Synthesis and pharmacological profile of a series of 2,5-substituted-*N*,*N*-dimethyltryptamine derivatives as novel antagonists for the vascular 5-HT$_{1B}$-like receptor

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The coronary 5-HT$_{1B}$-like receptor has been implicated in vasospasm and it is postulated that a 5-HT$_{1B}$-like antagonist may block the detrimental action of 5-HT whilst not interfering with normal blood vessel function. The synthesis and pharmacological profile of a novel series of 2-(*N*-heteroaryl)carboxamido-5-substituted-*N*,*N*-dimethyltryptamine derivatives 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), competitive and selective 5-HT$_{1B}$-like receptor antagonists is described. Modifications to the 2-carboxamido sidechain as well as the 5-ethylene linked heterocycle are explored. *N*-Furfuryl-5-[2-(*N*-phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (**34**) was discovered which fulfilled our *in vitro* selection criteria and which had a favourable pharmacokinetic profile. Compound **34** showed good affinity (pK_B = 7.38) for the vascular 5-HT$_{1B}$-like receptor and greater than 125 fold selectivity over α_1-adrenoceptor affinity. The selectivity of **34** and related compounds for the 5-HT$_{1B}$-like receptor over other receptor subtypes is discussed and a mode of binding for this class of compound to a pharmacophore model is proposed.

Introduction

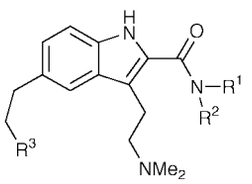
Our knowledge and understanding of the serotonin (5-HT) receptor family has continued to grow in recent years and it is now divided into seven major families based on pharmacological properties, second messenger coupling and sequence data.[1–3] Receptors 5-HT$_1$, 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$[4–9] comprise the main classes although gene products encoding other putative receptors such as 5-ht$_5$, 5-ht$_6$ and 5-HT$_7$ have been identified from cloning studies.[10–12] The 5-HT$_{1D}$ receptor has attracted considerable interest since it has been shown to be widely distributed in the central nervous system (CNS).[13] Vascular 5-HT$_1$ receptors very similar to the 5-HT$_{1B}$-like receptors in the brain have been identified in vascular smooth muscle and mediate contraction.[14] Studies by Weinshank and co-workers have identified two populations of human 5-HT$_{1D}$ receptors: 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors.[15] There have been a number of selective 5-HT$_{1D}$ agonists for vascular 5-HT$_{1D}$ receptors reported recently including sumatriptan,[16] zolmitriptan,[17,18] MSD AH 25086[19] and other related tryptamine derivatives.[20,21]

A series of benzanilides,[22] have been described as potent antagonists at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors and have been shown to block both peripheral and central responses mediated by both of these receptor types.[23] However, this compound is not a silent (as judged by the inability of angiotensin II to unmask 5-HT$_{1B}$-like receptor mediated agonist activity in the rabbit femoral artery) antagonist and behaves as a partial agonist at recombinant human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.[24] Moreover, the drug exhibits pseudo-irreversible pharmacodynamics, making it less than ideal for the quantitative study of 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.[23]

We recently reported a series of 2-ester-5-(2-ethyl-1-dioxoimidazolidinyl)-*N*,*N*-dimethyltryptamine derivatives as the first 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 receptors.[25] We also reported the discovery of some stable 2-*N*-(benzyl)carboxamido-5-(2-ethyl-1-dioxoimidazolidinyl)-*N*,*N*-dimethyltryptamine derivatives with similar pharmacological profiles.[26] Further to this work we now report on a related series of tryptamine derivatives with a range of heterocyclic 2-*N*-carboxamido substituents. 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. Compounds were sought which had high potency (pK_B > 7.0) and ideally 100 fold selectivity over other receptor subtypes, in particular the α_1-adrenoceptor so as to avoid hypotensive effects. It has been postulated that a compound fitting our biological profile may be a useful agent for the treatment of vasospastic disease states including Raynaud's phenomenon,[27–30] variant angina,[31,32] and intermittent claudication.[33–38] Present therapies for vasospastic angina include calcium channel blockers and nitrates which are non-specific and suffer from tolerance problems and cause peripheral vasodilation which can lead to hypotension and headaches. Neither of these treatments is effective in all patients, nor all the time in the same patient and so there is a need for a selective treatment with a low side effect profile, and a 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 vascular 5-HT_{1B}-like receptor antagonist may provide this.

We describe in this paper the synthesis, 5-HT_{1B}-like receptor activity and selectivity profile of a series of 2-*N*-carboxamido-5-substituted-*N*,*N*-dimethyltryptamine analogs **1** and related



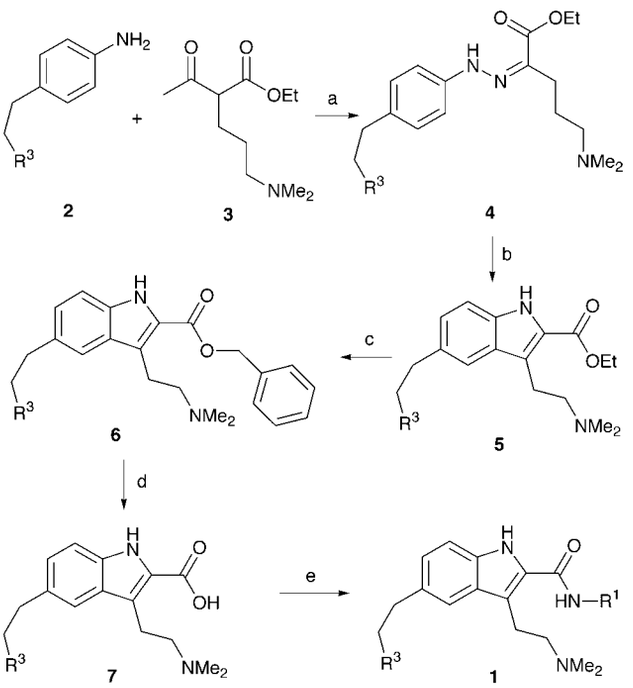
1

analogs. To explore the pharmacophore we have studied changes to the amide moiety R^1 and the heterocyclic moiety R^3 connected to the 5-position of the indole. Potential modes of binding to the pharmacophore model for several of the key compounds are discussed.

Results and discussion

Synthesis

The synthesis of the 2-*N*-carboxamido-5-substituted tryptamine derivatives proceeded *via* a Japp Klingemann indole synthesis as previously reported,[39,40] (Scheme 1). The desired

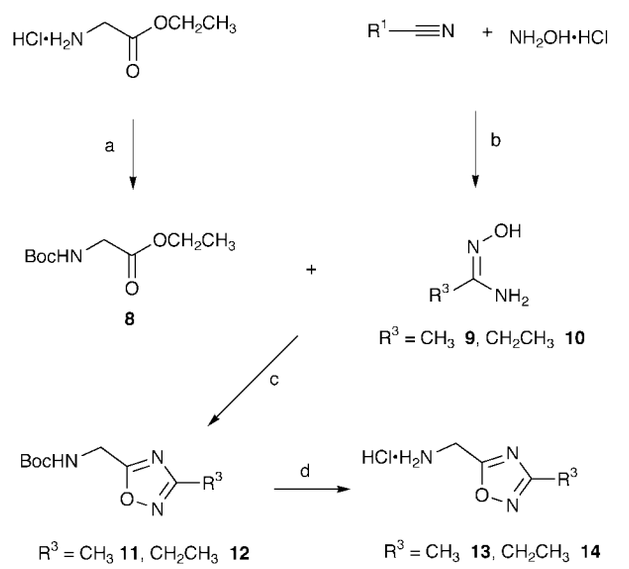


Scheme 1 *Reagents*: (a) $NaNO_2$, HCl, NaOH; (b) concentrated H_2SO_4, EtOH; (c) benzyl alcohol, $Ti(iOPr)_4$; (d) H_2, Pd–C (10%); (e) TBTU, DIPEA, R^1NH_2, DMF.

tryptamine derivatives were obtained in a 5-step pathway starting from a previously synthesized 4-substituted aniline derivative **2**.[25,26] Reaction with the β-keto ester **3** under basic conditions gave the hydrazone **4** which could be isolated and crystallized. Refluxing in ethanol in the presence of concentrated sulfuric acid gave the 2-ethyl ester tryptamine **5** which was then converted to the benzyl ester **6** by heating in benzyl alcohol in the presence of titanium tetraisopropoxide. Following trans-esterification, the 2-benzyl ester derivative was converted to the tryptamine-2-carboxylic acid **7** under hydrogenation conditions in the presence of 10% palladium on carbon at room temperature and atmospheric pressure. Amide coupling of the tryptamine-2-carboxylic acid with the desired methylamine derivative using TBTU and DIPEA in DMF gave the desired 2-*N*-carboxamido tryptamine **1**.

