Synthesis and Biological Activity of 3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-methyl]-1*H*-indole and Analogues: Agonists for the 5-HT_{1D} Receptor

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A novel series of 5-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)tryptamines was designed, synthesized, and evaluated as 5-HT_{1D} receptor agonists. Compounds such as **8d,f,k** were identified which had comparable affinity, potency, and receptor selectivity to that of the antimigraine drug sumatriptan. Both **8d,k** were found to be well absorbed in the rat with oral bioavailabilities of 66% and 62%, respectively. Additionally, **8d** was found to be selective over other non-serotonergic receptors and exhibited relatively low central nervous system penetration.

Introduction

Our knowledge and understanding of the serotonin (5-hydroxytryptamine, 5-HT) receptor system has been revolutionized in recent years through the extensive use of modern molecular biology and traditional biochemical and pharmacological techniques. In addition, the heterogeneity of this receptor (super)family,[1] with some 14 members now having been identified, offers the possibility of discovering selective ligands for each of these receptor subtypes to further delineate their role in several clinical disorders.[2] With the exception of the 5-HT_3 receptor, the other members have been shown, or are considered, to be part of the G-protein coupled receptor (GPCR) superfamily. Although pharmacophores have been generated for several of these subtypes,[3] a deeper understanding of the receptor topology and receptor activation is beginning to emerge through the combined utilization of site-directed mutagenesis[4] and receptor modeling.[3e,5]

The recent discovery that a selective 5-HT_{1D} receptor agonist such as sumatriptan (**4**) offers a new and clinically effective treatment for migraine headache[6] has intensified research in this area.[7] Although sumatriptan has been shown to be a selective vasoconstrictor of the cranial vasculature, doubts still exist about the mechanism of its antimigraine action.[8] On the basis of a simple analysis of the known 5-HT_{1D} receptor agonists **1**–**4**, we recently reported[9] that certain aromatic heterocycles were viable replacements for the hydrogen bond donor and/or acceptor groups attached to C-5 of these tryptamines. The previous study also allowed us to conclude that an H-bond acceptor, and not a donor, group was required for effective binding and activation of the 5-HT_{1D} receptor. Compounds such as the oxadiazolyl- and (aminothiadiazolyl)tryptamines **5** and **6**, respectively, are among the most potent agonists reported for this receptor subtype. Interestingly, **6** proved to be some 50-fold more potent in a functional assay than the corresponding oxadiazole analogue **7**.[10] These observations led us to consider a series of 5-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)tryptamines, **8**, as worthwhile targets, and herein we report on their synthesis and biological activity. As previously described,[9] compounds were sought which had high potency and receptor selectivity, good oral bioavailability, and low central nervous system (CNS) penetration. By analogy with sumatriptan, a relatively low log *D* was expected for the 5-(1,1-dioxo-1,2,5-thiadiazolidin-2-yl)tryptamines **8**, a property which could be advantageous in avoiding trespassing of the blood brain barrier. The majority of the compounds were evaluated as the *N,N*-dimethylamino derivatives because they were envisaged to have increased metabolic stability in biological fluids when compared to their primary amine analogues.

Chemistry

Three different approaches to the synthesis of the required substituted tryptamines **8** were developed in our laboratories. All of them required the utilization of the appropriately substituted cyclic sulfamides **10**, which could either be elaborated to the final product in a linear sequence or in a convergent manner. The majority of these sulfamides, **10a**–**i**, were easily accessible by the condensation of the corresponding diamines **9a**–**i** with sulfamide itself in refluxing pyridine (Scheme 1).[11] The reaction proceeds well with *N*-monoalkylated ethylenediamines except for the *N*-*tert*-butyl case, **9e**, probably due to steric congestion. Contrary to the reported literature,[12] the condensation can be achieved, albeit in low yield, with ethylenediamine itself. In spite of this low isolated yield of **10a**, the method is still comparable to the two-step procedure of Preiss.[13] When compared to ethylenediamine, (±)-2-methylethylenediamine and 2,2-dimethylethylenediamine afforded much better (50% and 85%) yields of the thiadiazolidine 1,1-dioxides **10g,h**, indicative of a favorable *gem*-(di)methyl effect.[14] The corresponding 6-membered analogue **10i** was also efficiently prepared by the above method. Cyclic sulfamides **10a,e** were also synthesized by the improved procedure shown in Scheme 2. Thus, reaction

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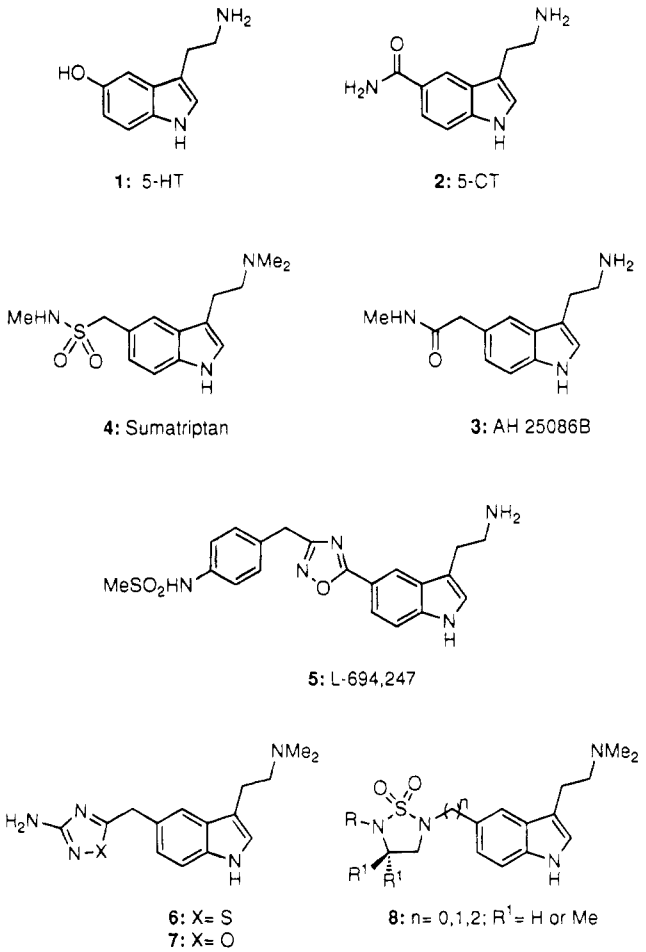
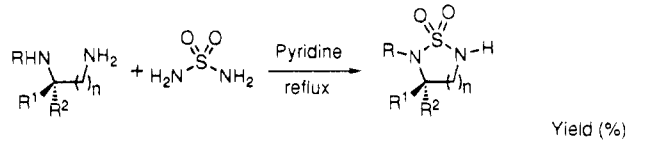
Chart 1

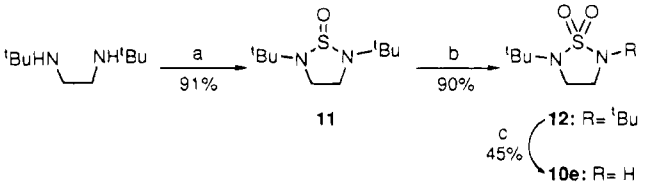


Scheme 1



	Yield (%)
10a: n= 1; R= R^1=R^2= H	11
10b: n= 1; R= Me; R^1= R^2= H	68
10c: n= 1; R= Et; R^1=R^2= H	59
10d: n= 1; R= ^{i}Pr; R^1=R^2= H	41
10e: n= 1; R= ^{t}Bu; R^1=R^2= H	13
10f: n= 1; R= Bn; R^1=R^2= H	79
10g: n= 1; R= R^1= H; R^2= Me	50
10h: n= 1; R= H; R^1= R^2= Me	85
10i: n= 2; R=Me; R^1=R^2= H	72

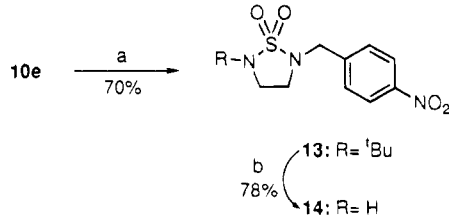
Scheme 2[a]



[a] Reagents: (a) $SOCl_2$, Et_3N, CH_2Cl_2, −78−25 °C; (b) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4−MeCN−H_2O, 0 °C; (c) TMSI, CH_2Cl_2, 25 °C.

of *N,N'*-di-*tert*-butylethylenediamine with thionyl chloride at low temperature[15] cleanly afforded 1,2,5-thiadiazolidine 1-oxide derivative **11** which was converted to the dioxo analogue **12** using Sharpless oxidation.[16] Reaction of **12** with TMSI at room temperature afforded **10e** in 45% yield together with 14% of **10a** and recovered starting material. Conversion of **12** into **10a** by TFA treatment is a known process.[13] The more complex thiadiazolidine 1,1-dioxide derivative **14** was synthesized as shown in Scheme 3.

