Novel 5-HT$_3$ Antagonists. Indole Oxadiazoles

C. J. Swain,*,† R. Baker,† C. Kneen, J. Moseley,† J. Saunders,† E. M. Seward,† G. Stevenson,† M. Beer,‡ J. Stanton,‡ and K. Watling‡

Department of Medicinal Chemistry and Department of Biochemistry, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, England. *Received March 21, 1990*

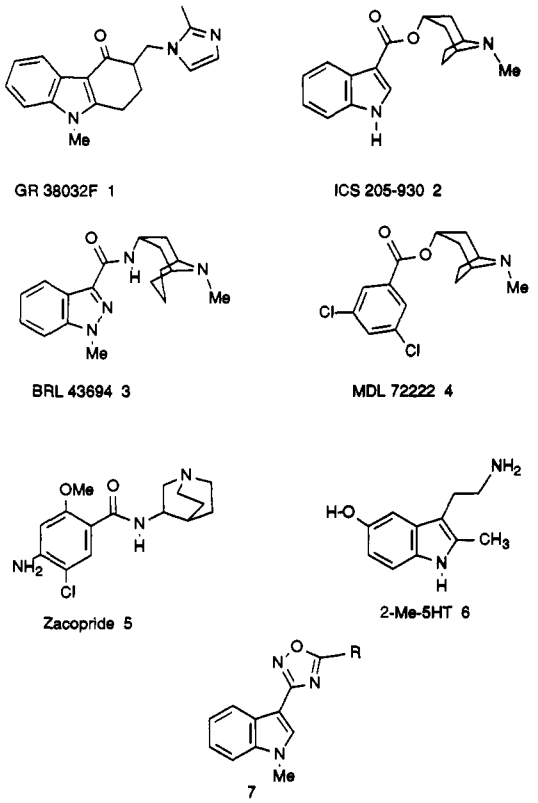
The synthesis and biochemical evaluation of a series of indole oxadiazole 5-HT$_3$ antagonists are described. The key pharmacophoric elements have been defined as a basic nitrogen, a linking group capable of H-bonding interactions, and an aromatic moiety. The steric limitations of the aromatic binding site have been determined by substitution about the indole ring. Variation of the heterocyclic linking group has shown that while two hydrogen-bonding interactions are possible, only one is essential for high affinity. The environment of the basic nitrogen has been investigated and shown to be optimal when constrained within an azabicyclic system. These results have been incorporated into a proposed binding model for the 5-HT$_3$ antagonist binding site, in which the optimum distance between the aromatic binding site and the basic amine is 8.4–8.9 Å and the steric limitations are defined by van der Waals difference mapping.

Introduction

Currently four broad classes of 5-HT (5-hydroxytryptamine) receptors are recognized (5-HT$_1$, 5-HT$_2$, 5-HT$_3$, 5-HT$_4$).[1a-d] While ligands for the first two receptors are well documented, recent attention has focused on the 5-HT$_3$ receptor. A number of potent 5-HT$_3$ receptor antagonists have been reported (GR 38032F (1),[2] ICS 205-930 (2),[3] BRL 43694 (3),[4] MDL 72222 (4),[5] Zacopride (5),[6]) (Chart I) and shown to be effective in the control of cancer chemotherapy-induced emesis.[7,8] In addition, evidence has been presented for the therapeutic roles of this class of compounds in migraine,[9] schizophrenia,[10] and anxiety.[11] If these results can be translated into clinical efficacy they would provide important new therapies. While a number of 5-HT$_3$ antagonists have been described, the only agonist showing selectivity for the 5-HT$_3$ receptor is 2-methyl-5-HT (6).[3]

The key pharmacophoric elements of the known 5-HT$_3$ antagonists can be regarded as an aromatic moiety (preferably indole), a linking acyl group, and a basic amine. This simple model can be further refined by consideration of the possible hydrogen-bonding interactions available. In the cases of 1, 2, and 4, the linking group is capable of accepting one or two hydrogen bonds. The amides 3 and 5 are also capable of taking part in two hydrogen-bonding interactions as acceptor and donor. It was speculated that it might be of advantage to design ligands that would offer the opportunity of participating in two hydrogen-bonding interactions and to use these systems to evaluate the contribution made to receptor binding by each of the possible hydrogen-bonding interactions. A number of five-membered heterocyclic rings were evaluated by comparison of their electrostatic maps, and the 1,2,4-oxadiazole selected as offering considerable similarity with the known systems. It has previously been demonstrated in both the cholinomimetic system[12] and the benzodiazepines[13] that the 1,2,4-oxadiazole is an excellent bioisosteric replacement for esters. While incorporation of a five-membered ring would increase the distance between the aromatic binding site and the basic nitrogen, it was felt that by varying the structure of the azacyclic system it would be possible to optimize this distance. In addition, most of the known 5-HT$_3$ receptor antagonists are ester or amide derivatives and are thus potentially susceptible to hydrolysis. This unwanted property could be obviated by incorporation of H-bond acceptors within a five-membered heteroaromatic ring. In this paper, we report the syntheses, receptor-binding properties and modeling data for a series of indole

Chart I



*To whom correspondence should be addressed.
†Department of Medicinal Chemistry.
‡Department of Biochemistry.

(1) (a) Richardson, B. P.; Engel, G. *Trends Neurosci.* 1986, *9*, 424–428. (b) Serotonin: Actions, Receptors, Pathophysiology. *Proceedings of the 1987 IUPHAR Congress Satellite Meeting*; Heron Island, Australia, 1987; Mylecharane, E. J., de la Lande, I. S., Angus, J. A., Humphrey, P. P. A. Eds.; Macmillan: London, 1987. (c) Peroutka, S. J. *Trends Neurosci.* 1988, *11*, 496–500. (d) Clarke, D. E.; Craig, D. A.; Fozard, J. R. *Trends Pharmacol. Sci.* 1989, *10*, 385–386.
(2) Butler, A.; Hill, J. M.; Ireland, S. J.; Jordan, C. C.; Tyers, M. B. *Br. J. Pharmacol.* 1988, *94*, 397–412.
(3) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* 1985, *316*, 126–131.
(4) Sanger, G. J.; Nelson, G. R. *Eur. J. Pharmacol.* 1989, *159*, 113–124.
(5) Fozard, J. R. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1984, *326*, 36–44.
(6) Smith, W. W.; Sancilio, L. F.; Owera-Atepo, J. B.; Naylor, R. J.; Lambert, L. J. *Pharm. Pharmacol.* 1988, *40*, 301–302.
(7) Leibundgut, U.; Lancranjan, I. *Lancet* 1987, No. i, 1198.

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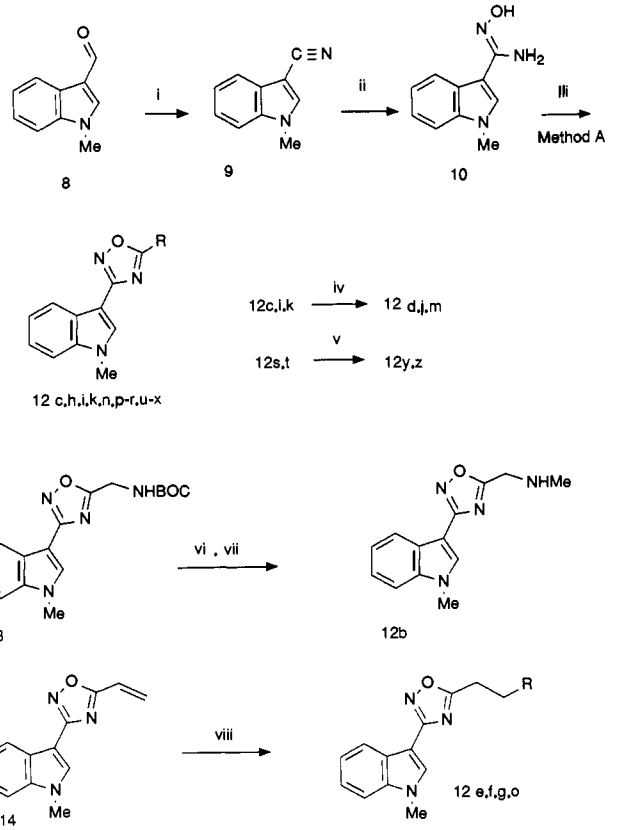
Scheme I[a]



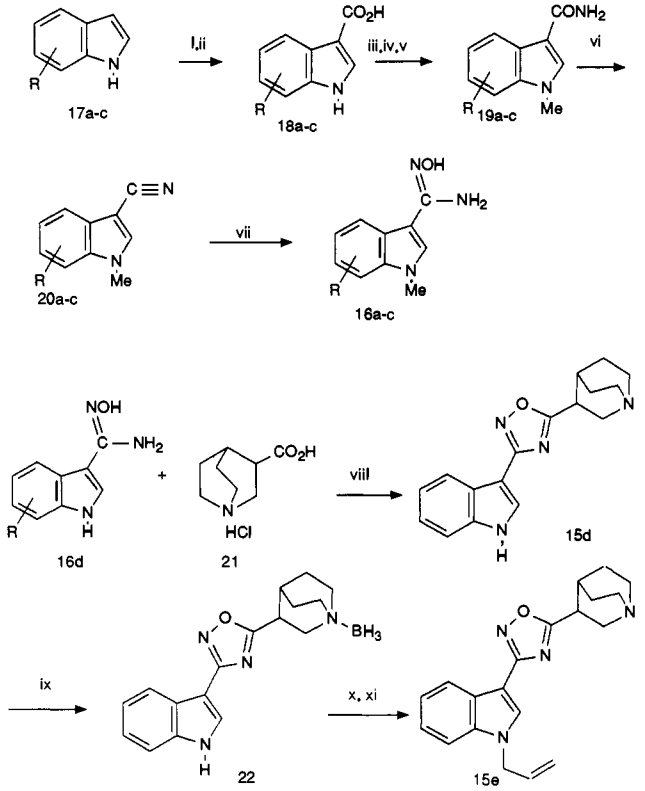
[a] Reagents: (i) ammonium phosphate dibasic, acetic acid, PrNO$_2$; (ii) H_2NOH·HCl, K_2CO_3, MeOH; (iii) NaH, THF, RCO_2R' (11); (iv) MeI, acetone; (v) CH_2O, HCO_2H; (vi) NaH, MeI; (vii) TFA; (viii) R'R''NH·MeOH.

oxadiazoles **7** and related analogues.

Results

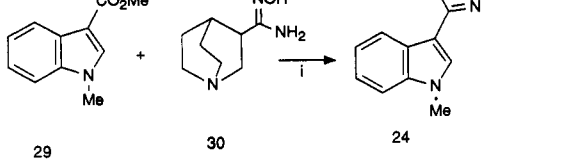
Synthetic Chemistry. 1-Methyl-1*H*-indole-3-carboxaldehyde (**8**) provided the starting point for the synthesis of the 3-indol-3-yl-1,2,4-oxadiazoles **7**. Treatment of the aldehyde **8** with diammonium hydrogen phosphate in nitropropane[14] (Scheme I) yielded the corresponding nitrile **9**; subsequent reaction with hydroxylamine afforded the amide oxime **10**. This was reacted in the presence of sodium hydride in tetrahydrofuran (method A) with a variety of esters **11** (Tables II and III) to yield the desired oxadiazoles **12c,h,i,k,n,p–r,u–x** (Scheme I); the esters were either commercially available or prepared by literature routes. The quaternary ammonium salts **12d,j,m** were

Scheme II[a]



[a] Reagents: (i) TFAA; (ii) NaOH, H_2O; (iii) KOH, MeI, acetone; (iv) $(COCl)_2$; (v) NH_3, CH_2ClCH_2Cl; (vi) TFAA, NEt_3, dioxan; (vii) H_2NOH, K_2CO_3, MeOH; (viii) NEt_3, isobutyl chloroformate; (ix) BH_3, THF; (x) NaH, THF, allyl bromide; (xi) MeOH, HCl.

