O), 49.5 (N–CH_2), 31.0 (CH_2CO_2 H); *m*/*z* 295 (M^+, 10%), 251 (17), 121 (100); (found: C, 72.7; H, 6.2; N, 4.4. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%).

1-Benzyl-5-methoxy-2-methylindole-3-acetic acid 13. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (328.8 mg, 1.5 mmol), benzyl chloride (207 μL, 1.8 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 144.0 mg, 3.6 mmol, 2.4 equiv) and DMF (4 mL). Flash column chromatography (chloroform/methanol 20:1) afforded the title compound as a pale yellow solid (175.0 mg, 37.7%).

Mp 169–173 °C; ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1700 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 6.73–7.25 (m, 8H, indole-H and Ph), 5.22 (s, 2H, N-CH_2), 3.81 (s, 3H, CH_3O), 3.69 (s, 2H, CH_2CO_2H), 2.26 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.6 (C=O), 154.3 (C5), 137.8, 153.2, 131.7, 128.1 (4×qC), 127.3 (*p*-Ph), 128.8, 125.9 (*o*- and *m*-Ph), 111.0, 109.9 (C4 and C6), 103.7 (C3), 100.4 (C7), 55.9 (CH_3O), 46.7 (N–CH_2), 30.5 (CH_2CO_2H), 10.4 (CH_3); *m*/*z* 309 (M^+, 82%), 264 (70), 173(37), 158 (38), 91 (100); (Found: C, 73.4; H, 6.15; N, 4.2. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%).

1-(4-Chlorobenzyl)-5-methoxy-2-methylindole-3-acetic acid 4. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (219.2 mg, 1 mmol), *para*-chlorobenzyl chloride (193.2 mg, 1.2 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 96.0 mg, 2.4 mmol, 2.4 equiv) and DMF (5 mL). Recrystallisation of the crude product (ether/ethanol) afforded the title compound as a pale yellow solid (141.1 mg, 41.1%).

Mp 185–187 °C; ν_{max} (KBr)/cm^{-1} 3200–2500 (OH), 1706 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 6.74–7.25 (m, 7H, indole-H and C_6H_4), 5.22 (s, 2H, N-CH_2), 3.84 (s, 3H, CH_3O), 3.72 (s, 2H, CH_2CO_2H), 2.29 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.3 (C=O), 154.4 (C5), 136.3 (*p*-Ph), 135.1, 133.1, 131.5, 128.1 (4×qC), 129.0, 127.3 (*o*- and *m*-Ph), 111.2, 109.8 (C4 and C6), 103.8 (C3), 100.5 (C7), 55.9 (CH_3O), 46.2 (N–CH_2), 30.4 (CH_2CO_2H), 10.4 (CH_3).

1-(4-Bromobenzyl)-5-methoxy-2-methylindole-3-acetic acid 7. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (328.8 mg, 1.5 mmol), *para*-bromobenzyl bromide (281.2 mg, 1.35 mmol, 0.9 equiv), which was added dropwise via syringe as a solution in DMF (1 mL), sodium hydride (60% dispersion in mineral oil; 144.0 mg, 3.6 mmol, 2.4 equiv) and DMF (4 mL). Flash column chromatography (chloroform/methanol 15:1) afforded the title compound as a pale yellow solid (119.6 mg, 20.5%).

Mp 191–192 °C; ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1700 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 6.77–7.35 (m, 7H, indole-H and C_6H_4), 5.20 (s, 2H, N–CH_2), 3.84 (s, 3H, CH_3O), 3.72 (s, 2H, CH_2CO_2H), 2.29 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.7 (C=O), 154.4 (C5), 136.8, 135.0, 132.3, 128.1 (4×qC), 132.5, 127.7 (*o*- and *m*-Ph), 121.1 (*p*-Ph), 111.1, 109.7 (C4 and C6), 104.0 (C3), 100.5 (C7), 55.9 (CH_3O), 46.2 (N–CH_2), 30.5 (CH_2CO_2H), 10.3 (CH_3); *m*/*z* 387, 389 (M^+[$^{79/81}$Br], 1%), 239 (25), 121 (68), 78 (94), 63 (100); (found: C, 59.0; H, 5.0; N, 3.9. $C_{19}H_{18}NBrO_3$ requires C, 58.8; H, 4.7; N, 3.6%).

1-(4-Fluorobenzyl)-5-methoxy-2-methylindole-3-acetic acid 14. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (328.8 mg, 1.5 mmol), *para*-fluorobenzyl bromide (187 μL, 1.5 mmol, 1.0 equiv), which was added dropwise via syringe, sodium hydride (60% dispersion in mineral oil; 144.0 mg, 3.6 mmol, 2.4 equiv) and DMF (5 mL). Flash column chromatography (chloroform/methanol 20:1) afforded the title compound as a white solid (140.8 mg, 28.7%).

Mp 167–169 °C; ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1686 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 6.74–7.07 (m, 7H, indole-H and C_6H_4), 5.21 (s, 2H, N–CH_2), 3.83 (s, 3H, CH_3O), 3.71 (s, 2H, CH_2CO_2H), 2.28 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.1 (C=O), 162.1 (d, J_{CF} 246, C4′), 154.4 (C5), 135.0, 133.5, 131.5, 128.1 (4×qC), 127.6 (d, $^3J_{CF}$ 8.7, C2′ and C6′), 115.7 (d, $^2J_{CF}$ 22.4, C3′ and C5′), 111.1, 109.8 (C4 and C6), 103.8 (C3), 100.5 (C7), 55.8 (CH_3O), 46.2 (N–CH_2), 30.4 (CH_2CO_2H), 10.4 (CH_3); *m*/*z* 327 (M^+, 2%), 283 (5), 205 (19), 109 (17), 84 (73), 49 (100); (found: C, 69.9; H, 5.6; N, 4.0; F, 5.7. $C_{19}H_{18}NFO_3$ requires C, 69.7; H, 5.5; N, 4.3; F, 5.8%).

1-(4-Methylthiobenzyl)-5-methoxy-2-methylindole-3-acetic acid 5. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (438.5 mg, 2 mmol), *para*-methylthiobenzyl chloride[17] (414.4 mg, 2.4 mmol, 1.2 equiv), which was added dropwise as a solution in DMF (1 mL), sodium hydride (60% dispersion in mineral oil; 192.0 mg, 4.8 mmol, 2.4 equiv) and DMF (5 mL). Flash column chromatography (chloroform/methanol 20:1) afforded a dark orange solid that was further purified by recrystallisation (dichloromethane/

hexane), giving the title compound as an off-white solid (119.2 mg, 16.8%).

Mp 159–160 °C (lit.[18] 155–56.5 °C); ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1709 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.74–7.16 (m, 7H, indole-H and C_6H_4), 5.22 (s, 2H, N-CH_2), 3.84 (s, 3H, CH_3O), 3.72 (s, 2H, CH_2CO_2H), 2.42 (s, 3H, CH_3S), 2.30 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.9 (C=O), 154.4 (C5), 137.5, 135.1, 131.6, 128.1 (4×qC), 134.8 (*p*-Ph), 127.2, 126.5 (*o*- and *m*-Ph), 111.1, 109.9 (C4 and C6), 103.6 (C3), 100.5 (C7), 56.0 (CH_3O), 46.4 (N–CH_2), 30.4 (*C*H_2CO_2H), 15.9 (CH_3S), 10.4 (CH_3); *m*/*z* 355 (M^+, 17%), 311 (12), 137 (100); (found: C, 67.5; H, 6.2; N, 4.2; S, 8.8. $C_{20}H_{21}NSO_3$ requires C, 67.6; H, 6.0; N, 3.9; S, 9.0%).

1-(4-Methylbenzyl)-5-methoxy-2-methylindole-3-acetic acid 15. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (400 mg, 1.82 mmol), *para*-methylbenzyl bromide (405 mg, 2.19 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil: 175.2 mg, 4.38 mmol, 2.4 equiv) and DMF (5 mL). Recrystallisation of the crude product (methanol) afforded the title compound as a white solid (70 mg, 12%).

Mp 189–190 °C; ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1698 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32–6.74 (m, 7H, indole-H and C_6H_4), 5.22 (s, 2H, N-CH_2), 3.84 (s, 3H, CH_3O), 3.72 (s, 2H, CH_2CO_2H), 2.30 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.8 (C=O), 154.2 (C5), 136.9, 135.2, 134.7, 131.6 (4×qC), 129.4, 125.9 (*o*- and *m*-Ph), 127.9 (*p*-Ph), 111.0, 110.0 (C4 and C6), 103.3 (C3), 100.2 (C7), 55.9 (CH_3O), 46.6 (N–CH_2), 30.5 (*C*H_2CO_2H), 21.0 (CH_3), 10.4 (CH_3); *m*/*z* 323 (M^+, 74%), 278 (67), 105 (100); (found: C, 73.91; H, 6.51; N, 4.17; $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.39; N, 4.33%).