A range of methylene linked heterocyclic groups R^1 were incorporated into the 2-sidechain to explore the effect of increased polarity within this series. It was of interest to explore a range of 5-membered heteroaromatic groups and observe the effect substituents of different sizes had on potency and selectivity at the vascular 5-HT_{1B}-like receptor.

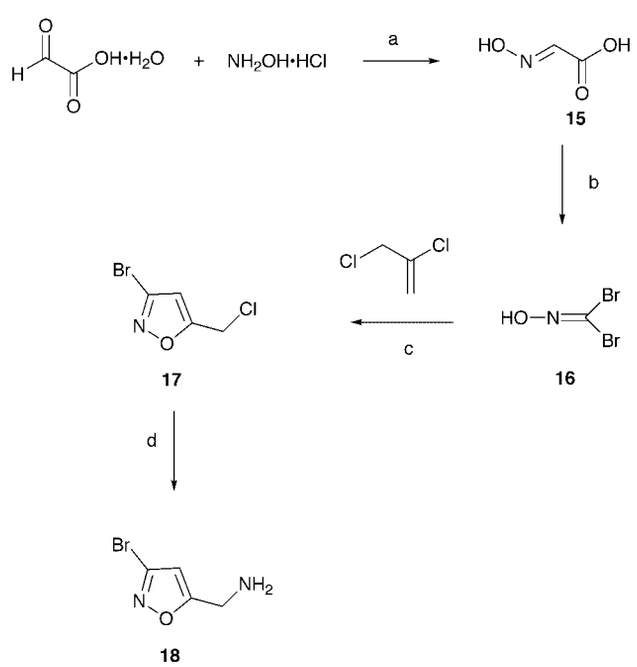
The heterocyclic methylamine derivatives required for the amide coupling were prepared in a variety of ways. The oxadiazole derivatives **13** and **14** were synthesized by coupling a previously formed oxime[41] with *tert*-butyloxycarbonyl protected glycine ethyl ester **8** (Scheme 2). Deprotection of the



Scheme 2 *Reagents*: (a) Boc_2O, CH_2Cl_2; (b) $NaOCH_3$, MeOH; (c) 3 Å sieves, NaH, THF; (d) TFA.

amines **11** and **12** with TFA afforded the desired methylamine derivatives **13** and **14** as TFA salts.[41]

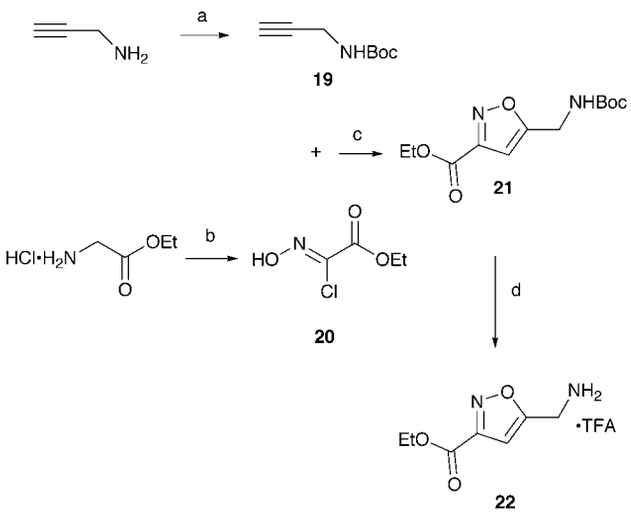
The isoxazole methylamine derivative **18** was synthesized *via* the method of Pevarello and Varasi (Scheme 3).[42] The bromo-



Scheme 3 *Reagents*: (a) H_2O, $NaHCO_3$, CH_2Cl_2; (b) Br_2; (c) $KHCO_3$, EtOAc; (d) 25% NH_4OH.

nitrile oxide **16** was formed by reaction of glyoxylic acid and hydroxylamine.[43,44] A 1,3-dipolar cycloaddition–elimination[44] of dibromoformaldoxime (**16**) with 2,3-dichloroprop-1-ene gave 5-chloromethyl-3-bromoisoxazole (**17**)[42] in good yield. Reaction of the alkyl chloride with 25% NH_4OH afforded the desired methylamino isoxazole **18**.[45]

The 3-ethyl ester isoxazole derivative **22** was synthesized by coupling of *tert*-butyloxycarbonyl protected propargylamine (prop-2-ynylamine) **19** with an ethyl oximino acetate derivative **20** (Scheme 4).[46] The oximino acetate **20** was previously formed



Scheme 4 *Reagents*: (a) Boc_2O, CH_2Cl_2; (b) concentrated HCl, $NaNO_2$, H_2O; (c) THF, Et_3N, Et_2O; (d) TFA.

by reaction of the ethyl ester of glycine with hydrochloric acid and sodium nitrite at ~5 °C. Deprotection of the intermediate isoxazole **21** with TFA afforded the desired aminomethyl isoxazole derivative **22** as the TFA salt.

A variety of heterocycles were incorporated onto the 5-sidechain to explore this area of the receptor including a range of hydantoin derivatives as well as several phthalimide derivatives (Table 1). The synthesis of these heterocyclic systems has been described previously.[25,26,47] The combination of the polar 5-membered heteroaromatic 2-*N*-carboxamido substituents and the various 5-ethylene linked heterocycles should afford more information about the vascular 5-HT_{1B}-like pharmacophore.

Activity

The compounds synthesized and their biological results are shown in Table 1.

In an effort to explain the biological results we have referred to a theoretical 5HT_{1B}-like receptor model which we have described previously.[18,25,26,47] This pharmacophore was constructed using the active analogue approach.[18,48] We have hypothesized that if the proposed important binding sites are occupied then the molecule will have high affinity and selectivity for the vascular 5-HT_{1B}-like receptor. The binding sites we refer to are a protonated amine site, an aromatic centre, a hydrophobic region, a hydrogen bonding acceptor site and a hydrogen bond donor–acceptor site and a 'selectivity' site for 5-HT_{1B}-like receptor over 5-HT_{2A} illustrated in Fig. 1.

As has been previously reported there is a spatial restriction on the size of the 2-carboxamido sidechain on the indole ring and bulkier groups result in steric interaction with the receptor.[25] We have postulated that in order to accommodate the large 2-substituent the molecule occupies a different position within the receptor or is 'displaced' resulting in the aromatic portion of the 2-sidechain occupying the aromatic binding site. The flexibility of the 5-ethyl linking chain allows the remainder

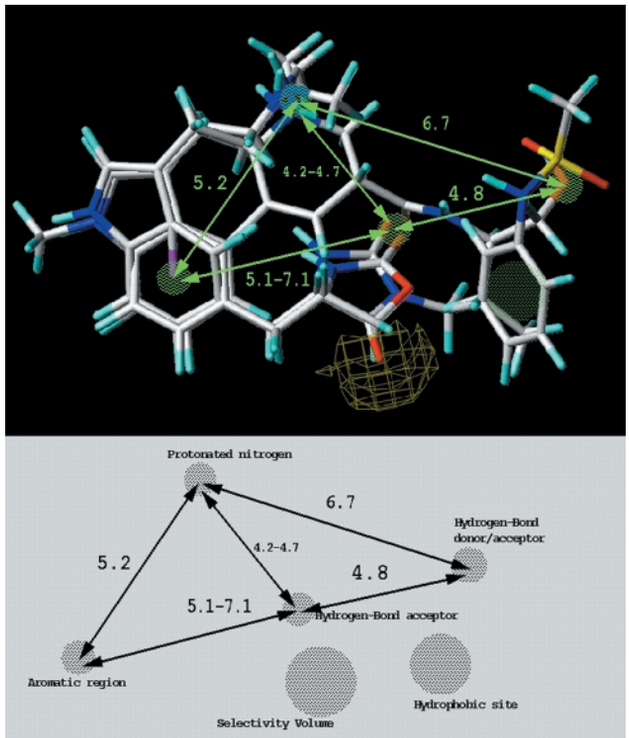


Fig. 1 Theoretical 5-HT_{1B}-like receptor model using *N*-benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-ethyl]-1*H*-indole-2-carboxamide (**24**)[26] as a reference and with methysergide as background.

of the molecule to orient so as to accurately interact with the remaining pharmacophoric sites.