Scheme III[a]



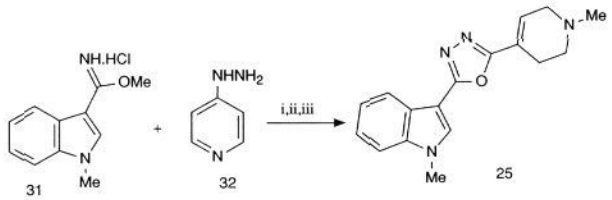
[a] Reagents: (i) NaH, THF.

prepared by treatment of the corresponding tertiary amines **12c,i,k** with methyl iodide. Amines **12a,l,s,t** were prepared from the *N*-BOC-protected esters **11a,l,s,t** according to method A; deprotection with trifluoroacetic acid afforded **12a,l,s,t** as the trifluoroacetate salts. Treatment of the protected amine **13** with sodium hydride and methyl iodide and subsequent deprotection with trifluoroacetic acid, afforded the secondary amine **12b**. Eschweiler–Clarke methylation of **12s,t** afforded **12y,z**. Amines **12e,f,g,o** were prepared by conjugate addition of the appropriate amine onto the intermediate alkene **14** (method B) which was prepared by condensation of **10** with methyl acrylate.

Substitution about the indole ring, affording **15a–c** (Table IV), was achieved by reaction of the substituted indole amide oximes **16a–c** and ester **11p** (method A) (Scheme II). The amide oximes **16a–c** were prepared from the substituted indoles **17a–c** by treatment with trifluoroacetic anhydride followed by base hydrolysis to afford the substituted acids **18a–c**. Methylation and subsequent conversion to the amides **19a–c** and dehydration afforded the appropriate nitriles **20a–c**. Reaction with

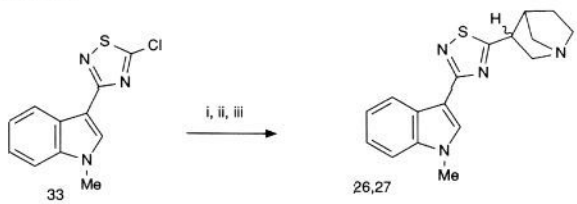
(8) Andrews, P. L. R.; Rapeport, W. G.; Sanger, G. J. *Trends Pharmacol. Sci.* **1988**, *9*, 334–341.
(9) Loisy, C.; Beorchia, S.; Centonze, V.; Fozard, J. R.; Schechter, P. J.; Tell, G. P. *Cephalagia* **1985**, *5*, 79–82.
(10) Costall, B.; Domeney, A. M.; Naylor, R. J.; Tyers, M. B. *Br. J. Pharmacol.* **1987**, *92*, 881–894.
(11) Jones, B. J.; Costall, B.; Domerey, A. M.; Kelly, M. E.; Naylor, R. J.; Oakley, N. R.; Tyers, M. B. *Br. J. Pharmacol.* **1988**, *93*, 985–993.
(12) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A.; Merchant, K.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 120.
(13) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Swain, C. J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282–2291.
(14) *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 656–658.

Scheme IV[a]



[a] Reagents: (i) MeOH; (ii) MeI, acetone; (iii) $NaBH_4$, MeOH.

Scheme V[a]



[a] Reagents: (i) LDA, **11u**, THF; (ii) NaOH; (iii) hydrochloric acid.

Table I. Displacement of [^{3}H]Q-ICS 205-930 (**36**) Binding to 5-HT_3 Recognition Sites in Rat Brain Membranes by Known 5-HT_3 Receptor Antagonists

no.	name	$pIC_{50} \pm SD$[a]
1	GR 38032F	8.71 ± 0.24
4	MDL 72222	7.66 ± 0.39
6	2-methyl-5-HT	6.19 ± 0.07

[a] SD, standard deviation from $n \geq 3$.

hydroxylamine then afforded the required amide oximes **16a–c** (Scheme II). Analogue **15d**, unsubstituted at the indole nitrogen, was prepared by condensation of the indole amide oxime **16d** and quinuclidine-3-carboxylic acid (**21**) in the presence of isobutyl chloroformate and triethylamine (Scheme II). The *N*-allyl-substituted analogue **15e** was prepared by treatment of the borane-protected compound **22** with sodium hydride and allyl bromide prior to treatment with methanolic hydrogen chloride (Scheme II). Analogues **15f–p** (Table IV), in which the 3-substituted indole is replaced by the 2-substituted indole or alternative aryl groups, were prepared from the corresponding amide oximes and ester **11p** according to method A. Demethylation of **15n–p** with boron tribromide afforded the phenolic derivatives **15q–s**.

The 5-indol-3-yl-1,2,4-oxadiazole **24** (Table V) was prepared according to method A from the indole ester **29** and the amide oxime **30**[15] (Scheme III). The 5-indol-3-yl-1,3,4-oxadiazole **25** (Table V) was prepared from the reaction of imino ether **31** with isonicotinic acid hydrazide (**32**); quaternization with methyl iodide and reduction with sodium borohydride gave the desired product (Scheme IV). The 3-indol-3-yl-1,2,4-thiadiazoles **26** and **27** (Table V) were prepared via nucleophilic attack of the enolate of ester **11u** onto the chlorothiadiazole **33**, followed by hydrolysis and decarboxylation (Scheme V). Thiazole **28** (Table V) was prepared by reaction of thioamide **34** with bromo ketone **35**, followed by quaternization and reduction (Scheme VI).

Interaction of Compounds with Central 5-HT_3 Recognition Sites. The affinity of a number of known ligands (Table I) and of each the new compounds **12a–z**, **15a–s**, and **24–28** (Tables II–V) for the 5-HT_3 antagonist

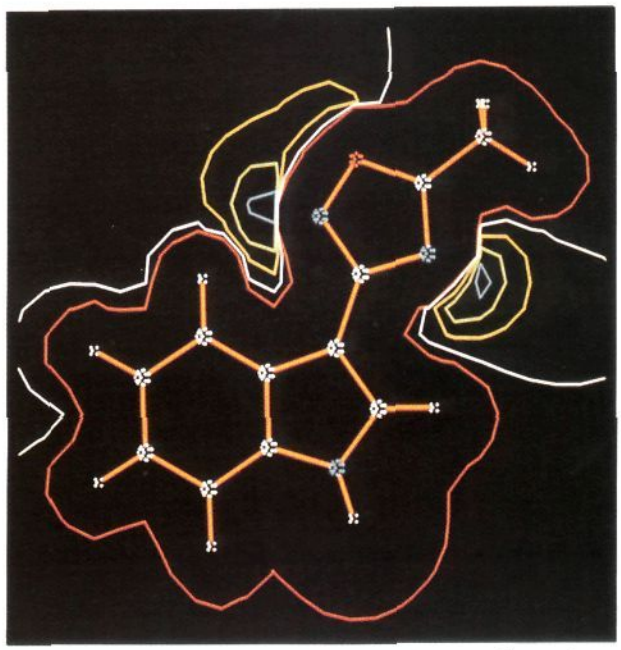
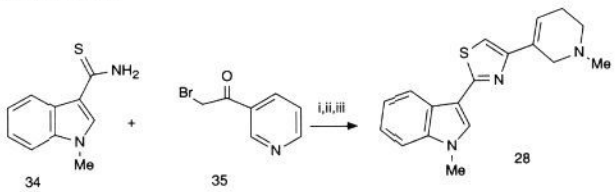


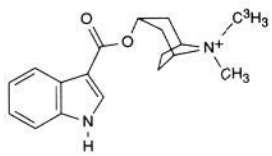
Figure 1. Electrostatic maps generated with use of denpot from charges calculated by using GAUSSIAN80 with the QM interface within CHEMX. Contours are as follows: -80, light blue; -60, blue; -40, light green; -20, yellow; 0, white; 20, red (kcal mol^{-1}).

Scheme VI[a]



[a] Reagents: (i) DMF, reflux; (ii) MeI, acetone; (iii) $NaBH_4$, MeOH.

binding site in rat cortical membranes was measured by its ability to displace the specific binding of the radiolabeled antagonist [^{3}H]Q-ICS 205-930 (**36**) by using previously described methods.[16] All compounds displaced



Q-ICS 205-930 **36**

the radioligand with a mass action profile and a Hill coefficient close to unity. All compounds behaved as antagonists in a variety of pharmacological models (von Bezold–Jarisch reflex, isolated rabbit heart, rat vagus nerve, and rat superior cervical ganglion) results of which will be reported separately.

Discussion

We first sought to optimize the environment of the charged nitrogen (Tables II and III) using the indole oxadiazole **12a** as the starting point for the structure–activity relationship (SAR). In the series bearing simple alkyl amino substituents (**12a–h**) increasing substitution re-

(15) The preparation of amide oxime **30** has been described in European Patent 239309, 1987.

(16) Watling, K. J.; Aspley, S.; Swain, C. J.; Saunders, J. *Eur. J. Pharmacol.* **1988**, *149*, 397.

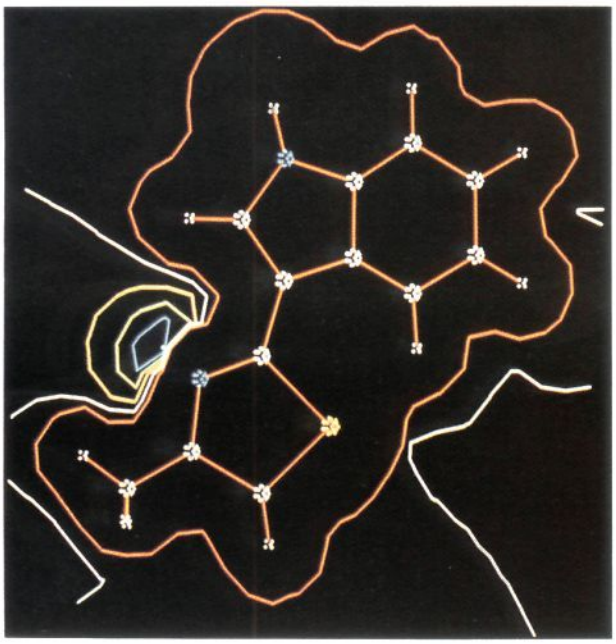


Figure 2. Electrostatic maps generated with use of denpot from charges calculated by using GAUSSIAN80 with the QM interface within CHEMX. Contours are as follows: -80, light blue; -60, blue; -40, light green; -20, yellow; 0, white; 20, red (kcal mol^{-1}).

sulted in increased affinity, and variation in the separation between oxadiazole and nitrogen indentified a two-carbon linkage to be optimal. Interestingly, while quaternization of the simple aminomethyl (**12a**, pIC_{50} 6.55; **12d**, pIC_{50} 9.15) increased affinity, in all other examples (**12i** and **12j**, **12k** and **12m**) quaternization resulted in a small decrease in affinity (Table II). This may be the result of unfavorable steric interactions arising from the longer linkage between the oxadiazole and nitrogen. It is more likely that this reflects the inductive effect of the oxadiazole ring causing a reduction in the pK_a of the basic nitrogen, (e.g. **12a–c** and **12e–g**). This effect would be more pronounced with the one-carbon linkage, and the quaternary compounds would be unaffected by the inductive effect. Constraining the charged amine within a six-membered ring (**12i–o**) maintained affinity. However, introduction of unsaturation into the ring (**12l,n**) caused a 10-fold reduction in binding affinity, possibly reflecting the reduction in pK_a of the basic nitrogen, (e.g. **12i** (pK_a 7.7[17]) and **12n** (pK_a 7.2[17]), Table II). It has previously been shown in the cholinomimetic area[12] that an azabicyclic system is an excellent bioisosteric replacement for the quaternary ammonium group of acetylcholine. Given the potency of the quaternary analogue (**12d**), introduction of an azabicyclic system was highly desirable to increase CNS penetration since the pK_a of the basic nitrogen (pK_a 8.4) would ensure a precentage of the unprotonated compound to be present at pH 7.4. As anticipated, constraining the nitrogen within an azabicyclic system yielded a number of very potent ligands (**12p–z**) (Table III). Highest affinity was observed for those systems having the nitrogen at the bridgehead position thus allowing the optimum in charge

(17) There is a high degree of correlation between the pK_a values of the indole oxadiazole series and an analogous series in which a methyl group replaces the indole moiety, see **12c,g,l,n** (Table II). The indole oxadiazoles **12i,k** were not sufficiently soluble in aqueous solution to enable pK_a values to be determined accurately; because of the high correlation noted above pK_a values of the analogous series were substituted for these two compounds.

