Centrally Acting α_1-Adrenoceptor Agonists Based on Hexahydronaphth[2,3-*b*]-1,4-oxazines and Octahydrobenzo[*g*]quinolines[1]

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Centrally acting α_1-agonists may be of therapeutic value in dementias and other CNS disorders characterized by symptoms of noradrenergic insufficiency. Therefore, on the basis of known peripherally acting α_1-agonists two new groups of centrally acting α_1-agonists with improved lipophilicity, the hexahydronaphth[2,3-*b*]-1,4-oxazines type A and the octahydrobenzo[*g*]quinolines type B were designed. The N-methylated derivatives **14** and **33** demonstrate potent, direct agonistic activity at postjunctional α_1-receptors. Ring substituent alterations in compounds of type A and B change the potency of compounds on the rabbit ear artery by over 3 orders of magnitude (pD_2 = 5.35–8.40). The efficacy of these compounds varies from 42 to 110%. Those α_1-agonists which were selective in the pithed rat increase vigilance in rats. Compound **14** was found to be a centrally acting α_1-agonist with good tolerability in different animal species and in healthy volunteers. Furthermore, **14** selectively stimulates the breakdown of phosphatidylinositol in rat cerebral cortex slices. In vivo, the compound reverses behavioral deficits in animals which received noradrenergic lesions following DDC or DSP_4 treatment. Oxazine **14** and its close derivatives are by far more lipophilic than commonly known α_1-agonists. This is demonstrated in a ClogP–PROBIS plot.

A variety of drugs which show selectivity for either α_1- or α_2-adrenoceptors are in clinical use. The α_2-agonists clonidine[2] **1** and guanfacine[3] **2** are centrally acting antihypertensives, whereas the purely peripherally acting α_1-agonists like phenylephrine[4] (**3**) and methoxamine[5] (**4**) are antihypotensives (Chart I). Due to their hydrophilic nature the classical α_1-agonists are penetrating poorly into the central nervous system. Within the last decade a second generation of more lipophilic, selective α_1-agonists has been described such as Sgd 101/75[6] (**5**), SKF 89748A[6] (**6**), cirazoline[6] (**7**), and ST 587[6] (**8**) (Chart II). Compound **8**, chemically related to clonidine, was characterized as a selective, full α_1-agonist which presumably penetrates to some extent into the central nervous system and causes only a moderate and transient blood pressure increase in anesthetized, normotensive cats.[7] This interesting finding clearly demonstrated that a lipophilic and potent α_1-agonist is not necessarily a strong vasoconstrictor. Indeed, a compound capable of central α_1-receptor activation without peripheral side effects could be of therapeutic value in the treatment of CNS disorders characterized by symptoms of noradrenergic insufficiency. Noradrenergic deficits are frequently caused by a neuronal decline in the locus coeruleus. The loss of these neurons constitutes a prominent histopathological change in senile dementia and severe depression.[8-10] With this background in mind, we

Chart I

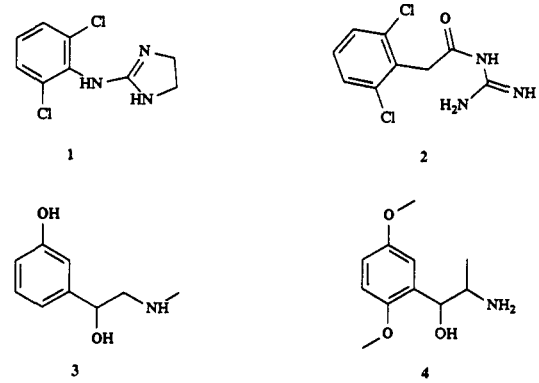
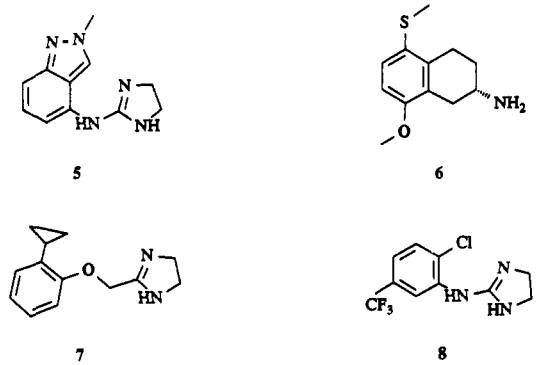
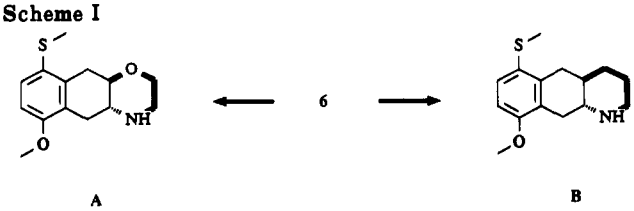


Chart II



Scheme I



(1) This paper has been presented in part: Dravid, A.; Hofmann, A.; Jaton, A.; Nozulak, J.*; Vigouret, J. M. SDZ NVI 085 - The rational design and pharmacological profile of a centrally acting α_1-agonist, 11th Int. Symp. Med. Chem., Jerusalem, Israel, Sep 2–7, 1990.

(2) Schmitt, H.; Laubie, M. Adrenoceptors and Central Cardiovascular Regulation. In *Adrenoceptors and Catecholamine Action*; Kunos, G., Ed.; Wiley-Interscience: New York, 1983; Vol. 1, Part B; pp 219–248.

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(5) For further references, see: *Pharmacology of adrenoceptors*; Szabadi, E., Bradshaw, C. M., Nahorski, S. R., Eds.; VCH Publishers: Weinheim, 1985.

(6) For further references, see: DeMarinis, R. M.; Wise, M.; Hieble, J. P.; Ruffolo, R. R. Structure-Activity Relationships for α_1-Adrenergic Receptor Agonists and Antagonists. In *The α_1-Adrenergic Receptors*; Ruffolo, R. R., Ed.; Humana Press: Clifton, NJ, 1987; pp 211–265.

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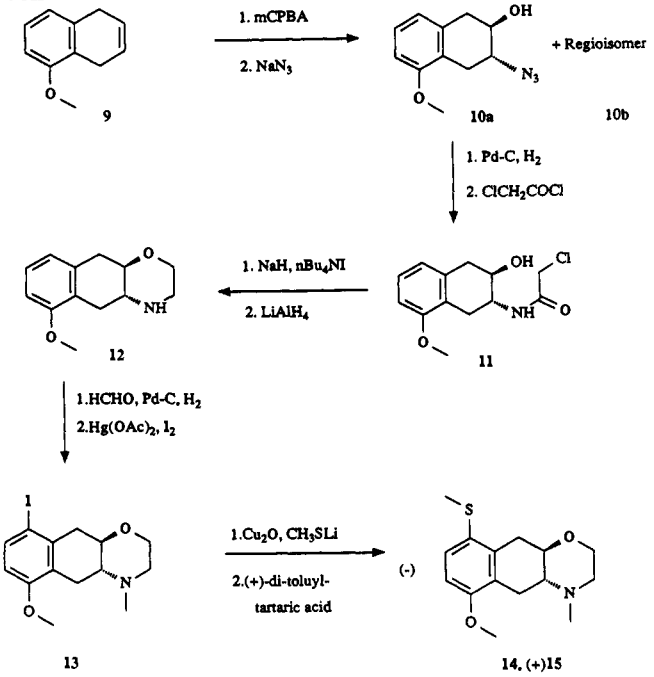
Scheme II



felt encouraged to start a new search for centrally acting α_1-agonists. The "conditio sine qua non" was the strict demand to identify an α_1-agonist which did not induce a blood pressure increase in humans at therapeutically useful doses. The tetralin **6** was selected as an attractive starting point for a medicinal chemistry strategy. The incorporation of the primary amine of the semirigid tetralin **6** into a condensed ring system was expected to enhance the overall lipophilicity of the molecule. This led to the design of the hexahydronaphth[2,3-*b*]-1,4-oxazine A and the octahydrobenzo[*g*]quinoline B systems (Scheme I). We assumed the active conformer of tetralin **6** would be frozen in the minimum-energy conformation of the trans stereoisomers of A and B. Therefore, we first prepared the N-methylated derivatives of A and B. Further derivation of the system A and to some extent of B was performed to improve the α_1-agonistic activity of the compounds.