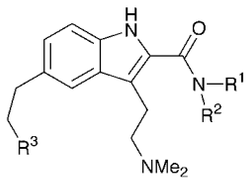
It was of interest to us to investigate the possibility of replacing the phenyl ring of the 2-*N*-carboxamido side chain with a range of heteroaromatic groups. Different heteroaromatic ring systems may result in molecules adopting varied conformations within the receptor and in turn have an impact on the compounds' pharmacological profiles. We also investigated a range of hydantoin-based ring systems in the 5-sidechain to assess the effect of subtle changes to the relative positions of important functional groups such as the hydantoin carbonyl groups on 5-HT_{1B}-like receptor potency.

Several pyridylmethylamido tryptamine derivatives were examined including **25** ($pK_B = 5.89$), **26** ($pK_B = 6.44$), **28** ($pK_B = 6.54$) and **29** ($pK_B = 6.38$). The biological results indicate that the inclusion of the nitrogen atom in the aromatic group of the 2-*N*-carboxamido sidechain is not well tolerated with affinity dropping by at least 0.5 log units relative to the 2-(*N*-benzyl)-carboxamido analog **24** ($pK_B = 7.09$).[26] It would appear that the differing electronic nature of the pyridyl group has a detrimental effect on 5-HT_{1B}-like receptor affinity a result which reflects the importance of the aromatic group of the 2-*N*-carboxamido sidechain in 5-HT_{1B}-like receptor binding.

A range of 2-furfurylamide derivatives were investigated. It would be expected that the slightly smaller 5-membered heteroaromatic group would result in a different conformation within the 5-HT_{1B}-like receptor relative to **24** which has a 2-(*N*-benzyl)carboxamido sidechain. Two compounds showed acceptable affinity at the 5-HT_{1B}-like receptor, **34** ($pK_B = 7.38$) containing a 5-ethylene linked phthalimide group and **36** ($pK_B = 7.16$) incorporating an *N*-benzyl substituted hydantoin group in the 5-sidechain. Both these compounds exhibited improved vascular 5-HT_{1B}-like receptor affinity relative to the 2-(*N*-benzyl)carboxamido tryptamine analogs.[26]

All other analogs containing hydantoin-based groups linked to the 5-position of the indole ring exhibited pK_B's < 7.0. It appears that the furan ring is able to substitute for the phenyl ring and bind at the aromatic binding site although with less

Table 1



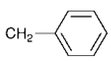
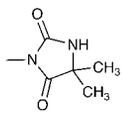
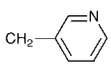
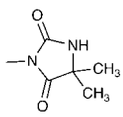
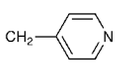
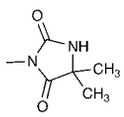
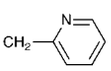
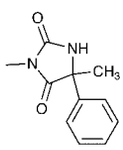
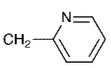
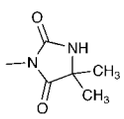
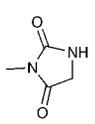
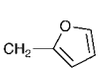
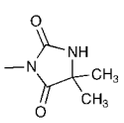
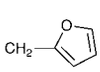
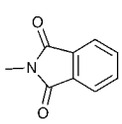
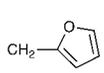
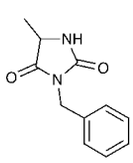
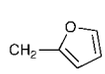
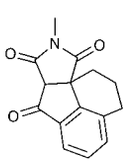
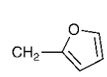
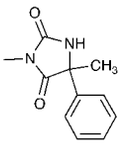
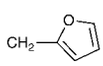
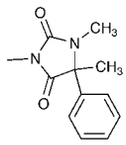
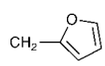
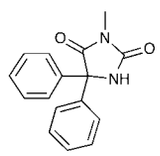
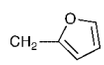
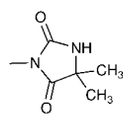
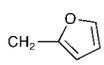
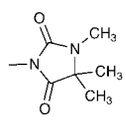
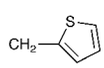
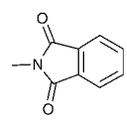
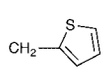
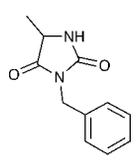
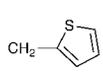
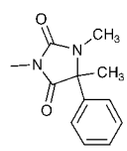
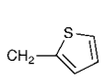
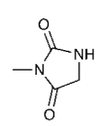
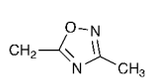
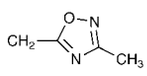
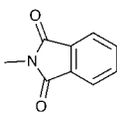
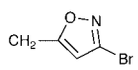
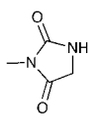
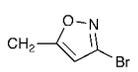
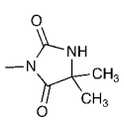
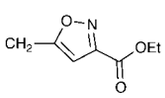
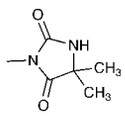
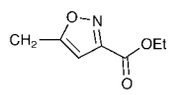
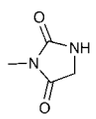
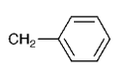
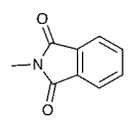
Compound Number	R^1	R^2	R^3	5-HT_{1B}-like RbSV[a] (pK_B)	$^{\alpha}$1 RbTA[a] (pK_B)
24[b]		H		7.09	5.20
25		H		5.89	4.8
26		H		6.44	<5.0
28		H		6.54	5.76
29		H		6.38	5.96
31		H		6.63	
32		H		6.75	
34		H		7.38	5.28
36		H		7.16	6.63
38		H		6.4	5.21
39		H		6.6	5.74
41		H		6.66	5.35
43		H		5.91	5.34
44		CH_3		<5.0	
45		CH_3		6.56	
46		H		7.22	5.45
47		H		6.83	5.94
48		H		6.69	5.24
49		H		7.25	5.97
50		H		5.61	
51		H		6.0	4.63

Table 1 (*Contd.*)

Compound Number	R^1	R^2	R^3	5-HT_{1B}-like RbSV[a] (pK_B)	α_1 RbTA[a] (pK_B)
52		H		7.23	5.47
53		H		6.15	5.25
54		H		6.39	
55		H		5.78	
56		H		5.61	
57[b]		H		7.33	5.55

[a] Affinity (pK_B : $-\log_{10}K_B$, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5-HT_{1B}-like receptor 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] Both compound **24**[26] and **57**[47] have been previously described.

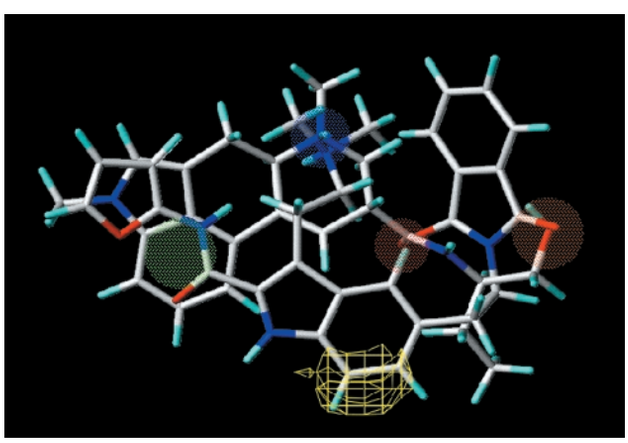


Fig. 2 Proposed conformation of **34** fitted to the 5-HT_{1B}-like receptor pharmacophore model.

potency than a phenyl ring. The improved potency of **34** and **36** may be due to the ability of the fused phenyl ring of the phthalimide group and the methyl-linked phenyl group of the *N*-benzylhydantoin ring system respectively to interact with a previously unreported hydrophobic pocket within the pharmacophore model. The proposed mode of binding of **34** is shown in Fig. 2.

In the conformation proposed in Fig. 2, the 3-ethylamine nitrogen can interact accurately with the amine binding site. The amide bond is slightly twisted from planarity but still energetically favourable allowing the furan ring to occupy the aromatic binding site. The 5-ethyl linked phthalimide sidechain is flexible and it is proposed that within the active site the sidechain adopts a conformation to allow one of the carbonyl groups to interact with the hydrogen bonding site. This conformation also allows for the other carbonyl of the hydantoin to interact with the proposed secondary hydrogen bonding site.[18,25] The selectivity site shown in yellow is occupied by part of the indole ring.