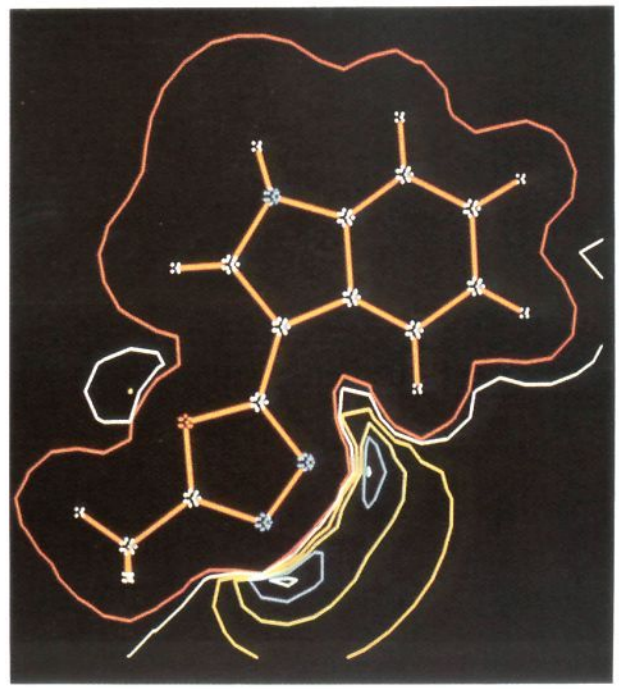


Figure 3. Electrostatic maps generated with use of denpot from charges calculated by using GAUSSIAN80 with the QM interface within CHEMX. Contours are as follows: -80, light blue; -60, blue; -40, light green; -20, yellow; 0, white; 20, red (kcal mol^{-1}).

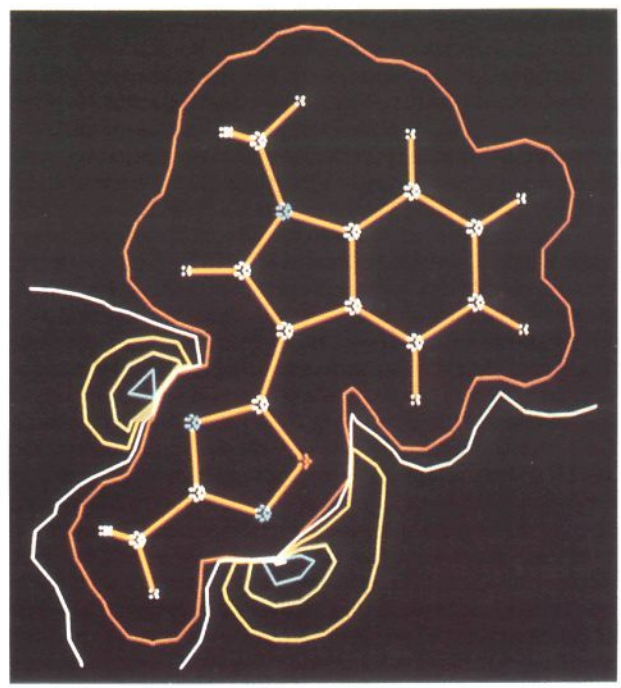
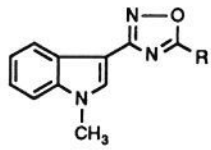
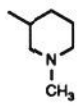
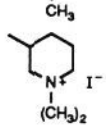
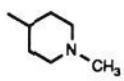
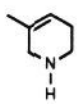
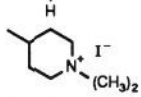
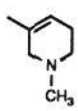
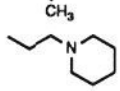


Figure 4. Electrostatic maps generated with use of denpot from charges calculated by using GAUSSIAN80 with the QM interface within CHEMX. Contours are as follows: -80, light blue; -60, blue; -40, light green; -20, yellow; 0, white; 20, red (kcal mol^{-1}).

distribution with the minimum of steric interference. The difference in affinity observed for the two isomeric [2.2.1] azabicyclic systems (**12v**, pIC_{50} 8.98) and (**12u**, pIC_{50} 8.12) is probably due to a reduction in a discrete region of lipophilic binding associated with the alkyl bridge rather than steric interactions because the [2.2.2] system retained high affinity (**12p**, pIC_{50} 8.86) (Table III). In general the tertiary amines are more potent than secondary amines (compare **12g** with **12f** and **12n** with **12l**), however in the

Table II. Displacement of [^{3}H]Q-ICS 205-930 (**36**) Binding to 5-HT$_3$ Recognition Sites in Rat Brain Membranes by Acyclic and Monocyclic Indole Oxadiazoles



no.	R	mp, °C	ester	formula	pK$_a$	pIC$_{50}$ ± SEM[g]
12a	CH_2NH_2	178[a]	$BOCRCO_2Et$	$C_{12}H_{12}N_4O$	6.4	6.55 ± 0.06
b	CH_2HNCH_3	195[a]	$BOCRCO_2Et$	$C_{13}H_{14}N_4O$	6.5	6.00 ± 0.05
c	$CH_2N(CH_3)_2$	197[b]	$BOCRCO_2Et$	$C_{15}H_{16}N_4O$	5.6 (5.6)[f]	6.78 ± 0.21
d	$CH_2N^+(CH_3)_3I$	218[c]	–	$C_{15}H_{19}N_4OI$	–	9.15 ± 0.12
e	$CH_2CH_2NH_2$	163[d]	–	$C_{13}H_{14}N_4O$	*e*	7.17
f	$CH_2CH_2NHCH_3$	190[d]	–	$C_{14}H_{16}N_4O$	8.8	7.07
g	$CH_2CH_2N(CH_3)_2$	180[d]	–	$C_{15}H_{18}N_4O$	7.7 (7.7)[f]	7.86
h	$CH_2CH_2CH_2N(CH_3)_2$	154[d]	RCO_2Me	$C_{14}H_{16}N_4O$	–	6.72 ± 0.14
i		217[d]	RCO_2Me	$C_{17}H_{20}N_4O$	*e* (7.7)[f]	7.89 ± 0.08
j		250	–	$C_{18}H_{23}N_4OI$	–	7.46 ± 0.09
k		198[d]	RCO_2Et	$C_{17}H_{20}N_4O$	*e* (8.5)[f]	7.88 ± 0.31
l		167[a]	RCO_2Et	$C_{16}H_{16}N_4O$	7.9 (7.9)[f]	6.33
m		246	–	$C_{18}H_{23}N_4OI$	–	7.45 ± 0.08
n		232[d]	–	$C_{17}H_{18}N_4O$	7.2 (7.2)[f]	6.68
o		186[d]	–	$C_{18}H_{22}N_4O$		6.43

[a] TFA salt. [b] HCl salt. [c] Decomposed. [d] Oxalate salt. [e] Value could not be determined because of poor water solubility. [f] Values quoted in parentheses refer to water-soluble analogues in which a methyl group replaces the indole moiety.[17] [g] SEM = standard error of the mean from $n \geq 3$. Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10% of the mean.

azabicyclic systems the secondary amines are more potent (compare **12s** with **12y** and **12t** with **12z**) perhaps due to the increased rigidity or the increased bulk of the azabicycle accentuating steric interactions.

Substitution at the 5- or 7-positions of the indole nucleus caused a reduction in binding affinity (**15a–c**) (Table IV) and while methyl was tolerated at the 1-position, any larger substituents decreased potency (**15e**). Replacement of indole by indazole (**15h**, pIC$_{50}$ 7.75) (Table IV) resulted in a reduction in affinity, a surprising result given that indazoles have been shown to be excellent bioisosteric replacements for indoles in other systems (BRL 43694 (**3**)).[4] A variety of alternative aromatic systems (Table IV) were evaluated in an effort to identify replacements for indole: replacement by naphthyl (**15k** and **15l**) or quinolyl (**15m**) all resulted in reduced affinity emphasizing the steric limitations of the aromatic binding site. Replacement of the indole by an unsubstituted aromatic ring resulted in dramatic drop in affinity (**15i**, pIC$_{50}$ 6.70) (Table IV); however, the affinity can be improved by introduction of the methoxy-substituent mimicking the electron-rich indole nucleus. While the 3-methoxy-substituted analogue (**15n**, pIC$_{50}$ 7.9) had the highest affinity and can thus be

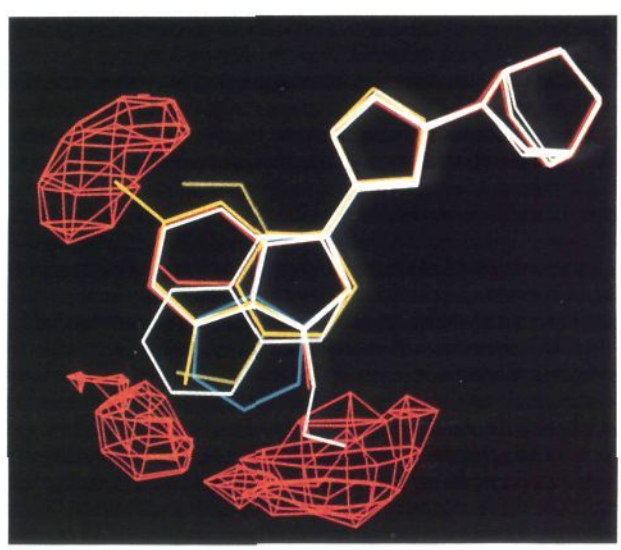
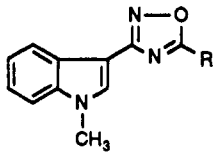
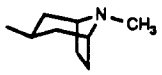
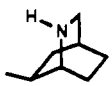
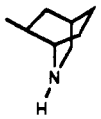
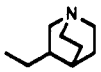
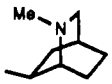


Figure 5. VDW difference map showing dissallowed volume: **12p**, white; **15n**, red; **15b**, yellow; **15c**, yellow; **15g**, dark blue; **15l**, light blue; **15o**, light green; **15p**, light green; **12e**, white.

Table III. Displacement of [^{3}H]Q-ICS 205-930 (**36**) Binding to 5-HT$_3$ Recognition Sites in Rat Brain Membranes by Azabicyclic Indole Oxadiazoles



no.	R	mp, °C	ester	formula	pIC$_{50}$ ± SEM[c]
12p		163[a]	RCO_2Me	$C_{18}H_{20}N_4O$	8.86 ± 0.25
q		210[a]	RCO_2Me	$C_{18}H_{20}N_4O$	6.89 ± 0.06
r		209[a]	RCO_2Me	$C_{19}H_{22}N_4O$	6.72 ± 0.02
s		145[a]	$BOCRCO_2Me$	$C_{18}H_{20}N_4O$	7.05
t		218[a]	$BOCRCO_2Me$	$C_{18}H_{20}N_4O$	7.88 ± 0.17
u		165[a]	RCO_2Me	$C_{17}H_{18}N_4O$	8.12 ± 0.27
v		153[a]	RCO_2Me	$C_{17}H_{18}N_4O$	8.98 ± 0.20
w		240[a]	RCO_2Me	$C_{18}H_{20}N_4O$	8.37
x		233[a]	RCO_2Et	$C_{19}H_{22}N_4O$	7.26 ± 0.18
y		125[b]		$C_{19}H_{22}N_4O$	6.65
z		133[b]		$C_{19}H_{22}N_4O$	7.07

[a] HCl salt. [b] Oxalate salt. [c] Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within ±10% of the mean.

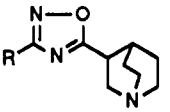
regarded as a good bioisosteric replacement for indole, the 2- and 4-substituted compounds possibly suffer from unfavorable steric interactions, since in these cases, demethylation improved affinity, (compare **15o**, pIC$_{50}$ 6.81 and **15r**, pIC$_{50}$ 7.38; **15p**, pIC$_{50}$ 5.80 and **15s** pIC$_{50}$ 6.83) (Table IV).