Scheme 3[a]

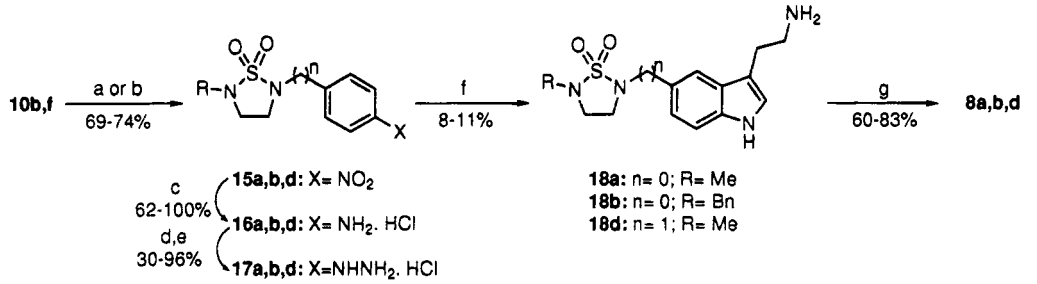


[a] Reagents: (a) *p*-nitrobenzyl bromide, K_2CO_3, DMF, 25 °C; (b) TFA−CH_2Cl_2, 25 °C.

The Fischer Approach. It was envisaged in the first instance that tryptamines **8** could be easily prepared by Fischer indolization[17] of suitable arylhydrazines which would in turn be accessible in a few steps from the cyclic sulfamides **10**. In practice, although this strategy produced the first compounds, **8a,b,d**, in the series, it suffered from a very low yield in the Fischer indolization step (Scheme 4), and the cyclization failed completely on the attempted preparation of **29**. This failure may be ascribed to instability of the indole product under the harsh acidic conditions employed. Alkylation of the sodium or potassium anions of **10b,f** with either 4-fluoronitrobenzene or 4-nitrobenzyl bromide afforded **15a,b,d**. Catalytic hydrogenation of the nitro group followed by a diazotization/reduction sequence gave hydrazines **17a,b,d** which were converted to tryptamines **18a,b,d** by reaction with 4-chlorobutanal dimethyl acetal in refluxing EtOH−H_2O.[18] *N,N*-Dimethylation of **18a,b,d** under standard conditions then yielded **8a,b,d**.

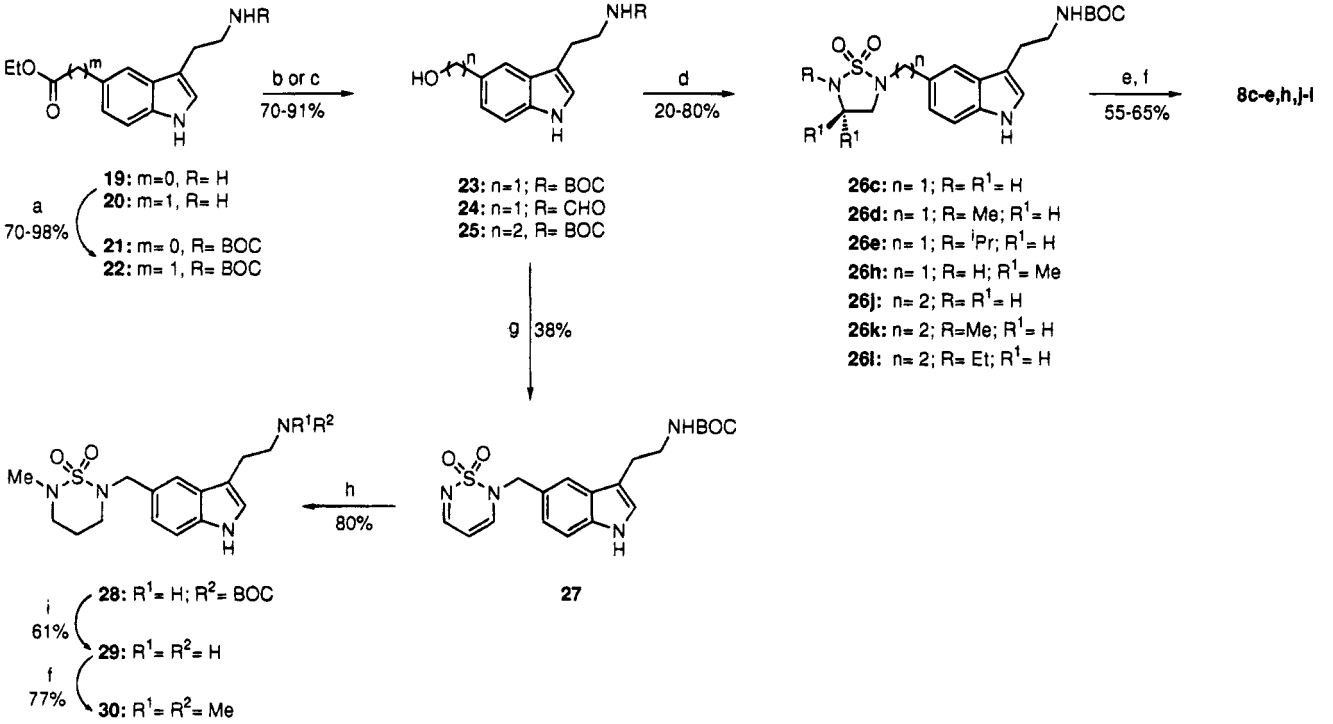
The Mitsunobu Approach. In order to overcome the extremely low-yielding indolization reaction, an alternative approach was sought where the cyclic sulfamide moiety could be appended under milder conditions to a preformed tryptamine. Because the Mitsunobu reaction[19] has been reported to mediate the coupling of alcohols with diverse nitrogen nucleophiles,[20] this methodology was next examined. The compounds would then be accessible from the common intermediate alcohols **23** and **25** and the appropriate sulfamides **10** in a convergent and, therefore, more attractive preparative strategy. Alcohols **23** and **25** were prepared by DIBAL-H reduction of tryptamine esters **21** and **22** (Scheme 5).[21] Although reduction of **21** proceeded normally to give **23** in high (91%) yield, reduction of **22** under the same conditions afforded a mixture of **25** and its aldehyde precursor, even at −10 °C and with a large excess of DIBAL-H. This surprising outcome probably results from enolization of the aldehyde under the reaction conditions. The crude mixture of alcohol/aldehyde was therefore reduced with $NaBH_4$/EtOH to give **25** in 70% overall yield. When the reduction of **21** was carried out at 0 °C, a 2:1 mixture of **23** and **24** was obtained (70% yield). Alcohols **23** and **25** were found to couple with **10b** under the normal Mitsunobu conditions (Ph_3P, DEAD, THF, 25 °C) to give **26d,k** in 53% and 80% yields, respectively. The higher yield of **26k** might reflect the increased stability of the intermediate oxyphosphonium salt derived from **25** compared to that

Scheme 4[a]



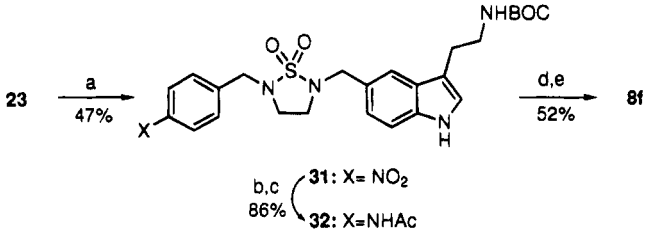
[a] Reagents: (a) NaH, 4-fluoronitrobenzene, DMF, reflux; (b) K_2CO_3, *p*-nitrobenzyl bromide, DMF, 25 °C; (c) H_2, 10% Pd–C, EtOH, 2 N HCl; (d) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (e) $SnCl_2 \cdot 2H_2O$, concentrated HCl, −10 °C; (f) 4-chlorobutanal dimethyl acetal, EtOH–H_2O (5:1), reflux; (g) CH_2O, $NaCNBH_3$, MeOH, AcOH, 25 °C.

Scheme 5[a]



[a] Reagents: (a) $(BOC)_2O$, Et_3N, CH_2Cl_2, 0–25 °C; (b) DIBAL-H, THF, −25 °C; (c) DIBAL-H, THF, −25 °C; then $NaBH_4$, EtOH, 25 °C; (d) **10a**, **10b**, **10c**, **10d**, or **10h**, Ph_3P, DEAD, THF, 25 °C; (e) 90% HCOOH, 25 °C; (f) CH_2O, $NaCNBH_3$, MeOH, 0–25 °C; (g) 1,2,6-thiadiazine 1,1-dioxide, Ph_3P, DEAD, THF–DMF, 25 °C; (h) **10i**, NaH, DMF, 80 °C; (i) TMSI, CH_2Cl_2, 25 °C.

