Synthesis and serotonergic activity of 2-oxadiazolyl-5-substituted-*N*,*N*-dimethyltryptamines: novel antagonists for the vascular 5-HT_{1B}-like receptor

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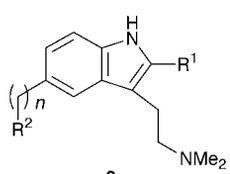
The synthesis and vascular 5-HT_{1B}-like receptor activity of a novel series of 2-oxadiazolyl-5-substituted tryptamine derivatives **2** is described. Modifications to the 2-oxadiazolyl group R^1, the heterocycle R^2 and the length of the



2

linking chain (*n*) have been explored. Several compounds were identified which exhibited moderate 5-HT_{1B}-like receptor affinity. In particular, 2-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (**20**) in which $n = 1$ had a $pK_B = 7.23$ at the 5-HT_{1B}-like receptor and >60 fold selectivity over α_1-adrenoceptor affinity. This contrasts with the higher homologue derivatives such as **10** and **11** where $n = 2$ which exhibited decreased potency and selectivity for the 5-HT_{1B}-like receptor. The 2-oxadiazolyl-5-substituted-*N*,*N*-dimethyltryptamine derivatives were found to be 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 competitive 5-HT_{1B}-like receptor antagonists with half lives of up to 1.5 hours in dog plasma and with good oral bioavailability.

Introduction

Serotonin (5-HT)[1] receptors have continued to generate interest as a major source of pharmaceutical targets. As new subtypes for the 5-HT receptor[1–6] have been discovered the search for novel selective agonists and antagonists as therapeutic agents has become increasingly attractive.

The 5-HT_1 class is diverse and comprises 5-HT_{1A}, 5-HT_{1B} (formally 5-$HT_{1D\beta}$),[7] 5-HT_{1D} (formally 5-$HT_{1D\alpha}$),[7] 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)[8–10] and more recently zolmitriptan,[11,12] avitriptan and others.[13–17]

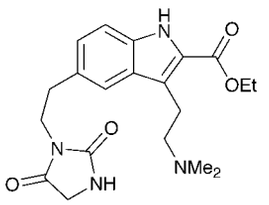
The objective of our research program was to develop a novel, silent (as judged by the inability of angiotensin II to unmask 5-HT_{1B}-like receptor mediated agonist activity in the rabbit femoral artery) and highly selective antagonist at vascular 5-HT_{1B}-like receptors with good oral bioavailability, 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.

The clinical interest here is related to the effects of serotonin on the human coronary artery. In human cerebral and coronary arterial blood vessels the constrictor effects of serotonin are mediated by the class of 5-HT_{1B}-like and 5-HT_{2A} receptors. The hyperactivity of vascular smooth muscle resulting in ischaemia or vasospasm may be involved in disease states such as angina pectoris,[18,19] cerebral vasospasm following sub-arachnoid haemorrhage, Raynaud's syndrome and intermittent claudication.[20–23] In these instances damage to the epithelial layer of the blood vessels may result in reduction of the pro-relaxant effects of 5-HT and an increase in the constrictive effects of exposed 5-HT_{1B}-like receptors.

Current therapies for angina pectoris (calcium channel blockers and nitrates) have extensive clinical utility but have

shortcomings of tolerance and peripheral vasodilation leading to hypotension and headaches due to their non-specific actions. There is thus the need for a selective peripheral vasoconstrictor antagonist with a lower side-effect profile and a selective 5-HT_{1B} antagonist may fulfill this need.

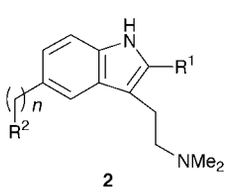
We recently reported the results of a drug discovery program directed toward 2-ester-5-substituted tryptamine derivatives as vascular 5-HT_{1B}-like receptor antagonists.[24] This work resulted in the discovery of several exciting compounds including ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)-ethyl]-1*H*-indole-2-carboxylate (**1**) which had good 5-HT_{1B}-like



1

potency (pK_b = 7.42), ~40 fold selectivity over 5-HT_{2A} receptor affinity and up to 100 fold selectivity over other monoamine receptor subtypes and ion channels both in the periphery and in the central nervous system (CNS).[21]

However, pharmacokinetic studies revealed that the 2-ester group of **2** and related compounds was susceptible to metabolism by esterases in animal plasma and that the half life of compounds from this series was typically less than 15 minutes in rat and mouse plasma.[24] A program was therefore initiated in our laboratories with the objective of replacing the 2-ester group of **2** with a stable isostere such as an oxadiazole moiety. It was hoped that the introduction of an oxadiazole or similar group would improve the pharmacokinetic properties of this series of compounds. Previous studies show that 5-membered heteroaromatic ring systems, in particular 1,2,4-oxadiazoles are excellent stable bioisosteric replacements for ester and amide groups.[25–28] This work should further extend our understanding of the structural and electronic requirements for effective binding to the 5-HT_{1B}-like receptor and thus aid the delineation of a pharmacophore of the 5-HT_{1B}-like receptor antagonist site. Compounds such as these could be used as tools to study the physiological function of the vascular 5-HT_{1B}-like receptor.



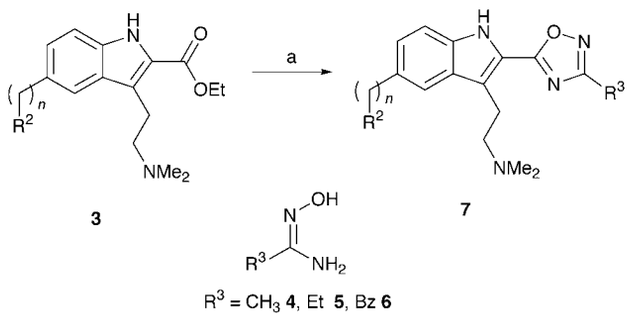
2

We describe in this paper the synthesis, vascular 5-HT_{1B}-like receptor activity and selectivity profile of a series of 2-oxadiazolyl-5-substituted-*N*,*N*-dimethyltryptamine derivatives **2** and related analogs. To explore the pharmacophore of the vascular 5-HT_{1B}-like recognition site we have studied changes in the length of the linking chain *n*, the 2-oxadiazole group R^1 and the 5-heterocycle R^2. The selectivity of these compounds for the 5-HT_{1B}-like receptor over other receptor subtypes is discussed as well as the proposed mode of binding to the 5-HT_{1B}-like receptor pharmacophore.

