6-Hydroxy-3-*n*-propyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and Analogs: New Centrally Acting 5-HT_{1A} Receptor Agonists

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The ring-closed phenylethylamine analogue 6-hydroxy-3-*n*-propyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1) is a 5-HT_{1A} receptor agonist of moderate potency, according to both in vivo biochemical data and in vitro binding data. The active compounds of this series also induce the 5-HT behavioral syndrome. Molecular modeling studies were performed with molecular mechanics calculations, and a tentative explanation for the relatively low potency of these serotonergic benzazepines is provided.

Introduction

In our continuous efforts to find new chemical structures with specific actions upon central neurotransmission, we synthesized 6-hydroxy-3-*n*-propyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1). This compound can be viewed very simplistically, and due to the symmetry of the benzazepine ring system, as being an analogue of both the potent dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT, 4)[1,2] and the potent 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT, 5) (see Chart I).[3,4] The benzazepine ring system is also found in mixed D_1/D_2 agonists and in D_1 antagonists[5-7] and in α_2 adrenergic antagonists.[8,9] At the same time they have affinity for 5-HT_{1A} binding sites.[10] This gives an indication that compound 1 may affect one or several of these receptor types. 6-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF86466; 6) was first classified as an α_2 adrenergic antagonist.[11] Recently it has been shown that compound 6 and analogues display 5-HT_{1A} binding affinity in [^{3}H]-8-OH-DPAT binding. In particular, the benzazepine–buspirone hybrid 7 has a high affinity in 5-HT_{1A} receptor binding.[10]

The benzazepines with D_1/D_2 effects have longer N–O distances than has compound 1. This is because they have their phenolic hydroxyls in positions 7 and/or 8 instead of in position 6, as in 1. Obviously, the N–O distance in compound 1 is closer to that of compound 5 in such a straightforward comparison. However, there is one potent DA agonist with an extremely short N–O distance, namely 4-hydroxy-2-(di-*n*-propylamino)indan (4-OH-DPAI; 8).[12,13] A distance geometry approach to the DA/5-HT_{1A} struc-

(1) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. Resolved monophenolic 2-aminotetralins and 1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolines: structural and stereochemical considerations for centrally acting pre- and postsynaptic dopamine-receptor agonists. *J. Med. Chem.* **1985**, *28*, 215–225.

(2) Liljefors, T.; Wikström, H. A molecular mechanics approach to the understanding of presynaptic selectivity for centrally acting dopamine receptor agonists of the phenylpiperidine series. *J. Med. Chem.* **1986**, *29*, 1896–1904.

(3) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. 8-Hydroxy-2-(dipropylamino)-tetralin, a new centrally acting 5-hydroxytryptamine receptor agonist. *J. Med. Chem.* **1981**, *24*, 921–923.

(4) Arvidsson, L.-E.; Hacksell, U.; Johansson, A.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. 8-Hydroxy-2-(alkylamino)tetralins and related compounds as central 5-hydroxytryptamine receptor agonists. *J. Med. Chem.* **1984**, *27*, 45–51.

(5) Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Bass, L. S.; Clardy, J. Absolute stereochemistry and dopaminergic activity of enantiomers of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine. *J. Med. Chem.* **1982**, *25*, 697–703.

(6) Ross, S. T.; Franz, R. G.; Wilson, J. W.; Brenner, M.; DeMarinis, R. M.; Hieble, J. P.; Sarau, H. M. Dopamine receptor agonists: 3-allyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diole and a series of related benzazepines. *J. Med. Chem.* **1986**, *29*, 733–740.

(7) Weinstock, J.; Oh, H.-J.; DeBrosse, C. W.; Eggleston, D. S.; Wise, M.; Flaim, K. E.; Gessner, G. W.; Sawyer, J. L.; Kaiser, C. Synthesis, conformation, and dopaminergic activity of 5,6-ethano-bridged derivatives of selective dopaminergic 3-benzazepines. *J. Med. Chem.* **1987**, *30*, 1303–1308.

(8) DeMarinis, R. M.; Krog, A. J.; Shah, D. H.; Lafferty, J.; Holden, K. G.; Hieble, J. P.; Matthews, W. D.; Regan, J. W.; Lefkowitz, R. J.; Caron, M. G. Development of an affinity ligand for purification of α2-adrenoceptors from human platlet membranes. *J. Med. Chem.* **1984**, *27*, 918–921.

(9) DeMarinis, R. M.; Pfeiffer, F. R. U.S. patent no. US 4683229, 1987.

(10) Clark, R. D.; Weinhardt, K. K.; Berger, J.; Fisher, L. E.; Brown, C. M.; MacKinnon, A. C.; Kilpatrick, A. T.; Spedding, M. 1,9-Alkano-bridged 2,3,4,5-tetrahydro-1H-3-benzazepines with affinity for the α_2-adrenoceptor and the 5-HT_{1A} receptor. *J. Med. Chem.* **1990**, *33*, 633–641.

(11) DeMarinis, R. M.; Hieble, J. P.; Matthews, W. D. 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine: a potent and selective antagonist of α_2-adrenoceptors. *J. Med. Chem.* **1983**, *26*, 1213–1214.

