Articles

Synthesis and Serotonergic Activity of Substituted 2,*N*-Benzylcarboxamido-5-(2-ethyl-1-dioxoimidazolidinyl)-*N*,*N*-dimethyltryptamine Derivatives: 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 substituted 2,*N*-benzylcarboxamido-5-(2-ethyl-1-dioxoimidazolidinyl)-*N*,*N*-dimethyltryptamine derivatives are described. Modifications to the 5-ethylene-linked heterocycle and to substituents on the 2-benzylamide side chain have been explored. Several compounds were identified which exhibited affinity at the vascular 5-HT$_{1B}$-like receptor of pK_B > 7.0, up to 100-fold selectivity over α_1-adrenoceptor affinity and 5-HT$_{2A}$ receptor affinity, and which exhibited a favorable pharmacokinetic profile. *N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (**23**) was identified as a highly potent, silent (as judged by the inability of angiotensin II to unmask 5-HT$_{1B}$-like receptor-mediated agonist activity in the rabbit femoral artery), and competitive vascular 5-HT$_{1B}$-like receptor antagonist with a plasma elimination half-life of ∼4 h in dog plasma and with good oral bioavailability. The selectivity of compounds from this series for the vascular 5-HT$_{1B}$-like receptors over other receptor subtypes is discussed as well as a proposed mode of binding to the receptor pharmacophore. It has been proposed that the aromatic ring of the 2,*N*-benzylcarboxamide group can occupy an aromatic binding site rather than the indole ring. The resulting conformation allows an amine-binding site to be occupied by the ethylamine nitrogen and a hydrogen-bonding site to be occupied by one of the hydantoin carbonyls. The electronic nature of the 2,*N*-benzylcarboxamide aromatic group as well as the size of substituents on this aromatic group is crucial for producing potent and selective antagonists. The structural requirement on the 3-ethylamine side chain incorporating the protonatable nitrogen is achieved by the bulky 2,*N*-benzylcarboxamide group and its close proximity to the 3-side chain.

Introduction

In recent times, serotonin (5-HT) receptors have been extensively investigated and classified into seven distinct receptor classes, 5-HT$_1$ to 5-HT$_7$.[1−3] Within these classes, 14 different 5-HT receptor subtypes have been identified.[1−3] In some cases, i.e., 5-ht$_{1E}$, 5-ht$_{1F}$, 5-ht$_5$, and 5-ht$_6$, only the gene products encoding putative serotonin receptor proteins have been identified, and although the recombinant proteins are functionally active when transfected into a mammalian host cell, true physiological roles have not been demonstrated. For this reason, these gene products are provisionally referred to using a lower case notation.[4] The 5-HT$_1$ class is diverse and comprises 5-HT$_{1A}$, 5-HT$_{1B}$ (formally 5-HT$_{1D\beta}$),[5] 5-HT$_{1D}$ (formally 5-HT$_{1D\alpha}$),[5] 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)[6−8] and more recently zolmitriptan,[9] rizatriptan, eletriptan, avitriptan, and others.[10,11]

Until recently, efforts to unambiguously characterize vascular 5-HT$_{1B}$-like receptors have been frustrated by the lack of selective antagonists. A series of benzanilides,[12] exemplified by GR 127935, have been described as potent antagonists at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors and have been shown to block both peripheral vascular and central responses mediated by both of these receptor types.[13] However, this compound is not a silent antago-

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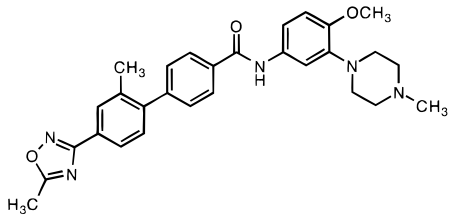
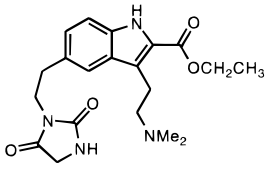


GR 127935

nist and behaves as a partial agonist at recombinant human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.[14] 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.[13]

The objective of our research program was to develop a novel, silent, and highly selective antagonist at vascular 5-HT$_{1B}$-like receptors with good oral bioavailability, a plasma half-life of at least 4 h, and low central penetration. Such a compound may have potential as a prophylactic treatment for unstable angina,[15,16] Raynaud's syndrome,[17−20] and a variety of other vasospastic conditions in which a pathophysiological role for 5-HT has been implicated. We recently published work leading to the discovery of ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate[21] (**1**).

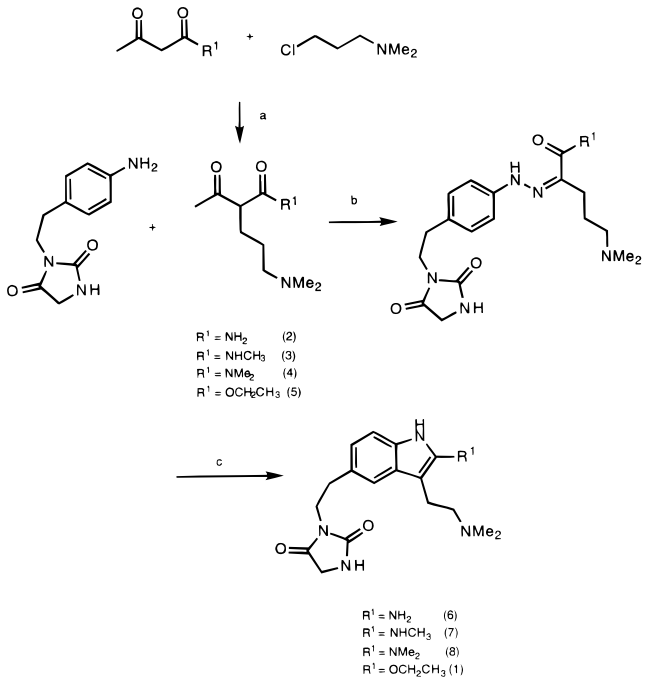


1

1 is a unique molecule in that it displays silent (as judged by the inability of angiotensin II to unmask 5-HT$_{1B}$-like receptor-mediated agonist activity in rabbit femoral artery), competitive antagonism at the vascular 5-HT$_{1B}$-like receptor with moderate affinity and shows no significant affinity at a wide variety of G-protein-coupled receptors in the periphery and/or CNS.[21] Unfortunately, pharmacokinetic studies revealed the poor stability of the 2-ester group in animal plasma, the major metabolic byproduct being the corresponding tryptamine-2-carboxylic acid derivative which was found to be relatively inactive. **1** was shown to be rapidly metabolized by plasma esterases in lower mammals ($t_{1/2}$ = 2−10 min) but showed reasonable stability in plasma from humans, dogs, and primates ($t_{1/2} \sim 2$ h). **1** had good oral bioavailability in the conscious dog (∼80%) but an elimination half-life of only 1 h. The poor pharmacokinetic properties of **1** precluded further development. Our chemical effort was therefore directed toward stable isosteres of the 2-ester group, and this work led to the development of a family of 2,*N*-benzylcarboxamidotryptamine derivatives.

We describe here the synthesis and vascular 5-HT$_{1B}$-like receptor activity of a series of 2,*N*-benzylcarboxamido-5-(2-ethyl-1-dioxoimidazolidinyl)-*N*,*N*-dimethyltryptamine derivatives and related analogues. To explore the pharmacophore of the vascular 5-HT$_{1B}$-like recognition site, we have studied changes in the 2,*N*-benzylcarboxamide substituent and the 5-ethylene-linked hydantoin side chain.

Scheme 1[a]



[a] Reagents: (a) NaOH, EtOH; (b) $NaNO_2$, HCl, NaOH; (c) concd H_2SO_4, EtOH.

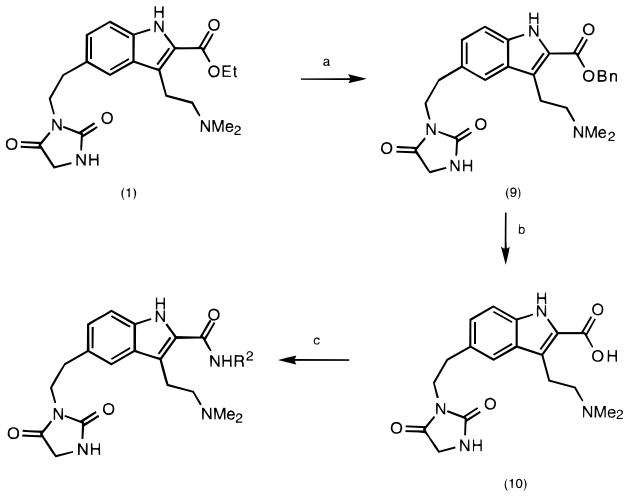
Chemistry

In the course of this study 2,5-substituted tryptamine derivatives have been synthesized in a variety of ways. At the commencement of this work most of these tryptamine derivatives were synthesized via a Japp Klingemann indole synthesis.[22,23] The simple amide derivatives **6**−**8** were synthesized according to this method using previously prepared amido ketone precursors **2**−**4,** Scheme 1. The remaining aliphatic amide derivatives **11**−**16** (Table 1) and many of the 2,*N*-benzylcarboxamido 5-substituted tryptamine compounds were also synthesized via the Japp Klingemann method using the *β*-keto ester intermediate **5** obtained by coupling of ethyl acetoacetate and (dimethylamino)-propyl chloride hydrochloride, Scheme 1.[21] The desired 2-ethyl ester tryptamine derivative **1** was then synthesized as described previously,[21] Scheme 1.

The ethyl ester is then converted to the 2-benzyl ester derivative **9** by refluxing in benzyl alcohol in the presence of titanium tetraisopropoxide, Scheme 2. Following trans-esterification, the 2-benzyl ester is converted to **10** under hydrogenation conditions in the presence of palladium on carbon (10%) at room temperature and atmospheric pressure. Amide coupling of **10** with an aliphatic or aromatic amine using TBTU and DIPEA in DMF affords the desired 2-amidotryptamine derivative, Scheme 2.

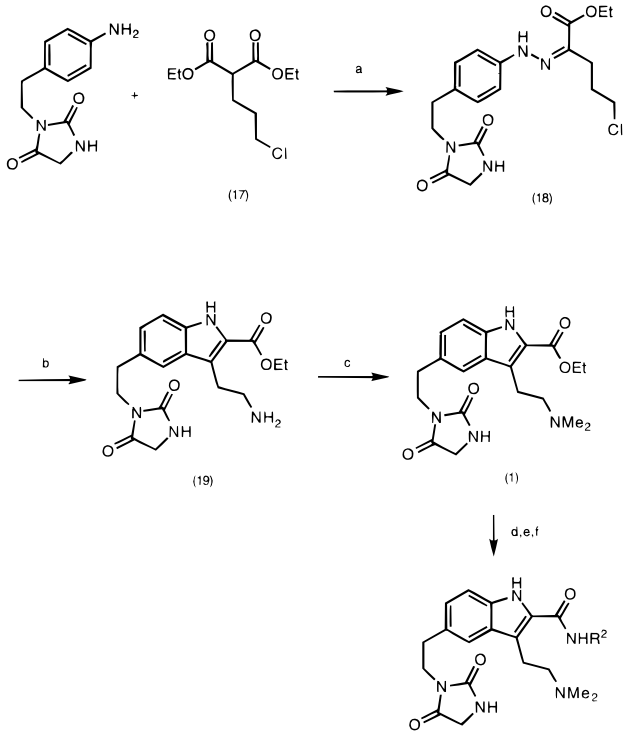
As the work continued attempts were made to improve the overall yield of this process as well as to decrease the number of steps required to produce the target tryptamine molecules. A variation of this procedure was applied which involved Japp Klingemann coupling of the diazotized aniline derivative with a malonate derivative **17**, Scheme 3. This afforded the

Scheme 2[a]



[a] Reagents: (a) $Ti(iOPr)_4$, benzyl alcohol; (b) H_2, Pd−C (10%); (c) TBTU, DIPEA, R^2NH_2, DMF.

Scheme 3[a]

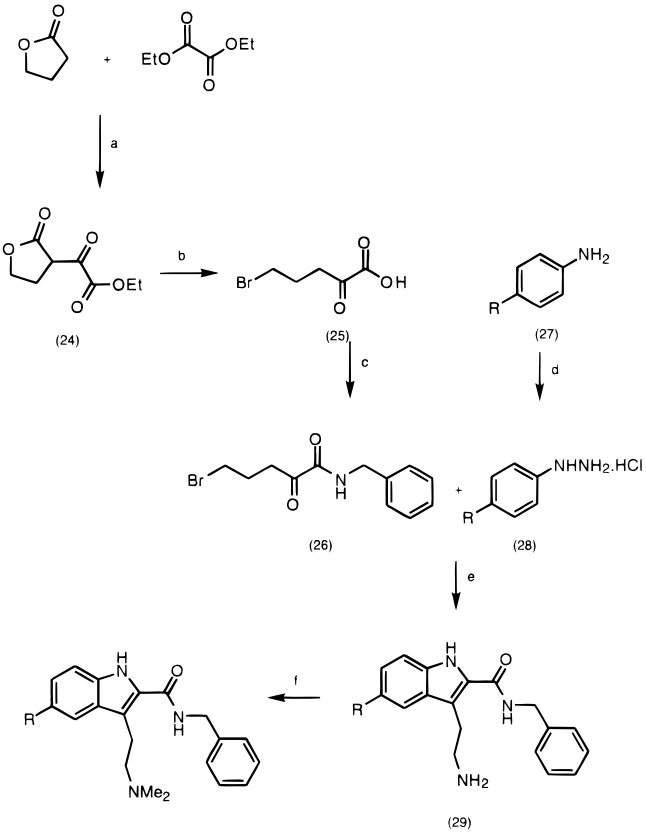


[a] Reagents: (a) $NaNO_2$, concd HCl; (b) butanol, water; (c) AcOH, CH_2O, $NaCNBH_3$, MeOH; (d) $Ti(iOPr)_4$, benzyl alcohol; (e) H_2, Pd−C (10%); (f) TBTU, DIPEA, R^2NH_2, DMF.

2-ester tryptamine derivative **19** in one step as the propyl chloride hydrazone intermediate **18** was not isolated. The ethylamine nitrogen was then methylated using CH_2O, AcOH, and $NaCNBH_3$. Conversion of the 2-ester group to the 2-amido side chain was performed as previously described. This method avoids synthesis of the diketone intermediate **5** which is a poor yielding step but does introduce the extra methylation step of the ethylamine nitrogen.

For several of the latter compounds a variation on the Fisher indole synthesis was employed.[24] This method required the synthesis of a 2-oxobenzylamide intermediate **26**, Scheme 4. Reaction of diethyl oxalate with

Scheme 4[a]



[a] Reagents: (a) NaH, EtOH; (b) AcOH, 45% HBr; (c) oxalyl chloride, benzylamine, pyridine; or benzyl alcohol, HBr, benzene; (d) $NaNO_2$, $SnCl_2 \cdot 2H_2O$; (e) EtOH, H_2O; (f) CH_2O, $NaCNBH_3$, AcOH, MeOH.

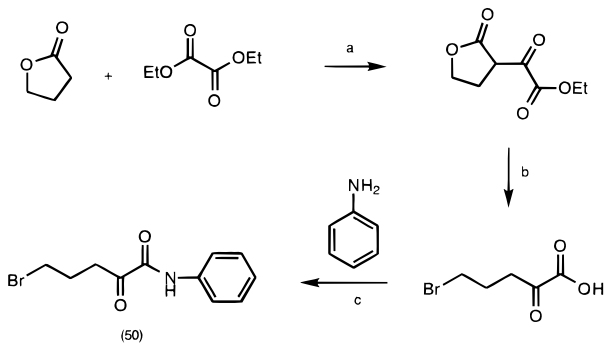
butyrolactone afforded ethyl 3-butyrolactone acetate (**24**) which was refluxed in 45% HBr in acetic acid to give 2-oxo-5-bromopentoic acid (**25**). The 2-keto acid was converted to the 2-ketobenzylamide **26** using TBTU and DIPEA in DMF. Meanwhile the aniline derivative **27** was converted to the corresponding hydrazine intermediate **28** with sodium nitrite and tin chloride dihydrate. This hydrazine intermediate was then reacted with the 2-oxobenzylamide intermediate **26** to give the 2-benzylamidotryptamine **29**. The primary ethylamine was then methylated to afford the desired *N*,*N*-dimethylaminotryptamine derivatives, Scheme 4.

The 2-phenylamidotryptamine derivative **52** was synthesized as described in Scheme 4 using a 2-oxophenylamide intermediate **50** in place of the 2-oxobenzylamide analogue. The phenylamide **50** was prepared as described in Scheme 5.

Many of the benzylamine derivatives required for the final amide coupling were synthesized as they were not commercially available. The sulfonamido benzylamide **57** required for the synthesis of **58** was synthesized as shown in Scheme 6. *tert*-Butyloxycarbonyl protection of 4-aminobenzylamine was followed by coupling with methanesulfonyl chloride to give **56**. Deprotection with TFA afforded the methylsulfonamido benzylamine intermediate **57**. A similar method was employed for the synthesis of the benzylamide derivatives required for the synthesis of **62**−**64**, respectively.

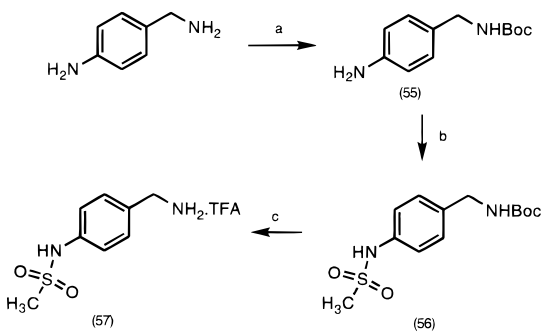
Other Hydantoin Side Chains. A range of hydantoin ring systems were investigated in an attempt to

Scheme 5[a]



[a] Reagents: (a) NaH, EtOH; (b) 45% HBr, AcOH; (c) TBTU, DIPEA, DMF.