1-(3-Chlorobenzyl)-5-methoxy-2-methylindole-3-acetic acid 16. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (219.2 mg, 1 mmol), *meta*-chlorobenzyl chloride (148 μL, 1.2 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 96.0 mg, 2.4 mmol, 2.4 equiv) and DMF (5 mL). Recrystallisation of the crude product (dichloromethane/hexane) afforded the title compound as a white solid (157.1 mg, 45.7%).

Mp 177–179 °C; ν_{max} (KBr)/cm^{-1} 3200–2500 (OH), 1710 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.74–7.22 (m, 7H, indole-H and C_6H_4), 5.23 (s, 2H, N-CH_2), 3.85 (s, 3H, CH_3O), 3.73 (s, 2H, CH_2CO_2H), 2.28 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.8 (C=O), 154.4 (C5), 139.9 (C3′), 135.0, 134.8, 131.5, 128.1 (4×qC), 130.1, 127.6, 126.1, 124.1 (C2′, C4′, C5′ and C6′), 111.2, 109.8 (C4 and C6), 103.9 (C3), 100.5 (C7), 55.9 (CH_3O), 46.3 (N–CH_2), 30.3 (*C*H_2CO_2H), 10.4 (CH_3); *m*/*z* 343 (M^+[^{35}Cl], 1%), 299 (12), 125 (16), 84 (68), 43 (100); (found: C, 65.9; H, 5.4; N, 4.0. $C_{19}H_{18}NClO_3$ requires C, 66.4; H, 5.3; N, 4.1%).

1-(2-Chlorobenzyl)-5-methoxy-2-methylindole-3-acetic acid 17. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (219.2 mg, 1 mmol), *ortho*-chlorobenzyl chloride (147 μL, 1.2 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 96.0 mg, 2.4 mmol, 2.4 equiv) and DMF (5 mL). Recrystallisation of the crude product (dichloromethane/hexane) afforded the title compound as a white solid (119.2 mg, 34.7%).

Mp 193–196 °C; ν_{max} (KBr)/cm^{-1} 3300–2400 (OH), 1702 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.98–7.41 (m, 5H, C_6H_4 and 4-H), 6.77 (dd, *J* 8.6, 2.4, 1H, 6-H), 6.23 (d, *J* 7.6, 1H, 7-H), 5.32 (s, 2H, N–CH_2), 3.85 (s, 3H, CH_3O), 3.76 (s, 2H, CH_2CO_2H), 2.28 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.7 (C=O), 154.6 (C5), 135.2 (C2′), 131.9, 131.6, 128.2 (3×qC), 129.4, 128.7, 127.4, 127.0 (C3′, C4′, C5′ and C6′), 111.3, 109.7 (C4 and C6), 103.9 (C3), 100.6 (C7), 55.9 (CH_3O), 44.6 (N–CH_2), 30.4 (*C*H_2CO_2H), 10.2 (CH_3); *m*/*z* 343 (M^+[^{35}Cl], 1%), 299 (8), 125 (19), 84 (75), 49 (100).

1-(3-Fluorobenzyl)-5-methoxy-2-methylindole-3-acetic acid 18. The procedure followed was as detailed above, using: 5-methoxy-2-methylindole-3-acetic acid (548.1 mg, 2.5 mmol), *meta*-fluorobenzyl bromide (363 μL, 3 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 240.0 mg, 6 mmol, 2.4 equiv) and DMF (5 mL). Recrystallisation (dichloromethane/hexane) afforded the title compound as a white solid (350.2 mg, 42.8%).

Mp 182–183 °C; ν_{max} (KBr)/cm^{-1} 3300–2200 (OH), 1702 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.61–7.26 (m, 7H, indole-H and C_6H_4), 5.25 (s, 2H, N-CH_2), 3.85 (s, 3H, CH_3O), 3.73 (s, 2H, CH_2CO_2H), 2.30 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.4 (C=O), 163.2 (d, J_{CF} 246, C3′), 154.4 (C5), 140.5 (d, $^3J_{CF}$ 7.5, C1′), 135.0, 131.5, 128.1 (3×qC), 130.4 (d, $^3J_{CF}$ 7.5, C5′), 121.5 (d, $^4J_{CF}$ 2.5, C6′), 114.3, 113.0 (2 d, $^2J_{CF}$ 21.2, $^2J_{CF}$ 21.2, C2′ and C4′), 111.2, 109.7 (C4 and C6), 103.9 (C3), 100.5 (C7), 55.9 (CH_3O), 46.4 (N–CH_2), 30.3 (*C*H_2CO_2H), 10.4 (CH_3); *m*/*z* 327 (M^+, 84%), 282 (100), 117 (88), 109 (77); (found: C, 70.1; H, 5.5; N, 4.3; F, 6.1. $C_{19}H_{18}NFO_3$ requires C, 69.7; H, 5.5; N, 4.3; F, 5.8%).

1-(4-Chlorobenzyl)-5-methoxyindole-3-acetic acid 19. The procedure followed was as detailed above, using: 5-methoxyindole-3-acetic acid (410.4 mg, 2 mmol), *para*-chlorobenzyl chloride (386.5 mg, 2.4 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 192.0 mg, 4.8 mmol, 2.4 equiv) and DMF (5 mL). Flash column chromatography (chloroform/methanol 20:1) afforded a pale yellow solid that was further purified by recrystallisation (dichloromethane/hexane), giving the title compound as a white solid (185.6 mg, 28.1%).

Mp 145–146 °C; ν_{max} (KBr)/cm^{-1} 3300–2400 (OH), 1706 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.81–7.27 (m, 8H, indole-H and C_6H_4), 5.20 (s, 2H, N-CH_2), 3.84 (s, 3H, CH_3O), 3.77 (s, 2H, CH_2CO_2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.3 (C=O), 154.3 (C5), 135.9 (*p*-Ph), 133.5, 131.7, 128.3 (3×qC), 128.7, 128.1 (*o*- and *m*-Ph), 127.8 (C2), 112.6, 110.6 (C4 and C6), 106.6 (C3), 100.9 (C7), 55.9 (CH_3O), 49.6 (N–CH_2), 31.0 (*C*H_2CO_2H); *m*/*z* 329, 331 (M^+[$^{35/37}$Cl], 14%), 284 (12), 127 (19), 125 (60), 69 (82), 41 (100); (found: C, 65.9; H, 5.2; N, 4.3;

Cl, 11.0. $C_{18}H_{16}NClO_3$ requires C, 65.55; H, 4.9; N, 4.25; Cl, 10.75%).

1-(4-Chlorobenzyl)-2-methylindole-3-acetic acid 20. The procedure followed was as detailed above, using: 2-methylindole-3-acetic acid (378.4 mg, 2 mmol), *para*-chlorobenzyl chloride (386.5 mg, 2.4 mmol, 1.2 equiv), sodium hydride (60% dispersion in mineral oil; 192.0 mg, 4.8 mmol, 2.4 equiv) and DMF (10 mL). Flash column chromatography (chloroform/methanol 20:1) afforded a pale yellow solid that was further purified by recrystallisation (dichloromethane/hexane), giving the title compound as a white solid (229.2 mg, 36.5%).

Mp 182–184 °C; ν_{max} (KBr)/cm^{-1} 3300–2200 (OH), 1706 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.86–7.58 (m, 8H, indole-H and C_6H_4), 5.26 (s, 2H, N–CH_2), 3.76 (s, 2H, CH_2CO_2H), 2.31 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.0 (C=O), 136.3 (*p*-Ph), 134.4, 133.2, 127.7 (3×qC), 129.0, 127.4 (*o*- and *m*-Ph), 121.5 (C5), 119.8, 118.2 (C4 and C6), 109.1 (C7), 104.2 (C3), 46.1 (N–CH_2), 30.3 (CH_2CO_2H), 10.3 (CH_3); *m*/*z* 313, 315 (M^+[$^{35/37}$Cl], 14%), 268 (20), 127 (36), 125 (100); (found: C, 69.1; H, 5.5; N, 4.6; Cl, 11.3. $C_{18}H_{16}NClO_2$ requires C, 68.9; H, 5.1; N, 4.5; Cl, 11.3%).

Acetaldehyde 4-methoxyphenylhydrazone 34.[16a] To a slurry of 4-methoxyphenylhydrazine (5.967 g, 43.2 mmol) in toluene (40 mL) under nitrogen at 0 °C was added a solution of acetaldehyde (3.62 mL, 64.8 mmol, 1.5 equiv) in toluene (7 mL) dropwise. Stirring at rt was continued for 30 min. The solution was decanted through a fluted filter paper into a RB-flask, evaporated and concentrated in vacuo. Bulb-to-bulb distillation (140 °C/0.6 mm Hg) afforded the title compound as a clear yellow liquid (4.5290 g, 63.8%; *E* and *Z* isomers formed in a 1:1 ratio).