In this paper we report the synthesis and pharmacological properties of a new class of α_1-agonists. The compounds were pharmacologically characterized using the pithed rat model, the isolated rabbit ear artery preparation, and a standardized rat primary observation test (POT). Full α_1-agonists, which increased vigilance and also displayed good tolerability in the POT, were selected for closer pharmacological studies. In particular the PI turnover, effects on noradrenergic lesioned rats, and action on blood pressure in cats and monkeys were examined. This screening strategy finally led to the development of the centrally acting α_1-agonist **14** (SDZ NVI 085). The detailed pharmacological characterization of **14** is described below.

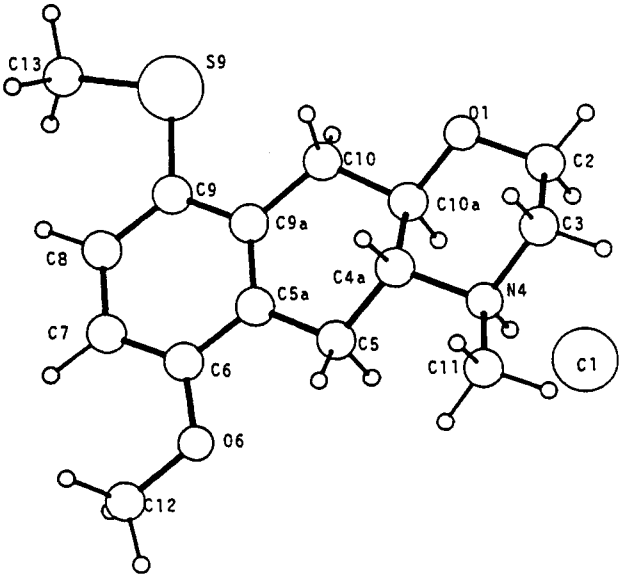
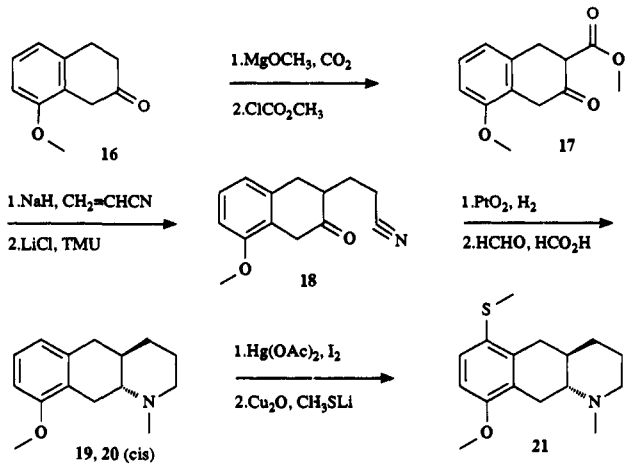


Figure 1. Single-crystal X-ray structure of **14**.

Scheme III



Chemistry

Hexahydronaphthoxazines were first described by Knorr[11] and later by Dantchev et al.[12,13] The new naphthoxazines discussed in this paper were prepared via the general reaction sequence depicted in Scheme II. The dihydronaphthalene[14] **9** was epoxidized and the oxirane ring opened by sodium azide giving a 1:1 mixture of the regioisomeric azido alcohols **10a,b**, which could be conveniently separated by a fractional crystallization from toluene/hexane. The azido alcohol **10a** was reduced, and the α-chloro amide was prepared. Intramolecular ring closure followed by reduction of the oxazinone yielded the

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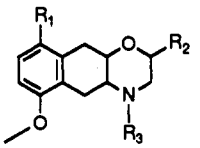
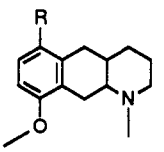
Table I. α_1-Agonists Based on Hexahydronaphth[2,3-*b*]-1,4-oxazines



no.	R_1	R_2	R_3	mp, °C	formula[a]	rabbit ea,[b] pD_2/E	pithed r,[c] pD_2/E; P/R	POT[d] vigilance
14	SCH_3	H	CH_3	244–246	$C_{15}H_{21}NO_2S$[e]	7.50/110	6.74/76; -79/-0	+2
15	SCH_3	H	CH_3	245–247	$C_{15}H_{21}NO_2S$[f]	5.40/100	6.19/23; -40/-22	0
22	NO_2	H	CH_3	254–256	$C_{14}H_{18}N_2O_4$	5.45/85	6.00/17; -22/-7	0
23	SCH_2CH_3	H	CH_3	>180 dec	$C_{16}H_{23}NO_2S$[e]	8.20/95	6.48/86; -80/-15	+1
24	Cl	H	CH_3	286–287	$C_{14}H_{18}ClNO_2$	5.97/89	5.89/40; -5/-17	+2
25	SCH_3	CH_3	CH_3	214–215	$C_{16}H_{23}NO_2S$	5.83/67	<4/-	0
26	SCH_3	H	CH_2CH_3	238–239	$C_{16}H_{23}NO_2S$	7.42/98	6.84/79; -84/-0	+1[g]
27	SCH_3	H	$(CH_2)_2CH_3$	244–246	$C_{17}H_{25}NO_2S$	6.78/98	6.18/38; -76/-35	+1[g]
28	SCH_3	CH_3	CH_2CH_3	231–232	$C_{17}H_{25}NO_2S$	6.47/93	6.45/29; -34/-31	+2
29	SCH_3	CH_2CH_3	CH_3	210–212	$C_{17}H_{25}NO_2S$	5.35/42	6.10/20; -0/-0	-1
6	SKF 89748A					7.48/98	7.92/73; -94/-5	+1
30	noradrenaline					7.7/100		

[a] C,H,N analysis and MS based; salt: hydrochloride. [b] Standard is noradrenaline. Values represent the means ± SEM: Potency ±0.1–0.25, efficacy ± 0–20%, n = 3–5. [c] Standard is noradrenaline. Values represent the means ± SEM: Potency ± 0.12–0.27, efficacy ± 2–20%, n = 3, prazosin/rauwolscine antagonism: ±3–22%. [d] Primary observation test, rat: vigilance score vs controls. Values represent the means of 6 experiments: ±0.2. [e] (*R,R*)-(-)-Antipode. [f] (*S,S*)-(+)-Antipode. [g] Strong serotoninergic stereotypes.

Table II. α_1-Agonists Based on Octahydrobenzo[*g*]quinolines



no.	type	R	mp, °C	formula[a]	rabbit ea,[b] pD_2/E	pithed r,[c] pD_2/E; P/R	POT[d] vigilance
31	trans	SCH_2CH_3	128–130	$C_{17}H_{25}NOS$	6.46/97	6.68/80; -93/-10	+1
32	cis	SCH_2CH_3	78–80	$C_{17}H_{25}NOS$	<4.00/-	6.12/18; -25/-36	0
33	trans[e]	SCH_3	133	$C_{16}H_{23}NOS$	8.40/109	7.36/85; -87/-12	+2
21	trans	SCH_3	157–158	$C_{16}H_{23}NOS$	nd	6.92/72; -79/-7	nd
34	cis	SCH_3	147–148	$C_{16}H_{23}NOS$	<4.00/-	<4.00/-; -/-	+1

[a] C,H,N analysis and MS based; all hydrogen malonates. [b] See Table I for statistical deviation of potency and efficacy. [c] See Table I for statistical deviation of potency, efficacy, and prazosin/rauwolscine antagonism. [d] Primary observation test, rat: vigilance score vs controls. See Table I for statistical deviation. [e] (-)-Antipode: $[\alpha]^{20}_D$ = 103° (c = 0.5, CH_2Cl_2).

oxazine **12**. N-Methylation of **12** was performed via Leuckart–Wallach reductive amination. The iodination with iodine and mercury(II) acetate gave rise to the 9-iodinated oxazine **13**. Heating **13** for 5 h in DMF in the presence of Cu_2O and CH_3SLi yielded a racemic oxazine which was resolved with (+)-di-*O,O'*-*p*-toluoyl-D-(-)-tartaric acid to obtain the enantiomerically pure oxazine **14**. Applying the antipode acid, **15** was obtained in analogous fashion (Scheme II). The absolute configuration of **14** was determined as *R,R* by anomalous single-crystal X-ray analysis (Figure 1). Lead derivation of the hexahydronaphthoxazine was performed in positions 2, 4, and 9. The introduction of a methyl or ethyl group at C-2 (**25**, **28**, **29**) was best accomplished by applying the appropriate α-chlorocarbonic acid chlorides to form derivatives of **11** (Scheme II). The oxazines **12** and **13** served as convenient precursors for the N-4 and C-9 variation.

