PERKIN 1

Synthesis and serotonergic activity of a series of 2-(*N*-benzyl)-carboxamido-5-substituted-*N*,*N*-dimethyltryptamine derivatives: novel antagonists for the vascular 5-HT$_{1B}$-like receptors

Gerard P. Moloney,*[a] Graeme R. Martin,[b] Neil Mathews,[c] Heather Hobbs,[c] Susan Dodsworth,[c] Pang Yih Sang,[c] Cameron Knight,[a] Miles Maxwell[d] and Robert C. Glen[e]

[a] *Department of Medicinal Chemistry, Victorian College of Pharmacy (Monash University), 381 Royal Parade, Parkville, Victoria, 3052 Australia. Fax: (03) 99039634; E-mail: Gerard.Moloney@vcp.monash.edu.au*
[b] *Molecular Pharmacology Department, Neurobiology Unit, Roche Bioscience, 3401 Hillview Avenue, R2-101, Palo Alto CA94304, USA*
[c] *Department of Medicinal Chemistry, GlaxoWellcome Research Group, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
[d] *Systems Pharmacology Unit, GlaxoWellcome Research Group, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
[e] *Tripos Inc., 1699 South Hanley Road, St Louis, MO 63144, USA*

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The synthesis and vascular 5-HT$_{1B}$-like receptor activity of a novel series of 2-(*N*-benzyl)carboxamido-5-substituted-*N*,*N*-dimethyltryptamine derivatives is described. Modifications to the 5-ethylene linked heterocycle are explored. Compounds such as *N*-benzyl-5-[2-(phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide **22** (pK_B = 7.33), the 2-aminobenzyl analogue **24** (pK_B = 7.19), which both contain a phthalimide group, and *N*-benzyl-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide **81** (pK_B = 7.05), which incorporates an *N*-benzylhydantoin moiety, have good 5-HT$_{1B}$-like affinity and indicate that there may be a hydrophobic binding pocket within the vascular 5-HT$_{1B}$-like receptor previously not considered. Compounds including *N*-benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,4-dioxo-1,3-thiazolidinyl)ethyl]-1*H*-indole-2-carboxamide **39** (pK_B = 7.35) and the dimethyl analogue **46** (pK_B = 7.48) which contain a 2,4-thiazolidinedione moiety have good vascular 5-HT$_{1B}$-like receptor affinity and show that the sulfur atom is well tolerated. Compound **61** which includes a methylsulfonyl substituent on the 1-nitrogen of the hydantoin ring system has the highest recorded 5-HT$_{1B}$-like affinity for this series (pK_B = 7.54) and it is proposed that this functional group can interact with a secondary hydrogen bonding region within the receptor. Compounds **22**, **24**, **39**, **46**, **61** and **81** also exhibited good selectivity over the α_1-adrenoceptors. The most selective compound from this series is **46** which contains a 5,5-dimethyl-thiazolidine-2,4-dione group and which is 66-fold selective over the α_1-adrenoceptors. This finding is consistent with the previous discovery that 5,5-dimethyl substitution on the hydantoin group in a related series of compounds afforded superior selectivity for 5-HT$_{1B}$-like receptors over α_1-adrenoceptors and other 5-HT receptors, in particular 5-HT$_{2A}$ receptors, relative to unsubstituted hydantoin analogues. The selectivity of these compounds for the vascular 5-HT$_{1B}$-like receptor is discussed. Structure–activity relationship indicated a significant steric requirement of the 5-HT$_{1B}$-like receptor subtype. Potential modes of binding for several of the compounds to a vascular 5-HT$_{1B}$-like receptor pharmacophore model are also proposed.

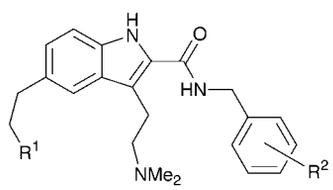
Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was discovered over 50 years ago[1] and continues to generate interest as one of the most attractive targets for medicinal chemists. The search for novel agonists and antagonists of 5-HT has become increasingly inviting as new receptor subtypes within the 5-HT family of receptors continue to be discovered.[2–5] Serotonin receptors have been classified into seven distinct receptor classes, 5-HT$_1$ to 5-HT$_7$.[3,4,6] Within these classes, fourteen different 5-HT receptor subtypes have been identified.[3,4,6] In some cases *i.e.* 5-ht$_{1E}$, 5-ht$_{1F}$, 5-ht$_5$ and 5-ht$_6$ only the gene products encoding putative serotonin receptor proteins have been identified and although the recombinant proteins are functionally active when transfected into a mammalian host cell, true physiological roles have not been demonstrated. For this reason, these gene products are provisionally referred to using a lower case notation.[7] The 5-HT$_1$ class is diverse and comprises 5-HT$_{1A}$, 5-HT$_{1B}$ (formally 5-HT$_{1D\beta}$),[8] 5-HT$_{1D}$ (formally 5-HT$_{1D\alpha}$),[8] 5-ht$_{1E}$ and 5-ht$_{1F}$ subtypes. Increasing evidence has indicated that the 5-HT$_{1B}$ receptor is likely to be the 5-HT receptor mediating vasoconstriction, but in the absence of ligands to make a definitive classification, it is referred to here as 5-HT$_{1B}$-like. The 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors have attracted considerable attention in recent times as putative targets for novel antimigraine drugs, leading to the development of 5-HT$_{1B/1D}$ receptor agonists such as sumatriptan (GR 43175)[9–11] and more recently zolmitriptan,[12,13] rizatriptan, eletriptan, avitriptan and others.[14–18]

The objective of our research program was to develop a novel, silent (as judged by the inability of angiotensin II to unmask 5-HT$_{1B}$-like receptor mediated agonist activity in the rabbit femoral artery) and highly selective antagonist at vascular 5-HT$_{1B}$-like receptors with good oral bioavailability, a plasma half-life of at least 4 hours and low central penetration. Such a compound may have potential as a prophylactic treatment for unstable angina,[19,20] Raynaud's syndrome[21–24] and a

variety of other vasospastic conditions in which a pathophysiological role for 5-HT has been implicated.

Recently, a class of benzanilides,[25] have been reported to block both the 5-HT_{1B} and 5-HT_{1D} receptors in the periphery and the central nervous system (CNS) vascular and central responses mediated by both of these receptor types.[25,26] However, studies have shown that these compounds behave as partial agonists at recombinant human 5-HT_{1B} and 5-HT_{1D} receptors.[27] We recently reported a series of 2-ester-5-substituted tryptamine derivatives[28] as well as some structurally related 2,*N*-benzylcarboxamido-5-(2-ethyldioxoimidazolidin-1-yl)-*N*,*N*-dimethyltryptamine analogues[29] which are both highly potent and selective antagonists for the vascular 5-HT_{1B}-like receptors. We describe in this paper the synthesis, 5-HT_{1B}-like activity and receptor selectivity profile of a related series of 2-(*N*-benzyl)carboxamido-5-substituted-*N*,*N*-dimethyltryptamine derivatives **1**. To explore the pharmacophore of the vas-

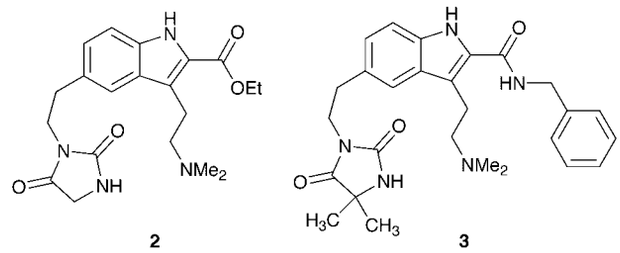


1

cular 5-HT-like recognition site we have studied variations to the heterocycle R^1 connected to the 5-position of the indole group by an ethylene linking chain. We have studied the mode of binding of several of the compounds to a pharmacophore model and attempt to explain changes in potency and selectivity in terms of changes in structure.

We report the discovery of several compounds, in particular **22**, **24**, **39**, **41**, **46**, **61** and **81** (Table 1) which have comparable potency to ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate (**2**)[28] and *N*-benzyl-3-(2-dimethylaminoethyl)-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (**3**)[29] (Chart 1).

The 2-(*N*-benzyl)carboxamido-5-substituted-*N*,*N*-dimethyltryptamine series we report here was also shown to possess a favourable pharmacokinetic profile comparable with **3**.[29]



2 **3**

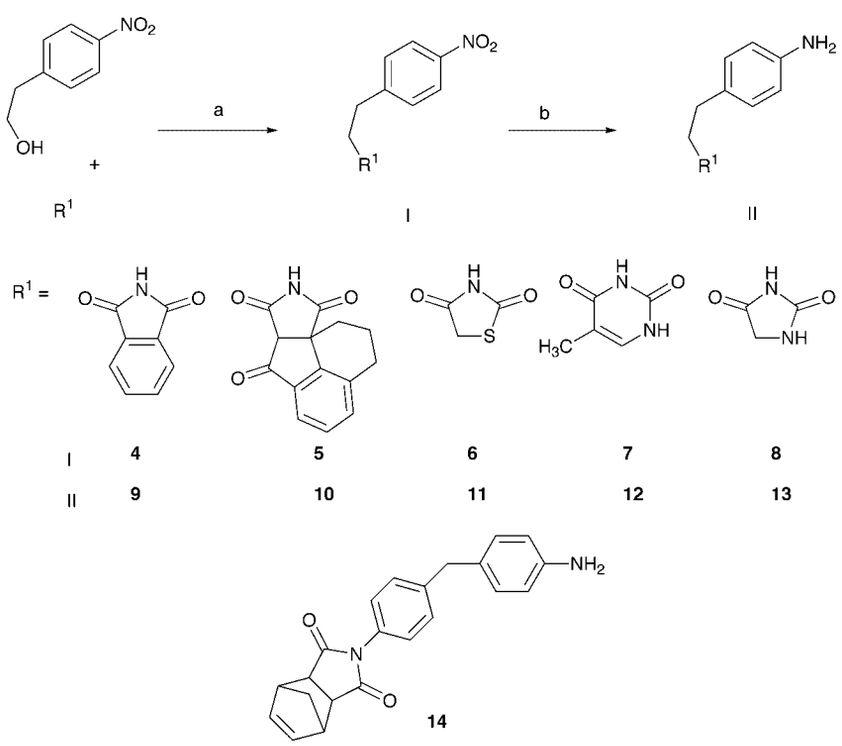
Chart 1

Results and discussion

Synthesis

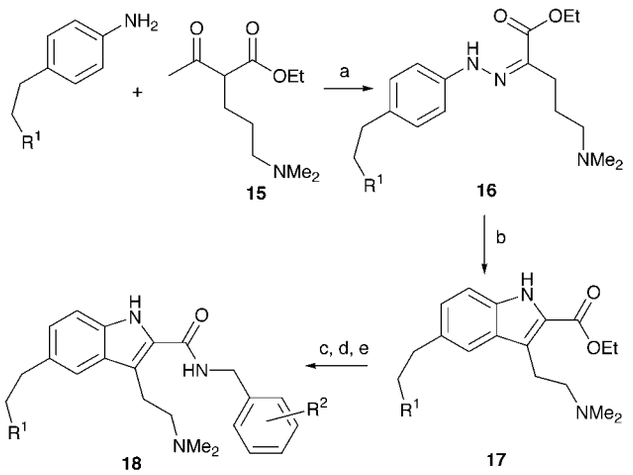
The 2,5-substituted tryptamine derivatives described here were synthesised using several different methods as previously outlined.[28,29] The synthesis of the nitro intermediates **4**–**8** followed the Mitsunobu procedure[30,31] used in the synthesis of a series of hydantoin derivatives previously reported (Scheme 1).[28,29]

The nitro intermediates **4**–**8** were converted to the aniline derivatives **9**–**13** by hydrogenation at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (Scheme 1). The aniline derivatives **9** and **10** as well as the commercially available norbornene derivative **14** were converted to the tryptamine target molecules *via* a Japp Klingemann indole synthesis[32,33] (Scheme 2). Diazotisation of the aniline derivative followed by reaction with the β-keto ester **15**[28] afforded the hydrazone intermediate **16**. Cyclization of the hydrazone to form the tryptamine **17** was achieved by refluxing with ethanol in the presence of a catalytic amount of concentrated H_2SO_4. The ethyl ester was then converted to a 2-benzyl ester derivative by refluxing in benzyl alcohol in the presence of titanium tetraisopropoxide. Following transesterification the 2-benzyl ester was converted to the tryptamine-2-carboxylic acid under hydrogenation conditions in the presence of palladium on carbon (10%) at room temperature and atmospheric pressure. Amide coupling of the tryptamine-2-carb-



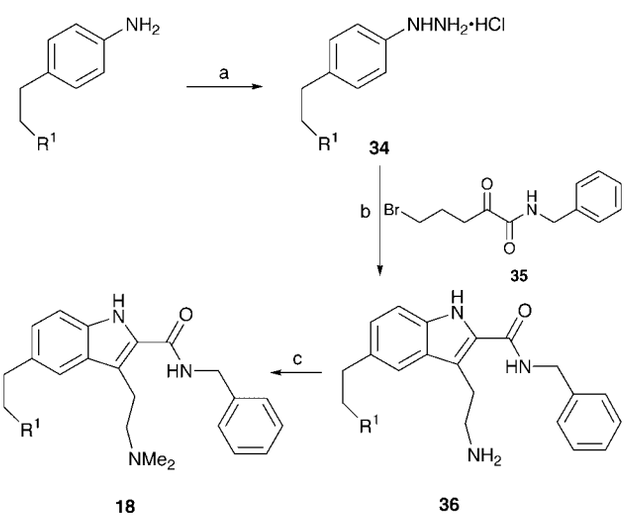
Scheme 1 *Reagents*: (a) Ph_3P, DIAD, THF, 0 °C; (b) H_2, Pd–C (10%), EtOH.

oxylic acid with benzylamine derivative using TBTU and DIPEA in DMF afforded the desired 2-(*N*-benzyl)carboxamido tryptamine **18** (Scheme 2).