ν_{max} (film)/cm^{-1} 3302 (NH), 2936 (CH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.75–7.06 (m, 5.5H, C_6H_4, NH and N=C*H*(CH_3) one isomer), 6.62 (q, *J* 5.7, 0.5H, N=C*H*(CH_3) one isomer), 3.74, 3.75 (2 s, 3H, CH_3O, *E* and *Z* isomers), 1.94, 1.81 (2 d, *J* 5.1, 5.7, 3H, N=CH(CH_3), *E* and *Z* isomers); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 153.8, 153.5 (*p*-Ph, *E* and *Z* isomers), 139.7, 139.5 (*i*-Ph, *E* and *Z* isomers), 138.3, 136.8 (*o*- and *m*-Ph), 114.1, 113.9 (C=N, *E* and *Z* isomers), 55.4 (CH_3O), 12.0 (CH_3).

Acetaldehyde phenylhydrazone 43. The procedure followed was as detailed above, using: phenylhydrazine (10.82 g, 0.1 mol), acetaldehyde (8.4 mL, 0.15 mol, 1.5 equiv) and toluene (40 mL). Bulb-to-bulb distillation of the crude product (66–80 °C/0.25–0.45 mm Hg) afforded a yellow oil, which upon trituration with hexane recrystallised. The title compound was obtained as a yellow crystalline solid by filtration (3.57 g, 26.6%; *E* and *Z* isomers formed in a 3:2 (or 2:3) ratio).

Mp 66–82 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.4–7.3 (m, 7H, C_6H_5, NH and N=C*H*(CH_3)), 1.7 [minor], 1.9 [major] (2 d, *J* 5, 3H, N=CH(CH_3), *E* and *Z* isomers).

Acetaldehyde N^1-benzoyl-N^1-(4-methoxyphenyl)hydrazone 38. To a solution of acetaldehyde 4-methoxyphenylhydrazone (1.00 g, 6.09 mmol) in pyridine (5 mL) under nitrogen at 0 °C was added benzoyl chloride (1.42 mL, 12.2 mmol, 2.0 equiv) in one portion. Stirring at rt was continued for 3 h. The reaction mixture was partitioned between water (50 mL) and dichloromethane (30 mL). A fine, white, insoluble solid was removed by suction filtration, washing with a portion of dichloromethane (20 mL). The filtrate was placed in a separatory funnel, the organic layer removed, dried ($MgSO_4$), evaporated and concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate 1:1) afforded the title compound as a clear, orange oil (0.88 g, 54.1%).

ν_{max} (film)/cm^{-1} 1660 (C=O); ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.9–8.2 (m, 9H, C_6H_4 and Ph), 6.8 (q, *J* 5, 1H, N=C*H*CH_3), 3.7 (s, 3H, CH_3O), 1.8 (d, *J* 5, 3H, N=CHCH_3).

Acetaldehyde N^1-(4-bromobenzoyl)-N^1-(4-methoxyphenyl) hydrazone 39. The procedure followed was as detailed above, using: acetaldehyde 4-methoxyphenylhydrazone (0.94 g, 5.74 mmol), 4-bromobenzoyl chloride (2.52 g, 11.47 mmol, 2.0 equiv), which was added in one portion, and pyridine (10 mL). Flash column chromatography (hexane/ethyl acetate 7:5) afforded the title compound as an orange solid (1.212 g, 60.8%).

ν_{max} (film)/cm^{-1} 1662 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67, 7.55 (ABq, *J* 10.0, 4H, $MeOC_6H_4$), 7.10, 7.01 (ABq, *J* = 8.9, 4H, BrC_6H_4), 6.82 (q, *J* = 5.4, 1H, N=C*H*CH_3), 3.84 (s, 3H, CH_3O), 1.88 (d, *J* = 5.1, 3H, N=CHCH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.2 (C=O), 159.9, 134.4, 124.7 (3×qC, 1 qC not seen), 131.4, 130.6, 130.3 (3×CH, 1 CH not seen), 115.4 (C=N), 55.5 (CH_3O), 18.5 (CH_3).

Acetaldehyde N^1-(4-chlorobenzoyl)-N^1-phenylhydrazone 44. The procedure followed was as detailed above, using: acetaldehyde phenylhydrazone (1.00 g, 7.45 mmol), 4-chlorobenzoyl chloride (0.95 mL, 7.45 mmol, 1.0 equiv), pyridine (0.60 mL, 7.45 mmol, 1.0 equiv) and ether (10 mL). Flash column chromatography (hexane/ethyl acetate 1:1) afforded the title compound as a clear, orange oil (1.3519 g, 66.5%).

ν_{max} (film)/cm^{-1} 1663 (C=O); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.0–7.8 (m, 9H, C_6H_4 and Ph), 6.7 (q, *J* = 5, 1H, N=C*H*CH_3), 1.8 (d, *J* = 5, 3H, N=CHCH_3).

N^1-Benzoyl-N^1-(4-methoxyphenyl)hydrazine hydrochloride 40. An excess of gaseous hydrogen chloride was bubbled through a solution of acetaldehyde N^1-benzoyl-N^1-(4-methoxyphenyl)hydrazone (442.0 mg, 1.65 mmol) in toluene (20 mL) and methanol (1 mL) at 0 °C for 1 h. Excess hydrogen chloride was removed under reduced pressure (ca 15 mm Hg) for 30 min and the solvent evaporated. The contents were swirled with a little toluene and filtered by suction affording the title compound as a white solid without further purification (267.0 mg, 58.1%).

Mp 170–172 °C; ν_{max} (KBr)/cm^{-1} 3300–2300 (NH_3^+), 1680 (C=O).

N^1-(4-Bromobenzoyl)-N^1-(4-methoxyphenyl)hydrazine hydrochloride 41. The procedure followed was as detailed above, using: acetaldehyde N^1-(4-bromobenzoyl)-N^1-(4-methoxyphenyl)hydrazone (1.212 g, 3.49 mmol), affording the title compound as a white solid without further purification (1.0216 g, 81.8%).

Mp 167–169 °C; ν_{max} (KBr)/cm^{-1} 3000–2500 (NH_3^+), 1670 (C=O).

N^1-(4-Chlorobenzoyl)-N^1-phenylhydrazine hydrochloride 45. The procedure followed was as detailed above, using: acetaldehyde N^1-(4-chlorobenzoyl)-N^1-phenylhydrazone (1.209 g, 4.43 mmol), affording the title compound as a white solid without further purification (1.120 g, 89.2%).

Mp 183–192 °C; ν_{max} (KBr)/cm^{-1} 3000–2500 (NH_3^+), 1680 (C=O).

1-Benzoyl-5-methoxy-2-methylindole-3-acetic acid 21. N^1-Benzoyl-N^1-(4-methoxyphenyl)hydrazine hydrochloride (338 mg, 1.21 mmol), levulinic acid (169 mg, 1.48 mmol, 1.2 equiv) and acetic acid (5 mL) were placed in a RB-flask fitted with a reflux condenser and heated at 80 °C under nitrogen for 3 h. The reaction solution was allowed to cool to rt overnight. The reaction mixture was partitioned between water (25 mL) and dichloromethane (25 mL), the organic layer removed and the aqueous extracted with a further portion of dichloromethane (25 mL). The combined organics were washed with water (3×25 mL) and extracted with saturated aqueous sodium bicarbonate solution (2×25 mL). The combined aqueous extracts were acidified (~20 mL 10% hydrochloric acid) and the resultant mixture extracted with dichloromethane (2×25 mL). The combined organic extracts were dried ($MgSO_4$), evaporated and concentrated in vacuo. Recrystallisation of the crude product (acetone/water) afforded the title compound as a white solid (180.6 mg, 46.2%).

Mp 175–176 °C (lit.[19] 176–177 °C); ν_{max} (KBr)/cm^{-1} 3500–3000 (OH), 1731 (carboxyl C=O), 1645 (amide C=O); ^{1}H NMR (270 MHz, $CDCl_3$/acetone-d_6) δ 7.48–7.72 (m, 5H, C_6H_5), 7.01 (d, J=2.4, 1H, 4-H), 6.91 (d, J=8.9, 1H, 7-H), 6.64 (dd, J=8.9, 2.4, 1H, 6-H), 3.82 (s, 3H, CH_3O), 3.69 (s, 2H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$/acetone-d_6) δ 171.5 (carboxyl C=O), 168.8 (amide C=O), 155.5 (C5), 135.3, 130.6, 130.2, 112.2 (4×qC, 1 qC not seen), 132.1 (*p*-Ph), 129.0, 128.2 (*o*- and *m*-Ph), 114.4, 111.0 (C4 and C6), 100.9 (C7), 55.0 (CH_3O), 12.6 (CH_3), α-CH_2 signal at δ ~29 ppm obscured by acetone-d_6 peaks; m/z 323 (M^+, 49%), 105 (100), 77 (21); (found: C, 70.2; H, 5.2; N, 4.4. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%).

