A Novel Series of 2,5-Substituted Tryptamine Derivatives as Vascular 5HT$_{1B/1D}$ Receptor Antagonists

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The design, synthesis, and activity of a novel series of 2,5-substituted tryptamine derivatives at vascular 5HT$_{1B}$-like receptors is described. Several important auxiliary binding sites of the 5HT$_{1B}$-like receptor have been proposed following various modifications to the 2-substituent and especially to the methylene- or ethylene-linked 5-side chain. Careful design of new molecules based on a proposed pharmacophoric model of the 5HT$_{1B}$-like receptor has resulted in the discovery of ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (**40**), a highly potent, silent, competitive, and selective antagonist which shows affinity at the vascular 5HT$_{1B}$-like receptors only. Changes to the size of the 2-ester substituent have a significant effect on affinity at the 5HT$_{1B}$-like receptor and other receptors. Prudent placement of the carbonyl substituent in the heterocycle of the 5-side chain is crucial for good affinity and selectivity over the 5HT$_{2A}$ and other receptors. Several key structural and electronic features were identified which are crucial for producing antagonism within a tryptamine-based series. An electron deficient indole ring system appears essential in order to achieve antagonism, and this is achieved by the inclusion of electron-withdrawing groups at the 2-position of the indole ring. The molecule displacement within the receptor resulting from the inclusion of the bulky 2-substituents also enhances antagonism as this results in the removal of the π electon density of the indole ring from the region of the receptor normally occupied by the indole ring of 5HT. There also appears to be a structural requirement on the side chain incorporating the protonatable nitrogen, and this is achieved by the inclusion of the bulky 2-ester group which neighbors the 3-ethylamine side chain.

Introduction

Fourteen subtypes of serotonin (5HT) receptors organized into seven distinct receptor classes, 5HT$_1$– 5HT$_7$, are now recognized.[1−3] In some cases, i.e., 5ht$_{1E}$, 5ht$_{1F}$, 5ht$_5$, and 5ht$_6$, only the genes 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 most diverse of the 5HT receptor classes is the 5HT$_1$ class, comprising 5HT$_{1A}$, 5HT$_{1B}$ (formally 5HT$_{1D\beta}$),[5] 5HT$_{1D}$ (formally 5HT$_{1D\alpha}$),[5] 5ht$_{1E}$, and 5ht$_{1F}$ subtypes. In addition, a well-characterized 5HT receptor mediating vasoconstriction has long been recognized. Increasing evidence indicates that this receptor is 5HT$_{1B}$, but in the absence of ligands to make a definitive classification, it is referred to here as 5HT$_{1B}$-like. Among these subtypes, the 5HT$_{1B}$ and 5HT$_{1D}$ receptors have attracted considerable attention as putative targets for novel

antimigraine drugs, leading to the development of 5HT$_{1B/1D}$ receptor selective agonists such as sumatriptan (GR43175)[6−8] and more recently zolmitriptan,[9] rizatriptan, eletriptan, avitriptan, and others.[10,11]

Until recently, efforts to characterize vascular 5HT$_{1B}$-like receptors have been frustrated by the lack of selectivity of the available antagonists, e.g., metergoline and methiothepin. A series of benzanilides,[12] exemplified by GR127935, have been described as potent antagonists at 5HT$_{1B}$ and 5HT$_{1D}$ receptors and have been shown to block both peripheral and central responses mediated by both of these receptor types.[13] However, this compound is not a silent antagonist and behaves as a partial agonist at recombinant human 5HT$_{1B}$ and 5HT$_{1D}$ receptors.[14] Moreover, the drug exhibits pseudoirreversible pharmacodynamics, making it less than ideal for the quantitative study of 5HT$_{1B}$ and 5HT$_{1D}$ receptors.[13]

Examination of molecules developed as selective 5HT$_{1B/1D}$ receptor agonists, e.g., sumatriptan,[6−8,15,16] MSD compounds,[17,18] and zolmitriptan,[9] together with work carried out in our laboratories have given some insight into the requirements for conversion of these potent agonists into antagonists. A program was initiated in our laboratories with the objective of identifying a novel series of potent and selective antagonists of the vascular 5HT$_{1B}$-like receptor as potential new drugs for the prophylactic treatment of various cardiovascular disease states including cerebral vasospasm following

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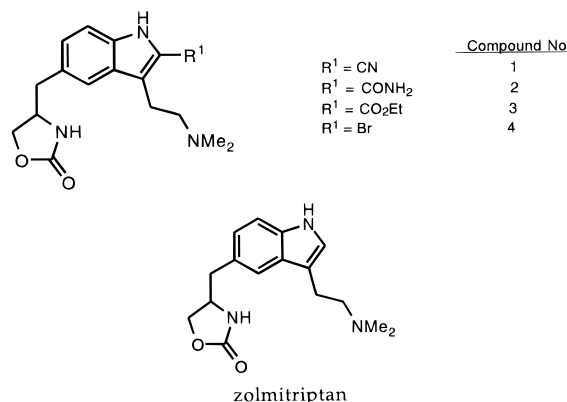[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

Figure 1. Four target tryptamine derivatives (**1**–**4**) designed as antagonists and zolmitriptan, a known selective and potent $5HT_{1B/1D}$ agonist.

Figure 2. Theoretical $5HT_{1B}$-like receptor model using zolmitriptan as a reference. The amine-binding site is represented by the blue sphere, the aromatic binding site by the green sphere, the hydrogen-bonding site by the red sphere, and the selectivity volume in yellow.

subarachnoid hemorrhage, Raynaud's syndrome, angina pectoris, and intermittent claudication.[19] Selective $5HT_{1B/1D}$ antagonists will also be useful as tools to study the physiological function of these receptors. The target molecule profile was one of a potent, silent, reversible antagonist with 100-fold selectivity over other mono-amine receptors and a pharmacokinetic profile consistent with the potential therapeutic applications outlined earlier.

Structure–activity relationships obtained from non-selective antagonists identified from previous work in our laboratories and from existing antagonists suggested that for tryptamine analogues an electron deficient aromatic system was important for antagonism. Moreover there appeared to be an association between antagonism and a conformational restriction of some nature on the 3-ethylamine side chain.[20] A consideration of the factors affecting selectivity and efficacy described elsewhere[21] led to the identification of the tryptamine analogues **1**–**4** as primary targets, Figure 1. The structure of these compounds is based on zolmitriptan, a selective partial $5HT_{1B/1D}$ receptor agonist.[9,21]

The proposed compounds differ from zolmitriptan in the electron-withdrawing groups attached to the indole in the 2-position. These substituents have been located in this position as this would create an electron deficient indole system while simultaneously conferring a conformational restriction on the ethylamine side chain. Biological results for these compounds were encouraging in that a series of silent, competitive antagonists were produced from selective agonists by incorporation of an electron-withdrawing group at the 2-position; however, potency and selectivity were not up to the desired level.

In the design of a novel series of 5HT ligands, we utilized computer graphics and computational chemistry. A theoretical model of the binding mode of high-affinity ligands to the vascular $5HT_{1B}$-like receptor has been postulated[21] based on the common pharmacophoric points displayed by a large number of diverse ligands with affinity at $5HT_{1B/1D}$ receptors. This pharmacophore model was constructed using the active analogue approach.[21,22] The elucidation of a series of common distance constraints between functional groups led to the hypothesis that a combination of a protonated amine, an aromatic center, a hydrophobic volume, a hydrogen-bonding acceptor site, and a donor–acceptor site coul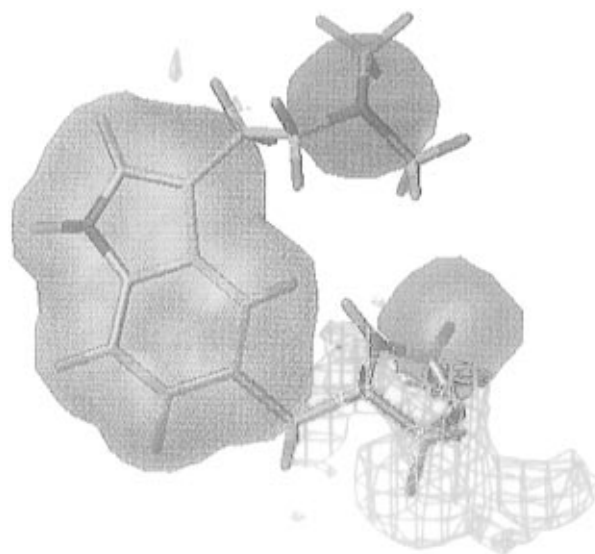d be occupied and result in affinity for the vascular $5HT_{1B}$-like receptor. In addition, a "selectivity volume" was deduced which, if occupied, resulted in selectivity for $5HT_{1B/1D}$ receptors over $5HT_{2A}$ receptors. A representation of the pharmacophore model is depicted in Figure 2.

Given the spatial distribution of the common pharmacophore points, it is possible to perform conformational analysis and least-squares fitting of novel compounds to the desired pharmacophoric points and hence suggest a binding mode for new compounds. The principal binding points were deduced to be the protonated amine and the hydrogen bond acceptor. In some cases, due to the conformational and geometric constraints present in some molecular structures, this mode of least-squares fitting results in displacement of the aromatic center of the indole (if present) from the aromatic site occupied by, for example, zolmitriptan. It was observed that in such cases the affinity of the compound could be high while its efficacy was greatly reduced. An extensive quantitative investigation of this effect (to be published elsewhere) implied that conformational constriction of the relationships between the protonated amine, hydrogen-bonding acceptor, and aromatic center would result in a displacement of the aromatic center from the volume normally occupied by the aromatic center in zolmitriptan and result in a loss of efficacy. Subsequent investigations narrowed the region which appears to be responsible for efficacy down to the double bond (π-density) region of the pyrrole of the indole indicated in Figure 3.

It thus appears that in order to design high-affinity antagonists occupation of the protonated amine site and the hydrogen-bonding site in addition to the aromatic center would be good for affinity while π-electron density in the region normally occupied by the indole double bond should be avoided to prevent an agonist response. The substitution in the 2-position of the indole causes restriction in the conformational flexibility of the ethylamine side chain, and in addition, we hypothesized that there may be a restriction in the size of substituents in the 2-position that could be accommodated by the
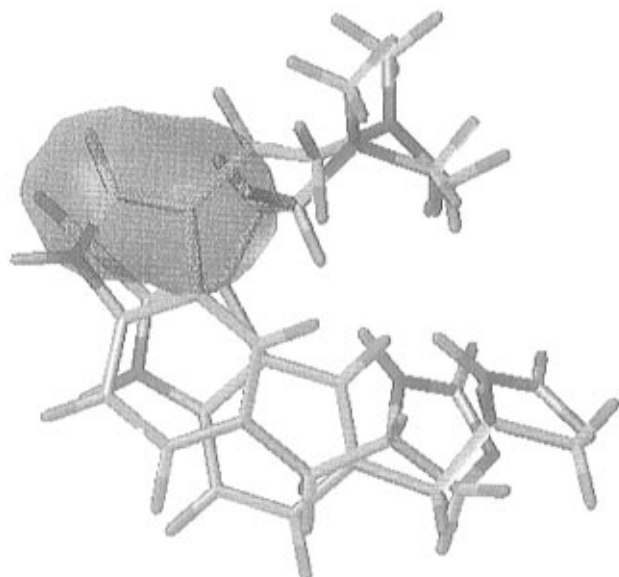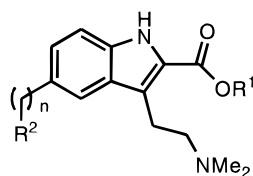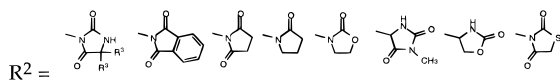
Figure 3. Overlay of zolmitriptan and the displaced tryptamine derivative **1**. The π-density region is indicated.

5: $n = 1, 2$; $R^1 = CH_3, CH_2CH_3, CH(CH_3)_2, CH_2C_6H_5, C_6H_{11}$

$R^2 =$

$R^3 = H, CH_3$

Figure 4. Series of 2,5-substituted tryptamine derivatives investigated with variation in structure occurring in the 2-ester substituent and the 5-linked heterocycle.

5HT$_{1B}$-like receptor. Bulk in this region may cause a displacement of the indole away from its usual position (as seen in **1**, Figure 3) resulting in loss of occupancy of the π-electron density region necessary to elicit an agonist response. The inclusion of this receptor essential volume explained the loss of agonism upon substitution of bulky substituents in the 2-position. If suitable modifications are made to the remainder of the molecule such that it can still accommodate the principal pharmacophoric binding points, then an antagonist may be obtained which has high affinity for the 5HT$_{1B}$-like receptor.

Examination of the tryptamine derivatives **1**−**4** in the pharmacophore model suggested that the molecules may better accommodate the pharmacophore binding points if the 5-side chain is increased in length hence allowing for more conformational freedom. A further series of compounds **5** were synthesized incorporating this change, Figure 4.

We describe in this paper the design, synthesis, and 5HT$_{1B}$-like activity of a series of 2,5-substituted tryptamine derivatives **5** and related analogues. Changes to the 2-substituent, the length of the linking chain (*n*), and the nature of the 5-linked heterocycle as well as the 3-side chain incorporating the protonatable nitrogen have been performed in an attempt to improve potency

Scheme 1^a
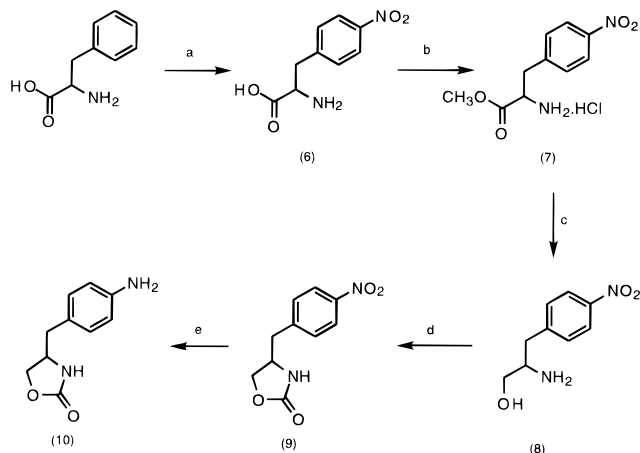
^{a} Reagents: (a) HNO$_3$/H$_2$SO$_4$; (b) SOCl$_2$, CH$_3$OH; (c) CH$_3$OH, NaBH$_4$; (d) COCl$_2$; (e) H$_2$, 10% Pd−C, EtOH.
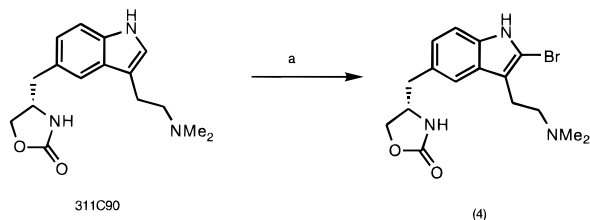
Scheme 2^a
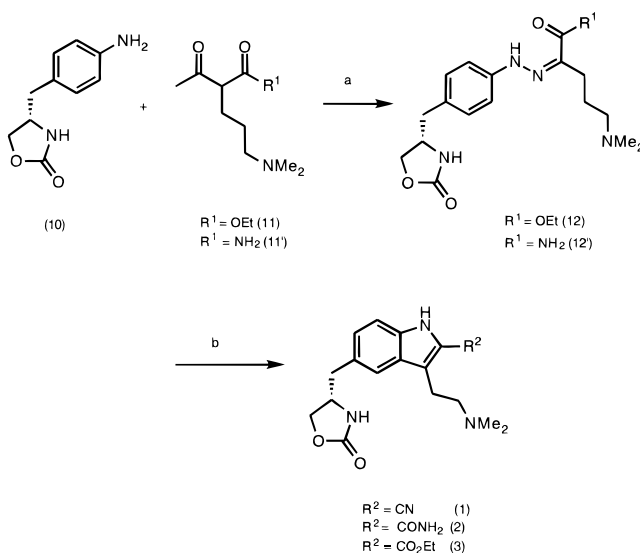
^{a} Reagents: (a) NaNO$_2$, HCl, NaOH; (b) PPE, CHCl$_3$ or *p*-toluenesulfonic acid, CHCl$_3$.

and selectivity and to explore the pharmacophore of the 5HT$_{1B}$-like recognition site.

Synthetic Chemistry

The tryptamine derivatives **1**−**4** were prepared from the aniline derivative **10** (Scheme 1). Nitration of phenylalanine followed by reaction with thionyl chloride and methanol gave the methyl ester intermediate **7**. The ester functionality was reduced to a methyl alcohol group with sodium borohydride. Cyclization of the alcohol and neighboring amine group with phosgene gave the oxazolidinone derivative **9** which was converted to the aniline derivative **10** by hydrogenation of the nitro group in the presence of 10% palladium on carbon.

The β-keto ester **11** or amide **11′** required for the Japp−Klingemann indole formation[23,24] was prepared by alkylation of ethyl acetoacetate[25] or acetoacetamide respectively with 3-(dimethylamino)propyl chloride hydrochloride, Scheme 2. Diazotization of the aniline derivative **10** followed by reaction with the prepared β-keto ester or amide afforded the hydrazone intermediate **12**. A number of different catalysts were used in attempts to force the final indole ring closure. Cycliza-

Scheme 3[a]

311C90 (4)

[a] Reagents: (a) (CH$_3$)$_3$SiBr, DMSO.