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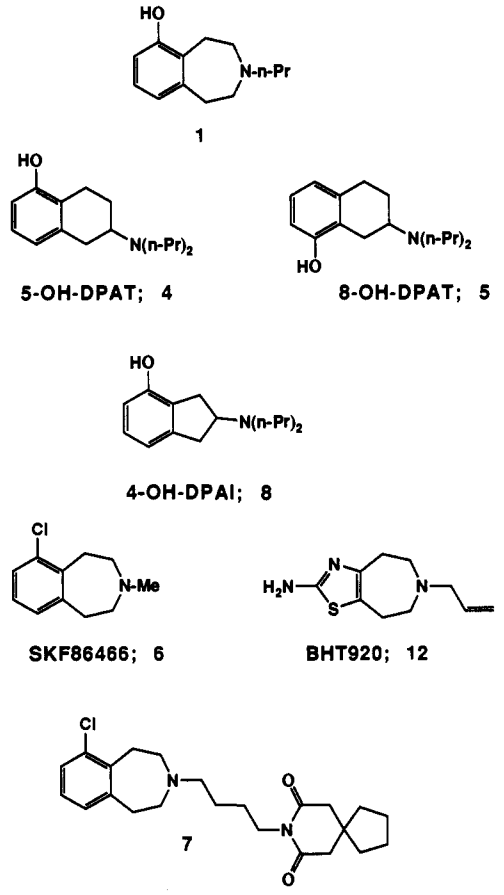
Chart I



ture–activity relationship (SAR) study is obviously an oversimplification.

Benzazepine ring conformations have previously been studied,[5,7] and there are three different conformations: chair, boat, and skew boat. The X-ray structure of quaternized (methiodide) (+)-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine displays the skew boat conformation, while the hydrochloride of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine shows the chair conformation in the crystal. According to molecular mechanics calculations (MM2-(85)), the lowest energy minimum of 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF38393) and its 7-chloro-3-methyl analogue (SCH23390) is calculated to be a chair conformation. The skew boat conformations are 1.3–2.6 kcal/mol (SCH23390) and 3.0–3.4 kcal/mol (SKF38393) higher in energy. The boat conformations are 2.3–4.4 kcal/mol (SCH23390) and 3.3–9.2 kcal/mol (SKF38393) higher in energy.[14]

The scope of this study has been to investigate the influence of the position of the OH group and the size of the *N*-alkyl substituent in this series of isomeric 2,3,4,5-tetrahydrobenzazepines. In addition, we have used molecular mechanics calculations to increase our understanding of the SAR in compounds displaying 5-HT$_{1A}$ receptor affinity and/or activity.

Chemistry

Compounds of this structural class have previously been synthesized from the corresponding *o*-phenylenediacetonitrile by two different ring closure reactions, namely through catalytic hydrogenation over Raney Ni at elevated temperature and pressure,[15] or through an acidic hydrolytic ring closure reaction yielding the imide product, which was subsequently reduced with diborane to a benzazepine ring system.[16] We used the first-mentioned strategy. The two methoxylated secondary amines 6- and 7-methoxy-2,3,4,5-tetrahydro-1*H*-benzazepine, used as starting materials for the preparation of all of the other analogues, have been described elsewhere.[8,17] N-Alkylation (methods A and B in the Experimental Section) gave the different N-alkylated analogues. Compound **3** was synthesized from the hydrochloride of compound **2** in EtOH with Br_2. The selective para-bromination in **3** was confirmed through a NOE experiment, which showed a 16% NOE on the high-field doublet at δ 6.63 ppm (H_7), and a small negative NOE on the other aromatic proton (H_8), upon selective irradiation of the OCH_3 resonance.[18] In addition, the irradiation of H_1 gave a small NOE on the H_7 proton.

The phenolic analogues were prepared from the corresponding methoxy derivatives with refluxing 48% aqueous HBr under nitrogen.

Computational Methods

Conformational energies and energy-minimized molecular geometries were calculated by using the molecular mechanics program MM2(87) developed by Allinger and co-workers.[19–22] Input structures for the MM2(87) calculations were constructed by using the molecular modeling program MacMimic.[23] The superimpositions were also performed with MacMimic.

Pharmacology

Biochemistry. The in vivo biochemical test utilizes the well-established phenomenon of receptor mediated feedback inhibition of the presynaptic neuron.[24] DA and norepinephrine (NE) have the same general biosynthetic pathway, and the synthesis rate of the catecholamines DA and norepinephrine (NE) is decreased by agonists (and

(12) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hjorth, S.; Carlsson, A.; Paalzow, L. Monophenolic 2-(dipropylamino)indans and related compounds: central dopamine-receptor stimulating activity. *J. Med. Chem.* **1981**, *24*, 429–434.

(13) Wikström, H.; Lii, J.-H.; Allinger, N. L. Conformational analysis of 2-aminoindans and 2-(aminomethyl)indans in relation to their central dopaminergic effects and a dynamic dopamine receptor concept. *J. Med. Chem.* **1987**, *30*, 1115–1120.

(14) Pettersson, I.; Liljefors, T.; Bøgesø, K. Conformational Analysis and Structure–Activity Relationships of Selective Dopamine D-1 Receptor Agonists and Antagonists of the Benzazepine Series. *J. Med. Chem.* **1990**, *33*, 2197–2204.

(15) Ruggli, P.; Bussemaker, B. B.; Müller, W.; Staub, A. Darstellung von m- und p-phenylen-di-äthylamin sowie benzohexamethylen-imin aus den drei phenylen-di-acetonitrilen. *Helv. Chim. Acta* **1935**, *18*, 1388–1395.

(16) Shetty, B. V. German patent no. DE 2207430, 1973.

(17) Pecherer, B.; Sunbury, R. C.; Brossi, A. The synthesis of some 7- and 7,8-substituted 2,3,4,5-tetrahydro-1H-3-benzazepines. *J. Heterocycl. Chem.* **1971**, *8*, 779–783.