Results and discussion

Synthetic chemistry

The 2-oxadiazolyl tryptamine derivatives were synthesized in one step by reaction of the corresponding tryptamine-2-ester derivatives **3** with an oxime intermediate in THF in the presence of sodium hydride and 3 Å sieves, Scheme 1.

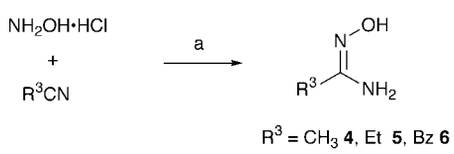


3 **7**

R^3 = CH_3 **4**, Et **5**, Bz **6**

Scheme 1 *Reagents*: (a) NaH (60%), 3 Å sieves, THF.

The synthesis of the tryptamine-2-ester intermediates **3** has been previously reported.[24,29,30] The synthesis of the oximes **4**, **5** and **6** followed a one step procedure outlined in Scheme 2.[31,32]



R^3 = CH_3 **4**, Et **5**, Bz **6**

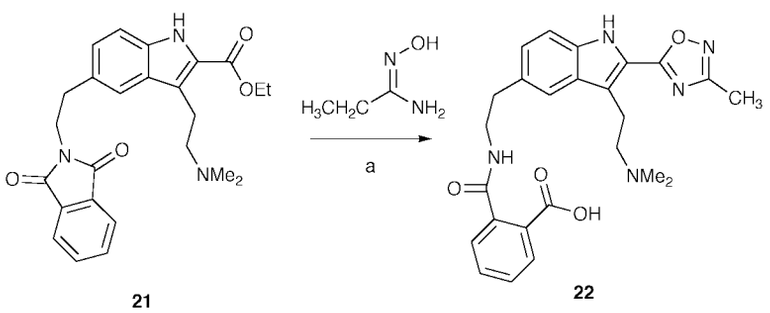
Scheme 2 *Reagents*: (a) $NaOCH_3$, CH_3OH.

An attempt was made to form a tryptamine-2-oxadiazole derivative with an ethyl-linked phthalimide group in the 5-position by reacting the phthalimide derivative **21** with the ethyl oxime **5** (Scheme 3). However the reaction conditions required to form the oxadiazole also resulted in opening of the phthalimide ring to form the benzoic acid derivative **22**.

Several 1,3,4-oxadiazole derivatives were synthesized from the *N*-hydrazide indole-2-carboxamide derivative **8** reported previously.[26] The amidohydrazide **8** was reacted with triethyl orthoformate and triethyl orthopropionate to give **24** and **25** respectively (Scheme 4).

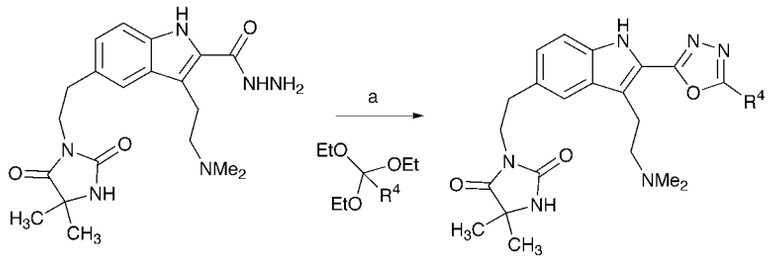
Biological results

The compounds synthesized and their biological results are shown in Table 1. For comparative purposes the biological



21 **22**

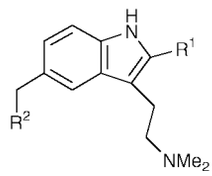
Scheme 3 *Reagents*: (a) NaH (60%), 3 Å sieves, THF.



23 R^4 = H **24**, CH_2CH_3 **25**

Scheme 4 *Reagents*: (a) Benzene.

Table 1 [a,b]



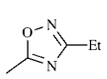
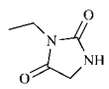
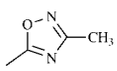
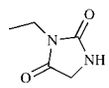
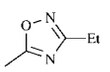
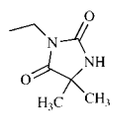
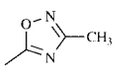
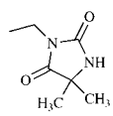
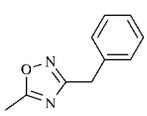
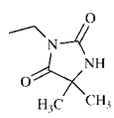
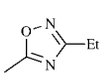
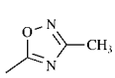
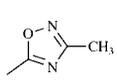
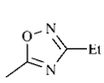
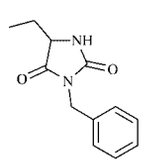
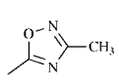
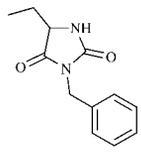
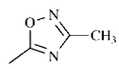
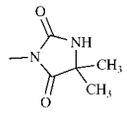
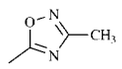
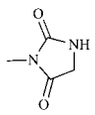
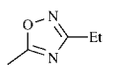
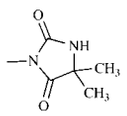
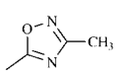
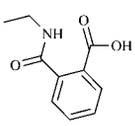
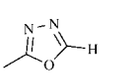
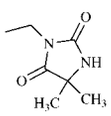
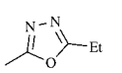
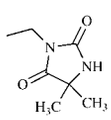
Compound number	R^1	R^2	5HT$_{1B}$-like RbSV (pK_B)	5HT$_{2A}$ RbA (pK_B)	α_1 RbTA (pK_B)
8			6.42 (7.42)[c]	6.28 (5.8)[c]	5.84
9			5.67 (6.97)[d]	5.33 (<5.0)[d]	5.7
10			6.76 (7.34)[e]	6.0 (5.23)[e]	5.01
11			6.49 (6.88)[f]	5.26 (5.02)[f]	<5.0
12			6.5 (7.91)[g]	6.25 (7.3)[g]	7.67
13			5.12 (6.78)[h]	5.69 (6.3)[h]	
14			6.06		5.69
15			5.14 (6.0)[i]	5.06 (<5)[i]	
16			6.1		5.67