1-(4-Bromobenzoyl)-5-methoxy-2-methylindole-3-acetic acid 22. The procedure followed was as detailed above, using: N^1-(4-bromobenzoyl)-N^1-(4-methoxyphenyl)hydrazine hydrochloride (0.500 g, 1.40 mmol), levulinic acid (0.195 g, 1.68 mmol, 1.2 equiv) and acetic acid (5 mL). The reaction mixture was heated at 70–80 °C for 6 h. Recrystallisation of the crude product (dichloromethane/hexane) afforded the title compound as a white solid (0.1923 g, 28.5%).

Mp 160–162 °C (lit.[20] 162–164 °C); ν_{max} (KBr)/cm^{-1} 3300–2500 (OH), 1697 (carboxyl C=O), 1677 (amide C=O); ^{1}H NMR (270 MHz, $CDCl_3$/acetone-d_6) δ 7.69, 7.61 (ABq, J=6.6, 4H, C_6H_4), 7.03 (d, J=2.7, 1H, 4-H), 6.93 (d, J=8.9, 1H, 7-H), 6.66 (dd, J=9.2, 2.4, 1H, 6-H), 3.82 (s, 3H, CH_3O), 3.69 (s, 2H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$/acetone-d_6) δ 171.0 (carboxyl C=O), 167.5 (amide C=O), 155.4 (C5), 134.9, 134.0, 130.1, 126.6, 112.3 (5×qC, 1 qC not seen), 131.6, 129.2 (*o*- and *m*-Ph), 114.1, 110.8 (C4 and C6), 100.8 (C7), 54.6 (CH_3O), 12.3 (CH_3), α-CH_2 signal at δ ~29 ppm obscured by acetone-d_6 peaks; m/z 401, 403 (M^+[$^{39/81}$Br], 51%), 185 (92), 183 (100); (found: C, 56.4; H, 4.3; N, 3.55; Br, 19.6. $C_{19}H_{16}NBrO_4$ requires C, 56.7; H, 4.0; N, 3.5; Br, 19.9%).

1-(4-Chlorobenzoyl)-2-methylindole-3-acetic acid 25. The procedure followed was as detailed above, using: N^1-(4-chlorobenzoyl)-N^1-phenylhydrazine hydrochloride (0.989 g, 3.49 mmol), levulinic acid (0.487 g, 4.19 mmol, 1.2 equiv) and acetic acid (5 mL). In this case the reaction was conducted at reflux for 5 h. Flash column chromatography (chloroform/methanol 10:1) afforded the title compound as a white solid (0.287 g, 27.6%).

ν_{max} (KBr)/cm^{-1} 3500–2500 (OH), 1686 (C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.83–7.58 (m, 8H, C_6H_4 and indole-H), 3.50 (s, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 178.3 (carboxyl C=O), 169.0 (amide C=O), 140.4 (*p*-Ph), 137.2, 136.3, 134.7, 130.5 (4×qC), 132.3, 130.0 (*o*- and *m*-Ph), 124.0, 123.6 (C4 and C5), 119.2 (C6), 114.5 (C7), 113.0 (C3), 31.0 (CH_2), 13.3 (CH_3).

Methyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate 23. To a solution of 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (358 mg, 1.0 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mol, 10 mol%) in dichloromethane (10 mL) at 0 °C was added, first, methanol (0.40 mL, 10 mmol, 10 equiv) in one portion, and second, a solution of dicyclohexylcarbodiimide (227 mg, 1.1 mmol, 1.1 equiv) in dichloromethane (10 mL) dropwise. Stirring was continued at rt for 2 h. The reaction mixture was cooled to 0 °C, filtered through Celite and the filtrate evaporated and concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate 3:1) afforded the title compound as a pale yellow solid (292 mg, 78.6%).

ν_{max} (KBr)/cm^{-1} 1732 (ester C=O), 1682 (amide C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.74, 7.56 (ABq, J=5.1, 4H, C_6H_4), 7.06 (d, J=2.4, 1H, 4-H), 6.96 (d, J=8.9, 1H, 7-H), 6.77 (dd, J=8.9, 2.7, 1H, 6-H), 3.93 (s, 3H, 5-CH_3O), 3.80 (ester CH_3O), 3.77 (s, 2H, CH_2), 2.48 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.2 (ester C=O), 168.2 (amide C=O), 156.1 (C5), 139.2, 135.9, 134.0, 130.8, 130.7, 112.5 (6×qC), 131.1, 129.4 (*o*- and *m*-Ph), 114.9, 111.6 (C4 and C6), 101.4 (C7), 55.7 (5-CH_3O), 52.1 (ester CH_3O), 30.1 (CH_2), 13.2 (CH_3).

***N*-Tolyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetamide 24.** To a solution of 1-(4-chlorobenzoyl)-5-

methoxy-2-methylindole-3-acetic acid (358 mg, 1.0 mmol), toluidine (118 mg, 1.1 mmol, 1.1 equiv), and 4-dimethylaminopyridine (12 mg, 0.1 mmol, 10 mol%), in dichloromethane (10 mL) at 0 °C was added a solution of dicyclohexylcarbodiimide (227.0 mg, 1.1 mmol, 1.1 equiv) in dichloromethane (5 mL) dropwise. Stirring at rt was continued for 3 h. The reaction mixture was cooled to 0 °C, filtered through Celite and the filtrate evaporated and concentrated in vacuo. Flash column chromatography (hexane/ethyl acetate 8:1, 4:1, 2:1 then 1:1) afforded an orange solid that was further purified by recrystallisation (ether/ethanol), giving the title compound as on off-white solid (142.6 mg, 31.9%).

ν_{max} (KBr)/cm^{-1} 3283 (NH), 1686 and 1654 (2×amide C=O); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68, 7.49 (ABq, J = 6.8, 4H, C_6H_4Cl), 7.05–7.29 (m, 4H, $C_6H_4CH_3$), 6.95 (d, J = 2.2, 1H, 4-H), 6.88 (d, J = 8.6, 1H, 7-H), 6.71 (dd, J = 9.0, 2.6, 1H, 6-H), 3.80 (s, 3H, CH_3O), 3.78 (s, 2H, CH_2), 2.44 (s, 3H, 2-CH_3), 2.28 (s, 3H, $C_6H_4CH_3$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 168.3, 168.0 (2×C=O), 156.4 (C5), 139.6, 136.6, 134.8, 134.3, 133.5, 130.9, 130.2, 115.2 (8×qC), 131.2, 129.4, 129.2, 120.2, 112.5 (5×CH, 1 CH not seen), 100.7 (C7), 55.7 (CH_3O), 33.2 (CH_2), 20.8 ($C_6H_4CH_3$), 13.3 (2-CH_3).

Methyl 3-(phenylmethyl)amino-2-pentenoate 47. A solution of methyl propionylacetate (12.6 mL, 0.1 mmol), benzylamine (11.4 mL, 0.105 mmol, 1.05 equiv) and *p*-toluenesulphonic acid monohydrate (0.95 g, 5 mmol, 5 mol%) in toluene (50 mL) was refluxed under Dean–Stark conditions under nitrogen for 3 h. The reaction solution was cooled in an ice-bath to ~10 °C, the fine white crystalline precipiate that formed was removed by filtration, and the filtrate evaporated and concentrated in vacuo affording the title compound as a clear orange liquid (21.1 g, 95.7%) that was used without subsequent purification.

^{1}H NMR (270 MHz, $CDCl_3$) δ 8.93 (s, 1H, NH), 7.18–7.37 (m, 5H, C_6H_5), 4.56 (s, 1H, C=CH–C=O), 4.43 (d, J = 6.2, 2H, N–CH_2), 3.64 (s, 3H, OCH_3), 2.23 (q, J = 7.5, 2H, CH_2CH_3), 1.12 (t, J = 7.4, CH_2CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.2 (C=O), 167.0 (C3), 138.8 (*i*-Ph), 128.7, 126.9, (*o*- and *m*-Ph), 127.4 (*p*-Ph), 81.0 (C2), 49.9 (N-CH_2), 25.1 (CH_2CH_3), 12.1 (CH_2CH_3).

Methyl 3-(phenylmethyl)amino-2-butenoate 46. The procedure followed was as detailed above, using: methyl acetoacetate (10.8 mL, 0.1 mol). The title compound was obtained as a clear orange liquid (20.1 g, 97.8%) that was used without subsequent purification.

^{1}H NMR (270 MHz, $CDCl_3$) δ 8.93 (s, 1H, NH), 7.13–7.38 (m, 5H, C_6H_5), 4.54 (s, 1H, C=CH–C=O), 4.42 (d, J = 6.2, 2H, N-CH_2), 3.63 (s, 3H, OCH_3), 1.91 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.9 (C=O), 161.9 (C3), 138.7 (*i*-Ph), 128.8, 126.7, (*o*- and *m*-Ph), 127.4 (*p*-Ph), 82.9 (C2), 50.0 (N-CH_2), 19.3 (CH_3).