Scheme 4[a]

(13)

(14) (19) (20)

(15) (16) (17)

(18)
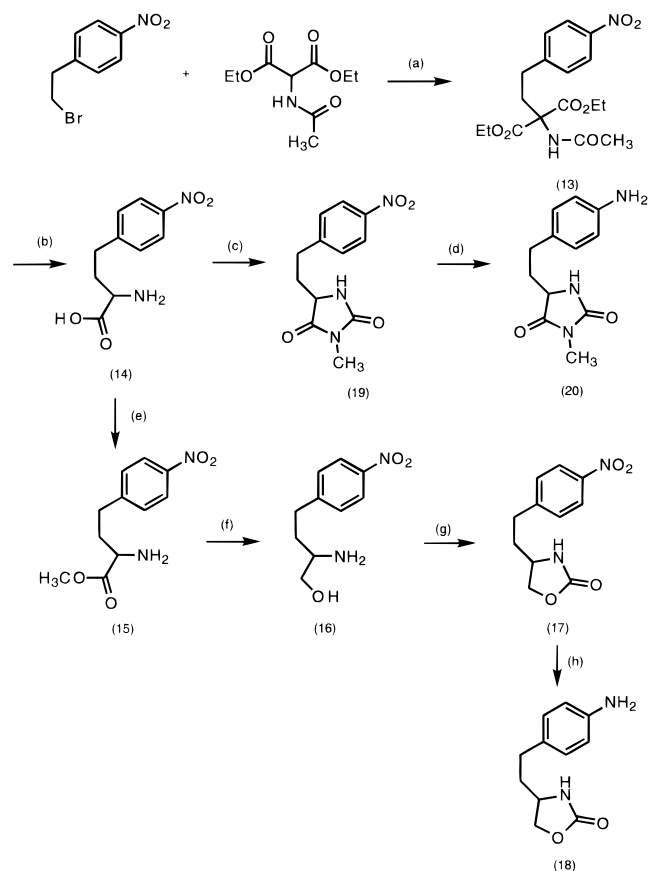
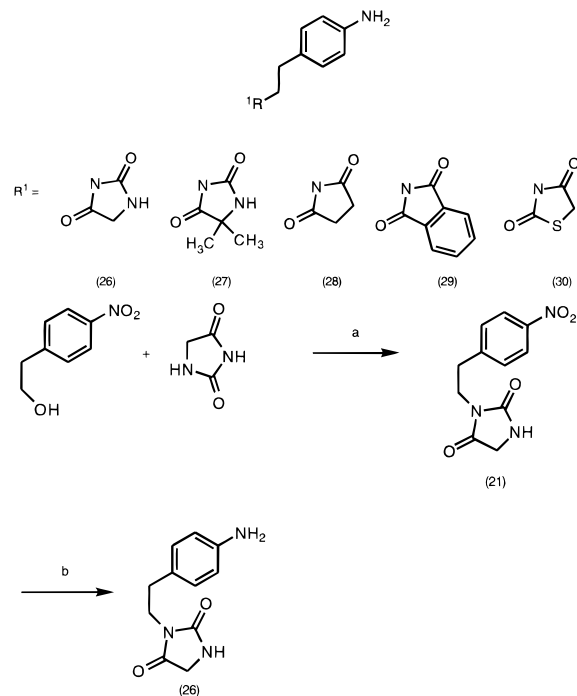[a] Reagents: (a) Na, EtOH; (b) 60% HBr; (c) KOH, H$_2$O, CH$_3$NCO, HCl; (d) H$_2$, Pd$-$C (10%), EtOH; (e) SOCl$_2$, CH$_3$OH; (f) CH$_3$OH, NaBH$_4$; (g) COCl$_2$; (h) H$_2$, Pd$-$C (10%), EtOH.

Scheme 5[a]

R^1 = (26) (27) (28) (29) (30)

(21)

(26)

[a] Reagents: (a) Ph$_3$P, DIAD, THF, 0 °C; (b) H$_2$, 10% Pd$-$C.

Scheme 6[a]

X = O (31)
X = CH$_2$ (32)

X = O (33)
X = CH$_2$ (34)

X = O (35)
X = CH$_2$ (36)

[a] Reagents: (a) THF, Et$_3$N; (b) 5 N NaOH, THF; (c) H$_2$, Pd$-$C (10%), EtOH.
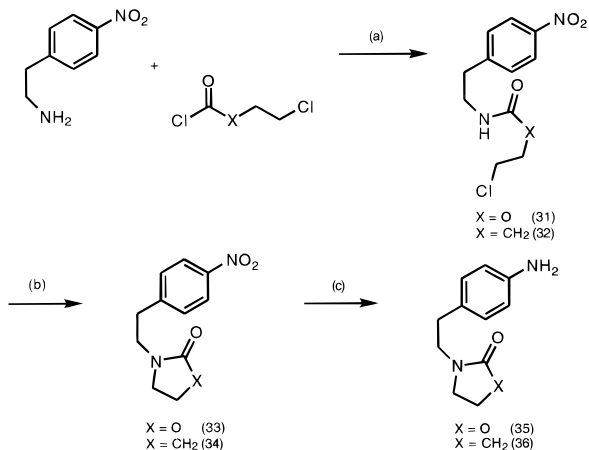
tion with polyphosphate ester in chloroform effected the formation of the indole and simultaneously dehydrated the amide to the required nitrile **1**. Cyclization of the hydrazone with *p*-toluenesulfonic acid gave the indole amide **2** and the indole ester **3**, Scheme 2.

The 2-bromo-substituted derivative **4** was prepared from the 2-unsubstituted tryptamine compound zolmitriptan by treatment with trimethylsilyl bromide, Scheme 3.

Other Aniline Intermediates Required for Indole Synthesis. A 5-ethylene-linked analogue of the 2-ester indole derivative **3** was prepared from the higher homologue of *p*-nitrophenylalanine which was obtained by a conventional amino acid synthesis, Scheme 4. 4-Nitrophenethyl bromide was coupled with diethyl acetoamidomalonate to give the diester derivative **13**. Refluxing in 60% HBr resulted in loss of CO$_2$ and formation of the amino acid **14** which was reacted on in an analogous way to that described in Scheme 1 to afford the oxazolidinone derivative **18**. The aniline derivative required to form a carbon-linked hydantoin

derivative was also synthesized from the amino acid **14**. Reaction with methyl isocyanate afforded the hydantoin derivative **19** which was converted to the aniline derivative **20** by hydrogenation in the presence of 10% palladium on carbon.

The hydantoin derivatives **26**−**30** were synthesized as shown in Scheme 5. Reaction of *p*-nitrophenethyl alcohol and the appropriate hydantoin derivative under Mitsunobu conditions[26−28] afforded the nitro intermediates **21**−**25**. Hydrogenation at room temperature and atmospheric pressure afforded the desired aniline derivatives **26**−**30**.

An oxazolidinone derivative (**35**) connected through the nitrogen was synthesized according to Scheme 6. *p*-Nitrophenethylamine was reacted with 2-chloroethyl chloroformate to give the amido halide **31**. Cyclization with NaOH followed by hydrogenation of the nitro group afforded the desired N-linked oxazolidinone aniline derivative **35**. The lactam aniline derivative **36** was
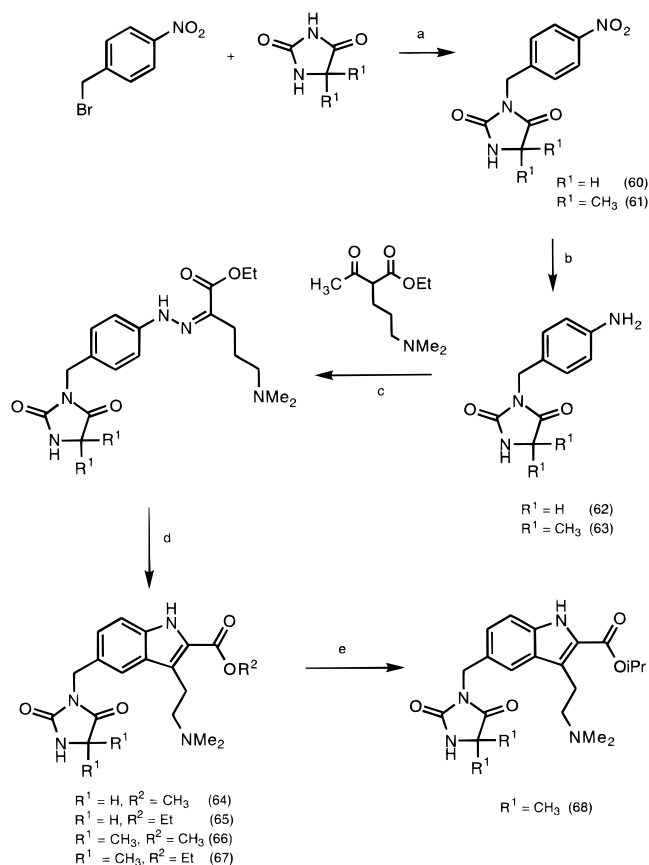
Scheme 7^a
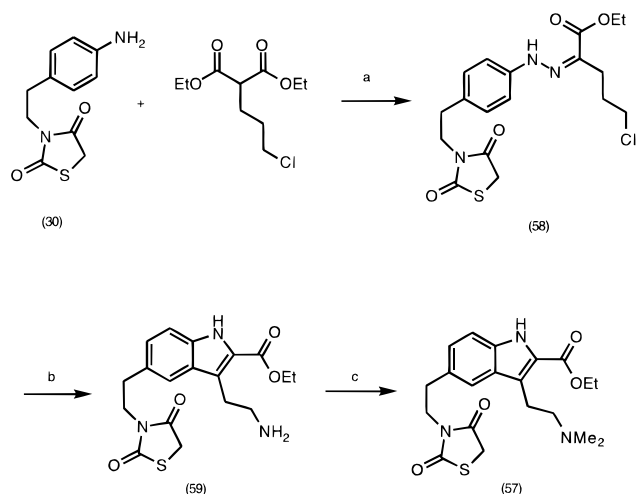
^{a} Reagents: (a) NaNO$_2$, H$_2$O, NaOAc; (b) *n*-BuOH; (c) NaC-NBH$_3$, CH$_2$O.

synthesized in a similar manner to **35** using instead 4-chlorobutyryl chloride in the alkylation step.

Conversion of all the aniline derivatives to the corresponding 2-substituted tryptamine derivatives proceeded as described in Scheme 2. Hydrazone formation followed the same reaction conditions as those utilized in the synthesis of compounds **1**−**3**; however, cyclization of the hydrazone intermediates was achieved by stirring in hot ethanol in the presence of sulfuric acid. A series of methyl ester derivatives was obtained by refluxing the hydrazone intermediate in hot methanol in the presence of sulfuric acid. The isopropyl ester and the cyclohexyl ester derivatives were formed by heating the appropriate tryptamine 2-ethyl ester derivative in isopropyl alcohol or cyclohexanol, respectively, in the presence of titanium tetraisopropoxide. Table 2 outlines the tryptamine derivatives synthesized.

In an attempt to improve the yields of the 2,5-substituted tryptamine derivatives, the thiazolidinone derivative **57** was synthesized in a different manner to the other tryptamine derivatives. The aniline derivative **30** was reacted with diethyl chloropropylmalonate[29] under Japp−Klingemann conditions to give the hydrazone derivative **58**, Scheme 7. Cyclization was achieved by heating the hydrazone in butanol to give the tryptamine intermediate **59** which was converted to the dimethyl derivative **57** by reaction with formaldehyde and sodium cyanoborohydride.

A series of lower homologue 5-ethylene-linked tryptamine derivatives was synthesized as outlined in Scheme 8. Reaction of *p*-nitrobenzyl bromide with the hydantoin derivative gave the required nitro hydantoin derivatives **60** and **61**. The nitro group was reduced with hydrogen in the presence of 10% palladium on carbon, and the resulting aniline derivative was reacted with the diketone under Japp−Klingemann conditions to give the desired hydrazone intermediate. Cyclization to form the 2-substituted tryptamine derivative was achieved by heating the hydrazone intermediate in ethanol and concentrated sulfuric acid. Heating of the ethyl ester in isopropyl alcohol in the presence of titanium tetraisopropoxide gave the desired isopropyl ester derivative **68**. The lower homologue compounds investigated are shown in Table 5.

Scheme 8^a

^{a} Reagents: (a) K$_2$CO$_3$, DMF; (b) H$_2$, Pd−C (10%); (c) HCl, NaNO$_2$, NaOH; (d) EtOH (or MeOH), cH$_2$SO$_4$; (e) (CH$_3$)$_2$CHOH, Ti(*i*-OPr)$_4$.

Scheme 9^a
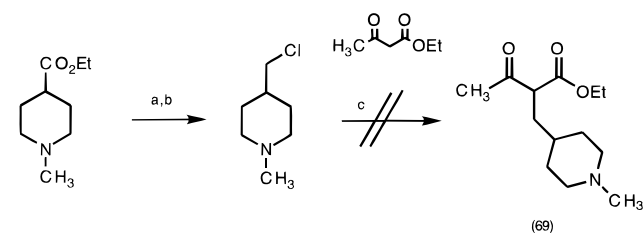
^{a} Reagents: (a) LiAlH$_4$, Et$_2$O; (b) PCl$_5$, CHCl$_3$; (c) Na, MeOH.

3-Piperidine Derivatives. A series of 3-piperidine derivatives was prepared in a slightly different manner to the corresponding 3-ethylamine derivatives. The substituted β-keto ester **69** containing a piperidine side chain could not be obtained in a manner analogous to that used to synthesize the diketone **11** shown in Scheme 2. Ethyl acetoacetate could not be persuaded to accept the piperidine alkyl halide as an electrophile, Scheme 9.

The desired β-keto ester was finally prepared by alkylation of ethyl acetoacetate with 4-picolyl chloride followed by quaternization with methyl iodide and hydrogenation of the aromatic ring under reduced pressure, Scheme 10.

Japp−Klingemann coupling of the diketone **69** with the aniline derivative **10** afforded the hydrazone intermediate **72** which was cyclized with *p*-toluenesulfonic acid in toluene to give the 3-piperidine analogue **73**, Scheme 11.

A series of higher homologues of the 3-piperidine derivative **73** were synthesized in a slightly different

Scheme 10[a]
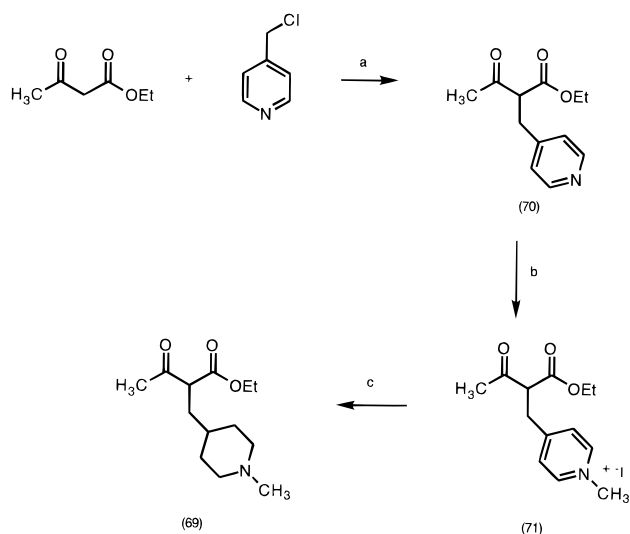
[a] Reagents: (a) Na, EtOH; (b) MeI, ether; (c) H$_2$, PtO$_2$, 50 atm.

Scheme 11[a]
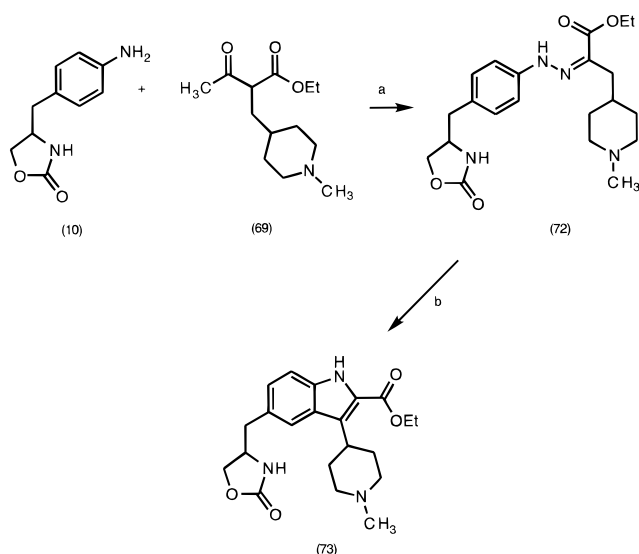
[a] Reagents: (a) HCl, NaNO$_2$, NaOH; (b) *p*-toluenesulfonic acid, toluene.

Scheme 12[a]

[a] Reagents: (a) HCl, NaNO$_2$, NaOH; (b) EtOH, cH$_2$SO$_4$; (c) MeI, THF; (d) NaBH$_4$, MeOH; (e) H$_2$, Pd (10%).