Scheme 2 *Reagents*: (a) $NaNO_2$, HCl, NaOH; (b) conc. H_2SO_4, EtOH; (c) $Ti(iOPr)_4$, benzyl alcohol; (d) H_2, Pd–C (10%); (e) TBTU, DMF, DIPEA.

The remaining tryptamine derivatives were synthesised by the general method outlined in Scheme 3. Reaction of the aniline

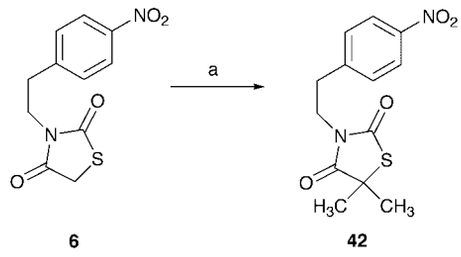


Scheme 3 *Reagents*: (a) $NaNO_2$, $SnCl_2{\cdot}2H_2O$; (b) EtOH, H_2O; (c) AcOH, MeOH, CH_2O, $NaCNBH_3$.

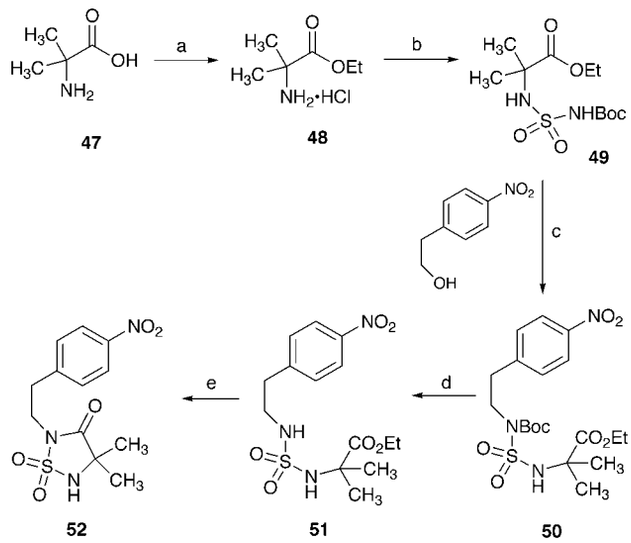
derivative with sodium nitrite and tin chloride dihydrate afforded the hydrazine intermediate **34** which was then reacted with the α-ketoamide **35**[28] under Fischer conditions[34] to afford the tryptamine intermediate **36**. Dimethylation of the 3-ethylamine nitrogen afforded the desired tryptamine molecule **18**.

The 5,5-dimethyl thiazolidinedione intermediate **42** required for the synthesis of the tryptamine derivative **46** was synthesised from reaction of the unsubstituted thiazolidinedione derivative **6** with potassium *tert*-butoxide and methyl iodide (Scheme 4). The 5,5-dimethyl thiazolidinedione derivative **42** was reacted further under the conditions described in Scheme 3 to give the desired tryptamine compound **46**.

The 2-(4-nitrophenyl)ethyl-4,4-dimethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide intermediate **52** required for the synthesis of the tryptamine derivative **56** was prepared as shown in Scheme 5. 2-Aminoisobutyric acid **47** was ethyl esterified with thionyl chloride in ethanol. Reaction of the amine with chlorosulfonyl-isocyanate and 2-methylpropan-2-ol in dichloromethane gave **49** which was Mitsunobu coupled to *p*-nitrophenethyl alcohol to give the Boc protected phenethylamine derivative **50**. Deprotection of the amine with trifluoroacetic acid in dichloromethane followed by cyclization using sodium hydroxide gave the 1,2,5-thiadiazolidin-3-one 1,1-dioxide intermediate **52**. This nitro intermediate was then reacted on as described in Scheme 3 to afford **56**.

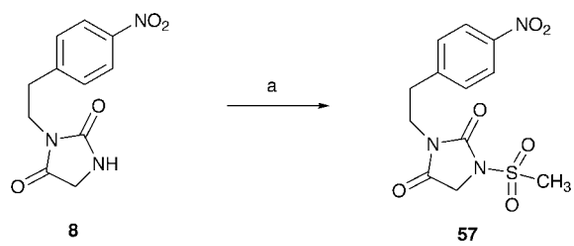


Scheme 4 *Reagents*: (a) K^{t}BuO, MeI.



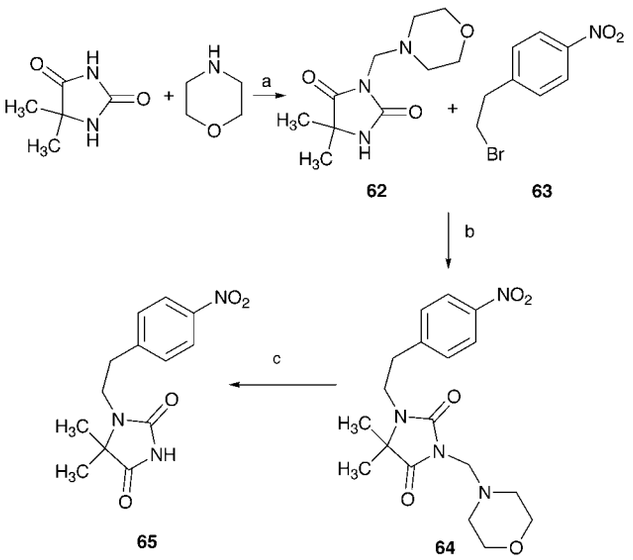
Scheme 5 *Reagents*: (a) $SOCl_2$, EtOH; (b) $ClSO_2N{=}C{=}O$, ^{t}BuOH, TEA; (c) Ph_3P, DEAD, DMF; (d) CH_2Cl_2, TFA; (e) NaOH.

The *N*-methylsulfonyl hydantoin derivative **57** required for the synthesis of **61** was synthesised by reacting the hydantoin intermediate **8** with methanesulfonyl chloride as shown in Scheme 6.



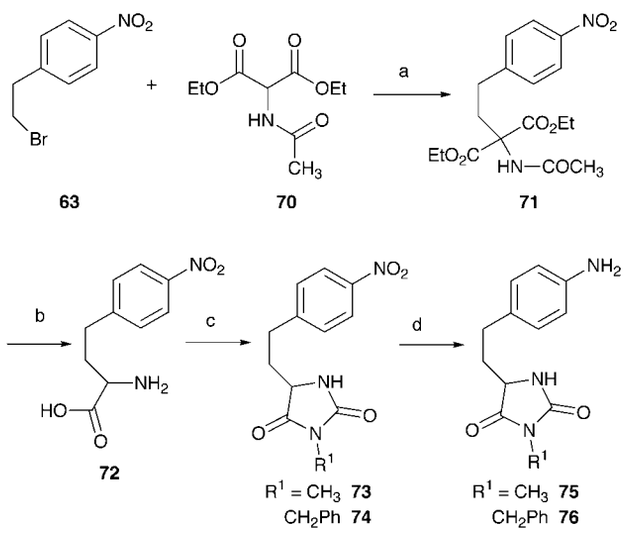
Scheme 6 *Reagents*: (a) methanesulfonyl chloride, Et_3N, toluene.

The 'rotated' hydantoin derivative **65** required for the synthesis of **69** was synthesised as shown in Scheme 7. This compound incorporates a 5-ethylene linked hydantoin sidechain connected through the 1-nitrogen. The 3-nitrogen of 5,5-dimethylhydantoin was protected with a methylene linked morpholine group by reaction with morpholine and formaldehyde to give **62**. The protected hydantoin derivative was then reacted with sodium hydride followed by *p*-nitrophenethyl bromide to give the *p*-nitrophenethyl derivative **64**. Deprotection with sodium hydroxide gave the desired *p*-nitrophenethyl analogue **65** connected through the 1-nitrogen. Conversion of the nitro derivative **65** to the desired *N*-benzylamido tryptamine derivative **69** then proceeded as outlined in Scheme 3.



Scheme 7 *Reagents*: (a) CH_2O, MeOH; (b) NaH, DMF; (c) NaOH.

The aniline intermediates required for the synthesis of the *N*-benzyl hydantoin derivative **81** and the *N*-methyl analogue **84** were prepared as outlined in Scheme 8. 4-Nitrophenethyl



Scheme 8 *Reagents*: (a) Na, EtOH; (b) 60% HBr; (c) KOH, H_2O, R^1NCO, HCl; (d) H_2, Pd–C (10%), EtOH.

bromide was coupled with diethyl acetamidomalonate **70** to give the diester derivative **71**. Refluxing in 60% HBr resulted in loss of CO_2 and formation of the amino acid **72**. Reaction with methyl isocyanate or benzyl isocyanate afforded the nitro hydantoin derivatives **73** and **74** which were reduced to the aniline derivatives **75** and **76** under hydrogenation conditions in the presence of 10% palladium on carbon. The aniline intermediates **75** and **76** were then converted to the tryptamine derivatives **81** and **84** respectively *via* the Japp Klingemann indole synthesis (Scheme 2).

Activity

Earlier studies towards vascular 5-HT_{1B}-like antagonists involved the investigation of a series of 2-(*N*-benzyl)carboxamido tryptamine derivatives containing a range of hydantoin ring systems connected to the 5-position of the indole ring.[29] A series of tryptamine derivatives with a range of heterocycles replacing the hydantoin ring system are the focus of this study. The primary reason for this study was to investigate the effects of differing substitution in this region of the receptor on

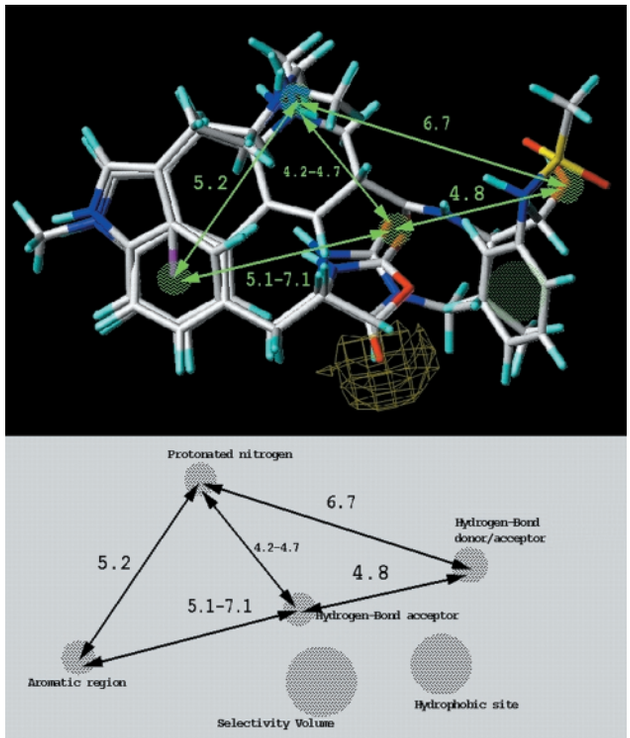


Fig. 1 Theoretical 5-HT_{1B}-like receptor model using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate (**2**),[28] *N*-benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (**3**)[29] as a reference with methysergide as background.

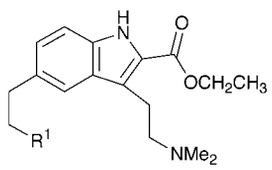
potency and selectivity. The compounds studied and their biological results are shown in Table 1.