The octahydrobenzo[*g*]quinolines were synthesized as shown by the general reaction sequence in Scheme III. The tetralone[15] **16** was regioselectively carboxylated according to S. W. Pelletier et al.,[16] and the resulting acid was esterified to give the β-keto ester **17** in good overall yield. Michael addition of **17** with acrylonitrile and subsequent demethoxycarbonylation gave access to the keto nitrile **18**. Reductive cyclization of **18**, followed by N-methylation, yielded the quinolines **19** and **20** as a 2:1 mixture of the cis and trans isomers. The (methylthio)-quinoline **21** was synthesized from **19** according to the procedure shown for **14**. Optically active quinolines could be obtained by resolution with (-)-ditoluoyltartaric acid.

Biological Results and Discussion

The α_1-adrenergic activity of the compounds was determined by measuring their potency and efficacy in the isolated rabbit ear artery. The rabbit ear artery contains postjunctional α_1-receptors with high receptor reserve.[17] Determination of the pD_2 values was performed in the presence of 2×10^{-6} M cocaine to prevent indirect noradrenergic activities. The α_1-/α_2-agonistic selectivity of the compounds was determined in pithed rats. Hypertensive responses were assessed by means of the α_1-selective an-

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Table III. Influence of 14 and Phenylephrine on the Accumulation of Inositol-1-phosphate in Rat Cerebral Cortex Slices

no.	pD_2	efficacy[a] (%)
14	6.1 ± 0.13	45 ± 4
3	5.1 ± 0.08	100

[a] Standard in phenylephrine, efficacy 100% per definition. The values represent the means ± SEM, $n = 3$. The stimulation of the PI response was completely inhibited by addition of 10^{-6} M prazosin. Rauwolscine was totally ineffective against the induced response.

tagonist prazosin or the α_2-selective antagonist rauwolscine. The results presented in Tables I and II give the pD_2 values and efficacies relative to noradrenaline. The tetralin **6** is listed for comparison. The naphthoxazine derivatives **14**, **23**, **26**, and **27** (Table I) with a methylthio or ethylthio group and no alkylation at position R_2 were among the most potent α_1-agonists on the rabbit ear artery and among the most selective ones in the pithed rat. The *S,S* enantiomer **15** still displayed full efficacy but was significantly less potent. The alkyl substitution at R_2 led to weak and/or unselective α_1-agonists. A stronger electron-withdrawing group, like nitro or halogen, at R_1 reduced the compounds potency on the rabbit ear artery. These compounds acted as partial agonists in the pithed rat. Increasing chain length of the *N*-alkyl substituent enhanced the α_1-agonistic activity. The compounds **14**, **23**, **26**, and **27** with high potency and efficacy on the rabbit ear artery and a clear-cut α_1-selectivity in the pithed rat caused a medium to strong vigilance increase in the rat (POT). The oxazines **26** and **27** exerted concomitantly strong serotoninergic stereotypical behavior in the rat (POT). The strong vigilance increase following the administration of **24** or **28** did not seem to be triggered by central α_1-receptor activation, as the α_1-profile especially in the pithed rat was far too weak to cause such a striking effect. Although interesting in their own right, these compounds were not further investigated. The trans configured octahydrobenzo[*g*]quinolines **31**, **33**, and **21** (Table II) were potent and selective α_1-agonists, whereas the cis diastereomers **32** and **34** were weak or almost inactive.

The typical behavioral changes induced by the new class of α_1-agonists are described below and correlated in their intensity with the potency and efficacy of the investigated compound. Immediately after administration of 10 mg/kg po or ip, a full α_1-agonist like **14** changed the behavior of the rats as compared to those in the control group. The compound decreased excitation during the initial exploratory phase. The treated animals were quiet but attentive to environmental stimuli. If the light was switched off, they immediately reacted without the excitation which is characteristic for control animals. One to two hours after administration, the control animals began to doze and sleep, whereas those treated with **14** maintained their vigilance; with their eyes wide open, they were immobile and calm. Their reactivity threshold to external stimuli remained excellent. These effects of **14** lasted for at least 6 h. When a 3-fold higher dose (30 mg/kg) was administered, pilierection and exophthalmosis of moderate intensity were observed. Salivation was sometimes intense in some rats. No dopaminergic or serotoninergic stereotypical behavior was observed even at 30 mg/kg po or ip.

The hexahydronaphth[2,3-*b*]-1,4-oxazine **14** demonstrated full α_1-agonism with no α_2-adrenergic activity in the pithed rat. The induction of a long-lasting vigilance increase in rats in the POT suggested a central noradrenergic action of **14**. This was further supported by the finding that **14** stimulated the α_1-receptor-coupled

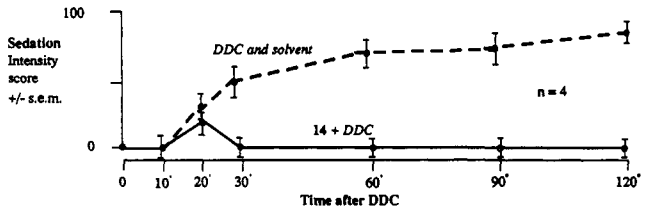

Figure 2. Antagonism of the DDC-induced sedation in rats with **14** (30 mg/kg po). The sedation was evaluated on a rating scale during 2 h after administration of DDC (300 mg/kg ip; 6 rats/treatment).

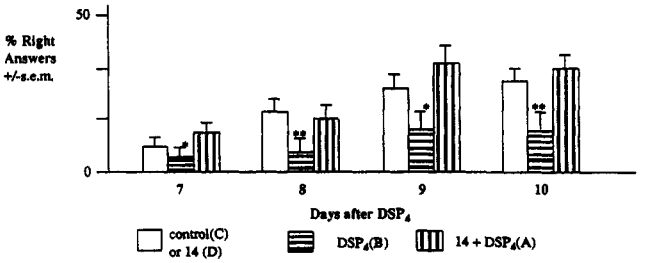

Figure 3. Antagonism of the DSP_4-induced (55 mg/kg, ip) cognitive impairment in rats ($n = 10$ rats/treatment) with **14** (10 mg/kg po). The performance decrease in learning and its antagonism was investigated by means of the shuttle box. The percentage of right answers of the groups A–D is shown from day 7 to day 10 after DSP_4 administration; $n = 4$, $*p < 0.05$, $**p < 0.01$.

breakdown of phosphatidyl inositol in rat cortex slices. Furthermore, this effect could be completely inhibited by the α_1-receptor antagonist prazosin. In comparison to phenylephrine (**3**), the oxazine **14** behaved like a partial agonist in the PI model (Table III). These results favor the involvement of α_1-receptor activation in the observed behavioral effects of **14**. Two in vivo experiments were performed to demonstrate the central noradrenergic action of **14**. In a first approach the dopamine-β-hydroxylase inhibitor DDC (diethyldithiocarbamate) was administered to rats. DDC induces a noradrenergic deficit in the brain by inhibition of the noradrenaline formation from dopamine, resulting in a strong sedation.[18] As depicted in the Figure 2, **14** was able to suppress the sedation induced by DDC, at a dose which alone did not induce motor stimulation.