Table 1

| compd no. | R^1 | pK$_B$[a] | |
		5HT$_{1B}$-like, RbSV	5HT$_{2A}$, RbA
1	CN	4.8	4.6
2	CONH$_2$	4.75	<4.5
3	CO$_2$Et	6.12	5.66
4	Br	5.86	<5.0

[a] Affinity (pK$_B$ = $-$log$_{10}$ K$_B$, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5HT$_{1B}$-like and 5HT$_{2A}$ receptors in the rabbit saphenous vein (Rb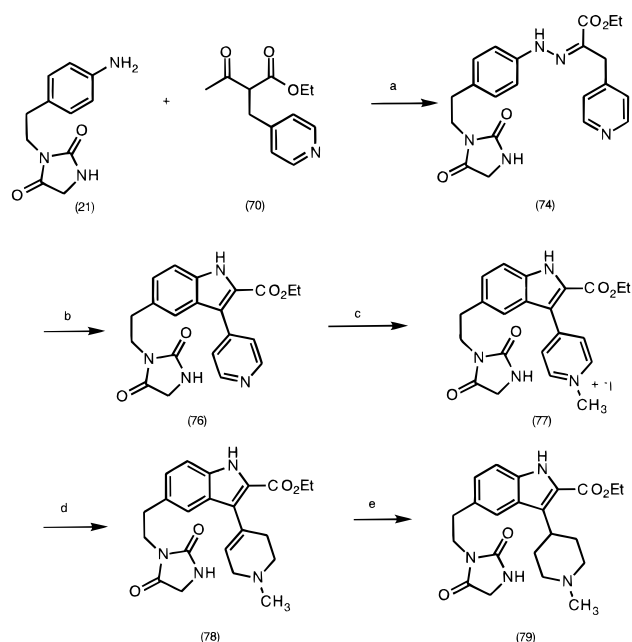SV) and aorta (RbA), respectively. Affinity values are the means of at least three separate estimates. Standard errors are omitted for clarity but in all cases were $\leq$0.2 log$_{10}$ unit.

manner, Scheme 12. The pyridine diketone derivative **70** was reacted directly with the aniline derivative to afford a pyridine hydrazone intermediate (**74**) which was cyclized in hot ethanol in the presence of sulfuric acid to give a 2-ethyl ester indole intermediate (**76**). Quaternization with methyl iodide followed by reduction with sodium borohydride afforded a tetrahydropyridine derivative (**78**). Reduction with hydrogen in the presence of 10% palladium on carbon gave the 3-piperidine derivative **79**, Scheme 12. Table 6 shows the 3-tetrahydropyridine and 3-piperidine derivatives investigated.

Results and Discussion

Structure$-$Activity Relationships. Table 1 shows biological data for the 2-substituted tryptamine derivatives **1**$-$**4**. It was encouraging to note that a highly selective agonist (zolmitriptan) had been converted to an antagonist by a simple structural manipulation. Clearly however the level of activity was modest, and a relative increase in affinity for the 5HT$_{2A}$ receptor was observed consistent with the displacement of the mol-

ecule from that predicted for zolmitriptan and the concomitant loss of occupancy of the selectivity volume. These compounds did however serve as good leads on which to base a potency and selectivity optimization program. Previous work in our laboratories suggested that the bulk of the 2-substituent resulted in displacement of the molecule from its preferred mode of binding within the receptor. Early modifications to take advantage of this displacement and maintain affinity involved the inclusion of a 5-ethylene linker between the 5-heterocycle and the indole ring allowing an increase in the degrees of freedom of the 5-side chain and allowing the molecule to more easily adopt a favorable conformation. From these preliminary results it was also apparent that the nitrile was poorly tolerated and that the ester group afforded significantly higher affinity. A large range of 2,5-substituted tryptamine derivatives incorporating a variety of heterocyclic ring systems connected to the 5-position of the indole group by an ethylene linker chain were investigated.

Table 2 shows biological results for this series of compounds. This series of 5-ethylene-linked tryptamine derivatives was a considerable improvement over the methylene-linked oxazolidinone derivatives of Table 1 with up to 40-fold increase in affinity at the 5HT$_{1B}$-like receptor in some cases. All the compounds were silent, competitive antagonists with the ethyl ester substituent at the 2-position affording more potent analogues than the methyl ester group. The best compounds with both good affinity at the 5HT$_{1B}$-like receptor and selectivity over 5HT$_{2A}$ are the hydantoin derivatives **40** and **44**, the phthalimide derivatives **55** and **56**, and the thiazolidinedione **57**. **40** was comprehensively investigated and found to be a silent, competitive antagonist at the 5HT$_{1B}$-like receptor. The compound was also found to have good selectivity over other monoamine receptor subtypes, Table 3.
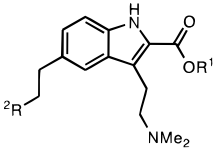
The affinity for **40** for amine-binding sites in the brain has also been examined, and the results are shown in Table 4. **40** has little affinity for any well-recognized brain receptor including other 5HT receptors. Thus **40** appears to be unique in its ability to discriminate between vascular 5HT receptors and central 5HT receptors. This has not been reported before and clearly calls into question the use of the appellant 1D for the 5HT receptor on the saphenous vein. This is not a species differentiation as has been demonstrated. **40** has been shown to antagonize the constrictor effects of 5HT in the human saphenous vein (pK_B = 7.4), in the dog saphenous vein (pK_B = 6.96), and in the rabbit femoral artery (pK_B = 7.24). The differences in affinity are ascribed to species differentiation and not different receptors. The lack of significant interaction with any of the recognized central binding sites suggests that there may not be a requirement to minimize the central penetration of these antagonists.

Preliminary studies in conscious beagle dogs showed that **40** is well absorbed after oral dosing (10 mg/kg, po) with oral bioavailability of at least 40%. Pharmacokinetic studies revealed **40** to undergo rapid metabolism in plasma exhibiting a half-life of $t_{1/2}$ =15 min in rat plasma and $t_{1/2}$ = 12 min in mouse plasma. However **40** was shown to survive longer in both human and dog plasma ($t_{1/2}$ = ~2 h in both human and dog). The short plasma half-life of **40** precluded further development of the compound.

The proposed mode of binding of **40** is shown in Figure 5. Following displacement of the molecule in order to accommodate the bulky 2-ethyl ester group, **40** is still able to access the amine-binding site, the aromatic binding site, and the hydrogen-bonding site, while the methylene protons of the 5-ethylene-linking chain can insert into the "selectivity site".

The biological results for the lower homologues of the hydantoin series shown in Table 5 were less encouraging with all compounds investigated failing to reach our desired pK_B level of 7.0. Evidence from earlier work in our laboratories had suggested that conformational restriction of the 3-substituent aided the ability of these molecules to take up an antagonist binding mode. Indeed that was one reason for siting the electron-withdrawing group on the 2-position of the indole. This conformational restriction can be enhanced by preparing a series of 3-piperidine and 3-tetrahydropyridine derivatives. Previous work in our department in a research

Table 2

compd no.	R^1	R^2	pK$_B$[a] 5HT$_{1B}$-like, RbSV	pK$_B$[a] 5HT$_{2A}$, RbA
37	H		6.17	<5.0
39	CH$_3$		6.97	<5.0
40	CH$_2$CH$_3$		7.42	5.8
41	CH(CH$_3$)$_2$		6.85	6.57
42	CH$_2$C$_6$H$_5$		7.91	7.30
43	CH$_3$		6.88	5.02
44	CH$_2$CH$_3$		7.34	5.23
45	CH(CH$_3$)$_2$		6.82	5.80
46	C$_6$H$_{11}$		5.95	4.77
47	CH$_2$CH$_3$		7.3	6.2
48	CH$_3$		6.61	5.88
49	CH$_2$CH$_3$		7.21	6.76
51	CH$_3$		6.0	<5.0
52	CH$_2$CH$_3$		6.78	6.30
53	CH$_2$CH$_3$		6.10	5.50
55	CH$_3$		7.39	5.66
56	CH$_2$CH$_3$		7.54	6.26
57	CH$_2$CH$_3$		7.72	7.56

[a] Affinity (pK_B = −log$_{10}$ K_B, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5HT$_{1B}$-like and 5HT$_{2A}$ receptors in the rabbit saphenous vein (RbSV) and aorta (RbA), respectively. 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.

Table 3

	5HT$_{1B}$-like	5HT$_{2B}$	5HT$_7$	5HT$_{2A}$	α_1	α_2	H$_1$	M$_3$
				receptor type[a]				
40	7.42	<5.0	5.50	5.80	5.43	<5.0	<5.0	<5.0

[a] Affinity (pK_B = −log$_{10}$ K_B, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5HT$_{1B}$-like receptor in rabbit saphenous vein (RbSV). Affinity at the 5HT$_{2A}$ receptors was measured in the rabbit aorta (RbA), at the 5HT$_{2B}$ receptors in the endothelium intact rabbit jugular vein, and at the 5HT$_7$ receptor in the endothelium denuded rabbit jugular vein. Affinity for both α_1 and H$_1$ was measured in the rabbit thoracic aorta and M$_3$ in the guinea pig trachea. 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.

Table 4

	5HT$_{1A}$	5HT$_{1D}$	5HT$_{2A}$	5HT$_{2C}$	D$_1$	D$_2$	α_1	α_2	β
				receptor type[a]					
40	5.03	5.0	5.1	5.26	4.49	4.97	4.95	5.25	4.34

[a] Affinity (pK_i) for 5HT$_{1A}$, 5HT$_{2A}$, 5HT$_{2C}$, D$_1$, D$_2$, α_1, α_2, and β was measured in rat cortex homogenates. 5HT$_{1D}$ is obtained from a calf caudate homogenate. 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.
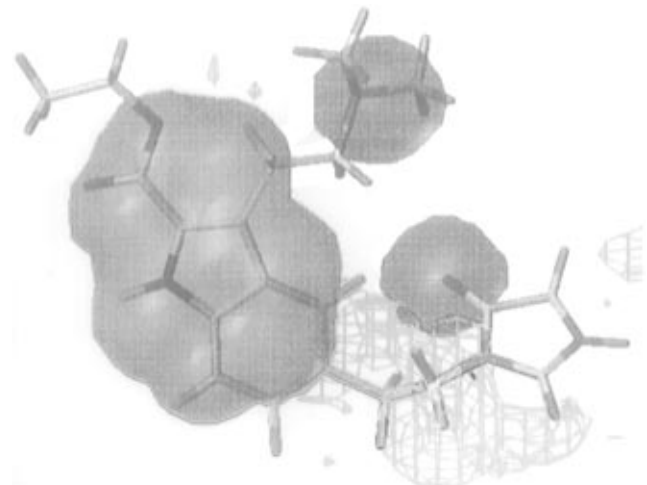

Figure 5. Proposed mode of binding of **40**. The amine-binding site is represented by the blue sphere, the aromatic binding site by the green sphere, the hydrogen-bonding site by the red sphere, and the selectivity volume in yellow.

program directed toward the discovery of compounds for the treatment of migraine had shown that replacement of the 3-ethylamine side chain with a cyclic structure produced compounds with slightly higher potency for the 5HT$_{1B}$-like receptor and with a longer half-life as the cyclic structures were less liable to oxidation by monoamine oxidases. The biological results for the compounds investigated shown in Table 6 clearly indicate that in the case of 2-substituted indole compounds, the bulky cyclic 3-substituents were not well tolerated, the best compound being **82** (pK_B = 6.42).

Steric restrictions clearly appear to further constrict the 2-substituent possibly in an unfavorable conformation for binding (out of the plane of the indole) and appeared to result in a loss of affinity. Thus from the variegated series of 2-ester-5-substituted tryptamine derivatives investigated as 5HT$_{1B}$-like antagonists, the more potent and selective compounds were those from the 3-ethylamine group. In particular **40** and its related dimethylhydantoin analogue **44** showed excellent po-

Table 5

compd no.	R^1	R^2	pK$_B$[a] 5HT$_{1B}$-like RbSV	5HT$_{2A}$ RbA
64	CH$_3$		5.41	5.15
65	CH$_2$CH$_3$		5.32	5.86
66	CH$_3$		6.45	5.03
67	CH$_2$CH$_3$		6.54	5.52
68	CH(CH$_3$)$_2$		5.62	5.62

[a] Affinity (pK_B = −log$_{10}$ K_B, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5HT$_{1B}$-like and 5HT$_{2A}$ receptors in the rabbit saphenous vein (RbSV) and aorta (RbA), respectively. 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$_{10}$ units.

tency and the desired selectivity over 5HT$_{2A}$ and other receptor types.
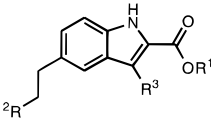
Conclusions

A series of novel, highly potent and selective vascular 5HT$_{1B}$-like receptor antagonists have been developed which are orally bioavailable. The compounds are in general tryptamine based with methyl or ethyl ester substituents at the 2-position and 5-methylene- and 5-ethylene-linked heterocyclic ring systems. In particular several compounds including **40** and the dimethyl-hydantoin analogue **44** were identified which differentiated between the central 5HT$_{1B}$-like receptors and the vascular 5HT$_{1B}$-like receptors. The less than desirable pharmacokinetics of the 2-ester tryptamine series precluded further development of compounds from this group, and future work which will be reported at a later date will be directed toward stable isosteres of the ester group.

Experimental Section

Biological Methods: 1. Rabbit Saphenous Vein (RbSV) Preparation. The vascular 5HT$_{1B}$-like receptor affinities of compounds were assessed using ring preparations of rabbit saphenous vein.[30] Vessels were removed from male New Zealand white rabbits killed by injecting pentobarbitone (80 mg/kg, iv) followed by exsanguination. After removing adhering connective tissue, ring segments (4−5 mm) were prepared and mounted between parallel tungsten wires. Tissues were suspended in 20 mL organ baths containing Krebs-Henseleit buffer at 37 °C, pH 7.4, and constantly gassed with 95% O$_2$: 5% CO$_2$. The Kreb-Henseleit solution used had the following composition (mM): NaCl 118.41, NaHCO$_3$ 25.00, KCl 4.75, KH$_2$PO$_4$ 1.19, MgSO$_4$ 1.19, glucose 11.10, and CaCl$_2$ 2.50. After application of a passive force (2 g), tissues were exposed to pargyline (500 μM) to inactivate monoamine oxidase. In order to prevent the direct or indirect activation of α-adrenorecep-

Table 6

compd no.	R^1	R^2	R^3	pK$_B$[a] 5HT$_{1B}$-like	pK$_B$[a] 5HT$_{2A}$
75	CH$_3$			non-surmountable	<5.0
76	CH$_2$CH$_3$			5.29	<5.0
79	CH$_2$CH$_3$		N-CH$_3$	<5.0	<5.0
78	CH$_2$CH$_3$		N-CH$_3$	5.88	<5.0
80	CH(CH$_3$)$_2$			5.25	<5.0
81	CH(CH$_3$)$_2$		N-CH$_3$	6.34	<5.0
82	CH$_2$CH$_3$		N-CH$_3$	6.42	5.02

[a] Affinity (pK$_B$ = $-$log$_{10}$ K$_B$, the dissociation equilibrium constant) estimates for novel compounds at the vascular 5HT$_{1B}$-like and 5HT$_{2A}$ receptors in the rabbit saphenous vein (RbSV) and aorta (RbA), respectively. 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.

tors, 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 5HT (1 μM) to determine viability. In the saphenous vein a cumulative concentration–effect (E/[A]) curve to 5HT 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 5HT 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/5HT maximum.

2. Rabbit Femoral Artery (RbFA) Preparation. 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 5HT as a reference) was constructed to determine vascular 5HT$_{1B}$-like agonist activity. Krebs solution containing prazosin, mepyramine, and spiperone (0.3 μM each) was used throughout to block possible effects mediated by α_1 adrenergic, H$_1$ histaminergic, and 5HT$_{2A}$ serotonergic receptor activation, respectively.

3. Rabbit Aorta (RbA) Preparation. Rings (3 mm) of rabbit thoracic aorta were exposed to pargyline (500 μM) for 30 min during which they were tensioned twice to 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 novels (30 μM) for 60 min prior to a cumulative E/[A] curve to L-Phe being constructed.

Receptor Binding Assays. Competition binding assays were performed to determine drug affinity (pK$_i$ or pIC$_{50}$) at the various receptors described. Briefly the appropriate radioligand ($\sim$K$_D$) and a wide range of test drug concentrations (in duplicate) were incubated with the relevant receptor preparation (brain homogenate or cell membranes) for 30 min at 27 °C—conditions determined previously to satisfy mass-action conditions. The assay buffer comprised 50 mM TRIS-HCl, 5 mM CaCl$_2$, 0.1% (w/v) ascorbate, and 10 mM pargyline. Nonspecific binding was defined using an excess of cold 5HT. Incubations were terminated by rapid filtration and washing with ice-cold buffer. Specifically bound radiolabel was measured by liquid scintillation spectroscopy.

