Synthesis and Serotonergic Activity of 3-[2-(Pyrrolidin-1-yl)ethyl]indoles: Potent Agonists for the h5-HT$_{1D}$ Receptor with High Selectivity over the h5-HT$_{1B}$ Receptor

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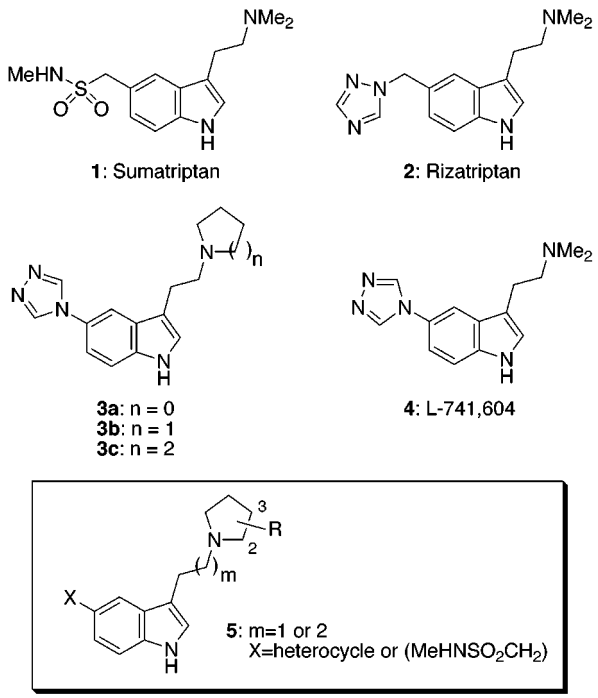
The design, synthesis, and biological evaluation of a novel series of 3-[2-(pyrrolidin-1-yl)ethyl]-indoles with excellent selectivity for h5-HT$_{1D}$ (formerly 5-HT$_{1D\alpha}$) receptors over h5-HT$_{1B}$ (formerly 5-HT$_{1D\beta}$) receptors are described. Clinically effective antimigraine drugs such as Sumatriptan show little selectivity between h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors. The differential expression of h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors in neural and vascular tissue prompted an investigation of whether a compound selective for the h5-HT$_{1D}$ subtype would have the same clinical efficacy but with reduced side effects. The pyrrolidine **3b** was initially identified as having 9-fold selectivity for h5-HT$_{1D}$ over h5-HT$_{1B}$ receptors. Substitution of the pyrrolidine ring of **3b** with methylbenzylamine groups gave compounds with nanomolar affinity for the h5-HT$_{1D}$ receptor and 100-fold selectivity with respect to h5-HT$_{1B}$ receptors. Modification of the indole 5-substituent led to the oxazolidinones **24a,b** with up to 163-fold selectivity for the h5-HT$_{1D}$ subtype and improved selectivity over other serotonin receptors. The compounds were shown to be full agonists by measurement of agonist-induced [^{35}S]GTPγS binding in CHO cells expressed with h5-HT receptors. This study suggests that the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors can be differentiated by appropriate substitution of the ligand in the region which binds to the aspartate residue and reveals a large binding pocket in the h5-HT$_{1D}$ receptor domain which is absent for the h5-HT$_{1B}$ receptor. The compounds described herein will be important tools to delineate the role of h5-HT$_{1D}$ receptors in migraine.

Introduction

The serotonin (5-HT) receptor agonist Sumatriptan (**1**; Chart 1) is the first of a new class of therapeutic agents for the acute treatment of migraine headaches.[1] Of the 13 currently identified human 5-HT receptors,[2] Sumatriptan exhibits binding selectivity for the h5-HT$_1$ subclass, particularly[3] for the h5-HT$_{1D}$ (formerly 5-HT$_{1D\alpha}$)[4] and h5-HT$_{1B}$ (formerly 5-HT$_{1D\beta}$) subtypes, and it is generally accepted that Sumatriptan's clinical efficacy is mediated through action at these receptors.[5] However, neither Sumatriptan nor the more recently developed compounds in the "triptan" class (Naratriptan, Zolmitriptan, Rizatriptan (**2**), Eletriptan) show much selectivity for either of these subtypes.

While the h5-HT$_{1D/1B}$ class of compounds is effective in the treatment of migraine, side effects have been documented,[6] including the potential[7] for coronary artery vasoconstriction which can preclude their use in patients with heart disease.[8] The possibility that the antimigraine activity of these compounds may be mediated through either one or the other of the h5-HT$_{1D/1B}$ receptors prompted us to investigate the possibility of identifying a second-generation compound that discriminated between these two receptors to give clinical efficacy with an improved side-effect profile.

Chart 1



The mechanism of action of Sumatriptan remains a matter of debate, and both vasoconstriction of intracranial, extracerebral blood vessels[9] and/or inhibition of

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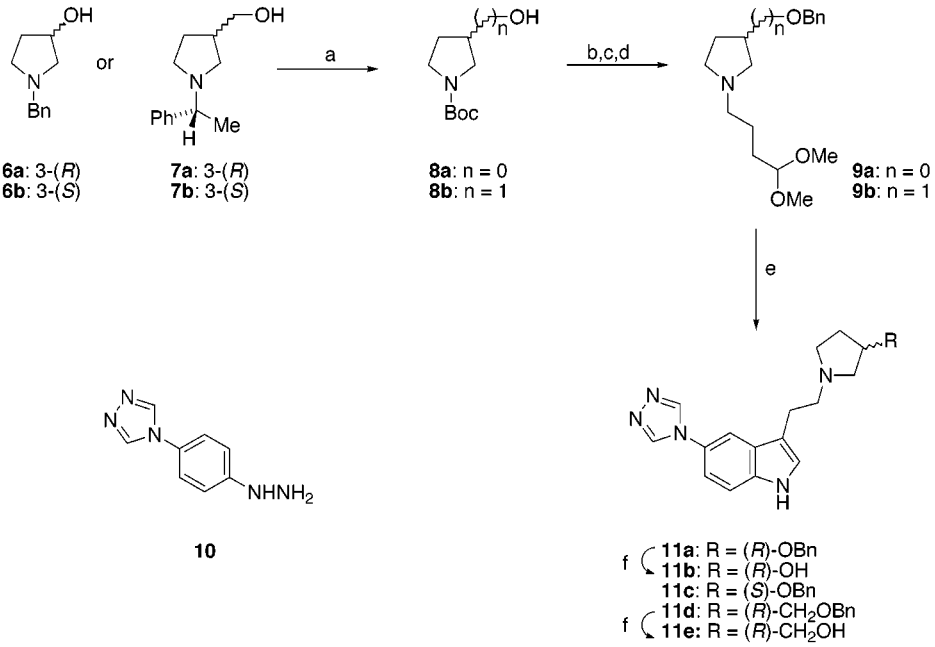
Table 1. h5-HT_{1D} Receptor Binding Selectivity and Functional Efficacy of Standard Compounds

compd[a]	IC_{50} (nM) h5-HT_{1D}[b]	IC_{50} (nM) h5-HT_{1B}[b]	selectivity	EC_{50} (nM) h5-HT_{1D}[c]	efficacy[d] (% 5-HT)
Sumatriptan (**1**)	6.7 ± 0.65	11 ± 1.8	2	14 ± 3.2	100 ± 5
L-741,604 (**4**)	0.30 ± 0.05	1.3 ± 0.20	4	0.40 ± 0.06	115 ± 6
3a	1.1 ± 0.20	4.4 ± 2.4	4		
3b	3.1 ± 0.72	28 ± 5.9	9	2.3 ± 0.88	120 ± 12
3c	200	570	3		

[a] Where applicable, all compounds are single enantiomers with absolute stereochemistry as drawn. [b] Displacement of [^{3}H]-5-HT binding from the cloned human 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in CHO cells. All values are the means of at least two independent determinations performed in duplicate; the standard error of the mean is given where $n \geq 3$. In each case the radioligand concentration used was at the k_D for the receptor. The maximum variance from the mean of the log IC_{50} values was 3.2%. [c] EC_{50} for the stimulation of [^{35}S]GTPγS binding in CHO cells expressing the h5-HT_{1D} receptor. [d] Maximum stimulation of [^{35}S]GTPγS binding expressed relative to the maximal effect produced by 5-HT. Values are the mean of at least two independent determinations; the standard error of the mean is given where $n \geq 3$.

Scheme 1[a]



[a] Reagents: (a) $Pd(OH)_2$, H_2, $(BOC)_2O$, MeOH/H_2O; (b) NaH, $PhCH_2Br$, THF; (c) 90% HCO_2H; (d) 4-chlorobutanal dimethyl acetal, K_2CO_3/THF or Na_2CO_3/NaI/DME, reflux; (e) **10**, 4% H_2SO_4, reflux; (f) HCO_2NH_4, Pd/C, MeOH or EtOH, 65 °C.

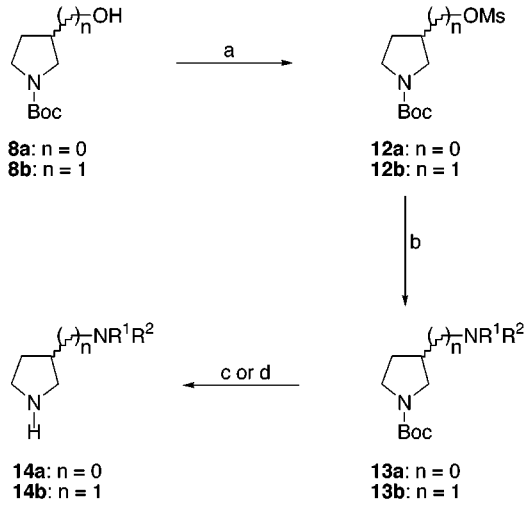
inflammation caused by inappropriate stimulation of the trigeminal ganglion[10] have been invoked. It has also been proposed that the antimigraine activity of some 5-HT agonists may have a centrally mediated component.[11] Receptor mapping studies[12] have revealed that the h5-HT_{1B} receptor is widely distributed in the central nervous system (CNS) and vascular tissues, while the h5-HT_{1D} receptor is restricted to neural tissues. This suggested to us that a h5-HT_{1D}-selective compound might lack the vasoconstrictor activity of unselective compounds such as Sumatriptan but retain their antimigraine efficacy. This paper describes in detail[13] the design, synthesis, and biological evaluation of a novel series of h5-HT_{1D} receptor agonists with up to 163-fold selectivity over the h5-HT_{1B} receptor.

Screening of the in-house collection of 5-substituted tryptamines, synthesized during the discovery of Rizatriptan, which explored primarily different electronic and steric properties of the indole 5-substituent, revealed many compounds with marginal h5-HT_{1D} over h5-HT_{1B} selectivity (3−5-fold). However, the C-3-modified pyrrolidine analogue **3b** had almost 1 order of magnitude higher binding affinity for the h5-HT_{1D} receptor compared to the h5-HT_{1B} receptor (Table 1), and this was used as a starting point for the medicinal chemistry program. The *N*,*N*-dimethylethylamine analogue of **3b**, L-741,604 (**4**),[14] has 10-fold higher affinity at h5-HT_{1D} receptors but arguably lower receptor selectivity.[15] This suggested that improvements in h5-HT_{1D} selectivity might be gained by exploring space around the pyrrolidine ring of **3b**. In so doing, it was anticipated that this would help to define the steric requirements for binding to the h5-HT_{1D} and h5-HT_{1B} receptors in the region of the aspartic acid binding domain.[16] Interestingly, the azetidine (**3a**) and piperidine (**3c**) analogues of **3b** have lower selectivity, coupled in the case of **3c** to substantially reduced affinity. Consequently, our initial efforts focused on the pyrrolidine series of compounds exemplified by **5**, and, in particular, on probing for improved h5-HT_{1B}/h5-HT_{1D} selectivity by substitution of the pyrrolidine ring. Modification of the indole 5-substituent was also explored as a further strategy to optimize the series.