It was interesting to note the considerable decrease in potency observed for the *N*-methyl derivative **44** ($pK_B = 5.0$) compared with **32** ($pK_B = 6.75$). The *N*-methyl group appears to cause steric hindrance between the 2 and 3-sidechains not allowing the groups to take up optimal positions for binding.

Four 2-carboxamidomethylthiophene derivatives were investigated. As with the furfurylamide derivatives there was a decrease in overall affinity compared with the corresponding 2-(*N*-benzyl)-carboxamido tryptamine derivatives though the decrease was less. The compound with highest affinity from this group was **49** ($pK_B = 7.25$) with an hydantoin moiety in the 5-sidechain. However, it exhibited ~20 fold selectivity over α_1-adrenoceptor affinity. The phthalimide compound **46** ($pK_B = 7.22$) had slightly lower affinity but superior selectivity (~60 fold) over α_1-adrenoceptor affinity. It may be that substitution of the phenyl ring with a thiophene group has produced the required hydrophobic interaction but without steric hindrance.

Three 2-carboxamidomethyloxadiazole tryptamine derivatives **50**–**52** were investigated and only one of the compounds had a pharmacological profile comparable to the corresponding 2-(*N*-benzyl)carboxamido tryptamine analog. The phthalimide containing analog **52** ($pK_B = 7.23$) has similar potency to the 2-(*N*-benzyl)carboxamido analog **57** ($pK_B = 7.33$) and similar selectivity over α_1-adrenoceptor affinity (~1.78 fold), Table 1.

Four 2-*N*-carboxamidomethylisoxazole derivatives **53**–**56** were investigated. All four compounds showed low 5-HT_{1B}-like receptor affinity and poor selectivity for the 5-HT_{1B}-like receptor over α_1-adrenoceptor affinity. One possible explanation for the poor biological profile observed for **53**–**56** is the extra size of the heteroaromatic groups containing the 3-bromo and 3-ethyl ester groups and the subsequent effect these groups have on the overall configuration of the molecules within the 5-HT_{1B}-like receptor.

Conclusion

In this study we have identified a novel series of 2-*N*-carboxamido-5-substituted-*N*,*N*-dimethyltryptamine derivatives as antagonists for the vascular 5-HT_{1B}-like receptor. *N*-Furfuryl-5-[2-(*N*-phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (**34**) exhibited high 5-HT_{1B}-like receptor affinity ($pK_B = 7.38$) and showed that the furfurylamido group can successfully replace the 2-(*N*-benzyl)carboxamide group and interact with the proposed aromatic binding site. From this series, the phthalimide moiety in the 5-sidechain provided the most potent compounds. Analog **36** with an *N*-benzyl substituted hydantoin ring in the 5-sidechain also showed high 5-

HT_{1B}-like receptor affinity (pK_B = 7.16). These results appear to indicate there may be a hydrophobic binding region in the pharmacophore previously unrecognised.[26] All other substituted hydantoin derivatives investigated resulted in compounds with relatively low 5-HT_{1B}-like receptor affinity (pK_B's < 7.0). These results indicate a size restriction in this region of the pharmacophore. Compounds such as **34** may prove to be useful pharmacological 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.[49] 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 minute 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 (a) 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.[50] 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

Computational chemistry was performed on a Silicon Graphics Iris Indigo II using the Sybyl[51] molecular modelling software.

Unless otherwise stated, all ^1H 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, ether 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. Microanalysis 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 multiwavelength 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.

***N*-(3-Pyridylmethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (25).** Method 1: 3-aminomethylpyridine (14.5 μL, 0.14 mmol) was added to a stirred solution of 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-ethyl]-1*H*-indole-2-carboxylic acid **23**[26] (50 mg, 0.13 mmol) and TBTU (46 mg, 0.14 mmol) in DMF (5 mL). DIPEA (27 μL, 0.16 mmol) was added and the solution was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure and the residue purified by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150 : 8 : 1) to give 48 mg (73%) of **25** as a white foam. MS *m*/*z* 477 $(M + 1)^+$; ^1H NMR δ 1.19 (6H, s, 2 × CH_3), 2.13 (6H, s, 2 × NCH_3), 2.54 (2H, m, CH_2NMe_2, under DMSO), 2.95 (2H, t, CH_2N, J 6.3 Hz), 3.08 (2H, m, 5-CH_2), 3.62 (2H, m, 3-CH_2), 4.55 (2H, d, CH_2NH), 7.05 (1H, d, H6), 7.32 (4H, m, H7, H4, 2 × ArH), 8.1 (1H, s, NH), 8.53 (2H, d, 2 × ArH), 9.79 (1H, t, NH), 11.17 (1H, s, NH); Found M^+ 476.25311. $C_{26}H_{32}N_6O_3$ requires M^+ 476.25359. HPLC retention time = 12.5 min.

***N*-(4-Pyridylmethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (26).** Method 1: cream powder, 10.5 mg (11%); MS *m*/*z* 476 (M^+); ^{1}H NMR δ 1.2 (6H, s, 2 × CH_3), 2.19 (6H, s, 2 × NCH_3), 2.6 (2H, m, CH_2NMe_2, under DMSO), 2.98 (2H, t, CH_2N, *J* 6.3 Hz), 3.12 (2H, m, 5-CH_2), 3.67 (2H, m, 3-CH_2), 4.6 (2H, d, CH_2NH), 7.09 (1H, d, H6), 7.38 (4H, m, H7, H4, 2 × ArH), 8.16 (1H, s, NH), 8.53 (2H, d, 2 × ArH), 9.77 (1H, t, NH), 11.25 (1H, s, NH); Found M^+ 476.25436. $C_{26}H_{32}N_6O_3$ requires M^+ 476.25359. HPLC retention time = 12.01 min.

***N*-(2-Pyridylmethyl)-5-[2-(4-phenyl-4-methyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (28).** Method 1 (using 3-[2-(dimethylamino)-ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxoimidazolidin-1-yl)-ethyl]-1*H*-indole-2-carboxylic acid **27**).[26] White lyophilate, 50 mg (83%) (mp 75–77 °C); MS *m*/*z* 539 $(M + 1)^+$; ^{1}H NMR δ 1.5 (3H, s, CH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.79 (6H, s, 2 × NCH_3), 2.95 (2H, t, CH_2N, *J* 6.3 Hz), 3.1 (2H, m, 5-CH_2), 3.3 (2H, m, 3-CH_2), 4.59 (2H, d, CH_2NH, *J* 5.2 Hz), 6.99–7.78 (12H, m, 12 × ArH); Found M^+ 538.27054. $C_{31}H_{34}N_6O_3$ requires M^+ 538.26924. HPLC retention time = 11.0 min.

***N*-(2-Pyridylmethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (29).** Method 1: purification by HPLC afforded 39 mg (42%) of the acetate salt of **29** as a white powder (mp 75–77 °C) (Found C, 59.93; H, 6.99; N, 14.97. $C_{26}H_{32}N_6O_3 \cdot 1.25H_2O \cdot 1.0CH_3CO_2H$ requires C, 63.14; H, 6.94; N, 15.03%); MS *m*/*z* 476 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (3H, s, CH_3CO_2H), 2.09 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.95 (2H, m, CH_2N), 3.05 (2H, m, 5-CH_2), 3.3 (2H, m, 3-CH_2, under water peak), 3.6 (2H, m, CH_2Hyd), 4.6 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.3 (4H, m, H7, H4, 2 × PyrH), 7.8 (1H, m, PyrH), 8.15 (1H, s, NH), 8.5 (1H, d, PyrH), 9.8 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{26}H_{32}N_6O_3 \cdot 1.25H_2O \cdot 1.0CH_3CO_2H$) C, H, N.

***N*-Furfuryl-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (31).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **30**).[26] HCl salt of **31** as a yellow lyophilate, 33 mg (53%); MS *m*/*z* 438 $(M + 1)^+$; ^{1}H NMR δ 2.07 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.86 (2H, t, CH_2N, *J* 8.1 Hz), 3.01 (2H, t, 5-CH_2, *J* 6.0 Hz), 3.15 (2H, m, 3-CH_2), 3.83 (2H, s, HydCH_2), 4.53 (2H, d, CH_2NH, *J* 5.1 Hz), 6.33 (1H, d, CH=C, *J* 3.3 Hz), 6.41 (1H, d, CH=C, *J* 1.8 Hz), 7.0 (1H, dd, H6, *J* 1.5, 8.4 Hz), 7.3 (2H, m, H7, H4), 7.98 (1H, s, CH=C), 8.3 (1H, s, NH), 9.92 (1H, t, NH, *J* 4.8 Hz), 11.24 (1H, s, NH); Found M^+ 437.20630. $C_{23}H_{27}N_5O_4 \cdot HCl$ requires M^+ 437.20661. HPLC retention time = 11.97 min.