Chemical Methods: General Directions. Computational chemistry was performed on a Silicon Graphics Iris Indigo II workstation using the Sybyl[31] 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 and pyridine were stored over sodium hydroxide. All solutions were dried over MgSO$_4$ or Na$_2$SO$_4$ 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, a 600 controller, and a series 600 pump with a 717 Plus autosampler. A Zorbax 4.6 mm × 250 mm, 5 μm column was used for analytical work, while a 22.4 mm × 250 mm, 7 μm C18 column was used for preparative work. A 10% H$_2$O/AcCN (10−90% gradient elution) (A)/0.1 M NH$_4$OAc (pH 4) (90−10%) (B) solvent system was used.

4-Nitrophenylalanine (6).[21] To a stirring mixture of phenylalanine (20.0 g, 0.095 mol) in concentrated sulfuric acid (27.8 mL, 0.28 mol) at 0 °C was gradually added concentrated nitric acid (5.55 mL, 0.095 mol) over 45 min. The reaction mixture was then stirred for a further 30 min at room temperature and poured onto ice/water (1.0 L), and stirring continued for a further 30 min. The yellow emulsion was extracted with ethyl acetate; the combined extracts were dried, filtered, and concentrated under vacuum. The solid was recrystallized from ethanol to give 9.8 g (53%) of **6** as yellow crystals (mp dec > 230 °C). Anal. (C$_9$H$_{10}$N$_2$O$_4$·1.0H$_2$O) C, H, N.

(S)-Methyl 4-Nitrophenylalanate Hydrochloride (7).[21] To a stirring solution of anhydrous methanol (50 mL) at −10 °C was added thionyl chloride (7.25 mL, 0.1 mol). The amino acid 6 (9.8 g, 0.05 mol) was added as a solid, and the reaction mixture was allowed to stir up to room temperature over 3 h. The mixture was warmed to 40 °C for 1 h and then cooled and the solvent removed under reduced pressure. The residue was taken up in water and extracted with ethyl acetate (3 × 50 mL). The extract was dried, and the filtrate was concentrated under vacuum to give 9.96 g (76%) of **7** as a white solid. Recrystallization of a small amount from ethanol afforded **7** as white needles (mp 227−228 °C): MS m/z (M$^+$) 224; ^{1}H NMR δ 3.3 (2H, m, CH$_2$), 3.7 (3H, s, OCH$_3$), 4.4 (1H, t, CH), 7.1 (2H, d, H3, H5, J = 7.2 Hz), 8.2 (2H, d, H2, H6, J = 7.2 Hz), 8.8 (3H, s, NH$_3$$^+$).

(S)-2-Amino-3-(4-nitrophenyl)propanol (8).[21] To a solution of sodium borohydride (4.93 g, 0.13 mol) in ethanol/water (1:1) (70 mL) was added dropwise a solution of the amino ester

7 (8.0 g, 0.031 mol) in ethanol/water (70 mL) at 0 °C. The mixture was refluxed for 4 h and then allowed to cool to room temperature. The solvent was decanted from the gray precipitate, and the ethanol was then removed under vacuum. The remaining water was extracted with ethyl acetate (3 × 50 mL) and the organic layer washed with brine and then water, dried, and concentrated. The yellow solid was recrystallized from ethanol to give 3.88 g (65%) of **8** as yellow crystals (mp 141−142 °C): ^{1}H NMR δ 2.52 (2H, m, CH$_2$O), 2.88 (2H, m, CH$_2$Ph), 3.22 (3H, m, CH, NH$_2$), 4.61 (1H, s, OH), 7.5 (2H, d, H3, H5, J = 7.3 Hz), 8.15 (2H, d, H2, H6, J = 7.3 Hz).

Method 1: General Procedure for Formation of the Oxazolidinone Ring of (*S*)-4-(4-Nitrobenzyl)-1,3-oxazolidin-2-one (9)[21] and Related Compound 17. The amino alcohol **8** (3.57 g, 0.018 mol) was suspended in toluene (55 mL) and cooled to 0 °C, and an aqueous potassium hydroxide solution (0.2 M, 41 mL) was added dropwise with stirring. To this solution was gradually added phosgene in toluene (1.25 M, 46 mL, 0.0576 mol) at 0 °C. The resulting solution was allowed to stir up to room temperature, and stirring continued for 2 h. A yellow solid was filtered off and dried over phosphorus pentoxide under vacuum. The compound was recrystallized from ethanol to give 2.97 g (75%) of **9** as yellow crystals: MS *m/z* 222 (M + 1)[+]; ^{1}H NMR δ 4.0 (2H, m, CH$_2$-Ph), 4.13 (1H, m, CH), 4.3 (2H, m, CH$_2$O), 7.55 (2H, d, H3, H5, J = 7.2 Hz), 7.74 (1H, s, NH), 8.16 (2H, d, H2, H6, J = 7.3 Hz). Anal. (C$_{10}$H$_{10}$N$_2$O$_4$) C, H, N.

Method 2: General Hydrogenation Procedure for the Preparation of the Aniline Derivative (*S*)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one (10) and Related Compounds 18, 20, 26−29, 35, 36, 62, and 63. A suspension of **9** (2.9 g, 13 mmol) in a mixture of ethanol (76 mL), water (60 mL), and 2 N HCl (12 mL) was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon (0.39 g) overnight. The catalyst was filtered through Celite and washed with ethanol (2 × 15 mL) and the solvent removed under vacuum. The remaining residue was azeotropically dried with absolute ethanol (50 mL) and further dried under vacuum to give 2.37 g (79%) of **10** as a white solid: MS *m/z* 193 (M + 1)[+]; ^{1}H NMR δ 4.0 (3H, m, CH$_2$Ph, CH), 4.28 (2H, m, CH$_2$O), 7.32 (4H, m, H2, H3, H5, H6), 7.8 (1H, s, NH), 10.3 (3H, br s, NH$_3$[+]).

Method 3: General Procedure for Formation of the β-Keto Ester Ethyl 2-Acetyl-5-(dimethylamino)pentanoate (11).[24] A sodium ethoxide solution was generated from absolute ethanol (175 mL) and sodium (9.2 g, 0.4 mol). To this stirring solution was added a solution of ethyl acetoacetate (26.0 g, 0.2 mol) and absolute ethanol (20 mL), and stirring continued for 1 h. A solution of (*N*,*N*-dimethylamino)propyl chloride hydrochloride (31.6 g, 0.2 mol) in absolute ethanol (50 mL) was gradually added and the resulting suspension refluxed for 18 h. The solution was cooled and the solvent removed under vacuum. Water (80 mL) was added and then extracted with ethyl acetate (3 × 100 mL). The organic extract was dried and concentrated to give a yellow oil. Purification was achieved by flash chromatography (CH$_2$Cl$_2$:EtOH:NH$_3$, 120:8:1) to give 10.8 g (25%) of **11** as a light yellow oil: MS *m/z* 215 (M[+]); ^{1}H NMR δ 1.17 (3H, t, CH$_3$, J = 7.1 Hz), 1.76 (2H, m, CH$_2$CH$_2$), 2.1 (6H, s, 2 × NCH$_3$), 2.19 (3H, s, CH$_3$CO), 2.26 (2H, t, CH$_2$C=, J = 6.5 Hz), 3.8 (2H, t, CH$_2$N, J = 6.4 Hz), 4.02 (2H, q, CH$_2$, J = 7.1 Hz), 5.01 (1H, s, OH).

2-Acetyl-5-(dimethylamino)pentamide (11′): method 3 (using ethyl acetoacetamide), 4.65 g (13%), bp 190 °C (2 mmHg); MS *m/z* 187 (M + 1)[+]; ^{1}H NMR δ (CDCl$_3$) 1.4−1.9 (4H, m, 2 × CH$_2$), 2.2 (9H, s, 2 × NCH$_3$, CH$_3$CO), 3.4 (2H, t, CH$_2$N, J = 6.1 Hz), 5.7 (1H, br s, NH), 6.5 (1H, br s, NH).

Method 4: General Method for the Formation of Ethyl 5-(Dimethylamino)-2-[[4-[(2-oxo-1,3-oxazolidin-4-yl)methyl]phenyl]hydrazin-2-ylidene]pentanoate (12) and Related Hydrazone Intermediates Required for the Synthesis of the Indole Derivatives 48 and 49. A stirring solution of **10** (0.97 g, 4.25 mmol) in concentrated hydrochloric acid (0.45 mL, 4.25 mmol) and ice (2.2 g) was cooled to −2 °C. A solution of sodium nitrite (0.29 g, 4.25 mmol) in ice water (0.5 mL) was added dropwise keeping the temperature below 0 °C, and the solution was stirred for 30 min. Meanwhile a

solution of potassium hydroxide (0.43 g, 7.6 mmol) in water (1.0 mL) was added to a solution of the diketone **11** (0.92 g, 4.25 mmol) in ice (3.88 g). This solution was stirred for 30 min and then added at once to the diazonium salt solution. The solution was left to stir for 30 min at 0−5 °C. Concentrated hydrochloric acid (0.33 mL) and ice (1.95 g) were then added, and the solution stirred at 10−15 °C overnight. The red suspension was basified with 2 N NaOH solution, extracted with CHCl$_3$, dried, and concentrated to give 0.9 g of a crude residue which was reacted on without further purification.

5-(Dimethylamino)-2-[[4-[(2-oxo-1,3-oxazolidin-4-yl)-methyl]phenyl]hydrazin-2-ylidene]pentanamide (12′). A stirring solution of **10** (1.0 g, 5.21 mmol) in concentrated hydrochloric acid (0.55 mL, 5.21 mmol) and ice (2.6 g) was cooled to −2 °C. A solution of sodium nitrite (0.36 g, 5.21 mmol) in ice water (0.5 mL) was added dropwise keeping the temperature below 0 °C, and the solution was stirred for 30 min. Meanwhile a solution of potassium hydroxide (0.52 g, 9.3 mmol) in water (1.4 mL) was added to a solution of the amide **11′** (0.97 g, 5.21 mmol) in ice (4.8 g). This solution was stirred for 30 min and then added at once to the hydrazine solution. The solution was left to stir for 30 min at 0−5 °C. Concentrated hydrochloric acid (0.4 mL) and ice (2.4 g) were then added, and the solution stirred up to room temperature for 2 h. The red suspension was then basified with 2 N NaOH, extracted with CHCl$_3$, dried, and concentrated to give a crude residue (0.86 g, 47%) which was reacted on without further purification.

(*S*)-2-[2-Cyano-5-[(2-oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indol-3-yl]dimethylethylamine (1). The crude hydrazone **12′** (0.4 g, 1.06 mmol) and polyphosphoric ester (5.7 g) in CHCl$_3$ (10 mL) were heated to reflux for 1 h. The reaction mixture was poured onto ice water, extracted with chloroform (3 × 300 mL), dried, and concentrated. The residue was purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH: NH$_3$ (240:8:1) to give 30 mg (8%) of **1** as an off-white powder. The solid was further purified by preparative HPLC to afford the acetate salt of **1** as a white lyophilate: t_R 13.1 min; IR CN stretch 2218; MS *m/z* 313 (M + 1)[+]; ^{1}H NMR δ 2.6 (6H, s, 2 × NCH$_3$), 2.72 (2H, m, CH$_2$NMe$_2$), 2.95 (2H, m, 5-CH$_2$), 3.12 (2H, m, 3-CH$_2$), 4.2 (3H, m, CH$_2$O, CH), 7.25 (1H, d, H6, J = 8.1 Hz), 7.32 (1H, d, H7, J = 8.2 Hz), 7.59 (1H, s, H4); found M[+] 312.3710, C$_{17}$H$_{20}$N$_4$O$_2$ requires M[+] 312.3714. Anal. Calcd (C$_{17}$H$_{20}$N$_4$O$_2$·2.0CH$_3$CO$_2$H·3.0H$_2$O): C, 51.8; H, 7.0; N, 11.7. Found: C, 51.9; H, 6.3; N, 12.5.

Method 5: General Method for Indole Formation Using *p*-Toluenesulfonic Acid. (*S*)-2-[2-Amido-5-[(2-oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indol-3-yl]dimethylethylamine (2). Hydrated *p*-toluenesulfonic acid monohydrate (0.6 g, 3.15 mmol) was dried by refluxing in toluene (20 mL) and then distilling off the toluene. A solution of dry *p*-toluenesulfonic acid in dry toluene (20 mL) was then added to the crude hydrazone **12′** (0.43 g, 12.4 mmol) and refluxed for 6 h. The toluene was evaporated, and the black residue was partially purified by flash chromatography eluting with CH$_2$-Cl$_2$:EtOH:NH$_3$ (90:8:1). Further purification was achieved with preparative HPLC to give 25 mg (6%) of the acetate salt of **2** as a white lyophylate: MS *m/z* 331 (M + 1[+]); found M[+] 330.3872, C$_{17}$H$_{22}$N$_4$O$_3$ requires M[+] 330.3867; ^{1}H NMR (CH$_3$-OH-d_4) δ 2.7 (6H, s, 2 × NCH$_3$), 2.96 (2H, m, CH$_2$NMe$_2$), 3.16 (2H, m, 5-CH$_2$), 3.4 (2H, m, 3-CH$_2$), 4.21 (2H, m, CH$_2$O), 4.38 (1H, m, CH), 7.19 (1H, d, H6, J = 8.4 Hz), 7.39 (1H, d, H7, J = 8.3 Hz), 7.52 (1H, s, H4). Anal. (C$_{17}$H$_{22}$N$_4$O$_3$·1.0CH$_3$-CO$_2$H·0.9H$_2$O) C, H, N.

(*S*)-Ethyl 3-[2-(Dimethylamino)ethyl]-5-[(2-oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indole-2-carboxylate (3). The crude hydrazone **12** (0.14 g, 0.4 mmol) and polyphosphoric ester (2.5 g) in CHCl$_3$ (8 mL) was heated to reflux for 8 h. The reaction mixture was cooled, poured onto ice water, basified to pH 8 with sodium hydrogen carbonate, and extracted with ethyl acetate. The organic layer was dried and concentrated to give a crude gum which was partially purified using flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (60:8:1). Further purification by preparative HPLC afforded 25 mg (20%) of the acetate salt of **3** as a white lyophylate: MS *m/z* 360 (M + 1)[+]; found M[+] 359.4249, C$_{19}$H$_{25}$N$_3$O$_4$ requires M[+] 359.4252;

^{1}H NMR δ 1.49 (3H, t, CH$_2$C*H$_3$*, $J = 7.0$ Hz), 2.48 (6H, s, 2 × NCH$_3$), 2.7 (2H, m, CH$_2$NMe$_2$), 3.0 (2H, m, 5-CH$_2$) 3.38 (2H, m, 3-CH$_2$), 4.25 (2H, q, C*H$_2$*CH$_3$, $J = 7.0$ Hz), 4.44 (3H, m, CH$_2$O, CH), 7.22 (1H, m, H6), 7.45 (1H, d, H7, $J = 8.0$ Hz), 7.61 (1H, d, H4, $J = 8.0$ Hz). Anal. Calcd (C$_{19}$H$_{25}$N$_3$O$_4$·1.3H$_2$O): C, 59.6; H, 7.2; N, 11.0. Found: C, 59.5; H, 6.4; N, 11.4.

(*S*)-2-[2-Bromo-5-[(2-oxo-1,3-oxazolidin-4-yl)methyl]-1*H*-indol-3-yl]dimethylethylamine (4). Trimethylsilyl bromide (0.4 mL, 3.1 mmol) was added to dimethyl sulfoxide (5.0 mL) and stirred for 15 min under nitrogen. A solution of the zolmitriptan^{9,21} (147 mg, 0.5 mmol) in dimethyl sulfoxide (2.0 mL) was added, and the resulting solution was stirred for 50 min at room temperature. The reaction mixture was poured onto ice water, adjusted to pH 9 with aqueous ammonium hydroxide, and then extracted with dichloromethane (4 × 20 mL), and the combined organic phases were washed with brine (3 × 10 mL). After drying, concentration gave a gummy solid which was dissolved in dichloromethane and filtered. Concentration in vacuo gave 65 mg (35%) of a pale gum. Further purification was achieved by preparative HPLC to afford 28 mg (13%) of the acetate salt of **4** as a beige lyophylate: t_R 9.25 min; MS *m/z* 366 (M + 1)$^+$; ^{1}H NMR δ 2.2 (6H, s, 2 × NCH$_3$), 2.42 (2H, m, CH$_2$NMe$_2$), 2.74 (2H, m, 5-CH$_2$), 2.8 (2H, m, 3-CH$_2$), 4.0 (3H, m, CH$_2$O, CH), 6.95 (1H, d, H6, $J = 7.9$ Hz), 7.18 (1H, d, H7, $J = 7.8$ Hz), 7.34 (1H, s, H4), 7.7 (1H, s, NHCO), 11.5 (1H, s, NH).