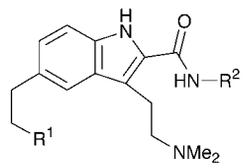
Several compounds with favourable pharmacological profiles were discovered from the 2-(*N*-benzyl)carboxamido tryptamine series previously reported including **3** (Table 1).[29] It was interesting to observe in this previous study that subtle changes to substitution at the 4-position of the hydantoin ring resulted in significant changes to affinity and selectivity for the 5-HT_{1B}-like receptor.[29] In particular, increased selectivity was observed for compounds incorporating a dimethyl hydantoin moiety compared with an unsubstituted hydantoin group. This was consistent with the observation that hydrophobicity in this region increased affinity and selectivity for 5-HT_{1D}.[13] In the present study we wished to investigate a range of heterocyclic systems which could be used to replace the hydantoin group linked to the 5-position of the indole ring and ideally enhance potency and selectivity for the 5-HT_{1B}-like receptor. Information from a range of compounds could also help to elucidate important pharmacophoric points within our 5-HT_{1B}-like receptor model.

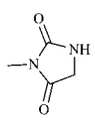
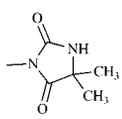
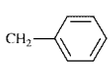
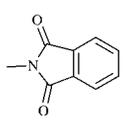
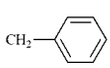
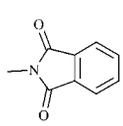
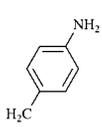
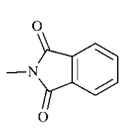
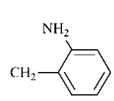
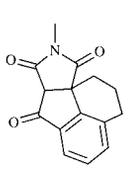
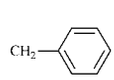
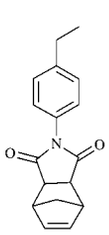
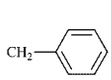
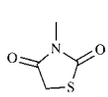
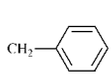
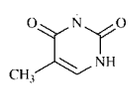
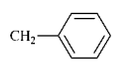
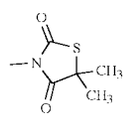
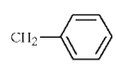
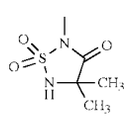
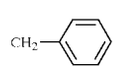
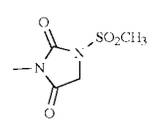
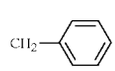
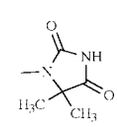
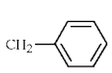
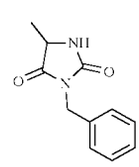
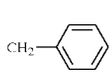
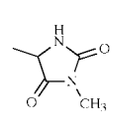
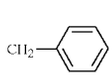
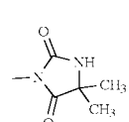
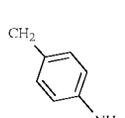
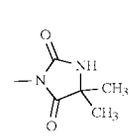
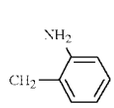
In order to explain the biological data we referred to our theoretical receptor model for the vascular 5-HT_{1B}-like receptor shown in Fig. 1. The theoretical receptor model is composed of a protonated amine, an aromatic binding site, a hydrogen-bond acceptor site, a 'selectivity' site for 5-HT_{1B}-like over 5-HT_{2A}, a hydrophobic site and an additional hydrogen bonding donor/acceptor site with associated inter-group distances. It was generated using systematic conformational searching of a series of analogues having a range of affinities and efficacies at both the 5-HT_{1B}-like and 5-HT_{2A} receptors.[12,13] This model proved to be qualitatively predictive for both affinity and selectivity and enabled the design of analogues having both affinity and selectivity at 5-HT_{1B}-like receptors.[28,29] Compounds which were selective for the 5-HT_{1B}-like receptor over 5-HT_{2A} were found to have occupied the 'selectivity site' with some part of the molecule.[13,28,29]

The important pharmacophoric points are illustrated using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-

Table 1





Compound Number	R^1	R^2	5-HT_{1B}-like RbSV[a] (pK_B)	α_1 RbTA[a] (pK_B)
2			7.42	5.43
3			7.09	5.2
22			7.33	5.55
23			6.73	
24			7.19	5.52
29			6.31	5.36
33			5.58	
39			7.35	5.76
41			7.07	5.27
46			7.48	5.66
56			6.29	5.0
61			7.54	5.96
69			6.85	5.35
81			7.05	5.18
84			6.6	
85[b]			6.19	4.52
86[b]			6.72	4.79

[a] Affinity (pK_B: $-\log_{10}K_B$, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5-HT_{1B}-like receptors in the rabbit saphenous vein (RbSV). α_1-Adrenoceptor affinity was measured in the rabbit thoracic aorta (RbTA) using phenylephrine as agonist. Affinity values are the means of at least 3 separate estimates. Standard errors are omitted for clarity, but in all cases were ≤ 0.2 $\log_{10}$ units. In each case affinity estimates were determined using the Gaddum–Schild equation and 5-HT as the receptor agonist. [b] Compounds **85** and **86** have been previously described.[29]

1-yl)ethyl]-1*H*-indole-2-carboxylate (**2**)[28] and *N*-benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (**3**)[29] and methysergide. The distances between each site are shown in angstroms. Methysergide ($pA_{50}/\alpha = 6.7/0.64$ at 5-HT_{1B}) was one of the structures used to deduce the theoretical model as it had restricted conformational freedom about the ethylamine sidechain.[13] A large range of structures were used to deduce the relative positions of pharmacophoric groups.[13] Methysergide is shown here as a reference structure for comparison purposes. Compound **3** is a previously selective 5-HT_{1B}-like receptor antagonist which can interact with the binding sites of the theoretical 5-HT_{1B}-like receptor model in a similar manner to the compounds of the present study.

Several compounds containing a phthalimide moiety were investigated. The results indicate that the phthalimide group does appear to enhance affinity within the 2-(*N*-benzyl)carboxamido tryptamine series. In particular the 2-amino substituted

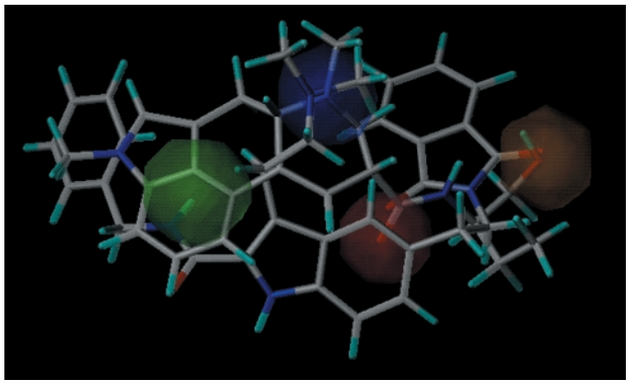


Fig. 2 The phthalimide derivative **22** fitted to the pharmacophore model with methysergide as background.

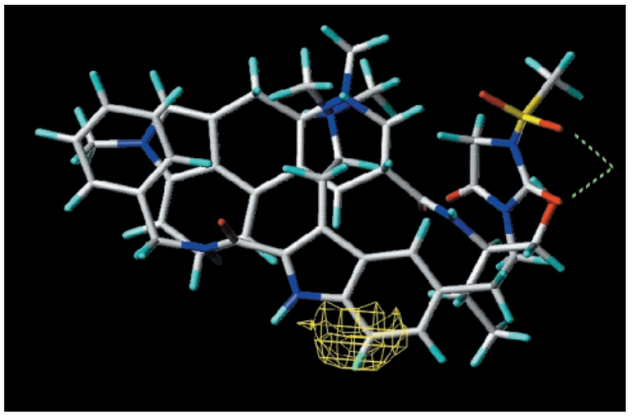


Fig. 3 Compound **61** overlaid on the vascular 5-HT_{1B}-like receptor pharmacophore model. The selectivity site is shown in yellow.

benzylamide derivatives **23** ($pK_B = 6.73$) and **24** ($pK_B = 7.19$) showed higher potency relative to the hydantoin analogues **85** ($pK_B = 6.19$) and **86** ($pK_B = 6.72$) Table 1.[29] Fig. 2 shows the proposed mode of binding for the phthalimide derivative **22** to the pharmacophore model using methysergide as background.

As postulated previously there appears to be a spatial restriction on the size of the 2-substituent on the indole ring, the receptor not tolerating large substituents at this position.[28] We therefore hypothesised that there was a steric interaction between the sidechain in the 2-position and the receptor and that the molecule is displaced by the steric interaction in order to accommodate the large 2-substituent. This would result in important functional groups not occupying optimal positions for binding at the proposed auxiliary binding sites.[13,28]

Following displacement of the molecule to accommodate the 2-benzylamido sidechain, the benzylamide phenyl group could potentially occupy the proposed aromatic binding site. The 5-ethylene linking chain could orientate so as to allow one of the carbonyls to interact with the hydrogen binding site while the other carbonyl group could interact with the secondary hydrogen binding site.[13] Another explanation for the enhanced affinity is that the fused aromatic ring of the phthalimide group may access a previously unrecognised hydrophobic pocket in the pharmacophore in the region between the protonated amine hydrogen bonding site and the secondary hydrogen bonding site.

The tetrahydrosuccinimide-like substituent of **29** resulted in poor affinity indicating that a size restriction exists for an ideal biological profile. The benzyl linked succinimide containing derivative **33** had poor affinity for the vascular 5-HT_{1B}-like receptor. It appears the inclusion of the benzyl group linking the indole ring to the succinimide-norbornene group does not allow for optimal interaction of the molecule with the receptor.

The two thiazolidinone derivatives **39** and **46** had excellent affinity at the 5-HT_{1B}-like receptor and approximately 66 fold selectivity over α_1-adrenoceptor activity. The sulfur atom appears to enhance binding possibly by accessing a hydrophobic region smaller than the phenyl ring of the phthalimide which may be advantageous and additionally by altering the exocyclic ring angles of the hydrogen bonding ketone.

The tryptamine derivative **41** which contains a pyrimidine ring in place of the five membered hydantoin ring system had good affinity at the 5-HT_{1B}-like receptor ($pK_B = 7.07$). This subtle structural change and relative movement of key functionality including the carbonyl groups within the active site appears to be well tolerated as the carbonyl groups can still access the hydrogen bonding sites.

The dioxothiazolidine derivative **56** showed poor 5-HT_{1B}-like affinity ($pK_B = 6.29$). It would appear that the two extra oxygens in the five membered ring system are not well tolerated. The *N*-methylsulfonyl substituted hydantoin derivative **61** had the highest recorded vascular 5-HT_{1B}-like affinity possibly for this series. The sulfonamide moiety appears to enhance affinity because of the extra hydrogen-bonding capabilities of the sulfonamide oxygens which may allow an additional hydrogen bonding interaction with the secondary hydrogen bonding site, Fig. 3. The $NHSO_2CH_3$ substituent in this position confers high affinity in the hydantoin series also (refer to **14** in Glen *et al.*[13])

The tryptamine derivative **69** with an hydantoin group connected through the 1-nitrogen had reduced affinity and selectivity. This observation is likely to be due to the altered relative position of the carbonyl groups of the hydantoin ring and the subsequent ability of the group to optimally interact with one of the hydrogen bonding sites.

The tryptamine derivatives **81** and **84** both include 5-ethylene linked hydantoin ring systems connected through the 5-carbon of the hydantoin ring. The hydantoin **81** had good affinity ($pK_B = 7.05$) and reasonable selectivity for the 5-HT_{1B}-like receptor over α_1-adrenoceptor affinity. The change in position of one of the carbonyl groups of the hydantoin ring (relative to the hydantoin derivatives connected through the 3-nitrogen) appears to be well tolerated. These results may reflect the flexibility of the 5-ethylene linking chain and the ability of the sidechain to position the attached heterocycle in an optimal position for good interaction.

Conclusions

This work has culminated in the discovery of a novel series of 2-(*N*-benzyl)carboxamido tryptamine derivatives which are potent, silent (as judged by the inability of angiotensin II to unmask 5-HT_{1B}-like receptor mediated agonist activity in the rabbit femoral artery), competitive and selective antagonists for the vascular 5-HT_{1B}-like receptor. The biological results for **22** and **24** indicate that a phthalimide group in the 5-sidechain enhances 5-HT_{1B}-like receptor affinity. The two thiazolidinedione derivatives **39** and **46** exhibited favourable 5-HT_{1B}-like affinity indicating that the sulfur atom is well tolerated. Dimethyl substitution on the thiazolidinedione moiety increased both affinity and selectivity consistent with the trend observed for a 5,5-dimethyl hydantoin analogue investigated previously.[28,29] The high affinity recorded for **61** containing an *N*-methylsulfonyl group was explained in terms of the ability of the sulfonyl atom to interact with the secondary hydrogen bonding site[13] giving further credibility to the proposed 5-HT_{1B}-like receptor pharmacophore. Compounds such as **22**, **39**, **46** and **61** will be useful biological probes for the vascular 5-HT_{1B}-like receptor.