Scheme 6[a]

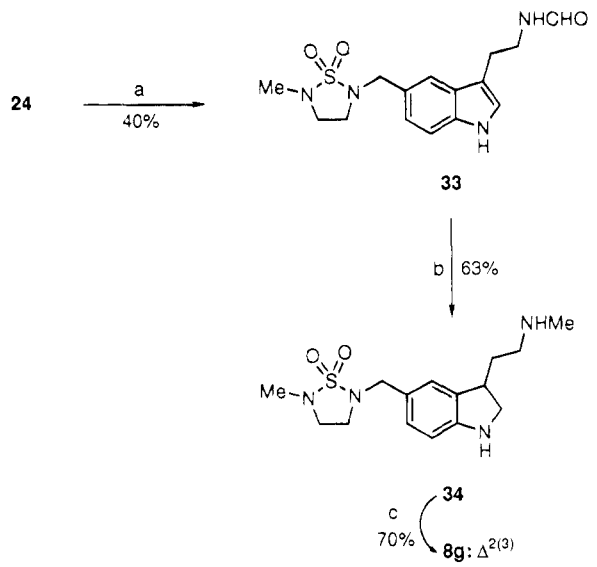


[a] Reagents: (a) **14**, Ph_3P, DEAD, THF, 25 °C; (b) H_2, 10% Pd–C, EtOH, 2 N HCl; (c) Ac_2O, Et_3N, CH_2Cl_2, 25 °C; (d) 90% HCOOH, 25 °C; (e) CH_2O, $NaCNBH_3$, MeOH, AcOH, 0–25 °C.

derived from **23** where the benzylic C–O bond is activated by donation of the indolic nitrogen lone pair into its σ^* orbital. The method was also applicable to cyclic sulfamides **10a,c,d** (Scheme 5) and **14** (Scheme 6) in comparable yields. Condensation of **23** and **10h** was, however, unsuccessful in THF although it proceeded in low yield (20%) in CH_2Cl_2.[22] Removal of the BOC group followed by *N,N*-dimethylation then gave **8c–e,h,j–l**. The 6-membered cyclic sulfamide **10i** failed to couple with **23** under any conditions (addition of reagents in different order; CH_2Cl_2 instead of THF; 1,1′-(azodicarbonyl)dipiperidine instead of DEAD[23]); in fact, **23** now coupled with reduced DEAD in high (78%) yield. The difference in behavior between **10b** and **10i** is probably a result of the increased pK_a for the latter.[24] In support of this notion is the observation that the more acidic 1,2,6-thiadiazine 1,1-dioxide[25] yielded the expected product **27** in moderate (38%) yield (Scheme 5). This latter compound was found, however, to decompose extremely easily in the presence of nucleophiles, and in fact, treatment of **27** with the sodium anion of **10i** in DMF at 80 °C cleanly produced **28**, which was conventionally converted to **30**.

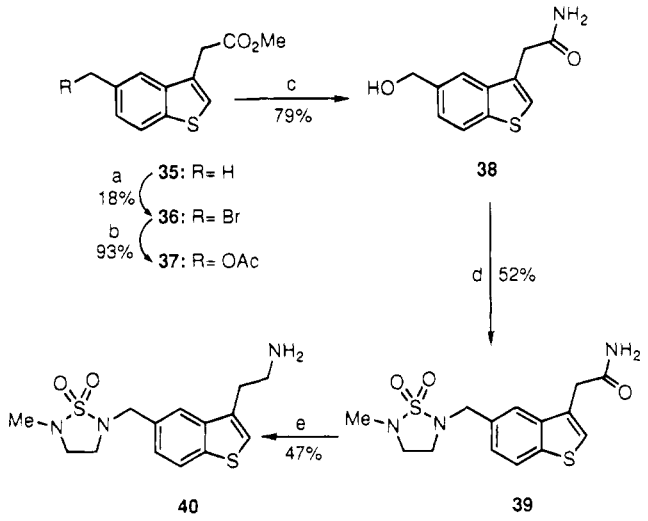
The monomethylated tryptamine **8g** was synthesized as shown in Scheme 7. Mitsunobu coupling of **24** and **10b** afforded **33** in moderate yield. Reduction of the formamido group with BH_3–THF gave a 1.4:1 mixture of indoline **34** and indole **8g**,[26] but benzeneseleninic anhydride[27] oxidation of the former afforded **8g** in good yield.

Scheme 7[a]



[a] Reagents: (a) **10b**, Ph_3P, DEAD, THF, 25 °C; (b) BH_3–THF, THF, 25 °C; (c) $(PhSeO)_2O$, Et_3N, indole, THF, 60 °C.

Scheme 8[a]

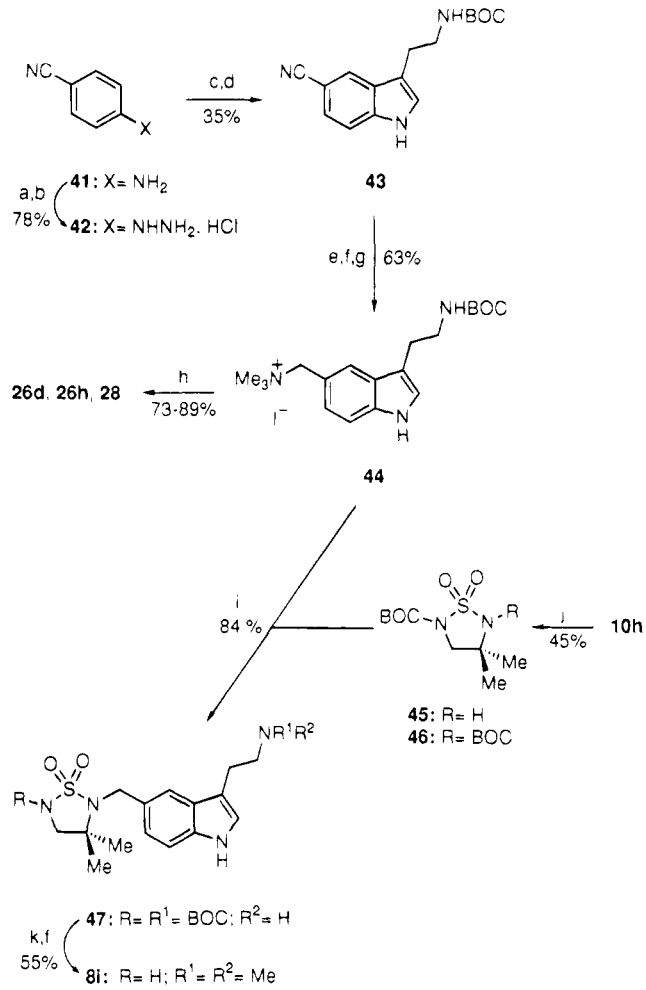


[a] Reagents: (a) NBS, CCl_4, reflux; (b) NaOAc, AcOH, 100 °C; (c) NH_3, MeOH, 0–100 °C; (d) **10b**, Ph_3P, DEAD, THF–DMF; (e) BH_3–THF, THF, 60 °C.

Synthesis of the benzothiophene **40** was carried out as described in Scheme 8. Allylic bromination of **35**[28] followed by reaction with sodium acetate afforded **37**. Removal of the acetyl group and conversion of the methyl ester to the primary carboxamide were cleanly achieved by treatment of **37** with ammonia to give **38**. Mitsunobu coupling of this alcohol and cyclic sulfamide **10b** then gave **39** which was converted to **40** by borane reduction.

The Methiodide Approach. Although most of the required compounds could be prepared by the above method, purification of the products from the Mitsunobu reactions was always difficult. It was therefore felt that a new method, overcoming this complication and producing increased yields of coupled product, would be desirable. By analogy with the quaternary salts of gramine, methiodide **44** was developed[29] which allowed the efficient preparation of **26d,h** and **28** (Scheme 9). The regioisomer analogue of **8h**, **8i**, was prepared using this methodology. Thus, reaction of the sodium anion

Scheme 9[a]



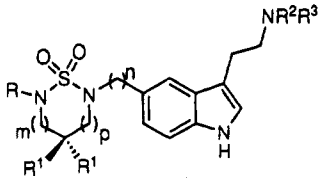
[a] Reagents: (a) $NaNO_2$, H_2O, concentrated HCl, −10 °C; (b) $SnCl_2 \cdot 2H_2O$, concentrated HCl, −10 °C; (c) 4-chlorobutanal dimethyl acetal, EtOH–H_2O (5:1), reflux; (d) $(BOC)_2O$, Et_3N, CH_2Cl_2, 0–25 °C; (e) H_2, PtO_2, EtOH–$CHCl_3$; (f) CH_2O, $NaCNBH_3$, MeOH, AcOH, 0–25 °C; (g) MeI, Et_2O; (h) **10b**, **10h**, or **10i**, NaH, DMF, 25–90 °C; (i) NaH, $(BOC)_2O$, DMF; (j) NaH, DMF, 25–90 °C; (k) 90% HCOOH.

of **10h** with $(BOC)_2O$ gave a 2:1 mixture of **45** and **46**. Coupling of the sodium anion of **45** with methiodide **44** cleanly produced **47** from which **8i** was obtained.