Scheme 6[a]



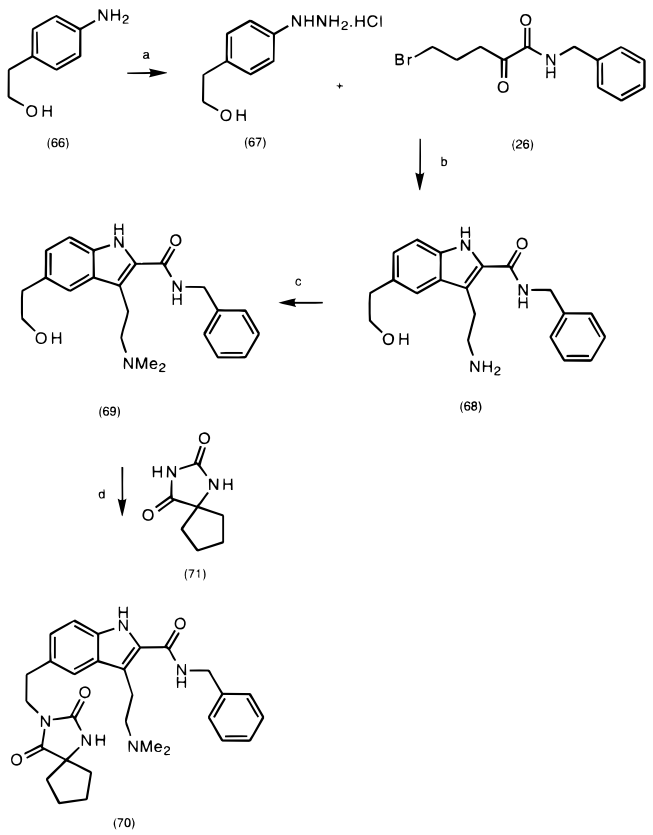
[a] Reagents: (a) Boc_2O; (b) CH_3SO_2Cl; (c) TFA.

improve potency and in particular secure 100-fold selectivity over other receptor subtypes. The spirocyclopentanylhydantoin derivative **70** was synthesized in two different ways. A variation on the method outlined in Scheme 4 provided the desired target molecule. In this method 4-aminophenethyl alcohol (**66**) was converted to the corresponding 4-hydrazinophenethyl alcohol intermediate **67** which in turn was reacted with the previously prepared 2-oxobenzylamide intermediate **26** to afford 2,*N*-benzylcarboxamido-5-(2-hydroxyethyl)-tryptamine (**68**), Scheme 7. The ethylamine nitrogen of **68** was methylated followed by Mitsunobu[25,26] coupling of the 5-ethyl alcohol tryptamine intermediate with the hydantoin derivative **71** to give the target molecule **70**.

The spirohydantoin derivative **70** was also synthesized as shown in Scheme 4. 5-Spirocyclopentanylhydantoin (**71**) required for the synthesis of **70** was synthesized as described in Scheme 8. The hydantoin was then coupled to 4-nitrophenethyl alcohol under Mitsunobu[25,26] conditions to afford the 4-nitrophenethylhydantoin derivative **72** which was converted under hydrogenation conditions to the aniline derivative **73**. Conversion of the aniline compound to the desired tryptamine derivative **70** then proceeded as shown in Scheme 4.

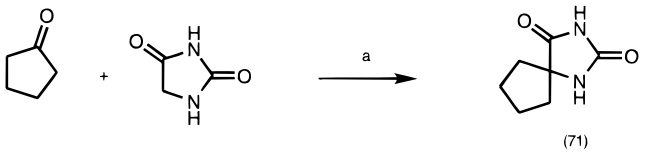
The trimethylenehydantoin analogue **82** was synthesized as shown in Scheme 9. Hydrocinnamic acid was nitrated with concentrated H_2SO_4 and concentrated HNO_3 followed by conversion of the carboxylic acid to the isocyanate using DPPA and triethylamine in dioxane. The isocyanate was reacted with proline to give **77** which was reacted with DCCI and *p*-nitrophenol in acetonitrile to force the ring closure and afford the trimethylenehydantoin intermediate **78**. The nitro compound was converted to the desired 2,*N*-benzylcarboxamidotryptamine derivative **82** under conditions previously described, Scheme 9.

Scheme 7[a]



[a] Reagents: (a) $NaNO_2$, $SnCl_2 \cdot 2H_2O$; (b) EtOH, H_2O; (c) CH_2O, $NaCNBH_3$, AcOH, MeOH; (d) Ph_3P, DIAD, DMF.

Scheme 8[a]



[a] Reagents: (a) NaCN, $(NH_4)_2CO_3$.

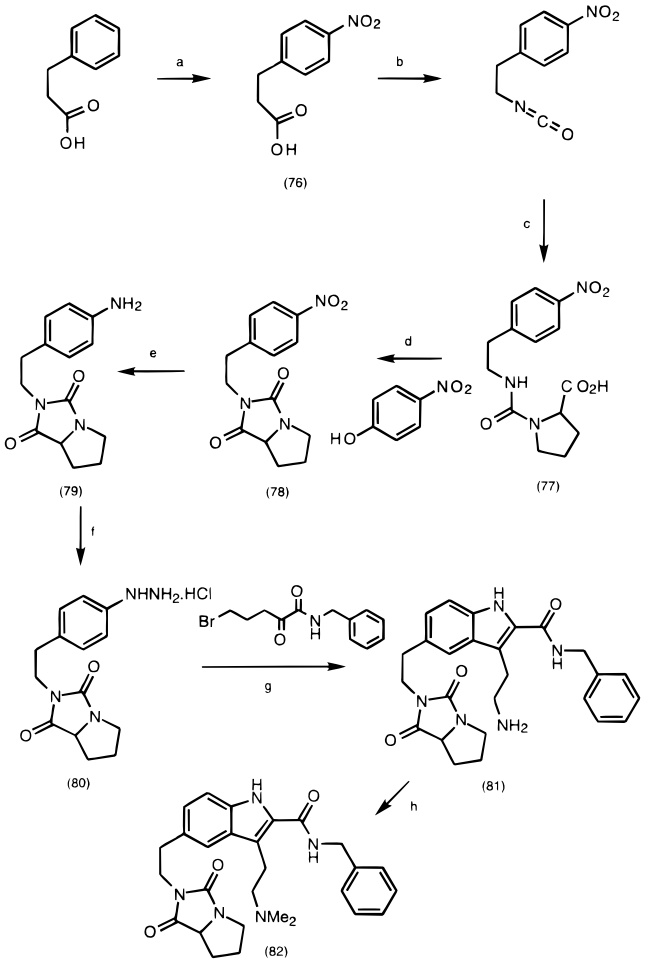
Several *N*-methylhydantoin derivatives were also investigated. The 3,4-dimethyl-4-phenylhydantoin derivative **85** used in the synthesis of **90** and **91** was synthesized by N-methylation of **83** with dimethyl sulfate, Scheme 10. Reduction of the nitro group under hydrogenation conditions gave the aniline intermediate which was reacted on as described in Scheme 1 to give the tryptamine derivatives **90** and **91**.

Results and Discussion

The tryptamine derivatives investigated are shown in Table 1.

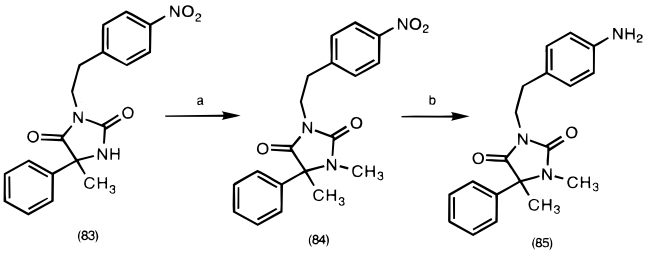
Following the poor pharmacokinetics observed for the 2-ester tryptamine series,[21] a series of 2-amidotryptamine derivatives were investigated. To explain the biological data, we referred to our theoretical receptor model for the vascular 5-HT$_{1B}$-like receptor shown in Figure 1. The theoretical receptor model which is composed of a protonated amine, an aromatic binding site, a hydrogen-bond acceptor site, a 'selectivity' site

Scheme 9[a]



[a] Reagents: (a) H_2SO_4, HNO_3; (b) DPPA, Et_3N, dioxane; (c) proline; (d) DCCI, CH_3CN; (e) H_2, Pd−C (10%); (f) $NaNO_2$, $SnCl_2 \cdot 2H_2O$; (g) EtOH, H_2O; (h) CH_2O, $NaCNBH_3$, MeOH, AcOH.

Scheme 10[a]



[a] Reagents: (a) NaH, $(CH_3)_2SO_4$, DMF; (b) H_2, Pd−C (10%).

for 5-HT_{1B}-like over 5-HT_{2A}, a hydrophobic site, and an additional hydrogen-bonding donor/acceptor site with associated intergroup distances was generated using systematic conformational searching of a series of analogues having a range of affinities and efficacies at both the 5-HT_{1B}-like and 5-HT_{2A} receptors.[27] This model proved to be qualitatively predictive for both affinity and selectivity and enabled the design of analogues having both affinity and selectivity at 5-HT_{1B}-like receptors. 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.[27] Additionally, due to the structural nature of the pharmacophore model, it was possible to use this model to design novel analogues (e.g., other than indole-based

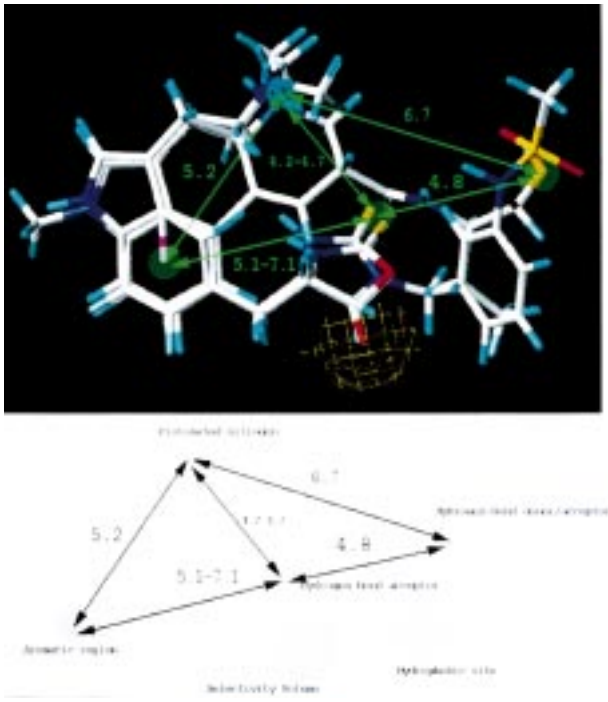
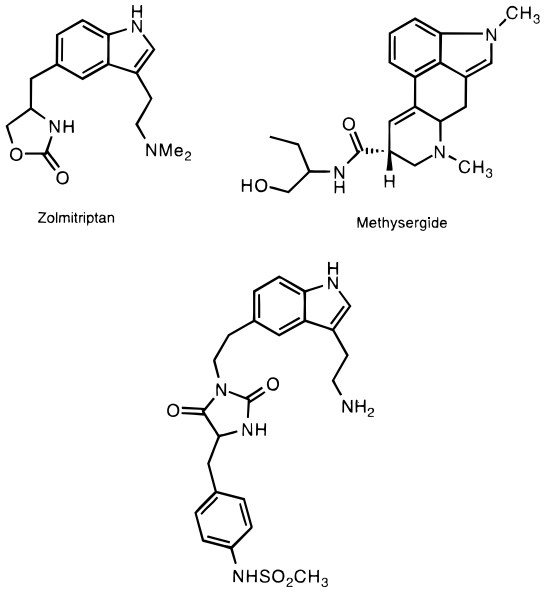


Figure 1. Theoretical 5-HT_{1B}-like receptor model using zolmitriptan[27] and compound **37** from Glen et al.[27] as references and with methysergide as background.

Chart 1



compounds) while maintaining affinity and selectivity for the 5-HT_{1B}-like receptor.

The principal regions responsible for affinity are overlaid using zolmitriptan,[27] another 5-HT_{1B}-like agonist (compound **37** from Glen et al.[27]), 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.[27]). Methysergide (pA_{50}/α = 6.7/0.64 at 5-HT_{1B}) was one of the structures chosen with restricted conformational freedom about the ethylamine side chain to deduce the theoretical model.[27] This was one of a larger number of structures used to deduce the relative posi-

tions of pharmacophoric groups. It is shown here as a reference structure for comparison purposes, with relevant new structures overlayed. Zolmitriptan is a selective 5-HT$_{1B}$ agonist (pA_{50}/α = 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.[27] Chart 1, represents a selective 5-HT$_{1B}$ agonist (pA_{50}/α = 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, hydrogen-bonding donor/acceptor sites, and hydrophobic binding site.[27]

As postulated previously there appears to be a spatial restriction on the size of the 2-substituent on the indole ring, the receptor not tolerating well large substituents at this position.[21] We therefore hypothesized that there was a steric interaction between the molecule 2-substituent and the receptor. If the molecule binds in a similar way, it would have to be pushed from the optimum binding position or displaced by the steric interaction between the 2-substituent and the receptor in order to accommodate the large 2-substituent. This would result in important functional groups not occupying optimal positions for binding at the proposed auxiliary binding sites.[21,27]

A range of aliphatic amides were initially examined. Compounds **6**−**8** and **11**−**16** all showed poor affinity for the 5-HT$_{1B-like}$ receptor. The poor affinity of the smaller 2-amidotryptamine derivatives would appear to indicate that unlike the 2-ester group, the 2-amide side chain does not contribute significantly to binding at the aromatic binding site following the proposed displacement. Figure 2 shows **1** displaced to accommodate the 2-ethyl ester group while still maintaining the pharmacophoric binding points previously proposed. **1** is capable of interacting with the principal binding sites affording the compound good affinity, efficacy, and selectivity.[21]

The amide side chain may not contribute significantly to binding at the aromatic binding site because of different electronic effects imposed by the amide side chain on the attached indole ring or because of the reduced conformational flexibility of the amide compared to the ester. As N-substitution of the amide group increases in size (>ethyl), the proposed molecule displacement within the pharmacophore model results in removal of the hydantoin carbonyl out of the hydrogen-bonding site and the indole ring out of the aromatic binding site, resulting in poor potency. Selectivity is also diminished as the proposed selectivity volume is no longer occupied. These results are entirely consistent with the proposed model and add validity to its use in compound design.

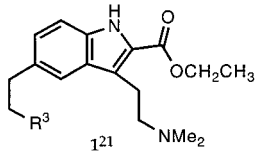
A series of 2,*N*-benzylcarboxamidotryptamine analogues were also investigated, the impetus for this series coming from the observed high affinity at the 5-HT$_{1B}$-like receptor of the 2-benzyl ester tryptamine derivative **9** (pK_B = 7.92).[21] The 2,*N*-benzylcarboxamidotryptamine derivatives investigated incorporated a 5-ethylene-linked hydantoin side chain. Following the observed 100-fold selectivity of **107**[21] for the 5-HT$_{1B}$-like receptor over 5-HT$_{2A}$ and other functional receptors, most of the compounds included 4,4-dimethyl substitution on the hydantoin ring. The dimethyl group increases penetration of the proposed 'selectivity' volume.[27] Several alkyl- and phenyl-substituted hydantoin derivatives were also investigated as well as several unsubstituted analogues in an effort to explore this region of the receptor. Substitution on the 2,*N*-benzylcarboxamido phenyl ring was also investigated, including groups of differing size and electronic nature.

Many of the compounds showed favorable affinity at the 5-HT$_{1B}$-like receptor and acceptable selectivity over the 5-HT$_{2A}$ and α_1-adrenoceptor. The 2,*N*-benzylcarboxamidotryptamine derivatives **20** (pK_B = 7.36) and **23** (pK_B = 7.09) showed high potency, **23** exhibiting 30-fold selectivity over 5-HT$_{2A}$ activity and ~80-fold selectivity over α_1-adrenoceptor activity. Good selectivity over α_1-adrenoceptor affinity was desired in order to avoid cardiovascular side effects.

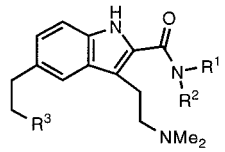
The 2,*N*-benzylcarboxamido side chain is bulkier than the 2-ethyl ester side chain. Molecular modeling and conformational search studies on the 2,*N*-benzylcarboxamidotryptamine series revealed that displacement of the molecule from the proposed binding sites of the receptor model was such that the indole ring could not occupy the aromatic binding site of the theoretical receptor model.[27] The high affinity of the 2,*N*-benzylcarboxamidotryptamine series can be explained in terms of the ability of the 2,*N*-benzylcarboxamido phenyl ring to substitute for the indole ring and occupy the aromatic binding site, Figure 3. This was predicted by the modeling studies and indicates the utility of the model. The 3-ethylamine nitrogen can still interact accurately with the amine-binding site even though the side chain comes from a different direction. In this conformation the amide bond is slightly twisted from planarity but still energetically favorable. The 5-ethyl-linked hydantoin side chain is flexible, and it is proposed that within the active site the side chain adopts a conformation to allow one of the carbonyl groups to interact with the hydrogen-binding site and the other with the hydrogen-bonding donor−acceptor site, Figure 3. The selectivity site shown in yellow is occupied by part of the indole ring.