In a second experiment a noradrenergic deficit in the rat brain was induced by the specific neurotoxin DSP_4 (*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine). DSP_4 induces a marked and long-lasting noradrenaline reduction, especially in the cerebral and cerebellar cortex and spinal cord in mice and rat CNS, leaving dopamine and serotonin neurons apparently unaffected.[19] DSP_4 also induces a strong performance impairment in learning tests in rats.[20] Therefore, the effect of **14** on learning (shuttle box) in rats with and without DSP_4 pretreatment was investigated. The learning performance over 4 days is shown in Figure 3. At the dose used, the treatment of control rats with **14** resulted in a learning performance which was comparable to those without **14** treatment. There was an even

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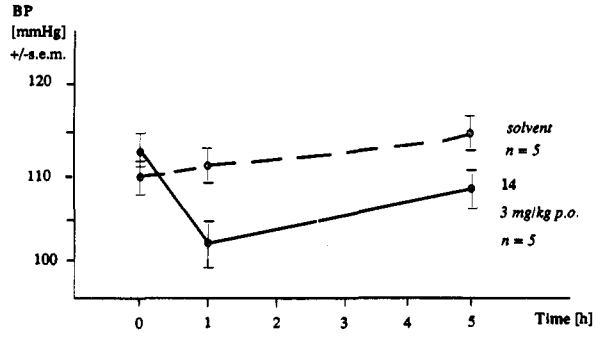

Figure 4. Action of 14 on the blood pressure in saimiri monkeys.

development of performance within the control group C and the 14 group D. The DSP_4 treated group B showed the expected, significant cognitive deficit. However, in group A, which was further treated with 14 (10 mg/kg po) after DSP_4 administration, a complete reversal of the DSP_4 effect occurred. The DSP_4 and the above DDC experiments strongly support a central noradrenergic mechanism of action of 14. Furthermore, the lack of effect on the reuptake or liberation of tritiated noradrenaline, dopamine, or serotonin even at the high concentration of 16 000 nM rules out possible presynaptic action of 14.[21] It can be concluded that 14 triggers central postsynaptic α_1-receptors selectively.

The oxazine 14 causes vasoconstriction in the isolated rabbit ear artery (pD_2 7.5; efficacy 110%) and in the pithed rat (pD_2 6.7; efficacy 76%). The compound was therefore tested for its cardiovascular activity in rats, cats, dogs, and saimiri monkeys. Experiments revealed that 14 slightly increased blood pressure in immobilized rats and dogs and decreased it in anesthetized cats.[22] In this paper only the presumably more relevant experiments and results with monkeys will be discussed. Compound 14 was administered to saimiri monkeys at doses of 0.3, 1, and 3 mg/kg po (n = 5/dose). The experiment with the highest dose is shown in Figure 4. The threshold for central stimulation comparable to the effects seen in rats was found to be 3 mg/kg po (monkey POT). Up to the highest dose tested no hypertension was observed, even during the first hour after drug administration. At the highest dose, there was a slight decrease in blood pressure concomitant with a moderate tachypnea, which might be due to central stimulation. In recent clinical studies with 14 in healthy young volunteers, there were no clinically relevant effects of 14 on blood pressure or heart rate up to a single dose of 24 mg.[23] It still remains an open question why 14 does not induce blood pressure increase following oral administration in saimiri monkeys and in humans. The immediate onset of action after po administration in rats (see POT) suggests a rapid gastrointestinal tract absorption followed by a prompt entry into the brain.

The structurally new class of centrally acting α_1-agonists like 14 and its derivatives shown in Table I and II differ significantly in terms of their lipophilic character from the known classically acting α_1-agonists previously discussed. Further, it was deemed desirable to quantitate these differences in hydrophobicity among α_1-agonists. Therefore, CLOGP[24] and PROBIS,[25] two recently described computational methods, were applied to calculate descriptors for a lipophilicity plot. The method provides a good correlation between the computationally derived log P and the hydrophobicity volume calculated by PROBIS (eq 1). As

$$[\text{CLogP}] = 0.011[\text{hydrophobic volume}] - 4.992$$
$$n = 17 \quad r = 0.91 \quad s = 0.64 \quad F = 69.06 \qquad (1)$$

shown in Table IV, the compounds exhibiting peripheral selectivity, **3**, **4**, **5**, and **30**, have low CLogP values and relatively small hydrophobic volumes and differ therefore significantly from those α_1-agonists which have the potential to penetrate the blood brain barrier (Figure 5). The favorable physicochemical characteristic of **14**, with a ClogP of 2.5 and a hydrophobic volume of 680 Å^3, is a strong basis for a purely pharmacokinetic explanation for the lack of effects on blood pressure as discussed above. A low concentration of free α_1-agonist in peripheral blood vessels due to high plasma albumin binding could be another or additional explanation. There could also be a pure pharmacodynamic rationale in which 14 acts concomitantly via another receptor as a functional "blood pressure" antagonist. Further studies are necessary to clarify this point.

In conclusion, 14 is one of a series of new CNS-active α_1-agonists. In animal studies, 14 facilitates maintenance of vigilance, increases attention, lowers sensory threshold, and reverses behavioral deficits induced by noradrenergic depletion.

Table IV. PROBIS Derived Hydrophobic Volumes and CLogP's of a Variety of Centrally and Peripherally Acting α_1-Agonists

no.	hydrophobic volume [Å^3]	CLogP	no.	hydrophobic volume [Å^3]	CLogP
3	439.3	−0.09	**25**	721.9	2.97
4	534.8	0.59	**26**	719.8	2.98
5	529.3	0.80	**27**	764.5	3.51
6	569.8	2.26	**28**	761.9	3.50
7	587.4	3.27	**29**	762.5	2.97
14	680.0	2.45	**30**	394.9	−1.06
22	626.5	1.89	**31**	744.9	4.25
23	726.8	2.98	**33**	698.1	3.72
24	630.3	2.70			

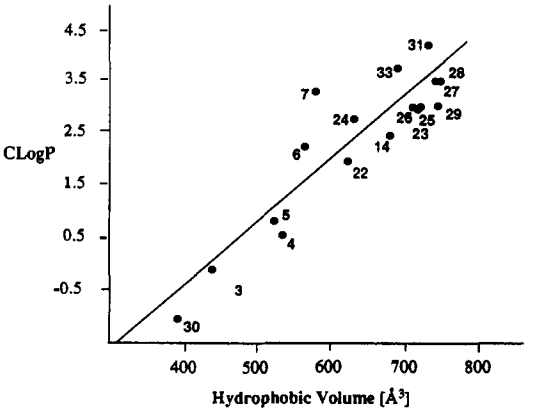

Figure 5. The linear dependence of computationally derived log P and hydrophobicity volume of a variety of α_1-agonists.