Synthetic Chemistry

Derivatives with the general structure **5** were prepared via either Fischer indolization or a palladium-catalyzed coupling reaction as shown in Schemes 1−5. Hydrogenation of the enantiomerically pure benzylpyrrolidines **6a,b** and **7a,b**[17] in the presence of $(Boc)_2O$ gave

Scheme 2[a]



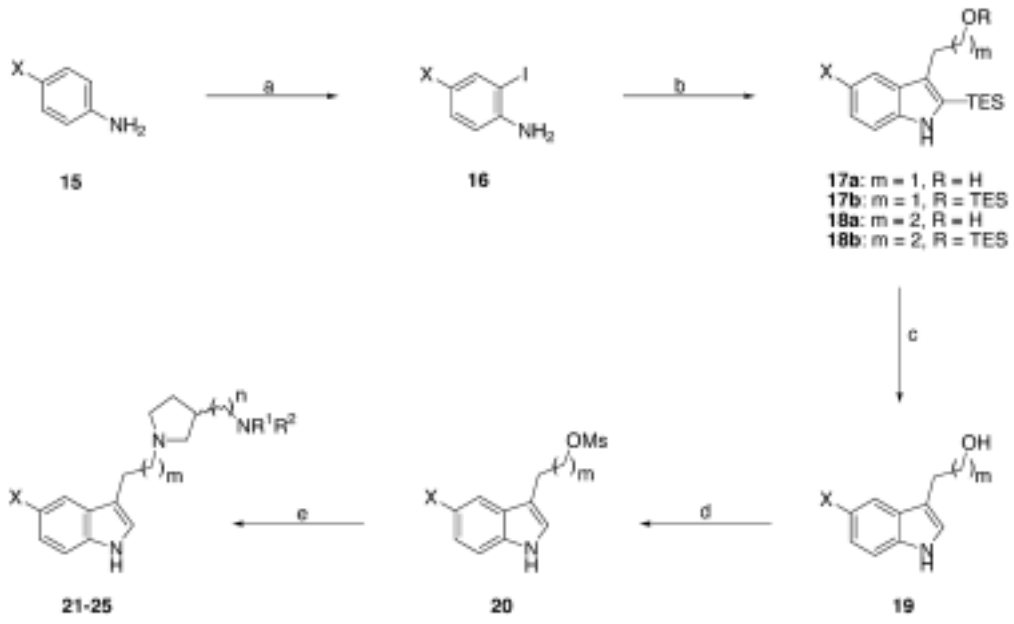
[a] Reagents: (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (b) R^1R^2NH, toluene, reflux or R^1R^2NH, toluene, 150 °C, sealed pressure tube; (c) 90% HCO_2H or CF_3CO_2H, CH_2Cl_2; (d) (i) HCHO, $NaCNBH_3$, AcOH, MeOH, (ii) 90% HCO_2H or CF_3CO_2H, CH_2Cl_2.

the Boc-pyrrolidines **8a,b** in excellent yield (Scheme 1). Alkylation with benzyl bromide followed by removal of the Boc protecting group and *N*-alkylation with 4-chlorobutanal dimethyl acetal[18] smoothly afforded the butanal dimethyl acetals **9a,b**. Fischer indolization of **9a,b** with hydrazine **10**[14] in refluxing 4% sulfuric acid afforded the indoles **11a,c,d** in 10−25% yield. Treatment of **11a**,**d** with HCO_2NH_4/Pd−C gave the debenzylated indoles **11b**,**e**, respectively.

The poor yields obtained in the Fischer reaction with **9a,b** prompted the design of an alternative synthetic route for the preparation of further *N*-substituted analogues. Since the indoles appeared to be unstable to prolonged heating in the acidic medium required for the Fischer cyclization, an improved strategy might be to construct the indole nucleus first and introduce the chiral pyrrolidine in the final step. In particular, coupling between a tryptophol or homotryptophol **19** and a suitably functionalized pyrrolidine **14a,b** to give the required indoles in a single step was envisaged.[19] The required chiral pyrrolidines **14a,b** were prepared as shown in Scheme 2. Mesylation of alcohols **8a,b** followed by reaction with the appropriate amine either in refluxing toluene or, for less reactive or volatile amines, in toluene at 150 °C in a sealed pressure tube gave the functionalized pyrrolidines **13a,b** in excellent yield.[20] Treatment of **13a,b** with formic acid or trifluoroacetic acid in dichloromethane gave the required N(H)-pyrrolidines **14a,b**. In cases where a *N*-methylamine required for coupling with **12a,b** was not commercially available, reaction of **13a,b** (R^2 = H) with $HCHO/NaCNBH_3/MeCO_2H$ prior to removal of the Boc group gave the required tertiary amine substituent (**13a,b**, R^2 = Me).

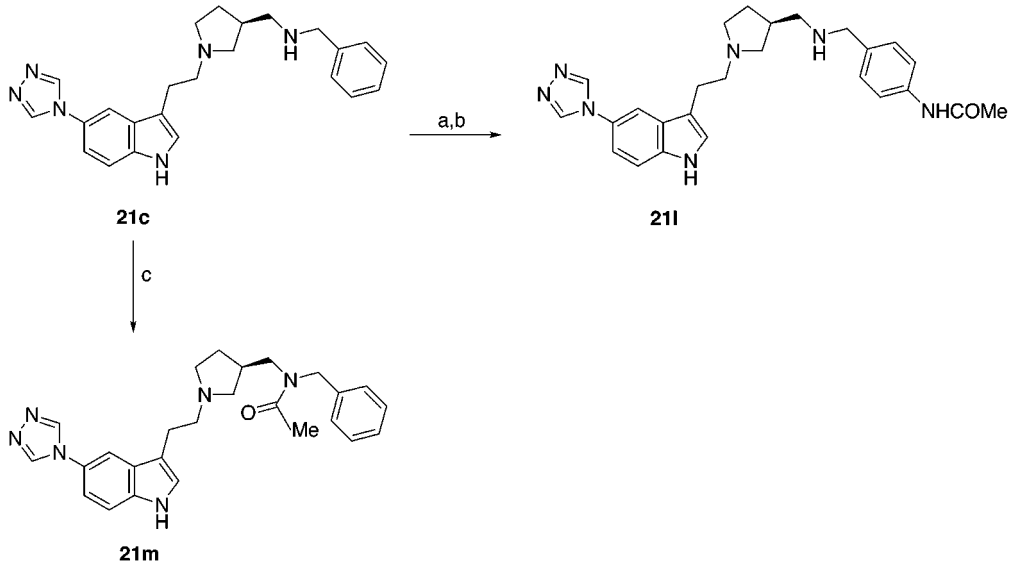
The indole alcohols **19**[21] were prepared starting from the differentially substituted anilines **15**[22] (Scheme 3). Iodination with ICl gave the *o*-iodoanilines **16**, and subsequent Larock reaction with 1,4-bis(triethylsilyl)-3-butyn-1-ol[19,23] and 1,5-bis(triethylsilyl)-4-pentyn-1-ol[23b] afforded the indoles **17a,b** and **18a,b**, respectively, in which partial cleavage of the *O*-TES group was observed. Treatment of the crude material with 5 N HCl in methanol gave the fully deprotected indole alcohols **19**. Conversion of **19** to the mesylates **20** followed by coupling with **14a,b** in boiling isopropyl alcohol in the presence of potassium carbonate gave the required indoles **21**−**25**. For indoles derived from **14a,b** (R^2 = H), coupling through the pyrrolidine nitrogen rather than through the exocyclic nitrogen was confirmed by NOE enhancement experiments. Saturation of the benzylic methylene of, for example, **21c** gave NOE enhancements of the C-3′ methylene protons and two phenyl protons, as well as enhancement (via the NH proton) of the signal due to residual water in the solvent, thus defining the regiochemistry of coupling. Indole **26** was

Scheme 3[a]



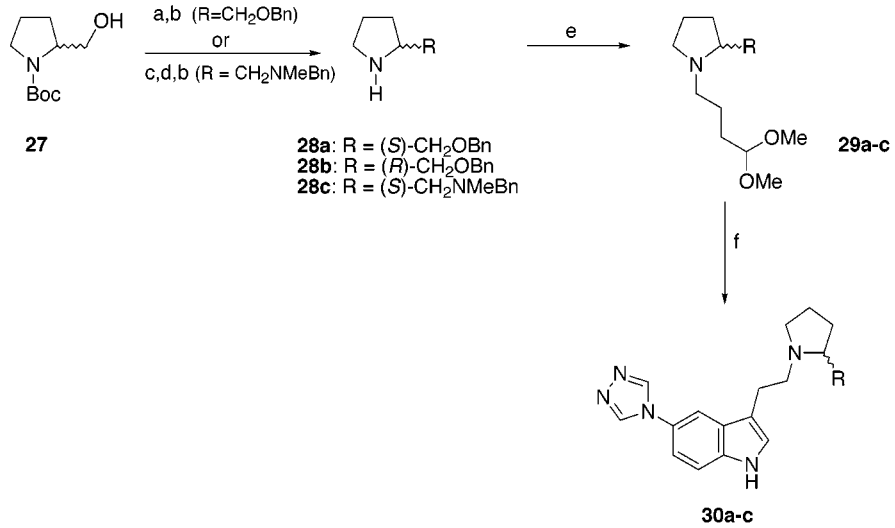
[a] Reagents: (a) ICl, $CaCO_3$, MeOH; (b) $TESCC(CH_2)_2OTES$ or $TESCC(CH_2)_3OTES$, $Pd(OAc)_2$, Na_2CO_3, DMF, 105 °C; (c) 5 N HCl, MeOH, rt or 60 °C; (d) $MeSO_2Cl$, pyridine or $MeSO_2Cl$, Et_3N, THF or CH_2Cl_2 or MeCN; (e) **14**, K_2CO_3, IPA, reflux.

Scheme 4[a]



[a] Reagents: (a) HCO_2NH_4, Pd/C, MeOH, 62 °C; (b) *p*-acetamidobenzaldehyde, $NaBH_4$, EtOH; (c) MeCOCl, Et_3N, CH_2Cl_2.

Scheme 5[a]



[a] Reagents: (a) NaH, $PhCH_2Br$, THF; (b) 90% HCO_2H; (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (d) $PhCH_2NHMe$, DMF, reflux; (e) 4-chlorobutanal dimethyl acetal, K_2CO_3/THF or Na_2CO_3/NaI/DME, reflux; (f) **10**, 4% H_2SO_4, reflux.

prepared from the homotryptophol **19** ($m = 2$) and the N(H)-pyrrolidine precursor of **9b**.

Derivatives of **21c** were prepared either by removal of the benzyl group followed by reductive alkylation with *p*-acetamidobenzaldehyde to give **21l** or by acylation with acetyl chloride to give **21m** (Scheme 4). The 2-substituted pyrrolidines **30a**−**c** were prepared from the enantiomerically pure Boc-prolinols **27** using the Fischer−indole methodology described above for **11** (Scheme 5).

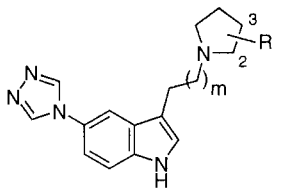
The optical purity of the target compounds of this study was confirmed by chiral HPLC analysis of indoles **11b**, **21a**,**c**,**d**, **30a**,**b** as representative examples of the different synthetic routes used.