Table 1 [a,b] (*Contd.*)

Compound number	R^1	R^2	$5HT_{1B}$-like RbSV (pK_B)	$5HT_{2A}$ RbA (pK_B)	α_1 RbTA (pK_B)
17			6.8		6.14
18			6.84 (6.45)[j]	5.21 (5.03)[j]	
19			6.04 (5.41)[k]		
20			7.23 (6.45)[l]		5.42
23			6.02		5.84
25			5.51		<4.5
26			6.13		<4.5

[a] Affinity (pK_B: $-\log_{10}K_B$, the dissociation equilibrium constant) estimates for novel compounds at the vascular $5HT_{1B}$-like and $5HT_{2A}$ receptors in the rabbit saphenous vein (RbSV) and aorta (RbA) respectively. α_1-Adrenoceptor affinity was also 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] Biological results for the corresponding 2-ester-5-tryptamine derivatives are shown in parentheses. [c] Compound **40** Moloney *et al.*[24] [d] **39**.[24] [e] **44**.[24] [f] **43**.[24] [g] **42**.[24] [h] **52**.[24] [i] **51**.[24] [j] **66**.[24] [k] **64**.[24] [l] **67**.[24]

results for the corresponding 2-ester-5-tryptamine derivatives are shown in parentheses.[24]

A survey of the biological results for the majority of the oxadiazole derivatives revealed that replacement of the methyl, ethyl or benzyl ester group with the corresponding methyl, ethyl or benzyl oxadiazole group resulted in a decrease in affinity and selectivity for the 5-HT_{1B}-like receptor. A possible explanation for their pharmacological profile becomes apparent when we consult a theoretical receptor model for the vascular 5-HT_{1B}-like receptor we have published previously, (Fig. 1).[24,29,33] The theoretical receptor model which 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 was generated using systematic conformational searching of a series of analogs having a range of affinities and efficacies at both the 5-HT_{1B}-like and 5-HT_{2A} receptors.[30] This model proved to be qualitatively predictive for both affinity and selectivity and enabled the design of analogs having both affinity and selectivity at 5-HT_{1B}-like receptors. 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.[33] Additionally, due to the structural nature of the pharmacophore model, it was possible to use this model to design novel analogs (*e.g.* other than indole based compounds) while maintaining affinity and selectivity for the 5-HT_{1B}-like receptor. The principal regions responsible for affinity are overlaid using zolmitriptan,[33] another 5-HT_{1B}-like agonist (compound **37** from Glen *et al.*[33]) and methysergide. The distances between each site are shown in angstroms. Chart 1 shows the classical 2D structures of zolmitriptan, methysergide and compound **37** (Glen *et al.*[33]). Methysergide ($pA_{50}/\alpha = 6.7/0.64$ at 5-HT_{1B}) was one of the structures chosen with restricted conformational freedom about the ethylamine sidechain to deduce the theoretical model.[33] This was one of a larger number of structures used to deduce the relative positions of pharmacophoric groups. It is shown here as a reference structure for comparison purposes,

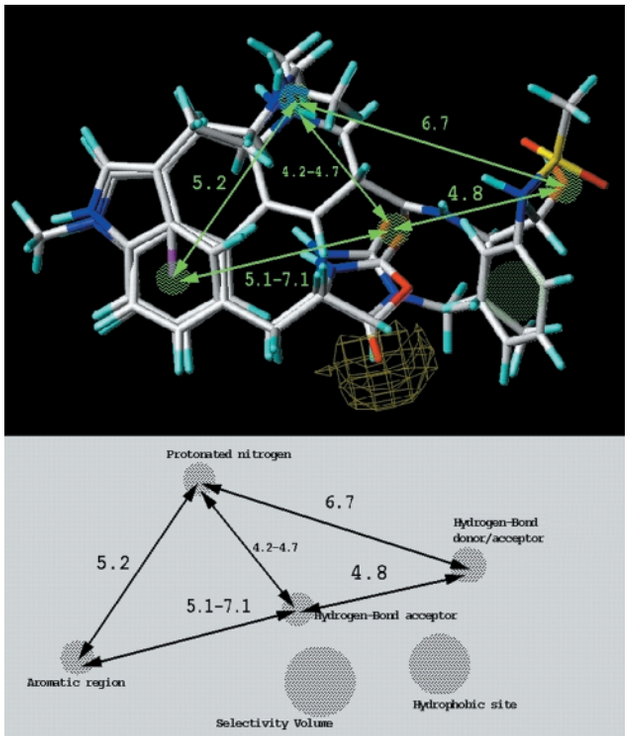


Fig. 1 Theoretical 5-HT_{1B}-like receptor model using zolmitriptan[30] and compound **37** from Glen *et al.*[30] as references and with methysergide as background.