Experimental

Biological methods

Definition: 'Intrinsic activity': the maximum effect of the test agonist relative to a standard (usually a full agonist).

Rabbit saphenous vein (RbSV) preparation. The vascular 5-HT_{1B}-like receptor affinities of compounds were assessed using ring preparations of rabbit saphenous vein.[35] Vessels were removed from male New Zealand White rabbits killed by injecting pentobarbitone (80 mg kg^{-1}, iv) followed by exsanguination. After removing adhering connective tissue, ring segments (4–5 mm) were prepared and mounted between parallel tungsten wires. Tissues were suspended in 20 mL organ baths containing Krebs–Henseleit buffer at 37 °C, pH 7.4 and constantly gassed with 95% O_2–5% CO_2. The Kreb–Henseleit solution used had the following composition: (mM) NaCl 118.41, $NaHCO_3$ 25.00, KCl 4.75, KH_2PO_4 1.19, $MgSO_4$ 1.19, glucose 11.10 and $CaCl_2$ 2.50. After application of a passive force (2 g) tissues were exposed to pargyline (500 μM) to inactivate monoamine oxidase. In order to prevent the direct or indirect activation of α_1-adrenoceptors, saphenous veins were simultaneously exposed to phenoxybenzamine (0.3 μM). After 30 minutes excess inhibitors were removed by several exchanges of the organ bath buffer and the tissues challenged with 5-HT (1 μM) to determine viability. In the saphenous vein a cumulative concentration–effect (E/[A]) curve to 5-HT was constructed followed by washout and after 60 minutes recovery by a second curve to the test compound. When the test compound failed to produce agonism, it was evaluated as a 5-HT antagonist, potency being determined as an apparent pK_B. When the test produced vascular contraction, potency estimates were determined as $p[A]_{50}$ and intrinsic activity (α) values determined from the ratio test maximum response/5-HT maximum.

Rabbit femoral artery (RbFA) preparation. Rings (2 mm) of rabbit femoral artery were used to determine whether or not novel compounds behaved as 'silent (as judged by the inability of angiotensin II to unmask 5-HT_{1B}-like receptor mediated agonist activity in the rabbit femoral artery) antagonists' *i.e.* were essentially devoid of agonist properties. This is possible in this preparation, since concomitant exposure to spasmogens such as thromboxane A_2 or angiotensin II unmasks activity at 5-HT_{1B}-like receptors that might not otherwise manifest agonist ligands with very low intrinsic efficacy.[36] Rings (2 mm) of rabbit femoral artery were exposed to pargyline (500 μM) for 30 minutes during which time they were progressively tensioned to 2.6 g. The tissues were exposed to 80 mM KCl to assess tissue viability and provide a reference contracture for subsequent data analysis. After washout, angiotension II was titrated to provide a contraction equivalent to ~45% of the KCl response. Once this was achieved a cumulative E/[A] curve to the novel compound (or 5-HT as a reference) was constructed to determine vascular 5-HT_{1B}-like agonist activity. Krebs solution containing prazosin, mepyramine and spiperone (0.3 μM of each) was used throughout to block possible effects mediated by α_1-adrenergic, H_1 histaminergic and 5-HT_{2A} serotonergic receptor activation respectively.

Rabbit aorta (RbA) preparation. Rings (3 mm) of rabbit thoracic aorta were used to assay for activity at α_1-adrenoceptors. α_1-Adrenoceptor activity was determined in tissues exposed to pargyline (500 μM for 30 minutes) during which they were tensioned twice to a resting force of 3.0 g. Exposure to L-phenylephrine (L-Phe, 10 μM) enabled tissue viability to be assessed and provided a reference contracture for subsequent data analysis. Following washout tissues were exposed to novel compounds (30 μM) for 60 minutes prior to a cumulative E/[A] curve to L-Phe being constructed.

Chemical methods: general directions

Computational chemistry was performed on a Silicon Graphics Iris indigo II using the Sybyl[37] molecular modelling software.

Unless otherwise stated, all ^{1}H NMR spectra were recorded at 200 MHz on a Bruker AC 200 spectrometer or at 300 MHz on a Bruker AM 300 spectrometer. Chemical shifts are in δ/ppm relative to TMS. Deuterated dimethyl sulfoxide (99.9%) was used as solvent unless otherwise stated. Mass spectra and high resolution mass spectra (HRMS) were obtained on a Kratos Concept IS (EIMS), a Kratos MS50 (FAB) mass spectrometer or a JEOL JMS DX-300 double focussing instrument. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Methanol and ethanol were distilled from iodine and magnesium and stored over type 3 Å molecular sieves. Anhydrous THF was freshly distilled over potassium and benzophenone. Anhydrous DMF, diethyl ether, benzene and toluene were stored over type 4 Å molecular sieves. Triethylamine, diisopropylethylamine and pyridine were stored over sodium hydroxide. All solutions were dried over $MgSO_4$ or Na_2SO_4 and concentrated on a Buchi rotary evaporator. Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254}). Infra red spectra were run in KBr disks on a Bruker IFS66 FTIR spectrometer. Microanalyses were performed on a VG Platform spectrometer and are within 0.4% of the theoretical values unless otherwise stated. HPLC was performed on a Waters Millenium system comprising a 490E Multi-wavelength detector, 600 controller, a series 600 pump with a 717 plus autosampler. A Zorbax 4.6 mm × 250 mm, 5 μm column was used for analytical work while a 22.4 mm × 250 mm, 7 μm C18 column was used for preparative work. A 10% H_2O–AcCN (10–90% gradient elution) (A)–0.1 M NH_4OAc (pH 4) (90–10%) (B) solvent system was used. The following chemical abbreviation definitions were used: DIAD diisopropyl azodicarboxylate; TBTU *O*-benzothiazol-1-yl-*N*,*N*,*N*′,*N*′,-tetramethyluronium tetrafluoroborate; DIPEA diisopropylethylamine; $NaCNBH_3$ sodium cyanoborohydride; K^{t}BuO potassium *tert*-butoxide; CH_2O formaldehyde; Ph_3P triphenylphosphine; TEA triethylamine; TFA trifluoroacetic acid; Et_3N triethylamine and $SOCl_2$ thionyl chloride. RT = HPLC retention time.

Benzyl 5-[2-(phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate (20). Method 1: A mixture of the ethyl ester **17**[29] (68.0 mg, 0.16 mmol) and titanium tetraisopropoxide (16.4 μL, 0.05 mmol) in benzyl alcohol (3.0 mL) was heated to 100 °C for 18 h. The solution was concentrated *in vacuo* to give a brown gum which was purified by flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (200 : 8 : 1) to give 70 mg (90%) of **20** as a white solid. MS *m*/*z* 496 (M^+); ^{1}H NMR δ 2.0 (6H, s, 2 × NCH_3), 2.20 (2H, m, CH_2NMe_2), 2.98 (4H, m, 5-CH_2, 3-CH_2), 3.83 (2H, t, CH_2Phth, *J* 7.0 Hz), 5.35 (2H, s, CH_2O), 7.12 (1H, d, H6, *J* 8.7 Hz), 7.3–7.5 (7H, m, H7, H4, 5 × ArH), 7.79 (4H, s, 4 × PhthH), 11.45 (1H, s, NH); Found M^+ 495.21576. $C_{30}H_{29}N_3O_4$ requires M^+ 495.21580.

5-[2-(Phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylic acid (21). Method 2: To a solution of the benzyl ester **20** (65 mg, 0.13 mmol) in ethanol (10 mL) was added 10% palladium on carbon (33 mg) and the suspension was hydrogenated at room temperature and atmospheric pressure for 48 h. The suspension was filtered through Celite and washed with ethanol. The filtrate was evaporated under reduced pressure to give **21** as a white powder which was reacted on without further purification. MS *m*/*z* 406 $(M + 1)^+$; ^{1}H NMR δ 2.35 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2), 2.97 (2H, m, 5-CH_2), 3.06 (2H, m, 3-CH_2), 3.79 (2H, m, CH_2Phth), 6.96 (1H, d, H6), 7.22 (2H, m, H7, H4), 7.8 (4H, m, 4 × ArH), 10.8 (1H, s, NH).

***N*-Benzyl-5-[2-(phthalimido)ethyl]-3-[2-(dimethylamino)-ethyl]-1*H*-indole-2-carboxamide (22).** Method 3: a solution of the carboxylic acid **21** (31.6 mg, 0.8 mmol), benzylamine (9.2 mg, 0.86 mmol) and TBTU (27.5 mg, 0.086 mmol) in DMF (33.0 mL) was stirred for 1 h. DIPEA (16.3 μL, 0.094 mmol) was added and the resulting solution was stirred at room temperature under nitrogen overnight. The solvent was evaporated

under reduced pressure and the residue taken up in water (10 mL) and extracted with ethyl acetate. The organic layer was dried, filtered and evaporated under reduced pressure to give a yellow solid which was further purified by flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (200 : 8 : 1) to give 26 mg (67%) of **22** as a yellow powder (Mp 142–143 °C); MS *m*/*z* 494 (M^+); ^{1}H NMR δ 1.93 (6H, s, 2 × NCH_3), 2.25 (2H, m, CH_2NMe_2), 2.88 (2H, m, 5-CH_2), 3.0 (2H, m, 3-CH_2), 3.85 (2H, t, CH_2Phth, *J* 7.0 Hz), 5.0 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.3 (2H, m, H7, H4), 7.5–7.6 (4H, m, 4 × ArH), 7.9–8.2 (4H, m, 3 × ArH, NH), 9.7 (1H, t, NH), 11.2 (1H, s, NH); Found M^+ 494.23456. $C_{30}H_{30}N_4O_3$ requires M^+ 494.23179.

***N*-(4-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)ethyl]-1*H*-indole-2-carboxamide (23).** Method 3 (using 4-aminobenzylamine): yellow solid, 40 mg (63%) (Found C, 66.81; H, 5.83; N, 12.54. $C_{30}H_{31}N_5O_3$·1.0HCl requires C, 65.99; H, 5.86; N, 12.83%); MS *m*/*z* 510 $(M + 1)^+$; ^{1}H NMR δ 1.89 (6H, s, 2 × NCH_3), 2.23 (2H, m, CH_2NMe_2), 2.86 (2H, t, 5-CH_2, *J* 6.8 Hz), 2.98 (2H, t, 3-CH_3, *J* 7.2 Hz), 3.82 (2H, m, CH_2Hyd), 4.3 (2H, d, CH_2NHCO, *J* 5.4 Hz), 4.9 (2H, s, NH_2), 6.5 (2H, d, H2′, H6′, *J* 8.4 Hz), 6.97 (2H, d, H3′, H5′, *J* 8.4 Hz), 7.0 (1H, d, H6, *J* 8.4 Hz), 7.23 (2H, m, H7, H4), 7.8 (4H, s, 4 × Phth-H), 9.51 (1H, t, NH, *J* 5.7 Hz), 9.5 (1H, s, NH), 11.15 (1H, s, NH); Found M^+ 509.23919. $C_{30}H_{31}N_5O_3$ requires M^+ 509.24269; Anal. ($C_{30}H_{31}N_5O_3$·1.0HCl) C, H, N. RT = 15.77 min.

***N*-(2-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)ethyl]-1*H*-indole-2-carboxamide (24).** Method 3 (using 2-aminobenzylamine): yellow lyophilate, 45 mg (72%) (Found C, 56.74; H, 5.77; N, 10.58. $C_{30}H_{31}N_5O_3$·2.0HCl·3.0H_2O requires C, 56.63; H, 6.13; N, 11.01%); MS *m*/*z* 510 $(M + 1)^+$; ^{1}H NMR δ 1.92 (6H, s, 2 × NCH_3), 2.22 (2H, m, CH_2NMe_2, *J* 6.0 Hz), 2.88 (2H, m, 5-CH_2), 2.97 (2H, t, 3-CH_2, *J* 6.6 Hz), 3.82 (2H, t, CH_2Hyd, *J* 6.6 Hz), 4.34 (2H, d, CH_2NHCO, *J* 5.4 Hz), 5.12 (2H, s, NH_2), 6.51 (1H, m, ArH, *J* 8.1 Hz), 6.61 (1H, d, ArH, *J* 7.2 Hz), 7.0 (3H, m, 2 × ArH, H6), 7.23 (2H, m, H7, H4), 7.79 (4H, s, 4 × PhthH), 9.65 (1H, t, NH, *J* 5.7 Hz), 11.2 (1H, s, NH); Found M^+ 509.23919. $C_{30}H_{31}N_5O_3$·1.0HCl requires M^+ 509.24269; Anal. ($C_{30}H_{31}N_5O_3$·2.0HCl·3.0H_2O) C, H, N. RT = 17.52 min.