(18) Tracy, M.; Acton, E. M. Synthesis of tetrahydrobenzo[b]phenazines as anthracyclinone N-isosteres. *J. Org. Chem.* **1984**, *49*, 5116–5124.

(19) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

(20) Sprague, J. T.; Tai, J. C.; Yuh, Y.; Allinger, N. L. The MMP2 Calculational Method. *J. Comp. Chem.* **1987**, *8*, 581–603.

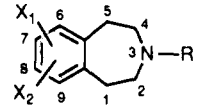
(21) Liljefors, T.; Tai, J. C.; Li, S.; Allinger, N. L. On the Out-of-Plane Deformation of Aromatic Rings, and Its Representation by Molecular Mechanics. *J. Comp. Chem.* **1987**, *8*, 1051–1056.

(22) Allinger, N. L.; Kok, R. A.; Imam, M. R. Hydrogen Bonding in MM2. *J. Comp. Chem.* **1988**, *9*, 591–595.

(23) Liljefors, T.; MacMimic, InStar Software, IDEON Research Park, S-223 70 Lund, Sweden, 1990.

(24) Andén, N.-E.; Carlsson, A.; Häggendal, J. Adrenergic mechanisms. *Annu. Rev. Pharmacol.* **1969**, *9*, 119–134.

Table I. Physical Data



compd	X_1	X_2	R	N-alkylation method[a]	yield,[b] %	mp, °C
13	6-OMe	H	Me	B	58	187–190[c] $C_{12}H_{17}NO\cdot HCl$[d]
14	6-OMe	H	Et	B	69	108–110[e] $C_{13}H_{19}NO\cdot HCl$[d]
2	6-OMe	H	*n*-Pr	A	66	205–207[c] $C_{14}H_{21}NO\cdot HCl$[d]
10	6-OMe	H	Δ-CH_2	A	72	170–173[c] $C_{15}H_{21}NO\cdot HCl$[d]
3	6-OMe	9-Br	*n*-Pr		70	258–260[e] $C_{14}H_{20}BrNO\cdot HCl$[d]
15	6-OH	H	Me		77	239–241[e] $C_{11}H_{15}NO\cdot HBr$[d]
16	6-OH	H	Et		59	162–164[c] $C_{12}H_{17}NO\cdot HBr$[d]
1	6-OH	H	*n*-Pr		86	230–231[f] $C_{13}H_{19}NO\cdot HBr$
9	6-OH	H	*n*-Bu		ND[g]	196–201[c] $C_{14}H_{21}NO\cdot HBr$
11	7-OH	H	*n*-Pr	A	54	214–216[f] $C_{13}H_{19}NO\cdot HBr$[d]
17	7-OH	H	*n*-Bu	B	ND	225–230[e] $C_{14}H_{21}NO\cdot HBr$

[a] The details on the N-alkylation methods A and B can be found in the Experimental Section. [b] The yield notation comes from the last synthetic step. [c] Recrystallization solvent was acetone/ether. [d] Identified through high-resolution MS, and the purity was assessed with HPLC. [e] Recrystallization solvent was EtOH/ether. [f] Recrystallization solvent was MeOH/ether. [g] ND means "not determined".

increased by antagonists) at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agonists.[25,26] The 5-HTP accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD 1015), was used as an indicator of the 5-HT synthesis rate in the three brain areas (Table II). In addition, the dopa accumulation was used as an indicator of the DA synthesis rate in the DA-rich areas (i.e. limbic system and corpus striatum) and the NE synthesis rate in the NE-rich hemispheres (mainly cortex). For this study we used reserpine-pretreated rats (5 mg/kg sc, 18 h), in which the synthesis rates of 5-HTP and dopa are raised (feedback regulation). This model is designed to detect directly acting agonists at central monoamine receptors through both biochemical and behavioral effects.

Locomotor Activity and Behavior. Postsynaptic agonistic effects of the test compounds were assessed by the increase in locomotor activity (reversal of reserpine induced hypokinesia). Postsynaptic 5-HT_{1A} effects induce forward locomotion and the 5-HT behavioral syndrome (flat body posture and forepaw treading), while postsynaptic dopaminergic effects induce locomotor activity and stereotypy. Motor activity recordings were carried out as previously described with the use of motility meters (Table III).[27] The behavior of the animals was observed through semitransparent glass windows, and the 5-HT behavioral syndrome was rated (Table III, footnote *a*).

In Vitro Binding. The abilities of the test compounds to displace the radioactively labeled ligands [^{3}H]-8-OH-DPAT and [^{3}H]spiperone from 5-HT_{1A} and D_2 receptor sites, respectively, in homogenized rat brain tissue were assessed in vitro.

Results and Discussion

Structure–Activity Relationships. The behavioral and biochemical testing of the present series of compounds show that the active compounds are those having the aromatic substituents 6-OH (**1**, **15**, **16**), 6-OMe (**2**, **10**), and 6-OMe,9-Br (**3**) (Tables II and III). These compounds also display 5-HT_{1A} receptor affinity (Table IV) and induce the 5-HT behavioral syndrome. These compounds can thus be classified as 5-HT_{1A} agonists. However, they are about 20–200 times less potent in vivo than the reference compound **5**.

The influence of the *N*-alkyl substituent upon the 5-HT_{1A} effect is similar in this series of compounds and in compounds related to **5**, i.e. potency increases with increasing chain length up to and including a *n*-Pr substituent. *N*-*n*-Bu substitution yields the inactive compound **9**. The 6-methoxylated analogue with a *N*-cyclopropylmethyl substituent (**10**) is equipotent to its *N*-*n*-propyl analogue (**2**). As is the case with the 8-substituted 2-aminotetralins, the hydroxy and methoxy 6-substituted compounds **1** and **2** are equipotent. This indicates that H-bond acception is sufficient for 5-HT_{1A} receptor interaction.