Changes in substitution on the 2,*N*-benzylcarboxamido group were made in an attempt to increase the selectivity for the 5-HT$_{1B}$-like receptor over 5-HT$_{2A}$ and other receptor subtypes to the desired 100-fold level. The results shown in Table 1 indicate that variations in substitution on the benzylamido side chain have a large impact on vascular 5-HT$_{1B}$-like receptor affinity. The size of the substituents may alter the conformational preference of the molecule within the active site as large substituents are proposed to result in greater displacement from the conformation adopted by compounds without substitution in the 2,*N*-benzylcarboxamido phenyl ring. The electronic nature of the substituents is also extremely significant as the 2,*N*-benzylcarboxamido phenyl ring is now crucial for binding at the aromatic binding site. Differences in electron density will have an effect on affinity and possibly efficacy. (It was proposed[21] that the ρ density of the indole double bond in the region normally occupied by 5-HT was responsible for the agonist properties of these molecules,

Table 1. Affinity Estimates for Novel Compounds at the Vascular 5-HT_{1B}-like and 5-HT_{2A} Receptors in the Rabbit Saphenous Vein (RbSV) and Aorta (RbA)[a]



1[21]



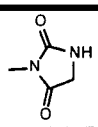
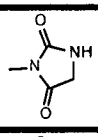
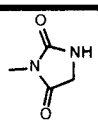
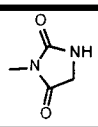
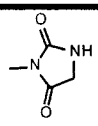
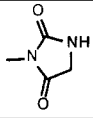
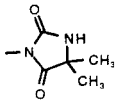
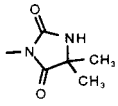
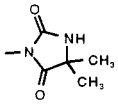
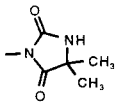
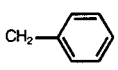
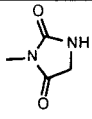
Compound Number	R^1	R^2	R^3	5-HT_{1B}-like RbSV (pK_B)	5-HT_{2A} RbA (pK_B)	α_1 RbTA (pK_B)
1				7.42	<5.0	5.43
6	H	H		<5.0	<5.0	
7	H	CH_3		5.94	<5.0	
8	CH_3	CH_3		5.0	<5.0	
11	OCH_3	CH_3		5.76	5.3	
12	$(CH_2)_3CH_3$	H		5.94	5.2	
13	$(CH_2)_2Ph$	H		5.57	5.35	
14	$(CH_2)_3CH_3$	H		5.47	<5.0	
15	CH_2-C≡CH	H		5.44		4.62
16	NH_2	H		5.48		<4.5
20		H		7.36	6.09	5.77

Table 1 (Continued)

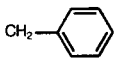
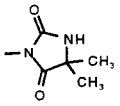
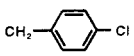
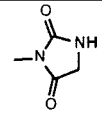
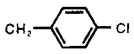
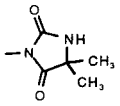
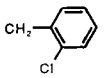
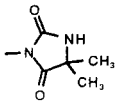
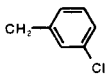
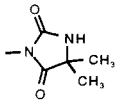
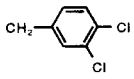
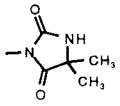
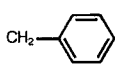
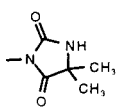
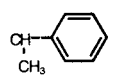
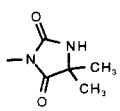
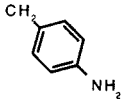
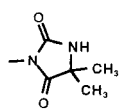
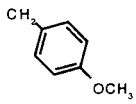
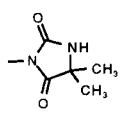
Compound Number	R^1	R^2	R^3	5-HT$_{1B}$-like RbSV (pK$_B$)	5-HT$_{2A}$ RbA (pK$_B$)	α_1 RbTA (pK$_B$)
23		H		7.09	5.6	5.2
30		H		7.74	6.31	6.47
31		H		7.59		5.86
32		H		5.81		5.35
33		H		6.45		
34		H		6.5		5.0
35		CH_3		5.8	6.03	5.8
36		H		5.5	5.59	4.65
37		H		6.19		4.52
38		H		6.54		4.73

Table 1 (Continued)

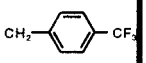
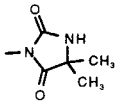
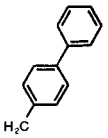
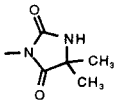
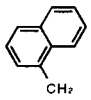
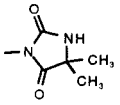
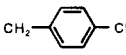
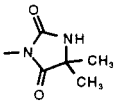
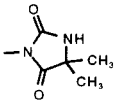
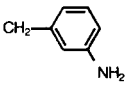
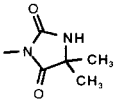
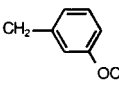
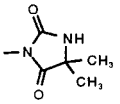
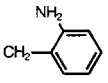
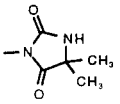
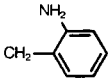
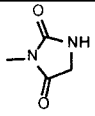
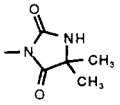
Compound Number	R^1	R^2	R^3	5-HT_{1B}-like RbSV (pK_B)	5-HT_{2A} RbA (pK_B)	α_1 RbTA (pK_B)
39		H		6.2		<5.0
40		H		5.77		5.0
41		H		5.5		
42		H		7.0		6.0
43		H		<5.0		
44		H		6.52		4.58
45		H		6.47		5.17
46		H		6.72		4.79
47		H		6.67		5.73
48	OCH_3	H		5.4		<4.5

Table 1 (Continued)

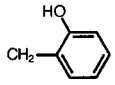
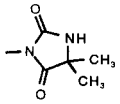
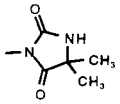
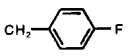
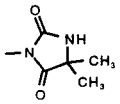
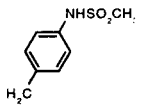
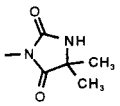
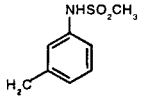
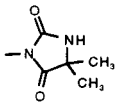
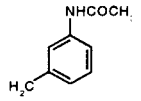
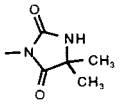
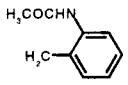
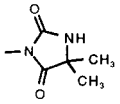
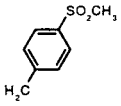
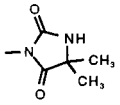
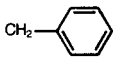
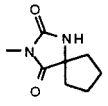
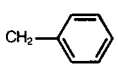
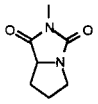
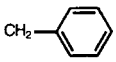
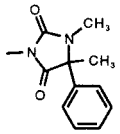
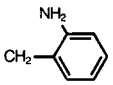
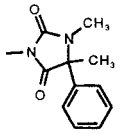
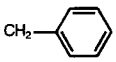
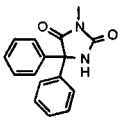
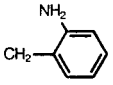
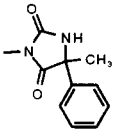
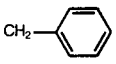
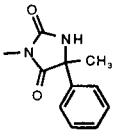
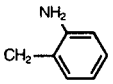
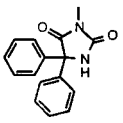
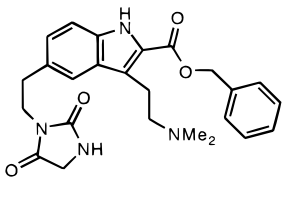
Compound Number	R^1	R^2	R^3	5-HT$_{1B}$-like RbSV (pK$_B$)	5-HT$_{2A}$ RbA (pK$_B$)	α_1 RbTA (pK$_B$)
49		H		6.61		5.0
52		H		5.21		4.86
54		H		7.3		5.46
58		H		5.65		<4.5
62		H		5.67		4.51
63		H		5.68		4.5
64		H		6.04		<5.0
65		H		5.91		4.52
70		H		7.2		5.48
82		H		6.66		5.31

Table 1 (Continued)

Compound Number	R^1	R^2	R^3	5-HT_{1B}-like RbSV (pK_B)	5-HT_{2A} RbA (pK_B)	α_1 RbTA (pK_B)
90		H		7.19		5.5
91		H		6.64		4.78
98		H		6.44		5.0
104		H		6.65		5.21
105		H		7.15		5.27
106		H		6.31		5.43

[a] pK_B : $-\log_{10} K_B$, the dissociation equilibrium constant. α_1-Adrenoceptor affinity was measured in the rabbit thoracic aorta (RbTA) using phenylephrine as agonist. Affinity values are the means of at least three separate estimates. Standard errors are omitted for clarity but in all cases were ≤ 0.2 $\log_{10}$ unit. In each case, affinity estimates were determined using the Gaddum−Schild equation and 5-HT as the receptor agonist.



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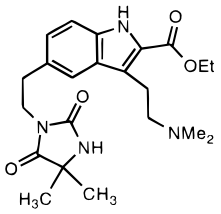

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and it should be noted that the ρ-electron density is low at the indole double-bond region for **23**.)

Several chloro-substituted 2,*N*-benzylcarboxamidotryptamine derivatives showed good affinity. The *para*-substituted analogue **30** exhibited high 5-HT_{1B}-like affinity (pK_B = 7.74) but poor selectivity over α_1-adrenoreceptors (pK_B = 6.47). The dimethylhydantoin **31** had slightly decreased affinity (pK_B = 7.59) but improved selectivity over α_1-adrenoceptor affinity (pK_B = 5.86). This observation is consistent with the superior selectivity of the dimethylhydantoin derivatives within the 2-ester tryptamine series.[21] The electronic effect and overall size of these halogen substituents appear to enhance the binding ability of these molecules. The most selective compound with affinity for 5-HT_{1B}-like receptor of $pK_B > 7.0$ was the 4-fluoro derivative **54** (pK_B = 7.3) which showed ~70-fold selectivity over α_1-adrenoceptor affinity. This would seem to indicate that halogen substitution is well-tolerated within this series.

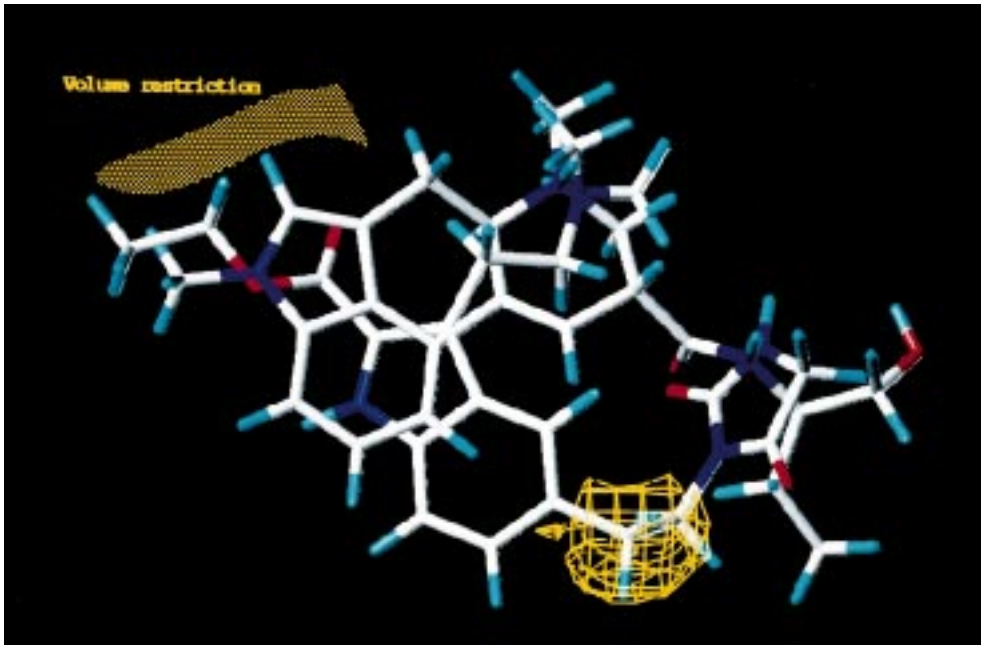

Figure 2. Proposed conformation of **1** overlayed on methysergide to show displacement.

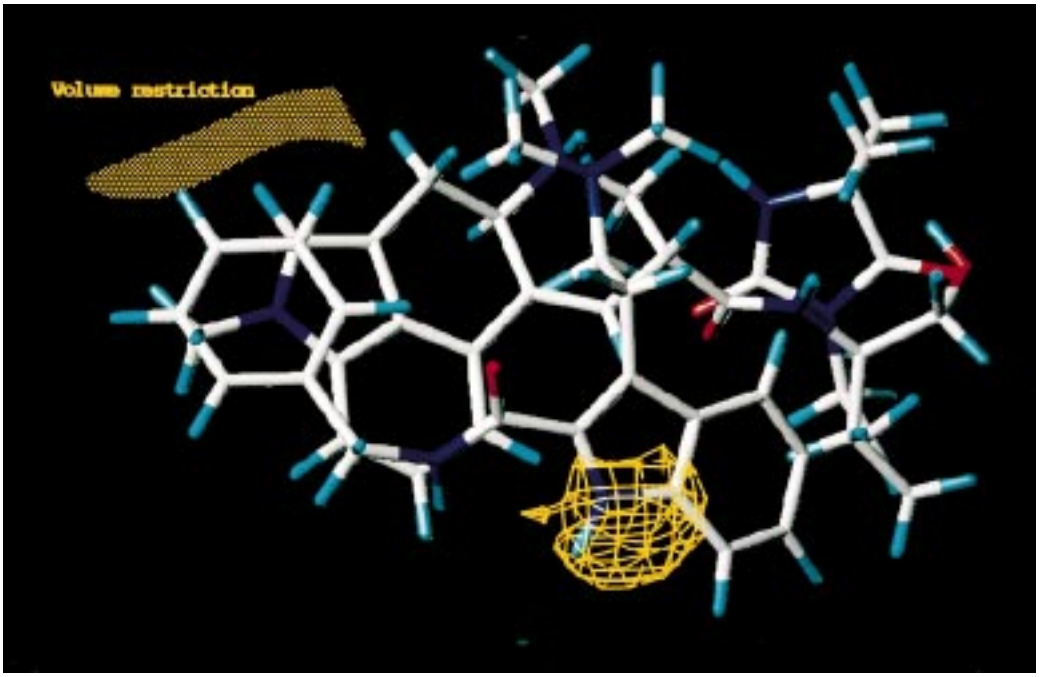

Figure 3. Proposed conformation of **23** fitted to the pharmacophore model with methysergide as background. The selectivity volume is represented by the yellow mesh.

Several of the amino-substituted 2,*N*-benzylcarboxamido derivatives proved interesting although the affinity of these derivatives was below our desired level of pK_B > 7: **37** (pK_B = 6.19), **44** (pK_B = 6.52), **46** (pK_B = 6.72), and **47** (pK_B = 6.67). The two phenyl-substituted hydantoin analogues containing an amino-substituted 2,*N*-benzylcarboxamido side chain, **91** (pK_B = 6.64) and **104** (pK_B = 6.65), had similar potency. The reduced potency of these derivatives may be due to the changes in the electron density distribution of the substituent phenyl ring making it more dissimilar from indole-like analogues. This is consistent with the original argument relating to the ideal affinity and efficacy of the ester series being achieved with a ρ-electron-deficient indole system. The decreased potency recorded for **91** is consistent with the biological profile of the 2-aminobenzylamide derivatives previously discussed. Although potency was low, both **44** and **46** had ~100-fold selectivity over 5-HT$_{2A}$ and α_1-adrenoceptor affinity. This improved selectivity may be due to a subtle change in orientation caused by the inclusion of the amino groups.

The 4-methylbenzylamide derivative **42** was originally synthesized because smaller substituents seemed to yield compounds of higher potency. The compound had the desired affinity (pK_B = 7.0) but poor selectivity over α_1-adrenoceptor affinity (pK_B = 6.0).

The 5-spirocyclopentanylhydantoin derivative **70** had good affinity (pK_B = 7.2) and ~50-fold selectivity over α_1-adrenoceptor affinity (pK_B = 5.48). It would appear

Table 2. Affinity Values[a]

	pK_i		
receptor type	5-HT_{1D}	5-HT_{1A}	5-HT_{2C}
20	5.88	4.17	5.72
23	5.42	4.83	5.66

[a] Affinity values for 5-HT_{1A} and 5-HT_{2C} were measured in rat cortex homogenates. 5-HT_{1D} affinity estimates were obtained from calf caudate homogenates. Affinity values are the means of at least three separate estimates. Standard errors are omitted for clarity but in all cases were ≤ 0.2 $\log_{10}$ unit.

that there is a reasonable amount of room in the receptor around the 4-position of the hydantoin once the molecule has adopted a conformation for binding.

The trimethylenehydantoin derivative **82** had reduced 5-HT_{1B}-like receptor affinity (pK_B = 6.66) and poor selectivity over α_1-adrenoceptor affinity (pK_B = 5.31) compared with the dimethylhydantoin analogue **23** and the unsubstituted derivative **20**. There may be a restriction on the functionality that can intrude on the space between the 1 and 5 positions. Several *N*-methylhydantoin analogues were also investigated as it was uncertain whether the reduced affinity and selectivity of the trimethylene derivative **82** was due to the masking of the hydantoin 3-NH or because of the crowding of the region in space between positions 1 and 5. **90** had good affinity for the 5-HT_{1B}-like receptor (pK_B = 7.19) indicating that the free hydantoin NH is not necessary for high potency.

Phenyl-substituted hydantoin derivatives investigated included the 4-phenyl derivative **104** (pK_B = 6.65) and the 4,4-diphenyl derivatives **98** (pK_B = 6.44) and **106** (pK_B = 6.31). Both compounds had reduced potency most likely due to steric problems associated with the bulky phenyl groups which were ill-fitting on the pharmacophore model. Again the 2-aminobenzylamide derivative **106** was less potent than the unsubstituted analogue which may be a reflection of the change in electron density of the phenyl ring while interacting with the aromatic binding site. It is also possible that the amino group may be interacting with other parts of the receptor resulting in less than optimal binding at the active site.

A range of sulfonamido- and acetamido-substituted 2,*N*-benzylcarboxamido derivatives were investigated to assess changes in size of the 2-side chain as well as changes on the electronic nature of the phenyl ring. All four compounds **58** (pK_B = 5.65), **62** (pK_B = 5.67), **63** (pK_B = 5.68), and **64** (pK_B = 6.04) showed poor affinity for the 5-HT_{1B}-like receptor further indicating the lack of room in this region of the receptor and the detrimental effect large groups have on potency. The best of these compounds is the *ortho*-substituted compound **64** possibly indicating that there is less displacement with this compound. The extra oxygens in these compounds may interact with regions previously untouched by other molecules, or the electronic effects of these substituents may not be well-tolerated.

The unsubstituted 2-benzylamide derivatives **20** and **23** were investigated in greater detail. Pharmacological evaluation of compounds **20** and **23** at both histamine (H_1) or muscarinic (M_3) receptors revealed no significant affinity (pK_b's < 5.0). CNS binding results for compounds **20** and **23** at several amine-binding sites have also been examined, results shown in Table 2. Both **20** and **23** have little affinity for these 5-HT receptors in the brain. Like **1** previously reported,[21] **20** and **23** appear to be able to discriminate between vascular and central 5-HT receptors.

Compounds from this series were thus found to meet the initial objectives set for this research. **20** and **23** were analyzed in vivo to obtain preliminary pharmacokinetics. These studies revealed that the 2,*N*-benzylcarboxamidotryptamine series was considerably more stable in animal plasma than the corresponding 2-ester series. **23** was found to have a half-life of 1.5 h in rat plasma and greater than 4 h in dog plasma. **23** was found to have 100% oral bioavailability at 10 mg/kg, while **20** was found to have ~50% oral bioavailability.