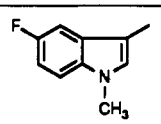
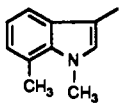
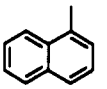
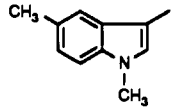
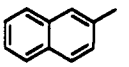
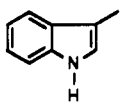
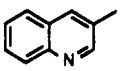
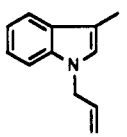
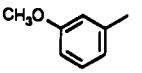
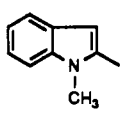
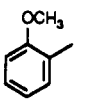
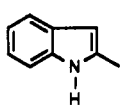
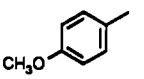
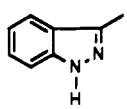
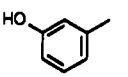
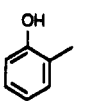
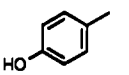
Modifications of the five-membered heterocyclic ring (Table V) confirmed the hypothesis of an essential hydrogen bonding interaction at N2 since transposition of N2 and O1 resulted in a reduction in affinity consistent with the loss of a hydrogen bond (e.g. **12p**, pIC$_{50}$ 8.96 and **24**, pIC$_{50}$ 7.62). While there is no direct analogue of the 1,3,4-oxadiazole (**25**, pIC$_{50}$ 6.19) (Table V) the observed SAR within the 1,2,4-oxadiazoles would suggest it should be comparable with **12n**, (pIC$_{50}$ 6.68) (Table II). This relatively small difference might be accounted for by the possibility of a second H-bonding interaction, however this interaction is not essential for high affinity. Interestingly, attempts to replace the oxadiazole with the corresponding thiadiazole resulted in a 10-fold reduction in affinity (e.g. **12u**, pIC$_{50}$ 8.13 and **27**, pIC$_{50}$ 7.69; **12v**, pIC$_{50}$ 8.98 and **26**, pIC$_{50}$ 7.85) (Tables II and V) while incorporation of a thiazole **28** resulted in an almost complete loss of activity.

These results are perhaps best explained by examination of the electrostatic potential maps generated using the GAUSSIAN80 program with CHEMX. Ab initio molecular orbital calculations[18] were carried out on these molecules with GAUSSIAN80[19] at the STO-3G level. The wavefunctions obtained were used in DENPOT80[20] to generate electrostatic potential maps using a two-dimensional grid consisting of 900 calculation points (30 × 30) over the molecule and surrounding space, in the plane of the aromatic ring. The electrostatic map (Figure 1) of the indole oxadiazole (with the basic amine replaced by methyl for clarity) shows two significant negative potentials associated with the two nitrogens of the oxadiazole ring. The oxadiazole is thus capable of accepting two hydrogen bonds; transposition of N2 and O1 results in a change in the position of the negative potential (Figure 2) and loss of the associated

(18) All quantum mechanical calculation were performed with the CHEMQM interface within the CHEMX program (Chemical Design Ltd., Oxford, U.K.).
(19) GAUSSIAN80 (QCPE 446) U. C. Singh and P. Kollman.
(20) DENPOT 80 (QCPE 483) D. Peters and M. Sana.

Table IV. Displacement of [^{3}H]Q-ICS 205-930 (**36**) Binding to 5-HT$_3$ Recognition Sites in Rat Brain Membranes by Azabicyclic Substituted Aromatic Oxadiazoles



no.	R	mp, °C	formula	pIC$_{50}$ ± SEM[c]	no.	R	mp, °C	formula	pIC$_{50}$ ± SEM[c]
15a		188[a]	$C_{18}H_{19}N_4OF$	7.34	j		146[b]	$C_{14}H_{16}N_4O$	5.53 ± 0.13
b		148[b]	$C_{19}H_{22}N_4O$	7.02	k		148[b]	$C_{19}H_{19}N_3O$	7.20
c		198[b]	$C_{19}H_{22}N_4O$	6.48 ± 0.27	l		187[a]	$C_{19}H_{19}N_3O$	5.83 ± 0.11
d		226[a]	$C_{17}H_{16}N_4O$	8.57 ± 0.36	m		138[a]	$C_{18}H_{16}N_4O$	5.82 ± 0.06
e		94[b]	$C_{20}H_{22}N_4O$	7.66 ± 0.11	n		156[a]	$C_{18}H_{19}N_3O$	7.90
f		189[a]	$C_{18}H_{20}N_4O$	6.17	o		260[a]	$C_{16}H_{19}N_3O_2$	6.81
g		181[a]	$C_{17}H_{16}N_4O$	6.16	p		266[a]	$C_{16}H_{19}N_3O_2$	5.80
h		215[b]	$C_{18}H_{17}N_4O$	7.75	q		239[a]	$C_{15}H_{17}N_3O_2$	7.09
i		150[b]	$C_{15}H_{17}N_3O$	6.70 ± 0.15	r		197[a]	$C_{15}H_{17}N_3O_2$	7.38
					s		263[a]	$C_{15}H_{17}N_3O_2$	6.83

[a] HCl salt. [b] Oxalate salt. [c] Where SEM is not quoted the figures are the mean of two independent determinations typically with the individual values within ±10% of the mean.

hydrogen bond. In the case of the 1,3,4-oxadiazole (Figure 3), while two negative potentials exist, that associated with the oxygen is relatively small. This difference would suggest that while a second hydrogen-bonding interaction is possible, it contributes little to the overall affinity. In the case of the thiazole (Figure 4) there is only a single negative potential and the complete loss in affinity emphasizes the requirement for a hydrogen-bonding interaction at N-2 of the oxadiazole. The electrostatic map (not shown) of the 2-indolyl derivative (**15f**) in the region of the oxadiazole shows little variation from the 3-indolyl analogue, suggesting the difference in affinity is best explained by unfavorable steric interactions.

Receptor Model. The simple model of the antagonist binding described above can now be refined to accommodate the SAR observed within the series of compounds. The effect of substitution in the indole ring serves to emphasize the steric restrictions of the aromatic binding site; this is illustrated by the VDW (van der Waals) difference map (Figure 5). This map was created by first superimposing the quinuclidine skeleton and oxadiazole ring of all the structures under consideration by using the least-squares fitting routine within CHEMX. A total VDW volume map of all the less active structures (**15b,c,e,g,l,o,p**) was generated from which was subtracted the total VDW volume for the active structures and (**12p**, **15n**), the result is shown in Figure 5. The position of the two possible hydrogen-bonding interactions to the five-membered ring can also be defined (A and B), with the hydrogen bond A being essential for high affinity. The optimum distance between the center of the benzene ring of the indole and the basic nitrogen appears to be within the range 8.4–8.9 Å. However, because of the conformational flexibility of these ligands, in particular rotation around the bond linking the oxadiazole and azacycle, it is not possible to identify the relative position of the binding site for the protonated nitrogen, or for the lipophilic interactions that appear to play an important role in the binding of the azabicyclic systems.

Receptor Selectivity. The pharmacological specificity

of one of the compounds (**12p**) for central 5-HT recognition sites was examined by investigating the compound in a wide variety of central binding assays. These included assays for serotonin receptors (5HT$_1$, [^{3}H]-8-OH-DPAT, 5-HT$_{1B}$ [^{125}I]-cyanopindolol, 5-HT$_{1D}$ [^{3}H]-5-HT, 5-HT$_2$, [^{3}H]-ketanserin), dopamine receptors ([^{3}H]-SCH 23390, [^{3}H]-spiperone), muscarinic receptors ([^{3}H]-NMS, [^{3}H]-oxo-M), adrenergic receptors ([^{3}H]-prazosin, [^{3}H]-rauwolscine, [^{125}I]-iodopindolol), histamine receptors ([^{3}H]-pyrilamine), amino acid receptors ([^{3}H]-glutamate, [^{3}H]-kainate, [^{3}H]-glycine, [^{3}H]-AMPA, [^{3}H]-GABA), channel blockers ([^{3}H]-strychnine, [^{3}H]-MK-801, [^{3}H]-ω-conotoxin, [^{125}I]-charybdotoxin, [^{3}H]-verapamil, [^{3}H]-nitrendipine, [^{3}H]-diltiazam, [^{3}H]-fluspirilene), peptide receptors ([^{125}]-BH-SP, [^{125}I]-BH-ELE, [^{125}]-BH-CCK) and [^{3}H]-Ro15-1788 (benzodiazepine), [^{3}H]-DTG (sigma), [^{3}H]-forskolin, and [^{3}H]-imipramine recognition sites. The apparent affinities, measured as pIC$_{50}$ values, for **12p** were all < 5, demonstrating that the compound was inactive at displacing binding to a large number of central recognition sites.

Experimental Section

Chemistry. General Directions. Except where otherwise stated, the following procedures were adopted: all ^{1}H NMR spectra were recorded at 360 MHz on a Brucker AM 360 instrument, mass spectra with a VG 70-250 mass spectrometer, and infrared spectra on a Perkin-Elmer 782 IR spectrophotometer. Organic solvents were purified when necessary by the methods described by D. D. Perrin, W. L. F. Armarego, and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon: Oxford, 1986) or were purchased from The Aldrich Chemical Co., Sureseal). All solutions were dried over anhydrous sodium sulfate and evaporated on a Buchi rotary evaporator, with a water bath temperature of 40 °C or below. Thin-layer chromatography and preparative chromatography were performed on silica, with use of plates (Merck Art No. 5719) and gravity columns (Merck Art No. 7734), or on alumina with use of plates (Merck Art No. 5550) and gravity columns (Woelm Alumina Act. 2). Melting points are uncorrected.

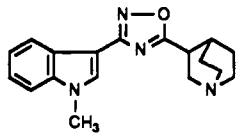
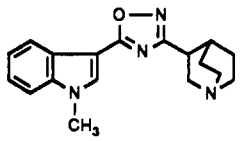
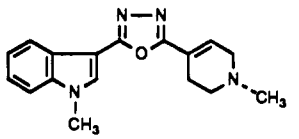
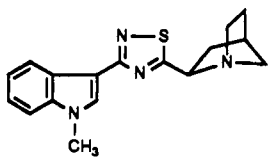
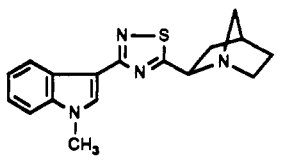
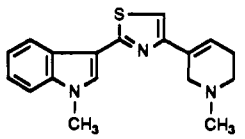
1-Methyl-1*H*-indole-3-carboxamide Oxime (10). A suspension of hydroxylamine hydrochloride (1.3 g, 18.7 mmol), potassium carbonate (3.5 g, 25.3 mmol), and 1-methyl-1*H*-indole-3-carbonitrile (**9**)[14] (2.0 g, 12.8 mmol) in absolute ethanol (100 mL) was heated at reflux for 8 h. The reaction mixture was cooled, filtered to remove inorganic salts, and was concentrated under vacuum. The residue was purified by column chromatography by use of a gradient elution of dichloromethane to 40% acetone in dichloromethane. The starting material was recovered in 40% yield, 0.8 g. The product was obtained as a clear oil which crystallized upon addition of ether, giving 0.95 g (40%) **10**: mp 189–190 °C; ^{1}H NMR ($CDCl_3$), δ 3.60 (s, 3 H, NCH_3), 6.8–7.0 (m, 2 H, H-5, H-6), 7.11 (d, J = 8 Hz, 1 H, H-7), 7.20 (s, 1 H, H-2), 7.90 (d, J = 8 Hz, 1 H, H-4); MS m/e 173 (M^+, 25), 158 (40), 156 (100). Anal. ($C_{10}H_{11}N_3O$) C, H, N.