Ethyl 2-(*N*-Acetamido)-2-(carboxyethyl)-4-(4-nitrophenyl)butanoate (13). To a stirring solution of sodium (5.0 g, 0.22 mol) dissolved in dry ethanol (600 mL) was added diethyl acetamidomalonate (47.2 g, 0.22 mol). The resulting solution was stirred for 5 min and then heated to reflux. To this solution was added dropwise 4-nitrophenethyl bromide (50.0 g, 0.22 mol) in dry ethanol (225 mL). The resulting solution was refluxed overnight and then allowed to cool. The solution was concentrated under vacuum to a smaller volume and the resultant precipitate filtered and dried to afford 54.9 g (55%) of **13** as white crystals: MS *m/z* 366 (M$^+$); ^{1}H NMR δ 1.16 (6H, t, 2 × CH$_2$C*H$_3$*, $J = 7.1$ Hz), 1.92 (3H, s, COCH$_3$), 2.5 (4H, m, CH$_2$CH$_2$), 4.12 (4H, q, 2 × CH$_2$, $J = 7.1$ Hz), 7.41 (2H, d, H3, H5, $J = 8.9$ Hz), 8.14 (2H, d, H2, H6, $J = 8.8$ Hz), 8.32 (1H, s, NH). Anal. (C$_{17}$H$_{22}$N$_2$O$_7$·0.23H$_2$O) C, H, N.

2-Amino-4-(4-nitrophenyl)butyric Acid (14). A solution of the diester **13** (17.0 g, 46.5 mM) in 60% hydrobromic acid (150 mL) was gently refluxed for 3 h. The solution was cooled and concentrated under vacuum, the residue dissolved in water (150 mL), and the solution adjusted to pH 7 with 5 N NaOH. The precipitate was filtered, washed with water, and dried under vacuum over phosphorus pentoxide to give 9.8 g (94%) of **14**: MS *m/z* 224 (M$^+$); ^{1}H NMR δ 2.81 (2H, m, CH$_2$Ph), 3.16 (2H, m, CH$_2$), 3.3 (1H, m, CH, blanketed by HDO peak), 7.5 (2H, d, H3, H5, $J = 8.3$ Hz), 8.18 (2H, d, H2, H6, $J = 8.5$ Hz).

Methyl 2-Amino-4-(4-nitrophenyl)butyrate (15). Thionyl chloride (10.4 g, 87.5 mmol) was added dropwise to a stirring solution of methanol (50 mL) at −10 °C under nitrogen. The amino acid **14** (9.8 g, 43.8 mmol) was gradually added and the reaction mixture allowed to stir up to room temperature overnight. The methanol was removed under vacuum; the solid was washed with diethyl ether, filtered, and dried to give 6.98 g (58%) of the hydrochloride salt of **15** as a white solid: MS *m/z* 239 (M + 1)$^+$; ^{1}H NMR δ 2.2 (2H, m, CH$_2$-Ph), 2.9 (2H, m, CH$_2$), 3.75 (3H, s, OCH$_3$), 4.02 (1H, m, CH), 7.55 (2H, d, H3, H5, $J = 9.0$ Hz), 8.2 (2H, d, H2, H6, $J = 9.2$ Hz), 8.88 (3H, s, NH$_3$$^+$).

2-Amino-4-(4-nitrophenyl)butanol (16). A solution of **15** (6.98 g, 25.4 mmol) in ethanol/water (1:1) (75 mL) was added dropwise to a stirring solution of sodium borohydride (3.95 g, 0.1 mol) in ethanol/water (1:1) (75 mL) at room temperature. The reaction mixture was refluxed for 4 h and then allowed to cool. The ethanol was removed under vacuum, and the remaining aqueous layer was extracted with ethyl acetate, washed with brine, dried, and filtered and the solvent removed to give 3.4 g (64%) of **16** as a yellow powder: MS *m/z* 211 (M + 1)$^+$; ^{1}H NMR δ 1.56 (2H, m, CH$_2$Ph), 2.7 (4H, m, C*H$_2$*CH, CH$_2$O), 3.2 (1H, m, CH), 7.48 (2H, d, H3, H5, $J = 8.2$ Hz), 8.13 (2H, d, H2, H6, $J = 8.3$ Hz).

4-(4-Nitrophenethyl)-1,3-oxazolidin-2-one (17): method 1, pale yellow crystals (53%); MS *m/z* 236 (M$^+$); ^{1}H NMR (CDCl$_3$) δ 1.9 (2H, m, CH$_2$Ph), 2.8 (2H, m, C*H$_2$*CH), 3.9 (1H, m, CH), 4.1 (1H, m, CH$_A$O), 4.52 (1H, m, CH$_B$O), 7.0 (1H, s, NH), 7.38 (2H, d, H3, H5, $J = 8.5$ Hz), 8.18 (2H, d, H2, H6, $J = 8.5$ Hz).

4-(4-Aminophenethyl)-1,3-oxazolidin-2-one hydrochloride (18): method 2, (85%); MS *m/z* 206 (M$^+$); ^{1}H NMR δ 1.75 (2H, m, CH$_2$Ph), 2.53 (2H, m, C*H$_2$*CH), 3.75 (1H, m, CH), 3.95 (1H, m, CH$_A$O), 4.4 (1H, m, CH$_B$O), 7.3 (4H, m, H2, H3, H5, H6), 7.86 (1H, s, NH), 10.3 (3H, br s, NH$_3$$^+$).

1-Methyl-4-[(4-nitrophenyl)ethyl]imidazolidine-2,5-dione (19). The amino acid **14** (2.8 g, 12.5 mmol) was added to a solution of potassium hydroxide (0.84 g, 15 mmol) in water (25 mL). The solution was cooled to 0 °C, and methyl isocyanate (0.86 g, 0.89 mL, 15 mmol) was added over 15 min at 0 °C. The solution was stirred at 60−70 °C for 2 h after which the urea was filtered off. The filtrate was acidified with concentrated hydrochloric acid and then filtered. The uncyclized hydantoic acid was collected and washed with water. The solid was suspended in concentrated HCl/water (1:1) (15 mL) and refluxed for 2 h. The solution was then cooled, diluted with water, filtered, washed with water, and dried in vacuo to give 2.63 g (80%) of **19** as a white powder: MS *m/z* 264 (M + 1)$^+$.

1-Methyl-4-[(4-anilino)ethyl]imidazolidine-2,5-dione (20):^{21} method 2, 2.38 g (92%); MS *m/z* 234 (M + 1)$^+$.

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-methyl-4-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (47).^{21} The previously prepared hydrazone was used crude. Water was azeotroped off by distillation of TsOH·H$_2$O in toluene. The TsOH/toluene solution was added to the crude hydrazone and refluxed for 2 h. The solution was cooled and the toluene evaporated under reduced pressure. The residue was dried and then purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (100:8:1) to give an orange solid. Further purification with preparative HPLC gave 30 mg (4%) of the acetate salt **47** as a white lyophylate: MS *m/z* 401 (M + 1)$^+$; ^{1}H NMR (CH$_3$OH-*d$_4$*) δ 1.42 (3H, t, CH$_2$C*H$_3$*, $J = 7.2$ Hz), 1.91 (3H, s, CH$_3$CO$_2$H), 2.15 (2H, m, C*H$_2$*CH), 2.69 (6H, s, 2 × NCH$_3$), 2.8 (5H, m, CH$_2$NMe$_2$, NCH$_3$), 3.1 (2H, m, 5-CH$_2$), 3.45 (2H, m, 3-CH$_2$), 4.1 (1H, m, CH), 4.45 (2H, q, C*H$_2$*-CH$_3$, $J = 7.1$ Hz), 7.2 (1H, d, H6, $J = 8.0$ Hz), 7.38 (1H, d, H7, $J = 8.2$ Hz), 7.53 (1H, s, H4). Anal. (C$_{21}$H$_{28}$N$_4$O$_4$·1.0CH$_3$-CO$_2$H·0.4H$_2$O) C, H, N.

Method 6: General Method for Indole Formation To Afford Methyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2-oxo-1,3-oxazilidin-4-yl)ethyl]-1*H*-indole-2-carboxylate (48). To a solution of the crude ethyl ester hydrazone (0.45 g, 1.15 mmol) prepared by method 4 in methanol (45 mL) was added dropwise concentrated hydrochloric acid (0.9 mL). The reaction mixture was stirred at 80 °C under nitrogen for 24 h. The solution was cooled, the solvent evaporated, water added (40 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 an orange solid which was purified by column chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (80:8:1) to give the product as a yellow solid. Further purification with preparative HPLC afforded 30 mg (8%) of **48** as the acetate salt: MS *m/z* 360 (M + 1)$^+$; ^{1}H NMR δ 1.74−1.9 (4H, m, C*H$_2$*-CH, CH$_2$NMe$_2$), 2.25 (6H, s, 2 × NCH$_3$), 2.44 (2H, m, 5-CH$_2$), 2.68 (2H, m, 3-CH$_2$), 3.75 (1H, m, CH), 3.88 (3H, s, OCH$_3$), 3.95 (1H, m, CH$_A$O), 4.31 (1H, m, CH$_B$O), 7.12 (1H, d, H6, $J = 7.9$ Hz), 7.21 (1H, d, H7, 8.0 Hz), 7.44 (1H, s, H4), 7.8 (1H, s, NHCO), 11.43 (1H, s, NH); found M$^+$ 359.1811, C$_{19}$H$_{25}$N$_3$O$_4$ requires M$^+$ 359.4252.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2-oxo-1,3-oxazilidin-4-yl)ethyl]-1*H*-indole-2-carboxylate (49): method 6 (using ethanol as solvent), white powder (free base) (17%) (mp 190−192 °C); MS *m/z* 373 (M$^+$); ^{1}H NMR δ 1.36 (3H, t, CH$_2$C*H$_3$*, $J = 7.4$ Hz), 1.78 (2H, m, C*H$_2$*CH), 2.21 (6H, s, 2 × NCH$_3$), 2.42 (2H, m, CH$_2$NMe$_2$), 2.69 (2H, m, 5-CH$_2$), 3.18 (2H, m, 3-CH$_2$), 3.75 (1H, m, CH), 3.94 (1H, m, CH$_A$O), 4.30 (1H, m, CH$_B$O), 4.31 (2H, q, C*H$_2$*CH$_3$, $J = 7.3$ Hz), 7.1 (1H, dd, H6,

J = 8.3 Hz), 7.3 (1H, d, H7, J = 8.2 Hz), 7.42 (1H, s, H4), 7.82 (1H, s, NH), 11.36 (1H, s, NH). Anal. ($C_{20}H_{27}N_3O_4\cdot0.25H_2O$) C, H, N.

Method 7: General Procedure for the Preparation of N-Linked Imidazolidine-2,5-diones. 5,5-Dimethyl-3-[2-(4-nitrophenyl)ethyl]imidazolidine-2,4-dione (22). To a solution of dry DMF (60 mL) were added 5,5-dimethylhydantoin (3.83 g, 0.029 mol), p-nitrophenethyl alcohol (5.0 g, 0.029 mol), and triphenylphosphine (7.84 g, 0.029 mol). The solution was stirred under nitrogen at 0 °C for 15 min; then diisopropyl azodicarboxylate (6.04 g, 6.2 mL, 0.029 mol) was added dropwise over 30 min with the temperature maintained at 0 °C. The solution was then allowed to warm up to room temperature overnight. The reaction mixture was poured onto ice water (250 mL) and stirred for 2 h. The white solid was filtered and recrystallized from ethanol to give 4.64 g (54%) of **22** as white needles (mp 159–160 °C): MS m/z 277 (M$^+$); ^{1}H NMR δ 1.16 (6H, s, 2 × CH$_3$), 2.9 (2H, m, CH$_2$N), 3.63 (2H, m, CH$_2$Ph), 7.43 (2H, d, H3, H5, J = 8.7 Hz), 8.13 (2H, d, H2, H6, J = 8.7 Hz), 8.2 (1H, s, NH); found M$^+$ 277.1058, $C_{13}H_{15}N_3O_4$ requires M$^+$ 277.2798. Anal. Calcd ($C_{13}H_{15}N_3O_4$): C, 56.3; H, 5.4; N, 15.1. Found: C, 56.9; H, 5.5; N, 14.3.

3-[2-(4-Nitrophenyl)ethyl]imidazolidine-2,4-dione (21): method 7, white crystals from ethanol (60%); MS m/z 250 (M$^+$); ^{1}H NMR δ 2.95 (2H, t, CH$_2$N, J = 7.1 Hz), 3.62 (2H, t, CH$_2$Ph, J = 7.1 Hz), 3.85 (2H, s, CH$_2$CO), 7.47 (2H, d, H3, H5, J = 8.4 Hz), 8.0 (1H, s, NH), 8.12 (2H, d, H2, H6, J = 8.3 Hz).

***N*-[2-(4-Nitrophenyl)ethyl]succinimide (23):** method 7, white crystals, 3.89 g (51%); MS m/z 249 (M + 1)$^+$; ^{1}H NMR δ 2.58 (4H, s, 2 × CH$_2$CO), 2.93 (2H, t, CH$_2$N, J = 7.26 Hz), 3.63 (2H, t, CH$_2$Ph, J = 7.2 Hz), 7.48 (2H, d, H3, H5, J = 8.67 Hz), 8.14 (2H, d, H2, H6, J = 8.7 Hz); found M$^+$ 248.2123, $C_{12}H_{12}N_2O_4$ requires 248.2383.

***N*-[2-(4-Nitrophenyl)ethyl]phthalimide (24):** method 7, white needles from ethanol, 5.64 g (64%) (mp 202–204 °C); MS m/z 297 (M + 1)$^+$; ^{1}H NMR δ 3.07 (2H, t, CH$_2$N, J = 6.9 Hz), 3.87 (2H, t, CH$_2$Ph, J = 7.0 Hz), 7.5 (2H, d, H3, H5, J = 8.5 Hz), 7.82 (4H, m, 4 × PhthAr), 8.1 (2H, d, H2, H6, J = 8.5 Hz). Anal. ($C_{16}H_{12}N_2O_4\cdot0.1H_2O$) C, H, N.

3-[2-(4-Nitrophenyl)ethyl]thiazolidine-2,4-dione (25): method 7, white crystals from ethanol, 0.5 g (75%); MS m/z 267 (M + 1)$^+$; ^{1}H NMR δ 3.0 (2H, t, CH$_2$N, J = 8.4 Hz), 3.8 (2H, t, CH$_2$Ph, J = 8.4 Hz), 4.2 (2H, s, CH$_2$S), 7.5 (2H, d, H3, H5, J = 8.0 Hz), 8.16 (2H, d, H2, H6, J = 8.0 Hz).

3-(4-Aminophenethyl)imidazolidine-2,4-dione (26): method 2, cream solid (94%) (mp 257–259 °C); MS m/z 219 (M$^+$); ^{1}H NMR δ 2.44 (2H, t, CH$_2$N, J = 6.9 Hz), 3.17 (2H, t, CH$_2$Ph, J = 7.0 Hz), 3.46 (2H, s, CH$_2$O), 6.84 (4H, m, H2, H3, H5, H6), 7.61 (1H, s, NH). Anal. ($C_{11}H_{13}N_3O_2\cdot0.2H_2O$) C, H, N.

3-(4-Aminophenethyl)-5,5-dimethylimidazolidine-2,4-dione (27): method 2, white needles, 2.05 g (45%) (mp 268–270 °C); MS m/z 247 (M$^+$); ^{1}H NMR δ 0.78 (6H, s, 2 × CH$_3$), 2.46 (2H, t, CH$_2$N, J = 7.0 Hz), 3.18 (2H, t, CH$_2$Ph, J = 6.9 Hz), 6.84 (4H, m, H2, H3, H5, H6), 7.74 (1H, s, NH). Anal. ($C_{17}H_{13}N_3O_2\cdot1.0HCl$) C, H, N.

***N*-(4-Aminophenethyl)succinimide (28):** method 2, hydrochloride salt as white needles from ethanol, 3.52 g (87%); MS m/z 219 (M + 1)$^+$; ^{1}H NMR δ 2.54 (4H, s, 2 × CH$_2$CO), 2.71 (2H, t, CH$_2$N, J = 7.7 Hz), 3.5 (2H, t, CH$_2$Ph, J = 7.8 Hz), 7.1 (2H, d, H2, H6, J = 8.3 Hz), 7.17 (2H, d, H3, H5, J = 8.3 Hz), 9.33 (3H, br s, NH$_3^+$). Anal. ($C_{12}H_{14}N_2O_2\cdot1.0HCl$) C, H, N.

***N*-(4-Aminophenethyl)phthalimide (29):** method 2, white needles of the hydrochloride salt from ethanol, 3.81 g (62%) (mp dec > 270 °C); MS m/z 266 (M$^+$); ^{1}H NMR δ 2.95 (2H, m, CH$_2$N), 3.75 (2H, m, CH$_2$Ph), 7.11 (4H, m, 4 × PhthAr), 7.7 (4H, s, H2, H3, H5, H6), 9.32 (3H, br s, NH$_3^+$). Anal. ($C_{16}H_{14}N_2O_2\cdot1.0HCl$) C, H, N.

3-(4-Aminophenethyl)thiazolidine-2,4-dione (30). The thiazolidinone **25** (5.0 g, 18.8 mmol) was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon (0.5 g) in acetic acid (100 mL) for 48 h. The catalyst was removed over Celite and the filtrate concentrated to a light brown powder which was triturated with ethyl acetate/diethyl ether (1:5) and isolated by filtration to give 3.73 g (67%) of

the amine salt as a white solid: MS m/z 237 (M + 1)$^+$; ^{1}H NMR δ 2.67 (2H, t, CH$_2$N, J = 8.9 Hz), 3.4 (3H, br s, NH$_3^+$), 3.66 (2H, t, CH$_2$Ph, J = 8.7 Hz), 4.18 (2H, s, CH$_2$S), 4.88 (1H, br s, NH), 6.5 (2H, d, H2, H6, J = 7.8 Hz), 6.82 (2H, d, H3, H5, J = 7.9 Hz). Anal. ($C_{11}H_{12}N_2O_2S\cdot0.27H_2O$) C, H, N.