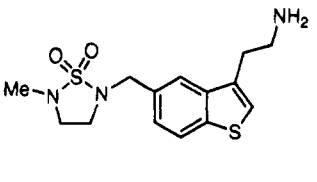
Results and Discussion

Structure–Affinity Relationships. The 5-HT_{1D} affinity of the compounds was measured by displacement of [^{3}H]-5-HT from pig caudate membranes in the presence of cyanopindolol and mesulergine to block interactions with 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} sites. The data in Table 1 shows that there is little change in 5-HT_{1D} receptor affinity when the length of the chain linking the cyclic sulfamide to the tryptamine nucleus is increased (**8a** vs **8d** vs **8k**) and that the 6-membered analogue **30** has the same affinity as **8d**. The desmethyl compounds **8c,j**, with comparable affinity to **8d,k**, respectively, reinforce the hypothesis that a hydrogen bond donor group is not required at C-5 of the tryptamine for binding to 5-HT_{1D} receptors. Somewhat surprisingly, the optimal activity was not obtained when the heterocycle was directly attached to the indole as previously reported.[9] Moreover, in the present case, *N,N*-dimethylation of the ethylamino side chain appears to be beneficial for 5-HT_{1D} affinity (**8d** vs **18d**), a result

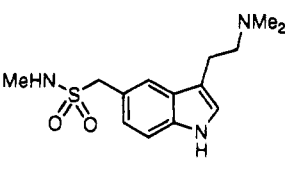
Table 1. Binding and *in Vitro* Functional Activities of (1,1-Dioxo-1,2,5-thiadiazolidin-2-yl)tryptamines and Analogues at Serotonin Receptors



8a-l, 30



40



4: Sumatriptan

								pIC$_{50}$[a]				pEC$_{50}$[a,f]	
compd	*n*	*m*	*p*	R	R^1	R^2	R^3	5-HT$_{1D}$[b]	5-HT$_{1A}$[c]	5-HT$_{2A}$[d]	5-HT$_3$[e]	(relative maximum[g])	log *D*[h]
8a	0	0	1	Me	H	Me	Me	7.0	6.2	<5.0		5.5 (0.31)	−0.92
8b	0	0	1	Bn	H	Me	Me	7.7	7.1	5.3			
8c	1	0	1	H	H	Me	Me	7.0	6.1	<5.0		5.6 (0.58)	−0.97
8d	1	0	1	Me	H	Me	Me	7.2	6.1	<5.0	<5.0	6.2 (0.74)	−0.68
8e	1	0	1	*i*-Pr	H	Me	Me	7.0	6.3	<5.0			0.16
8f	1	0	1	4-(AcNH)Bn	H	Me	Me	7.7	6.7	5.1		6.3 (0.72)	0.42
8g	1	0	1	Me	H	H	Me	7.0	6.1	<5.0		5.7 (0.79)	−1.71
18d	1	0	1	Me	H	H	H	6.5	6.2	<5.0			
30	1	1	1	Me	H	Me	Me	7.2	6.9	<5.0	<5.0	5.6 (0.57)	−0.02
8h	1	0	1	H	Me	Me	Me	7.0	6.6	<5.0		5.6 (0.54)	−0.39
8i	1	1	0	H	Me	Me	Me	6.7	6.0	<5.0		5.2 (0.72)	−0.78
8j	2	0	1	H	H	Me	Me	7.4	6.9	5.3			
8k	2	0	1	Me	H	Me	Me	7.4	6.7	5.6		5.8 (0.68)	−0.57
8l	2	0	1	Et	H	Me	Me	7.4	6.9	5.7		5.8 (0.69)	
40								6.4	5.7	5.7		4.9 (0.61)	
4 (sumatriptan)								7.7	6.3	<5.0	<5.0	6.2 (0.96)	−1.17

[a] The figures are the mean of two or three independent determinations typically with individual values within ±10−15% of the mean. [b] Displacement of [^{3}H]-5-HT binding to 5-HT$_{1D}$ recognition sites in pig caudate. [c] Displacement of [^{3}H]-8-OH-DPAT from pig cortex. [d] Displacement of [^{3}H]DOB from rat cortex homogenates. [e] Displacement of [^{3}H]Q-ICS 205−930 from rat cortex homogenates. [f] Contraction of New Zealand white rabbit saphenous vein. [g] Relative maximum = relative efficacy of the agonist with respect to 1 μM 5-HT. [h] log *P* measured at pH 7.4.

which contrasts with an earlier structure−affinity study[30] where the same transformation was found to be some 2−3-fold detrimental. Although the above compounds were found to have somewhat lower affinity than sumatriptan, incorporation of a benzyl group, optionally substituted with a further hydrogen bond donor/acceptor functionality, afforded compounds such as **8b,f** which had comparable affinity to sumatriptan. The small difference in affinity ($\Delta\Delta G$ < 1 kcal/mol) between sumatriptan and **8d** could either be due to the introduction of (minor) steric interactions with the ethylene bridge at the 5-HT$_{1D}$ receptor or be a direct result of the reduced hydrogen bond acceptor capability of the cyclic sulfamide moiety compared to the sulfonamide.[31] In support of the second hypothesis is the observation that increasing the steric bulk of the ethylene bridge, as in the case of the *gem*-dimethyl derivative **8h**, has no effect on the 5-HT$_{1D}$ affinity (**8h** vs **8c**). A slight (2-fold) reduction in affinity was however seen in the case of the other isomeric *gem*-dimethyl analogue **8i**.

In general, the compounds showed good selectivity (>100-fold) for 5-HT$_{1D}$ receptors over 5-HT$_2$, with the exception of **8k,l**. The selectivity over 5-HT$_{1A}$ was less pronounced and varied between 3- and 12-fold. Interestingly, the 6-membered analogue **30**, with the same 5-HT$_{1D}$ affinity as **8d**, showed significantly higher affinity (6-fold) for the 5-HT$_{1A}$ receptor, and a similar increase was observed with the introduction of a *gem*-dimethyl group in **8c** (**8c** vs **8h**). As a general trend, the compounds incorporating an ethylene link between the indole and the cyclic sulfamide moiety showed higher affinities for the 5-HT$_{1A}$ and 5-HT$_2$ receptors than their corresponding methylene-bridged analogues. Both **8d** and **30** also showed excellent selectivity over 5-HT$_3$ receptors.

Bioisosteric replacement of the indole nucleus by a benzo[*b*]thiophene[32] was studied in order to determine the effect on 5-HT$_{1D}$ receptor affinity and selectivity. Interestingly, compound **40** had the same 5-HT$_{1D}$ affinity as its indole analogue, **18d**, but it also showed significantly increased affinity for 5-HT$_2$ receptors.

Functional Activity. The functional activity of the compounds was assessed *in vitro* by measuring the contraction of the New Zealand white rabbit saphenous vein,[33] a response which is thought to be mediated by 5-HT$_1$-like receptors. The data in Table 1 show that these compounds appeared to behave as partial agonists in this preparation with relative efficacies ranging from 0.31 to 0.79 when compared to the maximum response elicited by 1 μM 5-HT. Sumatriptan is a full agonist in this model. **8d,f** were the most potent compounds derived from the present study, and they had pEC$_{50}$s identical to that of sumatriptan. Somewhat surprisingly, the introduction of the substituted benzyl side chain in **8d** to afford **8f**, which resulted in a 3-fold increase in the 5-HT$_{1D}$ affinity, did not improve its potency in the functional assay. The benzothiophene derivative **40** was the weakest of all the compounds tested.

Overall, **8d** proved to have the best *in vitro* profile (5-HT$_{1D}$ receptor binding, receptor selectivity, functional activity) of the compounds prepared. Moreover, **8d** was found to have no appreciable affinity for a variety of other receptors, including (pIC$_{50}$): adenosine (<5.0), adrenergic (<5.0), excitatory amino acids (<5.0), dopamine (<5.0), histamine (<5.0), muscarinic (<5.0), nicotinic (<5.0), and opiate (<5.0). Gratifyingly, **8d** was also

Table 2. Physical Data for (1,1-Dioxo-1,2,5-thiadiazolidin-2-yl)tryptamines[a]

no.	empirical formula	mp, °C
8a	$C_{15}H_{22}N_4O_2S \cdot (COOH)_2 \cdot 0.3H_2O$	169–176
8b	$C_{21}H_{26}N_4O_2S \cdot (COOH)_2 \cdot 0.6H_2O$	157–165
8c	$C_{15}H_{22}N_4O_2S \cdot (CH_2COOH)_2$	159–161
8d	$C_{16}H_{24}N_4O_2S \cdot (CH_2COOH)_2$	178–180
8e	$C_{18}H_{28}N_4O_2S \cdot (COOH)_2$	186–187
8f	$C_{24}H_{31}N_5O_3S \cdot (CH_2COOH)_2$	158–161
8g	$C_{15}H_{22}N_4O_2S \cdot (CH_2COOH)_2$	140–142
8h	$C_{17}H_{26}N_4O_2S \cdot (CH_2COOH)_2$	149–151
8i	$C_{17}H_{26}N_4O_2S \cdot 0.5(CH_2COOH)_2$	164–166
8j	$C_{16}H_{24}N_4O_2S \cdot (COOH)_2$	154–155
8k	$C_{17}H_{26}N_4O_2S \cdot (COOH)_2$	137–139
8l	$C_{18}H_{28}N_4O_2S \cdot (CH_2COOH)_2 \cdot 0.3H_2O$	144–145
18d	$C_{14}H_{20}N_4O_2S \cdot (COOH)_2$	172–180
30	$C_{17}H_{26}N_4O_2S \cdot 1.05(COOH)_2 \cdot 0.2(EtOH)$[b]	190–191

[a] All compounds were crystallized from EtOH, MeOH, or mixtures of these with Et_2O and gave satisfactory microanalysis for C, H, and N. [b] The ^1H NMR spectrum of this compound suggested that the salt had crystallized with solvent.

shown to have good oral bioavailability in the rat (66%) following a 3 mg/kg dose, and it exhibited relatively low CNS penetration, similar to that of sumatriptan. The homologated analogue of **8d**, **8k**, was also well absorbed after oral dosing (oral bioavailability 62%). By contrast, their equipotent benzyl-substituted analogue, **8f**, had very limited (*ca.* 1%) bioavailability in the same species.