2-(4-Nitrophenethyl)-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrole-1,3,4-trione (5). Method 4: 4-nitrophenethyl alcohol (3.33 g, 20 mmol) was dissolved in DMF (50 mL) and the succinimide derivative **10** (4.8 g, 20 mmol) was added. To the stirring solution was added triphenylphosphine (5.2 g, 20 mmol) and the solution was cooled to 0 °C. A solution of diisopropyl azodicarboxylate (4.02 g, 20 mmol) in DMF (20 mL) was added dropwise over 20 min and then the solution was stirred up to room temperature overnight. The solution was poured onto ice–water (250 mL) and stirring continued for 3 h to form a yellow gum. The solvent was decanted off and the yellow solid recrystallised from ethanol to give 6.06 g (78%) of **5** as yellow crystals (Mp 175–177 °C); MS *m*/*z* 390 (M^+); ^{1}H NMR δ 1.75 (2H, m, CH_2), 2.23 (2H, m, CH_2), 2.7 (1H, m, CH), 2.94 (2H, m, CH_2N), 3.11 (1H, m, CH), 3.64 (2H, m, CH_2), 3.92 (1H, s, CH), 7.23 (2H, d, H3, H5, *J* 8.5 Hz), 7.48 (3H, m, 3 × ArH), 7.93 (2H, d, H2, H6, *J* 8.0 Hz).

2-(4-Aminophenethyl)-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrole-1,3,4-trione (10). Method 5: a suspension of the nitro intermediate **5** (5.9 g, 15 mmol) in a mixture of ethanol (125 mL), water (96 mL) and 2 M HCl (7.6 mL) was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon (0.45 g) overnight. The catalyst was filtered through Celite, washed with ethanol (2 × 15 mL) and the solvent removed under vacuum. The remaining residue was azeotropically dried with absolute ethanol (50 mL) and triturated with diethyl ether. The solid was recrystallised from ethanol–ether and dried under vacuum to give 6.37 g (97%) of **10** as white crystals (Mp 177–180 °C) (Found C, 62.49; H, 5.60; N, 6.37. $C_{22}H_{20}N_2O_3$·1.0HCl·1.44H_2O requires C, 62.49; H, 5.45; N, 6.63%); MS *m*/*z* 361 $(M + 1)^+$; ^{1}H NMR δ 1.78 (2H, m, CH_2), 2.25 (1H, m, CH), 2.31 (1H, m, CH), 2.79 (2H, m, CH_2N), 3.39 (2H, m, CH_2), 3.57 (2H, m, CH_2), 3.95 (1H, s, CH), 7.1 (4H, m, H2, H3, H5, H6), 7.48 (3H, m, 3 × ArH), 9.6 (3H, br s, NH_3^+); Anal. ($C_{22}H_{20}N_2O_3$·1.0HCl·1.44 H_2O) C, H, N.

Ethyl 5-(dimethylamino)-2-{4-[2-(1,3,4-trioxo-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]phenyl}-hydrazin-2-ylidenepentanoate (25). Method 6: a stirring solution of the amine **10** (2.0 g, 5.0 mmol) in concentrated hydrochloric acid (1.05 mL, 9.5 mmol), ethanol (6.6 mL) and water (10.0 mL) was cooled to 0 °C. A solution of sodium nitrite (0.35 g, 5.0 mmol) in water (3.1 mL) was added dropwise keeping the temperature at ~0 °C and the solution was stirred for 30 min. Meanwhile, a solution of sodium acetate trihydrate (3.52 g, 25.9 mmol) in water (4.5 mL) was added to a solution of the diketone **15**[28] (1.08 g, 5.0 mmol) in ethanol (4.5 mL). This solution was stirred for 30 min and then added at once to the diazonium salt solution. The solution was left to stir for 30 min at 0–5 °C then allowed to stir at 10–15 °C overnight. The orange suspension was basified with 2 M NaOH solution, extracted with $CHCl_3$, dried and concentrated to give 1.5 g of a crude residue which was purified by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150 : 8 : 1) to give 1.1 g (40%) of **25** as an orange powder. MS *m*/*z* 545 $(M + 1)^+$; ^{1}H NMR δ 1.27 (3H, t, CH_2CH_3, *J* 7.2 Hz), 1.64 (2H, t, CH_2, *J* 6.3 Hz), 1.75 (2H, m, CH_2), 2.11 (6H, s, 2 × NCH_3), 2.25 (2H, m, CH_2), 2.52 (2H, m, CH_2), 2.69 (2H, m, CH_2), 2.72 (1H, m, CH), 2.83 (1H, m, CH), 3.31 (2H, m, CH_2), 3.53 (2H, m, CH_2), 3.94 (1H, s, CH), 4.12 (2H, q, CH_2CH_3, *J* 7.3 Hz), 6.87 (2H, d, H2, H6, *J* 8.4 Hz), 6.95 (2H, d, H3, H5, *J* 8.1 Hz), 7.41–7.55 (3H, m, 3 × ArH), 10.55 (1H, s, NH); Found M^+ 544.26844. $C_{31}H_{36}N_4O_5$ requires M^+ 544.26857.

Ethyl 5-[2-(1,3,4-trioxo-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate (26). Method 7: to a solution of the ethyl ester hydrazone **25** (1.1 g, 2.0 mmol) in ethanol (100 mL) was added dropwise concentrated hydrochloric acid (2.35 mL). The reaction was gently refluxed under nitrogen for 24 h. The solution was cooled, the solvent evaporated under reduced pressure, water added (30 mL) and the pH adjusted to 9 with potassium carbonate. The aqueous layer was extracted with ethyl acetate, dried, filtered and the solvent evaporated under reduced pressure to give an orange solid which was purified by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (80 : 8 : 1) to give 0.26 g (25%) of **26** as a white powder. MS *m*/*z* 528 $(M + 1)^+$; ^{1}H NMR δ 1.34 (3H, t, CH_2CH_3, *J* 7.2 Hz), 1.71 (2H, m, CH_2), 2.19 (1H, m, CH), 2.21 (6H, s, 2 × NCH_3), 2.25 (1H, m, CH), 2.39 (2H, m, CH_2), 2.65 (3H, m, CH_2, CH), 2.84 (3H, m, CH_2, CH), 3.6 (2H, m, CH_2), 3.9 (1H, s, CH), 4.33 (2H, q, CH_2CH_3, *J* 7.3 Hz), 6.9 (1H, d, H7, *J* 8.4 Hz), 7.18 (1H, d, H6, *J* 8.1 Hz), 7.23 (1H, s, H4), 7.37 (2H, m, 2 × ArH), 7.5 (1H, m, ArH), 11.34 (1H, s, NH); Found M^+ 527.24446. $C_{32}H_{33}N_3O_5$ requires M^+ 527.24202.

Benzyl 5-[2-(1,3,4-trioxo-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate (27). Method 1: yellow powder, 84 mg (43%); MS *m*/*z* 590 $(M + 1)^+$; ^{1}H NMR δ 1.7 (2H, m, CH_2), 2.1 (6H, s, 2 × NCH_3), 2.4 (2H, m, CH_2), 3.06 (4H, m, 2 × CH_2), 3.2 (4H, m, 2 × CH_2), 3.3 (2H, m, CH_2, under water peak), 3.6 (2H, m, CH_2NCO), 3.8 (1H, s, CH), 5.37 (2H, s, CH_2O), 6.9–7.5 (11H, m, H7, H4, 8 × ArH), 11.47 (1H, s, NH); Found M^+ 589.25654. $C_{36}H_{35}N_3O_5$ requires M^+ 589.25767.

5-[2-(1,3,4-Trioxo-2,3,5,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylic acid (28). Method 2: White powder, 36 mg (59%); MS *m*/*z* 500 $(M + 1)^+$; Found M^+ 500.21807. $C_{29}H_{30}N_3O_5$ requires M^+ 500.21854.

***N*-Benzyl 5-[2-(1,3,4-trioxo-2,3,4,6,10,10a-hexahydro-1*H*,4*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (29).** Method 3: yellow powder, 10.4 mg (42%); MS *m*/*z* 589 $(M + 1)^+$; ^{1}H NMR δ 1.7 (2H, m, CH_2), 2.0 (6H, s, 2 × NCH_3), 2.47 (2H, m, CH_2), 2.7–3.2 (8H, m, 4 × CH_2), 3.59 (3H, m, CH, CH_2), 4.51 (2H, d, CH_2NH, *J* 5.4 Hz), 6.86 (1H, d, H6), 7.1–7.7 (10H, m, H7, H4, 8 × ArH), 9.71 (1H, m, NH), 11.14 (1H, s, NH); Found M^+ 588.27473. $C_{36}H_{36}N_4O_4$ requires M^+ 588.27366.

Ethyl 5-(dimethylamino)-2-{3-[4-(4-azatricyclo[5.2.1.0^{2,6}]-dec-8-en-4-yl)phenyl]propyl}hydrazin-2-ylidenepentanoate (30). Method 6: orange solid, 0.91 g (61%); MS *m*/*z* 529 $(M + 1)^+$; ^{1}H NMR δ 1.25 (3H, t, CH_3CH_2, *J* 7.3 Hz), 1.58 (2H, s, CH_2), 1.64 (2H, m, CH_2), 2.11 (2H, m, CH_2), 2.14 (6H, s, 2 × NCH_3), 2.54 (2H, m, CH_2), 3.46 (2H, s, CH_2), 3.88 (2H, s, CH_2), 4.26 (2H, q, CH_2CH_3, *J* 6.9 Hz), 6.19 (2H, s, CH=CH), 6.99 (2H, d, H2, H6, *J* 8.1 Hz), 7.09 (4H, s, 4 × ArH), 7.25 (2H, d, H3, H5, *J* 8.0 Hz), 10.63 (1H, s, NH).

Ethyl 3-[2-(dimethylamino)ethyl]-5-{3-[4-(4-azatricyclo-[5.2.1.0^{2,6}]dec-8-en-4-yl)phenyl]propyl}-1*H*-indole-2-carboxylate (31). Method 7: yellow powder, 0.80 g (93%); MS *m*/*z* 512 $(M + 1)^+$; ^{1}H NMR δ 1.25 (3H, t, CH_3CH_2, *J* 6.3 Hz), 1.51 (2H, s, CH_2), 2.08 (2H, s, 2 × CH), 2.14 (6H, s, 2 × NCH_3), 2.40 (2H, m, CH_2), 2.43 (2H, s, CH_2), 3.08 (2H, m, CH_2), 3.24 (4H, s, 2 × CH_2), 3.88 (2H, s, CH_2), 4.26 (2H, q, CH_2CH_3, *J* 6.2 Hz), 6.12 (2H, s, CH=CH), 6.9–7.5 (7H, m, 7 × ArH), 11.34 (1H, s, NH).

Benzyl 3-[2-(dimethylamino)ethyl]-5-{3-[4-(4-azatricyclo-[5.2.1.0^{2,6}]dec-8-en-4-yl)phenyl]propyl}-1*H*-indole-2-carboxylate (32). Method 1: yellow solid, 780 mg (80%); MS *m*/*z* 574 $(M + 1)^+$; ^{1}H NMR δ 1.57 (2H, s, CH_2), 2.1 (6H, s, 2 × NCH_3), 2.41 (2H, m, CH_2), 3.14 (2H, m, CH_2), 3.3 (2H, m, CH_2 under HDO peak), 3.44 (2H, s, CH_2), 4.01 (2H, s, CH_2), 5.43 (2H, s, CH_2), 6.2 (2H, s, CH_2O), 6.96–7.5 (12H, m, 12 × ArH), 11.5 (1H, s, NH); Found M^+ 573.26241. $C_{36}H_{35}N_3O_4$ requires M^+ 573.26276.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-{3-[4-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)phenylpropyl}-1*H*-indole-2-carboxamide (33).** Method 2, method 3: white lyophilate, 3.5 mg (21%); MS *m*/*z* 573 $(M + 1)^+$; ^{1}H NMR δ 2.0 (6H, s, 2 × NCH_3), 3.06 (2H, m, CH_2), 3.1–3.5 (8H, m, 4 × CH_2, -CH_2-, 2 × CH), 4.07 (2H, m, 2 × CH_2), 4.51 (2H, d, CH_2NH, *J* 5.4 Hz), 6.9–7.6 (12H, m, 12 × ArH), 9.13 (1H, t, NH), 11.48 (1H, s, NH); Found M^+ 572.27568. $C_{36}H_{36}N_4O_3$ requires M^+ 572.27874.