***N*-[(2-Chloroethoxy)carbonyl]-2-(4-nitrophenyl)ethyl-amine (31).** To (4-nitrophenyl)ethylamine hydrochloride (2.5 g, 0.012 mol) in THF (200 mL) were added 2-chloroethyl chloroformate (1.78 g, 0.012 mol) and triethylamine (1.21 g, 0.012 mol), and the solution was stirred at room temperature for 48 h. The solution was evaporated under vacuum, the solid was taken up in ethyl acetate, and the salts were filtered off. The filtrate was evaporated under reduced pressure to give 1.87 g (61%) of **31** as yellow crystals: MS m/z 272 (M$^+$); ^{1}H NMR δ 2.54 (2H, swamped by DMSO peak, CH$_2$N), 2.85 (2H, m, CH$_2$Ph), 3.73 (2H, m, CH$_2$Cl), 4.2 (2H, m, CH$_2$O), 7.39 (1H, t, NH), 7.5 (2H, d, H3, H5, J = 8.7 Hz), 8.16 (2H, d, H2, H6, J = 8.7 Hz).

***N*-[2-(4-Nitrophenyl)ethyl]-1,3-oxazolidin-2-one (33).** To a stirring solution of **31** (2.0 g, 7.34 mmol) in THF (25 mL) was added 5 N NaOH (4.4 mL). The solution was refluxed overnight and cooled, the solvent evaporated, and the residue purified by flash chromatography eluting with chloroform/methanol (95:5). The resulting yellow solid was recrystallized from ethanol to give 1.3 g (75%) of yellow crystals (mp 128–130 °C): MS m/z 236 (M$^+$); ^{1}H NMR δ 2.95 (2H, t, CH$_2$N, J = 7.3 Hz), 3.47 (2H, t, CH$_2$Ph, J = 7.4 Hz), 3.55 (2H, dd, CH$_2$-CH$_2$O), 4.21 (2H, dd, CH$_2$O), 7.57 (2H, d, H3, H5, J = 8.6 Hz), 8.18 (2H, d, H2, H6, J = 8.6 Hz). Anal. ($C_{11}H_{12}N_2O_4$) C, H, N.

***N*-[2-(4-Aminophenyl)ethyl]-1,3-oxazolidin-2-one (35):** method 2, white foam, 1.03 g (97%); MS m/z 207 (M + 1)$^+$; ^{1}H NMR δ 2.8 (2H, t, CH$_2$N, J = 7.2 Hz), 3.4–3.55 (4H, m, CH$_2$N, CH$_2$Ph), 4.22 (2H, dd, CH$_2$O), 7.21 (2H, d, H2, H6, J = 8.4 Hz), 7.31 (2H, d, H3, H5, J = 8.4 Hz). Anal. ($C_{11}H_{14}N_2O_2\cdot1.0HCl\cdot1.5H_2O$) C, H, N.

***N*-[2-(4-Nitrophenyl)ethyl]-4-chlorobutylamide (32).** To a solution of (4-nitrophenyl)ethylamine hydrochloride (1.0 g, 4.93 mmol) in THF (100 mL) was added 4-chlorobutyryl chloride (0.696 g, 4.93 mmol) followed by triethylamine (0.8 g, 4.93 mmol). The solution was stirred at room temperature for 48 h and then evaporated under reduced pressure, water added, and the water layer extracted with ethyl acetate. The organic layer was dried, filtered, and evaporated under reduced pressure to give a yellow solid which was purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (150:8:1). The resulting yellow solid was recrystallized from ethanol to give 0.7 g (52%) of **32** as soft white crystals (mp 72–74 °C): MS m/z 271 (M + 1)$^+$; ^{1}H NMR δ 1.87 (2H, m, CH$_2$CH$_2$CH$_2$), 2.16 (2H, t, CH$_2$CO, J = 7.0 Hz), 2.84 (2H, t, CH$_2$N, J = 6.9 Hz), 3.34 (2H, m, CH$_2$Ph, blanketed by water peak), 3.54 (2H, t, CH$_2$Cl, J = 6.5 Hz), 7.48 (2H, d, H3, H5, J = 7.0 Hz), 7.97 (1H, t, NH), 8.14 (2H, d, H2, H6, J = 8.3 Hz). Anal. ($C_{12}H_{15}N_2O_3Cl\cdot0.5H_2O$) C, H, N.

***N*-[2-(4-Nitrophenyl)ethyl]-2-pyrrolidinone (34).** The alkyl halide **32** (1.79 g, 6.59 mmol) was added to a solution of 5 N NaOH (7.0 mL, 32.9 mmol) in THF (160 mL), and the resulting solution was refluxed for 24 h. The solution was cooled, concentrated, and diluted with water (50 mL). The aqueous layer was extracted with ethyl acetate, dried, and filtered and the solvent evaporated under reduced pressure to give an orange residue which was purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (300:8:1) to give 342 mg (22%) of the desired lactam as a white solid: MS m/z 235 (M + 1)$^+$; ^{1}H NMR δ 1.88 (2H, m, CH$_2$CH$_2$CH$_2$), 2.18 (2H, t, CH$_2$CO, J = 7.8 Hz), 2.93 (2H, t, CH$_2$N, J = 7.2 Hz), 3.34 (2H, m, CH$_2$Ph, blanketed by water peak), 3.5 (2H, t, CH$_2$O, J = 7.2 Hz), 7.54 (2H, d, H3, H5, J = 8.5 Hz), 8.19 (2H, d, H2, H6, J = 8.5 Hz). Anal. ($C_{12}H_{14}N_2O_3\cdot0.3H_2O$) C, H, N.

***N*-[2-(4-Aminophenyl)ethyl]-2-pyrrolidinone (36):** method 2, white solid, 294 mg (90%); MS m/z 205 (M + 1)$^+$; ^{1}H NMR δ 1.83 (2H, m, CH$_2$CH$_2$CH$_2$), 2.10 (2H, t, CH$_2$CO, J = 7.9 Hz), 2.71 (2H, t, CH$_2$N, J = 7.3 Hz), 3.23 (2H, t, CH$_2$Ph, J = 7.1 Hz), 3.5 (2H, m, CH$_2$NH, blanketed by water peak), 7.18 (2H, d, H2, H6, J = 8.5 Hz), 7.25 (2H, d, H3, H5, J = 8.5 Hz), 9.87 (3H, br s NH$_3^+$). Anal. ($C_{12}H_{16}N_2O\cdot1.25H_2O$) C, H, N.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (40): method 6 (using ethanol as solvent), cream solid (40%) (mp 210−211 °C); MS *m/z* 387 (M + 1)$^+$; ^{1}H NMR δ 1.35 (3H, t, CH$_3$CH$_2$, *J* = 7.6 Hz), 2.25 (6H, s, 2 × NCH$_3$), 2.49 (2H, m, CH$_2$NMe$_2$, under DMSO peak), 2.9 (2H, t, CH$_2$N, *J* = 6.9 Hz), 3.15 (3H, m, 5-CH$_2$), 3.6 (2H, t, 3-CH$_2$, *J* = 6.8 Hz), 3.85 (2H, s, CH$_2$NH), 4.4 (2H, q, CH$_2$CH$_3$, *J* = 7.4 Hz), 7.1 (1H, d, H6, *J* = 8.4 Hz), 7.35 (1H, d, H7, *J* = 8.5 Hz), 7.4 (1H, s, H4), 7.95 (1H, s, NHCO), 11.4 (1H, s, NH). Anal. (C$_{20}$H$_{26}$N$_4$O$_4$·0.25H$_2$O) C, H, N.

Benzyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (42). A mixture of **40** (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 in vacuo to give a brown gum which was purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (200:8:1) to give 1.1 g (98%) of **42** 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$_2$NMe$_2$), 2.92 (2H, m, CH$_2$N), 3.19 (2H, m, 5-CH$_2$), 3.62 (2H, m, 3-CH$_2$), 3.88 (2H, s, CH$_2$CO), 5.38 (2H, s, CH$_2$O), 7.11 (1H, d, H6, *J* = 8.0 Hz), 7.4 (7H, m, H7, H4, 5 × ArH), 7.95 (1H, s, NHCO), 11.4 (1H, s, NH). Anal. (C$_{25}$H$_{28}$N$_4$O$_4$·0.75H$_2$O) C, H, N.

3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylic Acid (37). A mixture of **42** (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, concentrated, and triturated with dichloromethane to give 86 mg (79%) of **37** as a white powder: MS *m/z* 359 (M + 1)$^+$; ^{1}H NMR δ 2.81 (6H, s, 2 × NCH$_3$), 2.95 (2H, m, CH$_2$NMe$_2$), 3.41 (4H, m, CH$_2$N, 5-CH$_2$), 3.75 (2H, m, 3-CH$_2$), 3.83 (2H, s, CH$_2$NH), 7.1 (1H, d, H6, *J* = 8.3 Hz), 7.3 (1H, d, H7, *J* = 8.1 Hz), 7.45 (1H, s, H4); *t*$_R$ 8.06 min.

Isopropyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (41): method 6 (using 2-propanol as solvent), white powder (40%) (mp 202−203 °C); MS *m/z* 401 (M + 1)$^+$; found M$^+$ 400.2145, C$_{21}$H$_{28}$N$_4$O$_4$ requires M$^+$ 401.4777; ^{1}H NMR δ 1.34 (6H, d, CH(CH$_3$)$_2$, *J* = 6.3 Hz), 2.25 (6H, s, 2 × NCH$_3$), 2.44 (2H, m, CH$_2$NMe$_2$), 2.9 (2H, m, CH$_2$N), 3.18 (2H, m, 5-CH$_2$), 3.59 (2H, m, 3-CH$_2$), 5.2 (1H, m, CH, *J* = 6.3 Hz), 7.1 (1H, d, H6, *J* = 8.1 Hz), 7.3 (1H, s, H4), 7.4 (1H, m, H6), 7.94 (1H, s, NHCO), 11.35 (1H, s, NH). Anal. (C$_{21}$H$_{32}$N$_4$O$_4$·0.3H$_2$O) C, H, N.

Method 8: General Procedure for the Formation of Methyl 5-(Dimethylamino)-2-[[4-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (38). To a stirring solution of **26** (1.0 g, 3.91 mmol) in ethanol (2.0 mL) and water (6.5 mL) 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 10 min; then the excess sodium nitrite was destroyed with urea (0.29 g, 4.8 mmol). Meanwhile the diketone **11** (0.79 g, 3.91 mmol) was stirred with sodium acetate trihydrate (2.77 g, 20 mmol) and ice (3.5 g). The diazonium salt was added quickly to the diketone solution, and the reaction mixture was stirred for 1.5 h up to room temperature. Concentrated HCl (100 μL) was added, and the solution stirred a further 20 min. The solution was adjusted to pH 9 with 10% NaOH and stirred for a further 10 min. The solution was extracted with ethyl acetate, dried, filtered, and evaporated to give an orange gum. Purification was achieved with flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (100:8:1). Recrystallization from ethanol afforded 0.77 g (51%) of **38** as orange needles (mp 158−160 °C): MS *m/z* 389 (M$^+$); ^{1}H NMR δ 1.75 (2H, m, CH$_2$), 2.12 (6H, s, 2 × NCH$_3$), 2.28 (2H, m, CH$_2$), 2.6 (2H, m, CH$_2$), 2.72 (2H, m, CH$_2$), 3.55 (2H, m, CH$_2$), 3.59 (3H, s, OCH$_3$), 3.85 (2H, s, CH$_2$NH), 7.12 (4H, m, H2, H3, H5, H6), 7.97 (1H, s, NH), 10.1 (1H, s, NH). Anal. (C$_{19}$H$_{27}$N$_5$O$_4$·0.65H$_2$O) C, H, N.

Methyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (39): method 6, purification by preparative HPLC gave 70 mg (8%) of

the acetate salt of **39** as a white lyophylate; MS *m/z* 373 (M + 1)$^+$; *t*$_R$ 9.51 min; ^{1}H NMR (CH$_3$OH-*d*$_4$) δ 1.9 (3H, s, CH$_3$CO$_2$H), 2.88 (6H, s, 2 × NCH$_3$), 3.08 (2H, m, CH$_2$NMe$_2$), 3.22 (2H, m, CH$_2$N), 3.53 (2H, m, 5-CH$_2$), 3.83 (2H, m, 3-CH$_2$), 4.0 (2H, s, CH$_2$NH), 7.22 (1H, d, H6, *J* = 8.0 Hz), 7.53 (1H, d, H7, *J* = 8.1 Hz), 7.62 (1H, s, H4). Anal. (C$_{19}$H$_{24}$N$_4$O$_4$·1.0CH$_3$CO$_2$H·2.0H$_2$O) C, H, N.

Methyl 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (43): method 6, 56 mg (22%); MS *m/z* 401 (M + 1)$^+$; found M$^+$ 400.21106, C$_{21}$H$_{28}$N$_4$O$_4$ requires M$^+$ 400.4777; ^{1}H NMR δ 1.15 (6H, s, 2 × CH$_3$), 2.21 (6H, s, 2 × NCH$_3$), 2.43 (2H, m, CH$_2$NMe$_2$), 2.91 (2H, m, CH$_2$N), 3.1 (2H, m, 5-CH$_2$), 3.57 (2H, m, 3-CH$_2$), 3.85 (3H, s, OCH$_3$), 7.06 (1H, d, H6, *J* = 7.6 Hz), 7.31 (2H, m, H7, H4), 8.11 (1H, s, NH), 11.45 (1H, s, NH).

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (44) (Method 6, using ethanol as solvent). To the required hydrazone intermediate (277 mg, 0.64 mmol) in ethanol (25 mL) was added concentrated H$_2$SO$_4$ (0.62 mL). The reaction mixture was gently refluxed at 90 °C overnight. The solution was cooled, the solvent evaporated, water added (40 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 an orange powder which was further purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (110:8:1). Recrystallization from ethanol gave 143 mg (54%) of **44** as a yellow powder (mp 142−144 °C): MS *m/z* 415 (M + 1)$^+$; found M$^+$ 414.2267, C$_{22}$H$_{30}$N$_4$O$_4$ requires M$^+$ 414.5046; ^{1}H NMR δ 1.09 (6H, s, 2 × CH$_3$), 1.3 (3H, t, CH$_2$CH$_3$, *J* = 7.5 Hz), 2.18 (6H, s, 2 × NCH$_3$), 2.38 (2H, m, CH$_2$NMe$_2$), 2.87 (2H, m, CH$_2$N), 3.06 (2H, m, 5-CH$_2$), 3.56 (2H, m, 3-CH$_2$), 4.31 (2H, q, CH$_2$CH$_3$, *J* = 7.5 Hz), 7.03 (1H, m, H6), 7.28 (2H, m, H7, H4), 8.11 (1H, s, NHCO), 11.4 (1H, s, NH).

Isopropyl 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (45): method 6 (using isopropyl alcohol as solvent), 25 mg (13%); MS *m/z* 429 (M + 1)$^+$; found M$^+$ 428.24236, C$_{23}$H$_{32}$N$_4$O$_4$ requires M$^+$ 428.5315; ^{1}H NMR δ 1.13 (6H, s, 2 × NCH$_3$), 1.36 (6H, d, CH(CH$_3$)$_2$, *J* = 6.2 Hz), 2.92 (2H, m, CH$_2$NMe$_2$), 3.18 (2H, m, CH$_2$N), 3.41 (2H, m, 5-CH$_2$), 3.62 (2H, m, 3-CH$_2$), 5.18 (1H, m, CH, *J* = 6.2 Hz), 7.1 (1H, m, H6), 7.35 (1H, d, H7, *J* = 8.4 Hz), 7.54 (1H, s, H4), 8.18 (1H, s, NH), 10.2 (1H, br s, NH$^+$CH$_3$), 11.61 (1H, s, NH). Anal. Calcd (C$_{23}$H$_{32}$N$_4$O$_4$·1.0HCl·3.0H$_2$O): C, 53.2; H, 7.5; N, 10.8. Found: C, 52.87; H, 6.81; N, 10.47.