***N*-Furfuryl-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (32).** Method 1: pale yellow solid, 81 mg (42%); MS *m*/*z* 466 $(M + 1)^+$; ^{1}H NMR δ 1.13 (3H, s, 2 × CH_3), 2.06 (6H, s, 2 × NCH_3), 2.85 (2H, m, CH_2NMe_2), 2.9 (2H, m, CH_2N), 3.0 (2H, m, 5-CH_2), 3.6 (2H, m, 3-CH_2, *J* 6.9 Hz), 4.5 (2H, d, CH_2NH, *J* 5.1 Hz), 6.34 (1H, d, CH=C, *J* 3.0 Hz), 6.41 (1H, d, CH=C, *J* 2.8 Hz), 7.0 (1H, d, H6, *J* 8.4 Hz), 7.28 (2H, m, H7, H4), 7.6 (1H, s, CHO), 8.1 (1H, s, NH), 9.9 (1H, t, NH), 11.2 (1H, s, NH); Found M^+ 465.23897. $C_{25}H_{31}N_5O_4$ requires M^+ 465.23760.

***N*-Furfuryl-5-[2-(phthalimido)ethyl]-3-[2-(dimethylamino)-ethyl]-1*H*-indole-2-carboxamide (34).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)-ethyl]-1*H*-indole-2-carboxylic acid **33**):[47] yellow powder, 22 mg (59%); MS *m*/*z* 485 $(M + 1)^+$; ^{1}H NMR δ 1.93 (6H, s, 2 × NCH_3), 2.22 (2H, m, CH_2NMe_2), 2.84 (2H, m, CH_2N), 2.93 (2H, m, 5-CH_2), 3.78 (2H, m, 3-CH_2), 4.44 (2H, d, CH_2NH, *J* 5.7 Hz), 6.25 (1H, d, CH=C, *J* 3.0 Hz), 6.35 (1H, d, CH=C, *J* 3.0 Hz), 7.01 (1H, d, H6, *J* 8.4 Hz), 7.2 (2H, m, H7, H4), 7.74 (4H, m, 4 × ArH), 8.05 (1H, s, NH), 9.8 (1H, t, NH), 11.15 (1H, s, NH); Found M^+ 484.21094. $C_{28}H_{28}N_4O_4$ requires M^+ 484.21106.

***N*-Furfuryl-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (36).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)-ethyl]-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid **35**):[47] yellow powder, 30 mg (79%); MS *m*/*z* 528 $(M + 1)^+$; ^{1}H NMR δ 1.93 (6H, s, 2 × NCH_3), 2.22 (2H, m, CH_2NMe_2), 2.84 (2H, m, CH_2N), 2.93 (2H, m, 5-CH_2), 3.78 (2H, m, 3-CH_2), 4.44 (2H, d, CH_2NH, *J* 5.7 Hz), 6.25 (1H, d, CH=C, *J* 3.0 Hz), 6.35 (1H, d, CH=C, *J* 3.0 Hz), 7.01 (1H, d, H6, *J* 8.4 Hz), 7.2 (2H, m, H7, H4), 7.74 (4H, m, 4 × ArH), 8.05 (1H, s, NH), 9.8 (1H, t, NH), 11.15 (1H, s, NH); Found M^+ 527.25198. $C_{30}H_{33}N_5O_4$ requires M^+ 527.25325.

***N*-Furfuryl-5-[2-(1,3,4-trioxo-2,3,5,6,10,10a-hexahydro-1*H*,*H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (38).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)ethyl]-5-[2-(1,3,4-trioxo-2,3,5,6,10,10a-hexahydro-1*H*, *H*-acenaptho[1,8a-*c*]pyrrolyl)ethyl]-1*H*-indole-2-carboxylic acid **37**):[47] yellow powder, 13.5 mg (47%); MS *m*/*z* 579 $(M + 1)^+$; ^{1}H NMR δ 1.59 (3H, s, CCH_3), 2.04 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.59 (3H, s, NCH_3), 2.97 (4H, m, CH_2N, 5-CH_2), 3.71 (2H, m, 3-CH_2), 4.51 (2H, d, CH_2NH, *J* 5.4 Hz), 6.34 (1H, m, CH=C), 6.41 (1H, m, CH=C), 7.01 (3H, m, H6, 2 × ArH), 7.24 (5H, m, 5 × ArH), 7.6 (1H, m, CH-O), 9.9 (1H, t, NH), 11.71 (1H, s, NH); Found M^+ 578.24901. $C_{34}H_{34}N_4O_5$ requires M^+ 578.25292.

***N*-Furfuryl-5-[2-(4-phenyl-4-methyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (39).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)-ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxoimidazolidin-1-yl)-ethyl]-1*H*-indole-2-carboxylic acid **27**):[26] HCl salt of **39** as a white lyophilate, 34 mg (58%); MS *m*/*z* 528 $(M + 1)^+$; ^{1}H NMR δ 1.23 (3H, s, CH_3), 2.82 (6H, s, 2 × NCH_3), 2.92 (2H, m, CH_2NMe_2), 3.15 (4H, s, CH_2N, 5-CH_2), 3.68 (2H, m, 3-CH_2), 4.51 (2H, d, CH_2NH, *J* 4.9 Hz), 6.36 (1H, m, CH=C), 6.43 (1H, m, CH=C), 7.03 (1H, d, H6, *J* 9.0 Hz), 7.27 (6H, m, H7, 5 × ArH), 7.46 (1H, s, CHO), 8.62 (1H, m, $NHMe_2$), 8.7 (1H, s, NH), 9.71 (1H, t, NH), 11.44 (1H, s, NH); Found M^+ 527.25123. $C_{30}H_{33}N_5O_4$ requires M^+ 527.25325.

***N*-Furfuryl-5-[2-(4-phenyl-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (41).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)ethyl]-5-[2-(4-phenyl-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **40**):[26] HCl salt of **41** as a fluffy white solid, 50 mg (66%) (Found C, 58.39; H, 5.88; N, 10.72. $C_{31}H_{35}N_5O_4 \cdot 1.0HCl$ requires C, 59.0; H, 6.60; N, 11.10%); MS *m*/*z* 542 $(M + 1)^+$; ^{1}H NMR δ 1.59 (3H, s, CCH_3), 2.04 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.59 (3H, s, NCH_3), 2.97 (4H, m, CH_2N, 5-CH_2), 3.71 (2H, m, 3-CH_2), 4.51 (2H, d, CH_2NH, *J* 5.4 Hz), 6.34 (1H, m, CH=C), 6.41 (1H, m, CH=C), 7.01 (3H, m, H6, 2 × ArH), 7.24 (5H, m, 5 × ArH), 7.6 (1H, m, CHO), 9.9 (1H, t, NH), 11.19 (1H, s, NH). Anal. ($C_{31}H_{35}N_5O_4 \cdot 1.0HCl$) C, H, N.

***N*-Furfuryl-5-[2-(4,4-diphenyl-2,5-dioxoimidazolidin-1-yl)-ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (43).** Method 1 (using furfurylamine and 3-[2-(dimethylamino)-ethyl]-5-[2-(4,4-diphenyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **42**):[26] HCl salt of **43** as a fluffy white solid, 27 mg (33%) (Found C, 55.89; H, 5.30; N, 9.12. $C_{35}H_{35}$-

N_5O_4·2.0HCl·5.0H_2O requires C, 55.84; H, 6.29; N, 9.30%); MS *m*/*z* 590 $(M + 1)^+$; ^{1}H NMR δ 2.02 (6H, s, 2 × NCH_3), 2.47 (2H, m, CH_2NMe_2), 2.80 (2H, m, NCH_2), 2.90 (2H, m, 5-CH_2), 3.73 (2H, m, 3-CH_2), 4.51 (2H, d, CH_2NH, *J* 5.4 Hz), 6.34 (1H, m, CH=C), 6.42 (1H, m, CH=C), 6.95 (1H, d, H6, *J* 8.4 Hz), 7.01–7.29 (13H, m, 12 × ArH, CH-O), 9.43 (1H, s, NH), 9.92 (1H, t, NH), 11.19 (1H, s, NH). Anal. ($C_{35}H_{35}N_5O_4$·2.0HCl·5.0H_2O) C, H, N.