3-[2-(4-Hydrazinophenyl)ethyl]-1,3-thiazolidine-2,4-dione (37). Method 8: A solution of the acetate salt of the amine **11**[28] (1.77 g, 5.9 mmol) in water (7.9 mL) was treated with concentrated HCl (15.3 mL) and cooled to −5 °C. A solution of sodium nitrite (0.4 g, 10.0 mmol) in water (4.2 mL) was added dropwise and stirring continued at 0 °C for 1 h. A solution of tin chloride dihydrate (7.75 g, 34.4 mmol) in concentrated HCl (12.8 mL) was added dropwise and stirring continued at room temperature overnight. The suspension was concentrated under reduced pressure and the residue resuspended in water. The aqueous phase was washed with dichloromethane and brought to pH 2.5. Filtration and concentration under reduced pressure afforded a solid which was triturated with ethanol. Filtration and recrystallisation from ethanol gave 1.7 g (98%) of the **37** as a white solid. MS *m*/*z* 252 $(M + 1)^+$; ^{1}H NMR δ 2.73 (2H, t, CH_2N, *J* 7.3 Hz), 3.65 (2H, t, CH_2Ph, *J* 7.2 Hz), 10.22 (3H, br s, NH_3^+).

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,4-dioxo-1,3-thiazolidin-3-yl)ethyl]-1*H*-indole-2-carboxamide (39).** Method 9: a refluxing solution of the hydrazine **37** (1.7 g, 5.9 mmol) in ethanol (40 mL) and water (4 mL) was treated dropwise with a solution of the benzylamide **35** (1.86 g, 6.6 mmol) in ethanol (20 mL) and reflux continued for 4 h. The solution was concentrated under reduced pressure and partitioned between 2 M HCl and ethyl acetate. The aqueous phase was neutralised (2 M NaOH) and extracted with ethyl acetate. The organic phase was dried and concentrated under reduced pressure to afford 198 mg (8%) of the primary amine intermediate **38** as an orange gum which was reacted on without further purification. Method 10: A solution of the **38** (198 mg, 4.5 mmol) in methanol (34 mL) was treated with acetic acid (0.12 mL, 2.1 mmol), formaldehyde (0.08 mL) followed by sodium cyanoborohydride (33 mg, 0.5 mmol) and the solution was stirred overnight. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic phase was concentrated under reduced pressure to afford a yellow oil which was purified by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (300 : 8 : 1) afforded 20 mg (10%) of **39** as a white solid. MS *m*/*z* 465 $(M + 1)^+$; ^{1}H NMR δ 2.08 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2, under DMSO peak), 2.9 (2H, m, CH_2NMe_2), 3.08 (2H, m, CH_2), 3.75 (2H, m, CH_2Hyd), 4.13 (2H, s, CH_2), 4.5 (2H, d, CH_2NHCO), 7.05 (1H, d, H6, *J* 7.8 Hz), 7.3–7.5 (7H, m, H7, H4, 5 × ArH), 9.8 (1H, t, NH), 11.42 (1H, s, NH); Found M^+ 464.18877. $C_{25}H_{28}N_4O_3S$ requires M^+ 464.18821. RT = 19.33 min.

3-(4-Nitrophenethyl)-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (7). Method 4: trituration with diethyl ether gave 1.9 g (28%) of an off-white solid which was reacted on without further purification. ^{1}H NMR δ 1.78 (3H, s, CH_3), 2.98 (2H, m, CH_2Ph), 4.05 (2H, t, CH_2N), 7.45–7.65 (5H, m, 5 × ArH), 8.16 (3H, m, 3 × ArH), 10.86 (1H, d, NH).

3-(4-Aminophenethyl)-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (12). Method 5: white solid, 1.0 g (59%). Mp = 208–210 °C; MS *m*/*z* 245 $(M)^+$; ^{1}H NMR δ 1.74 (3H, s, CH_3), 2.78 (2H, t, CH_2Ph, *J* 8.6 Hz), 3.95 (2H, t, CH_2N, *J* 8.3 Hz), 7.28 (4H, m, H2, H3, H5, H6), 10.3 (2H, br s, NH_2), 10.95 (1H, d, CH).

***N*-Benzyl-3-(2-aminoethyl)-5-[2-(2,6-dioxo-5-methyl-1,2,3,6-tetrahydropyrimidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (40).** Method 8, method 9: purification by HPLC afforded 200 mg (16%) of the acetate of salt of **40** as an off-white solid. MS *m*/*z* 446 $(M + 1)^+$; ^{1}H NMR δ 1.78 (3H, s, CH_3), 1.89 (3H, s, CH_3CO_2H), 2.09 (6H, S, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO peak), 2.88 (2H, m, 5-CH_2), 3.08 (2H, m, 3-CH_2), 4.05 (2H, m, CH_2Hyd), 4.55 (2H, d, CH_2NHCO), 7.08 (1H, d, H6), 7.28–7.4 (8H, m, H7, H4, 5 × ArH, NH), 9.7 (1H, t, NH), 11.23 (1H, s, NH). RT = 14.21 min.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,6-dioxo-5-methyl-1,2,3,6-tetrahydropyrimidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (41).** Method 10: purification by HPLC afforded **41** as a white solid (Found C, 57.45; H, 6.37; N, 11.32. $C_{27}H_{31}N_5O_3 \cdot 1.0CH_3CO_2H \cdot 4.0H_2O$ requires C, 57.52; H, 7.10; N, 11.57%); MS *m*/*z* 473 $(M)^+$; ^{1}H NMR δ 1.78 (3H, s, CH_3), 1.89 (3H, s, CH_3CO_2H), 2.09 (6H, S, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO peak), 2.88 (2H, m, 5-CH_2), 3.08 (2H, m, 3-CH_2), 4.05 (2H, m, CH_2Hyd), 4.55 (2H, d, CH_2NHCO), 7.08 (1H, d, H6), 7.28–7.4 (8H, m, H7, H4, 5 × ArH, NH), 9.7 (1H, t, NH), 11.23 (1H, s, NH); Found M^+ 473.24305. $C_{27}H_{31}$-

N_5O_3 requires M^+ 473.24269; Anal. ($C_{27}H_{31}N_5O_3 \cdot 1.0CH_3CO_2H \cdot 4.0\ H_2O$) C, H, N. RT = 15.41 min.

5,5-Dimethyl-3-[2-(4-nitrophenyl)ethyl]-1,3-thiazolidine-2,4-dione (42). A solution of 3-[2-(4-nitrophenyl)ethyl]-1,3-thiazolidine-2,4-dione **6** (5.0 g, 18.8 mmol) in THF (200 mL) was cooled to −78 °C. Potassium *tert*-butoxide (8.4 g, 75.0 mmol) was added and the solution stirred at −78 °C for 0.5 h. Methyl iodide (10.7 g, 4.6 mL, 75.0 mmol) was added and the solution allowed to warm gradually to room temperature. The reaction was quenched with aqueous ammonium chloride and extracted with dichloromethane. The organic layer was concentrated under reduced pressure and purified by flash chromatography eluting with petrol–ethyl acetate (4:1) to afford 3.7 g (67%) of **42** as white needles. MS *m/z* 295 $(M + 1)^+$; ^{1}H NMR δ ($CDCl_3$) 1.59 (6H, s, 2 × CH_3), 3.05 (2H, t, CH_2N), 3.8 (2H, t, CH_2-Ph), 7.35 (2H, d, H3, H5, *J* 8.7 Hz), 8.13 (2H, d, H2, H6, *J* 8.7 Hz).

5,5-Dimethyl-3-[2-(4-aminophenyl)ethyl]-1,3-thiazolidine-2,4-dione (43). A solution of **42** (3.7 g, 12.6 mmol) in ethanol (200 mL) was treated with concentrated HCl (12.6 mL) and 10% palladium on charcoal (200 mg) and stirred under an atmosphere of hydrogen at room temperature overnight. The solution was filtered through Celite and concentrated under reduced pressure to afford 3.15 g (83%) of **43** as a pale orange solid which was reacted on without further purification.

5,5-Dimethyl-3-[2-(4-hydrazinophenyl)ethyl]-1,3-thiazolidine-2,4-dione (44). Method 8: a suspension of the amine **43** (3.0 g, 10.0 mmol) in water (13.3 mL) was treated with concentrated HCl (24.4 mL) and cooled to −5 °C. A solution of sodium nitrite (0.68 g, 10.0 mmol) in water (6.5 mL) was added dropwise and stirring continued at 0 °C for 1 h. A solution of tin chloride dihydrate (11.1 g, 50.0 mmol) in concentrated HCl (19.8 mL) was added dropwise and stirring continued at room temperature overnight. The suspension was concentrated under reduced pressure and the residue resuspended in water. The aqueous phase was washed with dichloromethane and brought to pH 2.5. Filtration and concentration under reduced pressure afforded a solid which was triturated with ethanol. Filtration and concentration gave 1.8 g (57%) of **44** as an orange solid which was reacted on without further purification.

***N*-Benzyl-3-(2-aminoethyl)-5-[2-(5,5-dimethyl-2,4-dioxo-1,3-thiazolidin-3-yl)ethyl]-1*H*-indole-2-carboxamide (45).** Method 9: a solution of the hydrazine **44** (1.5 g, 5.3 mmol) in ethanol (20 mL) and water (2.0 mL) was heated to ~90 °C and the α-ketoamide **35** (1.0 g, 3.5 mmol) was added portionwise over 1 h. The solution was heated to reflux for 4 h and then stirred at room temperature overnight. The solution was concentrated under reduced pressure and the residue purified using flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150:8:1) to give 240 mg (15%) of **45** as an off-white solid (Found C, 63.04; H, 5.95; N, 11.74. $C_{25}H_{28}N_4O_3S \cdot 0.65H_2O$ requires C, 63.03; H, 6.16; N, 11.77%); MS *m/z* 465 $(M + 1)^+$; ^{1}H NMR δ 1.5 (6H, s, 2 × CH_3), 2.82–3.08 (6H, m, 3 × CH_2), 3.79 (2H, m, CH_2), 4.5 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.22–7.35 (9H, m, H7, H4, 5 × ArH, NH_2), 10.5 (1H, m, NH), 11.16 (1H, s, NH); Anal. ($C_{25}H_{28}N_4O_3S \cdot 0.65H_2O$) C, H, N.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(5,5-dimethyl-2,4-dioxo-1,3-thiazolidin-3-yl)ethyl]-1*H*-indole-2-carboxamide (46).** Method 10: pale yellow powder (Found C, 64.43; H, 6.41; N, 11.11. $C_{27}H_{32}N_4O_3S \cdot 0.6H_2O$ requires C, 64.44; H, 6.60; N, 11.14%); MS *m/z* 493 $(M + 1)^+$; ^{1}H NMR δ 1.45 (6H, s, 2 × CH_3), 2.05 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO peak), 2.93 (2H, m, 5-CH_2), 3.03 (2H, t, 3-CH_2), 3.82 (2H, t, CH_2Hyd), 4.53 (2H, d, CH_2NHCO), 6.99 (1H, d, H6), 7.22–7.39 (7H, m, H7, H4, 5 × ArH), 9.67 (1H, t, NH), 11.2 (1H, s, NH); Found M^+ 492.22109. $C_{27}H_{32}N_4O_3S$ requires M^+ 492.21951; Anal. ($C_{27}H_{32}N_4O_3S \cdot 0.6H_2O$) C, H, N.

Ethyl 2-aminoisobutyrate (48). A solution of 2-aminoisobutyric acid **47** (9.0 g, 93 mmol) in ethanol (100 mL) was treated with thionyl chloride (20 mL, 0.27 mol) and heated at reflux for 16 h. The solution was concentrated under reduced pressure and triturated with ethyl acetate–ethanol to afford 11.3 g (75%) of **48** as a white crystalline solid which was reacted on without further purification.

Ethyl 2-[*N*-(*tert*-butyloxycarbonyl)aminosulfonamido]-2-methylpropanoate (49). A solution of chlorosulfonyl isocyanate (4.4 g, 34.0 mmol) in dichloromethane (77 mL) was added to a solution of butan-2-ol (5.5 mL) in dichloromethane (30 mL) at 0 °C. This solution was warmed to room temperature and added to a stirring solution of the amino ester **48** (5.0 g, 31.0 mmol) in dichloromethane (15 mL) and triethylamine (5.0 mL, 36 mmol) was then added. The solution was stirred at room temperature for 3 h. The solution was then diluted with dichloromethane, washed with 2 M HCl and water. Concentration of the solution under reduced pressure afforded 5.0 g (58%) of **49** as a white solid which was reacted on without further purification.