The *p*-Br-substituted 6-OMe analogue **3** has a somewhat higher in vitro affinity for 5-HT_{1A} receptors than its nonhalogenated analogue **2** (Table III). The total lack of dopaminergic agonist effects of e.g. compounds **1** and/or **11** is puzzling in view of the DA partial agonist properties of the mixed D_2/α_2 receptor agonist BHT-920 (**12**).

Conformational Analysis and Molecular Modeling. The preferred conformation of the azepine ring (chair, boat, or skew boat) could not be deduced from NOE experiments. The ring methylenes were almost degenerate and no coupling information could be extracted to decide on such a conformation. This may be due to dynamic effects. Upon lowering the temperature in −50 °C a spectrum with exchange broadened and exchange shifted peaks resulted, thus confirming that the ring is very mobile at room temperature.

According to the molecular mechanics calculations on compound **15** (Chart II), the global energy minimum with respect to the seven-membered ring is found for the chair conformation. The skew boat conformations and the boat conformations are 3.2–3.3 kcal/mol and 2.7–8.1 kcal/mol higher in energy, respectively. Based on these calculations, the most likely receptor-active conformation of the benzazepines with 5-HT_{1A} activity is the chair conformation.

In an attempt to increase the understanding of the 5HT_{1A} activity of these benzazepines, molecular superimpositions have been performed. Four fitting points have

(25) Aghajanian, G. K.; Bunney, B. S.; Kuhar, M. J. *New Concepts Neurotransm. Regul., Proc. Symp. Drug Abuse Metab. Regul. Neurotransm.* **1972**, 115–134.

(26) Neckers, L. M.; Neff, N. H.; Wyatt, R. J. Increased serotonin turnover in corpus striatum following an injection of kainic acid: evidence for neuronal feedback regulation of synthesis. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1979**, *306*, 173–177.

(27) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. N-Alkylated 2-aminotetralins: central dopamine-receptor stimulating activity. *J. Med. Chem.* **1979**, *22*, 1469–1475.

Table II. In Vivo Biochemical Data

compd, adm route (dose, μmol/kg)	5-HTP acc: % of controls ± SEM and estd ED50 (μmol/kg)[a]		
	limb	stri	hem
1, sc (25)	76 ± 12*[b]	75 ± 2	72 ± 6**
1, sc (6.25)	51 ± 2*	67 ± 8	53 ± 1*
1, sc (1.56)	70 ± 27		73 ± 28
1, sc (0.39)	129 ± 9	135 ± 4	129 ± 3
1, sc (0.20)	117 ± 9	125 ± 9	115 ± 14
1, sc ED50	1.3	2.2	1.4
2, sc (50)	61 ± 8**	63 ± 9**	58 ± 6**
2, sc (12.5)	42 ± 3***	48 ± 1***	48 ± 4***
2, sc (3.1)	48 ± 1***	53 ± 6***	47 ± 1***
2, sc (0.78)	99 ± 15	74 ± 5*	92 ± 14
2, sc ED50	1.5	1.0	1.5
2, po (100)	47 ± 5**	56 ± 4*	53 ± 6***
2, po (25)	58 ± 9*	65 ± 6*	58 ± 2**
2, po (6.25)	77 ± 12	79 ± 9	84 ± 15
2, po (1.56)	99 ± 9	97 ± 9	101 ± 5
2, po ED50	7.0	10.0	13.0
3, sc (50)	48 ± 6	50 ± 9	43 ± 6
3, sc (3.1)	69 ± 10	71 ± 10	83 ± 13
3, sc (0.80)	118 ± 3	130 ± 7	111 ± 7
3, sc (0.20)	108 ± 6	117 ± 12	102 ± 7
3, sc ED50	2.7	3.2	5.0
3, po (50)	48 ± 4***	50 ± 7*	50 ± 3***
3, po (12.5)	76 ± 4*	77 ± 5	88 ± 7
3, po (3.1)	90 ± 3	96 ± 4	99 ± 4
3, po (0.80)	88 ± 11	112 ± 21	86 ± 10
3, po ED50	13	14	21
9, sc (50)	84 ± 6	111 ± 24	108 ± 17
10, sc (50)	42 ± 3***	ND[c]	43 ± 2**
10, sc (12.5)	56 ± 12***	60 ± 10*	85 ± 25
10, sc (3.1)	67 ± 3**	68 ± 7	77 ± 11
10, sc (0.78)	84 ± 9	88 ± 12	95 ± 11
10, sc ED50	1.7	2.5	4.0
10, po (50)	48 ± 8**	48 ± 9**	50 ± 10**
10, po (12.5)	83 ± 14	77 ± 9	89 ± 9
10, po (3.1)	70 ± 12	59 ± 4**	75 ± 11
10, po (0.80)	101 ± 10	102 ± 14	102 ± 8
10, po ED50	5.5	7.0	6.5
11, sc (100)	81 ± 13	77 ± 15	78 ± 13
11, sc (25)	105 ± 6	107 ± 2	113 ± 12
11, sc (1.56)	80 ± 7	110 ± 25	114 ± 19
11, sc (0.39)	121 ± 17	106 ± 15	119 ± 17
11, sc (0.20)	122 ± 11	118 ± 18	128 ± 9
11, sc ED50	ND	ND	ND
13, sc (50)	67 ± 9	72 ± 7	80 ± 7
13, sc (12.5)	86 ± 12	74 ± 9	76 ± 15
13, sc (3.1)	108 ± 9	89 ± 14	93 ± 8
13, sc (0.78)	93 ± 14	97 ± 4	81 ± 11
13, sc (0.20)	110 ± 4	98 ± 6	126 ± 44
13, sc ED50	ND	ND	ND
14, sc (50)	66 ± 5	66 ± 10	64 ± 9
15, sc (50)	57 ± 11**	54 ± 12**	58 ± 15**
15, sc (12.5)	72 ± 18	70 ± 15*	73 ± 11*
15, sc (3.1)	106 ± 7	104 ± 4	96 ± 4
15, sc ED50	10	11	12
16, sc (50)	46 ± 5**	54 ± 6*	48 ± 4**
16, sc (12.5)	48 ± 6**	56 ± 7*	49 ± 5**
16, sc (3.1)	89 ± 11	96 ± 16	101 ± 13
16, sc (0.80)	99 ± 8	100 ± 5	108 ± 8
16, sc ED50	5.0	6.5	6.0
17, sc (50)	119 ± 17	106 ± 17	114 ± 21
5, sc ED50	0.052	0.052	0.063
5, po ED50	3.0	7.9	7.6