Conclusions

A concise series of novel 5-HT_{1D} receptor agonists which incorporate a 1,1-dioxo-1,2,5-thiadiazolidin-2-yl moiety attached to C-5 of a tryptamine was developed. Compounds were identified which have comparable affinity, potency, and receptor selectivity to that of the antimigraine drug sumatriptan. In contrast with our previous studies, optimal activity was not achieved however with the cyclic sulfamide directly linked to the indole nucleus. Good oral bioavailability in the series was found with compounds having a methyl substituent on the cyclic sulfamide ring.

Experimental Section

Biological Methods. Detailed procedures for the radioligand binding assays and *in vitro* functional studies in the New Zealand white rabbit saphenous vein preparation have been previously reported.[9]

Chemical Methods: General Directions. Unless otherwise stated, all ^1H NMR spectra were recorded at 360 MHz on a Bruker AM 360 spectrometer or at 250 MHz on a Brucker AC250 instrument. Mass spectra and high-resolution mass spectra (HRMS) were obtained with a VG70-250 spectrometer. Melting points are uncorrected. Anhydrous THF, DMF, Et_2O, MeOH, and toluene were purchased from the Aldrich Chemical Co., Sureseal. Et_3N was distilled from CaH_2. All solutions were dried over Na_2SO_4 or $MgSO_4$ and concentrated on a Büchi rotary evaporator. Flash chromatography was performed on silica gel (Fluka Art. No. 60738). log *D*s were determined using 1-octanol and pH 7.4 buffer by the shake flask method.

1,2,5-Thiadiazolidine 1,1-Dioxide (10a). To a refluxing solution of sulfamide (14.4 g, 149.5 mmol) in anhydrous pyridine (200 mL) was added dropwise, over 3 h, anhydrous ethylenediamine (10 mL, 149.5 mmol). The resulting solution was refluxed for a further 20 h under nitrogen before it was cooled in an ice–water bath. The precipitated white solid was removed by filtration and washed with CH_2Cl_2 (50 mL) and Et_2O (2 × 50 mL). The filtrate was concentrated under vacuum, the residue was taken up into a hot mixture of $CHCl_3$ and MeOH (2.5:1; 350 mL), and the undissolved material was removed by filtration. Solvents were removed, and the residue was again taken up into the same hot solvent mixture (4:1; 250 mL), filtered, and concentrated. The remaining solid was then crystallized from EtOAc–hexane to give 1.9 g (10.4%) of **10a** as white needles: mp 53–54.5 °C; ^1H NMR ($CDCl_3$) δ 3.47 (4H, s).

General Procedure for the Preparation of Cyclic Sulfamides 10b–i. 3,3-Dimethyl-1,2,5-thiadiazolidine 1,1-Dioxide (10h). To a refluxing solution of sulfamide (27.25 g, 283 mmol) in anhydrous pyridine (300 mL) was added dropwise 1,2-diamino-2-methylpropane (25 g, 283 mmol) over 2 h. The resulting mixture was refluxed for a further 16 h under nitrogen before the solvent was removed under vacuum. The residue was triturated with hexane and the solid collected by filtration and purified by flash chromatography (CH_2Cl_2–MeOH, 96:4) to give 36.1 g (85%) of **10h** as a white solid: mp 80–83 °C; ^1H NMR (DMSO-d_6) δ 7.08 (1H, br t), 6.77 (1H, s), 3.04 (2H, d, J = 6.9 Hz), 1.24 (6H, s); MS (EI) *m/z* 151 (M^+ + 1). Anal. ($C_4H_{10}N_2O_2S$) C, H, N.

General Procedure for the 4-Nitrobenzylation of 10b,e. 2-*tert*-Butyl-5-(4-nitrobenzyl)-1,2,5-thiadiazolidine 1,1-Dioxide (13). A mixture of **10e**[13] (1.5 g, 7.3 mmol), anhydrous K_2CO_3 (1.03 g, 7.4 mmol), and 4-nitrobenzyl bromide (1.59 g, 7.4 mmol) in anhydrous DMF (12 mL) was stirred at room temperature for 15 h, under nitrogen. Water (20 mL) was added, and products were extracted with EtOAc (3 × 15 mL), dried, and concentrated. The residue was crystallized from EtOAc–hexane (40:60) to give 1.61 g (70%) of **13** as white needles: mp 113 °C; ^1H NMR ($CDCl_3$) δ 8.21 (2H, d, J = 8.7 Hz), 7.58 (2H, d, J = 8.7 Hz), 4.24 (2H, s), 3.40 (2H, t, J = 6.2 Hz), 3.17 (2H, t, J = 6.2 Hz), 1.44 (9H, s); MS (EI) *m/z* 313 (M^+).

2-(4-Nitrobenzyl)-1,2,5-thiadiazolidine 1,1-Dioxide (14). A solution of **13** (1.5 g, 4.78 mmol) in a mixture of anhydrous CH_2Cl_2 (10 mL) and trifluoroacetic acid (10 mL) was allowed to stand at room temperature for 48 h. Solvents were removed under vacuum, and the residue was azeotroped with MeOH (25 mL) and finally recrystallized from EtOAc–hexane to give 966 mg (78%) of **14** as a pale yellow solid: mp 113–117 °C; ^1H NMR ($CDCl_3$) δ 8.23 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 4.38 (1H, br t), 4.29 (2H, s), 3.54 (2H, q, J = 6.6 Hz), 3.34 (2H, t, J = 6.6 Hz); MS (CI) *m/z* 256 (M^+); HRMS calcd for $C_{13}H_{19}N_3O_4S$ 257.0470, found 257.0419.

General Procedure for the Coupling of 10b,f with 1-Fluoro-4-nitrobenzene. 4-(1,1-Dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)nitrobenzene (15a). To a solution of **10b** (2.02 g, 14.8 mmol) in anhydrous DMF (30 mL) was added NaH (60% dispersion in oil; 0.59 g), and the mixture was stirred at room temperature for 40 min under nitrogen. A solution of 1-fluoro-4-nitrobenzene (2.09 g, 14.8 mmol) in anhydrous DMF (15 mL) was then added, and the mixture was refluxed for 1 h. Water (200 mL) was added, and products were extracted with EtOAc (2 × 150 mL), dried, and concentrated. Crystallization from EtOAc afforded 2.61 g (68.7%) of **15a** as a pale orange solid: mp 155–163 °C; ^1H NMR (DMSO-d_6) δ 8.29 (2H, d, J = 9.3 Hz), 7.34 (2H, d, J = 9.3 Hz), 4.00 (2H, t, J = 6.4 Hz), 3.57 (2H, t, J = 6.4 Hz), 2.78 (3H, s); MS (EI) *m/z* 257 (M^+). Anal. ($C_9H_{11}N_3O_2S$) C, H, N.

General Procedure for the Preparation of Anilines 16a,b,d. 4-[(1,1-Dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-methyl]aniline Hydrochloride (16d). A suspension of **15d** (20 g, 74.72 mmol) in a mixture of EtOH (300 mL), EtOAc (150 mL), and 2 N HCl (39 mL, 78 mmol) was hydrogenated at 30 psi over 10% Pd–C (2 g) for 7 min. The catalyst was filtered off and washed with EtOH (2 × 30 mL), and solvents were removed under vacuum. The remaining residue was azeotropically dried with absolute EtOH (150 mL) and further dried under high vacuum to give 20.36 g (99.5%) of **16d** as a white solid. A sample recrystallized from EtOH showed the following: mp 153–156 °C (white needles); ^1H NMR (DMSO-d_6) δ 7.42 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 4.15 (2H, s), 3.27–3.17 (4H, m), 2.62 (3H, s); MS (CI) *m/z* 240 (M^- − 1). Anal. ($C_{10}H_{15}N_3O_2S \cdot HCl$) C, H, N.

General Procedure for the Preparation of Hydrazines 17a,b,d. 4-[(1,1-Dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)-methyl]phenylhydrazine Hydrochloride (17d). To a cooled (−10 °C) and stirred suspension of **16d** (20 g, 72.0 mmol) in a mixture of concentrated HCl (100 mL) and water (10 mL) was

added dropwise a solution of $NaNO_2$ (5.22 g, 75.6 mmol) in water (40 mL) at such a rate as to maintain the temperature below −5 °C. After a further 10 min, the mixture was quickly filtered to remove a small amount of solid and the filtrate was added portionwise to a cooled (−15 °C) and stirred solution of $SnCl_2 \cdot 2H_2O$ (81.2 g, 360 mmol) in concentrated HCl (60 mL) at such a rate as to maintain the temperature below −10 °C. The mixture was then allowed to warm to 0 °C, basified with 10 N KOH, and extracted with EtOAc (1 × 500 mL and 3 × 250 mL). The combined organic phases were washed with brine (100 mL), dried, and concentrated. Crystallization of the residue from EtOAc followed by flash chromatography purification of the mother liquors (EtOAc−MeOH, 98:2, and CH_2Cl_2−MeOH, 95:5) gave 6.5 g (35%) of **17d** free base as a yellow solid. The hydrochloride salt was prepared and recrystallized from EtOH: mp 152−153 °C; ^{1}H NMR (DMSO-d_6) δ 10.17 (3H, br s), 8.30 (1H, br s), 7.28 (2H, d, J = 8.5 Hz), 6.95 (2H, d, J = 8.5 Hz), 4.13 (2H, s), 3.23 (2H, t, J = 6.0 Hz), 3.14 (2H, t, J = 6.0 Hz), 2.61 (3H, s); MS (EI) m/z 256 (M^+). Anal. ($C_{10}H_{16}N_4O_2S \cdot HCl \cdot 0.2H_2O$) C, H, N.