Conclusions

A novel series of 5-HT_{1B}-like receptor antagonists has been identified. Several compounds were found to have acceptable potency and good selectivity. The theoretical receptor model which was previously described[21,27] has been a useful tool in the design of compounds from this series and has been successfully utilized in work which has culminated in the discovery of novel molecules which fit the desired biological profile. Several compounds have been identified with vascular 5-HT_{1B}-like affinity above the desired pK_B level of 7.0 and close to 100-fold selectivity over α_1-adrenoceptor affinity including **20, 23, 31, 70**, and **105**. Two other compounds (**44** and **46**) were found to have less than the desired vascular 5-HT_{1B}-like potency but achieved greater than 100-fold selectivity over α_1-adrenoceptor affinity. The mode of binding to a theoretical receptor model for the 2,*N*-benzylcarboxamidotryptamine series is different from that described for the less bulky 2-ester tryptamine series.[21] The discovery that the phenyl ring appears to be able to successfully replace the indole ring at the aromatic binding site increases the scope for design of other classes of vascular 5-HT_{1B}-like receptor antagonists both within the tryptamine series and through novel classes such as phenylpiperazine derivatives.[28] Compounds such as **23** are useful biological probes and will be invaluable in the classification of the 5-HT_{1B}-like receptor.

Experimental Section

Chemical Methods. Computational chemistry was performed on a Silicon Graphics Iris Indigo II computer using the Sybyl[29] molecular modeling 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) spectrometer, a Kratos MS50 (FAB) mass spectrometer, or a Joel JMX DX-300 double focusing instrument. Melting points were determined on a Gallencamp 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}). Infrared spectra were run in KBr disks on a Bruker IFS66 FTIR spectrometer. Microanalyses were performed on a VG Platform spectrometer and are within 0.4% of the theoretical values unless otherwise stated. HPLC was performed on a Waters Millenium system comprising a 490E multiwavelength detector, 600 controller, 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 over 20 min) (A)/0.1 M NH_4OAc (pH 4) (90−10%) (B) solvent system was used.

3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (6). Method 1: 3-(4-Aminophenethyl) imidazolidine-2,4-dione[21] (1.0 g, 3.91 mmol) was dissolved in a mixture of ethanol (2.0 mL) and water (6.5 mL), and to this solution was added concentrated HCl (0.78 mL, 7.42 mmol). The solution was cooled to 0 °C, and a solution of sodium nitrite (0.54 g, 7.82 mmol) in water (2.5 mL) was added. The solution was stirred for 30 min after which the excess sodium nitrite was destroyed with urea (0.29 g, 4.8 mmol). Meanwhile, the amide **2**[21] (0.72 g, 3.91 mmol) in ethanol (3.5 mL) was stirred with sodium acetate trihydrate (2.77 g, 20 mmol) in water (3.5 mL). This solution was stirred for 20 min at ∼0 °C after which it was added quickly to the cold diazonium solution. The solution was allowed to stir for a further 30 min at 0 °C and then allowed to stir up to room temperature over 1 h. The pH was adjusted to 9 with 10% sodium hydroxide solution and the solution left in the fridge overnight. The residue was extracted with ethyl acetate (3 × 30 mL), the organic layer dried and filtered, and the solvent evaporated to give a red gum which was purified by column chromatography to afford 300 mg of the desired hydrazone intermediate, ∼90% pure. A portion of the hydrazone (30 mg, 0.08 mmol) was dissolved in ethanol (3.0 mL), concentrated H_2SO_4 (0.13 mL) was added, and the solution was gently refluxed overnight. The solvent was evaporated under reduced pressure, water added, and the pH adjusted to 9 with potassium carbonate. The basic solution was extracted with ethyl acetate, dried, and filtered and the organic layer reduced to give a yellow residue which was further purified by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (50:8:1) to afford the desired tryptamine **6** as an off-white solid. Further purification using preparative HPLC gave 13.0 mg (24%) of the acetate salt of **6** as a white lyophylate: MS *m*/*z* 358 $(M + 1)^+$; ^{1}H NMR δ 1.9 (3H, s, CH_3CO_2H), 2.18 (6H, s, 2 × NCH_3), 2.85 (4H, m, 2 × CH_2), 3.15 (2H, m, CH_2), 3.6 (2H, m, CH_2), 3.8 (2H, s, CH_2NH), 7.0 (1H, dd, H6), 7.3 (1H, d, H7), 7.35 (1H, d, H4), 7.95 (1H, s, NH), 11.05 (1H, s, NH); found M^+ 357.17723, $C_{18}H_{23}N_5O_3$ requires M^+ 357.18008. Anal. ($C_{18}H_{23}N_5O_3$·1.0CH_3CO_2H). Calcd: C, 57.54; H, 6.52; N, 16.78. Found: C, 54.06; H, 6.24; N, 16.29.

***N*-Methyl-2-acetyl-5-(dimethylamino)pentamide (3). Method 2[30] (using *N*-methyl-3-ketobutyramide):** The yellow oil was distilled under reduced pressure, bp 180−200 °C at 0.2 mmHg. Further purification by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (90:8:1) afforded 5.3 g (13%) of **3** as a light-yellow oil: MS *m*/*z* 200 $(M)^+$; ^{1}H NMR δ 1.15−1.35 (2H, m, CH_2), 1.55−1.75 (2H, m, CH_2N), 2.1 (6H, s, 2 × NCH_3), 2.15 (3H, m, NCH_3), 2.6 (2H, m, CH_2), 3.3 (3H, s, CH_3CO), 4.1 (1H, br s, OH), 8.1 (1H, br s, NH).

***N*-Methyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (7).** Method 1 (using previous compound **3**)**:** 63.0 mg (38%) of the HCl salt as a white powder; mp 262−264 °C; MS *m*/*z* 372 $(M + 1)^+$; ^{1}H NMR δ 2.2 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2, under DMSO peak), 2.8 (3H, d, NHCH_3), 2.9 (2H, t, 5-CH_2), 3.05 (2H, t, 3-CH_2), 3.6 (2H, t, CH_2Hyd), 3.75 (2H, s, NHCH_2CO), 7.0 (1H, dd, H6), 7.25 (1H, d, H7), 7.3 (1H, s, H4), 8.95 (1H, s, NH), 9.0 (1H, br m, NH), 11.1 (1H, s, NH). Anal. ($C_{19}H_{25}N_5O_3$·0.1H_2O) C, H, N.

***N*,*N*-Dimethyl-2-acetyl-5-(dimethylamino)pentamide (4).** Method 2[30] (using *N*,*N*-dimethyl-3-ketobutyramide): purification by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (80:8:1) gave 5.16 g (12%) of **4** as a light-yellow oil; R_f 0.25; MS *m*/*z* 214 $(M)^+$; ^{1}H NMR δ 1.75 (2H, m, CH_2), 2.1 (6H, s, 2 × NCH_3), 2.15 (6H, s, 2 × NCH_3), 2.25 (2H, t, CH_2), 3.3 (3H, s, CH_3CO, under water peak), 3.8 (2H, t, CH_2), 5.3 (1H, s, OH).

***N*,*N*-Dimethyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (8).** Method 1 (using previous compound **4**): isolated the HCl salt as a white powder; MS *m*/*z* 385 $(M)^+$; ^{1}H NMR δ (CD_3OD) δ 2.3 (6H, s, 2 × NCH_3), 2.6 (2H, m, CH_2NMe_2), 2.95 (4H, m, 2 × CH_2), 3.1 (6H, s, CONMe_2), 3.7 (2H, m, CH_2), 3.8 (2H, s, CH_2NH), 7.1 (1H, dd, H6), 7.3 (1H, d, H7), 7.4 (1H, d, H4). Anal. ($C_{19}H_{27}N_5O_3$·2.0HCl·0.05H_2O) C, H, N.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (9). Method 3: A mixture of **1**[21] (962 mg, 2.49 mmol) and titanium tetraisopropoxide (0.24 mL, 0.87 mmol) in benzyl alcohol (20 mL) was heated to 100 °C for 24 h. The solution was concentrated under reduced pressure to give a brown gum which was purified by flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (200:8:1) to give 1.1 g (98%) of **9** as a yellow solid: mp 163−170 °C (softens); MS *m*/*z* 449 $(M + 1)^+$; ^{1}H NMR δ 2.15 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2Ph), 2.50 (2H, m, CH_2NMe_2, under DMSO peak), 2.92 (2H, m, 5-CH_2), 3.19 (2H, m, 3-CH_2), 3.62 (2H, m, CH_2Hyd), 3.88 (2H, s, CH_2CO), 5.38 (2H, s, CH_2O), 7.11 (1H, d, H6, J = 8.0 Hz), 7.4 (7H, m, H7, H4, H2′−H6′), 8.0 (1H, s, NH), 11.5 (1H, s, NH). Anal. ($C_{25}H_{28}N_4O_4$·0.75H_2O) C, H, N. HPLC retention time = 14.3 min.

3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylic Acid (10). Method 4: A mixture of **9** (137 mg, 0.3 mmol) and 10% palladium on carbon (30 mg) in ethyl acetate (10 mL) and ethanol (10 mL) was hydrogenated overnight at room temperature and atmospheric pressure. The catalyst was filtered through Celite; the solution was concentrated and triturated with dichloromethane to give 86 mg (79%) of **10** as a white powder: mp 250 °C dec; MS *m*/*z* 359 $(M + 1)^+$; ^{1}H NMR δ 2.81 (6H, s, 2 × NCH_3), 2.95 (2H, m, CH_2NMe_2), 3.41 (4H, m, CH_2-3, CH_2-5), 3.75 (2H, m, CH_2N), 3.83 (2H, s, CH_2NH), 7.1 (1H, d, H6, J = 8.3 Hz), 7.3 (1H, d, H7, J = 8.1 Hz), 7.45 (1H, s, H4). HPLC retention time = 8.06 min.

***N*-Methyl-*N*-methoxy-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (11). Method 5:** The acid **10** (50 mg, 0.14 mmol), TBTU (50 mg, 0.15 mmol), and MeONHMe·HCl (15 mg, 0.15 mmol) were dissolved in DMF (1.0 mL) and stirred vigorously, and DIPEA (48 μL, 0.28 mmol) was added. Stirring was continued for 3 h after which the solvent was evaporated under reduced pressure. Water was added and the solution extracted with ethyl acetate, dried, filtered, and evaporated under reduced pressure to give an off-white residue. Column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (100:8:1) gave **11** as a pink powder: mp 193−197 °C; MS *m*/*z* 401 (M^+); ^{1}H NMR δ 2.2 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.89 (2H, m, 5-CH_2), 3.02 (2H, m, 3-CH_2), 3.3 (3H, s, NCH_3), 3.6 (5H, m, CH_2, OCH_3), 3.87 (2H, s, CH_2CO), 7.0 (1H, dd, H6), 7.33 (1H, d, H7), 7.35 (1H, d, H4), 8.0 (1H, s, NH), 11.05 (1H, s, NH). Anal. ($C_{20}H_{27}N_5O_4$·0.5H_2O) C, H, N. HPLC retention time = 9.9 min.

***N*-Butyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (12).** Method 5: purification by preparative HPLC afforded the acetate salt of **12** as a white foam; MS *m*/*z* 414 $(M + 1^+)$; ^{1}H NMR δ 0.9 (3H, t, CH_3), 1.32 (2H, m, CH_2), 1.5 (2H, m, CH_2), 1.91 (3H, s, CH_3CO_2H), 2.2 (6H, s, 2 × NCH_3), 2.52 (2H, m, CH_2), 2.9 (2H, m, 5-CH_2), 3.08 (2H, m, 3-CH_2), 3.3 (2H, m, CH_2), 3.58 (2H, m, CH_2Hyd), 3.82 (2H, s, CH_2N), 7.02 (1H, dd, H6), 7.3 (1H, d, H4), 7.35 (1H, d, H7), 7.95 (1H, s, NH), 9.0 (1H, t, NH), 11.08 (1H, s, NH). Anal. ($C_{22}H_{31}N_5O_3$·1.0H_2O·1.0CH_3CO_2H) C, H, N. HPLC retention time = 12.81 min.

***N*-(2-Phenylethyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (13).** Method 5: yellow powder; purification by preparative HPLC afforded the acetate salt of **13** as a white

lyophylate; MS *m/z* 490 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.82 (5.5H, s, CH_3CO_2H), 2.02 (6H, s, 2 × NCH_3), 2.65−3.7 (12H, m, 6 × CH_2), 7.0 (1H, dd, H6), 7.25 (7H, m, H7, H4, 5 × ArH), 8.12 (1H, s, NH), 9.4 (1H, t, NH), 11.26 (1H, s, NH). Anal. ($C_{28}H_{35}N_5O_3 \cdot 2.8H_2O \cdot 1.85CH_3CO_2H$) C, H, N.

***N*-Butyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (14).** Method 5: yellow powder; purification by preparative HPLC afforded the acetate salt of **14** as a white lyophylate; MS *m/z* 442 $(M + 1)^+$. Anal. ($C_{24}H_{35}N_5O_3 \cdot 2.66H_2O \cdot 1.18CH_3CO_2H$) C, H, N.

***N*-(2-Propynyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (15).** Method 5: cream powder; MS *m/z* 424 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.25 (6H, s, 2 × NCH_3), 2.6 (2H, t, CH_2NMe_2, J = 7.0 Hz), 2.9 (2H, t, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.2 (1H, s, CH), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, m, CH_2NHCO), 7.0 (1H, d, H6, J = 7.5 Hz), 7.3 (2H, m, H7, H4), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{23}H_{29}N_5O_3 \cdot 0.75H_2O$) C, H, N. t_R = 11.81 min.

5-[2-(4,4-Dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]indole-2-carbohydrazide (16). Hydrazine hydrate (1 mL) was added to a suspension of ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (**107**)[21] (630 mg, 1.52 mmol) in ethanol (5 mL) and the suspension refluxed for 5 h. The reaction mixture was allowed to cool to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue purified by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (80:8:1) to afford 369 mg (61%) of **16** as a yellow powder: MS *m/z* 401 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.2 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, br s, CH_2NHCO), 7.0 (1H, dd, H6, J = 7.5 Hz), 7.3 (2H, m, H7, H4), 8.1 (1H, s, NH), 10.3 (1H, br s, NH), 11.1 (1H, s, NH). Anal. ($C_{20}H_{28}N_6O_3 \cdot 1.0\ H_2O$) C, H, N. HPLC retention time = 10.03 min.

Ethyl 3-(2-Aminoethyl)-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (19). Potassium hydroxide (271 mg, 4.8 mmol) was dissolved in absolute ethanol (3.0 mL) and added dropwise to a solution of diethyl chloropropylmalonate (0.94 mL, 4.6 mmol) in absolute ethanol (3.0 mL) at room temperature, and the solution was stirred for 2 h. Meanwhile 3-(4-aminophenethyl)imidazolidine-2,4-dione hydrochloride[21] (1.1 g, 4.3 mmol) was dissolved in water (5.0 mL) and concentrated HCl (1.25 mL). A solution of sodium nitrite (353 mg, 5.1 mmol) in water (0.8 mL) was added while maintaining the temperature at <5 °C. After 1 h, a clear solution was evident which was added dropwise to a solution of hydrolyzed ester precooled to −10 °C. After the addition, the mixture was adjusted to pH 7.5 by addition of aqueous sodium carbonate. After 1 h at 0 °C the pH was adjusted to ∼6 by addition of acetic acid and stirred overnight. The resulting red oil was extracted with dichloromethane, washed with 2 N NaOH and then water, dried, and concentrated to afford **18** as a crude red oil. The crude hydrazone **18** was heated in butanol (10 mL) at reflux for 8 h. The solution was then cooled to 0 °C and the precipitate isolated by filtration and washed with cold butanol. The solid was dried under vacuum to afford the tryptamine derivative **19** as a brown powder. Conversion to the hydrochloride salt and recrystallization from ethanol gave 237 mg (14%) of **19** as a light-yellow powder: mp 245−247 °C; MS *m/z* 359 $(M + 1)^+$. Anal. ($C_{18}H_{22}N_4O_4 \cdot 1.0HCl$) C, H, N. HPLC rentention time = 10.1 min.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (20).** Methods 3−5: HCl salt as a white powder; mp 208−209 °C; MS *m/z* 447 (M^+); ^{1}H NMR δ 2.05 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO), 2.89 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.58 (2H, t, CH_2Hyd, J = 7.0 Hz), 3.82 (2H, s, NHCH_2-CO), 4.55 (2H, d, CH_2Ph), 7.05 (1H, dd, H6), 7.32 (7H, m, H7, H4, 5 × ArH), 8.0 (1H, s, NH), 9.8 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{25}H_{29}N_5O_3 \cdot 1.0HCl \cdot 2.2H_2O$) C, H, N. t_R = 12.6 min.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (21). Method 3: A mixture of the ethyl ester **107**[21] (2.0 g, 4.8 mmol) and titanium tetraisopropoxide (0.5 mL, 1.68 mmol) in benzyl alcohol (50 mL) was heated to 100 °C for 18 h. The cooled reaction mixture was concentrated in vacuo at 0.1 mmHg and purified by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (150:8:1) to give **21** as a beige foam (1.52 g, 66%).

3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylic Acid (22). Method 4: 2.15 g (80%); mp 260 °C dec. Anal. ($C_{20}H_{26}N_4O_4 \cdot 1.6H_2O$) C, H, N.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (23).** Method 5: white powder; mp 182−183 °C; MS *m/z* 476 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.09 (6H, s, 2 × NCH_3), 2.52 (2H, m, CH_2NMe_2), 2.93 (2H, m, 5-CH_2), 3.06 (2H, m, 3-CH_2), 3.6 (2H, m, CH_2Hyd), 4.52 (2H, d, CH_2NH, J = 5.0 Hz), 7.05 (1H, d, H6, J = 7.5 Hz), 7.35 (7H, m, H7, H4, 5 × ArH), 8.1 (1H, s, NH), 9.64 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{33}N_5O_3$) C, H, N. HPLC retention time = 14.7 min.