Results and Discussion

The h5-HT_{1D} and h5-HT_{1B} receptor affinities of compounds were measured by displacement of [^{3}H]-5-HT binding from cloned human 5-HT_{1D} and 5-HT_{1B} receptors stably expressed in CHO cells.[24] Their intrinsic efficacy, expressed as percent relative to the maximal effect produced by 5-HT, was measured in the same cell lines using agonist-induced [^{35}S]GTPγS binding.[25,26] The data are presented in Tables 2−4.

The h5-HT_{1D} and h5-HT_{1B} affinities and efficacies of a series of pyrrolidines in which the C-3 position of the pyrrolidine ring of **3b** has been substituted are shown in Table 2. Substitution with a benzyloxy group improved h5-HT_{1D} over h5-HT_{1B} selectivity (**11a**: 1B/1D 23). The same effect was observed when this group was attached through a methylene spacer (**11d**: 1B/1D 37). In both cases, the increase in selectivity arises primarily through a substantial decrease in binding affinity at the h5-HT_{1B} receptor. Removal of the benzyl group of **11a**,**d**, to give the hydroxypyrrolidines **11b**,**e**, respectively, was detrimental to h5-HT_{1D} over h5-HT_{1B} selectivity, suggesting that a bulky substituent and/or high electron density is important in this region of space for differentiating the h5-HT_{1D} and h5-HT_{1B} receptors.

Table 2. h5-HT$_{1D}$ Receptor Binding Selectivity and Functional Efficacy of Substituted Pyrrolidines



compd[a]	m	position of subst[n]	R	IC$_{50}$ (nM) h5-HT$_{1D}$[b]	IC$_{50}$ (nM) h5-HT$_{1B}$[b]	selectivity	EC$_{50}$ (nM) h5-HT$_{1D}$[c]	efficacy[d] (% 5-HT)
3b	1		H	3.4 ± 0.72	28 ± 5.9	9	2.3 ± 0.88	120 ± 12
11a	1	3	OBn	6.3 ± 0.50	145 ± 21	23	15 ± 1.1	81 ± 3
11b	1	3	OH	9.0	93	10	7.8	103
11c	1	3	OBn	20	275	14	31	84
21a	1	3	NMeBn	37	209	6		
11d	1	3	CH$_2$OBn	2.3	85	37	2.1	68
11e	1	3	CH$_2$OH	26	93	4		
21b	1	3	CH$_2$NMeBn	0.70	32	46	1.5	102
21c	1	3	CH$_2$NHBn	0.50	47	94	0.8 ± 0.47	102 ± 5
21d	1	3	CH$_2$NHBn	1.6	47	29	4.1	103
21e	2	3	CH$_2$NMeBn	4.2	59	14		
26	2	3	CH$_2$OBn	2.1	33	16		
30a	1	2	CH$_2$OBn	0.81	2.7	3		
30b	1	2	CH$_2$OBn	95	575	6		
30c	1	2	CH$_2$NMeBn	0.80	15	19	3.0	106

[a–d] See corresponding footnotes of Table 1.

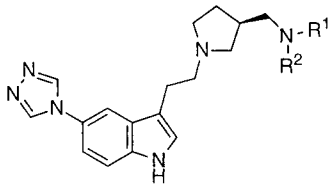
Both **11a**,**d** behave as partial agonists in the GTPγS binding assay when compared to serotonin. Since there is no definitive animal assay for migraine,[27] it was considered essential that an optimal selective compound should have comparable h5-HT$_{1D}$ efficacy to the unselective, clinically effective compounds[28] in order to determine whether h5-HT$_{1D}$ activity alone is sufficient to intervene in the migraine process. Replacement of the oxygen atom in **11a**,**d** by a methylated nitrogen, to give the benzylamines **21a**,**b**, respectively, appeared to be tolerated only in the latter case. This change, however, was beneficial for improving the efficacy of the compounds, and benzylamine **21b** was as efficacious as 5-HT in the in vitro functional assay with improved affinity relative to the benzyl ether **11d** and comparable selectivity. Removal of the methyl group on nitrogen in **21b** to give **21c** produced a further 2-fold increase in 1B/1D binding selectivity to give a 94-fold selective compound, while retaining subnanomolar affinity and full agonism at the h5-HT$_{1D}$ receptor.

The absolute stereochemistry of the pyrrolidine C-3 chiral center has an effect on both affinity and selectivity which is illustrated by comparison of the benzyl ethers **11a**,**c** and benzylamines **21c**,**d**. Notably, the same absolute stereochemistry of the pyrrolidine substituent is preferred whether the heteroatom is directly attached to the pyrrolidine ring or linked through a methylene spacer. Investigation of the length of chain linking the indole nucleus and pyrrolidine nitrogen showed that a two-carbon linker was optimal (e.g., **21b** vs **21e** and **11d** vs **26**). This is in direct contrast to the previously reported piperidine-[13] and piperazine[29]-derived 5-HT$_{1D}$ receptor agonists which favor a propylene chain and suggests that the benzyl substituents on the cyclic amines may be occupying different regions of space at the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors in the different series.

Data for an analogous series of 2-substituted pyrrolidines is also shown in Table 2. Compounds in the more active enantiomeric series derived from L-proline have the same relative disposition of the pyrrolidine substituent as the more active enantiomers in the 3-substituted pyrrolidine series. Interestingly, the 2-substituted series exhibits greater stereodifferentiation in terms of receptor binding than the 3-substituted series, possibly as a consequence of the closer proximity of the pyrrolidine substituent in the former to the pyrrolidine nitrogen atom which is believed to be crucial for binding. C-2-substituted pyrrolidines in the more active enantiomeric series showed excellent h5-HT$_{1D}$ affinity but reduced h5-HT$_{1B}$/h5-HT$_{1D}$ selectivity compared to their C-3-substituted counterparts (cf. **30a** vs **11d** and **30c** vs **21b**), although it was possible to introduce modest selectivity into the series by replacing the benzyl ether oxygen of **30a** with a methylated nitrogen (**30c**).

Having identified the optimal position for substitution of the pyrrolidine ring, the optimal enantiomeric series, and the preferred length of the linking chain, further

Table 3. h5-HT_{1D} Receptor Binding Selectivity and Functional Efficacy of Aminomethyl-Substituted Pyrrolidines



compd[a]	R^1	R^2	IC_{50} (nM) h5-HT_{1D}[b]	IC_{50} (nM) h5-HT_{1B}[b]	selectivity	EC_{50} (nM) h5-HT_{1D}[c]	efficacy[d] (% 5-HT)
21f	CH_2(2-pyridyl)	H	3.6	48	13		
21g	CH_2(3-pyridyl)	H	3.8 ± 0.8	62 ± 29	16		
21h	CH_2(4-pyridyl)	H	8.5	110	13	9.5	102
21i	CH_2(2-furyl)	H	1.5	20	13	2.8	102
21j	CH_2(3-furyl)	H	0.45	12	27	1.3	110
21k	$CH_2CH{=}CH_2$	H	17	325	19		
21l	CH_2(*p*-AcNHPh)	H	12	165	14	10	93
21m	CH_2Ph	Ac	1.1	11	10		
21n	Ph	H	9.1 ± 0.9	87 ± 28	10		
21o	CH_2CH_2Ph	H	2.6	125	48	6.2	92
21p	(*R*)-α-(Me)CHPh	H	0.72	74	103	2.1	101
21q	(*S*)-α-(Me)CHPh	H	0.45	41	91	0.63	90
21r	(*R*)-α-(CH_2OH)CHPh	H	1.4 ± 0.2	165 ± 4	118	1.8	110
21s	(*S*)-α-(CH_2OH)CHPh	H	8.3	270	33	8.7	102
21t	$C(Me)_2Ph$	H	1.0 ± 0.4	39 ± 6	39	0.3	92

[a–d] See corresponding footnotes of Table 1.

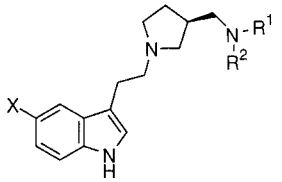
work focused on the 3-[2-(pyrrolidin-1-yl)ethyl]indole series. The importance of the benzyl substituent on the exocyclic nitrogen for optimum h5-HT_{1D} receptor affinity and selectivity is evident from the results shown in Table 3. Replacement of the phenyl ring with heterocycles was explored. All three pyridyl isomers (**21f**−**h**) had at least an order of magnitude lower affinity for h5-HT_{1D} receptors than **21c** and had only modest selectivity. The 2-furyl (**21i**) and 3-furyl (**21j**) derivatives showed high affinity but were compromised by moderate selectivity, although a full agonist profile was maintained. Replacement of the phenyl ring with an allyl group (**21k**) produced a large decrease in both affinity and selectivity, suggesting that both the steric bulk and electron density of the phenyl ring contribute to the outstanding binding and selectivity profile of **21c**. Substitution of the phenyl ring with polar functionality (e.g., **21l**) led to a 25-fold drop in affinity and only modest selectivity. The importance of a basic exocyclic nitrogen is evident from the decrease in selectivity seen for the *N*-acetyl derivative **21m** and, in the case of the aniline **21n**, the significantly reduced affinity and selectivity. Extension of the phenyl ring to the phenethyl derivative **21o** gave a 5-fold reduction in affinity compared to **21c** but retained good selectivity (48-fold).

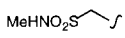
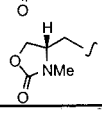
Substitution at the benzylic position with either a (*R*)-methyl or a (*S*)-methyl group (**21p**,**q**) retained the excellent affinity and selectivity (91−103-fold) of **21c**.[30] In contrast, substitution with a hydroxymethyl group was stereoselective: substitution to give (*R*)-stereochemistry (**21r**) resulted in improved selectivity (118-fold), albeit coupled with a 3-fold drop in affinity. On the other hand, the diastereomer **21s** showed a 17-fold drop in affinity and only moderate selectivity (33-fold), presumably a consequence of an unfavorable steric or electronic interaction with (primarily) the h5-HT_{1D} receptor. While monomethylation of the benzylic position in both diastereomeric series is tolerated, α,α-dimethylation of **21c** to give **21t** resulted in a significant decrease in selectivity (39-fold). However, both mono- and disubstitution retained the full agonist profile of **21c**.

Table 4 shows data for compounds in which the indole 5-substituent has been modified. Replacement of the N4-linked triazole of **21c**,**q** with a methylene-bridged N1-linked triazole to give **22a**,**b**, respectively, retained (**22a**) or improved (**22b**) h5-HT_{1B}/h5-HT_{1D} selectivity, although this was combined with a 6-fold drop in h5-HT_{1D} affinity. This decrease in affinity parallels our previously reported observation in the tryptamine series of unselective h5HT_{1D}/h5-HT_{1B} agonists.[14] *N*-Methylation of **22a**,**b** to give **22c**,**d**, respectively, retained excellent selectivity. Substitution of the indole 5-position with sulfonamide (**23a**) and oxazolidinone (**24a,b**) was tolerated; in particular, **24a**,**b** had subnanomolar affinity and improved selectivity (140−163-fold) compared to their triazole counterparts **21c**,**q**. Methylation of both the oxazolidinone and benzylic nitrogens of **24a** retained high affinity, but this was coupled with lower selectivity (41-fold). All C-5 modifications were achieved without compromising the full agonist profile of the series.