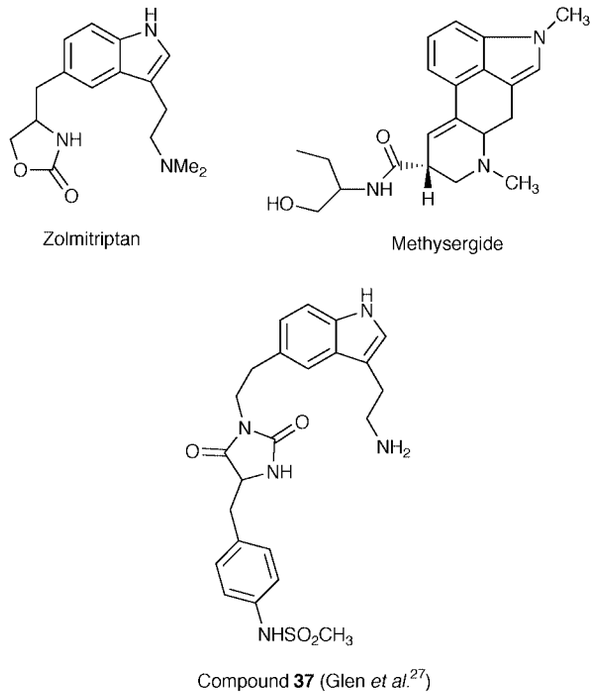


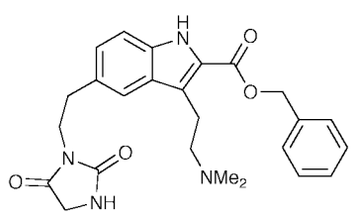
Chart 1

with relevant new structures overlayed. Zolmitriptan is a selective 5-HT_{1B} agonist ($pA_{50}/\alpha = 6.8/0.77$ at 5-HT_{1B}) with no substituent at the 2-position of the indole ring system. It is a good example of a tryptamine derivative which possesses functionality that can interact with important pharmacophore binding sites. Compound **37** from Glen *et al.*[33] represents a selective 5-HT_{1B} agonist ($pA_{50}/\alpha = 7.4/0.8$ at 5-HT_{1B}) which can also interact with the binding sites of the theoretical 5-HT_{1B} receptor model including the secondary binding sites, the hydrogen bonding donor–acceptor sites and hydrophobic binding site.[33]

Studies in our laboratories have described a spatial restriction on the size of the 2-substituent on the indole ring, the receptor not tolerating well large substituents at this position.[24,29] We have described modes of binding to the 5-HT_{1B}-like receptor for a series of tryptamine-2-ester and 2-(*N*-aryl)carboxamido tryptamine derivatives.[24,29] We hypothesised that there was a steric interaction between a region in the 5-HT_{1B}-like receptor and the 2-ester or 2-*N*-carboxamido group of the 2,5-substituted tryptamine derivatives. The molecules adopt a 'displaced' conformation (relative to agonists for the 5-HT_{1B}-like receptor such as zolmitriptan[33]) which has a proton in the 2-position. The conformation adopted in order to accommodate the 2-sidechain in the case of the 2-(*N*-aryl)carboxamido derivatives showed that the aromatic binding site could be occupied by the aromatic group other than an indole including phenyl and heteroaromatic groups such as furan, thiophene and oxadiazole groups.[29,34]

Various oxadiazole moieties have been investigated as potential replacements for the labile ester group of the 2-ester tryptamine derivatives typified by **2**.[24] The 1,2,4-oxadiazole derivative **10** containing an ethyloxadiazole group exhibited a 5-HT_{1B}-like affinity of $pK_B = 6.76$ which is below the desired level of $pK_b = 7.0$. However there was no significant affinity for the α_1 adrenoceptor. The decreased affinity of **10** may be explained in terms of the size of the 2-oxadiazole group and the subsequent configuration the molecule can adopt in the receptor following displacement from its preferred mode of binding.

The 3-benzyloxadiazole derivative **12** was synthesized in an attempt to improve affinity in a similar trend observed for the improved affinity recorded for the 2-benzylester tryptamine derivative **27** ($pK_B = 7.91$ at the 5-HT_{1B}-like receptor).[24]



27

The 5-HT_{1B}-like receptor affinity of **12** was moderate ($pK_B = 6.5$) and in addition **12** showed pronounced affinity at the α_1-adrenoceptor. Clearly the bulk of the benzyloxadiazole group was not well tolerated.

The *N*-benzylhydantoin derivative **16** was synthesized in the hope that the *N*-benzyl group may enhance affinity by accessing a proposed hydrophobic binding site suggested previously (see Fig. 1).[29,30] The low 5-HT_{1B}-like affinity ($pK_B = 6.1$) of **16** indicates that the 5-ethylene linked hydantoin moiety cannot optimally interact with important pharmacophore binding sites including the hydrogen bonding sites.

Molecular modelling studies were performed which suggested that a shorter 5-linking chain may permit more accurate interaction of important functional groups such as the hydantion carbonyl groups with the proposed pharmacophoric hydrogen bonding sites. A series of lower homologues were therefore investigated containing a 5-methylene linked sidechain. Two compounds from this series were found to have improved affinity and selectivity for the 5-HT_{1B}-like receptor. Within this series the dimethyl hydantoin moiety enhanced the 5-HT_{1B}-like receptor selectivity of these compounds which is consistent with the preference of a hydrophobic group in this position.[24] The ethyl oxadiazole derivative **20** has excellent affinity at the 5-HT_{1B}-like receptor ($pK_B = 7.23$) and >1.8 log units selectivity over α_1-adrenoceptor activity. The proposed mode of binding for **20** is shown in Fig. 2.