Alternative Synthesis for 23. Ethyl Oxalylbutyrolactone (24).[31,32] Diethyl oxalate (40 mL, 0.3 mol) was added dropwise to an ice/salt-chilled solution of sodium ethoxide in ethanol (prepared from sodium (7.4 g) in ethanol (150 mL)) under nitrogen. Butyrolactone (25 mL, 0.3 mol) in ethanol (50 mL) was added dropwise over 30 min. After 1 h the cold bath was removed and the mixture allowed to warm to room temperature overnight. The resulting suspension was concentrated under reduced pressure and partitioned between ether and water. The aqueous phase was cooled in ice and 1 N HCl added until the solution was acidic. The reaction mixture was then extracted with dichloromethane (5 × 200 mL), and the combined organic layers were dried and concentrated to afford 36.3 g (65%) of **24** as a pale-yellow oil: MS *m/z* 186 (M^+); ^{1}H NMR δ ($CDCl_3$) 1.21 (3H, t, CH_3CH_2), 3.12 (2H, t, CH_2), 4.2 (2H, q, CH_2CH_3), 4.32 (2H, t, CH_2). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

5-Bromo-2-oxovaleric Acid (25).[32] Ethyl oxalylbutyrolactone (39.0 g, 0.21 mol) was treated with 40% HBr in acetic acid (84 mL), and the resulting solution was heated to 120 °C for 1 h (CAUTION: gas evolved). A further 226 mL of the 40% HBr solution was added gradually to the refluxing solution over 5 h. The solution was refluxed for a further 1 h and then stirred at room temperature for 48 h. The brown solution was concentrated under vacuum to give a brown oil which was distilled under reduced pressure to give 30.9 g (76%) of **25** as a colorless oil which solidified on standing: bp 105−112 °C at 2 mmHg.[32]

***N*-Benzyl-2-oxo-5-bromovaleramide (26). Method 6:** The α-keto acid **25** (5.0 g, 25.6 mmol) was dissolved in dichloromethane under nitrogen and cooled to 0 °C. Oxalyl chloride (15.4 mL, 30.7 mmol) in dichloromethane (20 mL) was added dropwise, and 1 drop of DMF was added prior to warming to room temperature. The solution was stirred for 3 h, then transferred via cannula to a solution of benzylamine in pyridine at 0 °C, and stirred overnight. The reaction mixture was partitioned between dichloromethane and 2 N HCl. The organic layer was washed with 2 N HCl and saturated $NaHCO_3$, dried, and concentrated under vacuum. The residue was filtered through silica eluting with petroleum ether/ethyl acetate (4:1) and concentrated under vacuum to afford 3.65 g (50%) of **26** as an off-white solid. Recrystallization from hot ethanol gave an analytically pure sample as pale needles: mp 81−82 °C; MS *m/z* 284 (M^+); ^{1}H NMR δ ($CDCl_3$) 2.2 (2H, m, CH_2), 3.18 (2H, m, 3-CH_2), 3.48 (2H, m, 5-CH_2), 4.45 (2H, m, CH_2Ph), 7.25 (5H, m, 5 × ArH). Anal. ($C_{12}H_{14}NO_2Br$) C, H, N. HPLC retention time = 17.83 min.

Alternative Synthesis for 26. Method 7: A solution of the α-keto acid **25** (11.0 g, 56.4 mmol), benzyl alcohol (10 mL,

96.6 mmol), benzene (20 mL), and hydrogen bromide-saturated benzyl alcohol (1.0 mL) was heated to reflux for 6 h. The solution was cooled, concentrated under reduced pressure, and then passed through a plug of silica eluting with petroleum ether/ethyl acetate (80:1) to give **26** as a colorless oil which solidified on standing.

2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)ethylphenylhydrazine Hydrochloride (28). Method 8: The aniline hydrochloride **27** (20 g, 70.5 mmol) was dissolved in water (120 mL) and cooled to −5 °C. Concentrated HCl (220 mL) was added dropwise over 15 min maintaining the temperature at <0 °C. A solution of sodium nitrite (4.87 g) in water (60 mL) was added dropwise to the reaction mixture over 20 min, and stirring then continued for 30 min. The reaction mixture was added dropwise to a stirred suspension of tin(II) chloride (80 g) in concentrated HCl (180 mL) at −5−0 °C over 20 min and then allowed to warm to ambient temperature overnight, before being concentrated to dryness. The residue was taken up in water and the pH adjusted to 2.5 using 2 N NaOH. The resulting precipitate was concentrated, taken up into ethanol, and filtered once more. The filtrate was concentrated and the solid dried to give **28** as a cream solid (17.0 g, 92%).

***N*-Benzyl-3-(2-aminoethyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (29). Method 9:** The benzylamide **26** (7.72 g, 27.2 mmol) in ethanol (3.2 mL) was added dropwise to a refluxing solution of the hydrazine hydrochloride **28** (7.4 g, 28 mmol) in ethanol (100 mL) and water (8 mL). After a further 2 h, the cooled reaction mixture was concentrated and purified by flash chromatography eluting with CH_2Cl_2/ethanol/NH_3 (150:8:1) to afford **29** as a beige foam (1.5 g) which was used without further purification in the next step.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (23). Method 10:** Formaldehyde (225 μL of a 37% aqueous solution) in methanol (2.0 mL) was added dropwise to a mixture of **29** (563 mg, 1.26 mmol), sodium cyanoborohydride (95 mg, 1.5 mmol), acetic acid (360 μL, 6.3 mmol), and methanol (15 mL). After stirring for 16 h, the reaction mixture was concentrated and purified by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (150:8:1) to give a colorless gum which yielded **23** as a white crystalline powder on trituration with CH_2Cl_2/petroleum ether: 480 mg (80%); mp 183−184 °C; spectral data as previously described.

***N*-(4-Chlorobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (30).** Method 5: white needles from ethanol; 28 mg (21%); mp 238−239 °C; MS *m*/*z* 482 $(M + 1)^+$; ^{1}H NMR δ 2.1 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 3.82 (2H, s, $COCH_2N$), 4.5 (2H, d, CH_2NHCO, J = 5.0 Hz), 7.05 (1H, d, H6, J = 9.0 Hz), 7.3−7.4 (6H, m, H7, H4, 4 × ArH), 7.95 (1H, s, NH), 9.7 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{25}H_{28}ClN_5O_3$·0.23H_2O) C, H, N. HPLC retention time = 15.21 min.

***N*-(4-Chlorobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (31).** Method 5: white powder; mp 221−223 °C; MS *m*/*z* 511 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, d, CH_2NHCO, J = 5.0 Hz), 7.0 (1H, d, H6, J = 7.5 Hz), 7.3 (2H, m, H7, H4), 7.4 (4H, m, 4 × ArH), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{32}N_5O_3$·0.54 H_2O) C, H, N. HPLC retention time = 16.38 min.

***N*-(2-Chlorobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (32).** Method 5: white powder; mp 174−175 °C; MS *m*/*z* 509/511 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.0 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.6 (2H, m, CH_2Hyd), 4.6 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.3−7.5 (6H, m, H7, H4, 4 × ArH), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{32}ClN_5O_3$·0.9H_2O) C, H, N. HPLC retention time = 16.1 min.

***N*-(3-Chlorobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (33).** Method 5: white powder; mp 169−170 °C; MS *m*/*z* 509/511 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, d, CH_2NHCO, J = 5.0 Hz), 7.0 (1H, d, H6, J = 7.5 Hz), 7.3−7.5 (6H, m, H7, H4, 4 × ArH), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{32}ClN_5O_3$) C, H, N. HPLC retention time = 16.5 min.

***N*-(3,4-Dichlorobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (34).** Method 5: white powder; mp 210−211 °C; MS *m*/*z* 544 (M + 1); ^{1}H NMR δ 1.1 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, d, CH_2NHCO, J = 5.0 Hz), 7.0 (1H, d, H6, J = 7.5 Hz), 7.25−7.5 (3H, m, H7, H4, 1 × ArH), 7.6 (2H, m, 2 × ArH), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{31}Cl_2N_5O_3$·0.25H_2O) C, H, N. HPLC retention time = 17.71 min.

***N*-Benzyl-*N*-methyl-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (35).** Method 5 (using *N*-methylbenzylamine): purification by preparative HPLC gave the acetate salt of **35** as a white lyophylate; MS *m*/*z* 490 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (2.4H, s, CH_3CO_2H), 2.18 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.75−3.0 (4H, m, 5-CH_2, 3-CH_2), 2.82 (3H, s, NCH_3), 3.58 (2H, m, CH_2Hyd), 4.66 (2H, s, CH_2Ph), 6.98 (1H, dd, H6), 7.3 (7H, m, H7, H4, 5 × ArH), 8.1 (1H, s, NH), 11.2 (1H, s, NH). Anal. ($C_{28}H_{35}N_5O_3$·1.65H_2O·0.39CH_3CO_2H) C, H, N.

***N*-(1-Phenylethyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (36).** Method 5 (using D/L-methylbenzylamine): purification by preparative HPLC gave the acetate salt of **36** as a white lyophylate; MS *m*/*z* 490 $(M + 1)^+$; ^{1}H NMR δ 1.16 (6H, s, 2 × CH_3), 1.5 (3H, d, $CHCH_3$, J = Hz), 1.9 (∼3.9H, s, CH_3CO_2H), 2.09 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2-NMe_2 under DMSO peak), 2.8 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd), 5.2 (1H, m, CH), 7.0 (1H, dd, H6), 7.2−7.4 (7H, m, H7, H4, 5 × ArH), 8.1 (1H, s, NH), 9.3 (1H, m, NH), 11.15 (1H, s, NH). Anal. ($C_{28}H_{35}N_5O_3$·1.75H_2O·0.65 CH_3CO_2H) C, H, N.

***N*-(4-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (37).** Method 5: pale-yellow needles; mp 198−199 °C; MS *m*/*z* 490 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.05 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.0 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.3 (2H, d, CH_2NHCO, J = 5.0 Hz), 4.95 (2H, br s, NH_2), 6.5 (2H, d, H3′, H5′), 7.0 (3H, m, H6, H7, H4), 7.3 (2H, m, 2 × ArH), 8.1 (1H, s, NH), 9.5 (1H, br t, NH), 11.1 (1H, s, NH). Anal. ($C_{27}H_{34}N_6O_3$·0.8H_2O) C, H, N. HPLC retention time = 12.23 min.

***N*-(4-Methoxybenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (38).** Method 5: HPLC purification gave the acetate salt of **38** as a white lyophylate; MS *m*/*z* 505 (M^+); ^{1}H NMR δ 1.12 (6H, s, 2 × CH_3), 2.05 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.92 (2H, t, 5-CH_2, J = 7.0 Hz), 3.02 (2H, m, 3-CH_2), 3.57 (3H, s, OCH_3), 3.59 (2H, t, CH_2-Hyd), 4.45 (2H, d, CH_2NHCO, J = 5.2 Hz), 4.95 (2H, br s, NH_2), 6.92 (2H, d, H2′, H6′), 7.0 (1H, d, H6), 7.29 (4H, m, H7, H4, 2 × ArH), 8.1 (1H, s, NH), 9.61 (1H, br t, NH), 11.1 (1H, s, NH); found $(M + 1)^+$ 506.27668, $C_{28}H_{36}N_5O_4$ requires $(M + 1)^+$ 506.27673. HPLC retention time = 15.06.

***N*-[4-(Trifluoromethyl)benzyl]-3-[2-(dimethylamino)-ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (39).** Method 5: cream powder; mp 236−237 °C; MS *m*/*z* 543 (M^+); ^{1}H NMR δ 1.16 (6H, s, 2 ×

CH_3), 2.12 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.91 (2H, t, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.59 (2H, t, CH_2Hyd), 4.5 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.3 (2H, m, H7, H4), 7.6 (2H, d, H3′, H5′), 7.7 (2H, d, H2′, H6′), 8.1 (1H, s, NH), 9.7 (1H, m, NH), 11.2 (1H, s, NH); found M^+ 543.24599, $C_{28}H_{32}N_5O_3F_3$ requires M^+ 543.24572. Anal. ($C_{28}H_{32}N_5O_3F_3$) C, H, N. HPLC retention time = 14.76 min.

***N*-(4-Biphenylylmethyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (40).** Method 5: white powder; 49 mg (60%); mp 142−144 °C; MS *m*/*z* 552 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.52 (2H, m, CH_2NMe_2 under DMSO peak), 2.9 (2H, t, 5-CH_2, J = 7.0 Hz), 3.05 (2H, m, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.55 (2H, d, CH_2NHCO, J = 5.0 Hz), 7.05 (1H, d, H6, J = 7.5 Hz), 7.25−7.5 (7H, m, H7, H4, 5 × ArH), 7.65 (4H, d, 4 × ArH, J = 6.0 Hz), 8.1 (1H, s, NH), 9.7 (1H, br t, NH), 11.15 (1H, br s, NH). Anal. ($C_{33}H_{37}N_5O_3$·0.5H_2O) C, H, N. HPLC retention time = 19.19 min.

***N*-(1-Naphthylmethyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (41).** Method 5: white powder; mp 195−210 °C, softens; MS *m*/*z* 526 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.8 (6H, s, 2 × NCH_3), 2.45 (2H, m, CH_2NMe_2), 2.9 (2H, m, 5-CH_2), 3.0 (2H, t, 3-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 5.0 (2H, d, CH_2NHCO), 7.0 (1H, d, H6), 7.3 (2H, m, H7, H4), 7.5−7.6 (4H, m, 4 × ArH), 7.9−8.2 (4H, m, 3 × ArH, NH), 9.7 (1H, t, NH), 11.2 (1H, s, NH); found M^+ 525.27539, $C_{31}H_{35}N_5O_3$ requires M^+ 525.27399. Anal. ($C_{31}H_{35}N_5O_3$·0.80H_2O) C, H, N. HPLC retention time = 17.7 min.

***N*-(4-Methylbenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (42).** Method 5: white powder; mp 206−207 °C; MS *m*/*z* 490 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.05 (6H, s, 2 × NCH_3), 2.3 (3H, s, CH_3), 2.9 (2H, m, CH_2NMe_2), 3.05 (2H, t, 5-CH_2), 3.6 (2H, t, CH_2Hyd, J = 7.0 Hz), 4.5 (2H, d, CH_2NHCO), 7.07 (1H, dd, H6, J = 8.4 Hz), 7.2−7.4 (6H, m, H7, H4, 4 × ArH), 8.1 (1H, s, NH), 9.65 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{28}H_{35}N_5O_3$·0.25H_2O) C, H, N. HPLC retention time = 16.34 min.

***N*-(2-Methylamido)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (43).** Method 5 (using glycinamide hydrochloride): cream powder; MS *m*/*z* 443 $(M + 1)^+$; ^{1}H NMR δ 1.18 (6H, s, 2 × CH_3), 2.23 (6H, s, 2 × NCH_3), 2.55 (2H, m, CH_2NMe_2), 2.98 (2H, m, CH_2N), 3.1 (2H, m, 5-CH_2), 3.55 (2H, m, 3-CH_2), 3.95 (2H, d, $NHCH_2$), 7.08 (1H, d, H6), 7.09 (1H, br s, NH_A), 7.32 (2H, m, H7, H4), 7.42 (1H, br s, $NH_{A'}$), 8.13 (1H, s, NH), 9.2 (1H, t, $NHCH_2$), 11.2 (1H, s, NH); found M^+ 442.23082, $C_{22}H_{30}N_6O_4$ requires M^+ 442.23285. HPLC retention time = 9.98 min.

***N*-(3-Aminobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (44).** Method 5: cream powder; MS *m*/*z* 491 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.08 (6H, s, 2 × NCH_3), 2.52 (2H, m, CH_2NMe_2, under DMSO peak), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.52 (2H, m, CH_2Hyd), 4.36 (2H, d, CH_2NHCO), 5.05 (2H, br s, NH_2), 6.5 (3H, m, 3 × ArH), 7.0 (2H, m, 2 × ArH), 7.28 (2H, m, 2 × ArH), 8.1 (1H, s, NH), 9.62 (1H, t, NH), 11.15 (1H, s, NH); found M^+ 490.26866, $C_{27}H_{34}N_6O_3$ requires M^+ 490.26924. HPLC retention time = 12.86 min.

***N*-(3-Methoxybenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (45).** Method 5: purification by HPLC gave the acetate salt of **45** as a cream powder; MS *m*/*z* 505 (M^+); ^{1}H NMR δ 1.13 (6H, s, 2 × CH_3), 1.9 (4.5H, s, CH_3CO_2H), 2.08 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO peak), 2.92 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.61 (2H, m, CH_2Hyd), 3.75 (3H, s, OCH_3), 4.5 (2H, d, CH_2NHCO), 6.82 (1H, d, H6), 6.9−7.1 (3H, m, H7, H4, ArH), 7.25 (3H, m, 3 × ArH), 8.1 (1H, s, NH), 9.65 (1H, t, NH), 11.15 (1H, s, NH); found M^+ 505.26827, $C_{28}H_{35}N_5O_4$ requires M^+ 505.26891. Anal. ($C_{28}H_{35}N_5O_4$·1.0H_2O·1.5CH_3CO_2H) C, H, N. HPLC retention time = 15.66 min.

***N*-(2-Aminobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (46).** Method 5: white powder; mp 201−202 °C; MS *m*/*z* 490 (M^+); ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.50 (2H, m, CH_2NMe_2), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.62 (2H, m, CH_2Hyd), 4.5 (2H, d, CH_2NHCO), 5.1 (2H, br s, NH_2), 6.5 (1H, t, ArH, J = 7.5 Hz), 6.65 (1H, d, H6, J = 7.5 Hz), 6.9−7.1 (2H, m, 2 × ArH), 7.3 (2H, m, 2 × ArH), 8.1 (1H, s, NH), 9.55 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{34}N_6O_3$·0.5H_2O) C, H, N. HPLC retention time = 12.66 min.

***N*-(2-Aminobenzyl)-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (47).** Method 5: cream powder; mp 213−215 °C; MS *m*/*z* 463 $(M + 1)^+$; ^{1}H NMR δ 2.1 (6H, s, 2 × NCH_3), 2.92 (2H, m, CH_2NMe_2), 3.05 (2H, m, 5-CH_2), 3.6 (2H, m, CH_2Hyd), 3.8 (2H, s NCH_2CO), 4.4 (2H, d, CH_2NHCO), 5.1 (2H, br s, NH_2), 6.5 (1H, t, ArH, J = 7.5 Hz), 6.65 (1H, d, H6), 7.0 (3H, m, 3 × ArH), 7.3 (2H, m, 2 × ArH), 7.95 (1H, s, NH), 9.6 (1H, br t, NH), 11.2 (1H, s, NH). Anal. ($C_{25}H_{30}N_6O_3$·0.6H_2O) C, H, N. HPLC retention time = 11.3 min.