General Procedure for the Fischer Indolization of Hydrazines 17a,b,d. 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole (18d). A solution of **17d** free base (3.0 g, 11.70 mmol) and 4-chlorobutanal dimethyl acetal (1.78 g, 11.70 mmol) in a mixture of EtOH (100 mL), water (15 mL), and 2 N HCl (5.85 mL, 11.70 mmol) was refluxed for 2 h. The solvent was removed, and the residue was azeotroped with absolute EtOH (50 mL). The remaining residue was taken up into hot absolute EtOH (100 mL) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (CH_2Cl_2−MeOH-NH_3, 90:10:1) to give 288 mg of **18d** as a colorless thick oil. The oxalate salt was prepared and recrystallized from EtOH: mp 172−180 °C; ^{1}H NMR (DMSO-d_6) δ 10.98 (1H, s), 7.52 (1H, s), 7.35 (1H, d, J = 8.3 Hz), 7.23 (1H, d, J = 1.9 Hz), 7.09 (1H, dd, J = 8.3 and 1.3 Hz), 4.70 (2H, s), 3.22 (2H, m), 3.14 (2H, m), 3.01 (2H, m), 2.92 (2H, m), 2.63 (3H, s). Anal. ($C_{14}H_{20}N_4O_2S \cdot C_2H_2O_4$) C, H, N.

General Procedure for the Protection of Tryptamines 19 and 20. Ethyl 3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]-ethyl]-1*H*-indole-5-carboxylate (21). To a cooled (−10 °C) and stirred suspension of **19**[9] (26.9 g, 100 mmol) in anhydrous CH_2Cl_2 (900 mL) was added anhydrous Et_3N (28.7 mL, 200 mmol) followed by $(BOC)_2O$ (24 g, 110 mmol), under nitrogen. The mixture was stirred at this temperature for 30 min and at room temperature for 3 h before it was diluted with CH_2Cl_2 (300 mL). The organic phase was then washed with 2 N HCl (2 × 100 mL), 10% Na_2CO_3 (100 mL), and brine (100 mL), dried, and concentrated. Flash chromatography (CH_2Cl_2−MeOH, 96:4) of the residue followed by crystallization from EtOH afforded 23.3 g (70%) of **21** as white crystals: mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, s), 8.28 (1H, br s), 7.91 (1H, dd, J = 8.5 and 1.6 Hz), 7.36 (1H, d, J = 8.5 Hz), 7.09 (1H, br s), 4.61 (1H, br s), 4.40 (2H, q, J = 7.2 Hz), 3.48 (2H, m), 2.96 (2H, t, J = 6.8 Hz), 1.43 (9H, s), 1.42 (3H, t, J = 7.2 Hz); MS (EI) m/z 332 (M^+). Anal. ($C_{18}H_{24}N_2O_4$) C, H, N.

3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-(hydroxymethyl)-1*H*-indole (23). To a cooled (−50 °C) and stirred solution of **21** (17.4 g, 52.4 mmol) in anhydrous THF (650 mL) was added DIBAL-H (1 M in toluene; 168 mL) over 23 min, under nitrogen. After the solution was stirred at −25 °C for 1 h, additional DIBAL-H (40 mL) was added over 15 min, and stirring was continued for 30 min. MeOH (65 mL) was then added at −35 °C (CAUTION! H_2 evolution) followed by aqueous citric acid (10%; 450 mL), and the organic phase was decanted off. The aqueous layer was extracted with EtOAc (500 mL), and the combined organic solutions were washed with brine (200 mL), dried, and concentrated. Flash chromatography (CH_2Cl_2−MeOH, 97:3) of the residue gave 13.8 g (90.8%) of **23** as a white solid: mp 129−130 °C (CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 10.70 (1H, br s), 7.44 (1H, s), 7.26 (1H, d, J = 8.3 Hz), 7.10 (1H, s), 7.03 (1H, d, J = 8.3 Hz), 6.86 (1H, br t), 4.95 (1H, t, J = 5.6 Hz), 4.54 (2H, d, J = 5.6 Hz), 3.18 (2H, m), 2.78 (2H, t, J = 7.2 Hz), 1.38 (9H, s); MS (EI) m/z 290 (M^+). Anal. ($C_{16}H_{22}N_2O_3$) C, H, N.

3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-(2-hydroxyethyl)-1*H*-indole (25). To a cooled (−23 °C) and stirred solution of **22** (10.8 g, 31.17 mmol) in anhydrous THF (385 mL) was added DIBAL-H (1 M in toluene; 100 mL) over 25 min, under nitrogen. After the solution was stirred at this temperature for 1 h and at −10 °C for 1 h, additional DIBAL-H (25 mL) was added, and stirring was continued for 2.5 h at −5 °C. The mixture was cooled to −40 °C, and MeOH (40 mL) was added dropwise followed by aqueous citric acid (10%; 400 mL). The organic phase was decanted off, and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic solutions were washed with brine (200 mL), dried, and concentrated (temperature <30 °C). The remaining residue was dissolved in MeOH (250 mL) and treated portionwise with $NaBH_4$ (1.2 g, 31.72 mmol) over 1 h at room temperature. HCl (2 N; 20 mL) was added, and the resulting acidic solution was neutralized with saturated aqueous K_2CO_3 before the MeOH was removed under vacuum. The residue was diluted with water (150 mL), and products were extracted with EtOAc (2 × 200 mL) and washed with brine (100 mL) and then dried and concentrated. Flash chromatography (hexane−EtOAc, 50:50) of the residue afforded 6.6 g (69.6%) of **25** as a colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 8.03 (1H, br s), 7.44 (1H, s), 7.32 (1H, d, J = 8.3 Hz), 7.07 (1H, dd, J = 8.3 and 1.6 Hz), 7.02 (1H, d, J = 2.2 Hz), 4.60 (1H, br s), 3.89 (2H, t, J = 6.5 Hz), 3.45 (2H, m), 2.97 (2H, t, J = 6.5 Hz), 2.93 (2H, t, J = 6.8 Hz), 1.43 (9H, s); MS (CI) m/z 303 ($M^+ - 1$); HRMS calcd for $C_{17}H_{24}N_2O_3$ 304.1787, found 304.1759.

General Procedure for the Preparation of Tryptamines 26c−e,j−l, 27, 31, and 33 by Mitsunobu Couplings. 3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole (26d). To a cooled (−5 °C) and stirred solution of **23** (5.0 g, 17.22 mmol), Ph_3P (5.42 g, 20.66 mmol), and **10b** (2.81 g, 20.66 mmol) in anhydrous THF (100 mL) was added dropwise, under nitrogen, DEAD (3.6 g, 20.66 mmol) over 14 min. After the solution was stirred at 0 °C for 0.5 h and at room temperature for 16.5 h, the solvent was removed under vacuum and the residue triturated with EtOAc−Et_2O (1:2; 150 mL) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (CH_2Cl_2−MeOH, 98:2, and EtOAc−hexane, 60:40) to give 3.74 g (53.2%) of **26d** as a colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, br s), 7.54 (1H, s), 7.35 (1H, d, J = 8.4 Hz), 7.22 (1H, dd, J = 8.4 and 1.5 Hz), 7.06 (1H, s), 4.60 (1H, br s), 4.30 (2H, s), 3.44 (2H, m), 3.25 (2H, dd, J = 8.2 and 7.0 Hz), 3.15 (2H, dd, J = 8.2 and 7.0 Hz), 2.94 (2H, t, J = 6.8 Hz), 2.79 (3H, s), 1.43 (9H, s); MS (EI) m/z 408 (M^+); HRMS calcd for $C_{19}H_{28}N_4O_4S$ 408.1831, found 408.1807.

General Procedure for Removal of the BOC Group of Tryptamines 26c−e,h,j−l, 32, and 47. 3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole (18d). A solution of **26d** (3.7 g, 9.05 mmol) in 90% HCOOH (90 mL) was allowed to stand at room temperature for 40 min. Toluene (100 mL) and MeOH (50 mL) were added, and solvents were removed under vacuum. The remaining residue was azeotroped with toluene−MeOH (3:1; 100 mL), and the crude product was purified by flash chromatography (CH_2Cl_2−MeOH−NH_3, 80:20:2) to give 2.16 g of **18d** as a colorless thick oil.