Ethyl 2-methyl-2-[*N*-(4-nitrophenylethyl)-*N*-(*tert*-butyloxycarbonyl)aminosulfonamido]propanoate (50). A solution of **49** (4.5 g, 16.2 mmol) and triphenylphosphine (4.76 g, 18.1 mmol) in dry DMF (30 mL) was treated under nitrogen with diethyl azodicarboxylate (3.75 mL, 23.8 mmol) and stirred in the dark for 1 h. A solution of *p*-nitrophenethyl alcohol (2.7 g, 16.2 mmol) was added dropwise and stirring continued for 3 days. The solution was concentrated under reduced pressure and the residue purified by flash chromatography eluting with petrol–ethyl acetate (8:1) to give 5.58 g (75%) of **50** as a pale yellow powder. ^{1}H NMR δ ($CDCl_3$) 1.3 (3H, t, CH_2CH_3), 1.48 (9H, s, 3 × CH_3), 1.54 (6H, s, 2 × CH_3), 3.05 (2H, t, CH_2Ph), 3.88 (2H, m, CH_2N), 4.23 (2H, q, CH_2CH_3), 6.3 (1H, s, NH), 7.38 (2H, d, H3, H5), 8.14 (2H, d, H2, H6).

Ethyl 2-methyl-2-[(4-nitrophenyl)ethylaminosulfonamido]propanoate (51). Method 11: a solution of **49** (5.5 g, 1.2 mmol) in dichloromethane (20 mL) was treated with a solution of TFA (20 mL) in dichloromethane (20 mL) at 0 °C and stirred for 1 h then left at 4 °C overnight. The solution was concentrated under reduced pressure to give a yellow oil which was triturated with ether to afford a pale yellow solid. Recrystallisation from ether afforded 3.71 g (86%) of **51** as a pale yellow powder. MS *m/z* 359 (M^+); ^{1}H NMR δ ($CDCl_3$) 1.28 (3H, t, CH_2CH_3), 1.48 (6H, s, 2 × CH_3), 2.98 (2H, t, CH_2Ph), 3.4 (2H, m, CH_2N), 4.2 (2H, q, CH_2CH_3), 4.45 (1H, s, NH), 4.95 (1H, s, NH), 7.38 (2H, d, H3, H5), 8.15 (2H, d, H2, H6) (Found C, 44.01; H, 5.69; N, 11.24. $C_{14}H_{21}N_3O_6S \cdot 1.25H_2O$ requires C, 44.01; H, 6.15; N, 11.00%); Found M^+ 359.11564. $C_{14}H_{21}N_3O_6S$ requires M^+ 359.11511.

2-(4-Nitrophenyl)ethyl-(4,4-dimethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide) (52). The ethyl ester intermediate **51** (3.5 g, 9.7 mmol) was treated with an aqueous solution of 1.6 M sodium hydroxide (500 mL) and stirred at room temperature for 2 h prior to quenching with 10 M HCl until the solution reached pH 1. The precipitate was isolated by filtration to give 2.15 g (70%) of **52** as a white solid (Found C, 43.80; H, 4.82; N, 12.75. $C_{12}H_{15}N_3O_5S$ requires C, 43.75; H, 5.16; N, 12.75%), MS *m/z* 313 (M^+); ^{1}H NMR δ ($CDCl_3$) 1.31 (6H, s, 2 × CH_3), 3.0 (2H, m, CH_2Ph), 3.8 (2H, t, CH_2N), 7.5 (2H, d, H3, H5), 8.15 (2H, d, H2, H6); Anal. ($C_{12}H_{15}N_3O_5S$) C, H, N.

2-(4-Aminophenyl)ethyl-4,4-dimethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide (53). Method 5: cream powder (Found C, 57.46; H, 6.03; N, 14.59. $C_{12}H_{17}N_3O_3S$ requires C, 50.84; H, 6.05; N,

14.83%), MS *m/z* 284 $(M + 1)^+$; ^{1}H NMR δ ($CDCl_3$) 1.35 (6H, s, 2 × CH_3), 2.72 (2H, m, CH_2Ph), 3.58 (2H, t, CH_2N), 4.87 (1H, s, NH), 6.47 (2H, d, H2, H6), 6.86 (2H, d, H3, H5); Anal. ($C_{12}H_{17}N_3O_3S$) C, H, N.

2-(4-Hydrazinophenyl)ethyl-4,4-dimethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide (54). Method 8: a solution of the amine **53** (1.0 g, 3.53 mmol) in water (4.7 mL) was treated with concentrated HCl (8.6 mL) and cooled to −5 °C. A solution of sodium nitrite (0.24 g, 3.5 mmol) in water (3.0 mL) was added dropwise and stirred at −5 °C for 1 h. A solution of tin chloride dihydrate (3.9 g, 17.3 mmol) in concentrated HCl (7.0 mL) was added dropwise and the solution stirred at room temperature for 4 h. The reaction mixture was concentrated *in vacuo* and resuspended in water. The aqueous phase was washed with CH_2Cl_2 and adjusted to pH 2.5 with 2 M NaOH. Concentration under reduced pressure afforded a white solid which was triturated with ethanol and filtered. Concentration of the ethanol afforded 1.2 g (100%) of the hydrazine hydrochloride **54** as a pale yellow solid which was reacted on without further purification.

***N*-Benzyl-5-[2-(4,4-dimethyl-1,1,3-trioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-3-(2-aminoethyl)-1*H*-indole-2-carboxamide (55).** Method 9: a solution of the hydrazine hydrochloride **54** (1.0 g, 3.0 mmol) in ethanol (12 mL) and water (1.2 mL) was heated to reflux. The α-ketoamide **35** (0.95 g, 3.3 mmol) was added portion-wise and the solution was refluxed for 6 h. Concentration under reduced pressure and flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150 : 8 : 1) afforded 285 mg (20%) of **55** as a pale gum. ^{1}H NMR δ 1.25 (6H, s, 2 × CH_3), 2.95 (4H, m, CH_2NMe_2, 3-CH_2), 3.12 (2H, m, 5-CH_2), 3.6 (2H, m, CH_2N, under water peak), 4.51 (2H, d, NHCH_2Ph), 7.1 (1H, d, H6), 7.15–7.35 (7H, m, H7, H4, 5 × CH_2), 9.8 (1H, m, NH), 11.2 (1H, br s, NH).

***N*-Benzyl-5-[2-(4,4-dimethyl-1,1,3-trioxo-1,2,5-thiadiazolidin-2-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (56).** Method 10: purification by HPLC afforded 110 mg (41%) of the acetate salt of **56** as a white lyophilate (Found C, 57.36; H, 6.28; N, 12.20. $C_{26}H_{33}N_5O_4S{\cdot}1.0H_2O{\cdot}0.5CH_3CO_2H$ requires C, 57.41; H, 6.71; N, 12.40%); MS *m/z* 512 $(M + 1)^+$; ^{1}H NMR δ 1.35 (6H, s, 2 × CH_3), 1.9 (1.5H, s, CH_3CO_2H), 2.1 (6H, s, 2 × NCH_3), 2.55 (2H, m, CH_2NMe_2), 3.05 (4H, m, 5-CH_2, 3-CH_2), 3.75 (2H, t, CH_2Hyd), 4.5 (2H, d, CH_2), 7.1 (1H, d, H6), 7.3–7.4 (8H, m, H7, H4, 5 × ArH, NH), 9.7 (1H, t, NH), 11.2 (1H, s, NH); Found M^+ 511.22575. $C_{26}H_{33}N_5O_4S$ requires M^+ 511.22533; Anal. ($C_{26}H_{33}N_5O_4S{\cdot}1.0H_2O{\cdot}0.5CH_3CO_2H$) C, H, N. HPLC retention time = 17.08 min.

3-(4-Nitrophenethyl)-1-methylsulfonylimidazolidine-2,4-dione (57). Methanesulfonyl chloride (1.38 g, 0.93 mL, 12.0 mmol) was added dropwise to a suspension of the hydantoin derivative **8**[29] (2.5 g, 10.0 mmol) and triethylamine (2.0 g, 20.0 mmol) in toluene (50 mL). The solution was stirred at room temperature under nitrogen for 6 h. A further equivalent of triethylamine (1.39 mL) was added and the solution was stirred overnight. A solid was filtered off and the remaining filtrate was evaporated to dryness under reduced pressure. The solid residue was triturated with ethanol and water then filtered and eventually dried under vacuum to give 1.89 g (59%) of **57**. MS *m/z* 327 (M^+); ^{1}H NMR δ 3.0 (2H, t, CH_2N), 3.36 (3H, s, SO_2CH_3), 3.7 (2H, t, CH_2), 4.39 (2H, s, HydCH$_2$), 7.5 (2H, d, H3, H5, *J* 8.7 Hz), 8.18 (2H, d, H2, H6, *J* 8.7 Hz).

3-(4-Aminophenethyl)-1-methylsulfonylimidazolidine-2,4-dione (58). Method 5: yellow solid, 579 mg (32%); MS *m/z* 297 (M^+); ^{1}H NMR δ 2.85 (2H, t, CH_2N), 3.05 (2H, t, CH_2Ph), 3.32 (3H, s, SO_2CH_3), 4.39 (2H, s, HydCH$_2$), 7.15 (2H, d, H2, H6), 7.25 (2H, d, H3, H5).

3-(4-Hydrazinophenethyl)-1-methylsulfonylimidazolidine-2,4-dione (59). Method 8: white solid, 60 mg (69%); MS *m/z* 312 (M^+); ^{1}H NMR δ 2.76 (2H, m, CH_2N), 3.09 (2H, t, CH_2Ph), 3.32 (3H, s, SO_2CH_3), 4.38 (2H, s, HydCH$_2$), 6.92 (2H, d, H2, H6), 7.11 (2H, d, H3, H5).

***N*-Benzyl-3-[2-aminoethyl]-5-[2-(3-methylsulfonyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (60).** Method 9: white solid, 50 mg (10%); MS *m/z* 498 $(M + 1)^+$; ^{1}H NMR δ 2.9 (4H, m, CH_2NMe_2, 5-CH_2), 3.03 (2H, m, 3-CH_2), 3.32 (3H, s, CH_3SO_2), 3.65 (2H, m, CH_2NH_2), 4.39 (2H, s, HydCH$_2$), 4.52 (2H, d, CH_2NH, *J* 5.2 Hz), 7.03 (1H, d, H6), 7.3 (7H, m, H7, H4, 5 × ArH), 10.55 (1H, t, NH), 11.2 (1H, s, NH).

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(3-methylsulfonyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (61).** Method 10: purification by HPLC afforded 10 mg (18%) of the acetate salt of **61** as a white lyophilate; MS *m/z* 526 $(M + 1)^+$; ^{1}H NMR δ 1.9 (2.5H, s, CH_3CO_2H), 2.08 (6H, s, 2 × NCH_3), 2.55 (2H, m, CH_2NMe_2), 2.93 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.31 (3H, s, CH_3SO_2), 3.65 (2H, m, CH_2Hyd), 4.37 (2H, s, $COCH_2$N), 4.55 (2H, d, CH_2NHCO, *J* 5.4 Hz), 7.01 (1H, d, H6), 7.33 (7H, m, H7, H4, 5 × ArH), 9.75 (1H, t, NH), 11.24 (1H, s, NH); Found M^+ 525.20645. $C_{26}H_{31}N_5O_5S{\cdot}1.0CH_3CO_2H$ requires M^+ 525.20459.

1-(4-Nitrophenethyl)-5,5-dimethylimidazolidine-2,4-dione (65). Morpholine (0.05 mol, 4.37 mL) was added to a chilled solution of 5,5-dimethylhydantoin (6.4 g, 0.05 mol) in methanol (50 mL). Formaldehyde (4.1 mL, 0.05 mol) was added and the solution stirred for 2 h. The solution was concentrated to a white solid which was azeotroped with benzene, washed with petrol and dried *in vacuo* to give 11.2 g (98%) of **62**. A portion of the solid (5.5 g, 24 mmol) was dissolved in dry DMF (100 mL) chilled to 0 °C and sodium hydride (970 mg, 60% disp, 55.0 mmol) was added portion wise. The suspension was stirred at room temperature until evolution of H_2 ceased after which 4-nitrophenethyl bromide **63** (5.52 g, 0.05 mol) was gradually added and the reaction mixture was stirred under nitrogen overnight. The solution was concentrated under reduced pressure to give a black oil which was stirred with 2 M NaOH (75 mL) and THF (25 mL) for 1.5 h. The solution was acidified to pH 1 with 2 M HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried, concentrated and triturated with ethanol to give 1.19 g (18%) of **65** as a pale cream solid. (Mp 186–187 °C) which was reacted on without further purification. HPLC retention time = 14.38 min.