General Method A. 5-[(Dimethylamino)methyl]-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (12c). This procedure illustrates the general method for preparation of **12c,h,i,k,n,p–r,u,x**. The amide oxime **10** (0.94 g, 5 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL) containing 4-Å powdered molecular sieves (2 g). This mixture was stirred for 30 min. Sodium hydride (0.1 g of 80% dispersion in oil, 5.2 mmol) was added and the mixture was heated at 60 °C for 20 min or until evolution of hydrogen had subsided. The mixture was cooled to room temperature, and a solution of ethyl (dimethylamino)-glycine (1.31 g, 10 mmol) in tetrahydrofuran was added. The resulting mixture was heated at reflux for 1 h, cooled, and filtered, and the filtrate concentrated under vacuum. The residue was purified by chromatography on silica with dichloromethane in acetone as eluant to afford a colorless oil (0.7 g, 55%). A sample was further purified by dissolution in ether and a solution of ethanolic hydrogen chloride was added; the resulting precipitate was removed by filtration and was recrystallized from acetone to afford **12c** as a white crystalline solid: mp 197 °C; ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 6 H, NMe_3), 3.75 (s, 3 H, NMe), 4.79 (s, 2 H, CH_2N), 7.29 (m, 2 H, H-5, H-6), 7.47 (d, J = 8 Hz, 1 H, H-7), 7.73 (s, 1 H, H-2), 7.87 (d, J = 8 Hz, 1 H, H-7), 7.73 (s, 1 H, H-2), 7.87 (d, J = 8 Hz, 1 H, H-4); MS m/e 259 (M^+, free base, 20), 216 (30), 214 (55), 139 (100). Anal. ($C_{14}H_{17}N_4O_4Cl$) C, H, N.

[[3-(1-Methyl-1*H*-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl]trimethylammonium Iodide (12d). 12d,j,m, were prepared by quaternization of the corresponding tertiary amines **12c,i,k**; the procedure adopted for the synthesis of **12d** is described. Methyl iodide (164 mg, 1.1 mmol) was added to a stirred solution of **12c** (300 mg, 1.1 mmol) in anhydrous acetone (30 mL). This solution was stirred for 2 h; during this time the product precipitated as a white crystalline solid and was isolated by filtration (400 mg, 91%): mp 218 °C dec; ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 9 H, N^+Me_3) 3.93 (s, 3 H, NMe), 5.11 (s, 2 H, CH_2), 7.25–7.35 (m, 2 H, H-5, H-6), 7.80 (d, J = 8 Hz, H-7), 8.03 (d, J = 8 Hz, 1 H, H-4), 8.22 (s, 1 H, H-2). Anal ($C_{15}H_{19}N_4OI$) C, H, N.

5-(Aminomethyl)-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Trifluoroacetate (12a). Amines **12a,l,s,t** were prepared from the *N*-BOC-protected esters **11a,l,s,t** according to method A. The procedure adopted for the synthesis of **12a** is described. Ethyl *N*-(butoxycarbonyl)glycinate (**11a**) (2.0 g, 9.8 mmol) and **10** (0.94 g, 5 mmol) were reacted according to method A affording 5-[[(*tert*-butoxycarbonyl)amino]methyl]-3-(1-methyl-1*H*-indol-

Table V. Displacement of [^{3}H]Q-ICS 205-930 (**36**) Binding to 5-HT$_3$ Recognition Sites in Rat Brain Membranes by Azabicyclic Indole Heterocycles

compd	mp, °C	formula	pIC$_{50}$ ± SEM[c]
 **12p**	163[a]	$C_{18}H_{20}N_4O$	8.86 ± 0.25
 **24**	170[b]	$C_{18}H_{20}N_4O$	7.53
 **25**	270[a]	$C_{17}H_{18}N_4O$	6.30
 **26**	196[b]	$C_{18}H_{17}N_4S$	7.85
 **27**	171[b]	$C_{18}H_{17}N_4S$	7.69
 **28**	235[b]	$C_{18}H_{19}N_3S$	5.23

[a] Oxalate. [b] HCl. [c] Where SEM is not quoted the figures are the mean of two independent determinations typically with individual values within 10% of the mean.

3-yl)-1,2,4-oxadiazole (**13**) which was purified on silica with use of dichloromethane as eluant, affording a pale yellow solid (1.4 g, 90%): mp 150 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H, *t*-Bu), 3.83 (s, 3 H, NMe), 4.60 (br s, 2 H, CH_2N), 5.28 (br s, 1 H, NH), 7.25–7.37 (m, 3 H, H-5, H-6, H-7), 7.76 (s, 1 H, H-2), 8.20 (d, J = 7 Hz, 1 H, H-4). **13** (300 mg, 1 mmol), was dissolved in dichloromethane (10 mL) at 0 °C; trifluoroacetic acid (0.5 mL, 6 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 30 min. This was stirred for 12 h and was concentrated under vacuum. The residue was recrystallized from cold dichloromethane to afford **12a** as white crystals (150 mg, 44%): mp 178 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3 H, NMe), 4.58 (s, 2 H, CH_2N), 7.24–7.35 (m, 2 H, H-5, H-6), 7.60 (d, J = 7 Hz, 1 H, H-4), 8.07 (d, J = 7 Hz, 1 H, H-7), 8.10 (s, 1 H, H-2); MS m/e 228 (M^+, free base, 70), 171 (100), 156 (80). Anal ($C_{14}H_{13}N_4O_3F_3$) C, H, N.

5-[(Methylamino)methyl]-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Trifluoroacetate (12b). **13** (300 mg, 1 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and cooled to 0 °C under a nitrogen atmosphere. Sodium hydride (0.1 g, 50% dispersion in oil, 2 mmol) was added followed by methyl iodide (0.1 mL, 1.6 mmol); the mixture was warmed to room temperature and stirred for 30 min. It was diluted with ether (20 mL), washed with water (10 mL), and dried, and the solvent removed under vacuum. The residue was purified by column chromatography on silica with dichloromethane as eluant; this afforded a colorless oil (300 mg, 92%), 5-[(*tert*-butoxycarbonyl)methylamino]-methyl]-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole (**37**). By using the procedure described for **12a**, **37** (300 mg, 0.9 mmol) was deprotected with trifluoroacetic acid and afforded **12b** as a white crystalline solid (170 mg, 53%): mp 195 °C; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3 H, Me), 3.92 (s, 3 H, NMe), 4.71 (s, 2 H, CH_2), 7.25–7.35 (m, 2 H, H-5, H-6), 7.60 (d, J = 7 Hz, 1 H, H-7), 8.07 (d, J = 7 Hz, 1 H, H-4), 8.13 (s, 1 H, H-2); MS m/e 242 (M^+, free base, 90), 171 (100), 156 (80). Anal. ($C_{15}H_{15}F_3N_4O_3$) C, H, N.

5-Ethenyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole (14). The amide oxime **10** (1.89 g, 10 mmol) and methyl acrylate (0.9 mL, 10 mmol) were reacted according to method A affording **14** as a colorless oil. This was purified on silica with dichloromethane as eluant (0.5 g, 22%): mp 54–55 °C (ether/hexane); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3 H, NMe), 5.92 (dd, J = 11, 1 Hz, 1 H, C*H*=CH_2), 6.54 (dd, J = 18, 1 Hz, 1 H, CH=C*H*H), 6.74 (dd, J = 18, 11 Hz, 1 H, CH=CH*H*), 7.26–7.34 (m, 3 H, H-5, H-6, H-7), 7.76 (s, 1 H, H-2), 8.23–8.26 (m, 1 H, H-4); MS m/e 225 (M^+, 100). Anal. ($C_{13}H_{11}N_3O$) C, H, N.

General Method B. 5-[(Dimethylamino)ethyl]-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Oxalate (12e). **12e,f,g,o** were prepared by conjugate addition of the appropriate amine with **14** according to method B. The procedure for **12e** is described. **14** (0.34 g, 1.5 mmol) was dissolved in methanol (50 mL) and tetrahydrofuran (10 mL). The solution was cooled to 0 °C; dry ammonia gas was bubbled through the solution for 2 h. The flask was securely sealed at 0 °C and was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure affording a yellow oil (0.36 g, 99%). The crude oil was purified by treatment with 1 equiv of oxalic acid in dichloromethane which precipitated the monooxalate salt as a white powder; this was recrystallized from methanol/acetone: mp 140–141 °C; ^{1}H NMR (D_2O) δ 3.44 (t, J = 7 Hz, 2 H, CH_2CH_2NH_2), 3.59 (t, J = 7 Hz, 2 H, CH_2CH_2NH_2), 3.88 (s, 3 H, CH_3), 7.36 (dt, J = 7, 1 Hz, ArH), 7.43 (dt, J = 7, 1 Hz, 1 H, ArH), 7.59 (d, J = 7 Hz, 1 H, H-7), 7.94 (s, 1 H, H-2), 8.03 (d, J = 8 Hz, 1 H, H-4); MS m/e 242 (M^+, free base, 90). Anal. ($C_{15}H_{18}N_4O_5$) C, H, N.

5-(Azabicyclo[2.2.2]octan-3-yl)-3-(1,7-dimethyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (15b). **15a–c** were prepared according to method A from the corresponding substituted amide oximes **16a–c**. The preparation of **15b** is described.

(a) 7-Methyl-1*H*-indole-3-carboxylic Acid (18b). Trifluoroacetic anhydride (6.25 mL, 44 mmol) was added dropwise to a stirred solution of 7-methyl-1*H*-indole (**17b**) (5 g, 38 mmol) in dimethylformamide (50 mL) at 0 °C. After 3 h the mixture was poured into water (200 mL) and the product isolated by filtration. The residue was washed with water (3 × 50 mL). This was suspended in 20% aqueous NaOH (200 mL) and heated at reflux overnight. The mixture was cooled, washed with CH_2Cl_2 (2 × 100 mL), and acidified. The precipitate was isolated by filtration and dried over P_2O_5 under vacuum (4.3 g, 65%): mp 218 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H, CH_3), 3.34 (6s, 1 H, NH), 6.97 (d, J = 7.1 Hz, 1 H, H-6), 7.05 (t, J = 7.3 Hz, 1 H, H-4), 7.96 (d, J = 3.0 Hz, 1 H, H-2), 11.83 (6s, 1 H, COOH); MS m/e 175 (M^+, 100).

(b) 1,7-Dimethyl-1*H*-indole-3-carboxylic Acid. Methyl iodide (30.0 g, 0.2 mol) was added to a stirred mixture of 7-methyl-1*H*-indole-3-carboxylic acid (**18b**) (4.3 g, 24 mmol) and powdered potassium hydroxide (20.0 g, 0.35 mol) in anhydrous acetone (200 mL) at 0 °C. The resulting suspension was then stirred at room temperature overnight, then poured into water (500 mL), washed with dichloromethane (3 × 100 mL) and the aqueous phase acidified to pH 2 with hydrochloric acid. The product was isolated by filtration and dried under vacuum to afford white crystals (4.5 g, 97%): mp 243 °C; ^{1}H NMR (DMSO-d_6) δ 2.72 (s, 3 H, CH_3), 4.09 (s, 3 H, NMe), 6.92 (d, J = 6 Hz, H-6), 7.02 (t, J = 6 Hz, 1 H, H-2); MS m/e 189 (M^+, 100).

(c) 1,7-Dimethyl-1*H*-indole-3-carboxamide (19b). Oxalyl chloride (6.0 g, 48 mmol) was added dropwise to a stirred solution of 1,7-dimethyl-1*H*-indole-3-carboxylic acid (4.5 g, 24 mmol) in tetrahydrofuran (50 mL) at 0 °C. When the addition was complete the solution was stirred for 12 h at room temperature. The solvent was evaporated at reduced pressure, the residue was dissolved in dichloroethane (100 mL), and ammonia was bubbled through the solution for 5 h. The solvent was removed at reduced pressure, and the residue triturated with water (20 mL) to yield a white solid (4.4 g, 100%): mp 197 °C; ^{1}H NMR (DMSO-d_6) δ 2.72 (s, 3 H, CH_3), 4.03 (s, 3 H, NCH_3), 6.67 (d, J = 6 Hz, H-6), 6.96 (t, J = 6 Hz, 1 H, H-5), 7.86 (s, 1 H, H-2), 8.00 (d, J = 6 Hz, 1 H, H-4); MS m/e 188 (M^+, 55), 172 (100), 88 (40).