[a] Graphically determined ED50 value; $n = 4$. [b] Statistics: Anova followed by Fischer's test; * means $p < 0.01$; ** means $p < 0.001$; *** means $p < 0.0005$. [c] ND means that an ED50 value was not retrievable from the data achieved.

Table III. In Vivo Behavioral Data

compd, adm route	dose, μmol/kg	locomotor activity: acc counts per 30 min, mean ± SEM	5-HT syndr[a]
1, sc	25	102 ± 29*[b]	+
2, sc	50	197 ± 90*	+
2, po	100	40 ± 13*	+
3, sc	50	108 ± 31*	+
3, po	50	21 ± 10	(+)
9, sc	50	19 ± 6*	-
10, sc	50	107 ± 42*	(+) and (+) DA
10, po	50	31 ± 14	(+)
11, sc	100	ND	(+)
13, sc	50	8 ± 2	-
14, sc	50	62 ± 18*	(+)
15, sc	50	6 ± 1	(+)
16, sc	50	31 ± 8*	+
5, sc	0.2	66 ± 17*	+
control (reserpine + saline)		3 ± 1 ($n = 13$)	

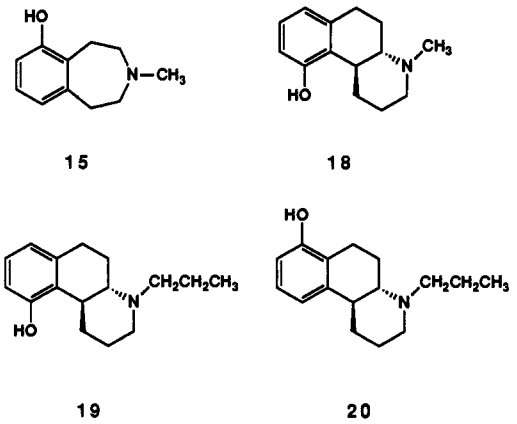
[a] The signs + and - indicate that the 5-HT behavioral syndrome was present or not, respectively. If in parentheses, this means that there were weak signs of the syndrome. [b] Statistics: Anova followed by Fischer's test; * means $p < 0.05$.

Table IV. In Vitro Binding Data

compd	IC$_{50}$ (nM)[a]	
	5-HT$_{1A}$	D$_2$
1	81 ± 14	>100000
2	63	3600
3	28 ± 7	680 ± 70
9	420	12000
10	120 ± 10	7600 ± 1800
11	4000	10000
13	480	2300
14	210	2200
15	1500	15000
16	630	14000
5	4	5800

[a] Most of the data come from single determinations; however, compounds 1, 3, and 10 were rerun in triplicate and are given as their mean ± SEM.

Chart II



been used: (i) the centroid of the aromatic ring, (ii) the oxygen atom of the hydroxy group, (iii) the nitrogen atom, and (iv) a point 2.8 Å from the nitrogen atom in the same direction as the nitrogen lone pair vector. This point is used to simulate a hydrogen-bonding site between the nitrogen atom in the substrate and the receptor. Compounds 18 and 19 (Scheme II) have been used as 5HT$_{1A}$ agonist templates for the superimpositions.[28]

Compounds 15 and 18 fit together well (Figure 1). If the nitrogen atom in the 5HT$_{1A}$ template is substituted with a *n*-propyl group, compound 19 (Scheme II), three

(28) Mellin, C.; Vallgårda, J.; Nelson, D. L.; Björk, L.; Yu, H.; Andén, N.-E.; Csöregh, I.; Arvidsson, L.-E.; Hacksell, U. A 3-D model for 5-HT$_{1A}$ agonists based on stereoselective methyl-substituted and conformationally restricted analogues of 8-hydroxy-2-(di-n-propylamino)tetralin. *J. Med. Chem.* 1991, *34*, 497–510.