***N*-Furfuryl-*N*-methyl-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (44).** Method 2: to a solution of **32** (59 mg, 0.11 mmol) in dry THF (3.0 mL) was added sodium hydride (4.3 mg, 0.11 mmol) and the solution was stirred at room temperature under nitrogen for 1.5 h. Dimethyl sulfate (11.0 μL, 0.11 mmol) was added and the reaction mixture stirred overnight. The solution was evaporated under reduced pressure and the residue suspended in water and extracted with ethyl acetate. The organic layer was dried, filtered and the solvent reduced *in vacuo* to give a yellow solid which was purified by flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (300 : 8 : 1) to give 15.6 mg (30%) of **44** as a yellow solid which was converted to the HCl salt. R_f = 0.26 (CH_2Cl_2–EtOH–NH_3, 150 : 8 : 1); MS *m*/*z* 480 $(M + 1)^+$; ^{1}H NMR ($(CD_3)_2CO$) δ 1.25 (6H, s, 2 × CH_3), 2.10 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2), 2.8 (3H, s, NCH_3), 3.43 (4H, m, CH_2N, 5-CH_2), 3.7 (2H, m, 3-CH_2), 4.55 (2H, d, CH_2NH, *J* 5.3 Hz), 6.35 (2H, m, 2 × CH=C), 7.25 (1H, d, H6, *J* 8.1 Hz), 7.45 (2H, m, H7, H4), 7.53 (1H, s, CHO), 10.3 (1H, br s, NH), 10.65 (1H, br s, NH); Found M^+ 479.25431. $C_{26}H_{33}N_5O_4$ requires M^+ 479.25325.

***N*-Furfuryl-*N*-methyl-5-[2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (45).** Method 2: purification by flash chromatography eluting with CH_2Cl_2–EtOH–NH_3 (300 : 8 : 1) gave 11.5 mg (22%) of **45** as a yellow solid which was converted to the HCl salt. R_f = 0.21 (CH_2Cl_2–EtOH–NH_3, 150 : 8 : 1); MS *m*/*z* 494 $(M + 1)^+$; ^{1}H NMR ($(CD_3)_2CO$) δ 1.21 (6H, s, 2 × CH_3), 2.06 (6H, s, 2 × NCH_3), 2.6 (2H, m, CH_2NMe_2), 2.81 (3H, s, NCH_3), 3.0 (4H, m, CH_2N, 5-CH_2), 3.7 (2H, m, 3-CH_2), 3.87 (3H, s, NCH_3), 4.61 (2H, d, NHCH_2, *J* 5.34 Hz), 6.4 (2H, m, 2 × CH=C), 7.15 (1H, d, H6, *J* 8.0 Hz), 7.35 (2H, m, H7, H4), 7.5 (1H, s, CHO), 10.45 (1H, br s, NH); Found M^+ 493.27268. $C_{27}H_{35}N_5O_4$ requires M^+ 493.26890.

***N*-(2-Methylthienyl)-5-[2-(phthalimido)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (46).** Method 1 (using methylaminothiophene and 3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)ethyl]-1*H*-indole-2-carboxylic acid **33**):[47] yellow powder, 23 mg (55%); MS *m*/*z* 501 $(M + 1)^+$; ^{1}H NMR δ 1.97 (6H, s, 2 × NCH_3), 2.26 (2H, m, CH_2NMe_2), 2.85 (2H, m, CH_2N), 2.95 (2H, m, 5-CH_2), 3.8 (2H, t, 3-CH_2, *J* 6.9 Hz), 4.65 (2H, d, CH_2NH, *J* 5.7 Hz), 6.96 (1H, m, CH=C), 7.04 (2H, m, CH=C, H6), 7.23 (2H, m, H7, H4), 7.39 (1H, m, CH-S), 7.79 (4H, s, PhthH), 9.9 (1H, t, *NH*CH_2, *J* 5.4 Hz), 11.12 (1H, s, NH); Found M^+ 500.19050. $C_{28}H_{28}N_4O_3S$ requires M^+ 500.18821.

***N*-(2-Methylthienyl)-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (47).** Method 1 (using methylaminothiophene and 3-[2-(dimethylamino)ethyl]-5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-1*H*-indole-2-carboxylic acid **35**):[47] Yellow powder, 20 mg (37%); MS *m*/*z* 544 $(M + 1)^+$; ^{1}H NMR δ 1.8 (2H, m, CH_2CH), 2.07 (6H, s, 2 × NCH_3), 2.51 (2H, m, CH_2NMe_2 under DMSO), 2.69 (2H, m, 5-CH_2), 3.01 (2H, m, 3-CH_2), 4.1 (1H, m, CH), 4.48 (2H, s, CH_2Ph), 4.67 (2H, d, CH_2NH, *J* 5.4 Hz), 7.02 (3H, m, 3 × ArH), 7.28 (8H, m, 8 × ArH), 8.52 (1H, s, NH), 10.02 (1H, t, NH), 11.19 (1H, s, NH); Found M^+ 543.23164. $C_{30}H_{33}N_5O_3S$ requires M^+ 543.23041.

***N*-(2-Methylthienyl)-5-[2-(4-phenyl-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (48).** Method 1 (using methylaminothiophene and 3-[2-(dimethylamino)ethyl]-5-[2-(4-phenyl-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **40**):[26] HCl salt of **48** as a fluffy white solid, 51 mg (71%) (Found C, 59.30; H, 6.11; N, 10.87. $C_{31}H_{35}N_5O_3$·1.0HCl·1.75H_2O requires C, 59.5; H, 6.11; N, 10.87%); MS *m*/*z* 558 $(M + 1)^+$; ^{1}H NMR δ 1.58 (3H, s, CH_3), 2.04 (6H, s, 2 × NCH_3), 2.47 (2H, m, CH_2NMe_2), 2.58 (3H, s, NCH_3), 2.98 (4H, m, 5-CH_2, NCH_2), 3.72 (2H, m, 3-CH_2), 4.68 (2H, d, CH_2NH, *J* 5.7 Hz), 6.98 (5H, m, H6, H7, 2 × CH=C, 1 × ArH), 7.24 (6H, m, H4, CHS, 4 × ArH), 10.03 (1H, t, *NH*CH_2, *J* 5.4 Hz), 11.25 (1H, s, NH). Anal. ($C_{31}H_{35}N_5O_3$·1.0HCl·1.75H_2O) C, H, N.

***N*-(Methylthienyl)-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (49).** Method 1 (using methylaminothiophene and 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **30**):[26] HCl salt of **49** as an off-white powder, 30.3 mg (48%); MS *m*/*z* 454 $(M + 1)^+$; ^{1}H NMR δ 2.08 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO), 2.87 (2H, m, CH_2N, *J* 8.1 Hz), 3.01 (2H, m, 5-CH_2, *J* 5.7 Hz), 3.57 (2H, m, 3-CH_2, *J* 6.9 Hz), 3.83 (2H, s, HydCH_2), 4.67 (2H, d, CH_2NH, *J* 5.7 Hz), 7.04 (3H, m, H6, H2′, H3′), 7.3 (3H, m, H7, H4, H4′), 7.97 (1H, s, NH), 10.02 (1H, t, NH, *J* 5.1 Hz), 11.24 (1H, s, NH); Found M^+ 453.18346. $C_{23}H_{27}N_5O_3S$·HCl requires M^+ 453.18151. HPLC retention time = 12.77 min.

(*N*-*tert*-Butyloxycarbonyl)glycine ethyl ester (8). Glycine ethyl ester (13.9 g, 0.1 mol) was combined with a mixture of water (191 mL), dioxane (350 mL) and 1 M NaOH (190 mL). To this mixture was added di-*tert*-butyl dicarbonate (24.0 g, 0.2 mol) dropwise while maintaining the mixture at 0–5 °C. The solution was stirred overnight at room temperature. Dioxane–water was removed under reduced pressure and the remaining residue was extracted with ethyl acetate, dried and the solvent evaporated under reduced pressure to give an oil which was distilled to give the 11.5 g (56%) of **8** as a clear oil. MS *m*/*z* 204 $(M + 1)^+$; ^{1}H NMR δ 1.17 (3H, t, CH_2CH_3, *J* 7.1 Hz), 1.38 (9H, s, 3 × CH_3), 3.59 (2H, d, CH_2NH, *J* 6.2 Hz), 4.07 (2H, q, CH_2CH_3, *J* 7.3 Hz), 7.17 (1H, br t, NH).