Cyclohexyl 3-[2-(dimethylamino)ethyl]-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (46): method 6 (using cyclohexanol as solvent), light brown powder purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (250:8:1), 60 mg (27%); MS *m/z* 469 (M + 1)$^+$; found M$^+$ 468.2749, C$_{26}$H$_{36}$N$_4$O$_4$ requires M$^+$ 468.5962; ^{1}H NMR δ 1.13 (6H, s, 2 × CH$_3$), 1.2−1.9 (10H, m, cyclohexyl methylenes), 2.21 (6H, s, 2 × NCH$_3$), 2.4 (2H, m, CH$_2$NMe$_2$), 2.9 (2H, m, CH$_2$N), 3.2 (2H, m, 5-CH$_2$), 3.6 (2H, m, 3-CH$_2$), 4.9 (1H, m, CH), 7.06 (1H, d, H6, *J* = 8.3 Hz), 7.32 (2H, m, H7, H4), 8.12 (1H, s, NHCO), 11.36 (1H, s, NH). Anal. Calcd (C$_{26}$H$_{36}$N$_4$O$_4$·1.1H$_2$O): C, 63.96; H, 7.83; N, 11.4. Found: C, 63.95, H, 7.49; N, 11.4.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-1H-indole-2-carboxylate (52): method 6 (using ethanol as solvent), light brown powder (8%); MS *m/z* 386 (M + 1)$^+$; found M$^+$ 385.1974, C$_{21}$H$_{27}$N$_3$O$_4$ requires M$^+$ 385.4631; ^{1}H NMR δ 1.4 (3H, t, CH$_2$CH$_3$, *J* = 7.2 Hz), 2.59 (10H, br s, 2 × NCH$_3$, 2 × CH$_2$CO), 2.84−2.96 (4H, m, CH$_2$NMe$_2$, CH$_2$N), 3.4 (2H, m, 5-CH$_2$), 3.7 (2H, m, 3-CH$_2$), 4.36 (2H, q, CH$_2$CH$_3$, *J* = 7.2 Hz), 7.15 (2H, m, H6, H7), 7.62 (1H, s, H4), 8.63 (1H, s, NH).

Ethyl 5-(dimethylamino)-2-[[4-[2-(N-phthalimido)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (54): method 8, light brown powder purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (180:8:1), 220 mg (20%); MS *m/z* 451 (M + 1)$^+$; ^{1}H NMR δ 2.1 (3H, t, CH$_2$CH$_3$, *J* = 6.9 Hz), 2.49 (2H, m, CH$_2$CH$_2$CH$_2$), 2.9 (6H, s, 2 × NCH$_3$), 3.39 (2H, m, CH$_2$NMe$_2$), 3.71 (2H, m, CH$_2$C=), 4.29 (2H, m, CH$_2$N), 4.6 (2H, m,

CH$_2$Ph), 5.0 (2H, q, C*H*$_2$CH$_3$, J = 6.9 Hz), 7.9 (4H, m, H2, H3, H5, H6), 8.6 (4H, s, 4 × PhthArH), 11.4 (1H, s, NH).

Methyl 3-[2-(dimethylamino)ethyl]-5-[2-(*N*-phthalimido)ethyl]-1*H*-indole-2-carboxylate (55): method 6, white crystals from ethanol, 50 mg (53%); MS *m/z* 420 (M + 1)$^+$; ^{1}H NMR δ 2.07 (6H, s, 2 × NCH$_3$), 2.21 (2H, m, CH$_2$NMe$_2$), 2.97 (4H, m, CH$_2$N, 5-CH$_2$) 3.79 (5H, m, 3-CH$_2$, OCH$_3$), 7.07 (1H, d, H6, J = 7.9 Hz), 7.24 (2H, m, H7, H4), 7.57 (4H, s, 4 × PhthArH), 11.4 (1H, s, NH); found M$^+$ 419.1851, C$_{24}$H$_{25}$N$_3$O$_4$ requires M$^+$ 419.4802.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(*N*-phthalimido)ethyl]-1*H*-indole-2-carboxylate (56): method 6 (using ethanol as solvent), white powder from ethyl acetate, 70 mg (67%); MS *m/z* 434 (M + 1)$^+$; found M$^+$ 433.1999, C$_{25}$H$_{27}$N$_3$O$_4$ requires M$^+$ 433.5071; ^{1}H NMR δ 1.28 (3H, t, CH$_2$C*H*$_3$, J = 7.2 Hz), 2.07 (6H, s, 2 × NCH$_3$), 2.19 (2H, m, CH$_2$NMe$_2$), 2.94 (4H, m, CH$_2$N, 5-CH$_2$), 3.79 (2H, m, 3-CH$_2$), 4.28 (2H, q, C*H*$_2$-CH$_3$, J = 7.1 Hz), 7.07 (1H, m, H6), 7.24 (2H, m, H7, H4), 7.76 (4H, s, 4 × PhthArH), 11.34 (1H, s, NH). Anal. Calcd (C$_{25}$-H$_{27}$N$_3$O$_4$·0.5H$_2$O): C, 67.8; H, 6.33; N, 9.4. Found: C, 67.8; H, 7.17; N, 8.7.

Methyl 5-(dimethylamino)-2-[[4-[2-(2-oxo-1,3-oxazilidin-4-yl)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (50): method 8, purified by flash chromatography eluting with CH$_2$-Cl$_2$:EtOH:NH$_3$ (30:8:1) to give 253 mg (31%) of the hydrazone as an orange powder; MS *m/z* 377 (M + 1)$^+$; ^{1}H NMR δ 1.66 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.18 (6H, s, 2 × NCH$_3$), 2.6 (2H, m, CH$_2$-NMe$_2$), 2.75 (2H, m, CH$_2$C=), 3.3–3.36 (4H, m, OCH$_2$C*H*$_2$N, PhCH$_2$C*H*$_2$N), 3.5 (2H, m, CH$_2$Ph), 3.75 (3H, s, OCH$_3$), 4.2 (2H, m, CH$_2$O), 7.17 (4H, m, H2, H3, H5, H6), 10.62 (1H, s, NH). Anal. Calcd (C$_{19}$H$_{28}$N$_4$O$_4$·0.1CH$_3$CH$_2$OH): C, 60.6; H, 7.57; N, 14.69. Found: C, 61.14; H, 7.57; N, 14.17.

Methyl 3-[2-(dimethylamino)ethyl]-5-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-1*H*-indole-2-carboxylate (51): method 6, purification by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (90:8:1) gave **51** as an orange powder; conversion to the hydrochloride salt with 0.2 N methanolic HCl gave 130 mg (54%) of **51** as white crystals; MS *m/z* 360 (M + 1)$^+$; ^{1}H NMR δ 2.2 (6H, s, 2 × NCH$_3$), 2.92 (2H, m, CH$_2$NMe$_2$), 2.96 (2H, m, CH$_2$N), 3.15 (2H, m, 5-CH$_2$), 3.35–3.55 (2H, m, 3-CH$_2$), 3.86 (3H, s, OCH$_3$), 4.17 (2H, m, CH$_2$O), 7.15 (1H, d, H6, J = 8.1 Hz), 7.35 (1H, d, H7, J = 8.0 Hz), 7.5 (1H, s, H4), 11.45 (1H, s, NH). Anal. Calcd (C$_{19}$H$_{25}$N$_3$O$_4$·1.0HCl·1.3H$_2$O): C, 54.42; H, 6.8; N, 10.02. Found: C, 54.02; H, 6.24; N, 9.69.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[2-(2-oxo-1-pyrrolidinyl)ethyl]-1*H*-indole-2-carboxylate (53): method 6 (using ethanol as solvent), purification by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$ (80:8:1) gave **53** as a glassy orange solid; conversion to the hydrochloride salt gave 7.0 mg (34%) of a light yellow powder; MS *m/z* 372 (M + 1)$^+$; found M$^+$ 371.2207, C$_{21}$H$_{29}$N$_3$O$_3$·HCl requires M$^+$ 371.4795; ^{1}H NMR δ 1.41 (3H, t, CH$_2$C*H*$_3$, J = 6.6 Hz), 1.93 (2H, m, CH$_2$C*H*$_2$-CH$_2$), 2.19 (2H, m, CH$_2$CO), 2.54 (6H, s, 2 × NCH$_3$), 2.88 (4H, m, 2 × CH$_2$N), 3.35–3.5 (4H, m, 5-CH$_2$, 3-CH$_2$, blanketed by water peak), 4.4 (2H, q, C*H*$_2$CH$_3$, J = 7.1 Hz), 7.21 (1H, d, H6, J = 8.2 Hz), 7.41 (1H, d, H7, J = 8.3 Hz), 7.6 (1H, s, H4), 11.7 (1H, s, NH).

Ethyl 5-Chloro-2-[[4-[2-(2,4-dioxo-3-thiazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]pentanoate (58). Potassium hydroxide (0.5 g, 8.93 mmol) in ethanol (6 mL) was added to a solution of diethyl chloropropylmalonate^{29} (1.86 mL, 8.54 mmol) in ethanol (6 mL), and the solution was stirred at room temperature for 3 h under nitrogen. The acetate salt of **30** (1.94 g, 6.57 mmol) was dissolved in water (15 mL) and concentrated HCl (1.97 mL, 19.7 mmol). Sodium nitrite (906 mg, 13.1 mmol) in water (4 mL) was added dropwise at 0 °C, and the solution was stirred for 24 h up to room temperature. The reaction mixture was diluted with water, extracted with dichloromethane, washed with 2 N NaOH and then water, and dried. The organic layer was concentrated to give ~2.0 g of **58** as a red oil which was used without further purification.

Ethyl 3-(2-Aminoethyl)-5-[2-(2,4-dioxo-3-thiazolidinyl)-ethyl]-1*H*-indole-2-carboxylate (59). The crude hydrazone **58** (2.0 g, 4.86 mmol) was heated in butanol (25 mL) and 2 drops of water for 18 h at reflux. The solution was allowed to cool to room temperature and the product isolated by filtration,

washed with butanol and diethyl ether, and dried in vacuo to give 764 mg (38%) of the product as a brown powder: MS *m/z* 376 (M + 1)$^+$; *m/z* 375 (M$^+$); ^{1}H NMR δ 1.4 (3H, t, CH$_2$C*H*$_3$, J = 7.6 Hz), 2.88 (2H, m, C*H*$_2$NH$_2$), 3.0 (2H, m, CH$_2$N), 3.36 (2H, m, 5-CH$_2$, blanketed by water peak), 3.77 (2H, m, 3-CH$_2$), 4.21 (2H, s, CH$_2$S), 4.38 (2H, q, C*H*$_2$CH$_3$, J = 7.5 Hz), 7.12 (1H, d, H6, J = 7.9 Hz), 7.38 (1H, d, H7, J = 8.0 Hz), 7.5 (1H, s, H4), 8.05 (2H, m, NH$_2$), 11.7 (1H, s, NH). Anal. (C$_{18}$H$_{21}$N$_3$O$_4$S·1.0HCl) C, H, N.

Ethyl 3-[2-(Dimethylamino)ethyl]-5-[2-(2,4-dioxo-3-thiazolidinyl)ethyl]-1*H*-indole-2-carboxylate (57). Formaldehyde (0.1 mL, 1.27 mmol) in methanol (1.0 mL) was added dropwise to a solution of the amine hydrochloride **59** (238 mg, 0.58 mmol), sodium cyanoborohydride (44 mg, 0.69 mmol), and glacial acetic acid (166 µL, 2.89 mmol) in methanol (10 mL). The solution was stirred for 3 h and concentrated and the residue purified by flash chromatography eluting with CH$_2$-Cl$_2$:EtOH:NH$_3$ (100:8:1) to give 143 mg (61%) of the product as a brown foam: MS *m/z* 404 (M + 1)$^+$; ^{1}H NMR δ 1.38 (3H, t, C*H*$_3$CH$_2$, J = 6.0 Hz), 2.25 (6H, s, 2 × NCH$_3$), 2.45 (2H, m, CH$_2$NMe$_2$), 2.9 (2H, m, CH$_2$N), 3.18 (2H, m, 5-CH$_2$), 3.7 (2H, m, 3-CH$_2$), 4.13 (2H, s, CH$_2$S), 4.32 (2H, q, C*H*$_2$CH$_3$, J = 6.2 Hz), 7.1 (1H, d, H6, J = 8.4 Hz), 7.3 (1H, d, H7, J = 8.4 Hz), 7.4 (1H, s, H4), 11.4 (1H, s, NH). Anal. (C$_{20}$H$_{25}$N$_3$O$_4$S·0.5H$_2$O) C, H, N.

Method 9: General Procedure for the Preparation of the 5-Methylene-Linked Hydantoin Derivatives 60 and 61. 4-[(2,5-Dioxo-1-imidazolidinyl)methyl]nitrobenzene (60). To a solution of hydantoin (9.25 g, 0.093 mol) in DMF (100 mL) was added potassium carbonate (12.8 g, 0.093 mol). The solution was stirred under nitrogen for 30 min; then *p*-nitrobenzyl bromide (22.0 g, 0.102 mol) was gradually added. The solution was stirred overnight at room temperature under nitrogen. The reaction mixture was poured onto water (300 mL), extracted with ethyl acetate, dried, and evaporated to give a white solid. Recrystallization from ethyl acetate gave 8.91 g (84%) of **60** as white crystals (mp 215−217 °C): MS *m/z* 205 (M$^+$); ^{1}H NMR δ 4.0 (2H, s, CH$_2$NH), 4.6 (2H, s, CH$_2$-Ph), 7.53 (2H, d, H3, H5, J = 9.0 Hz), 8.2 (3H, m, H2, H6, NH). Anal. (C$_{10}$H$_9$N$_3$O$_4$) C, H, N.

4-[(4,4-Dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]nitrobenzene (61): method 9, 7.53 g (68%) (mp 233−235 °C); MS *m/z* 263 (M$^+$); ^{1}H NMR δ 1.3 (6H, s, 2 × CH$_3$), 4.6 (2H, s, CH$_2$Ph), 7.47 (2H, d, H3, H5, J = 8.7 Hz), 8.2 (2H, d, H2, H6, J = 8.7 Hz), 8.4 (1H, s, NH). Anal. (C$_{12}$H$_{13}$N$_3$O$_4$) C, H, N.

4-[(2,5-Dioxoimidazolidin-3-yl)methyl]aniline (62): method 2, 5.0 g (97%) (mp 261−263 °C); MS *m/z* 205 (M$^+$); ^{1}H NMR δ 4.0 (2H, s, CH$_2$NH), 4.5 (2H, s, CH$_2$Ph), 7.25 (2H, d, H2, H6, J = 8.5 Hz), 7.3 (2H, d, H3, H5, J = 8.5 Hz), 8.1 (1H, s, NH), 9.0 (3H, br s, NH$_3$$^+$). Anal. (C$_{10}H_{11}N_3O_2$) C, H, N.

4-[(4,4-Dimethyl-2,5-dioxoimidazolidin-3-yl)methyl]-aniline (63): method 2, 7.0 g (87%) (mp dec > 200 °C, softens at 85−90 °C); MS *m/z* 233 (M$^+$); ^{1}H NMR δ 1.28 (6H, s, 2 × CH$_3$), 4.5 (2H, s, CH$_2$Ph), 7.21 (4H, m, H2, H3, H5, H6), 8.4 (1H, s, NH). Anal. (C$_{12}$H$_{15}$N$_3$O$_2$·HCl) C, H, N.

Methyl 3-[2-(dimethylamino)ethyl]-5-[(2,5-dioxo-1-imidazolidinyl)methyl]-1*H*-indole-2-carboxylate (64): method 6, 20 mg (12%); MS *m/z* 359 (M + 1)$^+$; found M$^+$ 358.1614, C$_{18}$H$_{22}$N$_4$O$_4$ requires M$^+$ 358.1641; ^{1}H NMR δ 2.07 (6H, s, 2 × NCH$_3$), 2.45 (2H, m, CH$_2$NMe$_2$), 3.13 (2H, m, CH$_2$N), 3.86 (3H, s, OCH$_3$), 3.93 (2H, s, 3-CH$_2$), 4.6 (2H, s, CH$_2$NH), 7.19 (1H, d, H6, J = 8.4 Hz), 7.33 (1H, d, H7, J = 8.4 Hz), 7.6 (1H, s, H4), 8.1 (1H, s, NH), 11.5 (1H, s, NH).

Ethyl 3-[2-(dimethylamino)ethyl]-5-[(2,5-dioxo-1-imidazolidinyl)methyl]-1*H*-indole-2-carboxylate (65): method 6 (using ethanol as solvent), 37 mg (19%); MS *m/z* 373 (M + 1)$^+$; ^{1}H NMR δ 1.34 (3H, t, CH$_2$C*H*$_3$, J = 7.5 Hz), 2.13 (2H, m, CH$_2$NMe$_2$), 2.25 (6H, s, 2 × NCH$_3$), 2.5 (2H, m, CH$_2$N), 3.9 (2H, s, 3-CH$_2$), 4.37 (2H, q, C*H*$_2$CH$_3$, J = 7.5 Hz), 4.6 (2H, s, CH$_2$NH), 7.2 (1H, d, H6, J = 8.5 Hz), 7.38 (1H, d, H7, J = 8.5 Hz), 7.6 (1H, s, H4), 8.1 (1H, s, NH), 11.6 (1H, s, NH). Anal. (C$_{19}$H$_{24}$N$_4$O$_4$·0.8H$_2$O) C, H, N.

Methyl 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-1*H*-indole-2-carboxylate (66): method 6, 115 mg (44%); MS *m/z* 387 (M + 1)$^+$; ^{1}H NMR δ 1.28 (6H, s, 2 × CH$_3$), 2.19 (6H, s, 2 × NCH$_3$), 2.4 (2H,

m, CH$_2$NMe$_2$), 3.1 (2H, m, CH$_2$N), 3.8 (3H, s, OCH$_3$), 4.6 (2H, s, 3-CH$_2$), 7.16 (1H, d, H6, J = 8.4 Hz), 7.34 (1H, d, H7, J = 8.4 Hz), 7.5 (1H, s, H4), 8.4 (1H, s, NH), 11.6 (1H, s, NH). Anal. (C$_{20}$H$_{26}$N$_4$O$_4$·0.5H$_2$O) C, H, N.