3-(2-Aminoethyl)-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1*H*-indole (29). To a stirred solution of **28** (95 mg, 0.225 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise, under nitrogen, TMSI (35 μL, 0.248 mmol). After 12 min, MeOH (1 mL) was added and solvents were removed under vacuum. Flash chromatography (CH_2Cl_2−MeOH−NH_3, 80:20:2) of the residue gave 44 mg (61%) of **29**: ^{1}H NMR ($CDCl_3$) δ 8.21 (1H, br s), 7.52 (1H, s), 7.33 (1H, d, J = 8.3 Hz), 7.18 (1H, d, J = 8.3 Hz), 7.05 (1H, br s), 4.35 (2H, s), 3.37 (2H, t, J = 5.8 Hz), 3.25 (2H, t, J = 5.6 Hz), 3.02 (2H, m), 2.91 (2H, m), 2.85 (3H, s), 1.74 (2H, m); MS (CI) m/z 323 ($M^+ + 1$).

General Procedure for the Preparation of *N,N*-Dimethyltryptamines 8a−f,h−l and 30. 3-[2-(Dimethylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole (8d). To a cooled (−2 °C) and stirred solution of **18d** (2.16 g, 7.0 mmol), $NaCNBH_3$ (880 mg, 14.0

mmol), and glacial AcOH (2.0 mL, 35.0 mmol) in MeOH (110 mL) was added dropwise, over 17 min, a solution of CH_2O (38% w/v aqueous solution; 1.38 mL) in MeOH (15 mL). After 20 min of stirring at 0 °C and 2.5 h at room temperature, saturated aqueous K_2CO_3 (40 mL) was added and the MeOH was removed under vacuum. The residue was diluted with water (40 mL), and the product was extracted with EtOAc (2 × 125 mL), washed with brine (2 × 40 mL), dried, and concentrated. Flash chromatography (CH_2Cl_2–MeOH–NH_3, 90:10:1) of the crude material afforded 1.95 g (83%) of **8d** as a colorless thick oil. The succinate salt was prepared and recrystallized from EtOH–Et_2O (1:1; 400 mL): mp 178–180 °C (white scales); ^1H NMR (DMSO-d_6) δ 10.85 (1H, br s), 7.51 (1H, s), 7.32 (1H, d, J = 8.3 Hz), 7.18 (1H, d, J = 1.8 Hz), 7.07 (1H, dd, J = 8.3 and 1.4 Hz), 4.17 (2H, s), 3.22 (2H, t, J = 6.1 Hz), 3.13 (2H, t, J = 6.1 Hz), 2.87 (2H, t, J = 6.9 Hz), 2.72 (2H, t, J = 6.9 Hz), 2.63 (3H, s), 2.38 (6H, s), 2.31 (4H, s, succinate); MS (EI) m/z 336 (M^+). Anal. ($C_{16}H_{24}N_4O_2S \cdot C_4H_6O_4$) C, H, N.

3-[2-(Methylamino)ethyl]-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]-1*H*-indole (8g). To a cooled (0 °C) and stirred solution of **33** (440 mg, 1.31 mmol) in anhydrous THF (10 mL) was added dropwise, under nitrogen, BH_3–THF (1 M in THF; 3.9 mL). The mixture was allowed to warm to room temperature, and it was stirred for 6 h before excess of borane was destroyed by dropwise addition of MeOH (4 mL). Solvents were removed under vacuum, and the residue was dissolved in a mixture of 2 N HCl (25 mL) and MeOH (25 mL) and stirred at room temperature for 0.5 h. After the mixture was basified with 2 N NaOH, the MeOH was removed and products were extracted with EtOAc (2 × 100 mL) and washed with brine (40 mL) and then dried and concentrated. Flash chromatography (Et_2O–MeOH–NH_3, 70:30:2) of the residue gave 100 mg (26%) of **8g** and 142 mg (37%) of indoline **34** as colorless thick oils.

The succinate salt of **8g** was prepared and recrystallized from EtOH–Et_2O: mp 140–142 °C; ^1H NMR (DMSO-d_6) δ 10.95 (1H, br s), 7.53 (1H, s), 7.35 (1H, d, J = 8.3 Hz), 7.23 (1H, s), 7.09 (1H, d, J = 8.3 Hz), 4.17 (2H, s), 3.24–3.20 (2H, m), 3.16–3.12 (2H, m), 3.06 (2H, t, J = 7.6 Hz), 2.95 (2H, t, J = 7.6 Hz), 2.62 (3H, s), 2.53 (3H, s), 2.27 (4H, s, succinate); MS (CI) m/z 323 ($M^+ + 1$). Anal. ($C_{15}H_{22}N_4O_2S \cdot C_4H_6O_4$) C, H, N.

Indoline 34: ^1H NMR ($CDCl_3$) δ 7.08 (1H, d, J = 1.3 Hz), 6.99 (1H, dd, J = 8.0 and 1.3 Hz), 6.58 (1H, d, J = 8.0 Hz), 4.12 (1H, d, J = 13.6 Hz), 4.07 (1H, d, J = 13.6 Hz), 3.71 (1H, t, J = 8.0 Hz), 3.40–3.10 (6H, m), 2.77 (3H, s), 2.72–2.63 (2H, m), 2.46 (3H, s), 2.10–1.94 (1H, m), 1.81–1.65 (1H, m); MS (CI) m/z 325 ($M^+ + 1$); HRMS calcd for $C_{15}H_{24}N_4O_2S$ 324.1620, found 324.1599.

Oxidation of Indoline 34 to Indole 8g. A solution of **34** (125 mg, 0.427 mmol), indole (169 mg, 1.44 mmol), and anhydrous Et_3N (134 μL, 0.96 mmol) in anhydrous THF (6 mL) was added to solid benzeneseleninic anhydride (90 mg, 0.250 mmol), under nitrogen. The resulting brown solution was refluxed for 30 min before it was concentrated. Flash chromatography (Et_2O–MeOH–NH_3, 70:30:2) of the residue afforded 86 mg (70%) of **8g**.

Methyl 5-(Bromomethyl)benzo[*b*]thiophene-3-acetate (36). To a solution of **35**[28] (1.0 g, 4.5 mmol) in CCl_4 (10 mL), purged with nitrogen, was added NBS (0.81 g, 4.5 mmol), and the mixture was refluxed for 6.5 h. After cooling, the mixture was filtered and the solvent was removed under vacuum. Flash chromatography (hexane–EtOAc, 95:5) of the residue gave 245 mg (18%) of **36** as a yellow solid: ^1H NMR ($CDCl_3$) δ 7.83 (1H, d, J = 8.3 Hz), 7.76 (1H, s), 7.40 (1H, d), 7.39 (1H, s), 4.66 (2H, s), 3.87 (2H, s), 3.72 (3H, s); MS (CI) m/z 300/298 ($M^+ + 1$).

Methyl 5-(Acetoxymethyl)benzo[*b*]thiophene-3-acetate (37). A solution of **36** (3.8 g, 12.7 mmol) in glacial AcOH (55 mL) was added dropwise to a solution of NaOAc (11.4 g, 140 mmol) in glacial AcOH (165 mL) at 100 °C, under nitrogen. The resulting solution was stirred at this temperature for 8 h before it was cooled to room temperature and water (200 mL) was added. Solvents were removed under vacuum, the residue was diluted with water (100 mL), and products were extracted with EtOAc (4 × 100 mL). The combined organic solutions were washed with water (4 × 150 mL), dried, and concentrated. Flash chromatography of the residue (hexane–EtOAc, 80:20) gave 3.3 g (93%) of **37** as an orange oil: ^1H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 8.2 Hz), 7.74 (1H, s), 7.39 (1H, s), 7.37 (1H, d), 5.24 (2H, s), 3.87 (2H, s), 3.72 (3H, s), 2.11 (3H, s); MS (CI) m/z 296 [$M + NH_4$]$^+$; HRMS calcd for $C_{14}H_{14}O_4S$ 278.0613, found 278.0618.

5-(Hydroxymethyl)benzo[*b*]thiophene-3-acetamide (38). Ammonia gas was bubbled through a cooled (0 °C) solution of **37** (1.5 g, 5.40 mmol) in anhydrous MeOH (15 mL) for 5 min. The mixture was then heated at 100 °C in a sealed tube for 8 h before the solvent was removed under vacuum. The residue was triturated with CH_2Cl_2 (30 mL) and the solid collected to give 945 mg (79%) of **38** as yellow crystals: mp 176–178 °C; ^1H NMR (DMSO-d_6) δ 7.89 (1H, d, J = 8.3 Hz), 7.76 (1H, s), 7.52 (1H, br s), 7.48 (1H, s), 7.33 (1H, d, J = 7.0 Hz), 6.95 (1H, br s), 5.24 (1H, t, J = 5.6 Hz), 4.61 (2H, d, J = 5.5 Hz), 3.64 (2H, s); MS (EI) m/z 221 (M^+). Anal. ($C_{11}H_{11}NO_2S \cdot 0.2H_2O$) C, H, N.