3-(Carbomethoxy)-2-ethyl-1-(phenylmethyl)-5-hydroxyindole 49. To a solution of freshly recrystallised benzoquinone (10.17 g, 93.9 mmol, 1.38 equiv) in nitromethane (40 mL) at rt under nitrogen was added a solution of methyl 3-(phenylmethyl)amino-2-pentenoate (15.00 g, 68.1 mmol) in nitromethane (20 mL) dropwise over 30 min. Stirring at rt was continued for 48 h. The reaction mixture was cooled to 0 °C in an ice-bath, filtered, washed with cold nitromethane (~50 mL) affording the title compound as a pale brown solid (11.32 g, 53.7%) after drying in vacuo that was used without subsequent purification. However, an analytical sample was obtained thus: a portion of the product (2.89 g) was suspended in 1,2-dichloroethane (10 mL) and the mixture refluxed for 30 min. Filtration of the hot mixture afforded a pale brown solid (1.68 g).

Mp 191–193 °C (lit.[21] 194–195 °C); ν_{max} (KBr)/cm^{-1} 3281, 1646, 1142; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.72-7.67 (m, 8H, indole-H and C_6H_5), 5.34 (s, 2H, N–CH_2), 3.93 (s, 3H, CO_2CH_3), 3.14 (q, J = 7.5, 2H, CH_2CH_3), 1.18 (t, J = 7.4, 3H, CH_2CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.3, (C=O), 155.6 (C5), 151.4, 136.6, 131.5, 127.9 (4×qC), 128.9, 125.8 (*o*- and *m*-Ph), 127.7 (*p*-Ph), 111.7, 110.7 (C4 and C6), 106.6 (C7), 103.1 (C3), 50.8 (CO_2CH_3), 46.7 (N–CH_2), 19.3 (CH_2CH_3), 13.8 (CH_2CH_3).

3-(Carbomethoxy)-2-methyl-1-(phenylmethyl)-5-hydroxyindole 48. The procedure followed was as detailed above, using: a solution of benzoquinone (14.54 g, 0.134 mol, 1.38 equiv) in nitromethane (50 mL) and a solution of methyl 3-(phenylmethyl)amino-2-butenoate (20.00 g, 0.974 mol) in nitromethane (25 mL). Stirring at rt under nitrogen was continued for 66 h. The title compound was obtained as a pale brown solid (13.73 g, 47.7%). A portion (2.50 g) was refluxed in 1,2-dichloroethane (5 mL) for 1 h and the resultant mixture filtered whilst hot to give an analytical sample (0.87 g) as a pale brown solid.

Mp 191–193 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3016, 1676, 1118; ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.99 (s, 1H, OH), 6.63–7.42 (m, 8H, indole-H and C_6H_5), 5.43 (s, 2H, N-CH_2), 3.81 (s, 3H, CO_2CH_3), 2.65 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 165.4, (C=O), 152.8 (C5), 144.9, 137.2, 136.5, 130.3 (4×qC), 128.6, 126.1 (*o*- and *m*-Ph), 127.2 (*p*-Ph), 111.6, 110.7 (C4 and C6), 105.4 (C7), 102.5 (C3), 50.3 (CO_2CH_3), 45.8 (N–CH_2), 11.8 (CH_3).

3-(Carbomethoxy)-2-ethyl-1-(phenylmethyl)-5-methoxyindole 51. To a mixture of 3-(carbomethoxy)-2-ethyl-1-(phenylmethyl)-5-hydroxyindole (11.31 g, 36.56 mmol) and tetrabutylammonium bromide (1.179 g, 3.66 mmol, 10 mol%) in water (100 mL) was added a 50% aq solution of sodium hydroxide (35 mL) and methyl iodide (6.83 mL, 0.110 mol, 3.0 equiv). This heterogeneous mixture was brought to reflux, resulting in a dark brown solution, and reflux continued for 30 min. Once cooled to rt, the reaction mixture was extracted with ethyl acetate (3×85 mL), the combined extracts washed with brine (150 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo to a pale brown solid (10.82 g). Recrystallisation of the crude product (*iso*-propanol) afforded the title compound as colourless crystals (7.160 g, 60.6%).

Mp 100–101 °C (lit.[21] 102–103 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2950, 1689, 1480, 1462, 1439, 1120; ^{1}H NMR (270 MHz,

DMSO-d_6) δ 6.78–7.53 (m, 8H, indole-H and C_6H_5), 5.51 (s, 2H, N–CH_2), 3.84 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CH_3O), 3.11 (q, $J=7.4$, 2H, CH_2CH$_3$), 1.06 (t, $J=7.4$, 3H, CH$_2$CH_3).

3-(Carbomethoxy)-2-methyl-1-(phenylmethyl)-5-methoxyindole 50. The procedure followed was as detailed above, using: 3-(carbomethoxy)-2-methyl-1-(phenylmethyl)-5-hydroxy-indole (12.99 g, 43.98 mmol), tetrabutylammonium bromide (1.418 g, 4.40 mmol, 10 mol%), water (125 mL), 50% aq sodium hydroxide solution (42 mL) and methyl iodide (8.21 mL, 0.132 mol, 3.0 equiv). The crude product was obtained as a pale brown solid that upon recrystallisation (*iso*-propanol) afforded the title compound as beige crystals (7.775 g, 57.2%).

Mp 127–128 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3007, 2950, 1688, 1482, 1415, 1119; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.78–7.54 (m, 8H, indole-H and C_6H_5), 5.48 (s, 2H, N-CH_2), 3.84 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CH_3O), 2.67 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 165.4, (C=O), 155.2 (C5), 145.2, 137.1, 131.1, 126.9 (4×qC), 128.7, 126.0 (*o*- and *m*-Ph), 127.3 (*p*-Ph), 111.3, 111.1 (C4 and C6), 103.3 (C7), 103.0 (C3), 55.3 (CH_3O), 50.5 (CO_2CH_3), 45.9 (N–CH_2), 11.8 (CH_3).

3-(Hydroxymethyl)-2-ethyl-1-(phenylmethyl)-5-methoxyindole 53. To a slurry of lithium aluminium hydride (2.46 g, 64.9 mmol, 3.0 equiv) in THF (50 mL) at rt under nitrogen was added a solution of 3-(carbomethoxy)-2-ethyl-1-(phenylmethyl)-5-methoxyindole (7.00 g, 21.6 mmol) in THF (15 mL) dropwise and stirring continued for 17 h. The reaction was quenched by the sequential addition of water (2.5 mL), 15% aq sodium hydroxide solution (2.5 mL) and water (7.5 mL). The resultant mixture was stirred at rt for 30 min during which the grey slurry was transformed to a fine white solid and a clear yellow solution. This mixture was filtered, the filtrate dried ($MgSO_4$), evaporated and concentrated in vacuo to give the title compound (4.24 g, 66.4%) without further purification as a yellow oil that solidified upon standing.

Mp 69–72 °C (lit.[21] 69–70 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1485, 1454, 1158; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.63–7.30 (m, indole-H and C_6H_5), 5.37 (s, 2H, N–CH_2), 4.61 (s, 3H, CH_2OH; accidental equivalence), 3.76 (s, 3H, CH_3O), 2.74 (q, $J=7.5$, 2H, CH_2CH$_3$), 1.05 (t, $J=7.6$, 3H, CH$_2$CH_3).

3-(Hydroxymethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole 52. The procedure followed was as detailed above, using: a slurry of lithium aluminium hydride (2.85 g, 75.2 mmol, 3.0 equiv) in THF (50 mL) and a solution of 3-(carbomethoxy)-2-methyl-1-(phenylmethyl)-5-methoxyindole (7.75 g, 25.1 mmol) in THF (30 mL). Work up in a similar fashion afforded the title compound as a yellow solid (4.45 g, 63.0%) without further purification.

ν_{max} (KBr)/cm^{-1} 3500–2700 (OH), 2923, 1447, 1147; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.61–7.30 (m, 8H, indole-H and C_6H_5), 5.33 (s, 2H, N–CH_2), 4.60 (s, 3H, CH_2OH; accidental equivalence), 3.75 (s, 3H, CH_3O), 2.31 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 153.4 (C5), 138.6, 134.9, 131.2, 128.0 (4×qC), 128.5, 126.2 (*o*- and *m*-Ph), 127.0 (*p*-Ph), 111.9 (C3), 109.9 (C4 and C6), 100.6 (C7), 55.3 (CH_3O), 53.9 (CH_2OH), 45.8 (N-CH_2), 10.0 (CH_3).

3-(Cyanomethyl)-2-ethyl-1-(phenylmethyl)-5-methoxyindole 55. To a solution of boron trifluoride etherate (4.06 mL, 32.1 mmol, 3.0 equiv) and cyanotrimethylsilane (5.70 mL, 42.7 mmol, 4.0 equiv) in dichloromethane (65 mL) at 0 °C under nitrogen in a three-necked RB-flask fitted with a thermometer and a dropping funnel was added a solution of 3-(hydroxymethyl)-2-ethyl-1-(phenylmethyl)- 5-methoxyindole (3.156 g, 10.7 mmol) in dichloromethane (15 mL) dropwise at such a rate that the internal temperature was maintained at <7 °C. Stirring at 0 °C was continued for 1 h. The reaction was quenched by the addition of satd aq sodium bicarbonate solution (10 mL) and stirring at rt continued for 45 min. The organic layer was separated, washed with 1 M hydrochloric acid (25 mL), satd aq sodium bicarbonate solution (25 mL) and brine (25 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo to a brown oil (2.194 g). Elution of the crude product through a silica gel plug with dichloromethane (500 mL) afforded the title compound, after evaporation and concentration in vacuo, as a light amber semi-solid (2.319 g, 71.3%).

ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2249, 1486, 1454, 1157; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.70–7.31 (m, 8H, indole-H and C_6H_5), 5.40 (s, 2H, N–CH_2), 4.04 (s, 2H, CH_2CN), 3.76 (s, 3H, CH_3O), 2.78 (q, $J=7.6$, 2H, CH_2CH$_3$), 1.05 (t, $J=7.4$, 3H, CH$_2$CH_3).

3-(Cyanomethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole 54. The procedure followed was as detailed above, using: a solution of boron trifluoride etherate (5.84 mL, 46.1 mmol, 3.0 equiv) and cyanotrimethylsilane (8.19 mL, 61.4 mmol, 4.0 equiv) in dichloromethane (90 mL) and a solution of 3-(hydroxymethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole (4.32 g, 15.4 mmol) in dichloromethane (25 mL). Work up in a similar fashion afforded the crude product as a dark red semi-solid (4.266 g) that, upon elution through a silica gel plug with dichloromethane (700 mL), gave the title compound as a light yellow semi-solid (3.233 g, 72.5%).

ν_{max} ($CHCl_3$)/cm^{-1} 3004, 2249, 1487, 1454, 1157; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.72–7.32 (m, 8H, indole-H and C_6H_5), 5.36 (s, 2H, N–CH_2), 4.03 (s, 2H, CH_2CN), 3.78 (s, 3H, CH_3O), 2.33 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 154.1 (C5), 138.5, 135.4, 131.4, 127.2 (4×qC), 128.9, 126.4 (*o*- and *m*-Ph), 127.4 (*p*-Ph), 119.6 (CN), 110.9, 110.8 (C4 and C6), 100.3 (C7), [C3 not seen], 55.7 (CH_3O), 46.2 (N–CH_2), 12.5 (CH_2CN), 10.2 (CH_3).

3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-5-methoxyindole 57. To a solution of 3-(cyanomethyl)-2-ethyl-1-(phenylmethyl)-5-methoxyindole (2.307 g, 7.58 mmol) in *tert*-butanol (30 mL) was added powdered potassium hydroxide (2.127 g, 37.9 mmol, 5.0 equiv) and the mixture refluxed under nitrogen for 1 h. Once cooled to rt, the

reaction mixture was partitioned between ethyl acetate (75 mL) and brine (75 mL). The organic layer was separated, washed with brine (75 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo. Flash column chromatography (dichloromethane/ethyl acetate 1:2) afforded the title compound as a pale yellow solid (1.680 g, 66.2%).

ν_{max} ($CHCl_3$)/cm^{-1} 3514, 3398, 3008, 1671 (C=O), 1485, 1154; ^1H NMR (270 MHz, DMSO-d_6) δ 6.63–7.30 (m, 10H, indole-H, C_6H_5 and NH_2), 5.36 (s, 2H, N–CH_2), 3.74 (s, 3H, CH_3O), 3.44 (s, 2H, 3-CH_2), 2.73 (q, J = 7.4, 2H, CH_2CH_3), 1.04 (t, J = 7.4, 3H, CH_2CH_3).

3-(Amidomethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole 56. The procedure followed was as detailed above, using: 3-(cyanomethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole (3.113 g, 10.7 mmol), powdered potassium hydroxide (3.01 g, 53.6 mmol, 5.0 equiv) and *tert*-butanol (40 mL). Work up in a similar fashion gave the crude product as a yellow solid (2.956 g). Recrystallisation (ethyl acetate) afforded the product as colourless crystals (1.139 g). Concentration of the mother liquor and subsequent recrystallisation (hexane/dichloromethane) afforded the product as pale yellow crystals (0.725 g). Concentration of the mother liquor and subsequent flash column chromatography (ethyl acetate then ethyl acetate/methanol 20:1) afforded the product as a pale yellow solid (0.463 g). Combination of the three materials afforded the title compound (2.327 g, 70.4%).

ν_{max} ($CHCl_3$)/cm^{-1} 3514, 3398, 3003, 1671 (C=O), 1486, 1454, 1154; ^1H NMR (270 MHz, DMSO-d_6) δ 6.64–7.30 (m, 10H, indole-H, C_6H_5 and NH_2), 5.33 (s, 2H, N–CH_2), 3.75 (s, 3H, CH_3O), 3.45 (s, 2H, 3-CH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 172.8 (C=O), 153.5 (C5), 138.5, 134.8, 131.2, 128.1 (4×qC), 128.2, 126.1 (*o*- and *m*-Ph), 126.9 (*p*-Ph), 109.7 (C4 and C6), 105.6 (C3), 100.8 (C7), 55.4 (CH_3O), 45.9 (N–CH_2), 31.6 (3-CH_2), 10.1 (CH_3).

3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-5-hydroxyindole 59. To a solution of 3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-5-methoxyindole (1.622 g, 5.03 mmol) in dichloromethane (35 mL) at 0 °C under nitrogen was added boron tribromide (1.0 M solution in dichloromethane; 15.1 mL, 15.1 mmol, 3.0 equiv) dropwise. Stirring at rt was continued for 3 h. The reaction solution was diluted with dichloromethane (50 mL) and quenched with water (75 mL). The organic layer was separated, washed with sat. aq ammonium chloride solution (75 mL), brine (75 mL), dried (Na_2SO_4), evaporated and concentrated in vacuo affording the title compound as a pale brown solid (1.551 g, 98.2%) without further purification.

ν_{max} ($CHCl_3$)/cm^{-1} 3500–3100 (OH), 3512, 3396, 3006, 1668 (C=O), 1482, 1454, 1153; ^1H NMR (270 MHz, DMSO-d_6) δ 8.61 (br s, 1H, OH), 6.49–7.30 (m, 10H, indole-H, C_6H_5 and NH_2), 5.31 (s, 2H, N–CH_2), 3.39 (s, 2H, 3-CH_2), 2.70 (q, J = 7.4, 2H, CH_2CH_3), 1.03 (t, J = 7.4, 3H, CH_2CH_3).

3-(Amidomethyl)-2-methyl-1-(phenylmethyl)-5-hydroxyindole 58. The procedure followed was as detailed above, using: 3-(amidomethyl)-2-methyl-1-(phenylmethyl)-5-methoxyindole (2.32 g, 7.52 mmol) in dichloromethane (25 mL) and boron tribromide (1.0 M solution in dichloromethane; 22.6 mL, 22.6 mmol, 3.0 equiv). Work-up in a similar fashion (a further portion of dichloromethane, ~125 mL, was added prior to the aqueous washes to effect complete dissolution of the crude product) afforded the title compound as a brown solid (1.941 g, 87.7%) without further purification.

ν_{max} ($CHCl_3$)/cm^{-1} 3600–3100 (OH), 3513, 3398, 3008, 1669 (C=O), 1483, 1454, 1153; ^1H NMR (270 MHz, DMSO-d_6) δ 8.59 (br s, 1H, OH), 6.50–7.31 (m, 10H, indole-H, C_6H_5 and NH_2), 5.29 (s, 2H, N–CH_2), 3.37 (s, 2H, 3-CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 172.8 (C=O), 150.6 (C5), 138.8, 134.4, 130.6 (3×qC, 1 qC not seen), 128.5, 126.2 (*o*- and *m*-Ph), 126.9 (*p*-Ph), 110.2, 109.5 (C4 and C6), 105.1 (C3), 102.7 (C7), 45.8 (N–CH_2), 31.7 (3-CH_2), 10.2 (CH_3).

Dimethyl (3-bromopropyl)phosphonate 64.[22] Trimethylphosphite (2.38 mL, 20.1 mmol) and 1,3-dibromopropane (10.2 mL, 0.105 mol, 5.0 equiv) were placed in a RB-flask fitted with a reflux condenser and heated to 150 °C (external temperature) in an oil-bath for 30 min. Once cooled to rt, the excess dibromopropane was removed by distillation (60–62 °C/~15 mm Hg) and the title compound obtained by bulb-to-bulb distillation (120 °C/0.1 mm Hg) as a clear, colourless liquid (1.668 g, 35.9%).