An oxadiazole group attached to the 2-position of the indole ring appears to result in the molecules adopting a different overall conformation within the theoretical receptor model

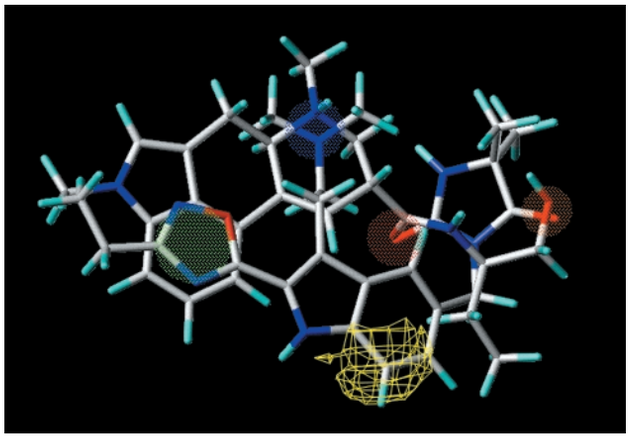


Fig. 2 A proposed conformation for **20** fitted to the 5-HT_{1B}-like pharmacophore model. The selectivity volume is shown in yellow.

compared with the 2-ester tryptamine series.[24] For optimum interaction between one of the carbonyl groups of the hydantoin moiety of this series and the putative hydrogen bonding site of the 5-HT_{1B}-like pharmacophore a 5-methylene linking chain is preferred.

Two 1,3,4-oxadiazole derivatives **25** and **26** were investigated but found to have inferior affinity for the 5-HT_{1B}-like receptor compared with the 1,2,4-oxadiazole derivatives (see Table 1). However, 5-methylene linked analogs of this series have yet to be examined and may improve the affinity and selectivity of this series for the 5-HT_{1B}-like receptor.

It was of interest to investigate the stability in plasma and the oral bioavailability of the 2-oxadiazole tryptamine class of compounds in the early stages of this work in order to ensure that the replacement of the 2-ester group with a 2-oxadiazole moiety was successful in improving the overall pharmacokinetic properties of these molecules. Pharmacokinetic studies on the ethyl oxadiazole derivative **10** revealed a half life of ~90 minutes in rat plasma and 1.2 hours in dog plasma. The stability of the 2-oxadiazole tryptamine series was superior to the 2-ester tryptamine series ($t_{1/2}$ = 15 min) in rat plasma.[24] However the 2-oxadiazole series had slightly decreased stability in dog plasma compared with the 2-ester tryptamine series ($t_{1/2}$ = ~2 hours). In rats, **10** was found to have 100% oral bioavailability at an oral dose of 10 mg kg^{-1}.

Conclusion

A novel series of 5-HT_{1B}-like receptor antagonists has been identified. Our findings support previous studies which show that 5-membered heteroaromatic rings, in particular 1,2,4-oxadiazoles are excellent stable bioisosteric replacements for ester and amide groups.[25–28] The 1,2,4-oxadiazole group was shown to improve the half-life of this series of 2,5-substituted tryptamine derivatives in rat plasma, compound **10** having a half-life of ~90 minutes in rat plasma compared with a half life for a related 2-ester derivative of $t_{1/2}$ = 15 min.[24] The 5-HT_{1B}-like affinity of **10** is however below the desired level required by the program objectives with a pK_B = 6.76. Importantly though there is no significant affinity for the α_1 adrenoceptor which is necessary to avoid possible hypotensive action. The decreased affinity of **10** may be explained in terms of the size of the 2-oxadiazole group and the subsequent position of the molecule following displacement from its preferred mode of binding. Compound **10** was also found to exhibit 100% oral bioavailibility in rats.

Several 5-methylene linked compounds were investigated following molecular modelling studies which suggested that a shorter 5-linking chain may allow the 5-linked hydantoin group to access the hydrogen bonding site and selectivity volume more accurately than an ethylene linked hydantoin group. One compound from this series, 2-(3-ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (**20**) was found to have the desired potency at the 5-HT_{1B}-like receptor (pK_B = 7.23) and showed >60 fold selectivity over α_1-adrenoceptor affinity. The mode of binding to the receptor for the 2-oxadiazolyl tryptamine series has been described and it was shown that a 5-methylene linking chain is preferred for optimum binding to the hydrogen bonding site and the selectivity volume.

Compounds from the 2-oxadiazole tryptamine series such as **20** will be useful biological probes for the vascular 5-HT_{1B}-like receptor and will help in the classification of the 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-adrenoreceptors, 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 (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.

Pharmacokinetic methods

These studies followed a protocol previously outlined.[37] Pharmacokinetic experiments were performed in Wistar rats and cynomolgous monkeys.[38] Animals were dosed orally with test drug and the time-course for appearance in the plasma measured using (GC-MS).

Chemical methods: general directions

Computational chemistry was performed on a Silicon Graphics Iris indigo II using the Sybyl[39] 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, ether, toluene and benzene 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 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; $SOCl_2$ thionyl chloride.

***N*-Hydroxypropanimidamide (5).**[32] Method 1: sodium (2.3 g, 0.1 mol) was added to methanol (50 mL) to provide sodium methoxide. Hydroxylamine hydrochloride (6.9 g, 0.1 mol) in methanol (100 mL) was then added and the solution was stirred for 40 min at room temperature. A precipitate was filtered off and the filtrate was treated with propionitrile (8.0 mL, 0.1 mol). The reaction mixture was refluxed for 18 h then cooled and the solvent evaporated under reduced pressure. The residue was taken up in diethyl ether and filtered. The ether filtrate was reduced *in vacuo* and the residue was passed through a silica column eluting with ethyl acetate to provide 3.7 g (33%) of the oxime as a yellow oil. MS *m*/*z* 89 $(M + 1)^+$; ^{1}H NMR δ 1.0 (3H, t, CH_3, *J* 7.4 Hz), 1.96 (2H, q, CH_2, *J* 7.6 Hz), 5.26 (2H, br s, NH_2), 8.65 (1H, br s, OH).

***N*-Hydroxyethanimidamide (4).**[31] Method 1: 3.84 g (48%); MS *m*/*z* 75 $(M + 1)^+$; ^{1}H NMR δ 1.64 (3H, s, CH_3), 5.57 (2H, br s, NH_2), 8.81 (1H, br s, OH).