(d) 1,7-Dimethyl-1*H*-indole-3-carbonitrile (20b). Trifluoroacetic anhydride (20.0 g, 0.14 mmol) was added dropwise to a stirred solution of the amide (**19b**) (4.4 g, 23 mmol) in dioxane (200 mL) and triethylamine (19 g, 0.19 mmol) at 0 °C. The resulting mixture was stirred for 12 h at room temperature. It was then diluted with dichloromethane (500 mL) and washed with water (3 × 200 mL), the organic phase was dried, and the solvent was removed at reduced pressure. The residue was purified by chromatography on silica, with dichloromethane as eluant; this afforded a white solid (3.0 g, 75%): mp 116 °C; ^{1}H NMR ($CDCl_3$) 2.75 (s, 3 H, CH_3), 4.08 (s, 3 H, CH_3), 7.02 (d, J = 6 Hz, 1 H, H-6), 7.14 (t, J = 6 Hz, 1 H, H-5), 7.43 (s, 1 H, H-2), 7.56 (d, J = 6 Hz, H-4); HRMS m/e 170.0840 (M^+, $C_{11}H_{10}N_2$ requires 170.0844, 100).

(e) 1,7-Dimethyl-1*H*-indole-3-carboxamide Oxime (16b). Potassium carbonate (6.0 g, 43 mmol), **20b** (2.7 g, 15.8 mmol), and hydroxylamine hydrochloride (2.0 g, 28.7 mmol) in dry methanol were reacted as in the preparation of **10**, affording **16b** (0.5 g, 16%): mp 177–180 °C; ^{1}H NMR (DMSO-d_6) δ 2.74 (s, 3 H, CH_3), 4.02 (s, 3 H, NCH_3), 6.13–6.90 (m, 2 H, H-5, H-6), 7.58 (s, 1 H, H-2), 7.91 (d, J = 6 Hz, 1 H, H-4); MS m/e 203.1070 (M^+, $C_{11}H_{13}N_3O$ requires 203.1059, 80).

(f) 5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1,7-dimethyl-1*H*-indol-3-yl)-1,2,4-oxadiazole (15b). Amide oxime **16b** (0.35 g, 1.7 mmol) and ester **11p** (0.5 g, 2.9 mmol) were reacted in tetrahydrofuran (50 mL) at reflux for 4 h according to method A, giving a yellow oil. This was purified by chromatography on alumina with CH_2Cl_2/methanol (98:2) as eluant. Formation of the oxalate salt in acetone in the presence of excess oxalic acid furnished the title compound **15b** which was recrystallized from acetone (450 mg, 64%) as white crystals: mp 146 °C; ^{1}H NMR (DMSO-d_6) δ 1.75–2.2 (m, 4 H, 2 × CH_2), 2.54 (br s, 1 H, CH), 2.77 (s, 3 H, CH_3), 3.2–3.3 (m, 4 H, 2 × CH_2), 3.65–3.85 (3 H, $CHCH_2$), 4.15 (s, 3 H, NCH_3), 6.98 (d, J = 6.0 Hz, 1 H, H-6), 7.08 (t, J = 6.0 Hz, 1 H, H-5), 7.88 (d, J = 6.0 Hz, 1 H, H-4), 8.06 (s, 1 H, H-2); MS m/e 322 (M^+, free base, 30), 170 (100). Anal. ($C_{19}H_{22}N_4O\cdot 2(COOH)_2\cdot 0.5H_2O$) C, H, N.

5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (15d). **(a) 1*H*-Indole-3-carboxamide Oxime (16b).** Potassium carbonate (49.7 g, 0.36 mol), 1*H*-indole-3-carbonitrile (25.4 g, 0.18 mol), and hydroxylamine hydrochloride (18.7 g, 0.27 mol) in dry ethanol (600 mL) were reacted as in the preparation of **10**, affording the amide oxime **16d**: mp 154–156 °C; ^{1}H NMR (DMSO-d_6) δ 5.56 (s, 2 H, NH_2), 7.00 (dt, J = 8, 1 Hz, 1 H, CH), 7.10 (dt, J = 8, 1 Hz, 1 H, CH), 7.36 (d, J = 8 Hz, 1 H, CH), 7.75 (d, J = 2 Hz, CH), 8.05 (d, J = 8 Hz, 1 H, CH), 9.18 (s, 1 H, NH), 11.20 (s, 1 H, OH); MS m/e

175 (M^+). Anal. ($C_9H_9N_3O \cdot 0.025H_2O$) C, H, N.

(b) 5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (15d). 1-Azabicyclo[2.2.2]octane-3-carboxylic acid hydrochloride (**21**) (5.24 g, 28 mmol) was dissolved in dry dimethylformamide (30 mL) under nitrogen; to this was added molecular sieves (6 g, powdered) and triethylamine (8.0 mL, 56 mmol). The mixture was cooled to −20 °C and isobutyl chloroformate (3.6 mL, 56 mmol) was added, and after 10 min the amide oxime **16d** (4.9 g, 56 mmol) in DMF (30 mL) was added. The mixture was stirred at room temperature overnight. The mixture was filtered, fresh molecular sieves (3.0 g) were added, and the mixture was heated to 120 °C for 10 h. Acetic acid (5 mL) was added. The mixture was filtered and evaporated to dryness. The residue was dissolved in aqueous acid, washed with dichloromethane, basified, and extracted with dichloromethane; the organic layer was washed with water, dried, and evaporated. The residue was purified by column chromatography on silica with 0–10% methanol in dichloromethane as eluant. The product (0.15 g, 3%) was isolated and recrystallized from ethanol. It was further purified by formation of the hydrochloride salt in ethanolic HCl. This was evaporated and the salt was recrystallized from 2-propanol/ether: mp 226–228 °C; ^1H NMR (D_2O) δ 1.88–2.04 (m, 2 H, CH_2), 2.14–2.28 (m, 2 H, CH_2), 2.68–2.74 (m, 1 H, CH), 3.36–3.54 (m, 4 H, 2 × CH_2), 3.78–3.96 (m, 3 H, CH_2, CH), 7.34–7.42 (m, 2 H, 2 × CH), 7.65 (d, J = 7 Hz, 1 H, CH), 8.07 (d, J = 6 Hz, CH), 8.08 (s, 1 H, CH); MS m/e 294 (M^+).

5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1-allyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (15e). (a) 5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1*H*-indol-3-yl)-1,2,4-oxadiazole–Borane Complex (22). Oxadiazole **15d** (0.1 g, 0.34 mol) was stirred in tetrahydrofuran (20 mL) under nitrogen and cooled to −20 °C. Borane–tetrahydrofuran (1.0 mL, 1 mmol) was added, and the solution was allowed to warm to room temperature. Methanol (5 mL) was added, and the solution was evaporated, yielding a colorless crystalline product: mp 200–202 °C; ^1H NMR ($CDCl_3$) δ 1.0–2.0 (br, 3 H, BH_3), 1.63–1.74 (m, 1 H, C-H), 1.78–1.90 (m, 1 H, CH), 1.90–2.08 (m, 2 H, CH), 2.52–2.58 (m, 1 H, CH), 3.02–3.18 (m, 3 H, CH), 3.20–3.30 (m, 1 H, CH), 3.40–3.52 (m, 2 H, CH), 3.73–3.84 (m, 1 H, CH), 7.26–7.33 (m, 2 H, H-5, H-6), 7.42–7.50 (m, 1 H, 7-H), 7.97 (d, J = 2.9 Hz, 1 H, H-2), 8.20–8.26 (m, 1 H, H-4), 8.54 (bs, 1 H, NH); MS m/e 294 (M^+). Anal. ($C_{17}H_{18}N_4O \cdot BH_3$) C, H, N.

(b) 5-(1-Azabicyclo[2.2.2]octan-3-yl)-3-(1-allyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Hydrochloride (15e). The borane complex (**22**) (0.23 g, 0.75 mmol) was dissolved in tetrahydrofuran (20 mL) under nitrogen. Sodium hydride (35 mg, 0.8 mmol) was added, and the mixture was stirred for 30 min. When all gas evolution was complete allyl bromide (0.065 mL, 0.75 mmol) was added, and the mixture was stirred at room temperature overnight. TLC revealed the presence of one product. The mixture was filtered, and the filtrate was evaporated. The residue was taken up in ether, washed with water, dried, and evaporated. The resulting product was triturated in hexane, yielding (0.27 g, 96%) of the borane-protected product. This was dissolved in methanolic hydrogen chloride and heated at reflux overnight to remove the borane moiety. The methanol was evaporated, and the residue was made basic with aqueous potassium carbonate. This was then extracted with dichloromethane (3 × 20 mL). The organic extracts were combined, washed with water, dried, and evaporated. The residue was purified by formation of the hydrochloride salt with ethereal hydrogen chloride: mp 94–97 °C; ^1H NMR (D_2O) δ 1.80–2.00 (m, 2 H, CH), 2.08–2.26 (m, 2 H, CH), 2.62–2.68 (m, 1 H, CH), 3.34–3.54 (m, 4 H, CH), 3.74–3.94 (m, 3 H, CH), 4.87 (d, J = 5.1 Hz, 2 H, $NCH_2CH{=}CH_2$), 5.08 (d, J = 16.9 Hz, 1 H, CH=C*H*H), 5.26 (d, J = 9.5 Hz, 1 H, CH=CH*H*), 6.04–6.16 (m, 1 H, C*H*=CH_2), 7.36 (t, J = 8.6Hz, 1 H) and 7.41 (t, J = 6.4 Hz, 1 H, H-5, H-6), 7.57 (d, J = 8.0 Hz, 1 H, H-7), 7.95 (s, 1 H, H-2), 8.02 (d, J = 7.3 Hz, 1 H, H-4); MS m/e 334 (M^+). Anal. ($C_{20}H_{22}N_4O \cdot HCl \cdot 1.5H_2O$) C, H, N.

3-(1-Azabicyclo[2.2.2]octan-3-yl)-5-(2-methoxyphenyl)-1,2,4-oxadiazole Hydrochloride (15o). Compounds **15f–p** were prepared from the corresponding substituted amide oximes and ester **12p** according to method A; the procedure for the preparation of **15o** is described. 2-Methoxyphenylcarboxamide oxime (1.70 g, 10 mmol) and ester **12p** (1.50 g, 9 mmol) were reacted in tetrahydrofuran (50 mL) at reflux according to method A giving **15o** (0.57 g, 20%). This was treated with methanolic hydrogen chloride and recrystallized from methanol to give the hydrochloride salt: mp 259–261 °C; ^1H NMR (D_2O) δ 1.88–2.06 (m, 2 H, CH_2), 2.14–2.32 (m, 2 H, CH_2), 2.72–2.78 (m, 1 H, CH), 3.38–3.58 (m, 4 H, CH_2N), 3.98 (s, 3 H, OCH_3), 3.86–4.06 (m, 3 H, CH_2N, CH), 7.21 (dd, J = 7.6, 7.5 Hz, 1 H, ArH), 7.29 (d, J = 8.4 Hz, ArH), 7.65 (ddd, J = 9.0, 7.6, 1.8 Hz, 1 H, ArH), 7.95 (dd, J = 7.7, 1.7 Hz, 1 H ArH); MS m/e 285 (M^+, 100). Anal. ($C_{16}H_{19}N_3O_2 \cdot HCl$) C, H, N, Cl.