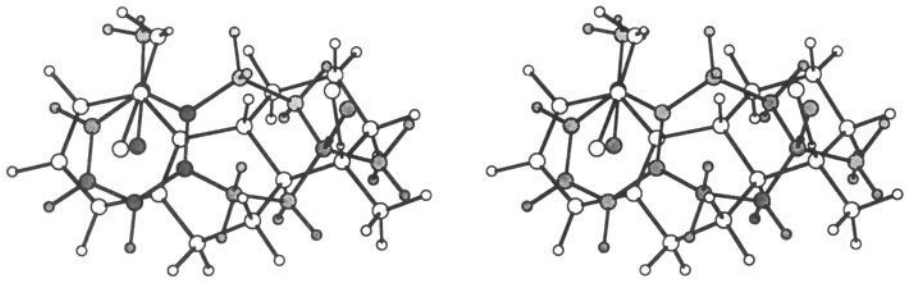


Figure 1. A stereoview of the superimposition between compounds **15** and **18**. The rms value is 0.60.

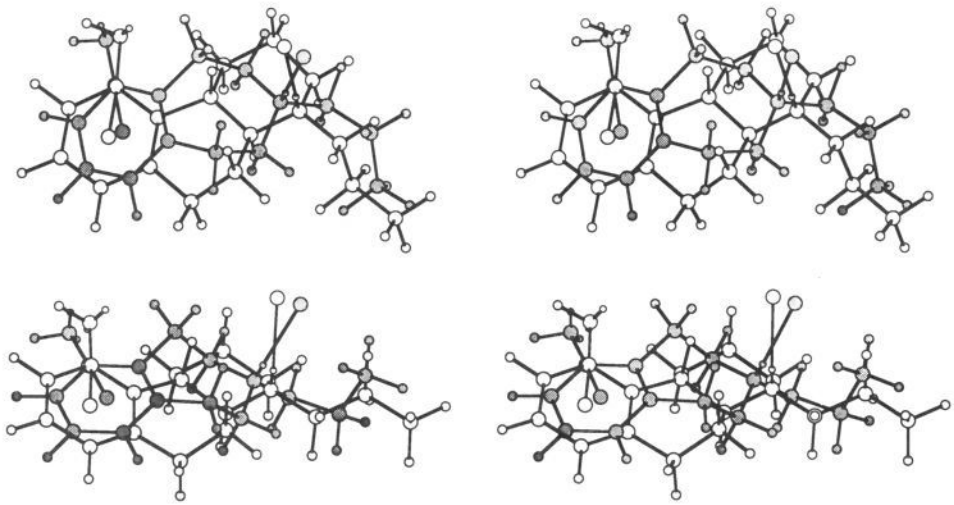


Figure 2. (a, top) A stereoview of the superimposition between compound **19** with the *n*-propyl group in an anti,anti conformation and compound **1** with the *n*-propyl group in a gauche$^+$,gauche$^+$ conformation (gray). The rms value is 0.58. (b, bottom) A stereoview of the superimposition between compound **19** with the *n*-propyl group in a gauche$^-$,anti conformation and compound **1** with the *n*-propyl group in a gauche$^+$,gauche$^-$ conformation (gray). The rms value is 0.59.

different low-energy conformations for the *n*-propyl group are obtained from the calculations (anti,anti (0.0 kcal/mol), gauche$^-$,anti (0.2 kcal/mol) and gauche$^-$,gauche$^+$ (0.5 kcal/mol)). The first-mentioned torsional angle of the *n*-propyl group is defined as lp–N–C–C and the second as N–C–C–C. The other conformations are 2.5–3.3 kcal/mol higher in energy. This is in agreement with the results obtained by others.[28] The *n*-propyl group in compound **1** can adopt nine different conformations, five of which are low-energy conformations (anti,anti; gauche$^+$,anti; gauche$^+$,gauche$^-$; gauche$^-$,anti; gauche$^-$,gauche$^+$) with about equal energy. The other four conformations are 2.6–3.1 kcal/mol higher in energy. Since compound **19** has a high affinity for 5HT$_{1A}$ binding sites, it is reasonable to assume that the biologically active conformation of this compound is one of the low-energy conformations. Compound **1** with the *n*-propyl group in a gauche$^+$,gauche$^+$ conformation can be superimposed on compound **19** with the *n*-propyl group in an anti,anti conformation (Figure 2a). In this fit compound **19** is in its global energy minimum conformation, while the conformational energy of compound **1** in this fitting conformation is 2.6 kcal/mol. Compound **1** with the *n*-propyl group in a gauche$^+$,gauche$^-$ conformation can be superimposed on **19** with the *n*-propyl group in a gauche$^-$,anti conformation (Figure 2b). Both of these conformations are low-energy conformations (0.2 kcal/mol for both compounds). However, in this fit the *n*-propyl groups are not overlapping as well as they are in Figure 2a. Finally, compound **19** with the *n*-propyl group in a gauche$^-$,gauche$^+$ conformation has the alkyl group pointing toward the hydrogen-bonding site. This does probably not represent a biologically active conformation.

In summary, based on molecular mechanics calculations and superimpositions between compounds **1** and **19**, we suggest that there are two different, plausible combinations of conformations for such superimpositions (Figure 2, parts a and b). In these conformations the seven-membered ring of compound **1** adopts a chair conformation and its *N*-*n*-propyl group a gauche$^+$,gauche$^+$ or a gauche$^+$,gauche$^-$ arrangement. The conformational energy penalty for compound **1** in the chair, gauche$^+$,gauche$^+$ conformation is 2.6 kcal/mol (see above). This energy penalty for such a fitting conformation of compound **1** can provide a tentative explanation for the lower 5-HT$_{1A}$ affinity and biochemical potency of this compound, as compared to the very high affinity and potency of compounds **5** and (4a*S*,10b*S*)-**19**.[28] Similar conformational considerations with regard to the comparison between the benzazepines and the DA agonist template (4a*S*,10b*S*)-**20** were less conclusive.