ν_{max} (film)/cm^{-1} 3464, 2955, 1232, 1031; ^1H NMR (270 MHz, $CDCl_3$) δ 3.76 (d, $^3J_{PH}$ 11.0, 6H, $(CH_3O)_2P$=O), 3.48 (t, J = 7.4, 2H, CH_2Br), 1.83–2.01, 2.06–2.24 (2 m, 4H, CH_2CH_2P=O); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 52.4 (d, $^2J_{CP}$ 6.2, $(CH_3O)_2P$=O), 33.4 (d, $^2J_{CP}$ 18.6, CH_2CH_2P=O), 25.9 (d, $^3J_{CP}$ = 4.9, CH_2Br), 23.5 (d, $^1J_{CP}$ 142.9, CH_2P=O).

Ethyl 4[3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl]oxy]butanoate 61. To a solution of 3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-5-hydroxyindole (894 mg, 2.90 mmol) in DMF (5 mL) at rt under nitrogen was added sodium hydride (60% dispersion in mineral oil; 139 mg, 3.48 mmol, 1.2 equiv) in one portion. Stirring at rt was continued for 1 h. Ethyl 4-bromobutyrate (415 μL, 2.90 mmol) was added in one portion and stirring at rt was continued for 2 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (15 mL). The organic layer was separated, the aqueous layer extracted with dichloromethane (10 mL), the combined organics washed with water (3×25 mL) and brine (25 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo to a brown oil. Flash column chromatography (dichloromethane/*iso*-propanol 20:1, 10:1 then 5:1) afforded the title compound as a beige solid (600.5 mg, 49.0%; 57.6% based on recovered starting material) and unreacted starting material was recovered (133.3 mg).

^1H NMR (270 MHz, DMSO-d_6) δ 6.62–7.30 (m, 10H, indole-H, C_6H_5 and NH_2), 5.35 (s, 2H, N–CH_2), 4.07 (q, J = 7.1, 2H, CH_3CH_2OC=O), 3.96 (t, J = 6.2, 2H, γ-CH_2), 3.43 (s, 2H, 3-CH_2), 2.73 (q, J = 7.4, 2H, 2-CH_2CH_3),

2.47 (t, $J=7.0$, 2H, α-CH_2), 1.97 (qn, $J=6.8$, 2H, β-CH_2), 1.18 (t, $J=7.2$, 3H, $CH_3CH_2OC=O$), 1.03 (t, $J=7.4$, 3H, 2-CH_3CH_2).

Ethyl 4-[3-(amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl]oxy]butanoate 60. The procedure followed was as detailed above, using: 3-(amidomethyl)-2-methyl-1-(phenylmethyl)-5-hydroxyindole (950 mg, 3.23 mmol) in DMF (10 mL), sodium hydride (60% dispersion in mineral oil; 155 mg, 3.87 mmol, 1.2 equiv) and ethyl 4-bromobutyrate (415 μL, 3.23 mmol). Work up in a similar fashion gave the crude product as a brown oil. Flash column chromatography (dichloromethane/*iso*-propanol 20:1, 10:1 then 5:1) afforded the title compound as a beige solid (506.5 mg, 38.4%; 47.3% based on recovered starting material) and unreacted starting material was recovered (178.6 mg).

ν_{max} ($CHCl_3$/cm^{-1} 3514, 3399, 3002, 1727 (ester C=O), 1672 (amide C=O), 1485, 1156; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.67–7.35 (m, 10H, indole-H, C_6H_5 and NH_2), 5.38 (s, 2H, N–CH_2), 4.12 (q, $J=7.1$, 2H, $CH_3CH_2OC=O$), 4.01 (t, $J=6.3$, 2H, γ-CH_2), 3.47 (s, 2H, 3-CH_2), 2.52 (t, $J=7.3$, 2H, α-CH_2), 2.34 (s, 3H, CH_3), 2.02 (qn, $J=6.8$, 2H, β-CH_2), 1.22 (t, $J=7.3$, 3H, $CH_3CH_2OC=O$); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 172.7, 172.5 (2×C=O), 152.4 (C5), 138.6, 134.8, 131.2, 128.1 (4×qC), 128.4, 126.1 (*o*- and *m*-Ph), 126.9 (*p*-Ph), 110.1, 109.7 (C4 and C6), 105.7 (C3), 101.9 (C7), 67.0 (γ-CH_2), 59.7 ($CH_3CH_2OC=O$), 45.8 (N-CH_2), 31.5 (3-CH_2), 30.2 (α-CH_2), 24.5 (β-CH_2), 14.0 ($CH_3CH_2OC=O$), 10.2 (CH_3).

Dimethyl [3-[3-(amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl]oxy]-propyl]phosphonate 62. The procedure followed was as detailed above, using: 3-(amidomethyl)-2-methyl-1-(phenylmethyl)-5-hydroxyindole (1.103 g, 3.75 mmol) in DMF (10 mL), sodium hydride (60% dispersion in mineral oil; 180 mg, 4.50 mmol, 1.2 equiv) and dimethyl (3-bromopropyl)phosphonate (0.866 g, 3.75 mmol). Work up in a similar fashion gave the crude product as a light brown oil. Flash column chromatography (dichloromethane/*iso*-propanol 9:1 then 9:2) afforded the title compound as an off-white solid (0.964 g, 57.9%).

ν_{max} ($CHCl_3$)/cm^{-1} 3515, 3399, 3002, 1671 (C=O), 1485, 1156, 1039; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.71–7.37 (m, 10H, indole-H, C_6H_5 and NH_2), 5.40 (s, 2H, N–CH_2), 4.05 (t, $J=5.5$, 2H, γ-CH_2), 3.68 (d, $^3J=_{PH}$ 15.1, 6H, $(CH_3O)_2P=O$), 3.48 (s, 2H, 3-CH_2), 2.35 (s, 3H, CH_3), 1.90–2.06 (m, 4H, α- and β-CH_2); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 174.2 (C=O), 153.9 (C5), 140.1, 136.4, 132.9, 129.7 (4×qC), 130.0, 127.8 (*o*- and *m*-Ph), 128.5 (*p*-Ph), 111.8, 111.3 (C4 and C6), 107.3 (C3), 103.7 (C7), 69.3 (d, $^3J=_{CP}$ 16.2, γ-CH_2), 53.5 (d, $^2J=_{CP}$ 6.2, $(CH_3O)_2P=O$), 47.4 (N-CH_2), 33.1 (3-CH_2), 23.9 (d, $^2J_{CP}=3.7$, β-CH_2), 22.0 (d, $^1J_{CP}=139$, α-CH_2), 11.7 (CH_3).

Dimethyl [3-[3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl]oxy]-propyl]phosphonate 63. The procedure followed was as detailed above, using: 3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-5-hydroxyindole (2.513 g, 8.15 mmol) in DMF (20 mL), sodium hydride (60% dispersion in mineral oil; 0.391 g, 9.78 mmol, 1.2 equiv) and dimethyl (3-bromopropyl)phosphonate (1.883 g, 8.15 mmol). Work up in a similar fashion gave the crude product as a light brown solid. A portion (100 mg) of this material was purified by flash column chromatography (dichloromethane/*iso*-propanol 7:1 then 5:1) affording an analytically pure sample (63.8 mg, overall yield 64.8%).

^{1}H NMR (270 MHz, DMSO-d_6) δ 6.65–7.31 (m, 10H, indole-H, C_6H_5 and NH_2), 5.35 (s, 2H, N–CH_2), 4.00 (t, $J=5.7$, 2H, γ-CH_2), 3.64 (d, $^3J_{PH}=14.8$, 6H, $(CH_3O)_2P=O$), 3.44 (s, 2H, 3-CH_2), 2.73 (q, $J=7.4$, 2H, 2-CH_2CH_3), 1.80–2.01 (m, 4H, α- and β-CH_2), 1.04 (t, $J=7.4$, 3H, 2-CH_2CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 172.7 (C=O), 152.4 (C5), 140.5, 138.7, 131.3, 128.3 (4×qC), 128.4, 125.9 (*o*- and *m*-Ph), 126.9 (*p*-Ph), 110.5, 110.0 (C4 and C6), 105.3 (C3), 102.4 (C7), 67.8 (d, $^3J_{CP}=17.4$, γ-CH_2), 51.9 (d, $^2J_{CP}=6.2$, $(CH_3O)_2P=O$), 45.9 (N-CH_2), 31.4 (3-CH_2), 22.3 (d, $^2J_{CP}=4.9$, β-CH_2), 20.2 (d, $^1J_{CP}=139$, α-CH_2), 17.3 (2-CH_2CH_3), 14.4 (2-CH_2CH_3).

4-[3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl]-oxy]butanoic acid 27. To a solution of ethyl 4-[3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl]oxy] butanoate (403.9 mg, 0.956 mmol) in ethanol (15 mL) at rt was added a 1 M aq solution of sodium hydroxide (2 mL). Stirring at rt was continued for 2 h. The reaction mixture was evaporated to dryness, water (10 mL) added and the resultant mixture acidified with 10% hydrochloric acid (~1 mL). The crude product was extracted with ethyl acetate (~200 mL), the organic layer separated, washed with brine (50 mL), dried ($MgSO_4$), evaporated and concentrated in vacuo. This material was swirled with ether/methanol (3–4 mL/6 drops), allowed to settle, the liquor carefully removed by pipette, and the residual solid dried in vacuo to give the title compound as an off-white solid (254.2 mg, 67.4%).