An integral part of this study was to use the selective compounds we had designed to help define the steric requirements for binding to the h5-HT_{1D} and h5-HT_{1B}

Table 4. h5-HT$_{1D}$ Receptor Binding Selectivity and Functional Efficacy of 1-Triazole-, Sulfonamide-, and Oxazolidinone-Substituted Indoles



compd[a]	X	R^1	R^2	IC_{50} (nM) h5-HT$_{1D}$[b]	IC_{50} (nM) h5-HT$_{1B}$[b]	selectivity	EC_{50} (nM) h5-HT$_{1D}$[c]	efficacy[d] (% 5-HT)
22a		CH_2Ph	H	3.2	260	81	4.9	105
22b		(*S*)-α-(Me)CHPh	H	2.5	305	122	3.0 ± 1.8	92 ± 5
22c		CH_2Ph	Me	7.7	575	82	11 ± 1.3	87 ± 6
22d		(*S*)-α-(Me)CHPh	Me	0.70	87	124	4.5 ± 1.0	86 ± 4
23a		CH_2Ph	H	1.1	62	56	3.5	92
24a		CH_2Ph	H	0.35	49	140	1.7	98
24b		(*S*)-α-(Me)CHPh	H	0.30 ± 0.06	49 ± 2	163	0.50	98
25a		CH_2Ph	Me	1.70	69	41	3.2	95

[a–d] See corresponding footnotes of Table 1.

receptors in the region of the aspartate residue binding domain. The results in Tables 2−4 clearly demonstrate that C-3 substitution of the pyrrolidine ring of **3b** with a group bearing a terminal phenyl ring is critical for h5-HT$_{1B}$/h5-HT$_{1D}$ selectivity. Moreover, the length of chain linking the pyrrolidine and phenyl rings appears to control the level of selectivity. An overlay of the indoles **21a,c,n,o** for which this linking chain is 2−4 atoms in length is shown in Figure 1,[31] highlighting that for each of the compounds the phenyl ring occupies a different region of space. In-house mutagenesis studies[32] have identified a selectivity-producing region between helices 2, 3, and 7 of the 5-HT$_{1D}$ receptor for which important binding residues are an isoleucine at position 113 on helix 3 and a tyrosine at position 98 on helix 2; a phenylalanine residue occupies position 113 on helix 3 of the 5-HT$_{1B}$ receptor. Figure 2 shows the proposed docking of **21a,c,n,o** into a speculative model of the 5-HT$_{1D}$ receptor.[33] It is proposed that the phenyl ring of selective compounds such as **21c**,**o** interacts favorably with the isoleucine residue of the 5-HT$_{1D}$ receptor, whereas interaction with the larger and electron-rich phenylalanine residue of the 5-HT$_{1B}$ receptor would be predicted to be less favored. Figure 2 clearly shows that the less-selective compounds **21a**,**n** do indeed have a poorer interaction with the selectivity-producing region. The model also suggests an explanation for the lower selectivity of the 2-substituted pyrrolidines **30a−c**, since for these compounds the important phenyl-bearing substituent is located away from this critical region of the receptor.

In addition to showing selectivity in the binding assay, the compounds of this study also showed selectivity in the functional assay for the h5-HT$_{1D}$ receptor.[34] Selected compounds were further screened against other cloned serotonin receptors using radioligand binding techniques (Table 5). All compounds showed excellent selectivity over 5-HT$_{2A}$ receptors (5000−9000-fold). The benzylamine **21c** showed good selectivity for 5-HT$_{1D}$ receptors over 5-HT$_{1A}$ receptors (11-fold), and replacement of the triazole group with sulfonamide (**23a**) and oxazolidinone (**24a**) further improved 5-HT$_{1A}$/5-HT$_{1D}$ selectivity to 37- and 49-fold, respectively. Additionally, both **21c** and the oxazolidinone **24b** had >500-fold selectivity over 100 other GPCRs, ion channels, and proteins in a broader range of receptor and enzyme assays.[35]

Pharmacokinetics

Pharmacokinetic studies of a number of compounds presented in Tables 2 and 3 indicated that they had poor oral bioavailability in rats, and measurement of hepatic portal vein plasma concentrations after oral dosing revealed this to be a consequence of poor absorption

Figure 1. Overlay of **21a** (red), **21c** (black), **21n** (magenta), and **21o** (green) with van der Waals contacts shown. See text for details.

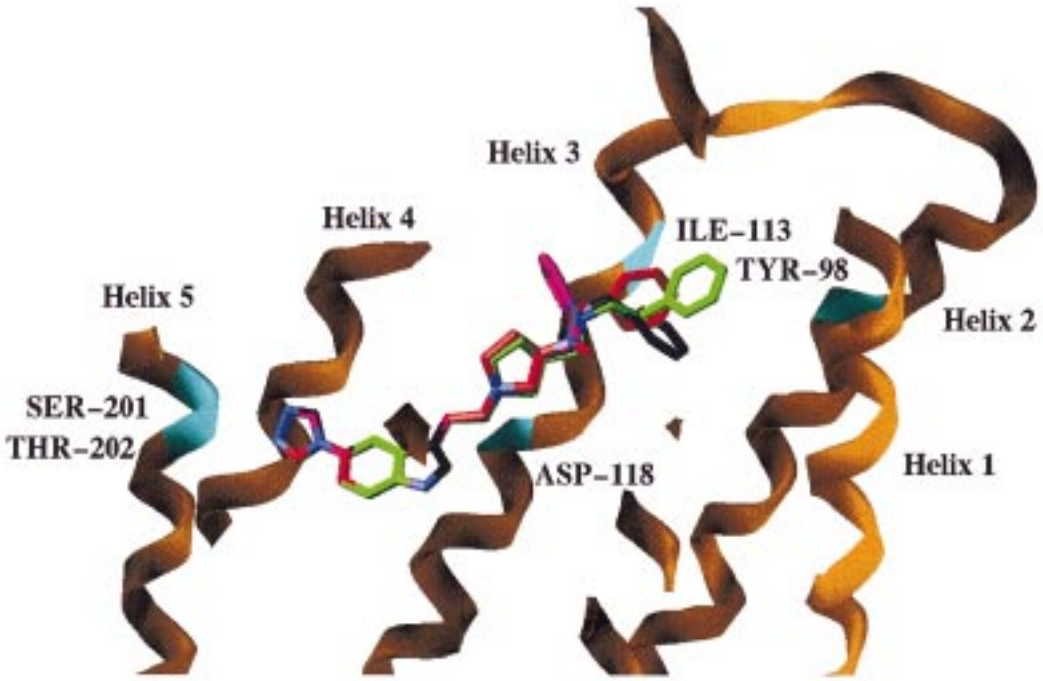


Figure 2. Proposed docking of **21a** (red), **21c** (black), **21n** (magenta), and **21o** (green) into the 5-HT_{1D} receptor model showing residues involved in binding. Helices 6 and 7 and hydrogens have been omitted for clarity.

rather than extensive first-pass metabolism. We have previously reported that L-741,604 (**4**) has lower bioavailability than Rizatriptan (**2**),[14] and an inference may be that the N4-linked triazole of compounds such as **21c** may be adversely affecting oral absorption perhaps due to a less favorable interaction with the cells of the intestinal membranes.[36] Consequently, two strategies were adopted to improve the oral absorption of compounds in the series. First, the N4-linked triazole at C-5 of the indole was replaced by alternative groups which retained the hydrogen-bonding properties required for high h5-HT_{1D}/h5-HT_{1B} affinity. A second approach was to increase lipophilicity and reduce the potential of the pyrrolidine C-3 substituent for hydrogen bonding by *N*-methylation in order to enhance absorption by a transcellular route. The effect of these two approaches is summarized in Table 6. Gratifyingly, the N1-linked triazole **22a** showed significantly improved hepatic portal vein plasma levels compared to **21c**. In addition, the more lipophilic *N*-methyl analogues **22c**,**d** showed enhanced absorption relative to the analogous N−H derivatives **22a**,**b**. The fully methylated oxazolidinone

Table 5. Comparison of 5-HT Receptor Affinities of Selected Pyrrolidine Derivatives

compd	IC$_{50}$ (nM)[a] h5-HT$_{1D}$	IC$_{50}$ (nM)[a] h5-HT$_{1B}$	IC$_{50}$ (nM)[a] h5-HT$_{1A}$	IC$_{50}$ (nM)[a] r5-HT$_{2A}$
21c	0.50	47	5.4	4400
23a	1.1	62	41	5800
24a	0.35	49	17	3000
24b	0.30 ± 0.06	50 ± 2.0	8.7	2200

[a] All values are the mean of at least two independent determinations performed in triplicate.

Table 6. Hepatic Portal Vein Plasma Concentrations after Oral Dosing of Selected Pyrrolidine Derivatives[a]

compd	plasma concn (ng/mL) 0.5 h postdose	plasma concn (ng/mL) 2 h postdose
21c	<5	<5
22a	<25	55 ± 17
22b	<10	52 ± 9
22c	39 ± 17	114 ± 31
22d	34 ± 14	117 ± 32
24a	<2	4 ± 2
25a	74 ± 24	280 ± 95

[a] For details of the experimental protocol, see text.

25a showed further improved plasma concentrations compared to the desmethyl analogue **24a**, and a full pharmacokinetic study revealed modest bioavailability in rats (9%).

Although this combination of strategies served to enhance oral absorption, none of the highly selective compounds had appreciable oral bioavailability in animals, and this prevented their further development. This issue has been addressed in further series of selective h5-HT$_{1D}$ agonists which will be the subject of forthcoming publications.

Conclusions

A novel series of high-affinity h5-HT$_{1D}$ receptor full agonists has been identified which has up to 163-fold selectivity over the h5-HT$_{1B}$ receptor. The results suggest that the h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors can be differentiated by appropriate substitution of the ligand in the region which binds to the aspartate residue. Whereas relatively bulky substituents are tolerated by the h5-HT$_{1D}$ receptor, the h5-HT$_{1B}$ receptor tolerates minimal substitution, suggesting that the binding pocket of the h5-HT$_{1D}$ receptor which accommodates benzylamine substitution is not present for the h5-HT$_{1B}$ receptor. The pyrrolidines **21c** and **24a,b** show very good selectivities over a range of other serotonin and non-serotonin receptors and therefore constitute useful new tools to define the role of h5-HT$_{1D}$ receptors in migraine.

Experimental Section

Chemical Methods: General Directions. Except where otherwise stated, the following procedures were adopted. ^{1}H NMR spectra were recorded at 250 or 360 MHz on Bruker AC 250 and AM 360 instruments, respectively. Mass spectra were recorded with a VG70-250 mass spectrometer. Anhydrous solvents were purchased from the Sigma-Aldrich Co. Ltd., Sureseal. All solutions were dried over magnesium sulfate or sodium sulfate and evaporated at reduced pressure on a Buchi rotary evaporator. Thin-layer chromatography and flash chromatography were performed on silica, with use of plates (Merck Art. No. 5719) and columns (40−63 μm silica gel). Microanalyses were performed by Butterworth Laboratories Ltd., Middlesex, U.K., and are within ±0.4% unless otherwise noted. Melting points are uncorrected.

General Procedure for the Preparation of *N*-(*tert*-Butyloxycarbonyl)pyrrolidines (*R*)-8a, (*S*)-8a, (*R*)-8b, and (*S*)-8b. (3*R*)-*N*-(*tert*-Butyloxycarbonyl)pyrrolidin-3-ol ((*R*)-8a). A mixture of (3*R*)-*N*-benzylpyrrolidin-3-ol (5.00 g, 28.2 mmol), di-*tert*-butyl dicarbonate (7.39 g, 33.8 mmol), methanol (200 mL), and water (20 mL) was hydrogenated over Pearlmans catalyst (0.55 g) in a Parr shake apparatus at 40 psi for 2 h. The catalyst was removed by filtration through Celite, and the solvents were evaporated in vacuo. The crude product was chromatogaphed on silica gel eluting with ethyl acetate/hexane (1:1) to give **(*R*)-8a** (4.55 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (9H, s, OC(Me)$_3$), 1.87−2.03 (2H, m, CH$_2$), 2.07 (1H, s, OH), 3.33−3.50 (4H, m, 2 of CH$_2$), 4.42−4.48 (1H, m, C*H*-OH).