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[(2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (8). Method 2: propionamide oxime **5** (70 mg, 0.79 mmol) was added to a stirred suspension of powdered 3 Å molecular sieves (100 mg) in THF (5.0 mL) under an atmosphere of nitrogen. After 15 min sodium hydride (31 mg, 0.79 mmol) was added and stirring continued for 45 min. The 2-ester tryptamine derivative **2**[24] (150 mg, 0.39 mmol) in THF (10 mL) was added and the resulting mixture heated to reflux for 2 h. The solution was then allowed to cool and acetic acid (0.1 mL) added. The solution was partitioned between CH_2Cl_2 and sodium hydrogen carbonate, the organic layer washed with water and brine and dried. The organic layer was concentrated under reduced pressure to give a yellow gum. Crystallisation with ethyl acetate followed by recrystallisation from CH_2Cl_2 and ethyl acetate gave 21 mg (13%) of **8** as a white powder (Mp 174–175 °C) (Found C, 54.30; H, 5.95; N, 17.47. $C_{21}H_{26}N_6O_3{\cdot}0.50H_2O{\cdot}0.7CH_2Cl_2$ requires C, 54.20; H, 5.98; N, 17.47%).

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)-ethyl]-5-[(2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (9). Method 2 (using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate):[24] cream solid, 120 mg (47%) (Found C, 61.41; H, 6.09; N, 20.09. $C_{20}H_{24}N_6O_3$ requires C, 61.45; H, 6.38; N, 20.47%); MS *m*/*z* 397 $(M + 1)^+$; ^{1}H NMR δ 2.4 (6H, s, 2 × NCH_3), 2.71 (2H, m, CH_2NMe_2), 2.91 (2H, m, CH_2N), 3.3 (2H, m, 5-CH_2, under water peak), 3.59 (2H, m, 3-CH_2), 3.82 (2H, s, HydCH_2), 7.15 (1H, d, H6), 7.38 (1H, d, H7), 7.52 (1H, s, H4), 8.06 (1H, s, NH), 12.06 (1H, s, NH); Found M^+ 396.19077. $C_{20}H_{24}N_6O_3$ requires M^+ 396.19099. Anal. ($C_{21}H_{26}N_6O_3{\cdot}0.5H_2O{\cdot}0.7CH_2Cl_2$) C, H, N.

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole (10). Method 2 (using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate):[24] purification by HPLC afforded 429 mg (81%) of the acetate salt of **10** as a white solid (Found C, 59.31; H, 6.66; N, 16.40. $C_{23}H_{30}N_6O_3S{\cdot}0.40H_2O{\cdot}0.50CH_3CO_2H$ requires C, 63.03; H, 6.16; N, 11.77); MS *m*/*z* 439 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.3 (3H, t, CH_2CH_3, *J* 7.7 Hz), 2.31 (6H, s, 2 × NCH_3), 2.58 (2H, m, CH_2NMe_2), 2.8 (2H, q, CH_2CH_3, *J* 7.8 Hz), 2.91 (2H, m, CH_2N), 3.26 (2H, m, 5-CH_2), 3.55 (2H, m, 3-CH_2), 7.08 (1H, d, H6), 7.39 (2H, m, H7, H4), 8.13 (1H, s, NH), 11.95 (1H, s, NH); Anal. ($C_{23}H_{30}N_6O_3{\cdot}0.5CH_3CO_2H{\cdot}0.4H_2O$) C, H, N.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole (11). Method 2: purification by HPLC afforded 163 mg (80%) of the acetate salt of **11** as a white foam (Found C, 57.96; H, 6.49; N, 17.47. $C_{22}H_{28}N_6O_3{\cdot}1.10H_2O{\cdot}0.50CH_3CO_2H$ requires C, 58.23; H, 6.84; N, 17.71); MS *m*/*z* 425 $(M + 1)^+$; ^{1}H NMR δ 1.14 (6H, s, 2 × CH_3), 1.9 (1.5H, s, 0.5CH_3CO_2H), 2.25 (6H, s, 2 × NCH_3), 2.45 (3H, s, OxadCH_3), 2.52 (2H, m, CH_2NMe_2), 2.92 (2H, m, CH_2N), 3.23 (2H, m, 5-CH_2), 3.6 (2H, m, 3-CH_2), 7.12 (1H, d, H6), 7.34 (1H, d, H7), 7.4 (1H, s, H4), 8.2 (1H, s,

NH), 11.91 (1H, s, NH); Anal. ($C_{22}H_{28}N_6O_3$ .0.5 CH_3CO_2H·1.1H_2O) C, H, N.

2-(3-Benzyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-1*H*-indole (12). Method 2: purification by preparative HPLC afforded 28 mg (23%) of **12** as a white foam; MS *m*/*z* 501 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (0.6H, s, 0.2CH_3CO_2H), 2.21 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.92 (2H, m, CH_2N), 3.21 (2H, m, 5-CH_2), 3.62 (2H, m, 3-CH_2), 4.18 (2H, s, CH_2Ph), 7.11 (1H, d, H6), 7.31 (1H, m, H7, H4, 5 × ArH), 8.12 (1H, s, NH), 11.9 (1H, s, NH); Found M^+ 500.25516. $C_{28}H_{32}N_6O_3$ requires M^+ 500.25359.