5-[(1,1-Dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]benzo[*b*]thiophene-3-acetamide (39). To a solution of **38** (500 mg, 2.26 mmol), **10b** (370 mg, 2.71 mmol), and Ph_3P (710 mg, 2.71 mmol) in a mixture of anhydrous THF (15 mL) and anhydrous DMF (1 mL) was added dropwise, under nitrogen, DEAD (0.43 mL, 2.71 mmol) over 5 min. After the solution was stirred at room temperature for 1.5 h, solvents were removed under vacuum and the residue was purified by flash chromatography (CH_2Cl_2–MeOH, 95:5) to give 400 mg (52%) of **39** as a white solid: mp 153–159 °C; ^1H NMR ($CDCl_3$) δ 7.87 (1H, d, J = 8.3 Hz), 7.74 (1H, s), 7.44 (1H, d, J = 8.3 Hz), 7.41 (1H, s), 5.51 (1H, br s), 5.34 (1H, br s), 4.35 (2H, s), 3.83 (2H, s), 3.25 (4H, m), 2.79 (3H, s); MS (CI) m/z 340 ($M^+ + 1$).

3-(2-Aminoethyl)-5-[(1,1-dioxo-5-methyl-1,2,5-thiadiazolidin-2-yl)methyl]benzo[*b*]thiophene (40). To a stirred suspension of **39** (125 mg, 0.367 mmol) in anhydrous THF (5 mL) was added BH_3–THF (1 M in THF; 1.29 mL), and the resulting clear solution was refluxed for 4 h under nitrogen. Saturated NaCl solution (2 mL) was then added, and the mixture was stirred for 16 h before the organic phase was separated. The aqueous layer was extracted with THF (10 mL), and the combined organic solutions were dried and concentrated. Flash chromatography (CH_2Cl_2–MeOH, 80:20–70:30) of the residue afforded 55 mg (47%) of **40**. The oxalate salt was prepared. **40**: mp 170–178 °C (MeOH–Et_2O); ^1H NMR (D_2O) 8.03 (1H, d, J = 8.5 Hz), 7.90 (1H, s), 7.53 (1H, s), 7.50 (1H, d, J = 8.3 Hz), 4.42 (2H, s), 3.27–3.44 (8H, m), 2.76 (3H, s); MS (CI) m/z 326 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{19}N_3O_2S_2 \cdot C_2H_2O_4$: C, 46.25; H, 5.09; N, 10.11. Found: C, 46.14; H, 5.21; N, 11.49.

4-Cyanophenylhydrazine Hydrochloride (42). To a cooled (−15 °C) and stirred suspension of 4-aminobenzonitrile (50 g, 423 mmol) in concentrated HCl (550 mL) was added dropwise a solution of $NaNO_2$ (31.5 g, 457 mmol) in water (200 mL) at such a rate as to maintain the temperature below −10 °C. After the addition was finished, the reaction mixture was quickly filtered to remove solids and the filtrate was added portionwise to a cooled −20 °C) and stirred solution of $SnCl_2 \cdot 2H_2O$ (477 g, 2.1 mol) in concentrated HCl (370 mL) at such a rate as to keep the temperature below −10 °C. After a further 15 min, the solid was collected, washed with Et_2O (4 × 250 mL), and dried to give 56 g (78%) of **42**: mp 235–237 °C (EtOH–H_2O, 1:1); ^1H NMR (DMSO-d_6) δ 10.50 (3H, br s), 9.10 (1H, br s), 7.71 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz); MS (CI) m/z 132 ($M^- - 1$). Anal. ($C_7H_7N_3 \cdot HCl \cdot 0.1H_2O$) C, H, N.

3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-cyano-1*H*-indole (43). A mixture of **42** (50 g, 292 mmol) and 4-chlorobutanal dimethyl acetal (45 g, 295 mmol) in EtOH–H_2O (5:1; 2 L) was refluxed for 18 h. Solvents were removed under vacuum, and the residue was azeotroped with toluene to give a brown solid. Crystallization from MeOH afforded 23 g (35%) of 3-(2-aminoethyl)-5-cyano-1*H*-indole hydrochloride as a yellow solid: mp 270–274 °C; ^1H NMR (DMSO-d_6) δ 11.60 (1H, br s), 8.17 (1H, d, J = 1.1 Hz), 7.97 (3H, br s), 7.54 (1H,

d, J = 8.5 Hz), 7.46 (1H, s), 7.44 (1H, dd, J = 8.5 and 1.1 Hz), 3.05 (4H, br s); MS (CI) m/z 184 ($M^+ - 1$). Anal. ($C_{11}H_{11}N_3$·HCl·0.3H_2O) C, H, N.

Protection of the ethylamino side chain of the above tryptamine as the (*tert*-butyloxy)carbonyl derivative was carried out using the general method described for **21**. Crystallization from hexane–EtOAc afforded **43** as white prisms: mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (1H, br s), 7.93 (1H, s), 7.41 (2H, s), 7.12 (1H, d, J = 2.2 Hz), 4.71 (1H, br s), 3.44 (2H, q, J = 6.9 Hz), 2.94 (2H, t, J = 6.9 Hz), 1.45 (9H, s); MS (CI) m/z 286 ($M^+ + 1$). Anal. ($C_{16}H_{19}N_3O_2$) C, H, N.

3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-[(trimethylammonium)methyl]-1*H*-indole Iodide (44). A solution of **43** (11.3 g, 39.5 mmol) in EtOH (750 mL) and $CHCl_3$ (22 mL) was hydrogenated at 50 psi over PtO_2 (1 g) for 28 h. The catalyst was filtered off, and solvents were removed under vacuum. The residue was purified by flash chromatography (CH_2Cl_2–MeOH–NH_3, 90:10:1) to give 9.5 g (82%) of 5-(aminomethyl)-3-[2-[*N*-[(*tert*-butyloxy)carbonyl]amino]ethyl]-1*H*-indole as a white solid: mp 147–149 °C (EtOAc–Et_2O); ^{1}H NMR ($CDCl_3$) δ 8.04 (1H, br s), 7.52 (1H, s), 7.33 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.03 (1H, s), 4.61 (1H, br s), 3.96 (2H, s), 3.45 (2H, br q), 2.95 (2H, t, J = 6.8 Hz), 1.43 (9H, s); MS (CI) m/z 288 ($M^+ - 1$). Anal. ($C_{16}H_{23}N_3O_2$) C, H, N.

N,*N*-Dimethylation of the above amine using the conditions described for **8d** proceeded in 71% yield to give 3-[2-[*N*-[(*tert*-butyloxy)carbonyl]amino]ethyl]-5-[(dimethylamino)methyl]-1*H*-indole as a colorless thick oil: HRMS calcd for $C_{18}H_{27}N_3O_2$ 317.2103, found 317.2111.

A solution of the above *N*,*N*-dimethylamino compound (2.9 g, 9.13 mmol) in a mixture of anhydrous Et_2O (170 mL) and MeI (36 mL) was allowed to stand at room temperature for 16 h, in the dark. The white solid was collected, washed with Et_2O, and dried over P_2O_5 at 50 °C, under high vacuum, to give 4.2 g (100%) of **44** as a white solid: mp 199–202 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.09 (1H, br s), 7.69 (1H, s), 7.44 (1H, d, J = 8.3 Hz), 7.26 (1H, s), 7.19 (1H, d, J = 8.3 Hz), 6.89 (1H, br t), 4.57 (2H, s), 3.23 (2H, q, J = 7.6 Hz), 3.01 (9H, s), 2.83 (2H, t, J = 7.6 Hz), 1.37 (9H, s). Anal. ($C_{19}H_{30}IN_3O_2$) C, H, N.

General Procedure for the Coupling of Methiodide 44 with Cyclic Sulfamides 10b,h,i and 45. 3-[2-[*N*-[(*tert*-Butyloxy)carbonyl]amino]ethyl]-5-[(1,1-dioxo-6-methyl-3,4,5,6-tetrahydro-1,2,6-thiadiazin-2-yl)methyl]-1*H*-indole (28). To a solution of **10i** (360 mg, 2.40 mmol) in anhydrous DMF (6 mL) was added NaH (60% dispersion in oil; 87 mg, 2.18 mmol), and the mixture was stirred at room temperature for 25 min under nitrogen. A solution of **44** (500 mg, 1.09 mmol) in anhydrous DMF (4 mL) was then added, and the pale yellow solution was heated at 90 °C for 1 h. After cooling, water (60 mL) was added and the product was extracted with Et_2O (2 × 70 mL), washed with brine (25 mL), dried, and concentrated. Flash chromatography (Et_2O) of the residue gave 352 mg (76.5%) of **28** as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, br s), 7.51 (1H, s), 7.35 (1H, d, J = 8.5 Hz), 7.21 (1H, dd, J = 8.5 and 1.5 Hz), 7.05 (1H, d, J = 2.1 Hz), 4.60 (1H, br s), 4.36 (2H, s), 3.45 (2H, br q), 3.38 (2H, t, J = 5.7 Hz), 3.26 (2H, t, J = 5.8 Hz), 2.94 (2H, t, J = 6.9 Hz), 2.86 (3H, s), 1.80–1.70 (2H, m), 1.43 (9H, s); MS (EI) m/z 422 (M^+); HRMS calcd for $C_{20}H_{30}N_4O_4S$ 421.1910, found 421.1933.

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Supplementary Material Available: Experimental procedures for the preparation of **11**, **12**, **10e**, **24**, **27**, and **28**, characterization data for final products **8a–c,e,f,h–l**, **30**, and **45**, and a table of microanalytical data for novel compounds (7 pages). Ordering information is given on any current masthead page.

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