(*R*)-8b: prepared from (3*R*)-*N*-[(*R*)-1-phenylethyl]-3-(hydroxymethyl)pyrrolidine[17] (100%); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.39 (9H, s, OC(Me)$_3$), 1.31−1.64 (2H, m, CH$_2$), 1.85 (1H, m, CH), 2.25 (1H, m, CH of CH$_2$), 2.95 (1H, dd, J = 10.7 and 7.0 Hz, CH of CH$_2$), 3.11−3.35 (4H, m, 2 of CH$_2$), 4.67 (1H, t, J = 5.3 Hz, OH).

General Procedure for the Preparation of 4-(Pyrrolidin-1-yl)butanal Dimethyl Acetals (*R*)-9a, (*S*)-9a, (*R*)-9b, and 29a,b. (3*R*)-4-[3-(Benzyloxy)pyrrolidin-1-yl]butanal Dimethyl Acetal ((*R*)-9a). A solution of **(*R*)-8a** (2.25 g, 12.0 mmol) in anhydrous THF (10 mL) was added dropwise to a slurry of sodium hydride (60% dispersion in oil, 0.63 g, 13.8 mmol) in THF (35 mL) at 0 °C under nitrogen and the mixture stirred for 0.3 h at 0 °C. A solution of benzyl bromide (2.37 g, 13.8 mmol) in THF (2 mL) was added and the mixture warmed to room temperature and stirred for 18 h. Water (20 mL) was added and the mixture extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. The crude product was chromatographed on silica gel eluting with MeOH/

Table 7. Physical Data for 3-[(Pyrrolidin-1-yl)alkyl]indoles[a]

compd	empirical formula	mp (°C)	compd	empirical formula	mp (°C)
11c	$C_{23}H_{25}N_5O\cdot(COOH)_2\cdot0.65H_2O\cdot0.025(Et_2O)$[b]	102−104	**21q**	$C_{25}H_{30}N_6\cdot2.5(COOH)_2\cdot0.6H_2O\cdot0.1(Et_2O)$[b]	191−193
21a	$C_{24}H_{28}N_6\cdot(CH_2COOH)_2\cdot0.6H_2O$	75−77	**21r**	$C_{25}H_{30}N_6O\cdot2.4(COOH)_2\cdot0.1H_2O$	158
21b	$C_{25}H_{30}N_6\cdot1.5(COOH)_2\cdot0.3H_2O$	116−117	**21s**	$C_{25}H_{30}N_6O\cdot2.4(COOH)_2\cdot0.1H_2O$	155
21d	$C_{24}H_{28}N_6\cdot2.5(COOH)_2\cdot0.5(Et_2O)$[b]	230−232	**21t**	$C_{26}H_{32}N_6\cdot2.45(COOH)_2\cdot0.1(Et_2O)$[b]	172−174
21e	$C_{26}H_{32}N_6\cdot2(COOH)_2\cdot0.5H_2O\cdot0.4(Et_2O)$[b]	90−94	**22a**	$C_{25}H_{30}N_6\cdot2.4(COOH)_2$	154−156
21f	$C_{23}H_{27}N_7\cdot3(COOH)_2\cdot0.5H_2O\cdot0.1(Et_2O)$[b]	218−220	**22b**	$C_{26}H_{32}N_6\cdot2.35(COOH)_2\cdot0.3H_2O\cdot0.1(Et_2O)$[b]	195−197
21g	$C_{23}H_{27}N_7\cdot3.3(COOH)_2\cdot0.2H_2O$	226	**22c**	$C_{26}H_{32}N_6\cdot2.5(COOH)_2$	154−155
21h	$C_{23}H_{27}N_7\cdot3(COOH)_2\cdot0.7H_2O\cdot0.2(Et_2O)$[b]	213−215	**22d**	$C_{27}H_{34}N_6\cdot2(COOH)_2\cdot0.17(Et_2O)$[b]	148−149
21i	$C_{22}H_{26}N_6O\cdot2.5(COOH)_2\cdot0.5H_2O$	229−231	**23a**	$C_{24}H_{32}N_4SO_2\cdot2.1(COOH)_2\cdot0.7(Et_2O)$[b]	224−226
21j	$C_{22}H_{26}N_6\cdot2.5(COOH)_2\cdot0.5H_2O$	205−207	**24a**	$C_{26}H_{32}N_4O_2\cdot3(COOH)_2$	196−197
21k	$C_{20}H_{26}N_6\cdot2.5(COOH)_2\cdot0.25H_2O\cdot0.2(MeOH)$[b]	232−234	**24b**	$C_{27}H_{34}N_4O_2\cdot2.4(COOH)_2$	115−117
21n	$C_{23}H_{26}N_6\cdot1.8(COOH)_2\cdot0.1H_2O$	145	**25a**	$C_{28}H_{36}N_4O_2\cdot1.5(COOH)_2\cdot0.5H_2O$	102−104
21o	$C_{25}H_{30}N_6\cdot2.5(COOH)_2\cdot H_2O$	189−190	**26**	$C_{25}H_{29}N_5O\cdot(COOH)_2\cdot1.4H_2O$	121−123
21p	$C_{25}H_{30}N_6\cdot2.5(COOH)_2\cdot0.5H_2O\cdot0.2(Et_2O)$[b]	192−194	**30a**	$C_{24}H_{27}N_5O\cdot1.5(CH_2COOH)_2\cdot0.4H_2O$	76−78

[a] All compounds were crystallized from MeOH, EtOH, ^{i}PrOH or mixtures of these with Et_2O and gave satisfactory microanalyses for C, H, and N. [b] ^{1}H NMR of these compounds suggested that the salt had crystallized with solvent.

CH_2Cl_2 (gradient 0:100 to 3:97) to give (3*R*)-*N*-(*tert*-butyloxycarbonyl)-3-(benzyloxy)pyrrolidine (2.53 g, 76%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (9H, s, $OC(Me)_3$), 1.87−2.11 (2H, m, CH_2), 3.42−3.50 (4H, m, 2 of CH_2), 4.13 (1H, m, C*H*OCH_2Ph), 4.53 (2H, s, OCH_2Ph), 7.26−7.39 (5H, m, Ph).

A solution of (3*R*)-*N*-(*tert*-butyloxycarbonyl)-3-(benzyloxy)-pyrrolidine (5.0 g, 18.0 mmol) in 90% formic acid (150 mL) was stirred at 0 °C for 0.3 h and then at room temperature for 2.5 h. The solvent was evaporated in vacuo and the residue neutralized by addition of saturated potassium carbonate solution and extracted with *n*-butanol (2 × 40 mL). The solvent was evaporated in vacuo and the residue azeotroped with ethanol (×2) and chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give (3*R*)-*N*(H)-3-(benzyloxy)-pyrrolidine (2.62 g, 82%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.85−1.93 (2H, m, CH_2), 2.79−2.89 (2H, m, CH_2), 3.07−3.17 (2H, m, CH_2), 4.11 (1H, m, C*H*OCH_2Ph), 4.53 (2H, s, OCH_2Ph), 7.24−7.38 (5H, m, Ph).

A mixture of (3*R*)-*N*(H)-3-(benzyloxy)pyrrolidine (2.60 g, 15.0 mmol), 4-chlorobutanal dimethyl acetal[18] (2.29 g, 15.0 mmol), and potassium carbonate (2.23 g, 16.0 mmol) in THF (40 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature, water (70 mL) was added, and the mixture was extracted with ethyl acetate (3 × 70 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo and the residue chromatographed on silica gel eluting with MeOH/CH_2Cl_2 (5:95) to give **(*R*)-9a** (1.9 g, 44%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.57−1.67 (4H, m, 2 of CH_2), 1.90 (1H, m, CH of CH_2), 2.10 (1H, m, CH of CH_2), 2.46−2.74 (5H, m, 2 of CH_2 and CH of CH_2), 2.89 (1H, dd, J = 10.3 and 6.1 Hz, CH of CH_2), 3.31 (6H, s, CH(O*Me*)$_2$), 4.14 (1H, m, C*H*OBn), 4.38 (1H, t, J = 5.2 Hz, C*H*(OMe)$_2$), 4.48 (2H, q, J = 11.9 Hz, OCH_2Ph), 7.24−7.38 (5H, m, Ph).

(*R*)-9b: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.24−1.56 (6H, m, 3 of CH_2), 1.82 (1H, m, CH), 2.21−2.55 (6H, m, 3 of CH_2), 3.20 (6H, s, CH(O*Me*)$_2$), 3.30 (2H, d, J = 7.1 Hz, CH_2OBn), 4.34 (1H, t, J = 5.3 Hz, C*H*(OMe)$_2$), 4.45 (2H, s, OCH_2Ph), 7.24−7.39 (5H, m, Ph).

29b: prepared from Boc-D-prolinol; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.56−1.90 (8H, m, 4 of CH_2), 2.17−2.30 (2H, m, 2 of CH), 2.64 (1H, m, CH), 2.86 (1H, m, CH), 3.15 (1H, m, CH), 3.31 (6H, s, CH(O*Me*)$_2$), 3.36 (1H, m, CH), 3.49 (1H, m, CH), 4.37 (1H, t, J = 5.4 Hz, C*H*(OMe)$_2$), 4.53 (2H, t, J = 12.2 Hz, CH_2Ph), 7.25−7.35 (5H, m, Ph).

4′-(Triazol-4-yl)phenylhydrazine (10). A mixture of 4′-aminoacetanilide (3.52 g, 23.4 mmol), *N*,*N*-dimethylformamide azine[37] (3.33 g, 23.4 mmol), and *p*-toluenesulfonic acid monohydrate (0.223 g, 1.17 mmol) in anhydrous toluene (100 mL) was heated at reflux for 17 h. The beige-colored precipitate was filtered off, washed with toluene and dichloromethane, and dried in vacuo to give 4′-(1,2,4-triazol-4-yl)acetanilide (4.29 g, 91%): ^{1}H NMR (250 MHz, MeOH-d_4/DMSO-d_6) δ 2.14 (3H, s, Me), 7.60 (2H, d, J = 8.8 Hz, 2 of Ar−H), 7.78 (2H, d, J = 8.8 Hz, 2 of Ar−H), 8.96 (2H, s, 2 of Ar−H).

A solution of 4′-(1,2,4-triazol-4-yl)acetanilide (4.91 g, 24.3 mmol) in 5 N HCl (100 mL) was heated at 125 °C for 1.5 h. The mixture was cooled to 0 °C, basified with concentrated aqueous NaOH solution, and extracted with dichloromethane (×5). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give 4′-(1,2,4-triazol-4-yl)aniline (2.94 g, 76%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.80 (2H, s, NH_2), 6.71 (2H, d, J = 8.8 Hz, 2 of Ar−H), 7.08 (2H, d, J = 8.8 Hz, 2 of Ar−H), 8.36 (2H, s, 2 of Ar−H).