***N*-Methoxy-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (48).** Method 5: off-white powder; mp 148−150 °C; MS *m*/*z* 416 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.22 (6H, s, 2 × NCH_3), 2.55 (2H, m, CH_2), 2.90 (2H, m, CH_2NMe_2), 3.05 (2H, m, 5-CH_2), 3.60 (2H, m, CH_2Hyd), 3.72 (3H, s, OCH_3), 7.05 (1H, d, H6, J = 7.5 Hz), 7.25−7.35 (2H, m, H7, H4), 8.1 (1H, s, NH), 11.18 (1H, s, NH); found M^+ 415.22458, $C_{21}H_{29}N_5O_4$ requires M^+ 415.22195. HPLC retention time = 10.11 min.

***N*-(2-Hydroxybenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (49).** Method 5: white solid; mp 198−200 °C; MS *m*/*z* 492 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.9 (2H, m, CH_2NMe_2), 3.05 (2H, m, 5-CH_2), 3.6 (2H, m, CH_2Hyd), 4.4 (2H, d, CH_2NHCO), 6.8 (2H, m, 2 × ArH), 7.0 (2H, m, 2 × ArH), 7.25 (3H, m, 3 × ArH), 8.1 (1H, s, NH), 9.55 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{27}H_{33}N_5O_4$·0.25H_2O·0.5C_2H_5OH) C, H, N. HPLC retention time = 12.93 min.

***N*-Phenyl-2-oxo-5-bromopentamide (50).** Method 6: isolated as a yellow wax; MS *m*/*z* 269, 271 $(M^+, M + 2)^+$); ^{1}H NMR δ ($CDCl_3$) 2.25 (2H, m, 4-CH_2), 3.23 (2H, m, 5-CH_2), 3.5 (2H, m, 3-CH_2), 3.65 (2H, m, CH_2Hyd), 7.19 (1H, m, ArH), 7.36 (2H, m, 2 × ArH), 7.68 (2H, m, 2 × ArH), 8.66 (1H, s, NH); found M^+ 269.00603, $C_{11}H_{12}BrNO_2$ requires M^+ 269.00514. HPLC retention time = 18.31 min.

***N*-Phenyl-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-(2-aminoethyl)-1*H*-indole-2-carboxamide (51).** Method 9: white solid; MS *m*/*z* 434 $(M + 1)^+$; ^{1}H NMR δ 1.17 (6H, s, 2 × CH_3), 2.95 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.38 (2H, m, CH_2NMe_2), 3.65 (2H, m, CH_2Hyd), 7.11 (2H, m, H6, ArH), 7.35 (3H, m, H7, 2 × ArH), 7.5 (1H, s, H4), 7.85 (4H, m, 2 × ArH, NH_2), 8.15 (1H, s, NH), 10.5 (1H, s, NH), 12.08 (1H, s, NH); found M^+ 433.21112, $C_{24}H_{27}N_5O_3$ requires M^+ 433.21139. HPLC retention time = 13.69 min.

***N*-Phenyl-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (52).** Method 10: white solid; MS *m*/*z* 462 $(M + 1)^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.2 (6H, s, 2 × NCH_3), 2.61 (2H, m, CH_2NMe_2), 2.95 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.65 (2H, m, CH_2Hyd), 7.08 (2H, m, H6, ArH), 7.35 (4H, m, H7, H4, 2 × ArH), 7.66 (2H, d, 2 × ArH), 8.15 (1H, s, NH), 10.95 (1H, s, NH), 11.35 (1H, s, NH); found M^+ 461.24100, $C_{26}H_{31}N_5O_3$ requires M^+ 461.24269. Anal. ($C_{26}H_{31}N_5O_3$) C, H, N. HPLC retention time = 15.39 min.

***N*-(4-Fluorobenzyl)-3-(2-aminoethyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (53).** Methods 6 and 9: The α-keto acid **25** (1.79 g, 10.0 mmol) and 1 drop of dry DMF were dissolved in dry dichlo-

romethane (10 mL). A solution of oxalyl chloride (1.27 g, 10.0 mmol) in dichloromethane (5 mL) was then gradually added and the reaction left to stir at room temperature for 1 h. The solution was concentrated under reduced pressure and the residue dissolved in dry dichloromethane (20 mL). This solution was added dropwise to a solution of 4-fluorobenzylamine (1.14 mL, 10.0 mmol) and pyridine (1.0 mL, 11.0 mmol) in dichloromethane (40 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. Acid/base workup and concentration gave 1.3 g of a brown oil which was dissolved in ethanol/water (9:1, 100 mL). 2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)ethylphenylhydrazine hydrochloride (2.44 g, 10 mmol) was then added and the solution stirred for 2 h at room temperature and then heated to reflux for 2 h. The solution was cooled, filtered, concentrated, and partitioned between 2 N HCl and ethyl acetate (3 × 50 mL). The combined organic phases were dried and concentrated to give a yellow gum which was purified by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (100:8:1) to give 316 mg (8%) of the free base of **53** as a pale-yellow gum which was used without further purification.

***N*-(4-Fluorobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (54).** Method 10: cream powder; mp 175 °C; MS *m*/*z* 493 (M^+); ^{1}H NMR δ 1.12 (6H, s, 2 × CH_3), 2.21 (6H, s, 2 × NCH_3), 2.65 (2H, m, CH_2NMe_2), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.7 (2H, t, CH_2Hyd), 4.5 (2H, m, CH_2NHCO), 7.0 (1H, dd, H6), 7.05−7.45 (6H, m, H7, H4, 4 × ArH), 8.1 (1H, s, NHHyd), 9.49 (1H, br t, NH), 11.1 (1H, s, NH); found M^+ 493.24672, $C_{27}H_{32}N_5O_3F$ requires M^+ 493.24891. HPLC retention time = 15.27 min.

***N*-(*tert*-Butyloxycarbonyl)-4-aminobenzylamine (55). Method 11:** A solution of di-*tert*-butyl dicarbonate (19.0 g, 87.0 mmol) and 4-aminobenzylamine (9.0 mL, 79.0 mmol) in THF (150 mL) was stirred for 24 h. The reaction mixture was concentrated and triturated with ether/petroleum ether to give 14 g (80%) of **55** as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s, 3 × CH_3), 4.18 (2H, d, CH_2Ph), 4.68 (2H, br s, NH_2), 6.6 (2H, d, H2, H6), 7.06 (2H, d, H3, H5).

***N*-(*tert*-Butyloxycarbonyl)-4-methylsulfonamidobenzylamine (56). Method 12:** Methanesulfonyl chloride (0.57 mL, 7.36 mmol) was added dropwise to a solution of *N*-(*tert*-butyloxycarbonyl)-4-aminobenzylamine (**55**) (1.35 g, 6.1 mmol) in dry pyridine (10 mL) under nitrogen at 0 °C, and the reaction was allowed to warm to room temperature with stirring overnight. Water was added, the solution was acidified with 1 N HCl, and the solution was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried, filtered, and concentrated under reduced pressure. The residue was recrystallized from chloroform/hexane to give 1.23 g (67%) of **56** as a pale-pink solid: mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (9H, s, 3 × CH_3), 3.0 (3H, s, SO_2CH_3), 4.28 (2H, d, CH_2Ph), 4.82 (1H, br s, $NHSO_2$), 6.55 (1H, br s, NH), 7.16 (2H, d, H2, H6), 7.28 (2H, d, H3, H5). HPLC retention time = 15.22 min.

4-Methylsulfonamidobenzylamine Trifluoroacetate (57). Method 13: *N*-(*tert*-Butyloxycarbonyl)-4-methylsulfonamidobenzylamine (1.2 g, 4.0 mmol) was suspended in dichloromethane (20 mL) and cooled to 0 °C, and trifluoroacetic acid (5.0 mL) was added dropwise. The resulting yellow solution was stirred for 1.5 h at 0 °C and then concentrated under reduced pressure to give an orange gum. Trituration with ether/chloroform gave 1.2 g (96%) of the product as a yellow-orange solid: mp 130−132 °C; ^{1}H NMR δ 3.01 (3H, s, SO_2CH_3), 4.0 (2H, br s, CH_2Ph), 7.22 (2H, d, H2, H6), 7.42 (2H, d, H3, H5), 8.25 (3H, br s, NH_3^+). HPLC retention time = 3.38 min.

***N*-(4-Methylsulfonamidobenzyl)-3-[2-(dimethylamino)-ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (58).** Method 5: light-brown powder; MS *m*/*z* 569 (M + 1)$^+$; ^{1}H NMR δ 1.2 (6H, s, 2 × CH_3), 2.08 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.91 (2H, t, 5-CH_2), 2.98 (3H, s, SO_2CH_3), 3.05 (2H, m, 3-CH_2), 3.61 (2H, t, CH_2Hyd), 4.5 (2H, d, CH_2NHCO), 7.05 (1H, d, H6), 7.18−7.38 (6H, m, H7, H4, 4 × ArH), 8.12 (1H, s, NH), 9.63 (2H, m, 2 × NH), 11.13 (1H, br s, NH); found M^+ 568.24751, $C_{28}H_{36}N_6O_5S$ requires 568.24679. HPLC retention time = 12.73 min.

***N*-(*tert*-Butyloxycarbonyl)-3-aminobenzylamine (59).** Method 11: trituration of the resulting solid with ether/petroleum ether gave 1.88 g (45%) of **59** as an off-white solid; ^{1}H NMR δ 1.4 (9H, s, 3 × CH_3), 4.0 (2H, d, CH_2NH), 4.95 (1H, br s, NH_2), 6.49 (3H, m, 3 × ArH), 6.9 (1H, m, ArH), 7.15 (1H, t, NHCO). Anal. ($C_{12}H_{18}N_2O_2$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-3-methylsulfonamidobenzylamine (60).** Method 12: residue was triturated with ether and filtered to give 925 mg (68%) of **60** as a cream solid; mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (9H, s, 3 × CH_3), 2.95 (3H, s, SO_2CH_3), 4.1 (2H, d, CH_2Ph), 7.0 (3H, m, 3 × ArH), 7.21 (1H, m, ArH), 7.32 (1H, t, NH), 9.7 (1H, s, NH). Anal. ($C_{13}H_{20}N_2O_4S$) C, H, N.

3-Methylsulfonamidobenzylamine Trifluoroacetate (61). Method 13: trituration with ether gave 884 mg (94%) of the trifluoroacetate salt of **61** as a pale-brown solid; mp 130−132 °C; ^{1}H NMR δ 3.01 (3H, s, SO_2CH_3), 4.0 (2H, br s, CH_2-Ph), 7.22 (2H, d, H2, H6), 7.42 (2H, d, H3, H5), 8.25 (3H, br s, NH_3^+). Anal. ($C_8H_{12}N_2O_2S$·1.0CF_3CO_2H) C, H, N.

***N*-(3-Methylsulfonamidobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (62).** Method 5: white powder; dec > 80 °C; MS *m*/*z* 569 (M + 1)$^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.15 (6H, s, 2 × NCH_3), 2.59 (2H, m, CH_2) (under DMSO peak), 2.95 (2H, m, CH_2NMe_2), 2.99 (3H, s, SO_2CH_3), 3.08 (2H, m, 5-CH_2), 3.6 (2H, m, CH_2Hyd), 4.5 (2H, d, CH_2NHCO), 7.02 (1H, d, H6, *J* = 7.5 Hz), 7.1−7.32 (6H, m, H7, H4, 4 × ArH), 8.1 (1H, s, NH), 9.68 (1H, t, NH), 11.18 (1H, s, NH). Anal. ($C_{28}H_{36}N_6O_5S$·0.75H_2O·0.5Et_2O) C, H, N.

***N*-(3-Acetamidobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (63).** Method 5: acetate salt as white powder (dec > 80 °C); purification by preparative HPLC gave **63** as a white lyophylate; MS *m*/*z* 533 (M + 1)$^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 2.1 (6H, s, 2 × NCH_3), 2.50 (2H, m, CH_2NMe_2, under DMSO peak), 2.9 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.6 (2H, m, CH_2Hyd), 4.6 (2H, d, CH_2NHCO), 7.0 (1H, d, H6, *J* = 7.5 Hz), 7.2−7.5 (5H, m, H7, H4, 3 × ArH), 7.75 (1H, d, ArH), 7.9 (2H, br s, NH_2), 8.1 (1H, s, NH), 9.7 (1H, t, NH), 11.2 (1H, s, NH). Anal. ($C_{29}H_{36}N_6O_4$·2.0H_2O·1.0 CH_3CO_2H) C, H, N.

***N*-(2-Acetamidobenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (64).** Method 5: purification by preparative HPLC gave the acetate salt of **64** as a white lyophylate; MS *m*/*z* 533 (M + 1)$^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (1.5H, s, CH_3CO_2H), 2.12 (3H, s, $COCH_3$), 2.26 (6H, s, 2 × NCH_3), 2.67 (2H, m, CH_2NMe_2), 2.93 (2H, m, 5-CH_2), 3.12 (2H, m, 3-CH_2), 3.62 (2H, m, CH_2Hyd), 4.5 (2H, d, CH_2-NHCO, *J* = 5.4 Hz), 7.05 (1H, d, H6), 7.1−7.35 (5H, m, H7, H4,3 × ArH), 7.62 (1H, d, ArH), 8.12 (1H, s, NH), 9.55 (1H, t, NH), 9.82 (1H, br s, NH), 11.25 (1H, s, NH); found M^+ 532.27941, $C_{29}H_{36}N_6O_4$·1.0CH_3CO_2H requires M^+ 532.27980. HPLC retention time = 11.8 min.

***N*-(4-Mesylbenzyl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl) ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (65).** Method 5: purification by HPLC gave the acetate salt of **65** as a white powder; MS *m*/*z* 554 (M + 1)$^+$; ^{1}H NMR δ 1.15 (6H, s, 2 × CH_3), 1.9 (1.6H, s, CH_3CO_2H), 2.1 (6H, s, 2 × NCH_3), 2.48 (2H, m, CH_2NMe_2, under DMSO peak), 2.9 (2H, t, 5-CH_2, *J* = 7.0 Hz), 3.03 (2H, m, 3-CH_2), 3.14 (3H, s, SO_2CH_3), 3.6 (2H, m, CH_2Hyd, blanketed by water peak), 4.6 (2H, d, CH_2Ph, *J* = 5.0 Hz), 7.0 (1H, d, H6, *J* = 7.5 Hz), 7.26 (2H, m, H7, H4), 7.6 (2H, d, H3′, H5′), 7.88 (2H, d, H2′, H6′). Anal. ($C_{28}H_{35}N_5O_5S$ ·0.5H_2O·0.53CH_3CO_2H) C, H, N.

4-Hydrazinophenethyl Alcohol (67). A solution of 4-aminophenethyl alcohol (10.0 g, 0.73 mol) in water (10 mL) was treated with concentrated HCl (178.4 mL) and cooled to 0 °C. A solution of sodium nitrite (5.0 g, 0.73 mol) in water (48 mL) was added dropwise and stirring continued for a further 30

min. The solution was allowed to warm to room temperature and stirring continued for 4 h. The solution was concentrated in vacuo and the residue dissolved in water and washed with dichloromethane. The aqueous phase was adjusted to pH 2.5 with 2 N NaOH, and the precipitate was removed by filtration. The aqueous filtrate was concentrated and the residue triturated with ethanol. The solid residue was removed by filtration and the filtrate concentrated to give 10.5 g (73%) of **67** as a white solid which was used without further purification.

***N*-Benzyl-3-(2-aminoethyl)-5-(2-hydroxyethyl)-1*H*-indole-2-carboxamide (68).** A solution of the hydrazine **67** (365 mg, 2.4 mmol) and the benzylamide **26** (750 mg, 2,64 mmol) in ethanol (10 mL) and water (1 mL) was heated at reflux for 24 h. The solution was concentrated in vacuo, and flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (50:8:1) gave 150 mg (19%) of **68** as a pale-yellow solid: MS *m*/*z* 337 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.95 (2H, m, CH_2NMe_2), 3.09 (4H, m, 5-CH_2, 3-CH_2), 3.88 (2H, t, CH_2OH), 4.63 (2H, d, $NHCH_2Ph$), 7.12 (1H, dd, H6), 7.25−7.45 (7H, m, H4, H7, 5 × ArH), 9.02 (1H, br s, NH), 10.65 (1H, br s, NH); found M^+ 337.17867, $C_{20}H_{23}N_3O_2$ requires M^+ 337.17903.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-(2-hydroxyethyl)-1*H*-indole-2-carboxamide (69).** Method 10: white solid; 100 mg (74%); MS *m*/*z* 365 (M^+); ^{1}H NMR δ 2.01 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.78 (2H, m, 5-CH_2), 3.04 (2H, m, 3-CH_2), 3.64 (2H, t, CH_2OH), 4.52 (2H, d, $NHCH_2Ph$), 7.0 (1H, dd, H6), 7.25−7.45 (7H, m, H4, H7, 5 × ArH), 9.68 (1H, t, NH), 11.15 (1H, s, NH); found M^+ 365.20984, $C_{22}H_{27}N_3O_2$ requires M^+ 365.21032. HPLC retention time = 13.43 min.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidine-4-spirocyclopentan-1-yl)ethyl]-1*H*-indole-2-carboxamide (70).** A suspension of the indole **69** (100 mg, 0.28 mmol), the spirohydantoin **71** (64 mg, 0.41 mmol), and triphenylphosphine (106 mg, 0.41 mmol) in dry DMF under nitrogen was treated with diisopropyl azodicarboxylate (85 μL, 0.43 mmol) in the dark. Stirring was continued in the dark for 18 h. Concentration in vacuo and flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (200:8:1) gave 20 mg (15%) of **70** as a white solid: MS *m*/*z* 501 (M^+); ^{1}H NMR δ 1.65 (8H, m, 4 × CH_2), 2.09 (6H, s, 2 × NCH_3), 2.5 (2H, m, CH_2NMe_2 under DMSO peak), 2.92 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.62 (2H, t, CH_2Hyd), 4.52 (2H, d, $NHCH_2Ph$), 7.0 (1H, dd, H6), 7.29 (3H, m, 3 × ArH), 7.47 (4H, m, 4 × ArH), 8.31 (1H, s, NH), 9.68 (1H, t, NH), 11.15 (1H, s, NH); found M^+ 501.27313, $C_{29}H_{35}N_5O_3$ requires M^+ 501.27399. Anal. ($C_{29}H_{35}N_5O_3 \cdot 1.0H_2O \cdot 0.33CH_3CO_2H$) C, H, N. HPLC retention time = 14.97 min.