1-(4-Hydrazinophenethyl)-5,5-dimethylimidazolidine-2,4-dione (67). Method 5: MS *m/z* 248 $(M + 1)^+$; ^{1}H NMR δ 1.19 (6H, s, 2 × CH_3), 2.95 (2H, t, CH_2N, *J* 7.1 Hz), 3.42 (2H, t, CH_2Ph, *J* 7.1 Hz), 7.25 (2H, d, H3, H5, *J* 8.3 Hz), 7.35 (2H, d, H2, H6, *J* 8.3 Hz), 10.8 (1H, s, NH). RT = 8.29 min. Method 8: The amine hydrochloride **66** (3.9 g, 13.7 mmol) prepared from the nitro intermediate **65** *via* method 2 was dissolved in water (24 mL) and cooled to −5 °C. Concentrated HCl (43 mL) was added dropwise maintaining the temperature at 0–5 °C. $NaNO_2$ (0.95 g, 13.8 mmol) in water (12 mL) was added dropwise at −2 °C. The solution was stirred for 30 min after which the diazonium salt formed was added dropwise to a solution of tin chloride dihydrate (13.0 g, 57.7 mmol) in concentrated HCl (35 mL) over 30 min at ~0 °C. The solution was allowed to warm to room temperature then concentrated under reduced pressure, redissolved in water and basified to pH 3 with 2 M NaOH. The suspension was filtered and the filtrate concentrated to give 3.87 g (94%) of **67** as a cream solid which was reacted on without further purification. HPLC retention time = 7.87 min.

***N*-Benzyl-5-[2-(5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)-ethyl]-3-[2-aminoethyl]-1*H*-indole-2-carboxamide (68).** Method 9: the α-ketoamide **35** (617 mg, 21.7 mmol) was added to a stirred suspension of hydrazine hydrochloride **67** (650 mg, 22.0 mmol) in ethanol–water (1 : 1) (25 mL). The solution was stirred for 15 min at room temperature then heated to reflux for 4 h. Concentration under reduced pressure and flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (60 : 8 : 1) gave 189 mg (20%) of **68** as a pale foam which was reacted on without further purification.

***N*-Benzyl-5-[2-(5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)-ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (69).** Method 10: white powder, 35 mg (20%). MS *m*/*z* 476 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.05 (6H, s, 2 × NCH_3), 2.55 (2H, m, CH_2NMe_2), 2.95 (2H, m, CH_2), 3.06 (2H, m, 5-CH_2), 3.39 (2H, m, 3-CH_2), 4.52 (2H, d, CH_2NHCO), 7.1 (1H, d, H6, *J* 7.5 Hz), 7.3 (1H, s, NH), 7.35–7.41 (2H, m, H7, H4), 9.75 (1H, t, NH), 11.17 (1H, s, NH); Found M^+ 475.25689. $C_{27}H_{33}N_5O_3$ requires M^+ 475.25834. HPLC retention time = 15.19 min.

1-Benzyl-4-[(4-nitrophenyl)ethyl]imidazolidine-2,5-dione (74). The amino acid **72**[29] (2.8 g, 12.5 mmol) was added to a solution of potassium hydroxide (0.84 g, 15.0 mmol) in water (25 mL). The solution was cooled to 0 °C and benzyl isocyanate (1.99 g, 1.85 mL, 15 mmol) was added over 20 min maintaining the temperature at 0 °C. The solution was stirred at 60–70 °C for 2 h after which the urea was filtered off. The filtrate was acidified with concentrated HCl then filtered. The uncyclised hydantoic acid was collected and washed with water. The solid was suspended in concentrated HCl–water (1 : 1) (15 mL) and refluxed for 2 h. The solution was then cooled, diluted with water, filtered, washed with water and dried *in vacuo* to give 4.23 g (83%) of **74** as a white powder which was reacted on without further purification. MS *m*/*z* 339 $(M + 1)^+$; ^{1}H NMR δ 1.83 (1H, m, CH_A), 2.01 (1H, m, $CH_{A'}$), 2.8 (2H, m, CH_2Ph), 4.12 (1H, m, CH), 4.54 (2H, s, NCH_2Ph), 7.28 (5H, m, 5 × ArH), 7.51 (2H, d, H3, H5), 8.15 (2H, d, H2, H6), 8.49 (1H, s, NH).

1-Benzyl-4-[2-(4-anilino)ethyl]imidazolidine-2,5-dione (76). Method 5: 3.68 g (85%); MS *m*/*z* 310 $(M + 1)^+$; ^{1}H NMR δ 1.84 (1H, m, CH_A), 2.02 (1H, m, $CH_{A'}$), 2.65 (2H, m, CH_2Ph), 4.09 (1H, m, CH), 4.5 (2H, s, NCH_2Ph), 7.3 (9H, m, 9 × ArH), 8.5 (1H, s, NH), 10.2 (3H, br s, NH_3^+).

Ethyl 5-(dimethylamino)-2-{4-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]phenyl}hydrazin-2-ylidenepentanoate (77). Method 6: to a stirring solution of **76** (1.59 g, 4.59 mmol) in ethanol (6.0 mL) and water (9.1 mL) was added concentrated HCl (0.96 mL, 8.68 mmol). The solution was cooled to 0 °C and a solution of sodium nitrite (0.32 g, 4.59 mmol) in water (2.8 mL) was added and the solution was stirred for 10 min. Meanwhile a solution of the diketone **15** (0.98 g, 4.59 mmol) in ethanol (4.0 mL) was stirred with sodium acetate trihydrate (3.2 g, 23.6 mmol) and ice (4.0 g). The diazonium salt was added quickly to the diketone solution and the reaction was stirred for 5.0 h up to room temperature. The solution was adjusted to pH 9 with 10% NaOH and stirred for a further 10 min. The solution was extracted with ethyl acetate, dried, filtered and evaporated under reduced pressure to give an orange gum. Purification by flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (200 : 8 : 1) afforded 0.57 g (26%) of **77** as a yellow powder (Mp 142–143 °C) (Found C, 65.20; H, 6.89; N, 13.82. $C_{27}H_{35}N_5O_4 \cdot 0.10H_2O$ requires C, 65.46; H, 7.16; N, 14.13%); MS *m*/*z* 494 $(M + 1)^+$; ^{1}H NMR δ 1.24 (3H, t, CH_2CH_3, *J* 7.2 Hz), 1.64 (2H, m, CH_2), 2.0 (2H, m, CH_2), 2.1 (2H, m, CH_2), 2.14 (6H, s, 2 × NCH_3), 2.5 (4H, m, 2 × CH_2), 4.0 (1H, m, CH), 4.1 (2H, q, CH_2CH_3, *J* 7.0 Hz), 4.6 (2H, d, NCH_2Ph, *J* 4.4 Hz), 7.09 (4H, s, H2, H3, H5, H6), 7.24–7.34 (5H, m, 5 × ArH), 8.5 (1H, s, NH), 10.63 (1H, s, NH); Found $(M + 1)^+$ 494.27664. $C_{27}H_{36}N_5O_4$ requires $(M + 1)^+$ 494.27673. Anal. ($C_{27}H_{35}N_5O_4 \cdot 0.1H_2O$) C, H, N.

Ethyl 5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate (78). Method 7: yellow powder, 0.32 g (58%); MS *m*/*z* 477 $(M + 1)^+$; ^{1}H NMR δ 1.34 (3H, t, CH_2CH_3, *J* 6.9 Hz), 1.88 (2H, m, CH_2Hyd), 2.21 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.71 (2H, m, 5-CH_2), 3.1 (2H, t, 3-CH_2), 4.1 (1H, m, CH), 4.36 (2H, q, CH_2CH_3, *J* 7.0 Hz), 4.5 (2H, s, NCH_2Ph), 7.09 (1H, d, H6, *J* 8.6 Hz), 7.2–7.4 (7H, m, H7, H4, 5 × ArH), 8.5 (1H, s, NH), 9.77 (1H, t, NH), 11.4 (1H, s, NH); Found M^+ 476.24520. $C_{27}H_{32}N_4O_4$ requires M^+ 476.24236.

Benzyl 5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate (79). Method 1: purification by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150 : 8 : 1) gave 0.18 g (60%) of **79** as a yellow powder. MS *m*/*z* 539 $(M + 1)^+$; ^{1}H NMR δ 1.98–2.01 (2H, m, CH_2Hyd), 2.2 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2), 2.71 (2H, m, 5-CH_2), 3.13 (2H, t, 3-CH_2, *J* 8.1 Hz), 4.1 (1H, m, CH), 4.5 (2H, m, NCH_2Ph), 5.36 (2H, s, OCH_2Ph), 7.09 (1H, d, H6, *J* 8.7 Hz), 7.2–7.5 (12H, m, H7, H4, 10 × ArH), 8.51 (1H, s, NH), 11.5 (1H, s, NH); Found $(M + 1)^+$ 539.26580. $C_{32}H_{35}N_4O_4$ requires $(M + 1)^+$ 539.26583.

5-[2-(1-Benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylic acid (80). Method 2: white solid, 93 mg (95%); MS *m*/*z* 449 $(M + 1)^+$; ^{1}H NMR δ 1.8–2.0 (2H, m, CH_2Hyd), 2.52 (6H, s, 2 × NCH_3), 2.68 (2H, m, CH_2NMe_2), 2.98 (2H, m, 5-CH_2), 3.15 (2H, m, 3-CH_2), 4.1 (1H, m, CH), 4.5 (2H, s, CH_2Ph), 6.99 (1H, d, H6, *J* 8.0 Hz), 7.3 (7H, m, H7, H4, 5 × ArH), 8.5 (1H, s, NH), 11.0 (1H, s, NH); Found $(M + 1)^+$ 449.21845. $C_{25}H_{28}N_4O_4$ requires $(M + 1)^+$ 449.21888.

***N*-Benzyl-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (81).** Method 3: purification by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (100 : 8 : 1) gave 30 mg (77%) of **81** as a yellow powder. MS *m*/*z* 538 $(M + 1)^+$; ^{1}H NMR δ 1.7–1.9 (2H, m, CH_2Hyd), 2.02 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2), 2.69 (2H, m, 5-CH_2), 3.03 (2H, m, 3-CH_2, *J* 6.9 Hz), 4.1 (1H, m, CH), 4.5 (4H, m, HydCH_2Ph, CONHCH_2Ph), 7.02 (1H, d, H6, *J* 8.1 Hz), 7.3 (12H, m, H7, H4, 10 × ArH), 8.5 (1H, s, NH), 9.77 (1H, t, NH), 11.2 (1H, s, NH); Found M^+ 537.27126. $C_{32}H_{35}N_5O_3$ requires M^+ 537.27399.

Benzyl 3-[2-(dimethylamino)ethyl]-5-[2-(1-methyl-2,5-dioxoimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxylate (82). Method 1: (from ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-methylimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxylate[28,29]): white solid, 51 mg (79%); MS *m*/*z* 463 $(M + 1)^+$; ^{1}H NMR δ 1.90 (2H, m, CH_2CH), 2.0 (6H, s, 2 × NCH_3), 2.39 (2H, m, CH_2NMe_2), 2.72 (2H, m, 5-CH_2), 2.76 (3H, s, NCH_3), 3.13 (2H, m, 3-CH_2), 3.96 (1H, m, CH), 5.36 (2H, s, CH_2O), 7.12 (1H, d, H6, *J* 8.2 Hz), 7.3–7.5 (7H, m, H7, H4, 5 × ArH), 8.38 (1H, s, NH), 11.42 (1H, s, NH).

3-[2-(Dimethylamino)ethyl]-5-[2-(1-methyl-2,5-dioxoimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid (83). Method 2: white solid, 35 mg (87%); MS *m*/*z* 373 $(M + 1)^+$; ^{1}H NMR δ 1.87 (2H, m, CH_2), 2.28 (6H, s, 2 × NCH_3), 2.68 (2H, t, CH_2NMe_2, *J* 7.8 Hz), 2.77 (3H, s, NCH_3), 3.16 (2H, m, 3-CH_2), 3.3 (2H, m, 5-CH_2), 3.97 (1H, m, CH), 6.94 (1H, d, H6, *J* 8.7 Hz), 7.24 (1H, m, H7), 7.32 (1H, s, H4).

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(1-methyl-2,5-dioxoimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxamide (84).** Method 3: HCl salt of **84** as a white lyophilate, 14 mg (55%);

MS *m/z* 462 $(M + 1)^+$; ^{1}H NMR δ 1.83 (2H, m, CH_2CH), 2.03 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2 under DMSO), 2.68 (2H, t, 5-CH_2, *J* 8.1 Hz), 2.73 (3H, s, NCH_3), 3.01 (2H, m, 3-CH_2, *J* 6.3 Hz), 3.97 (1H, m, CH), 4.5 (2H, d, CH_2NHCO, *J* 5.7 Hz), 7.04 (1H, d, H6, *J* 8.7 Hz), 7.27 (7H, m, H7, H4, 5 × ArH), 8.3 (1H, s, NH), 9.76 (1H, t, NH, *J* 5.7 Hz), 11.24 (1H, s, NH); Found M^+ 461.24319. $C_{26}H_{31}N_5O_3$·1.0HCl requires M^+ 461.24269; R_f = 0.46 CH_2Cl_2–EtOH–NH_3 (60 : 8 : 1).

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