A solution of sodium nitrite (0.69 g, 9.99 mmol) in water (8 mL) was added to a cooled (−21 °C) solution of 4′-(1,2,4-triazol-4-yl)aniline (1.60 g, 9.99 mmol) in concentrated HCl/H_2O (23 and 3 mL, respectively), at such a rate that the temperature did not exceed −10 °C. The mixture was stirred for 0.3 h and then filtered rapidly through a sinter, under vacuum. The filtrate was added to a cooled (−20 °C) solution of tin(II) chloride dihydrate (9.02 g, 40.0 mmol) in concentrated HCl (17 mL). The mixture was stirred at −20 °C for 0.25 h and then at room temperature for 1.25 h. The resulting solid was filtered off, washed with ether, and dried in vacuo. The crude product was dissolved in water, basified with concentrated aqueous NaOH, and extracted with ethyl acetate (×5). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to afford **10** (0.95 g, 54%): ^{1}H NMR (250 MHz, $CDCl_3$/MeOH-d_4) δ 3.98 (3H, br s, NH and NH_2), 6.97 (2H, d, J = 12.0 Hz, 2 of Ar−H), 7.25 (2H, J = 12.0 Hz, 2 of Ar−H), 8.48 (2H, s, 2 of Ar−H).

General Procedure for the Preparation of Indoles 11a,c,d, and 30a−c. (3*R*)-3-(Benzyloxy)-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine Hydrogen Oxalate Hemihydrate (11a). A solution of **10** (1.25 g, 7.1 mmol) and **(*R*)-9a** (1.90 g, 6.48 mmol) in 4% H_2SO_4 (25 mL) was heated at reflux for 48 h. The mixture was cooled to room temperature, basified with K_2CO_3, and extracted into ethyl acetate (×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (90:8:1) to give **11a** (0.50 g, 22%).The hydrogen oxalate hemihydrate salt was prepared. **11a**: mp 97−98 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.96−2.22 (2H, m, CH_2), 3.02−3.10 (2H, m, CH_2), 3.12−3.35 (6H, m, 3 of CH_2), 4.27 (1H, m, C*H*OBn), 4.50 (2H, s, CH_2Ph), 7.29−7.38 (7H, m, 7 of Ar−H), 7.52 (1H, d, J = 8.6 Hz, Ar−H), 7.88 (1H, d, J = 1.8 Hz, Ar−H), 9.02 (2H, s, 2 of Ar−H), 11.25 (1H, s, NH); MS *m*/*z* 388 $[MH]^+$. Anal. ($C_{23}H_{25}N_5O\cdot C_2H_2O_4\cdot 0.5H_2O$) C, H, N.

The following indoles were prepared using the general procedure.

(3*R*)-3-(Benzyloxymethyl)-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine hydrogen oxalate hemihydrate (11d): mp 145 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.71 (1H, m, CH of CH_2), 2.10 (1H, m, CH of CH_2), 2.66 (1H, m, CH), 3.04−3.50 (10H, m, 5 of CH_2), 4.49 (2H, s, OCH_2Ph), 7.27−7.40 (7H, m, 7 of Ar−H), 7.52 (1H, d, J = 8.6 Hz, Ar−H), 7.90 (1H, d, J = 2.0 Hz, Ar−H), 9.04 (2H, s, 2 of Ar−H), 11.30 (1H, s, NH); MS *m*/*z* 402 $[MH]^+$. Anal. ($C_{24}H_{27}N_5O\cdot C_2H_2O_4\cdot 0.6H_2O$) C, H, N.

(2*R*)-2-(Benzyloxymethyl)-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine sesquioxalate (30b): mp 114−116 °C; ^{1}H NMR (360 MHz, D_2O) δ 1.79 (1H, m, CH of CH_2), 2.03 (1H, m, CH of CH_2), 2.12−2.32 (2H, m, 2 of CH of CH_2), 3.10−3.44 (4H, m, 4 of CH), 3.67 (1H, m, CH), 3.77−3.82 (4H, m, 4 of CH), 4.32 (1H, d, J = 11.8 Hz, 1 of CH_2Ph), 4.36 (1H, d, J = 11.7 Hz, 1 of CH_2Ph), 7.10−7.17 (5H, m, Ph), 7.27 (1H, dd, J = 8.6 and 2.1 Hz, Ar−H), 7.38 (1H, s, Ar−H), 7.55 (1H, d, J = 1.9 Hz, Ar−H), 7.61 (1H, d, J = 8.7 Hz, Ar−H), 8.72 (2H, s, 2 of Ar−H); MS *m*/*z* 402 $[MH]^+$. Anal. ($C_{24}H_{27}N_5O\cdot 1.4(C_2H_2O_4)\cdot 0.1H_2O$) C, H, N. Optical purity 96.8% ee (measured on a Chiralpak AD column eluting with 30% EtOH in hexane/0.5% DEA at 1 mL/min; retention time of **30b** 5.4 min, retention time of **30a** 4.7 min).

(2*S*)-2-[(*N*-Benzyl-*N*-methylamino)methyl]-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine sesquisuccinate sesquihydrate (30c): mp 70−72 °C; ^{1}H NMR (360 MHz, D_2O) δ 1.74 (1H, m, CH of CH_2), 1.89 (1H, m, CH of CH_2), 2.12 (1H, m, CH of CH_2), 2.22 (3H, s, Me), 2.28 (1H, m, CH of CH_2), 2.68−2.79 (2H, m, CH_2), 3.12−3.76 (9H, m, CH and 4 of CH_2), 7.01−7.03 (2H, m, 2 of Ar−H), 7.15−7.21 (3H, m, 3 of Ar−H), 7.32 (1H, dd, J = 8.6 and 2.1 Hz, Ar−H), 7.47 (1H, s, Ar−H), 7.64 (1H, d, J = 2.1 Hz, Ar−H), 7.67 (1H, d, J = 8.6 Hz, Ar−H), 8.70 (2H, s, 2 of Ar−H); MS *m*/*z* 415 $[MH]^+$. Anal. ($C_{25}H_{30}N_6\cdot 1.5(C_4H_6O_4)\cdot 1.5H_2O$) C, H, N.

General Procedure for the Preparation of Indoles 11b,e. (3*R*)-3-Hydroxy-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine Hydrogen Oxalate Hydrate (11b). A mixture of **11a** (90 mg, 0.23 mmol), ammonium formate (81 mg, 1.3 mmol), and 10% palladium/carbon (90 mg) in methanol (10 mL) was heated at 60−65 °C for 6.5 h. The mixture was cooled to room temperature and filtered through Hyflo and the solvent evaporated in vacuo. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give **11b** (62 mg, 86%). The hydrogen oxalate salt was prepared. **11b**: mp 110−112 °C; ^{1}H NMR (360 MHz, D_2O) δ 1.96−2.44 (2H, m, CH_2), 3.17−3.90 (8H, m, 4 of CH_2), 4.65 (1H,

m, CH), 7.29 (1H, dd, J = 8.6 and 2.0 Hz, Ar−H), 7.44 (1H, s, Ar−H), 7.61 (1H, d, J = 8.6 Hz, Ar−H), 7.72 (1H, d, J = 1.9 Hz, Ar−H), 8.81 (2H, s, 2 of Ar−H); MS m/z 298 $[MH]^+$. Anal. ($C_{16}H_{19}N_5O \cdot C_2H_2O_4 \cdot H_2O \cdot 0.1C_4H_{10}O_2$) C, H, N. Optical purity 97.6% ee (measured on a Chiralpak AD column eluting with 10% EtOH in hexane/0.1% DEA at 2 mL/min; retention time of **11b** 12.2 min, retention time of enantiomer 10.6 min).

The following indole was prepared using the general procedure.

(3*R*)-3-(Hydroxymethyl)-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine hydrogen oxalate hemihydrate (11e): mp 120 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.68 (1H, m, CH of CH_2), 2.00 (1H, m, CH of CH_2), 2.44 (1H, m, CH), 2.92−3.48 (10H, m, 5 of CH_2), 7.33−7.40 (2H, m, 2 of Ar−H), 7.52 (1H, d, J = 8.6 Hz, Ar−H), 7.90 (1H, d, J = 2.0 Hz, Ar−H), 9.05 (2H, s, 2 of Ar−H); MS m/z 312 $[MH]^+$. Anal. ($C_{18}H_{21}N_5O \cdot C_2H_2O_4 \cdot 0.7H_2O$) C, H, N.

General Procedure for the Preparation of Mesylates 12a,b. (3*R*)-*N*-(*tert*-Butyloxycarbonyl)-3-(methylsulfonyloxymethyl)pyrrolidine ((*R*)-12b). A solution of methanesulfonyl chloride (3.37 g, 29.4 mmol) in CH_2Cl_2 was added dropwise to a solution of **(*R*)-8b** (5.4 g, 26.7 mmol) and triethylamine (2.97 g, 29.4 mmol) in CH_2Cl_2 at −15 °C under nitrogen. The mixture was warmed to room temperature and stirred for 16 h before adding saturated potassium carbonate solution (50 mL) and diluting with CH_2Cl_2 (100 mL). The aqueous was separated and extracted further with CH_2Cl_2 (2 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give **(*R*)-12b** (7.5 g, 100%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.46 (9H, s, OC(Me)$_3$), 1.73 (1H, m, CH of CH_2), 2.07 (1H, m, CH of CH_2), 2.65 (1H, m, CH), 3.04 (3H, s, Me), 3.08−3.62 (4H, m, 2 of CH_2), 4.11−4.33 (2H, m, CH_2OMs).

General Procedure for the Preparation of Amines 13a,b. General Method A. (3*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-[(*N*-benzylamino)methyl]pyrrolidine ((*S*)-13b) (R^1 = CH_2Ph, R^2 = H). This procedure illustrates the general method for the preparation of adducts of **12a**,**b** with benzylamine, *N*-benzylmethylamine, 2-(aminomethyl)pyridine, 3-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, 2-furanmethylamine, 3-furanmethylamine,[38] (*R*)-α-methylbenzylamine, (*S*)-α-methylbenzylamine, and phenethylamine. A solution of **(*R*)-12b** (5.00 g, 17.9 mmol) and benzylamine (9.8 mL, 90 mmol) in toluene (25 mL) was heated at reflux for 18 h. The mixture was evaporated under high vacuum and the residue taken up in ethyl acetate (200 mL) and washed with water (×3). The organic layer was dried ($MgSO_4$) and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (98:2) to give **(*S*)-13b (R^1 = CH_2Ph, R^2 = H)** (4.9 g, 94%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (9H, s, OC(Me)$_3$), 1.58 (1H, m, CH of CH_2), 2.00 (1H, m, CH of CH_2), 2.33 (1H, m, CH), 2.60−2.68 (2H, m, CH_2), 3.00 (1H, m, CH of CH_2), 3.18−3.60 (3H, m, CH_2 and CH of CH_2), 3.80 (2H, s, CH_2Ph), 7.26−7.36 (5H, m, Ph).

General Procedure for the Preparation of Amines 13b. General Method B. (3*S*)-*N*-(*tert*-Butyloxycarbonyl)-3-[[(*R*)-α-(hydroxymethyl)benzyl]aminomethyl]pyrrolidine ((*S*)-13b) (R^1 = (*R*)-α-(hydroxymethyl)benzyl, R^2 = H). This procedure illustrates the general method for the preparation of adducts of **12b** with (*R*)-(−)-phenylglycinol, (*S*)-(+)-phenylglycinol, allylamine, aniline, and α,α-dimethylbenzylamine.[39] A solution of (*R*)-(−)-phenylglycinol (2.20 g, 16.1 mmol) and **(*R*)-12b** (1.00 g, 3.58 mmol) in toluene (20 mL) was heated at 150 °C for 6 h in a sealed pressure tube. The solvent was removed in vacuo and the residue taken up into ethyl acetate (200 mL) and washed with water (×4). The organic layer was dried ($MgSO_4$) and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH (97:3) to give **(*S*)-13b (R^1 = (*R*)-α-(hydroxymethyl)benzyl, R^2 = H)** (1.00 g, 87%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (9H, s, OC(Me)$_3$), 1.52−2.60 (5H, m, CH and 2 of CH_2), 2.90−3.76 (7H, m, CH and 3 of CH_2), 7.25−7.39 (5H, m, Ph).