Experimental Section

Chemistry. Melting points (uncorrected) were determined with a melting point microscope (Reichert Thermovar). ^{1}H NMR spectra were recorded with a Varian VXR 300S or a Bruker 500-MHz spectrometer (Me_4Si), using a spectral width of 8.5 ppm and an acquisition time of 2.5 s. T_1 relaxation times were estimated from signal nulling in an inversion-recovery experiment. Steady-state NOE difference spectra were measured using an 8-s presaturation. All spectra were run at 21 °C, except the low-temperature data spectrum, which was run at −50 °C.

GC was performed with a HP5830A instrument with a flame-ionization detector. A fused silica column (11 m, 0.22 mm i.d.) coated with cross-linked SE-54 (film thickness 0.3 μm, gas H_2, gas velocity 40 cm/s) was used throughout.

GC/MS spectra were recorded on a HP 5970A Mass Selective Detector working at 70 eV and interfaced with a HP 5700A gas chromatograph. High-resolution MS spectra were recorded on a ZAB-HF mass spectrometer (VG-Analytical) with direct inlet, working in the EI mode (60 eV). All spectra were in accordance with the assigned structures.

The elemental analyses for new crystalline substances (C, H, N) were within 0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different systems. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained (see Table I). In addition, HPLC purity tests were performed on a Supelco pKb-100 column using MeOH/buffer (10–100% MeOH gradient) and acetonitrile/buffer (10–100% acetonitrile gradient) as the two mobile phases. The buffer composition was 25 mM HOAc and 25 mM sodium acetate. The pressure working range was 1500–2000 psi and the flow rate was 1.5 mL/min. Detection was made using a Waters Model 440 UV monitor. The purity was estimated by comparing peak areas.

6-Methoxy-3-*n*-propyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2) (Method A). To a solution of the base of 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzazepine[8] (1.0 g, 5.6 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (4 mL) and propionic acid chloride (2.00 mL, 23 mmol). The mixture was stirred at room temperature and the reaction was followed by GC. After 2 h the starting material was consumed and 10% HCl (25 mL) was added. The organic layer was separated, washed with Na_2CO_3 (10%), dried, and filtered and the solvent was evaporated. The resulting product was chromatographed (SiO_2 0.040–0.063 mm) using light petroleum/ether (2:3) as eluant, yielding 1.00 g (4.6 mmol, 76%) of a white solid melting at 63–66 °C. This product was dissolved in anhydrous ether (25 mL) and added dropwise to a slurry of $LiAlH_4$ (0.500 g, 13.2 mmol) in anhydrous ether (10 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by adding 0.5 mL of H_2O, 0.5 mL of 10% NaOH, and 1.5 mL of H_2O. The solid was filtered and washed with ether and the solvent of the filtrate was removed by evaporation. The product was chromatographed (SiO_2 0.040–0.063 mm) using light petroleum/Et_3N (98:2) as eluant, yielding a white solid, which was converted to the hydrochloride with HCl-saturated EtOH. The volatiles were evaporated, and the residue was crystallized from acetone/ether to give 2 (650 mg; 66%) of white crystals melting at 205–207 °C.

6-Hydroxy-3-*n*-butyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9) (Method B). To a solution of 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzazepine[8] (50.0 mg, 0.280 mmol) in CH_2Cl_2 (5 mL) was added butyraldehyde (0.050 mL, 0.569 mmol) and $NaBH_3CN$ (20.0 mg, 0.320 mmol). After stirring at room temperature for 1 h, glacial acetic acid was added dropwise until pH was about 5. When the starting material was consumed according to GC, the reaction was quenched with 10% HCl (10 mL) (**caution**: toxic HCN(g) evolves) and the acidic water was washed with CH_2Cl_2. The acidic water phase was basified with Na_2CO_3 (10%) and the product was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and filtered, and the solvent was evaporated, yielding an oil, which was chromatographed (SiO_2 0.040–0.063 mm) using CH_2Cl_2/MeOH (9:1) as eluant. The fractions containing pure product were pooled and the solvent was evaporated, yielding 6-methoxy-3-*n*-butyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine as an oil (30 mg, 46%), which was used without further purification in the ether cleavage step, consisting of reflux for 2 h in 48% HBr under N_2(g). The acid was evaporated at 80 °C and to the residue was added absolute EtOH, which was subsequently evaporated. This procedure was repeated two more times and the residue was crystallized from MeOH/ether, yielding 9·HBr as crystals melting at 196–201 °C.

9-Bromo-6-methoxy-3-*n*-propyl-2,3,4,5-tetrahydro-1*H*-benzazepine (3). Compound 2·HCl (125 mg, 0.49 mmol) was dissolved in absolute EtOH (5 mL) and, with stirring, 1.3 mL of a solution of Br_2 in CH_2Cl_2 (0.49 mmol/mL) was added. The reaction mixture was worked up by the addition of 10% Na_2CO_3 and ether extraction. The organic phase was dried (Na_2SO_4) and filtered, and the solvent of the filtrate was evaporated under reduced pressure, yielding 180 mg of an oil, which was chromatographed (SiO_2, 0.040–0.063 mm), eluting with acetone. The fractions containing pure material were collected, and evaporation of the solvent, addition of HCl-saturated EtOH, and evaporation yielded 115 mg (34%) of an oil. Crystals (30 mg) melting at 258–260 °C were obtained from EtOH/ether after 2 days in room temperature. The mother liquor was collected as an oil in vials. GC/MS showed $M^+/M + 2$ at m/e = 297/299. Other prominent peaks were found at m/e = 268 (100%)/279 (96%) (M – Et and its isotope). ^{1}H NMR (the base in $CDCl_3$): δ 0.90 (t, 3 H), 1.55 (m, 2 H), 2.40 (m, 2 H), 3.10 (m, 2 H), 3.20 (m, 2 H), 3.80 (s, 3 H), 6.6 (d, 1 H, 9 Hz), 7.3 (d, 1 H, 9 Hz). For comparison, the ^{1}H NMR of the aromatic protons in 4-bromo-1-methoxy-2,3-dimethylbenzene shows 6.58 (d, 1 H, 9 Hz), 7.34 (d, 1 H, 9 Hz).[18]

Pharmacology. Animals. Animals used in the biochemical and motor activity experiments were male rats of the Sprague-Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were kept five per cage with free access to water and food, at least 1 week from arrival until used in the experiments.