Alternative Synthesis for 70. 5-Spirocyclopentanylhydantoin (71). A suspension of cyclopentanone (5.5 g, 65.0 mmol), sodium cyanide (4.78 g, 97.5 mmol), and ammonium carbonate (22.0 g, 0.23 mol) in ethanol (65 mL) and water (65 mL) was heated at 60 °C for 5 h. The ethanol was removed in vacuo and the crude product removed by filtration. The product was recrystallized from aqueous ethanol to afford 3.51 g (35%) of **71** as a white solid: MS *m*/*z* 154 (M^+); ^{1}H NMR (CD_3OD) δ 1.8 (6H, m, 3 × CH_2), 2.07 (2H, m, CH_2).

3-[2-(4-Nitrophenyl)ethyl]-5-spirocyclopentanylimidazolidine-2,4-dione (72). Method 14: A solution of *p*-nitrophenethyl alcohol (2.72 g, 16.3 mmol), spirohydantoin **71** (3.77 g, 24.5 mmol), and triphenylphosphine (6.42 g, 24.5 mmol) was stirred under nitrogen in dry DMF (50 mL). To the ice-cooled solution was gradually added diethyl azodicarboxylate (4.54 g, 26.1 mmol), and the resultant solution was stirred in the dark for 24 h. The reaction mixture was poured into water (300 mL), and a solution of ether/ethyl acetate (4:1) (200 mL) was added. The mixture was stirred rapidly for 0.5 h and filtered. The precipitate was dried and recrystallized from ethanol to give 5.7 g (79%) of **72** as white crystals: MS *m*/*z* 303 (M^+); ^{1}H NMR δ 1.5−1.9 (8H, m, 4 × CH_2), 2.98 (2H, t, CH_2N, J = 7.1 Hz), 3.64 (2H, t, CH_2Ph, J = 7.1 Hz), 7.41 (2H, d, H3, H5, J = 8.0 Hz), 8.16 (2H, d, H2, H6, J = 8.3 Hz), 8.39 (1H, s, NH).

3-[2-(4-Aminophenyl)ethyl]-5-spirocyclopentanylimidazolidine-2,4-dione (73). Method 4: white solid; 2.5 g, 62%; MS *m*/*z* 303 $(M + 1)^+$; ^{1}H NMR δ 1.5−1.9 (8H, m, 4 × CH_2), 2.72 (2H, t, CH_2N, J = 7.1 Hz), 3.48 (2H, t, CH_2Ph, J = 7.1 Hz), 4.81 (2H, s, NH_2), 6.48 (2H, d, H2, H6, J = 8.1 Hz), 6.77 (2H, d, H3, H5, J = 8.0 Hz), 8.32 (1H, s, NH). Anal. ($C_{15}H_{19}N_3O_2 \cdot 0.44H_2O$) C, H, N.

3-[2-(4-Hydrazinophenyl)ethyl]-5-spirocyclopentanylimidazolidine-2,4-dione (74). Method 8: white solid; 2.4 g, 100%; MS *m*/*z* 289 $(M + 1)^+$; ^{1}H NMR δ 1.5−1.9 (8H, m, 4 × CH_2), 2.73 (2H, t, CH_2N), 3.49 (2H, t, CH_2Ph), 6.8 (2H, d, H2, H6), 7.0 (2H, d, H3, H5), 8.37 (1H, s, NH).

***N*-Benzyl-3-(2-aminoethyl)-5-[2-(4-spirocyclopentanyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (75).** Method 9: white powder; 280 mg (15%); MS *m*/*z* 474 $(M + 1)^+$; ^{1}H NMR δ 1.5−1.9 (8H, m, 4 × CH_3), 2.83 (4H, m, CH_2NH_2, CH_2N), 3.0 (2H, m, 5-CH_2), 3.6 (2H, m, 3-CH_2), 4.5 (2H, br s, NH_2), 7.0 (1H, d, H6), 7.2−7.4 (7H, m, H7, H4, 5 × ArH), 8.3 (1H, s, NH), 10.4 (1H, s, NH), 11.2 (1H, s, NH).

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxoimidazolidine-4-spirocyclopentan-1-yl)ethyl]-1*H*-indole-2-carboxamide (70).** Method 10: same spectral data as previously described.

4-Nitrohydrocinnamic Acid (76). Hydrocinnamic acid (5.0 g, 33.3 mmol) was taken up in concentrated H_2SO_4 (9.84 mL) and cooled in an ice/salt bath. Concentrated HNO_3 (1.9 mL) was added slowly and the reaction mixture stirred at 0 °C for 1 h. The ice bath was then removed and the reaction mixture stirred at room temperature for 0.5 h. The orange oil was poured into ice and water and stirred to dissolve the ice. The white solid produced was filtered off and dried under vacuum to give the product. Further purification using column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (200:8:1) afforded 3.33 g (51%) of **76** as a white solid which was used directly in the next step.

***N*-[*N*-[2-(4-Nitrophenyl)ethyl]amido]proline (77).** To a solution of the acid **76** (3.33 g, 17.0 mmol) in dioxane were added triethylamine (1.72 g, 2.37 mL, 1.0 mmol) and diphenyl phosphorazidate (4.68 g, 3.66 mL, 17.0 mmol), and the reaction mixture was refluxed overnight. The solution was cooled to room temperature, proline (1.96 g, 17.0 mmol) was added, and the reaction mixture was stirred at room temperature overnight. Excess proline was filtered off, and the residues were concentrated in vacuo. The residue was taken up in ethyl acetate and washed with water and then 2 N NaOH. The aqueous layers were combined, extracted with ethyl acetate, dried, and concentrated to give 3.57 g (68%) of **77** as an orange oil which was used without further purification: MS *m*/*z* 308 $(M + 1)^+$.

1,5-Trimethylene-3-[2-(4-nitrophenyl)ethyl]-2,4-imidazolidinedione (78). The proline derivative **77** (3.57 g, 11.6 mmol) was taken up in acetonitrile, and DCCI (2.22 g, 11.6 mmol) was added. The solution was refluxed for 3 h. *p*-Nitrophenol (3.22 g, 23.2 mmol) was added, and the reaction mixture was refluxed overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography to give 1.38 g (41%) of **78** as a white solid which was reacted on without further purification: MS *m*/*z* 290 $(M + 1)^+$.

1,5-Trimethylene-3-[2-(4-aminophenyl)ethyl]-2,4-imidazolidinedione (79). Method 4: purification by column chromatography eluting with hexane/ethyl acetate (1:1, 1% NH_3) afforded 0.5 g (40%) of **79** as a white powder; MS *m*/*z* 260 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$) δ 1.51 (1H, m, CH), 2.0 (2H, m, CH_2), 2.15 (1H, m, CH), 2.8 (2H, m, CH_2), 3.2 (1H, m, CH), 3.59 (5H, m, CH, 2 × CH_2, NH_2), 3.99 (1H, m, CH), 6.68 (2H, d, H2, H6), 6.95 (2H, d, H3, H5). Anal. ($C_{14}H_{17}N_3O_2$) C, H, N. HPLC retention time = 9.72 min.

1,5-Trimethylene-3-[2-(4-hydrazinophenyl)ethyl]-2,4-imidazolidinedione (80). Method 8: yellow powder; 0.7 g (93%); MS *m*/*z* 274 $(M)^+$; ^{1}H NMR δ 1.51 (1H, m, CH), 2.1 (3H, m, CH, CH_2), 2.75 (2H, m, CH_2), 3.08 (1H, m, CH), 3.45 (6H, m, CH, CH_2, NH, NH_2), 3.49 (1H, m, CH), 6.81 (2H, d, H2, H6), 6.95 (2H, d, H3, H5). HPLC retention time = 8.61 min.

***N*-Benzyl-3-(2-aminoethyl)-5-[2-(3,4-trimethylene-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (81).** Method 9: white powder; MS *m*/*z* 460 $(M + 1)^+$; ^{1}H

NMR ($CDCl_3$) δ 1.49 (1H, m, CH), 1.85 (2H, m, CH_2), 2.1 (3H, m, CH, CH_2), 2.9−3.1 (6H, m, CH_2-5, CH_2-3, CH_2), 3.5−3.8 (4H, m, 2 × CH_2), 3.9 (1H, m, CH), 4.56 (2H, d, CH_2NHCO), 7.05 (1H, d, H6), 7.1−7.35 (7H, m, H7, H4, 5 × ArH), 10.6 (1H, s, NH). HPLC retention time = 14.89 min.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(3,4-trimethylene-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (82).** Method 10: The tryptamine **81** (158 mg, 0.34 mmol) was dissolved in methanol (10 mL); then acetic acid (99 μL, 1.72 mmol) and sodium cyanoborohydride (26 mg, 0.41 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen overnight. The reaction mixture was quenched with water, adjusted to pH 10 with 2 N NaOH, and then extracted with ethyl acetate. The organic layer was then dried and concentrated in vacuo and the residue purified by flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (400:8:1) to give 77.4 mg (46%) of **82** as a pink solid: MS *m*/*z* 487 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.49 (1H, m, CH), 1.91 (2H, m, CH_2), 1.94 (6H, s, 2 × NCH_3), 2.12 (1H, m, CH), 2.61 (2H, m, CH_2-NMe_2), 3.05 (4H, m, CH_2-5, CH_2-3), 3.2 (1H, m, CH), 3.61 (1H, m, CH), 3.75 (2H, m, CH_2Hyd), 3.98 (1H, m, CH), 4.64 (2H, d, CH_2NHCO), 7.12 (1H, d, H6), 7.22−7.4 (7H, m, H7, H4, 5 × ArH), 9.26 (1H, s, NH), 10.95 (1H, t, NH). Anal. ($C_{28}H_{33}N_5O_3$·0.5H_2O) C, H, N. HPLC retention time = 16.17 min.

3-(4-Nitrophenethyl)-5-methyl-5-phenyl-2,4-imidazolidinedione (83). Method 14: To a solution of dry DMF (130 mL) were added 5-methyl-5-phenylhydantoin (10 g, 52.6 mmol), *p*-nitrophenethyl alcohol (8.78 g, 52.6 mmol), and triphenylphosphine (13.8 g, 52.6 mmol). The solution was stirred under nitrogen at 0 °C for 20 min; then diisopropyl azodicarboxylate (10.6 g, 52.6 mmol) was added dropwise over 30 min with the temperature maintained at 0 °C. The solution was then allowed to warm to room temperature overnight. The reaction mixture was poured onto ice water (350 mL) and stirred for 2 h. The white solid was filtered and recrystallized from ethanol to give 12.9 g (73%) of **83** as white needles: mp 136−138 °C; MS *m*/*z* 340 (M + 1)$^+$; ^{1}H NMR δ 1.55 (3H, s, CH_3), 2.98 (2H, t, CH_2N, *J* = 6.6 Hz), 3.67 (2H, m, CH_2Ph), 7.32 (7H, m, H3, H5, 5 × ArH), 7.97 (2H, d, H2, H6, *J* = 8.6 Hz), 8.84 (1H, s, NH); found M^+ 339.12188, $C_{18}H_{17}N_3O_4$ requires M^+ 339.12191.

3-(4-Nitrophenethyl)-1,5-dimethyl-5-phenyl-2,4-imidazolidinedione (84). The nitro compound **83** (5.51 g, 16.3 mmol) was dissolved in dry THF (150 mL), and to the stirring solution was added sodium hydride (0.65 g, 16.3 mmol) under nitrogen. Dimethyl sulfate (2.05 g, 1.54 mL, 16.3 mmol) was gradually added, and the resulting solution was stirred for 72 h at room temperature. The reaction mixture was concentrated under vacuum, the residue suspended in ethyl acetate and filtered, and the filtrate concentrated under vacuum to give a yellow solid. Purification by column chromatography eluting with chloroform gave **84** as an off-white solid: 4.39 g (76%); MS *m*/*z* 354 (M + 1)$^+$; ^{1}H NMR δ 1.64 (3H, s, CCH_3), 2.64 (3H, s, NCH_3), 3.0 (2H, m, CH_2N), 3.77 (2H, m, CH_2Ph), 7.08 (2H, m, 2 × ArH), 7.33 (3H, m, 3 × ArH), 7.42 (2H, d, H3, H5, *J* = 7.2 Hz), 8.05 (2H, d, H2, H6, *J* = 7.3 Hz); found M^+ 354.14488, $C_{19}H_{20}N_3O_4$ requires M^+ 354.14539.

3-(4-Aminophenethyl)-1,5-dimethyl-5-phenyl-2,4-imidazolidinedione (85). Method 4: white solid as the HCl salt; 4.24 g (95%); MS *m*/*z* 324 (M + 1)$^+$; ^{1}H NMR δ 1.65 (3H, s, CCH_3), 2.49 (3H, s, NCH_3), 2.89 (2H, t, CH_2N, *J* = 6.9 Hz), 3.67 (2H, m, CH_2Ph, *J* = 7.0 Hz), 7.12 (2H, m, 2 × ArH), 7.22 (4H, m, 4 × ArH), 7.38 (3H, m, 3 × ArH), 10.0 (3H, br s, NH_3^+). Anal. ($C_{19}H_{21}N_3O_2$·1.0HCl·1.5H_2O) C, H, N.

Ethyl 5-(Dimethylamino)-2-[[4-[2-(3,4-dimethyl-3-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (86). Method 15: To a stirring solution of **85** (3.3 g, 9.18 mmol) in ethanol (6.5 mL) and water (16.0 mL) was added concentrated HCl (2.02 mL, 19.3 mmol). The solution was cooled to 0 °C, and a solution of sodium nitrite (0.69 g, 9.18 mmol) in water (6.0 mL) was added. The solution was stirred at ∼ −5 °C for 45 min. Meanwhile, the diketone **5** (1.97 g, 9.18 mmol) in ethanol (9.0 mL) was stirred with sodium acetate trihydrate (6.3 g, 46.3 mmol) and ice water (9.0 mL). The diazonium salt was added quickly to the diketone solution, and the reaction was stirred for 2.0 h at 0 °C and then up to room temperature over 1 h. The solution was adjusted to pH 9 with 10% NaOH and stirred a further 10 min. Water (150 mL) was added, and the solution was extracted with ethyl acetate, dried, filtered, and evaporated to give an orange gum. Purification was achieved with flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (200:8:1). Recrystallization from ethanol afforded 1.51 g (32%) of **86** as an orange solid: MS *m*/*z* 508 (M + 1)$^+$; ^{1}H NMR δ 1.26 (3H, t, CH_2CH_3, *J* = 6.9 Hz), 1.67 (3H, s, CCH_3), 2.14 (6H, s, NMe_2), 2.56 (2H, m, CH_2), 2.62 (3H, s, NCH_3), 2.81 (2H, t, CH_2, *J* = 6.9 Hz), 3.63 (2H, m, CH_2Ph, *J* = 7.0 Hz), 4.14 (2H, q, CH_2-CH_3, *J* = 7.0 Hz), 7.04 (3H, m, 3 × ArH), 7.12 (3H, m, 3 × ArH), 7.34 (3H, m, 3 × ArH), 10.57 (1H, s, NH); found M^+ 508.29377, $C_{28}H_{38}N_5O_4$ requires M^+ 508.29239.

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(3,4-dimethyl-4-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (87). Method 16: To the hydrazone **86** (1.51 g, 2.98 mmol) in ethanol (135 mL) was added concentrated H_2SO_4 (2.52 mL). The reaction mixture was gently refluxed at 90 °C overnight. The solution was cooled, the solvent evaporated under reduced pressure, water added (250 mL), and the pH adjusted to 9 with potassium carbonate. The aqueous layer was extracted with ethyl acetate, dried, and filtered and the solvent evaporated under reduced pressure to give a yellow solid which was further purified by flash chromatography eluting with CH_2Cl_2/EtOH/NH_3 (200:8:1). Recrystallization from ethanol gave 0.78 g (54%) of **87** as an off-white solid: MS *m*/*z* 491 (M + 1)$^+$; ^{1}H NMR δ 1.34 (3H, t, CH_2CH_3, *J* = 7.2 Hz), 1.62 (3H, s, CCH_3), 2.35 (6H, s, NMe_2), 2.37 (2H, m, CH_2-NMe_2), 2.6 (3H, s, NCH_3), 2.99 (2H, m, 5-CH_2), 3.13 (2H, m, 3-CH_2), 3.71 (2H, m, CH_2Hyd), 4.34 (2H, q, CH_2CH_3, *J* = 7.0 Hz), 7.0−7.37 (8H, m, 8 × ArH), 11.4 (1H, s, NH); found M^+ 491.25775, $C_{28}H_{38}N_5O_4$ requires M^+ 491.25800. Anal. ($C_{28}H_{38}$-N_5O_4) C, H, N.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(3,4-dimethyl-4-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (88). Method 3: purification by column chromatography eluting with CH_2Cl_2/EtOH/NH_3 (100:8:1) afforded 520 mg (59%) of **88** as a pale-yellow powder: MS *m*/*z* 553 (M + 1)$^+$; ^{1}H NMR δ 1.58 (3H, s, CH_3), 2.1 (6H, s, NMe_2), 2.33 (2H, m, $CH_2$$NMe_2$), 2.5 (3H, s, NCH_3), 2.95 (2H, m, 5-CH_2), 3.05 (2H, m, 3-CH_2), 3.8 (2H, m, CH_2Hyd), 5.38 (2H, s, CH_2O), 6.9−7.48 (13H, m, 13x ArH), 11.47 (1H, s, NH); found M^+ 553.28057, $C_{33}H_{37}N_4O_4$ requires M^+ 553.28149.