3-(1-Azabicyclo[2.2.2]octan-3-yl)-5-(2-hydroxyphenyl)-1,2,4-oxadiazole Hydrochloride (15r). **15q–s** were prepared by demethylation of **15n–p** with boron tribromide; the procedure for the synthesis of **15r** is described. A solution of **15o** (0.79 g, 2.8 mmol) in dichloromethane (50 mL) was cooled to −78 °C under nitrogen and boron tribromide (1.0 M solution in dichloromethane, 15 mL, 15 mmol) was added with stirring. The solution was allowed to warm to room temperature and stirred for 3 h. This mixture was then cooled to −78 °C, and methanol (25 mL) was added dropwise. This was evaporated to dryness, the residue was dissolved in methanol, made basic with aqueous ammonium hydroxide solution and was evaporated. The product was purified by chromatography on silica with dichloromethane/methanol/NH_4OH (90:10:1) as eluant, giving **15r** (0.45 g, 59%). Treatment with methanolic hydrogen chloride gave the hydrochloride salt: mp 197–9 °C; ^1H NMR (D_2O) δ 1.86–2.04 (m, 2 H, CH_2), 2.12–2.30 (m, 2 H, CH_2), 2.72–2.80 (m, 1 H, CH), 3.36–3.58 (m, 4 H, NCH_2 and NCH_2), 3.86–4.06 (m, 3 H, NCH_2 and CH), 7.10–7.18 (m, 2 H, CH), 7.50–7.56 (m, 1 H, CH), 7.95 (dd, J = 8.0, 1.7 Hz, 1 H, CH); MS m/e 271 (M^+). Anal. ($C_{15}H_{17}N_3O_2 \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl.

3-(1-Azabicyclo[2.2.2]octan-3-yl)-5-(1-methyl-1*H*-indol-3-yl)-1,2,4-oxadiazole Sesqui(hydrogen oxalate) (24). Azabicyclo[2.2.2]octane-3-carboxamide oxime[15] (**30**) (508 mg, 3 mmol) and methyl 1-methyl-1*H*-indole-3-carboxylate (**29**) (1.7 g, 9 mmol) in tetrahydrofuran (50 mL) were reacted according to method A. The product was purified by column chromatography on alumina with methanol/ethyl acetate as eluant (450 mg, 49%). The white solid (150 mg, 0.5 mmol) was converted to the monooxalate salt by dissolution of the free base in hot methanol and treatment of this solution with 1 equiv of oxalic acid in ether, whereupon the salt crystallized on standing (140 mg, 70%): mp 170–171 °C (methanol); ^1H NMR (DMSO-d_6) δ 1.1–2.1 (m, 4 H, CH_2), 2.50 (m, 1 H, CH), 3.2–3.4 (m, 4 H, CH_2N), 3.60–3.75 (m, 3 H, CH_2NCH), 3.94 (s, 3 H, NMe), 7.31–7.39 (m, 2 H, H-5, H-6), 7.64 (d, J = 7 Hz, 1 H, H-7), 8.11 (dd, J = 7 Hz, 1 H, H-4), 8.44 (s, 1 H, H-2): MS m/e (CI^+) 308 (M^+, free base, 30), 225 (40), 158 (100). Anal. ($C_{21}H_{23}N_4O_7$) C, H, N.

4-[2-(1-Methyl-1*H*-indol-3-yl)-1,3,4-oxadiazol-5-yl]-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (25). (a) 2-(1-Methyl-1*H*-indol-3-yl)-5-pyrid-3-yl-1,3,4-oxadiazole. The imino ether **31** (3.0 g, 13.4 mmol) and isonicotinic acid hydrazide (**32**) (1.84 g, 13.4 mmol) were dissolved in absolute ethanol (100 mL), heated at reflux for 60 h, cooled to room temperature, and evaporated to dryness. The residue was taken up in water (200 mL), extracted with dichloromethane (4 × 100 mL), and dried, and the solvent was removed giving a yellow solid. Recrystallization from ethanol gave the product as white needles (1.7 g, 46%): mp 212–214 °C; ^1H NMR ($CDCl_3$) δ 3.02 (s, 3 H, NCH_3), 7.3–7.45 (m, 3 H, H-4, H-5, H-6), 7.89 (s, 1 H, H-2), 7.99 (dd, J = 5, 1 Hz, C*H*=CHN), 8.27–8.34 (M, 1 H, H-7), 8.83 (dd, J = 5, 1 Hz, 2 H, CH=C*H*N); MS m/e (M^+, 30), 276 (30), 158 (100). Anal. ($C_{18}H_{12}N_4O$) C, H, N.

(b) 4-[2-(1-Methyl-1*H*-indol-3-yl)-1,3,4-oxadiazol-5-yl]-1-methylpyridinium Iodide. The aforementioned 1,3,4-oxadiazole (50 mg, 0.18 mmol) was dissolved in dry acetone (10 mL); methyl iodide (127 mg, 2 mmol) was added, and the resulting solution was heated at reflux for 24 h under nitrogen. The solution was cooled, and the yellow solid was isolated by filtration. Recrystallization from acetone afforded (70 mg, 93%): mp 290 °C dec; ^1H NMR (DMSO-d_6) δ 3.98 (s, 3 H, NCH_3), 4.43 (s, 3 H, CH_3N^+), 7.38 (m, 2 H, H-5, H-6), 7.68 (m, 1 H, H-4), 8.24 (m, 1 H, H-7), 8.49 (s, 1 H, H-2), 8.70 (d, J = 8 Hz, H, CH=C*H*N), 9.18 (d, 2 H, J = 8 Hz, 2 H, C*H*=CHN); MS m/e (M^+, free base, 60), 276 (60), 158 (100). Anal. ($C_{17}H_{16}N_4O_5I$) C, H, N.

(c) 4-[2-(1-Methyl-1*H*-indol-3-yl)-1,3,4-oxadiazol-5-yl]-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (25). The

iodide (1.0 g, 2.4 mmol) was suspended in a mixture of ethanol (50 mL) and water (5 mL) with vigorous stirring. Sodium borohydride (200 mg, 5 mmol) was added portionwise until the solution was colorless. The solution was stirred for 1 h at room temperature. HCl (2 N, 10 mL) was added, followed by aqueous ammonia to pH 12; the resulting solution was extracted into dichloromethane (4 × 100 mL), dried, and evaporated. The residue was purified by chromatography on silica with methanol in dichloromethane (2:98) as eluant. The isolated product was treated with ethereal HCl; recrystallization from absolute methanol yielded the final product as white crystals: mp 245–250 °C; ^{1}H NMR (D_2O) δ 2.67 (m, 2 H, CH_2NCH_3), 3.07 (s, 3 H, NCH_3), 3.4 (m, 2 H, CH_2NCH_3), 3.55 (s, 3 H, CH_3N), 3.48 (m, 2 H, CH_2CH_2N), 6.27 (m, 1 H, C=$CHCH_2$), 7.09 (m, 2 H, H-5, H-6), 7.11 (d, J = 5 Hz, 1 H, H-4), 7.22 (s, 1 H, H-2), 7.35 (d, J = 5 Hz, H-7); MS m/e 294 (M^+, free base, 100), 158 (40). Anal. ($C_{17}H_{18}N_4OCl$) C, H, N.

***exo*- and *endo*-5-(1-Azabicyclo[2.2.2]heptan-3-yl)-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-thiadiazole Oxalate (26 and 27, Respectively).** **(a) Methyl 1-Methyl-1*H*-indole-3-carboximidate Hydrochloride (31).** Dry hydrogen chloride was bubbled through a solution of **9** (17.0 g, 0.11 mmol) in dry methanol (100 mL). This solution was allowed to stand at room temperature for 24 h; the solvent was removed at reduced pressure. The residue was triturated with cold ether/methanol to afford **31** as white crystals (18.0 g, 73%): mp 156–158 °C; ^{1}H NMR (DMSO-d_6) δ 3.40 (s, 1 H, NH), 3.90 (s, 3 H, NMe), 4.30 (s, 3 H, OMe), 7.30 (dt, J = 7, 1 Hz, ArH), 7.40 (dt, J = 8, 2 Hz, 1 H, ArH), 7.70 (d, J = 8 Hz, ArH), 7.90 (dd, J = 7, 1 Hz, ArH), 9.0 (s, 1 H, H-2); MS m/e 188 (M^+, free base).

(b) 1-Methyl-1*H*-indole-3-carboxamidine Hydrochloride (38). Dry ammonia gas was bubbled through a solution of imidate (**31**) (8.0 g, 35.6 mmol) in dry methanol (120 mL) for 2 h. This solution stood at room temperature for 24 h; the solvent was removed at reduced pressure affording a buff-colored solid (7.5 g). This solid contained ~20% of 1-methyl-1*H*-indole-3-carboxamide (*39*) by ^{1}H NMR, but was used in subsequent reactions without further purification: mp 245–250 °C; ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3 H, NMe), 7.25–7.42 (m, 2 H, H-5, H-6), 7.61–7.67 (dd, J = 10, 2 Hz, 1 H, H-7), 7.67–7.92 (dd, J = 10, 2 Hz, 1 H, H-4), 8.40 (s, 1 H, H-2), 8.9–9.0 (m, 3 H, NH_2 and NH); MS m/e 173 (M^+, free base, 25), 157 (100).

(c) 5-Chloro-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-thiadiazole (33). A solution of NaOH (5.5 g, .13 mol) in water (30 mL) was added over 1 h to an ice-cold, rapidly stirred two-phase mixture of crude amidine (7.2 g, 27.6 mmol) and perchloromethyl mercaptan (5.1 g, 27.5 mmol) in water (30 mL). The mixture was allowed to warm to room temperature over 4 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic phase was dried and concentrated, and the resulting orange oil was purified by chromatography on silica by using hexane in dichloromethane to yield a yellow crystalline solid (4.2 g, 61%): mp 93–94 °C; ^{1}H NMR δ 3.67 (s, 3 H, NMe), 7.21–7.29 (m, 3 H, ArH), 7.74 (s, 1 H, H-2), 7.40–7.43 (m, 1 H, H-4); MS m/e 249 (M^+, 100).

(d) *exo*- and *endo*-5-(1-Azabicyclo[2.2.1]heptan-3-yl)-3-(1-methyl-1*H*-indol-3-yl)-1,2,4-thiadiazole Oxalate (26 and 27, Respectively). Lithium diisopropylamide (5.0 mL of a 2.5 M solution in cyclohexane) was added to a stirred solution of (**11u**) (1.80 g, 11.6 mmol) in anhydrous tetrahydrofuran (30 mL) at ~78 °C. This was stirred for 1 h under nitrogen. **33** (2.58 g, 10.3 mmol) in dry tetrahydrofuran (30 mL) was added dropwise and allowed to stir at −78 °C for 1.5 h; the mixture was allowed to warm to room temperature smoothly over 2 h. Solvents were removed at reduced pressure to afford the ester as a viscous oil. This crude ester was hydrolyzed immediately; it was dissolved in methanol (40 mL) and tetrahydrofuran (30 mL) and treated with aqueous sodium hydroxide (30 mL × 2 N) and stirred therein at 0 °C for 3 h. The solution was concentrated at reduced pressure, and the aqueous solution was extracted into ethyl acetate (3 × 30 mL). The aqueous solution was made acidic (pH 2) with concentrated hydrochloric acid and stirred for 2 h at room temperature to effect decarboxylation. This solution was made basic with saturated potassium carbonate solution and was extracted into dichloromethane (5 × 50 mL). The combined organic extracts were dried, and the solvent was evaporated at reduced pressure, affording a brown oil which was purified by flash chromatography on alumina with dichloromethane/methanol (99:1) as eluant. This afforded a glass which was a mixture of the two diastereoisomers by TLC. This was purified and the isomers separated by flash silica gel chromatography, with dichloromethane/methanol as eluant, to afford the less polar exo isomer (0.18 g, 5.6%) (**26**) and the more polar endo isomer (0.49 g, 15.3%) (**27**) as crystalline solids. The oxalate salts were prepared by addition of an ethereal solution of oxalic acid to the free bases in a minimum of dichloromethane. Exo isomer **26**: mp 171–172 °C; ^{1}H NMR (D_2O) δ 1.9–2.0 and 2.2–2.3 (M, 2 H, CH_2), 3.1–3.8 (m, 8 H, 3 × CH_2N, 2 × CH), 3.81 (s, 3 H, NMe), 7.25–7.40 (m, 2 H, ArH), 7.49 (d, J = 8 Hz, 1 H, H-7), 7.81 (s, 1 H, H-2), 8.14 (d, J = 7 Hz, H-4); MS 310 (M^+, free base, 100). Endo isomer **27**: mp 195–196 °C; ^{1}H NMR (D_2O) δ 1.7–1.8 and 2.0–2.1 (m, 2 H, CH_2), 3.4–3.1 (m, 5 H, 2 × CH_2N, CH), 3.7–3.8 (m, 1H, CH_2N), 3.85 (s, 3 H, NMe), 3.8–4.0 (m, 1 H, CH_2N), 4.25–4.35 (m, 1 H, CH), 7.25–7.40 (m, 2 H, ArH), 7.54 (d, J = 8 Hz, 1 H, H-7), 7.94 (s, 1 H, H-2), 8.24 (d, J = 7 Hz, H-4); MS m/e 310 (M^+, free base, 100).