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[2-(succinimido)ethyl]-1*H*-indole (13). Method 3: the amido oxime **4** (68 mg, 0.62 mmol) was added to a stirring suspension of crushed 3 Å sieves (95 mg) in THF (7.0 mL). After 15 min sodium hydride (60% disp, 25 mg, 0.62 mmol) was added and the suspension was stirred for 45 min. Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate **2** [24] (120 mg, 0.31 mmol) dissolved in THF (4.0 mL) was added and the mixture was refluxed for 2.5 h. The reaction mixture was partitioned between CH_2Cl_2 and water and separated. Solid $NaHCO_3$ was added to the aqueous phase and extracted further with CH_2Cl_2. The combined organic phases were back extracted with water, dried, filtered, concentrated under reduced pressure and dried over P_2O_5. The residue was purified by flash chromatography eluting with $CHCl_3$–MeOH (98 : 2) to afford 64 mg (51%) of **13** as a yellow–grey powder. Further purification by HPLC afforded the acetate salt of **13** as a white lyophilate. MS *m*/*z* 410 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (0.6H, s, 0.2CH_3CO_2H), 2.21 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.92 (2H, m, CH_2N), 3.21 (2H, m, 5-CH_2), 3.62 (2H, m, 3-CH_2), 4.18 (2H, s, CH_2Ph), 7.1 (1H, d, H6), 7.5 (1H, d, H7), 7.6 (1H, s, H4), 8.12 (1H, s, NH), 11.93 (1H, s, NH); Found M^+ 409.21277. $C_{22}H_{27}N_5O_3$ requires M^+ 409.21139.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)-ethyl]-5-[2-(succinimido)ethyl]-1*H*-indole (14). Method 2 (using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate [24]): purification by HPLC afforded 17 mg (11%) of the acetate salt of **14** as a white powder; MS *m*/*z* 396 $(M + 1)^+$; ^{1}H NMR δ 1.85 (2.4H, s, 0.79CH_3CO_2H), 2.22 (6H, s, 2 × NCH_3), 2.43 (2H, m, CH_2NMe_2, under DMSO), 2.59 (3H, s, OxadCH_3), 2.85 (2H, m, CH_2N), 3.26 (2H, m, 5-CH_2), 3.60 (2H, m, 3-CH_2), 7.13 (1H, dd, H6), 7.35 (1H, d, H7), 7.5 (1H, s, H4), 11.95 (1H, s, NH); Found M^+ 395.19498. $C_{21}H_{25}N_5O_3$ requires M^+ 395.19579.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)-ethyl]-5-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-1*H*-indole (15). Method 2: (using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2-oxopyrrolidin-1-yl)ethyl]-1*H*-indole-2-carboxylate): [24] flash chromatography gave 29 mg (75%) of the free base of **15** as a glassy solid. Further purification by HPLC afforded the acetate salt of **15** as a white solid; MS *m*/*z* 384 $(M + 1)^+$; ^{1}H NMR δ 1.62 (1.8H, s, 0.6CH_3CO_2H), 2.26 (6H, s, 2 × NCH_3), 2.45 (3H, s, OxadCH_3), 2.55 (2H, m, CH_2NMe_2, under DMSO), 2.91 (2H, m, NCH_2), 3.45 (4H, m, NCH_2, 5-CH_2), 3.55 (2H, m, 3-CH_2), 4.2 (2H, m, CH_2O), 7.2 (1H, dd, H6), 7.4 (1H, d, H7), 7.55 (1H, s, H4), 11.92 (1H, s, NH); Found M^+ 383.19461. $C_{20}H_{20}N_5O_3$ requires M^+ 383.19574.

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-[2-(1-benzyl-2,5-dioxo-imidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole (16). Method 2: (using ethyl 5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate): [24] column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (200 : 8 : 1) gave 17 mg (23%) of **16** as a yellow powder; MS *m*/*z* 501 $(M + 1)^+$; ^{1}H NMR δ 1.3 (3H, t, CH_3CH_2), 2.05 (2H, m, CH_2CH), 2.22 (6H, s, 2 × NCH_3), 2.50 (2H, m, CH_2NMe_2, under DMSO), 2.81 (4H, m, CH_2CH_3, 5-CH_2), 3.42 (2H, m, 3-CH_2), 4.21 (1H, m, CH), 4.5 (2H, m, CH_2Ph), 7.1–7.7 (8H, m, H6, H7, H4, 5 × ArH), 8.85 (1H, s, NH), 11.92 (1H, s, NH); Found M^+ 500.25354. $C_{28}H_{32}N_6O_3$ requires M^+ 500.25374.

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-[2-(1-benzyl-2,5-dioxo-imidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole (17). Method 2: (using ethyl 5-[2-(1-benzyl-2,5-dioxoimidazolidin-4-yl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxylate): [24] column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (200 : 8 : 1) gave 20 mg (55%) of **17** as a yellow powder; MS *m*/*z* 487 $(M + 1)^+$; ^{1}H NMR δ 1.85 (2H, m, CH_ACH), 2.09 (2H, m, CH_BCH), 2.22 (6H, s, 2 × NCH_3), 2.41 (3H, s, OxadCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 2.72 (2H, m, 5-CH_2), 3.3 (2H, m, 3-CH_2, under water peak), 4.09 (1H, m, CH), 4.5 (2H, m, CH_2Ph), 7.12–7.5 (8H, m, H6, H7, H4, 5 × ArH), 8.62 (1H, s, NH), 11.92 (1H, s, NH); Found M^+ 486.24149. $C_{27}H_{30}N_6O_3$ requires M^+ 486.23794.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)-ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (18). Method 2: (using ethyl 3-[2-(dimethylamino)-ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole-2-carboxylate): [24] column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (60 : 8 : 1) gave 34.5 mg (24%) of **18** as a yellow powder; MS *m*/*z* 411 $(M + 1)^+$; ^{1}H NMR δ 1.25 (6H, s, 2 × CH_3), 2.22 (6H, s, 2 × NCH_3), 2.4 (3H, s, OxadCH_3), 3.1 (2H, m, CH_2NMe_2), 3.25 (2H, m, 3-CH_2), 4.6 (2H, m, 5-CH_2), 7.2 (1H, d, H6), 7.4 (1H, d, H7), 7.5 (1H, s, H4), 8.3 (1H, s, NH), 12.0 (1H, s, NH); Found M^+ 410.20905. $C_{21}H_{26}N_6O_3$ requires M^+ 410.20664.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)-ethyl]-5-[(2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (19). Method 2: (using ethyl 3-[2-(dimethylamino)ethyl]-5-[(2,5-dioxoimidazolidin-1-yl)methyl]-1H-indole-2-carboxylate): [24] column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (60 : 8 : 1) gave 9.5 mg (52%) of **19** as a light brown powder; MS *m*/*z* 383 $(M + 1)^+$; ^{1}H NMR δ 2.21 (6H, s, 2 × NCH_3), 2.42 (3H, s, OxadCH_3), 2.49 (2H, m, CH_2NMe_2, under DMSO), 3.3 (2H, m, 3-CH_2), 3.95 (2H, s, HydCH_2), 4.6 (2H, m, 5-CH_2), 7.22 (1H, d, H6, *J* 8.1 Hz), 7.37 (1H, d, H7, *J* 8.4 Hz), 7.61 (1H, s, H4), 8.08 (1H, s, NH), 12.0 (1H, s, NH); Found M^+ 382.17416. $C_{19}H_{22}N_6O_3$ requires M^+ 382.17534.