Experimental Section

Chemistry. ^{1}H NMR spectra were measured on a Bruker Spectrospin 360-MHz (WH-360) or 90-MHz (HX-90) instrument

(21) For a description of the method, see: Enz, A.; Hefti, F.; Frick, W. Actue Administration of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Reduces Dopamine and Serotonin but Accelerates Norepinephrine Metabolism in the Rat Brain. Effect of Chronic Pretreatment with MPTP. *Eur. J. Pharmacol.* **1984**, *101*, 37–44.
(22) Hofmann, A.; Wiederhold, K.; Menninger, K. Sandoz Pharma Ltd., Basel, unpublished results.
(23) Dravid, A. R. Sandoz Pharma Ltd., Basel, unpublished results.
(24) CLOGP was calculated applying the MEDCHEM software by Daylight Chemical Information Systems, Inc., Irvine, CA.
(25) Walkinshaw, M. D.; Floersheim, P. Hydrophilicity of Proteins and DNA. *J. Mol. Struct.* **1990**, *237*, 63–73.

or on a Varian Gemini 200-MHz spectrometer using Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer-297 spectrophotometer and mass spectra on a Finnigan MAT 212. Melting points were determined on a Buchi 512 apparatus and were not corrected. Elemental analysis were within ±0.4% of theoretical values. All reactions were followed by TLC carried out on Merck 60 F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Buchi rotary evaporator at low pressure (Milt PVK 600 vacuum controller). Column chromatography was performed with silica gel (Merck 60, 230–400 mesh ASTM) applying a medium performance solvent pump (Matkemi RP). A more polar solvent (usually MeOH) was added during the second part of the chromatography. The determination of the enantiomeric excess (ee) was performed by means of ^1H NMR spectroscopy using a solution of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Aldrich) in $CDCl_3$. Salts of bases were generally prepared by adding the particular acid to the base dissolved in acetone or MeOH.

(±)-*trans*-3-Azido-1,2,3,4-tetrahydro-5-methoxy-2-naphthol (10a). A solution of 1,4-dihydro-5-methoxynaphthalene[14] (3.0 g, 0.02 mol) in CH_2Cl_2 (50 mL) was cooled to 0 °C. mCPBA (3.1 g, 0.02 mol) was added to the solution over the course of 1 min. The reaction was subsequently stirred for 15 h at room temperature. The suspension was then added to a mixture of 20 mL of 10% NaOH and 40 g of ice. The organic layer was separated, and the H_2O fraction was extracted twice with CH_2Cl_2. The combined organic fractions were washed with H_2O and NaCl solution, dried, and concentrated by evaporation. The purification by column chromatography (CH_2Cl_2) and crystallization from hexane afforded 2.4 g (68%) of the epoxide, mp 49.5–50.5 °C. *The following procedure was carried out using an efficient hood.* The epoxide was dissolved in DMSO (30 mL). NaN_3 (7.2 g, 0.11 mol) was suspended in DMSO (30 mL), and concentrated H_2SO_4 (2.0 g, 0.02 mol) was dissolved in DMSO (30 mL). The solutions and suspensions were combined and subsequently stirred for 15 h at 60 °C. CH_2Cl_2 (150 mL) was added to the reaction mixture, and the suspension was filtered through hyflo. The rose-colored solution was concentrated by evaporation at 60 °C (10 mm) and then at 80 °C (0.01 mm). The regioisomers were separated by fractional crystallization (toluene/hexane) to yield 1.2 g (40%) of **10a**, mp 83–84 °C, and 1.1 g (37%) of **10b**, mp 145–147 °C. ^1H NMR (200 MHz, $CDCl_3$) of **10a**: δ 1.61 (s, 1 H), 2.60 (dd, 1 H, *J* = 10.6, 17.0 Hz), 2.84 (dd, 1 H, *J* = 10.1, 15.9 Hz), 3.19 (dd, 1 H, *J* = 5.3, 15.9 Hz), 3.37 (dd, 1 H, *J* = 5.8, 17.0 Hz), 3.70 (m, 1 H), 3.84 (s, 3 H), 3.89 (m, 1 H), 6.70 (m, 2 H), 7.17 (t, 1 H, *J* = 8.0 Hz). **10b**: δ 1.60 (s, 1 H), 2.57 (dd, 1 H, *J* = 9.5, 17.0 Hz), 2.88 (dd, 1 H, *J* = 10.6, 17.0 Hz), 3.21 (dd, 1 H, *J* = 5.3, 17.0 Hz), 3.31 (dd, 1 H, *J* = 5.6, 17.0 Hz), 3.72 (m, 1 H), 3.84 (s, 3 H), 3.90 (m, 1 H), 6.72 (m, 2 H), 7.16 (t, 1 H, *J* = 8.0 Hz). Anal. ($C_{11}H_{13}N_3O_2$) C, H, N, O.

(±)-*trans*-2-Chloro-*N*-(1,2,3,4-tetrahydro-2-hydroxy-5-methoxy-3-naphthyl)acetamide (11). A 4.0-g sample of palladium on charcoal (10%) was coated with EtOH (100 mL). **10a** (8.8 g, 0.04 mol) was dissolved in EtOH (100 mL), and the solution was added to the catalyst suspension. The mixture was subsequently hydrogenated at 20 °C at 13 psi of H_2 pressure. The reaction mixture was then filtered through a G 4 hyflo suction filter. The catalyst was washed with CH_2Cl_2, and the filtrate was concentrated by evaporation and purified by column chromatography (CH_2Cl_2/10% MeOH). Crystallization from Et_2O yielded 6.0 g (78%) of the amino alcohol: mp 130–132 °C; MS *m/e* 193 (M^+). This was dissolved in dry CH_2Cl_2 (300 mL). Et_3N (4.8 g, 0.05 mol) was added, and the mixture was left to cool to 0 °C. At this temperature, chloroacetyl chloride (4.1 g, 0.04 mol, dissolved in 30 mL dry CH_2Cl_2) was added dropwise over the course of 5 min, and the mixture was stirred for 2 h at room temperature. The reaction mixture was subsequently washed once with 1 N HCl and once with ice H_2O. The aqueous fractions were reextracted with CH_2Cl_2. The combined organic fractions were dried, and the solution was concentrated by evaporation. The crude product was purified by column chromatography (CH_2Cl_2/2% MeOH) and crystallized from CH_2Cl_2/Et_2O to yield 5.8 g (79%) of 11: mp 176–178 °C; MS *m/e* 269 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 2.55 (dd, 1 H, *J* = 10.8, 17.4 Hz), 2.86 (s, 1 H), 2.90 (dd, 1 H, *J* = 9.6, 17.4 Hz), 3.20 (dd, 1 H, *J* = 6.0, 17.4 Hz), 3.34 (dd, 1 H, *J* = 6.0, 17.4 Hz), 3.82 (s, 3 H), 3.93 (m, 1 H), 4.12 (d, 2 H, *J* = 6.0 Hz), 4.15 (m, 1 H), 6.72 (m, 3 H), 7.16 (t, 1 H, *J* = 7.8 Hz). Anal. ($C_{13}H_{16}ClNO_3$) C, H, N, O.

(±)-*trans*-3,4,4a,5,10,10a-Hexahydro-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazine (12). NaH (0.9 g, 0.04 mol) and tetrabutylammonium iodide were suspended in dry THF (100 mL). A solution of 11 (8.8 g, 0.03 mol) in dry THF (300 mL) was subsequently added dropwise at room temperature over the course of 15 min, and the mixture was stirred for 18 h at room temperature under an Ar atmosphere. The solution was subsequently concentrated by evaporation, and the residue was taken up in CH_2Cl_2/ice water (1:1, 100 mL). The H_2O layer was removed, and the organic layer was extracted with 1 N HCl and H_2O. The entire H_2O fractions were again extracted with CH_2Cl_2. The combined organic fractions were dried and concentrated by evaporation to afford raw crystals, which were recrystallized from CH_2Cl_2/acetone/Et_2O to yield 6.4 g (92%) of the oxazinone: mp 237–240 °C; IR (CH_2Cl_2) ν 1675 cm^{-1} (C=O); MS *m/e* 233 (M^+). This oxazinone (5.9 g, 0.025 mol) was dissolved in dry THF (300 mL) and was added in drops to a suspension of $LiAlH_4$ (3.9 g, 0.1 mol) in dry THF (100 mL). The reaction mixture was refluxed for 2 h and then cooled to −20 °C. Ice (100 mL) and CH_2Cl_2 (200 mL) were then added, and the mixture stirred for 15 min. The suspension was then filtered through hyflo, the CH_2Cl_2 layer was separated, and the residue of filtration was washed with CH_2Cl_2. The combined organic fractions were dried and concentrated by evaporation. The residue was purified by column chromatography (CH_2Cl_2/1–3% MeOH) to obtain as an oil 4.2 g (76%) of 12: MS *m/e* 219 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 1.85 (broad singlet, 1 H), 2.34 (dd, 1 H, *J* = 12.0, 17.0 Hz), 2.78–3.16 (m, 6 H), 3.50 (3 d, 1 H, *J* = 5.2, 6.8, 10.5 Hz), 3.74 (m, 1 H), 3.81 (s, 3 H), 3.94 (m, 1 H), 6.70 (m, 2 H), 7.16 (t, 1 H, *J* = 7.6 Hz). Anal. ($C_{13}H_{17}NO_2$) C, H, N, O.