Materials. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 mL/kg, and all solutions had neutral pH at the time of injection (except for the solutions of reserpine, which had a pH of about 4).

Biochemistry. The biochemical experiments and the determinations of 5-HTP and dopa by means of HPLC with electrochemical detection were performed according to a modification of a previously described method.[29,30] Separate dose–response curves based on four to six dose levels (n = 4) for each substance (sc administration) and each brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease (ED50 value) of the 5-HTP (the maximal effect, expressed as percent of controls, was as follows: limbic system, striatum, and the hemispheres = –50%) and the dopa (the maximal effect, expressed as percent of controls, was as follows: limbic system = –65%, striatum = –80%, and the hemispheres = –50%) levels were estimated separately (Table II). Control values for the 5-HTP data were (ng/g, mean ± SEM, n = 4) as follows: limbic system = 163 ± 22, striatum = 125 ± 14, and the hemisphere 99 ± 13. The dopa values are not shown.

Motor Activity. The motor activity was measured by means of photocell recordings (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm) as previously described.[27] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were subcutaneously injected in the neck region with reserpine (5 mg/kg). The different test compounds were also administered subcutaneously in the neck region (n = 4). Immediately after drug administration, the rats were placed in the test cages (one rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min (control values 3 ± 1 counts/30 min, mean ± SEM; n = 13) (Table III). Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors.

5-HT$_{1A}$ Radioligand Binding.[31] Male Sprague-Dawley rats (160–225 g) were killed by decapitation, and the whole brain with the exception of the brainstem and cerebellum was rapidly removed, weighed, and chilled in ice-cold 0.9% NaCl. Each brain was homogenized (Ultra-Turrax for 20 s) in 10 mL of ice-cold 50 mM Tris buffer (pH 8.0 at 25 °C) containing 120 mM NaCl, 4 mM $CaCl_2$, and 4 mM $MgCl_2$ and centrifuged at 20000g at 4 °C for 10 min. Pellets were resuspended in 10 mL of fresh buffer and preincubated for 10 min at 37 °C (water bath) and then recentrifuged. Final pellets were homogenized in 100 volumes (w/v) of Tris buffer (as described above) containing 10 μM pargyline. The incubation tubes were kept on ice in triplicates and received 100 μL of drug solution in water (or water for total binding) and 1000 μL of membrane suspension (corresponds to

(29) Shum, A.; Sole, M. J.; van Loon, G. R. Simultaneous measurement of 5-hydroxytryptophan and L-dihydroxyphenylalanine by high performance liquid chromatography with electrochemical detection. Measurement of serotonin and catecholamine turnover in discrete brain regions. *J. Chromatogr.* **1982**, *228*, 123–130.

(30) Svensson, K., University of Göteborg, Sweden, ISBN 91-7900-078-9, Dopamine autoreceptor antagonists. A new class of central stimulants. 1986.

(31) Hyttel, J., personal communication.

10 mg of original tissue). The binding experiment was initiated by addition of 100 μL of [^{3}H]-8-OH-DPAT (specific activity 143–158 Ci/mmol) in ascorbic acid (the final incubation concentration was 1 nM [^{3}H]-8-OH-DPAT in 0.1% ascorbic acid). After incubation for 15 min at 37 °C, the reaction was terminated by separation of the free radioligand from bound by rapid vacuum filtration using a cell harvester equipment (O.M. Teknik, Denmark). The tubes were rinsed with 4 mL, and the filters (Whatman GF/F 25 mm) were washed twice with 4 mL, ice-cold 0.9% NaCl.

The radioactivity of the filters was measured in a liquid scintillation counter (efficiency 41%) in 5 mL of PicofluorTM15. Specific binding (70–75% of total binding) was defined as the radioactivity displaced by 10 μM 5-HT. IC50 values were calculated by semi-log plot and linear regression analysis.

D_2 Radioligand Binding. Binding of [^{3}H]spiperone (specific activity 21–24 Ci/mmol) to rat striatal membranes was, with a few exceptions, determined as described by Hyttel and Arnt.[32] Briefly, membranes were isolated in 50 mM potassium phosphate buffer (pH 7.4 at 25 °C) by homogenization and centrifugation at 25000*g*. The final pellets were homogenized in 1300 volumes of 50 mM potassium phosphate buffer, and the membrane suspension was incubated with 0.5 nM [^{3}H]spiperone in a final volume of 4.2 mL (3 mg of original tissue) for 10 min at 37 °C. Specific binding was 70–80% of total binding and was obtained by adding 10 μM 6,7-ADTN to the membrane suspension.

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(32) Hyttel, J.; Arnt, J. Characterization of binding of [^{3}H]-SCH23390 to dopamine D1 receptors. Correlation to other D-1 and D-2 measures and effect of selective lesions. *J. Neural Transm.* 1987, *68*, 171–189.