(3*R*)-*N*-(*tert*-Butyloxycarbonyl)-3-[(*N*-methyl-*N*-(*S*)-(α-methylbenzyl)amino)methyl]pyrrolidine ((*R*)-13b) (R^1 = (*S*)-α-methylbenzyl, R^2 = Me). Glacial acetic acid (0.9 mL, 15.7 mmol) and sodium cyanoborohydride (0.495 g, 7.88 mmol) were added successively to a stirred solution of **(*S*)-13b (R^1 = (*S*)-α-methylbenzyl, R^2 = H)** (1.92 g, 6.31 mmol) in methanol (150 mL) at 0 °C. A solution of formaldehyde (0.623 g of a 38% w/v solution, 7.88 mmol) in methanol (50 mL) was added dropwise over 0.1 h. The mixture was stirred at 0 °C for 4.5 h and then at room temperature for 1.25 h before adding saturated potassium carbonate solution (25 mL) and evaporating the solvent in vacuo. The residue was taken up in ethyl acetate (100 mL), washed with water (×1), saturated potassium carbonate solution (×1), and brine (×1), dried ($MgSO_4$), and evaporated in vacuo. The crude material was chromatographed on silica gel, eluting wtih CH_2Cl_2/MeOH (95:5) to give **(*R*)-13b (R^1 = (*S*)-α-methylbenzyl, R^2 = Me)** (2.02 g, 100%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (3H, d, J = 6.7 Hz, Me), 1.44 (9H, s, OC(Me)$_3$), 1.64 (1H, m, CH), 1.93 (1H, sextet, J = 6.1 Hz, CH), 2.19−2.36 (6H, m, Me and 3 of CH), 2.89 (1H, m, CH), 3.18−3.57 (4H, m, 4 of CH), 7.20−7.31 (5H, m, Ph).

General Procedure for the Preparation of Amines 14a,b. (3*S*)-*N*(H)-3-[(*N*-Benzylamino)methyl]pyrrolidine ((*S*)-14b) (R^1 = CH_2Ph, R^2 = H). A solution of **(*S*)-13b (R^1 = CH_2Ph, R^2 = H)** (4.90 g, 16.8 mmol) in 90% formic acid (90 mL) was stirred at room temperature for 18.5 h. Methanol was added, and the solvents were removed in vacuo. The residue was dissolved in a minimum volume of water, basified with saturated potassium carbonate solution, and extracted with *n*-butanol (3 × 100 mL). The combined extracts were evaporated in vacuo and the inorganics removed by trituration with CH_2Cl_2 and filtration. The filtrate was dried ($MgSO_4$) and evaporated in vacuo to give **(*S*)-14b (R^1 = CH_2Ph, R^2 = H)** (3.24 g, 100%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.39 (1H, m, CH of CH_2), 1.94 (1H, m, CH of CH_2), 2.25 (1H, septet, J = 7.3 Hz, CH), 2.56−2.65 (3H, m, CH_2 and CH of CH_2), 2.87−2.98 (2H, m, CH_2), 3.09 (1H, dd, J = 10.9 and 7.6 Hz, CH of CH_2), 3.79 (2H, m, CH_2Ph), 7.22−7.39 (5H, m, Ph).

General Procedure for the Preparation of Iodoanilines 16. 2-Iodo-4-(1,2,4-triazol-4-yl)aniline. A solution of iodine monochloride (22.3 g, 137 mmol) in methanol (300 mL) was added over 0.75 h to a stirred suspension of 4-(1,2,4-triazol-4-yl)aniline (20.0 g, 125 mmol) and calcium carbonate (25.0 g, 250 mmol) in methanol (800 mL) at −30 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 16 h before filtering through a pad of Celite. The filtrate was evaporated in vacuo and the residue dissolved in ethyl acetate and washed with 50% w/w sodium bisulfite solution. The precipitated product was filtered off, the ethyl acetate dried ($MgSO_4$), and evaporated in vacuo, and the resultant solid combined with the precipitated material to give the title product (23.9 g, 67%): mp 202−203 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.54 (2H, br s, NH_2), 6.84 (1H, d, J = 8.7 Hz, Ar−H), 7.38 (1H, dd, J = 2.6 and 8.7 Hz, Ar−H), 7.87 (1H, d, J = 2.5 Hz, Ar−H), 8.92 (2H, s, 2 of Ar−H).

2-Iodo-4-[(*N*-methylamino)sulfonylmethyl]aniline: prepared from 4-[(*N*-methylamino)sulfonylmethyl]aniline;[22a,23a] ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.51 (3H, d, J = 7.4 Hz, Me), 4.11 (2H, s, CH_2), 5.29 (2H, s, NH_2), 6.72 (1H, d, J = 8.3 Hz, Ar−H), 6.81 (1H, q, J = 7.4 Hz, NH), 7.06 (1H, dd, J = 2.0 and 8.3 Hz, Ar−H), 7.53 (1H, d, J = 2.0 Hz, Ar−H).

(*S*)-4-(3-Iodo-4-aminobenzyl)-1,3-oxazolidin-2-one: prepared from (*S*)-4-(4-aminobenzyl)-1,3-oxazolidin-2-one;[22b,23a] ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.55−2.60 (2H, m, CH_2), 3.90−3.99 (2H, m, CH_2O), 4.19−4.28 (1H, m, C*H*NH), 5.09 (2H, s, NH_2), 6.69 (1H, d, J = 8.2 Hz, Ar−H), 6.95 (1H, dd, J = 1.9 and 8.2 Hz, Ar−H), 7.44 (1H, d, J = 1.9 Hz, Ar−H), 7.74 (1H, s, NH).

(*S*)-3-Methyl-4-(3-iodo-4-aminobenzyl)-1,3-oxazolidin-2-one: prepared from (*S*)-3-methyl-4-(4-aminobenzyl)-1,3-oxazolidin-2-one;[22c,23a] ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.45−2.53 (1H, m, CH of CH_2), 2.72 (3H, s, Me), 2.82 (1H, dd, J = 14.4 and 3.7 Hz, CH of CH_2), 3.78−3.89 (2H, m, CH_2O), 4.12 (1H, m, CHN), 5.07 (2H, br s, NH_2), 6.66 (1H, d, J = 8.2 Hz, Ar−H), 6.92 (1H, dd, J = 8.2 and 2.0 Hz, Ar−H), 7.43 (1H, d, J = 1.9 Hz, Ar−H); MS m/z 333 $[MH]^+$.

General Procedure for the Preparation of Tryptophols 19. 2-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]ethyl Alcohol. A mixture of 2-iodo-4-(1,2,4-triazol-4-yl)aniline (35.0 g, 122 mmol), 1,4-bis(triethylsilyl)-3-butyn-1-ol[23] (47.5 g, 159 mmol), sodium carbonate (65.1 g, 614 mmol), and magnesium sulfate (22.4 g, 186 mmol) in DMF (350 mL) was degassed with nitrogen for 0.5 h. A suspension of palladium(II) acetate (1.4 g, 6.2 mmol) in DMF was added and the mixture heated at 110 °C for 16 h. The reaction mixture was diluted with ethyl acetate (300 mL) and filtered to remove the inorganic solids. The filtrate was diluted with water (200 mL) and filtered through a pad of Celite. The organic layer was separated and the aqueous layer extracted with ethyl acetate (×1) and methanol/dichloromethane (5:95) (×2). The combined organic layers were evaporated in vacuo, the residue was taken up in methanol (420 mL), and 5 N HCl (150 mL) was added. After the mixture stirred at room temperature for 3 h, 5 N HCl (130 mL) was added and the mixture stirred at room temperature for a further 16 h. The methanol was evaporated in vacuo and the residue basified to pH 9 with 4 N sodium hydroxide solution. The mixture was stored at 0 °C for 72 h and the resulting precipitate filtered off and washed successively with cold water and cold 2-propanol. A second crop was obtained by evaporation in vacuo of the mother liquors to approximately half-volume and recooling to 0 °C. The combined batches were dried in vacuo to give the title product (17.3 g, 61%): ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.88 (2H, t, J = 7.2 Hz, CH_2), 3.68 (2H, m, CH_2), 4.66 (1H, br s, OH), 7.23−7.32 (2H, m, 2 of Ar−H), 7.48 (1H, d, J = 8.5 Hz, Ar−H), 7.81 (1H, d, J = 2.1 Hz, Ar−H), 9.03 (2H, s, 2 of Ar−H), 11.2 (1H, br s, NH).

2-{5-[(*N*-Methylamino)sulfonylmethyl]-1*H*-indol-3-yl}-ethyl alcohol: mp 114−116 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.54 (3H, d, J = 4.8 Hz, Me), 2.83 (2H, t, J = 7.5 Hz, CH_2CH$_2$OH), 3.60−3.69 (2H, m, CH$_2$CH_2OH), 4.34 (2H, s, CH_2), 4.65 (1H, t, J = 5.4 Hz, OH), 6.78 (1H, q, J = 4.8 Hz, MeN*H*), 7.06 (1H, dd, J = 2.2 and 8.3 Hz, Ar−H), 7.16 (1H, d, J = 2.2 Hz, Ar−H), 7.31 (1H, d, J = 8.3 Hz, Ar−H), 7.51 (1H, s, Ar−H), 10.86 (1H, s, NH).

(*S*)-2-[5-(2-Oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethyl alcohol: ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.74−2.91 (4H, m, 2 of CH_2), 3.64 (2H, t, J = 7.3 Hz, CH_2), 4.00−4.08 (2H, m, CH_2), 4.23 (1H, m, CH), 6.92 (1H, dd, J = 1.4 and 8.2 Hz, Ar−H), 7.10 (1H, s, Ar−H), 7.25 (1H, d, J = 8.2 Hz, Ar−H), 7.36 (1H, s, Ar−H), 7.75 (1H, s, NH), 10.69 (1H, s, NH).

(*S*)-2-[5-(3-Methyl-2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethyl alcohol: ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.72−2.84 (6H, m, Me, CH_2 and CH of CH_2), 3.13 (1H, dd, J = 3.8 and 13.5 Hz, CH of CH_2), 3.61−3.67 (2H, m, CH_2), 3.94−4.02 (2H, m, CH_2), 4.14 (1H, m, CH), 4.58 (1H, t, J = 5.3 Hz, OH), 6.93 (1H, dd, J = 1.5 and 8.3 Hz, Ar−H), 7.10 (1H, d, J = 1.5 Hz, Ar−H), 7.26 (1H, d, J = 8.3 Hz, Ar−H), 7.38 (1H, s, Ar−H), 10.72 (1H, s, NH).

3-[5-(1,2,4-Triazol-4-yl)-1*H*-indol-3-yl]propyl alcohol: prepared from 2-iodo-4-(1,2,4-triazol-4-yl)aniline and 1,5-bis-(triethylsilyl)-4-pentyn-1-ol;[23b] mp 205−207 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.81 (2H, quintet, J = 7.5 Hz, CH_2), 2.74 (2H, t, J = 7.6 Hz, CH_2), 3.47 (2H, m, CH_2), 4.42 (1H, t, J = 5.2 Hz, OH), 7.26−7.31 (2H, m, 2 of Ar−H), 7.47 (1H, d, J = 8.7 Hz, Ar−H), 7.77 (1H, d, J = 2.1 Hz, Ar−H), 9.01 (2H, s, 2 of Ar−H), 11.05 (1H, br s, NH); MS m/z 243 [MH]$^+$.