(±)-*trans*-3,4,4a,5,10,10a-Hexahydro-9-iodo-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (13). Palladium (2 g) on charcoal (10%) were suspended in MeOH (100 mL). To this were added 12 (4.8 g, 0.02 mol) and 23.7 mL formalin (37%), both dissolved in MeOH (200 mL). The mixture was subsequently hydrogenated at 20 °C, at 13 psi of H_2 pressure. After 6 h the reaction mixture was filtered through a hyflo suction filter and washed with CH_2Cl_2 (100 mL), and the filtrate was concentrated by evaporation. The residue was taken up again in CH_2Cl_2 (100 mL) and washed once each time with saturated K_2CO_3 solution (20 mL) and H_2O. The CH_2Cl_2 fraction was dried and concentrated by evaporation. The residue was purified by column chromatography (CH_2Cl_2/1% MeOH). Crystallization from hexane yielded 4.1 g (88%) of the amine: mp 67–68 °C; MS *m/e* 233 (M^+). This amine (2.9 g, 0.01 mol) was dissolved in concentrated HOAc (60 mL) and warmed to 50 °C. I_2 (7.9 g, 0.06 mol) and separately $Hg(OAc)_2$ (5.1 g, 0.02 mol) were dissolved in concentrated HOAc (335 mL, 310 mL, respectively) and simultaneously added dropwise to the amine solution, while the reaction temperature was kept between 45 and 55 °C. There was always a small excess of I_2. The reaction mixture was stirred for 15 min at 50 °C, cooled down to room temperature, and stirred for additional 2 h. The precipitated Hg salt was filtered off the solution, and the HOAc was evaporated. The residue was taken up in an aqueous KI solution, and the crude product was recovered by filtration. The crystalline product was dissolved in concentrated NH_3 and extracted with CH_2Cl_2/H_2O. The organic fraction was dried and evaporated. The purification by crystallization from acetone/Et_2O yielded 3.9 g (88%) of 13 as base: mp >165 °C dec; ^1H NMR (360 MHz, $CDCl_3$) δ 2.04 (m, 1 H), 2.32 (dd, 1 H, *J* = 11.0, 18.0 Hz), 2.41 (s, 3 H), 2.49 (m, 1 H), 2.62 (dd, 1 H, *J* = 11.0, 17.0 Hz), 2.76 (m, 1 H), 3.12 (dd, 1 H, *J* = 6.0, 17.0 Hz), 3.33 (dd, 1 H, *J* = 5.6, 17.0 Hz), 3.56 (m, 1 H), 3.81 (s, 3 H), 3.88 (m, 2 H), 6.47 (d, 1 H, *J* = 9.0 Hz), 7.66 (d, 1 H, *J* = 9.0 Hz). Compound 13 as HCl salt: mp >285 °C dec. Anal. ($C_{14}H_{18}INO_2$·HCl) C, H, N, O, Cl, I.

(−)-(4a*R*,10a*R*)-3,4,4a,5,10,10a-Hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (14). To a suspension of CH_3SLi (3.7 g, 0.07 mol) in DMSO (70 mL) were added the solution of 13 (3.1 g, 0.008 mol) in DMSO (35 mL) and Cu_2O (16.4 g, 0.11 mol). The reaction mixture was subsequently stirred for 5 h at 80 °C under an Ar atmosphere. The preparation was then filtered through hyflo and washed with CH_2Cl_2, and the filtrate was concentrated by

evaporation. The residue was taken up in CH_2Cl_2/ice, the organic layer was separated, and the H_2O fraction was reextracted with CH_2Cl_2. The combined organic fractions were dried and concentrated by evaporation. The crude product was purified by column chromatography (CH_2Cl_2/5% MeOH) to yield the thioether as an oil: 1.7 g (78%); ^1H NMR (200 MHz, $CDCl_3$) δ 2.09 (m, 1 H), 2.32 (dd, 1 H, J = 10.5, 16.5 Hz), 2.39 (s, 3 H), 2.41 (s, 3 H), 2.45–2.80 (m, 3 H), two overlapping double-doublets 3.27–3.40 (2 dd, 2 H, J = 5.0, 6.0, 16.0, 16.5 Hz), 3.60 (m, 1 H), 3.82 (s, 3 H), 3.90 (m, 2 H), 6.72 (d, 1 H, J = 8.5 Hz), 7.14 (d, 1 H, J = 8.5 Hz). Splitting of the racemic form: The thioether (1.7 g, 0.006 mol) was dissolved in acetone (50 mL). To this was added a solution of (+)-di-*O,O'*-*p*-toluoyl-D-(-)-tartaric acid (2.5 g, 0.006 mol) in acetone (30 mL). The precipitating salt was stirred for 1 h at room temperature and filtered off. The salt was recrystallized three times from CH_2Cl_2/MeOH (1:1). The salt was subsequently taken up in a mixture of 50 mL of ice/5 mL of concentrated NH_3/10 mL of CH_2Cl_2. The organic layer was separated, and the H_2O fraction was reextracted twice with CH_2Cl_2. The combined organic fractions were dried and concentrated by evaporation to yield as an oil 0.6 g (36%) of 14 as free base: $[\alpha]_D$ -121.3° (c = 0.5, CH_2Cl_2/MeOH, 1:1), ee >99%. 14 as HCl salt: mp 237–239 °C; $[\alpha]_D$ -117.4° (c = 0.5, CH_2Cl_2/MeOH, 1:1). Anal. ($C_{15}H_{21}NO_2S$·HCl) C, H, N, O, S, Cl.

(+)-(4a*S*,10a*S*)-3,4,4a,5,10,10a-Hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (15). The *S,S*-(+) enantiomer 15 was obtained following the same procedure, using the (-)-antipode acid.

(±)-3-(Methoxycarbonyl)-8-methoxy-2-tetralone (17). Magnesium chips (13.5 g, 0.56 mol) were suspended in MeOH, and the mixture was warmed up to 55 °C while stirring. After 0.5 h additional Mg chips (20.5 g, 0.84 mol) were added and the reaction mixture was kept for 1.5 h at 55 °C. This step was repeated. Then the MeOH was evaporated, DMF (1100 mL) was added, and the mixture was kept for 12 h under an Ar atmosphere at room temperature. Subsequently the solution was saturated with CO_2 gas (4 h). A solution of 8-methoxy-2-tetralone[15] (55 g, 0.31 mol) in DMF (100 mL) was added in drops. Afterwards the reaction mixture was heated to 133 °C for 4 h while still keeping it under Ar. For the workup the mixture was divided into two equal portions and each cooled to -10 °C. In each one, 1500 mL of HCl (10%) was added dropwise, and the mixtures were stirred for 30 min at -10 °C. The combined products were recovered by filtration and washed with ice/H_2O. The crystalline mass was stirred in MeOH (100 mL) and then filtered off, and the residue was washed with Et_2O/petroleum ether (1:1) and dried to obtain 49.8 g (73%) of the acid: mp >117 °C dec; MS m/e 220 (M^+). This acid (49.5 g, 0.22 mol) was added to cooled CH_2Cl_2 (550 mL, 0 °C). Methyl chloroformate (21.1 g, 0.22 mol) was added to the solution, and the mixture was kept at 5 °C while Et_3N (34 mL, dissolved in 50 mL CH_2Cl_2) was added, and stirring was continued for 2 h at 5 °C. Subsequently, H_2O (125 mL) was added dropwise, and the organic layer was separated and evaporated. The residue was treated with MeOH, and the precipitated product was recovered by filtration and purified by recrystallization from MeOH/acetone to yield 31.9 g (62%) of 17 as pale brown crystals: mp 111–113 °C; IR (CH_2Cl_2) ν 1655 cm^{-1} (C=O, enol form); MS m/e 234 (M^+); ^1H NMR (90 MHz, $CDCl_3$) δ 3.60 (m, 4 H), 3.83 (2 s, 6 H), 6.71 (2 t, 2 H, J = 8.0 Hz), 7.15 (t, 1 H, J = 8.0 Hz), 12.20 (s, 1 H). Anal. ($C_{13}H_{14}O_4$) C, H, O.