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (20). Method 2: (using ethyl 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole-2-carboxylate): [24] column chromatography eluting with CH_2Cl_2–EtOH–NH_3 (150 : 8 : 1) gave 36 mg (35%) of **20** as a pale yellow powder; MS *m*/*z* 425 $(M + 1)^+$; ^{1}H NMR δ 1.31 (3H, t, CH_3CH_2, *J* 7.5 Hz), 1.31 (6H, s, 2 × CH_3), 2.21 (6H, s, 2 × NCH_3), 2.78 (2H, t, CH_2CH_3), 3.23 (2H, m, CH_2NMe_2), 3.39 (2H, m, 3-CH_2), 4.61 (2H, s, CH_2N), 7.17 (1H, d, H6, *J* 8.8 Hz), 7.39 (1H, d, H7, *J* 8.4 Hz), 7.5 (1H, s, H4), 8.3 (1H, s, NH), 12.0 (1H, s, NH); Found M^+ 424.22510. $C_{22}H_{28}N_6O_3$ requires M^+ 424.22221.

2-{2-[3-(2-Dimethylaminoethyl)-2-(3-methyl-1,2,4-oxadiazol-5-yl)indol-5-yl]ethylcarbamoyl}benzoic acid (23). Method 2: (using ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(*N*-phthalimido)-ethyl]-1*H*-indole-2-carboxylate): [24] flash chromatography gave 11.4 mg (22%) of the free base of **23** as an off-white solid. Further purification by HPLC afforded the acetate salt of **23** as a white powder; MS *m*/*z* 462 $(M + 1)^+$; ^{1}H NMR δ 2.43 (3H, s,

OxadCH$_3$), 2.5 (6H, s, 2 × NCH$_3$), 2.8-2.9 (6H, m, NCH$_2$, 5-CH$_2$, 3-CH$_2$), 4.2 (2H, m, *CH*$_2$NH), 7.15 (1H, d, ArH), 7.36 (3H, m, 3 × ArH), 7.67 (2H, m, 2 × ArH), 7.98 (1H, br s, CO$_2$H), 11.99 (1H, s, NH); Found M$^+$ 461.20443. $C_{25}H_{27}N_5O_4$ requires M$^+$ 461.20630.

2-(1,3,4-Oxadiazol-5-yl)-3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (25). Method 4: the hydrazide **21**[29] (100 mg, 0.25 mmol), triethyl orthoformate (1.5 mL, 1.34 g, 9.0 mmol) and benzene (5.0 mL) were heated at reflux for 16 h. The reaction mixture was allowed to cool and the solvent removed under reduced pressure to afford a yellow gum which was purified using preparative HPLC to give 22 mg (22%) of the acetate salt of **25** as a white foam; MS *m*/*z* 411 (M + 1)$^+$; ^{1}H NMR δ 1.13 (6H, s, 2 × CH$_3$), 1.9 (1.2H, s, 0.4*CH*$_3$CO$_2$H), 2.22 (6H, s, 2 × NCH$_3$), 2.55 (2H, m, *CH*$_2$NMe$_2$), 3.05 (2H, m, CH$_2$N), 3.3 (2H, m, 5-CH$_2$, under water peak), 3.74 (2H, m, 3-CH$_2$), 7.35 (1H, d, H6), 7.59 (1H, d, CH=N), 8.05 (1H, d, H7), 8.1 (1H, s, H4), 8.95 (1H, s, NH), 11.6 (1H, s, NH); Found M$^+$ 410.20663. $C_{21}H_{26}N_6O_3$ requires M$^+$ 410.20664.

2-[2-Ethyl(1,3,4-oxadiazol-5-yl)]-3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)methyl]-1*H*-indole (26). Method 4 (using triethyl orthopropionate): purification by HPLC afforded the acetate of **26** as a pale yellow glassy solid (Found C, 56.47; H, 7.23; N, 15.61. $C_{23}H_{30}N_6O_3 \cdot 0.20H_2O \cdot 1.0CH_3CO_2H$ requires C, 56.16; H, 7.17; N, 15.72); MS *m*/*z* 439 (M + 1)$^+$; ^{1}H NMR δ 1.18 (6H, s, 2 × CH$_3$), 1.37 (3H, t, *CH*$_3$CH$_2$), 1.9 (3H, s, *CH*$_3$CO$_2$H), 2.26 (6H, s, 2 × NCH$_3$), 2.48 (2H, m, *CH*$_2$NMe$_2$), 2.92 (2H, m, CH$_2$N), 2.97 (2H, q, *CH*$_2$CH$_3$), 3.18 (2H, m, 5-CH$_2$), 3.61 (2H, m, 3-CH$_2$), 7.07 (1H, d, H6), 7.34 (1H, d, H7), 7.38 (1H, s, H4), 8.14 (1H, s, NH), 11.24 (1H, s, NH); Found M$^+$ 438.23944. $C_{23}H_{30}N_6O_3$ requires M$^+$ 438.23794. Anal. ($C_{23}H_{30}N_6O_3 \cdot 1.0CH_3CO_2H \cdot 0.2H_2O$) C, H, N.

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