3-[2-(1-Methyl-1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (28). **(a) 1-Methyl-1*H*-indole-3-thiocarboxamide (34).** Lawesson's reagant (0.7 g, 1.7 mmol) was added to a suspension of 1-methyl-1*H*-indole-3-carboxamide (**39**) (0.6 g, 3.4 mmol) in toluene (20 mL), and the mixture was heated at reflux under nitrogen for 30 min until dissolution occurred. The solution was cooled, and toluene was removed under reduced pressure. The orange residue was purified by column chromatography on alumina with dichloromethane as eluant; this afforded an orange crystalline material, (0.5 g, 77%): ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 3 H, NCH_3), 7.18 and 7.23 (2 × dt, J = 7, 1 Hz, H-5 and H-6), 7.49 (d, J = 7.5 Hz, 1 H, H-7), 8.08 (s, 1 H, H-2), 8.59 (d, J = 7 Hz, 1 H, H-4), 8.76 (br s, 2 H, NH_2); MS m/e 190 (M^+ 100).

(b) 3-[2-(1-Methyl-1*H*-indol-3-yl)-1,3-thiazol-4-yl]pyridine Hydrobromide (39). The thioamide **34** (0.5 g, 2.6 mmol) was dissolved in anhydrous dimethylformamide (5 mL). This solution was added to a stirred suspension of 3-(bromoacetyl)pyridine hydrobromide (**35**) (1.1 g, 3.9 mmol) in anhydrous dimethylformamide (2 mL). This was stirred for 10 min at room temperature, isolated by filtration, and washed thoroughly with ether, (0.5 g, 50%): ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3 H, NCH_3), 7.2–7.4 (m, 2 H, H-5, H-6), 7.58 (d, J = 7 Hz, H-7), 8.03 (dd, J = 8, 5 Hz, 1 H, H-5″ β-pyr), 8.26 (s, 1 H, H-5 thiazole), 8.36 (d, 1 H, H-4), 8.38 (s, 1 H, H-2), 8.83 (mc, 1 H, H-4″ γ-pyr), 8.99 (d, J = 8 Hz, 1 H, H-6″ α-pyr), 9.47 (mc, 1 H, H-2″ α-pyr); MS m/e 291 (M^+, 100).

(c) 3-[2-(1-Methyl-1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1-methylpyridinium Iodide (40). The free base, liberated from **39** (0.6 g, 2 mmol, was dissolved in acetone (25 mL), and methyl iodide (1 mL) was added to the stirred solution. After 5 min a yellow crystalline precipitate was observed. This was isolated by filtration and was washed with ether, yielding **40** (0.85 g, 95%): mp 250 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.91 (s, NCH_3), 4.48 (s, 3 H, N^+CH_3), 7.29–7.36 (m, 2 H, H-5, H-6), 7.59 (dd, J = 6, 2 Hz, 1 H, H-7), 8.22 (dd, J = 6, 6 Hz, H-5″ β-pyr), 8.27 (s, 1 H, H-5 thiazole), 8.40 (dd, 1 H, H-4), 8.41 (s, 1 H, H-2), 8.94 (d, J = 6 Hz, 1 H, H-4″ β-pyr), 9.13 (d, J = 8 Hz, H-6″ α-pyr), 9.59 (s, 1 H, H-2″ α-pyr); MS m/e 291 (M^+, 40), 169 (100). Anal. ($C_{18}H_{18}N_3SI$) C, H, N.

(d) 3-[2-(1-Methyl-1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1-methyl-1,2,5,6-tetrahydropyridine Hydrochloride (28). The pyridinium iodide **40** (0.8 g, 1.8 mmol) was suspended in ethanol (20 mL) and water (1 mL). Sodium borohydride (0.1 g) was added in portions with much evolution of hydrogen. After 30 min the intense yellow coloration of the solution was replaced by a light brown hue. Hydrochloric acid (5 M) was added dropwise to quench excess sodium borohydride. The flask contents were poured onto saturated sodium bicarbonate and this was extracted with dichloromethane (4 × 150 mL). The organic layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography on silica with 10% methanol in dichloromethane as eluant (0.4 g, 70%). This was treated with methanolic HCl, and the resulting precipitate was recrystallized from aqueous ethanol: mp 235 °C dec; ^{1}H NMR (D_2O) δ 2.6–2.8 (m, 2 H, β-pyr), 3.08 (s, 3 H, NCH_3 pyr), 3.16–3.28 (m, 1 H, α-pyr), 3.65 (mc, 1 H, α-pyr), 3.74 (d, J = 16 Hz, 1 H, H-1″ α-pyr), 4.14

(d, J = 16 Hz, 1 H, H-1″ α-pyr), 6.53 (mc, 1 H, H-4″ γ-pyr), 7.09 (s, 1 H, SCH), 7.23 and 7.30 (2 × t, J = 8 Hz, H-5, H-6), 7.37 (d, J = 8 Hz, 1 H, CH), 7.53 (d, J = 8 Hz, 1 H), 7.75 (s, 1 H, H-2); MS m/e 309 (M^+, free base, 100).

Biochemical Methods. (a) Brain Membrane Preparation. Cerebral cortices of male Sprague-Dawley rats (250–300 g) were dissected on ice, weighed, and promptly transferred to 10–15 vol (weight/vol) of ice cold 0.32 M sucrose. The tissue was then homogenized by using ten strokes of a motor driven Teflon/glass homogenizer (Janke and Kunkel) at 500 rpm. The homogenate was centrifuged at 1000g at 4 °C for 10 min and the supernatant then recentrifuged at 48000g, 4 °C for 21 min. The supernatant was discarded and the pellet resuspended in 10–15 vol of 2.5 mM Hepes (pH 7.4 at room temperature) and left to stand at room temperature for 15 min. Finally, the homogenate was recentrifuged for a further 21 min at 48000g, 4 °C, and the resulting pellet stored on ice.

(b) [^{3}H]Q-ICS 205-930 Binding Assay. Cortical membranes were prepared freshly on the day of the assay. Immediately prior to use the pellet was resuspended in 30 vols of the assay buffer (10 mM Hepes containing 10 μM pargyline and 0.1% ascorbate, pH 7.1 at room temperature). The membranes, [^{3}H]Q-ICS 205–930 and displacing drugs were prepared in assay buffer. A 400-μL aliquot of the membrane suspension (approximately 400 μg, protein) was incubated on ice with 0.5–0.7 nM [^{3}H]Q-ICS 205-930 (**36**) plus displacing drug in polypropylene tubes, (final assay volume 1 mL). All assays were carried out in duplicate. Nonspecific binding was defined with 10 μM MDL 72222 (4). The reaction was initiated by adding the membrane suspension and was terminated after 15 min of incubation at 4 °C by rapid filtration through Whatman GF/B glass fiber filters by using a Brandel M24-R cell-harvester followed by 2 × 4 mL washes with cold 5 mM Hepes (pH 7.4 at room temperature). The filters had previously been soaked in 0.3% polythylenimine/0/5% Triton X100 for a minimum of 1 h to reduce nonspecific binding. Radioactivity was determined by liquid scintillation counting at 41% efficiency. Potencies for displacement (pIC_{50}) were determined from data obtained by using at least nine concentrations of the displacing ligand by computer-assisted iterative curve fitting.

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Supplementary Material Available: Microanalytical data and NMR data for each compound in Tables 2–5 (9 pages). Ordering information is given on only current masthead page.

1,2,4-Triazolo[4,3-*a*]pyrazine Derivatives with Human Renin Inhibitory Activity. 3.[1] Synthesis and Biological Properties of Aminodeoxystatine and Difluorostatone Derivatives

Robert H. Bradbury* and Janet E. Rivett

Department of Chemistry, ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.
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Two series of 1,2,4-triazolo[4,3-*a*]pyrazine derivatives with human renin inhibitory activity have been synthesized which incorporate the transition-state mimetics (3*S*,4*S*)- and (3*R*,4*S*)-5-cyclohexyl-3,4-diaminopentanoic acid ((*S*)- and (*R*)-CDAPA), and (4*S*)-4-amino-5-cyclohexyl-2,2-difluoro-3-oxopentanoic acid (ACDFOPA). Several compounds in these series, for example **13a**, **19c**, and **19f**, were highly potent inhibitors of partially purified human renin (IC_{50} values of 3.9, 1.6, and 1.4 nM, respectively). The ACDFOPA-based compounds **19c** and **19f** contain no natural amino acid fragments and have molecular weights which compare well with those of previously reported inhibitors of nanomolar in vitro potency. When administered intravenously to anesthetized, sodium-depleted marmosets at doses of 3 mg/kg, compounds **13a** and **19c** caused a marked reduction in mean arterial pressure, but in the same animal model at 30 mg/kg, oral activity was not seen.

Despite the efforts of many research groups during recent years,[2] the target has yet to be achieved of a long-acting, orally effective inhibitor of human renin as a potential alternative to blockade of angiotensin converting enzyme (ACE) for the treatment of hypertension and congestive heart failure. In an attempt to overcome the problems associated with known peptidic inhibitors, such as poor oral absorption, proteolytic instability, short duration of action, and rapid excretion,[3] we sought a nonpeptidic ligand which might bind in the S_4–S_2 region of human renin. As a consequence of the work, we recently reported[1] inhibitors containing a 2-(8-alkyl-6-aryl-1,2,4-triazolo[4,3-*a*]pyrazin-3-yl)-3-pyridin-3-ylpropionyl moiety linked to transition-state mimetics such as cyclohexylstatine (ACHPA[4]) and the hydroxyethylene isostere Cha$\overset{OH}{—}$Val.[4] Structure–activity relationships for these series of compounds, for example **1** and **2** (Figure 1), were consistent with the substituted heterocyclic propionyl unit spanning the S_4–S_2 sites of the enzyme and thus acting as

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(4) ACHPA = (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid; Cha$\overset{OH}{—}$Val = (2*S*,4*S*,5*S*)-5-amino-6-cyclohexyl-4-hydroxy-2-isopropylhexanoic acid; (*S*)-CDAPA = (3*S*,4*S*)-5-cyclohexyl-3,4-diaminopentanoic acid; (*R*)-CDAPA = (3*R*,4*S*)-5-cyclohexyl-3,4-diaminopentanoic acid; (*RS*)-CDAPA = (3*RS*,4*S*)-5-cyclohexyl-3,4-diaminopentanoic acid; ACDFOPA = (4*S*)-4-amino-5-cyclohexyl-2,2-difluoro-3-oxopentanoic acid; ACDFHPA = (3*R*,4*S*)-4-amino-5-cyclohexyl-2,2-difluoro-3-hydroxypentanoic acid; N_3-Z-N_4-Boc-(*S*)-CDAPA = (3*S*,4*S*)-3-[(benzyloxycarbonyl)amino]-4-[(*tert*-butoxycarbonyl)amino]-5-cyclohexylpentanoic acid; N_3-Z-N_4-Boc-(*R*)-CDAPA = (3*R*,4*S*)-3-[(benzyloxycarbonyl)amino]-4-[(*tert*-butoxycarbonyl)amino]-5-cyclohexylpentanoic acid; N_3-Z-(*S*)-CDAPA = (3*S*,4*S*)-4-amino-3-[(benzyloxycarbonyl)-amino]-5-cyclohexylpentanoic acid.

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