(±)-3-(2-Cyanoethyl)-8-methoxy-2-tetralone (18). To a solution of 17 (2.3 g, 0.01 mol) in dry toluene (50 mL) and dry MeOH (14 mL) were added acrylonitrile (0.8 g, 0.02 mol) and NaH (10 mg, 55% dispersion in oil) under Ar. The reaction mixture was stirred at room temperature for 20 h. Subsequently, the mixture was adjusted to pH 1 by the addition of methanolic HCl. The solvent was then evaporated. The residue was purified by column chromatography (CH_2Cl_2/0.8% MeOH) and crystallization from acetone/petroleum ether to obtain 1.1 g (40%) of the nitrile as yellow crystals: mp 120–121 °C; IR (Nujol) ν 1700 and 1735 (C=O), 2240 cm^{-1} (CN); MS m/e 287 (M^+). This nitrile (1.1 g, 0.004 mol) was dissolved in HMPA (30 mL) at 75 °C. LiCl (0.4 g, 0.01 mol) was added, and the mixture was stirred at 75 °C for 20 h. Afterwards the reaction mixture was poured on H_2O (200 mL) and extracted with Et_2O. The organic fraction was washed with water, dried, and evaporated. The oily residue was purified by column chromatography (CH_2Cl_2) and crystallized from acetone/Et_2O/petroleum ether to yield 0.6 g (68%) of 18 as colorless crystals: mp 74–75 °C; MS m/e 229 (M^+); IR (CH_2Cl_2) ν 1710 (C=O), 2240 cm^{-1} (CN); ^1H NMR (360 MHz, $CDCl_3$) δ 1.75 (m, 1 H), 2.20 (seven line multiplet, 1 H, J = 7.0 Hz), 2.56 (t, 2 H, J = 7.0 Hz), 2.74 (m, 1 H), 2.87 (dd, 1 H, J = 12.0, 15.0 Hz), 3.12 (dd, 1 H, J = 6.0, 15.0 Hz), 3.44 (d, 1 H, J = 22.5 Hz), 3.69 (d, 1 H, J = 22.5 Hz), 3.85 (s, 3 H), 6.78 (d, 1 H, J = 7.5 Hz), 6.82 (d, 1 H, J = 7.5 Hz), 7.21 (t, 1 H, J = 7.5 Hz). Anal. ($C_{14}H_{15}NO_2$) C, H, N, O.

(±)-*trans*- and *cis*-9-Methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (19, 20). To a solution of 18 (6.6 g, 0.03 mol) in EtOH (150 mL) and $CHCl_3$ (5 mL) was added PtO_2 (0.6 g), and the suspension was hydrogenated while shaking for 30 h under an initial H_2 pressure of 40 psi. The mixture was subsequently filtered off, the solvent was evaporated, and the residue was extracted with 1 N aqueous $NaHCO_3$/CH_2Cl_2. The organic layer was separated, dried, and evaporated. The crude, oily mixture of the isomers (5.8 g, 0.03 mol) was dissolved in 6.4 mL of formalin (37%) and 4.3 mL of HCOOH. The reaction mixture was heated up to 70 °C and stirred for 1.5 h under Ar. The solution was then extracted with H_2O/concentrated NH_3, H_2O/ice, and CH_2Cl_2. The organic fraction was dried and evaporated. The residue was purified, and the isomers separated, by column chromatography (CH_2Cl_2/1% MeOH/0.1% concentrated NH_3) to obtain 4.4 g (63%) of 19: mp 85–87 °C; MS m/e 231 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 1.11 (eight line multiplet, 1 H), 1.65–1.98 (m, 5 H), 2.21 (dt, 1 H, J = 2.0, 12.0 Hz), 2.35 (dd, 1 H, J = 10.5, 17.0 Hz), 2.44 (s, 3 H), 2.49 (dd, 1 H, J = 12.0, 18.0 Hz), 2.77 (dd, 1 H, J = 6.0, 16.5 Hz), 2.98 (m, 1 H), 3.29 (dd, 1 H, J = 6.0, 17.5 Hz), 3.83 (s, 3 H), overlapping doublets 6.66 (d, 1 H, J = 7.0 Hz), 6.68 (d, 1 H, J = 7.0 Hz), 7.09 (t, 1 H, J = 7.0 Hz). The cis isomer 20 was obtained as an oil: 1.5 g (22%); MS m/e 231 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 1.44 (m, 2 H), 1.63 (10 line multiplet, 1 H), 1.76 (m, 1 H), 2.14 (m, 1 H), 2.38 (s, 3 H), 2.39 (m, 1 H), 2.61–2.97 (m, 6 H), 3.83 (s, 3 H), 6.65 (d, 1 H, J = 7.5 Hz), 6.70 (d, 1 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 7.5 Hz). Anal. ($C_{15}H_{21}NO$) C, H, N, O.

(±)-*trans*-9-Methoxy-*N*-methyl-6-(methylthio)-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydromalonate (21). The iodination procedure described for 13 was followed, using 19 (3.5 g, 0.015 mol). The crude iodinated product was obtained as a brownish foam, 3.4 g (64%), MS m/e 357 (M^+) (for characterization: the corresponding hydromalonate crystallized from MeOH/CH_2Cl_2/acetone/Et_2O, mp 154–155 °C). The crude product (3.3 g, 0.009 mol) was transposed with CH_3SLi in the presence of Cu_2O according to the procedure described for 14. Purification by recrystallization from acetone/Et_2O yielded 2.0 g (79%) of 21 as free base: mp 113–115 °C; MS m/e 277 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 1.15 (10 line multiplet, 1 H), 1.57–1.98 (m, 5 H), 2.18 (dt, 1 H, J = 2.0, 12.0 Hz), overlapping double-doublets 2.28 (dd, 1 H, J = 10.0, 18.0 Hz), 2.33 (dd, 1 H, J = 8.0, 18.0 Hz), 2.40 (s, 6 H), 2.94 (m, 1 H), 3.03 (dd, 1 H, J = 6.0, 18.0 Hz), 3.28 (dd, 1 H, J = 6.0, 18.0 Hz), 3.82 (s, 3 H), 6.70 (d, 1 H, J = 7.5 Hz), 7.09 (d, 1 H, J = 7.5 Hz). The base 21 was converted into the hydrogen malonate salt and recrystallized from MeOH/acetone/CH_2Cl_2 to obtain 1.6 g (45%) of 21, mp 157–158 °C. Anal. ($C_{16}H_{23}NOS$·$C_3H_4O_4$) C, H, N, O, S.