Mp 196–198 °C (lit.[12b] 196–199 °C); ν_{max} (KBr)/cm^{-1} 3548 (NH), 3600–2200 (OH), 2965, 1715 (carboxyl C=O), 1644 (amide C=O), 1487, 1044; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.63–7.35 (m, 10H, indole-H, C_6H_5 and NH_2), 5.35 (s, 2H, N–CH_2), 3.96 (t, $J=6.3$, 2H, γ-CH_2), 3.44 (s, 2H, 3-CH_2), 2.73 (q $J=7.4$, 2H, CH_2CH_3), 2.40 (t, $J=7.2$, 2H, α-CH_2), 1.91–2.03 (m, 2H, β-CH_2), 1.04 (t, $J=7.4$, 3H, CH_2CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 174.1, 172.7 (2×C=O), 152.5 (C5), 140.4, 138.7, 131.2, 128.2 (4×qC), 128.4, 125.9 (*o*- and *m*-Ph), 126.8 (*p*-Ph), 110.4, 110.0 (C4 and C6), 105.2 (C3), 102.0 (C7), 67.1 (γ-CH_2), 45.8 (N–CH_2), 31.4 (3-CH_2), 30.2 (α-CH_2), 24.5 (β-CH_2), 17.3 (CH_2CH_3), 14.4 (CH_2CH_3); (found: C, 69.9; H, 6.9; N, 7.4. $C_{23}H_{26}N_2O_4$ requires C, 70.0; H, 6.6; N, 7.1%).

4-[3-(Amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl]-oxy]butanoic acid 26. To a solution of ethyl 4-[3-(amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl]oxy]-butanoate (495.9 mg, 1.21 mmol) in ethanol (40 mL) at rt was added a 1 M aq solution of sodium hydroxide (3 mL). Stirring at rt was continued for 19 h. The reaction

mixture was evaporated to dryness, water (10 mL) added and the resultant mixture acidified with 10% hydrochloric acid (~1 mL). The crude product was obtained by filtration, stirred with boiling ethyl acetate (50 mL) for 5 min, cooled to ~5 °C and filtered to give, after drying (50 °C/1.0 mm Hg, 3 h), the title compound as an off-white solid (368.0 mg, 79.7%).

Mp 232–234 °C (lit.[12b] 218–221 °C); ν_{max} (KBr)/cm^{-1} 3548 and 3345 (NH), 3600–2200 (OH), 2962, 2917, 1729 (carboxyl C=O), 1641 (amide C=O), 1578, 1473, 1161, 1038; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.65–7.33 (m, 10H, indole-H, C_6H_5 and NH_2), 5.35 (s, 2H, N–CH_2), 3.97 (t, J = 6.3, 2H, γ-CH_2), 3.44 (s, 2H, 3-CH_2), 2.40 (t, J = 7.2, 2H, α-CH_2), 2.31 (s, 3H, CH_3), 1.90–2.01 (m, 2H, β-CH_2); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 174.1, 172.6 (2×C=O), 152.5 (C5), 138.5, 134.7, 131.3, 128.1 (4×qC), 128.4, 126.1 (*o*- and *m*-Ph), 126.9 (*p*-Ph), 110.2, 109.7 (C4 and C6), 105.7 (C3), 101.9 (C7), 67.2 (γ-CH_2), 45.8 (N–CH_2), 31.5 (3-CH_2), 30.4 (α-CH_2), 24.6 (β-CH_2), 10.1 (CH_3).

[3-[3-(Amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl] oxy]propyl]phosphonic acid 28. To a solution of sodium iodide (2.55 g, 10.0 mmol, 9.0 equiv) in acetonitrile (13 mL) at rt under nitrogen in a 20 mL narrow, straight-walled flask (a new B19 cone sealed at the end by a glassblower is ideal) was added chlorotrimethylsilane (2.16 mL, 17.0 mmol, 9.0 equiv) in one portion. A fine white precipitate formed immediately and was allowed to settle over 15 min affording a clear yellow solution of iodotrimethylsilane. To a solution of dimethyl [3-[3-(amidomethyl)-2-methyl-1-(phenylmethyl)-indol-5-yl]-oxy]propyl]-phosphonate (842 mg, 1.89 mmol) in dichloromethane (20 mL) at rt under nitrogen was added a portion of the iodotrimethylsilane solution (5 mL, 3.0 equiv) in one portion. Stirring at rt was continued for 1.5 h. The reaction contents were evaporated to dryness and the residue stirred with methanol (10 mL) for 10 min, resulting in a white suspension. Evaporation and concentration in vacuo afforded the crude product. Recrystallisation (ethyl acetate/acetonitrile/acetic acid/water 21:7:7:9) afforded the title compound as a white solid (531 mg, 67.3%).

Mp 201–203 °C (lit.[12b] 201–203 °C); ν_{max} (KBr)/cm^{-1} 3600–2400 (OH), 3455 (N–H), 2928, 1655 (C=O), 1489, 1154; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.66–7.32 (m, 10H, indole-H, C_6H_5 and NH_2), 5.34 (s, 2H, N–CH_2), 4.01 (t, J = 6.5, 2H, γ-CH_2), 3.44 (s, 2H, 3-CH_2), 2.31 (s, 3H, CH_3), 1.83–2.01, 1.64–1.76 (2 m, 4H, α- and β-CH_2); ^{13}C NMR (100.54 MHz, DMSO-d_6) δ 174.9 (C=O), 153.1 (C5), 138.8, 135.9, 131.9, 128.6 (4×qC), 129.1, 126.7 (*o*- and *m*-Ph), 127.7 (*p*-Ph), 111.0, 110.5 (C4 and C6), 105.6 (C3), 102.6 (C7), 69.0 (d, $^3J_{CP}$ = 17.7, γ-CH_2), 46.5 (N–CH_2), 31.9 (3-CH_2), 24.4 (d, $^1J_{CP}$ = 137, α-CH_2), 23.3 (s, $^2J_{CP}$ = 0, β-CH_2), 10.6 (CH_3); ^{31}P NMR (161.83 MHz, DMSO-d_6, phosphoric acid external reference) δ 27.5; (found: C, 60.3; H, 5.9; N, 6.3. $C_{21}H_{25}N_2PO_5$ requires C, 60.6; H, 6.05; N, 6.7%).

[3-[3-(Amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl] oxy]propyl]phosphonic acid 29. The procedure followed was as detailed above, using: sodium iodide (5.86 g, 39.1 mmol, 6.0 equiv), chlorotrimethylsilane (4.96 mL, 39.1 mmol, 6.0 equiv) and acetonitrile (35 mL). A portion of the iodotrimethylsilane solution (20 mL, 3.0 equiv) was added to a solution of dimethyl [3-[3-(amidomethyl)-2-ethyl-1-(phenylmethyl)-indol-5-yl]oxy]propyl] phosphonate (3.793 g, 6.51 mmol) in dichloromethane (50 mL) in one portion and stirring at rt under nitrogen continued for 1.5 h. Work up in a similar fashion gave the crude product as an orange solid. Recrystallisation (ethyl acetate:acetonitrile:acetic acid:water 21:7:7:9) afforded the title compound as a pale brown solid (0.970 g, 34.6%).

Mp 190–192 °C (lit.[21] 194–196 °C); ν_{max} (KBr)/cm^{-1} 3600–2400 (OH), 3457 (N–H), 2361, 1654 (C=O), 1487, 1154; ^{1}H NMR (270 MHz, DMSO-d_6) δ 6.64–7.38 (m, 10H, indole-H, C_6H_5 and NH_2), 5.35 (s, 2H, N–CH_2), 4.00 (t, J = 6.3, 2H, γ-CH_2), 3.44 (s, 2H, 3-CH_2), 2.73 (q, J = 7.4, 2H, 2-CH_2CH$_3$), 1.63–1.78, 1.87–2.00 (2 m, 4H, α- and β-CH_2), 1.04 (t, J = 7.4, 3H, 2-CH_2CH_3); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 172.8 (C=O), 152.5 (C5), 140.4, 138.7, 131.2, 128.2 (4×qC), 128.4, 125.9 (*o*- and *m*-Ph), 126.8 (*p*-Ph), 110.4, 110.0 (C4 and C6), 105.2 (C3), 102.3 (C7), 68.2 (d, $^3J_{CP}$ = 16.1, γ-CH_2), 45.8 (N–CH_2), 31.4 (3-CH_2), 24.1 (d, $^1J_{CP}$ = 145, α-CH_2), 23.1 (s, $^2J_{CP}$ = 0, β-CH_2), 17.3 (2-CH_2CH$_3$), 14.4 (2-CH_2CH_3); (found: C, 61.6; H, 6.3; N, 6.4. $C_{22}H_{27}N_2PO_5$ requires C, 61.4; H, 6.3; N, 6.5%).

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