3-[2-(Dimethylamino)ethyl]-5-[2-(3,4-dimethyl-4-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylic Acid (89). Method 4: pale-yellow powder; 386 mg (89%); R_f = 0.05 (CH_2Cl_2/EtOH/NH_3 (150:8:1); MS *m*/*z* 463 (M + 1)$^+$; ^{1}H NMR δ 1.63 (3H, s, CH_3), 2.52 (6H, s, NMe_2), 2.9 (3H, s, NCH_3), 2.96 (2H, m, $CH_2$$NMe_2$), 3.19 (4H, m, 5-$CH_2$, 3-$CH_2$), 3.75 (2H, m, CH_2Hyd), 7.0 (3H, m, 3 × ArH), 7.31 (5H, m, 5 × ArH), 11.06 (1H, s, NH); found M^+ 463.23581, $C_{26}H_{31}N_4O_4$ requires M^+ 463.23453.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(3,4-dimethyl-4-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (90).** Method 5: white solid as the HCl salt; MS *m*/*z* 552 (M + 1)$^+$; ^{1}H NMR δ 1.62 (3H, s, CH_3), 2.48 (6H, s, 2 × NCH_3), 2.6 (3H, s, NCH_3), 2.7 (4H, m, $CH_2$$NMe_2$, 5-$CH_2$), 2.9 (2H, m, 3-$CH_2$), 3.75 (2H, m, CH_2Hyd), 4.52 (2H, d, CH_2-NHCO, *J* = 5.4 Hz), 6.99 (3H, m, 3 × ArH), 7.2−7.4 (10H, m, 10 × ArH), 8.8 (1H, m, NH), 9.7 (1H, br s, NH), 11.5 (1H, s, NH); found M^+ 551.28951, $C_{33}H_{37}N_5O_3$·1.0HCl requires M^+ 551.28964. Anal. ($C_{33}H_{37}N_5O_3$·1.0HCl·4.0H_2O) C, H, N.

***N*-(2-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(3,4-dimethyl-4-phenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (91).** Method 5: HCl salt as a white lyophylate; MS *m*/*z* 567 (M + 1)$^+$; ^{1}H NMR δ 1.62 (3H, s, CH_3), 2.6 (3H, s, NCH_3), 2.81 (6H, s, 2 × NCH_3), 2.99 (2H, m, $CH_2$$NMe_2$), 3.1 (2H, m, 5-$CH_2$), 3.2 (2H, m, 3-$CH_2$, under water peak), 3.78 (2H, m, CH_2Hyd), 4.45 (2H, d, CH_2NHCO, *J* = 5.4 Hz), 6.9−7.4 (12H, m, 12 × ArH), 8.8 (1H, t, NH), 9.8 (1H, br s, NH), 11.6 (1H, s, NH); found M^+ 566.30172,

$C_{33}H_{38}N_6O_3 \cdot 1.0HCl$ requires M^+ 566.30054. Anal. ($C_{33}H_{38}N_6O_3 \cdot 2.0HCl \cdot 1.9H_2O$) C, H, N.

3-(4-Nitrophenethyl)-5,5-diphenyl-2,4-imidazolidinedione (92). Method 14: 5.83 g (49%); MS *m/z* 402 $(M + 1)^+$; ^1H NMR δ 3.03 (2H, t, CH_2N, $J = 6.5$ Hz), 3.78 (2H, t, CH_2Ph, $J = 6.7$ Hz), 7.15 (4H, m, 4 × ArH), 7.3 (8H, m, 8 × ArH), 7.90 (2H, d, H2, H6, $J = 7.05$ Hz), 9.55 (1H, s, NH).

3-(4-Aminophenethyl)-5,5-diphenyl-2,4-imidazolidinedione (93). Method 4: 4.66 g (79%); MS *m/z* 372 $(M + 1)^+$; ^1H NMR δ 2.86 (2H, t, CH_2N, $J = 6.8$ Hz), 3.68 (2H, t, CH_2Ph, $J = 6.7$ Hz), 7.05 (2H, d, H2, H6, $J = 8.4$ Hz), 7.12 (2H, d, H3, H5, $J = 8.3$ Hz), 7.21 (4H, m, 4 × ArH), 7.37 (5H, m, 5 × ArH), 9.49 (1H, s, NH).

Ethyl 5-(Dimethylamino)-2-[[4-[2-(3,3-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]-pentanoate (94). Method 15: 1.59 g (25%); MS *m/z* 556 $(M + 1)^+$; ^1H NMR δ 1.26 (3H, t, CH_2CH_3, $J = 6.9$ Hz), 1.66 (3H, s, CH_2), 2.17 (8H, s, CH_2, NMe_2), 2.55 (2H, m, CH_2), 2.79 (2H, s, CH_2, $J = 6.6$ Hz), 3.64 (2H, m, CH_2Ph, $J = 7.0$ Hz), 4.18 (2H, q, CH_2CH_3, $J = 7.0$ Hz), 6.97 (4H, m, H2, H3, H5, H6), 7.17 (5H, m, 5 × ArH), 7.34 (5H, m, 5 × ArH), 9.46 (1H, s, NH), 10.55 (1H, s, NH); found $(M + 1)^+$ 556.29360, $C_{32}H_{38}N_5O_4$ requires $(M + 1)^+$ 556.29236.

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (95). Method 16: 0.76 g (50%); MS *m/z* 539 $(M + 1)^+$; ^1H NMR δ 1.35 (3H, t, CH_2CH_3, $J = 7.2$ Hz), 2.18 (6H, s, NMe_2), 2.32 (2H, m,CH_2NMe_2), 2.99 (4H, m, 5-CH_2, 3-CH_2), 3.73 (2H, m, CH_2Hyd), 4.34 (2H, q, CH_2CH_3, $J = 7.0$ Hz), 7.07 (5H, m, 5 × ArH), 7.24 (8H, m, 8 × ArH), 9.46 (1H, s, NH), 11.4 (1H, s, NH); found M^+ 539.26576, $C_{32}H_{35}N_4O_4$ requires M^+ 539.26583.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (96). Method 3: white solid; MS *m/z* 601 $(M + 1)^+$; ^1H NMR δ 2.08 (6H, s, 2 × NCH_3), 2.27 (2H, m, CH_2NMe_2), 2.97 (4H, m, 5-CH_2, 3-CH_2), 3.74 (2H, m, CH_2Hyd), 5.38 (2H, s, CH_2O), 7.05 (6H, m, 6 × ArH), 7.23 (8H, m, 8 × ArH), 7.49 (3H, m, 3 × ArH), 7.52 (1H, d, ArH), 9.46 (1H, s, NH), 11.48 (1H, s, NH); found M^+ 600.27341, $C_{37}H_{36}N_4O_4$ requires M^+ 600.27366.

3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylic Acid (97). Method 4: white powder; 204 mg (70%); MS *m/z* 511 $(M + 1)^+$; ^1H NMR δ 2.18 (6H, s, 2 × NCH_3), 2.36 (2H, m, CH_2NMe_2), 2.92 (2H, m, 5-CH_2), 3.15 (2H, m, 3-CH_2), 3.67 (2H, m, CH_2-Hyd), 6.79 (1H, d, H7, $J = 8.1$ Hz), 7.06−7.35 (12H, m, 12 × ArH), 9.45 (1H, s, NH), 10.4 (1H, s, NH); found M^+ 511.23250, $C_{30}H_{31}N_4O_4$ requires M^+ 511.23453.

***N*-Benzyl-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (98).** Method 5: HCl salt as a white solid; MS *m/z* 600 $(M + 1)^+$; ^1H NMR δ 1.23 (6H, s, 2 × NCH_3), 2.1 (4H, m, CH_2-NMe_2, 5-CH_2), 2.97 (2H, m, 3-CH_2), 3.72 (2H, m, CH_2Hyd), 4.52 (2H, d, CH_2NHCO, $J = 5.4$ Hz), 6.9−7.3 (18H, m, Arom), 9.4 (1H, s, NH), 9.6 (1H, br s, NH), 11.3 (1H, s, NH); found M^+ 599.29237, $C_{37}H_{37}N_5O_3 \cdot 1.0HCl$ requires M^+ 599.28964. Anal. ($C_{37}H_{37}N_5O_3 \cdot 1.0HCl$) C, H, N.

3-(4-Aminophenethyl)-5-phenyl-5-methyl-2,4-imidazolidinedione (99). Method 4: white powder; 8.08 g (62%); mp 175−177 °C; MS *m/z* 310 $(M + 1)^+$; ^1H NMR δ 1.57 (3H, s, CH_3), 2.83 (2H, t, CH_2N, $J = 6.9$ Hz), 3.59 (2H, t, CH_2Ph, $J = 6.9$ Hz), 7.15 (4H, s, H2, H3, H5, H6), 7.34 (5H, m, 5 × ArH), 8.4 (1H, s, NH), 9.82 (3H, br s, NH_3^+).

Ethyl 5-(Dimethylamino)-2-[[4-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (100). Method 15: afforded **100** as a glassy yellow solid; 4.12 g (72%); MS *m/z* 494 $(M + 1)^+$; ^1H NMR δ 1.23 (3H, t, CH_2CH_3, $J = 7.0$ Hz), 1.54 (3H, s, CH_3), 1.86 (2H, m, CH_2), 2.34 (6H, s, NMe_2), 2.57 (2H, m, CH_2), 2.75 (2H, s, CH_2, $J = 6.6$ Hz), 3.54 (2H, m, CH_2Ph), 4.16 (2H, q, CH_2CH_3, $J = 7.1$ Hz), 6.96 (2H, d, H2, H6, $J = 8.4$ Hz), 7.05 (2H, d, H3, H5, $J = 8.1$ Hz), 7.31 (5H, m, 5 × ArH), 8.79 (1H, s, NH), 10.46 (1H, s, NH), 11.86 (1H, s, NH).

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (101). Method 16: yellow glassy solid; 1.53 g (80%); MS *m/z* 477 $(M + 1)^+$; ^1H NMR δ 1.34 (3H, t, CH_2CH_3, $J = 7.2$ Hz), 1.53 (3H, s, CH_3), 2.2 (6H, s, 2 × NCH_3), 2.39 (2H, m, CH_2NMe_2), 2.93 (2H, m, 5-CH_2), 3.12 (2H, m, 3-CH_2), 3.64 (2H, m, CH_2Hyd), 4.34 (2H, q, CH_2CH_3, $J = 7.1$ Hz), 7.0 (1H, d, H6, $J = 8.0$ Hz), 7.26 (7H, m, H7, H4, 15 × ArH), 8.7 (1H, br s, NH), 11.47 (1H, br s, NH); found M^+ 476.24000, $C_{27}H_{32}N_4O_4$ requires M^+ 476.24236.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (102). Method 3: white powder; 610 mg (49%); MS *m/z* 539 $(M + 1)^+$; ^1H NMR δ 1.52 (3H, s, CH_3), 2.17 (6H, s, 2 × NCH_3), 2.49 (2H, m, CH_2NMe_2), 2.93 (2H, m, 5-CH_2), 3.07 (2H, m, 3-CH_2), 3.64 (2H, m, CH_2Hyd), 5.37 (2H, s, CH_2O), 7.02 (1H, d, H6, $J = 8.1$ Hz), 7.23−7.5 (12H, m, H7, H4, 10 × ArH), 8.78 (1H, s, NH), 11.47 (1H, s, NH).

3-[2-(Dimethylamino)ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylic Acid (103). Method 4: white powder; 297 mg (55%); MS *m/z* 449 $(M + 1)^+$; ^1H NMR δ 1.55 (3H, s, CH_3), 2.5 (6H, s, 2 × NCH_3), 2.94 (4H, m, CH_2NMe_2, 5-CH_2), 3.12 (2H, m, 3-CH_2), 3.63 (2H, m, CH_2Hyd), 6.93 (1H, d, H6, $J = 8.7$ Hz), 7.28 (7H, m, H7, H4, 5 × ArH), 8.76 (1H, s, NH), 11.05 (1H, s, NH).

***N*-(2-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (104).** Method 5: HCl salt as a white lyophylate; MS *m/z* 553 $(M + 1)^+$; ^1H NMR δ 1.57 (3H, s, CH_3), 2.81 (6H, s, 2 × NCH_3), 2.94 (2H, m, CH_2NMe_2), 3.1 (2H, m, 5-CH_2), 3.3 (2H, m, 3-CH_2, under H_2O Peak), 3.6 (2H, m, CH_2-Hyd), 4.41 (2H, d, CH_2NHCO, $J = 5.4$ Hz), 6.75 (2H, m, H6, 1 × ArH), 7.01 (2H, m, H7, H4), 7.16−7.3 (9H, m, 9 × ArH), 7.5 (1H, s, NH), 8.76 (2H, s, 2 × NH), 9.8 (1H, br s, NH), 11.6 (1H, s, NH); found M^+ 552.29011, $C_{32}H_{36}N_6O_3 \cdot 2.0HCl \cdot 3.0H_2O$ requires M^+ 552.28489. Anal. ($C_{32}H_{36}N_6O_3 \cdot 2.0HCl \cdot 3.0H_2O$) C, H, N.

***N*-Benzyl-5-[2-(4-phenyl-4-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-3-[2-(dimethylamino)ethyl]-1*H*-indole-2-carboxamide (105).** Method 5: HCl salt as a white lyophylate; MS *m/z* 538 $(M + 1)^+$; ^1H NMR δ 1.55 (3H, s, CH_3), 2.48 (6H, s, 2 × NCH_3), 2.78 (2H, m, CH_2), 2.95 (2H, m, CH_2NMe_2), 3.1 (2H, m, CH_2), 3.67 (2H, m, CH_2Hyd), 4.52 (2H, d, CH_2-NHCO), 7.02 (1H, d, H6, $J = 8.1$ Hz), 7.25−7.45 (12H, m, H7, H4, 10 × ArH), 8.8 (1H, s, NH), 9.6 (1H, t, NH), 11.42 (1H, s, NH); found M^+ 537.27399, $C_{32}H_{35}N_5O_3 \cdot 1.0HCl$ requires M^+ 537.27399. Anal. ($C_{32}H_{35}N_5O_3 \cdot 1.0HCl \cdot 1.0H_2O$) Calcd: C, 64.91; H, 6.47; N, 11.83. Found: C, 64.88; H, 6.24; N, 11.32.

***N*-(2-Aminobenzyl)-3-[2-(dimethylamino)ethyl]-5-[2-(4,4-diphenyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxamide (106).** Method 5: HCl salt as an off-white powder; MS *m/z* 615 $(M + 1)^+$; ^1H NMR δ 2.53 (8H, m, 2 × NCH_3, CH_2NMe, under DMSO peak), 3.01 (2H, m, 5-CH_2), 3.22 (2H, m, 3-CH_2, under H_2O Peak), 3.76 (2H, m, CH_2Hyd), 4.39 (2H, d, CH_2NHCO, $J = 5.4$ Hz), 5.1 (2H, br s, NH_2), 6.5−6.65 (2H, m, H6, 1 × ArH), 7.0−7.15 (7H, m, H7, H4, 5 × ArH), 7.25 (7H, m, 7 × ArH), 7.5 (1H, m, 1 × ArH), 9.58 (1H, s, NH), 11.4 (1H, s, NH); found M^+ 614.30588, $C_{37}H_{38}N_6O_3 \cdot 1.0HCl$ requires M^+ 614.30054. Anal. ($C_{37}H_{38}N_6O_3 \cdot 1.0HCl \cdot 0.5H_2O$) Calcd: C, 67.31; H, 6.11; N, 12.73. Found: C, 67.25; H, 5.65; N, 12.22.

Biological Methods. Rabbit saphenous vein (RbSV) preparation: The vascular 5-HT_{1B}-like receptor affinities of compounds were assessed using ring preparations of rabbit saphenous vein.[33] Vessels were removed from male New Zealand white rabbits killed by injecting pentobarbitone (80 mg/kg, iv) followed by exsanguination. After adhering connective tissue was removed, 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. To prevent the direct or indirect activation of α_1-adrenoceptors, saphenous veins were simultaneously exposed to phenoxybenzamine (0.3 μM). After 30 min 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 min 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 novel compounds behaved as 'silent 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.[30] Rings (2 mm) of rabbit femoral artery were exposed to pargyline (500 μM) for 30 min 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 and histamine H$_1$ receptors. α_1-Adrenoceptor activity was determined in tissues exposed to pargyline (500 μM for 30 min) 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 min prior to construction of a cumulative E/[A] curve to L-Phe. Activity at H$_1$ receptors was assessed using a similar protocol, except that tissues were not exposed to pargyline and histamine (10 μM) was used to provide the reference contracture prior to construction of a cumulative E/[A] curve to histamine.[31]

Guinea pig trachea (GPT) preparation: Ring segments of guinea pig trachea were used to assay for activity at M$_3$ receptors. Ring segments (2 mm) were opened into a strip by cutting through the cartilage opposite the trachealis smooth muscle. Indomethacin (3 μg/mL) was included in the Krebs Henseleit solution to prevent formation of cyclooxygenase products. A tension of 1 g was applied to each strip during a 30-min equilibration period, after which carbachol (10 μM) was added to enable viability to be assessed and provide a reference contracture for subsequent data analysis. Following washout, tissues were exposed to novel compounds (30 μM) for 60 min prior to construction of a cumulative E/[A] curve to carbachol.[36]

Receptor binding assays: Competition binding assays were performed to determine drug affinity (pK_i or IC$_{50}$) at the various receptors described. The radioligands used in the receptor binding assays were 5-HT$_{1D}$, [^{3}H]5-HT in the presence of 8-OH-DPAT (100 nM) to mask 5-HT$_{1A}$ binding and mesulargine (100 nM) to mask 5-HT$_{2C}$ binding; 5-HT$_{1A}$, [^{3}H]8-OH-DPAT; 5-HT$_{2C}$, [^{3}H]mesulergine. Briefly the appropriate radioligand (~K_D) and a wide range of test drug concentrations (in duplicate) were incubated with the relevant receptor preparation for 30 min at 27 °C—conditions determined previously to satisfy mass-action conditions. (5-HT$_{1A}$ receptor binding was conducted using membranes prepared from human recombinant 5-HT$_{1A}$ receptors expressed in CHO-K1 cells. 5-HT$_{1D}$ receptor binding was determined using membranes prepared from calf caudate nucleus. 5-HT$_{1C}$ receptor binding was determined using membranes prepared from rat whole brain.) The assay buffer comprised 50 mM TRIS-HCl, 5 mM $CaCl_2$, 0.1% w/v ascorbate, and 10 mM paragyline. Nonspecific binding was defined using an excess of cold 5-HT. Incubations were terminated by rapid filtration and washing with ice-cold buffer. Specifically bound radiolabel was measured by liquid scintillation spectroscopy.

Pharmacokinetic Methods. These studies followed a protocol previously outlined.[36] 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 was measured using (GC/MS).

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