(*N*-*tert*-Butyloxycarbonyl)-3-methyl-1,2,4-oxadiazol-5-ylmethylamine (11). Method 3: the oxime **9** (1.44 g, 19.0 mmol) was added to a stirred suspension of powdered 3 Å sieves (3.0 g) in THF (200 mL) under nitrogen. After 15 min sodium hydride (1.3 g, 32.0 mmol) was added and stirring continued for a further 40 min. The amino acid **8** (2.0 g, 9.7 mmol) in THF (40 mL) was added and the reaction mixture was refluxed overnight. The reaction mixture was cooled, filtered over Celite and the solvent removed under reduced pressure. The resulting oil was partitioned between CH_2Cl_2 and water. The combined organic extracts were dried and the solvent removed. The crude product was purified by column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (300 : 8 : 1) to give 1.14 g (55%) of **11** as a pale yellow oil. MS *m*/*z* 214 $(M + 1)^+$; ^{1}H NMR δ 1.38 (9H, s, 3 × CH_3), 2.3 (3H, s, CH_3), 4.36 (2H, d, CH_2NH), 7.61 (1H, br t, NH).

(*N*-*tert*-Butyloxycarbonyl)-3-ethyl-1,2,4-oxadiazol-5-ylmethylamine (12). Method 3 (using *N*-hydroxypropanimidamide **10**): bp 150 °C at 0.1 mmHg (145 °C at 0.05 mmHg).[41] MS *m*/*z* 203 (M^+).

3-Methyl-1,2,4-oxadiazolylmethylamine[41] (13). Method 4: to the *N*-protected oxadiazole derivative **11** (0.34 g, 1.6 mmol) was added 1,4-dioxane (24 mL) and 1 M HCl (28 mL). The mixture was allowed to stir at room temperature for 2 h. The solvent was removed under vacuum and the resultant oil was triturated with

acetonitrile to afford white crystals. Conversion to the HCl salt and recrystallisation from acetonitrile afforded 0.11 g (61%) of the HCl salt of **13** as white crystals (mp 177 °C (dec)) (Found C, 31.93; H, 5.25; N, 27.41. $C_4H_7N_3O{\cdot}1.0HCl{\cdot}0.3H_2O$ requires C, 31.8; H, 5.39; N, 27.83%); MS *m*/*z* 114 $(M + 1)^+$; ^{1}H NMR δ 2.3 (3H, s, CH_3), 4.45 (2H, s, CH_2), 8.67 (3H, s, NH_3^+). Anal. ($C_4H_7N_3O{\cdot}1.0HCl{\cdot}0.3H_2O$) C, H, N.

3-Ethyloxadiazolymethylamine (14). Method 4: HCl salt of **14**, 120 mg (70%); mp 160–162 °C (lit.,[41] mp 158–161 °C); MS *m*/*z* 127 (M^+) (Found C, 36.10; H, 5.99; N, 25.44. $C_5H_9N_3O{\cdot}1.0HCl$ requires C, 35.80; H, 5.84; N, 24.86).

***N*-[5-(3-Methyl)-1,2,4-oxadiazolymethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (50).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **23**):[26] HCl salt of **50** as a yellow lyophilate, 51.7 mg (92%); MS *m*/*z* 482 $(M + 1)^+$; ^{1}H NMR δ 1.12 (6H, s, 2 × CH_3), 2.16 (6H, s, 2 × NCH_3), 2.31 (3H, s, OxadCH_3), 2.53 (2H, m, CH_2NMe_2), 2.91 (2H, t, CH_2N, *J* 7.5 Hz), 3.02 (2H, t, 5-CH_2, *J* 5.7 Hz), 3.59 (2H, t, 3-CH_2, *J* 6.9 Hz), 4.76 (2H, d, CH_2NH, *J* 5.4 Hz), 7.0 (1H, dd, H6, *J* 1.5, 6.9 Hz), 7.27 (2H, m, H7, H4), 8.11 (1H, s, NH), 10.31 (1H, t, NH, *J* 5.7 Hz), 11.29 (1H, s, NH); Found M^+ 481.25404 $C_{24}H_{31}N_7O_4{\cdot}HCl$ requires M^+ 481.24378. HPLC retention time = 10.81 min.

***N*-[5-(3-Methyl)-1,2,4-oxadiazol-5-ylmethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4-methyl-4-phenyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (51).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(4-methyl-4-phenyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **27**):[26] HCl salt of **51** as a yellow lyophilate, 24 mg (35%); MS *m*/*z* 544 $(M + 1)^+$; ^{1}H NMR δ 1.53 (3H, s, HydCH_3), 2.15 (6H, s, 2 × NCH_3), 2.32 (3H, s, OxadCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.91 (2H, m, CH_2N), 2.99 (2H, m, 5-CH_2), 3.65 (2H, m, 3-CH_2), 4.77 (2H, d, CH_2NH, *J* 5.1 Hz), 6.98 (1H, d, H6, *J* 8.1 Hz), 7.28 (7H, m, H7, H4, 5 × ArH), 8.75 (1H, s, NH), 10.3 (1H, t, NH), 11.23 (1H, s, NH); Found M^+ 543.25337. $C_{29}H_{33}N_7O_4{\cdot}HCl$ requires M^+ 543.25940. R_f = 0.37 CH_2Cl_2–EtOH–NH_3 (80 : 8 : 1).

***N*-[5-(3-Methyl)-1,2,4-oxadiazol-5-ylmethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)ethyl]-1*H*-indole-2-carboxamide (52).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(phthalimido)ethyl]-1*H*-indole-2-carboxylic acid **33**):[47] HCl salt of **52** as a white lyophilate, 14 mg (23%); MS *m*/*z* 501 $(M + 1)^+$; ^{1}H NMR δ 2.07 (6H, s, 2 × NCH_3), 2.27 (3H, s, OxadCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.98 (4H, m, CH_2N, 5-CH_2), 3.38 (2H, m, 3-CH_2), 4.74 (2H, d, CH_2NH, *J* 5.7 Hz), 7.06 (1H, d, H6, *J* 6.6 Hz), 7.28 (2H, m, H7, H4), 7.8 (4H, s, 4 × ArH), 10.32 (1H, t, NH, *J* 5.4 Hz), 11.29 (1H, s, NH); Found M^+ 500.21297. $C_{27}H_{28}N_6O_4{\cdot}HCl$ requires M^+ 500.21720. R_f = 0.7, CH_2Cl_2–EtOH–NH_3 (80 : 8 : 1).

Dibromoformaldoxime (16).[42,43,45] Yellow solid, 19.8 g (45%) (mp 68–70 °C, lit.,[42] 65–66 °C) (Found C, 5.37; H, 0.43; N, 6.41. $CHNOBr_2$ requires C, 5.37; H, 0.70; N, 6.72%); MS *m*/*z* 197 (M^+) 203 (1:3:1); ^{1}H NMR δ 12.83 (1H, s, OH). Anal. ($CHNOBr_2{\cdot}0.3H_2O$) C, H, N.

5-Chloromethyl-3-bromoisoxazole (17).[42] Yellow oil, 6.19 g (80%); MS *m*/*z* 197 $(M + 1)^+$; ^{1}H NMR δ 4.63 (2H, s, CH_2Cl), 6.43 (1H, s, CH=C).

5-Aminomethyl-3-bromoisoxazole (18).[42] Yellow crystals, 417 mg (70%) (mp 117–118 °C); MS *m*/*z* 176 $(M + 1)^+$; ^{1}H NMR δ 3.75 (2H, s, CH_2), 6.53 (1H, s, CH=C), 9.74 (2H, s, NH_2); Found M^+ 176.00451. $C_4H_5N_2OBr$ requires M^+ 175.95852.

***N*-[5-(3-Bromo)-1,2-oxazol-5-ylmethyl]-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (53).** Method 1 (using 3-[2-(dimethylamino)-ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **30**):[26] HCl salt of **53** as a white lyophilate, 8.5 mg (12%); MS *m*/*z* 517, 519 $(M + 1)^+$, $(M+3)^+$; ^{1}H NMR δ 2.14 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO), 2.86 (2H, m, CH_2N, *J* 7.0 Hz), 3.03 (2H, m, 5-CH_2), 3.56 (2H, m, 3-CH_2, *J* 6.6 Hz), 3.82 (2H, s, HydCH_2), 4.6 (2H, d, CH_2NH, *J* 5.1 Hz), 6.74 (1H, s, CH=CBr), 7.05 (1H, m, H6), 7.31 (2H, m, H7, H4), 7.98 (1H, s, NH), 10.17 (1H, t, $NHCH_2$, *J* 5.0 Hz), 11.31 (1H, s, NH); Found M^+ 516.10881. $C_{22}H_{25}N_6O_4Br{\cdot}HCl$ requires M^+ 516.11206. HPLC retention time = 12.56 min.