General Procedure for the Preparation of Pyrrolidines 21a−k,n−t, 22a−d, 23a, 24a,b, and 25a. (3*S*)-3-[(*N*-Benzylamino)methyl]-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine 2.6 Hydrogen Oxalate (21c). Methanesulfonyl chloride (0.97 mL, 12.6 mmol) was added dropwise to a stirred suspension of 2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl alcohol (1.91 g, 8.38 mmol) in pyridine (60 mL) at −20 °C under nitrogen. The mixture was stirred at −20 °C for 0.5 h and then allowed to warm slowly to room temperature and stirred for 2 h. The solvent was evaporated in vacuo and the residue partitioned between dichloromethane (75 mL) and water (100 mL). The aqueous was separated and reextracted with dichloromethane (2 × 75 mL), and the combined extracts were dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography of the residue on silica gel, eluting with methanol/dichloromethane (10:90) gave **20** (1.50 g, 60%). A solution of **(*S*)-14b (R^1 = CH$_2$Ph, R^2 = H)** (1.119 g, 5.881 mmol) in IPA (25 mL) was added to a stirred mixture of **20** (1.060 g, 3.460 mmol) and potassium carbonate (1.435 g, 10.38 mmol) in IPA (80 mL) at room temperature under nitrogen. The mixture was heated at reflux for 4 h and then cooled to room temperature and the solvent evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and water and the aqueous layer separated and reextracted with CH_2Cl_2 (×1). The combined organic layers were washed with water (×1), dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1), to give **21c** (0.774 g, 53%). The dihydrogen oxalate salt was prepared. **21c**: mp 228−230 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.76 (1H, m, CH of CH_2), 2.17 (1H, m, CH of CH_2), 2.73 (1H, m, CH), 3.00−3.11 (5H, m, CH and 2 of CH_2), 3.34−3.60 (5H, m, CH and 2 of CH_2), 4.13 (2H, s, CH_2Ph), 7.35−7.54 (8H, m, 8 of Ar−H), 7.90 (1H, s, Ar−H), 9.04 (2H, s, 2 of Ar−H), 11.29 (1H, br s, NH); MS m/z 401 [MH]$^+$. Anal. ($C_{24}H_{28}N_6$·2.6(COOH)$_2$·0.1H_2O) C, H, N. Optical purity >96% ee (measured on a Chiralpak AD column eluting with 15% IPA in hexane/0.1% DEA at 2 mL/min; retention time of **21c** 19.0 min, retention time of **21d** 22.3 min).

(3*S*)-3-{[4-(Acetylamino)benzylamino]methyl}-1-{[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine 2.6 Hydrogen Oxalate (21l). A mixture of **21c** (277 mg, 0.639 mmol), ammonium formate (218 mg, 3.46 mmol), and 10% palladium/carbon (280 mg) in methanol (20 mL) was stirred at 62 °C under nitrogen for 0.75 h. The mixture was cooled to room temperature and filtered through a pad of Celite and the solvent evaporated in vacuo. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1) to give the required primary amine (145 mg, 68%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.54 (1H, m, CH of CH_2), 2.09 (1H, m, CH of CH_2), 2.29−2.41 (2H, m, 2 of CH), 2.63−3.02 (9H, m, CH and 4 of CH_2), 7.14 (1H, dd, J = 2.1 and 8.6 Hz, Ar−H), 7.21 (1H, s, Ar−H), 7.49 (1H, d, J = 8.6 Hz, Ar−H), 7.60 (1H, d, J = 2.1 Hz, Ar−H), 8.54 (2H, s, 2 of Ar−H).

A solution of the amine (140 mg, 0.452 mmol) in ethanol (10 mL) was treated with *p*-acetamidobenzaldehyde (74 mg, 0.45 mmol) and the mixture stirred at room temperature for 16 h. Sodium borohydride (17 mg, 0.46 mmol) was added and the solution stirred for a further 1 h. The solvent was evaporated in vacuo and the residue taken up in water and acidified with 2 N HCl. The mixture was then basified with saturated potassium carbonate solution and extracted with ethyl acetate (×4). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (70:8:1) to give **21l** (73 mg, 35%). The dihydrogen oxalate salt was prepared. **21l**: mp 197−199 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.76 (1H, m, CH of CH_2), 2.05 (3H, s, Me), 2.19 (1H, m, CH of CH_2), 2.62−3.58 (11H, m, CH and 5 of CH_2), 4.06 (2H, s, CH_2N), 7.34−7.42 (4H, m, 4 of Ar−H), 7.52 (1H, d, J = 8.6 Hz, Ar−H), 7.61 (2H, d, J = 8.4 Hz, 2 of Ar−H), 7.90 (1H, d, J = 2.0 Hz, Ar−H), 9.05 (2H, s, 2 of Ar−H), 10.08 (1H, s, NH), 11.30 (1H, s, NH); MS m/z 458 [MH]$^+$. Anal. ($C_{26}H_{31}N_7O$·2.6(COOH)$_2$·0.1H_2O) C, H, N.

(3*S*)-3-[(*N*-Acetyl-*N*-benzylamino)methyl-1-{2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethyl}pyrrolidine Dihydrogen Oxalate (21m). Acetyl chloride (0.024 mL, 0.34 mmol) was added to a stirred solution of **21c** (114 mg, 0.285 mmol) and triethylamine (0.048 mL, 0.34 mmol) in CH_2Cl_2 (5 mL) at −30 °C under nitrogen. The mixture was warmed gradually to 0 °C over 2.5 h and then stirred at room temperature for 2.25 h. Water was added, and the mixture was basified with saturated potassium carbonate solution and extracted with CH_2Cl_2 (×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1), to give **21m** (58 mg, 46%). The dihydrogen oxalate salt was prepared. **21m**: mp 132−134 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.69 (1H, m, CH of CH_2), 1.98−2.12 (4H, m, Me and CH of CH_2),

2.66 (1H, m, CH), 2.98−3.11 (3H, m, CH of CH_2 and CH_2), 3.26−3.44 (7H, m, CH of CH_2 and 3 of CH_2), 4.59 (2H, s, CH_2-Ph), 7.19−7.36 (7H, m, 7 of Ar−H), 7.52 (1H, d, J = 8.6 Hz, Ar−H), 7.82 (1H, s, Ar−H), 8.90 (2H, s, 2 of Ar−H), 11.11 (1H, br s, NH); MS m/z 443 $[MH]^+$. Anal. ($C_{26}H_{30}N_6O\cdot1.9(COOH)_2$) C, H, N.

(2*S*)-*N*(H)-2-[(*N*-Benzyl-*N*-methylamino)methyl]pyrrolidine (28c): prepared from Boc-L-prolinol using the general procedures; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (1H, m, CH of CH_2), 1.54−1.89 (3H, m, CH_2 and CH of CH_2), 2.13−2.38 (4H, m including s at δ 2.17, Me and CH), 2.52−2.81 (3H, m, 3 of CH), 3.20−3.55 (3H, m, CH and CH_2Ph), 7.12−7.35 (5H, m, Ph).

(2*S*)-4-{3-[(*N*-Benzyl-*N*-methylamino)methyl]pyrrolidin-1-yl}butanal Dimethyl Acetal (29c). A mixture of **28c** (1.73 g, 8.48 mmol), 4-chlorobutanal dimethyl acetal[18] (1.29 g, 8.48 mmol), sodium iodide (1.27 g, 8.48 mmol), and sodium carbonate (0.99 g, 9.33 mmol) in DME (20 mL) was heated at reflux for 18 h. The mixture was cooled to room temperature, water was added, and the mixture was extracted with ethyl acetate (4 × 50 mL) and dichloromethane (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give **29c** (1.54 g, 57%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49−1.76 (8H, m, 4 of CH_2), 1.89−2.36 (6H, m including s at δ 2.20, Me and 3 of CH), 2.44−2.54 (2H, m, 2 of CH), 2.85 (1H, m, CH), 3.13 (1H, m, CH), 3.31 (6H, s, 2 of MeO), 3.42 (1H, d, J = 13.1 Hz, CH of CH_2Ph), 3.57 (1H, d, J = 13.1 Hz, CH of CH_2Ph), 4.38 (1H, t, J = 5.4 Hz, CH(OMe)$_2$), 7.20−7.31 (5H, m, 5 of Ar−H).

Pharmacokinetic Methods. For each compound studied, eight rats (deprived of food for at least 12 h and weighing approximately 300 g) were assigned to either a 0.5- or 2-h blood sampling time (four rats per time point). The rats were dosed orally (3 mg/kg and 5 mL/kg dose volume) with an aqueous formulation of the test compound. Each rat was anesthetized with isoflurane at its preselected blood sampling time point, and blood samples were taken from the hepatic portal vein (typically 0.5 mL). Plasma was separated from the blood by centrifugation and stored at −20 °C until analysis. Extracts of plasma were prepared either by liquid−liquid extraction or solid-phase extraction and were analyzed by reversed-phase HPLC employing UV or fluorescence detection.

Biochemical Methods. 1. h5-HT$_{1D}$/h5-HT$_{1B}$ Radioligand Binding. Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors were harvested in PBS, homogenized in ice-cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron, and centrifuged at 48000g at 4 °C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10-min incubation at 37 °C. Finally the tissue was recentrifuged at 48000g, 4 °C for 11 min, and the pellet resuspended in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, $CaCl_2$ 4, ascorbate 0.1%, pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg of protein/mL). Incubations were carried out for 30 min at 37 °C in the presence of 0.02−150 nM [^{3}H]-5-HT for saturation studies or 2−5 nM [^{3}H]-5-HT for displacement studies. The final assay volume was 1 mL. 5-HT (10 μM) was used to define nonspecific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/0.5% Triton X) followed by 2 × 4-mL washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by nonlinear, least-squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. IC_{50} values calculated were the mean of at least two independent determinations performed in duplicate.

2. h5-HT$_{1D}$/h5-HT$_{1B}$ GTPγS Binding. Studies were performed essentially as described in *Br. J. Pharmacol.* **1993**, *109*, 1120. CHO clonal cell lines expressing the human cloned 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors were harvested in PBS and homogenized using a Kinematica polytron in ice-cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40000g, 4 °C for 15 min. The pellet was then resuspended in ice-cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature, and recentrifuged at 40000g, 4 °C for 15−25 min. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, $MgCl_2$ 10, pargyline 0.01, ascorbate 0.1%, pH 7.4 at room temperature) at a concentration of 40 μg of protein/mL for the h5-HT$_{1D}$ receptor transfected cells and 40−50 μg of protein/mL for the h5-HT$_{1B}$ receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 mL, with GDP (100 μM for h5-HT$_{1D}$ receptor transfected cells, 30 μM for the h5-HT$_{1B}$ receptor transfected cells) and test compound at 30 °C for 20 min and then transferred to ice for a further 15 min. [^{35}S]GTPγS was then added at a final concentration of 100 pM, and the samples were incubated for 30 min at 30 °C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washing with 5 mL of water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a nonlinear, least-squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Values calculated were the mean of at least two independent determinations.

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(34) Representative data: **21c** EC_{50} h5-HT_{1D} 0.8 nM, h5-HT_{1B} 463 nM; **24b** EC_{50} h5-HT_{1D} 0.50 nM, h5-HT_{1B} 910 nM.
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