Ethyl 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-1H-indole-2-carboxylate (67): method 6 (using ethanol as solvent), 61 mg (23%) (mp 192−194 °C); MS m/z 401 (M + 1)$^+$; ^{1}H NMR δ 1.28 (6H, s, 2 × CH$_3$), 1.3 (3H, t, CH$_2$CH_3, J = 6.6 Hz), 2.2 (6H, s, 2 × NCH$_3$), 2.48 (2H, m, CH$_2$NMe$_2$), 3.2 (2H, m, CH$_2$N), 4.32 (2H, q, CH_2CH$_3$, J = 6.8 Hz), 4.6 (2H, s, 3-CH$_2$), 7.2 (1H, d, H6, J = 8.4 Hz), 7.35 (1H, d, H7, J = 8.5 Hz), 7.5 (1H, s, H4), 8.4 (1H, s, NH), 11.5 (1H, s, NH). Anal. (C$_{21}$H$_{28}$N$_4$O$_4$·0.2H$_2$O) C, H, N.

Isopropyl 3-[2-(dimethylamino)ethyl]-5-[(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)methyl]-1H-indole-2-carboxylate (68): method 6 (using 2-propanol as solvent), 14 mg (24%); MS m/z 415 (M + 1)$^+$; found M$^+$ 414.2250, C$_{22}$H$_{30}$N$_4$O$_4$ requires M$^+$ 414.2267; ^{1}H NMR (CH$_3$OH-d_4) δ 1.46 (12H, m, 2 × CH$_3$, CH(CH_3)$_2$), 2.46 (6H, s, 2 × NCH$_3$), 2.7 (2H, m, CH$_2$-NMe$_2$), 3.35 (2H, m, CH$_2$N), 4.7 (2H, m, 3-CH$_2$), 5.3 (1H, m, CH(CH$_3$)$_2$), 7.31 (1H, d, H6, J = 8.2 Hz), 7.42 (1H, d, H7, J = 8.1 Hz), 7.7 (1H, s, H4).

Ethyl 2-Acetyl-3-(4-pyridinyl)propanoate (70). Sodium (9.2 g, 0.4 mol) was dissolved in dry ethanol (130 mL); then ethyl acetoacetate (26.0 g, 0.2 mol) in dry ethanol (130 mL) was added dropwise. The solution was stirred for 30 min; then 4-picolylchloride hydrochloride (32.8 g, 0.2 mol) in dry ethanol (250 mL) was added dropwise over 30 min. The resulting solution was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the oily residue was taken up in water (100 mL), extracted with ethyl acetate, dried, filtered, and evaporated to give a yellow oil which was purified by flash chromatrography eluting with hexane:ethyl acetate (8:2) to give 14.1 g (32%) of the diketone as a light yellow oil: MS m/z 222 (M + 1)$^+$; ^{1}H NMR δ 1.1 (3H, t, CH$_3$, J = 7.2 Hz), 2.2 (3H, s, CH$_3$CO), 3.05 (2H, m, CH_2CH), 4.1 (3H, m, CH_2CH$_3$, CHCH$_2$), 7.2 (2H, d, H2, H6, J = 6.6 Hz), 8.45 (2H, d, H3, H5, J = 6.5 Hz). Anal. (C$_{12}$H$_{15}$-NO$_3$·0.65H$_2$O) C, H, N.

Method 10: General Procedure for Methylation of the Pyridine Nitrogen Using Methyl Iodide. Ethyl 2-Acetyl-3-[N-(methyliodo)pyridin-4-yl]propanoate (71). A solution of the diketone **70** (3.0 g, 13.5 mmol) and methyl iodide (2.3 g, 16.2 mmol) in dry diethyl ether (80 mL) was stirred at room temperature under nitrogen for 18 h. The solvent was decanted off to leave an orange precipitate which was washed with ether and dried under vacuum to give 2.5 g (51%) of **71** as an orange solid: MS m/z 236 (M + 1)$^+$; found M$^+$ 235.1239, C$_{13}$H$_{17}$NO$_3$ requires M$^+$ 235.2828; ^{1}H NMR δ 1.18 (3H, t, CH$_2$CH_3, J = 6.8 Hz), 2.27 (3H, s, CH$_3$CO), 3.35 (2H, m, CHCH_2), 4.1 (2H, q, CH_2CH$_3$, J = 6.8 Hz), 4.3 (3H, s, NCH$_3$), 4.4 (1H, m, CHCH$_2$), 8.0 (2H, d, H2, H6, J = 8.3 Hz), 8.88 (2H, d, H3, H5, J = 8.4 Hz). Anal. (C$_{13}$H$_{18}$NO$_3$I·1.0H$_2$O) C, H, N.

Ethyl 2-Acetyl-3-(N-methylpiperidin-4-yl)propanoate (69). A mixture of **71** (2.16 g, 5.9 mmol) in ethanol (50 mL) in the presence of platinum oxide (135 mg) was hydrogenated at room temperature and 50 atm overnight. The catalyst was filtered through Celite and the solvent removed under vacuum to give 2.1 g (95%) of a yellow gum which was dried and stored under vacuum: MS m/z 242 (M + 1)$^+$; ^{1}H NMR δ 1.2 (3H, t, CH$_2$CH_3, J = 7.3 Hz), 1.3−1.9 (6H, m, 3 × CH$_2$), 2.25 (3H, s, CH$_3$CO), 2.77 (3H, s, NCH$_3$), 2.9 (1H, m, CHCH$_2$), 3.45 (4H, m, 2 × CH$_2$N), 3.7 (1H, m, CHCH$_2$), 4.2 (2H, q, CH_2CH$_3$, J = 7.2 Hz).

(S)-Ethyl 3-(N-methylpiperidin-4-yl)-5-[(2-oxo-1,3-oxazilidin-4-yl)methyl]-1H-indole-2-carboxylate (73): method 5, purification by preparative HPLC afforded 222 mg (27%) of **73** as the acetate salt; t_R 12 min; MS m/z 386 (M + 1)$^+$; found M$^+$ 385.1988, C$_{21}$H$_{27}$N$_3$O$_4$ requires M$^+$ 385.4631; ^{1}H NMR δ 1.4 (3H, t, CH$_2$CH_3, J = 7.1 Hz), 1.7−2.4 (8H, m, 4 × CH$_2$), 2.4 (3H, s, NCH$_3$), 3.82 (1H, m, CH$_2$CHCH$_2$), 4.38 (3H, m, CH_2-CH$_3$, CHNH), 4.2 (2H, m, CH$_2$O), 7.1 (1H, d, H6, J = 8.2 Hz), 7.38 (1H, d, H7, J = 8.4 Hz), 7.85 (1H, s, H4), 8.55 (1H, s, NH).

Ethyl 3-(4-pyridinyl)-2-[[4-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]phenyl]hydrazin-2-ylidene]propanoate (74): method 8, purification by flash chromatography gave 950 mg (58%) of the hydrazone; recrystallization from ethanol gave the hydrazone as yellow needles (mp 192−193 °C); MS m/z 410 (M + 1)$^+$; ^{1}H NMR δ 1.2 (3H, t, CH$_2$CH_3, J = 6.9 Hz), 2.75 (2H, m, CH$_2$N), 3.52 (2H, m, CH$_2$Ph), 3.83 (2H, s, CH$_2$Pyr), 4.0 (2H, s, CH_2NH), 4.16 (2H, q, CH_2CH$_3$, J = 7.1 Hz), 7.15 (6H, m, 6 × ArH), 7.8 (1H, s, NHPh), 8.45 (2H, d, 2 × CHN), 10.3 (1H, s, NH). Anal. (C$_{21}$H$_{23}$N$_5$O$_4$·0.12H$_2$O) C, H, N.

Ethyl 3-(4-pyridinyl)-5-[2-(2,5-dioxo-1-imidazolidinyl)-ethyl]-1H-indole-2-carboxylate (76): method 6 (using ethanol as solvent), white crystals purified by flash chromatography eluting with CH$_2$Cl$_2$:EtOH:NH$_3$, 226 mg (94%) (mp 243−245 °C); MS m/z 393 (M + 1)$^+$; ^{1}H NMR δ 1.21 (3H, t, CH$_2$CH_3, J = 6.8 Hz), 2.88 (2H, m, CH$_2$N), 3.57 (2H, m, 5-CH$_2$), 3.82 (2H, s, CH$_2$NH), 4.26 (2H, q, CH_2CH$_3$, J = 6.6 Hz), 7.2 (1H, d, H6, J = 8.0 Hz), 7.3 (1H, s, H4), 7.5 (3H, m, H7, H3′, H5′), 7.96 (1H, s, NH), 8.64 (2H, d, 2 × CHN, J = 6.3 Hz), 12.1 (1H, s, NH). Anal. (C$_{21}$H$_{20}$N$_4$O$_4$·0.7H$_2$O) C, H, N.

Ethyl 3-[4-(N-methyliodo)pyridinyl]-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (77): method 10 (using THF instead of ether), yellow crystals from ethanol, 88 mg (59%) (mp 225−226 °C); MS m/z 407 (M + 1)$^+$; ^{1}H NMR δ 1.3 (3H, t, CH$_2$CH_3, J = 6.7 Hz), 2.9 (2H, m, CH$_2$N), 3.58 (2H, m, 5-CH$_2$), 3.82 (2H, s, CH$_2$NH), 4.3 (2H, q, CH_2-CH$_3$, J = 6.8 Hz), 4.36 (3H, s, NCH$_3$), 7.25 (1H, d, H6, J = 8.4 Hz), 7.48 (1H, s, H4), 7.55 (1H, d, H7, J = 8.3 Hz), 7.94 (1H, s, NH), 8.27 (2H, d, H3′, H5′, J = 6.4 Hz), 8.93 (2H, d, H2′, H6′, J = 6.6 Hz). Anal. (C$_{22}$H$_{23}$N$_4$O$_4$I·1.0H$_2$O) C, H, N.

Method 11: General Procedure for Reduction of an N-Methylpyridine Ring to an N-Methyltetrahydropyridine Derivative. Ethyl 3-(N-Methyltetrahydropyridin-4-yl)-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (78). The indole **77** (42 mg 0.078 mmol) was dissolved in methanol (5 mL) and cooled to ~5 °C. Sodium borohydride (12.0 mg, 0.32 mmol) was gradually added, and the solution was stirred for 30 min. The reaction mixture was diluted with water, extracted with ethyl acetate, dried, and evaporated under reduced pressure to give 32 mg (100%) of **78** as a yellow powder (mp 94 °C): MS m/z 410 (M$^+$); ^{1}H NMR δ 1.35 (3H, t, CH$_2$CH_3, J = 6.9 Hz), 2.31 (3H, s, NCH$_3$), 2.4−2.6 (4H, m, 2 × CH$_2$), 2.85 (2H, m, CH$_2$N), 3.05 (2H, m, CH$_2$), 3.52 (2H, m, 5-CH$_2$), 3.82 (2H, s, CH$_2$NH), 4.27 (2H, q, CH_2-CH$_3$, J = 7.1 Hz), 5.61 (1H, m, CH=), 7.07 (1H, d, H6, J = 8.5 Hz), 7.28 (1H, s, H4), 7.32 (1H, d, H7, J = 8.6 Hz), 7.95 (1H, s, NH), 11.57 (1H, s, NH). Anal. (C$_{22}$H$_{26}$N$_4$O$_4$·1.0HCl·0.5H$_2$O) C, H, N.

Ethyl 3-(N-Methylpiperidin-4-yl)-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (79). A stirring suspension of the tetrahydropyridine derivative **78** (25 mg, 61.0 mmol) and 10% palladium on carbon (10 mg) in methanol (10 mL) was hydrogenated overnight at room temperature and atmospheric pressure. The suspension was filtered through Celite and the solvent evaporated under reduced pressure to give a yellow residue which was purified by preparative HPLC to give 6.0 mg (21%) of **79** as the acetate salt: MS m/z 413 (M + 1)$^+$; found M$^+$ 412.2071, C$_{22}$H$_{28}$N$_4$O$_4$·1.0CH$_3$CO$_2$H requires M$^+$ 412.4887; ^{1}H NMR δ 1.35 (3H, t, CH$_2$CH_3, J = 6.9 Hz), 1.61 (2H, m, CH$_2$), 1.95 (2H, m, CH$_2$), 2.22 (3H, s, NCH$_3$), 2.85 (6H, m, 2 × CH$_2$, CH$_2$N), 3.6 (3H, m, 5-CH$_2$, CH), 3.95 (2H, s, CH$_2$NH), 4.3 (2H, q, CH_2CH$_3$, J = 7.0 Hz), 7.05 (1H, dd, H6, J = 8.1 Hz), 7.37 (1H, d, H7, J = 8.3 Hz), 7.5 (1H, s, H4), 7.95 (1H, s, NH), 11.35 (1H, s, NH); t_R 11 min.

Isopropyl 3-(4-Pyridinyl)-5-[2-(2,5-dioxo-1-imidazolidinyl)ethyl]-1H-indole-2-carboxylate (80) (Method 6, using 2-propanol as solvent). The required hydrazone was synthesized from the aniline hydrochloride **22** and the β-keto ester **70**. The hydrazone was purified by flash chromatography eluting with CHCl$_3$:MeOH (97:3) and was used directly to form the indole derivative **80**, 60 mg (33%): MS m/z 435 (M + 1)$^+$; ^{1}H NMR δ 1.04 (6H, s, 2 × CH$_3$), 1.19 (6H, d, CH(CH_3)$_2$, J = 6.3 Hz), 2.9 (2H, m, CH$_2$N), 3.5 (2H, m, 5-CH$_2$), 5.1 (1H, m, CH), 7.14 (1H, d, H6, J = 8.2 Hz), 7.2 (1H, s, H4), 7.46 (3H,

m, H7, H3′, H5′), 8.1 (1H, s, NH), 8.62 (2H, d, H2′, H6′, $J =$ 5.1 Hz), 12.0 (1H, s, NH). Anal. ($C_{24}H_{26}N_4O_4$·0.75H_2O) C, H, N.

Isopropyl 3-(*N*-Methyltetrahydropyridin-4-yl)-5-[2-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-1*H*-indole-2-carboxylate (81). The methyl iodide quaternary salt of **80** was synthesized by method 9 and reacted on without purification via method 10 to give 40 mg (52%) of the desired tetrahydropyridine derivative **81**: MS m/z 453 (M + 1)$^+$; ^{1}H NMR δ 1.1 (6H, s, 2 × CH_3), 1.28 (6H, d, CH(CH_3)$_2$, $J =$ 6.3 Hz), 2.28 (3H, s, NCH$_3$), 2.38 (2H, m, CH$_2$), 2.56 (2H, m, CH$_2$), 2.86 (2H, m, CH$_2$N), 3.0 (2H, m, CH$_2$), 3.54 (2H, m, 5-CH$_2$), 5.1 (1H, m, CH(CH$_3$)$_2$), 5.6 (1H, s, CH=), 7.0 (1H, d, H6, $J =$ 8.1 Hz), 7.2 (1H, s, H4), 7.3 (1H, d, H7, $J =$ 8.1 Hz), 8.1 (1H, s, NH), 11.5 (1H, s, NH). Anal. ($C_{25}H_{32}N_4O_4$·1.0H_2O) C, H, N.

Ethyl 3-(*N*-Methyltetrahydropyridin-4-yl)-5-[2-(*N*-phthalimido)ethyl]-1*H*-indole-2-carboxylate (82). The required hydrazone was synthesized by method 7, indole closure was achieved using method 6, and the pyridine nitrogen was methylated using method 9. Reduction of the N-methylated pyridine ring to a tetrahydropyridine substituent was achieved using method 10. In each reaction the intermediates were not isolated and purified but were reacted on greater than 90% pure to ultimately afford 63 mg (23%) of **82** as an orange solid after purification by flash chromatography eluting with CH_2Cl_2:EtOH:NH$_3$ (150:8:1): MS m/z 458 (M + 1)$^+$; ^{1}H NMR δ 1.28 (3H, t, CH$_2$CH_3, $J =$ 6.9 Hz), 1.76 (2H, m, CH$_2$), 2.26 (3H, s, NCH$_3$), 2.8 (2H, m, CH$_2$), 2.95 (2H, m, CH$_2$N), 3.6 (2H, m, CH$_2$), 3.8 (2H, m, 5-CH$_2$), 4.25 (2H, q, CH_2CH$_3$, $J =$ 6.7 Hz), 6.1 (1H, t, CH=), 7.1 (1H, d, H6, $J =$ 8.2 Hz), 7.3 (1H, d, H7, $J =$ 8.3 Hz), 7.6 (1H, s, H4), 7.8 (4H, s, Phth Ar), 11.5 (1H, s, NH); found M$^+$ 457.2016, $C_{27}H_{27}N_3O_4$ requires M$^+$ 457.2002.

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