***N*-[5-(3-Bromo)-1,2-oxadiazol-5-ylmethyl]-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (54).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **23**):[26] HCl salt of **54** as a white solid, 15 mg (21%); MS *m*/*z* 545, 547 $(M + 1)^+$, $(M+3)^+$; ^{1}H NMR δ 1.06 (6H, s, 2 × CH_3), 2.14 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.91 (2H, t, CH_2N, *J* 6.9 Hz), 3.02 (2H, m, 5-CH_2), 3.59 (2H, m, 3-CH_2, *J* 6.9 Hz), 4.66 (2H, d, CH_2NH, *J* 5.4 Hz), 6.74 (1H, s, CH=C), 7.01 (1H, d, H6, *J* 8.4 Hz), 7.27 (2H, m, H7, H4), 8.11 (1H, s, NH), 10.15 (1H, t, NH, *J* 5.1 Hz), 12.75 (1H, s, NH); Found M^+ 544.14126. $C_{24}H_{29}N_6O_4Br{\cdot}HCl$ requires M^+ 544.14126. HPLC retention time = 13.83 min.

***N*-(*tert*-Butyloxycarbonyl)propargylamine (19).** To an ice cooled solution of propargylamine (5.0 g, 0.09 mol) and triethylamine (12.7 mL, 0.09 mol) in diethyl ether (70 mL) was added Boc_2O in diethyl ether (30 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was washed with saturated ammonium chloride (150 mL) followed by water then dried. The solvent was evaporated under reduced pressure to give a yellow oil which was distilled (bp 170 °C at 14 mmHg) to give the propargylamine derivative **19** as a clear oil. 13.9 g (90%); MS *m*/*z* 155 (M^+); ^{1}H NMR δ 1.36 (9H, s, 3 × CH_3), 1.45 (1H, s, CH=C), 3.67 (2H, d, CH_2NH, *J* 5.7 Hz), 7.22 (1H, br s, NH).

Ethyl 2-chloro-2-hydroxyiminoacetate (20).[46] Glycine ethyl ester (20 g, 0.143 mol) was dissolved in water (30 mL) and cooled to ~5 °C. Concentrated HCl (16.3 mL, 0.14 mol) was added to the stirring solution. After a further 5 min stirring, sodium nitrite (9.87 g, 0.14 mol) in water (15 mL) was added. A further equivalent of concentrated HCl (16.3 mL) was added followed by another equivalent of sodium nitrite (9.87 g) in water (15 mL). Following evolution of a brown gas, stirring was continued for 1 h. A white precipitate was filtered off and the filtrate was left to sit in the fridge overnight after which a second crop of the desired compound was filtered. The compound was dried to give 8.0 g (36%) of the desired oximino ester as a white crystalline solid (Mp 79–80 °C, lit.,[46] mp 80 °C); MS *m*/*z* 152, 154 $(M + 1)^+$, $(M+3)^+$ (3 : 1); ^{1}H NMR δ 1.26 (3H, t, CH_3, *J* 7.2 Hz), 4.29 (2H, q, CH_2, *J* 7.2 Hz), 13.5 (1H, s, OH); Found M^+ 151.00362. $C_4H_6NO_3Cl$ requires M^+ 151.00306.

Ethyl [*N*-(*tert*-butyloxycarbonyl)-5-aminomethyl]isoxazole-3-carboxylate (21). Ethyl 2-chloro-2-hydroxyiminoacetate **20** (5.0 g, 0.033 mol) was dissolved in THF (35 mL). A solution of the *N*-protected propargylamine **19** (5.86 g, 0.038 mol) and triethylamine (5.27 mL, 0.038 mol) in diethyl ether (140 mL) was added dropwise at room temperature. The solution was left to stir at room temperature overnight. The ether solution was washed with dilute ammonium chloride solution followed by water then dried. The ether was evaporated under reduced pressure to give a yellow oil which was dried under vacuum. Purification by column chromatography eluting with chloroform–

hexane (1 : 1) followed by chloroform to afford 1.42 g (16%) of **21** as a viscous yellow oil. MS *m*/*z* 271 $(M + 1)^+$; ^{1}H NMR δ 1.28 (3H, t, CH_3, *J* 7.0 Hz), 1.37 (9H, s, 3 × CH_3), 4.33 (4H, m, CH_2CH_3, CH_2NH), 6.62 (1H, s, CH=C), 7.57 (1H, t, NH, *J* 5.5 Hz).

Ethyl 5-aminomethylisoxazole-3-carboxylate (22). A stirring solution of the ester **21** (416 mg, 1.5 mmol) in dichloromethane (7.5 mL) was cooled to 0 °C. TFA (1.5 mL, 2.22 g, 19.4 mmol) was added dropwise and the solution was allowed to stir up to room temperature over 5 h. The solvent was then evaporated under reduced pressure and diethyl ether (20 mL) was added. The oil solidified and was then filtered and washed several times with ether. The solid was dried under vacuum to afford 341 mg (80%) of the trifluoroacetate salt of the **22** as an off-white solid. MS *m*/*z* 171 $(M + 1)^+$; Found M^+ 170.06914. $C_7H_{10}N_2O_3 \cdot CF_3CO_2H$ requires M^+ 170.06895; ^{1}H NMR δ 1.32 (3H, t, CH_3, *J* 8.7 Hz), 4.37 (4H, m, 2 × CH_2), 6.96 (1H, s, CH=C), 8.41 (3H, br s, NH_3^+).

***N*-[5-(3-Ethoxycarbonyl)isoxazol-5-ylmethyl]-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (55).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **23**):[26] HCl salt of **55** as a yellow lyophilate, 44 mg (63%); MS *m*/*z* 539 $(M + 1)^+$; ^{1}H NMR δ 1.14 (6H, s, 2 × CH_3), 1.29 (3H, t, CH_2CH_3, *J* 7.2 Hz), 2.84 (6H, s, 2 × NCH_3), 2.94 (2H, m, CH_2NMe_2), 3.23 (2H, m, CH_2N), 3.36 (2H, m, 5-CH_2), 3.62 (2H, m, 3-CH_2), 4.35 (2H, q, CH_2CH_3, *J* 7.2 Hz), 4.72 (2H, d, CH_2NH, *J* 5.4 Hz), 6.84 (1H, s, CH=C), 7.09 (1H, d, H6, *J* 8.4 Hz), 7.34 (2H, d, H7, *J* 8.4 Hz), 7.5 (1H, s, H4), 8.17 (1H, s, NH), 9.09 (1H, t, $NHCH_2$, *J* 5.4 Hz), 9.85 (1H, br s, NH(+)Me_2), 11.63 (1H, s, NH); Found M^+ 538.25134. $C_{27}H_{34}N_6O_6 \cdot HCl$ requires M^+ 538.25398.

***N*-[5-(3-Ethoxycarbonyl)isoxazol-5-ylmethyl]-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxamide (56).** Method 1 (using 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylic acid **30**).[26] HCl salt of **56** as a yellow lyophilate, 30 mg (40%); MS *m*/*z* 511 $(M + 1)^+$; ^{1}H NMR δ 1.29 (3H, t, CH_2CH_3, *J* 7.2 Hz), 2.15 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.87 (2H, m, CH_2N), 3.05 (2H, m, 5-CH_2), 3.58 (2H, m, 3-CH_2), 3.82 (2H, s, $HydCH_2$), 4.34 (2H, q, CH_2CH_3, *J* 7.3 Hz), 4.72 (2H, d, CH_2NH, *J* 5.4 Hz), 6.78 (1H, s, CH=C), 7.03 (1H, d, H6, *J* 7.2 Hz), 7.33 (2H, m, H7, H4), 7.97 (1H, s, NH), 10.12 (1H, t, $NHCH_2$, *J* 5.0 Hz), 11.28 (1H, s, NH); Found M^+ 510.22144. $C_{25}H_{30}N_6O_6 \cdot HCl$ requires M^+ 510.22268.

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