(±)-*trans*-3,4,4a,5,10,10a-Hexahydro-6-methoxy-4-methyl-9-nitro-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (22). The oxazine 12 was N-methylated according to the procedure described for 13. This tertiary amine (2.3 g, 0.01 mol) was cooled to 0 °C, and concentrated HNO_3 (5 mL) was added slowly. Subsequently the dark blue mixture was cooled and stirred for 2 h. Then ice was added, and the reaction mixture was neutralized with concentrated NH_3. The product was extracted with CH_2Cl_2, and the organic layer was washed with water, dried, and evaporated to obtain a reddish foam. The crude product was purified by column chromatography (CH_2Cl_2/0.5–1% MeOH) to yield pale yellow crystals: MS m/e 278 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 2.10 (dt, 1 H, J = 1.0, 6.0 Hz), 2.33 (dd, 1 H, J = 11.5, 18.0 Hz), 2.42 (s, 3 H), 2.51 (dt, 1 H, J = 4.0, 12.0 Hz), 2.76 (m, 1 H), 3.07 (dd, 1 H, J = 11.5, 18.0 Hz), overlapping double-doublets 3.34 (dd, 1 H, J = 6.0, 18.0 Hz), 3.39 (dd, 1 H, J = 6.0, 18.0 Hz), 3.50 (dt, 1 H, J = 1.0, 6.0 Hz), 3.85 (dt, 1 H, J = 2.0, 9.0 Hz), 3.92 (dt, 1 H, J = 2.0, 9.0 Hz), 3.94 (s, 3 H), 6.77 (d, 1 H, J = 9.0 Hz), 7.99

(d, 1 H, J = 9.0 Hz). The base was converted into the HCl salt and recrystallized from CH_2Cl_2/acetone to obtain 0.5 g (17%) of **22**, mp 254–256 °C. Anal. ($C_{14}H_{18}N_2O_4$·HCl) C, H, N, O, Cl.

(−)-(4a*R*,10a*R*)-9-(Ethylthio)-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (23). The procedure described for 14 was followed, using **13** (10.8 g, 0.03 mol), Cu_2O (57.9 g, 0.41 mol), and EtSLi (16.3 g, 0.24 mol). The base was converted into the HCl salt and recrystallized from MeOH/acetone/Et_2O to yield 2.3 g (23%) of **23**: mp >180 °C dec; $[\alpha]_D$ −121° (c = 0.6, MeOH/CH_2Cl_2, 1:1); ee >99%; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7.0 Hz), 2.64 (dd, 1 H, J = 11.0, 17.5 Hz), 2.78 (q, 2 H, J = 7.0 Hz), 2.93 (s, 3 H), 3.02 (dt, 1 H, J = 3.0, 7.0 Hz), 3.10 (dt, 1 H, J = 3.0, 12.0 Hz), 3.25 (dd, 1 H, J = 11.0, 17.5 Hz), 3.45 (dd, 1 H, J = 6.5, 18.0 Hz), 3.47 (m, 1 H), 3.59 (dd, 1 H, J = 6.0, 17.5 Hz), 3.81 (s, 3 H), 4.05 (dd, 1 H, J = 3.0, 12.5 Hz), 4.34 (dt, 1 H, J = 6.0, 12.0 Hz), 4.55 (dt, 1 H, J = 1.0, 12.5 Hz), 6.70 (d, 1 H, J = 7.5 Hz), 7.30 (d, 1 H, J = 7.5 Hz). Anal. ($C_{16}H_{23}NO_2S$·HCl) C, H, N, O, S, Cl.

(±)-*trans*-9-Chloro-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (24). Compound **12** was N-methylated according to the procedure described for **13**. The tertiary amine (1.4 g, 0.006 mol) was dissolved in CH_2Cl_2 (7 mL) and concentrated HOAc (11 mL) and cooled to 0 °C. At this temperature a solution of SO_2Cl_2 (1.0 g, 0.007 mol) in CH_2Cl_2 (4 mL) was added dropwise. After 3 h and then 5 h supplemental SO_2Cl_2 (0.2 g, 0.002 mol) was added. After 7 h the reaction mixture was poured into a beaker and cooled to 0 °C, and an aqueous Na_2CO_3 (10%) solution was added carefully for neutralization. The mixture was extracted with CH_2Cl_2, and the organic fraction was washed with H_2O/ice, dried, and evaporated. The crude product was obtained as a light yellow oil, and converted into the HCl salt. Recrystallization from MeOH/acetone/Et_2O afforded 1.5 g (83%) of **24**: mp 286–287 °C; MS m/e 267 (M^+); ^{1}H NMR (360 MHz, $CDCl_3$, of the free base) δ 2.05 (dt, 1 H, J = 6.0, 10.5 Hz), 2.31 (dd, 1 H, J = 10.0, 18.0 Hz), 2.40 (s, 3 H), 2.50 (dt, 1 H, J = 4.0, 10.5 Hz), 2.62 (dd, 1 H, J = 11.5, 17.5 Hz), 2.77 (broad doublet, 1 H, J = 12.0 Hz), 3.25 (dd, 1 H, J = 6.0, 18.0 Hz), 3.34 (dd, 1 H, J = 6.0, 17.5 Hz), 3.59 (dt, 1 H, J= 3.0, 10.5 Hz), 3.82 (s, 3 H), 3.90 (m, 2 H), 6.64 (d, 1 H, J = 8.0 Hz), 7.20 (d, 1 H, J = 8.0 Hz). Anal. ($C_{14}H_{18}ClNO_2$·HCl) C, H, Cl, N, O.

(±)-*trans*-3,4,4a,5,10,10a-Hexahydro-6-methoxy-2,4-dimethyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (25). The procedure described for **11** was followed, using 2-chloropropionyl chloride (5.1 g, 0.04 mol). The crude product was purified by recrystallization from Et_2O to obtain 7.7 g (88%) of the chloro amide, mp 191–193 °C. This product was cyclized according to the procedure described for **12**. To >90% a unique diastereomer was formed and purified by recrystallization from CH_2Cl_2/Et_2O to yield 4.7 g (70%) of the oxazinone: mp 192–194 °C; IR (CH_2Cl_2) ν 1670 cm^{-1} (C=O). This product was reduced analogously to **12** and purified by column chromatography (CH_2Cl_2/2–4% MeOH) to yield 3.8 g (86%) of the oxazine as an oil, MS m/e 233 (M^+). The oxazine was N-methylated according to the procedure described for **13** to obtain 3.8 g (94%) of the slightly impure, solid tertiary amine (all recrystallization trials failed), MS m/e 247 (M^+). This amine was iodinated according to **13** [3.3 g, 57% yield; crystallization from Et_2O/petroleum ether; mp 118–120 °C; MS m/e 373 (M^+)], and the SCH_3 group was introduced as described for **14**. The base was converted into the HCl salt and recrystallized from MeOH/acetone/Et_2O to afford 2.0 g (67%) of **25**: mp 214–215 °C; MS m/e 293 (M^+); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.84 (d, 3 H, J = 7.0 Hz), 2.40 (s, 3 H), 2.60 (dd, 1 H, J = 11.0, 17.0 Hz), 2.96 (s, 3 H), 2.98 (m, 1 H), 3.20–3.50 (m, 5 H), 3.80 (s, 3 H), 4.39 (m, 2 H), 6.73 (d, 1 H, J = 8.0 Hz), 7.18 (d, 1 H, J = 8.0 Hz). Anal. ($C_{16}H_{23}NO_2S$·HCl) C, H, N, O, S, Cl.

(±)-*trans*-4-Ethyl-3,4,4a,5,10,10a-hexahydro-6-methoxy-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (26). The oxazine **12** (9.5 g, 0.04 mol) was dissolved in CH_2Cl_2 (100 mL), and $Et(iPr)_2N$ (18.1 mL, 0.1 mol) was added. Acetyl chloride (6.2 mL, 0.09 mol) in CH_2Cl_2 (100 mL) was added, while the reaction temperature was kept at 20 °C. Stirring was continued for 1 h at room temperature. Subsequently the reaction mixture was diluted with CH_2Cl_2 and washed with 2 N HCl/ice, 2 N NaOH/ice, and H_2O. The organic fraction was dried and evaporated to obtain pale brown foamy crystals. This residue was purified by column chromatography (CH_2Cl_2/2% MeOH) and recrystallized from acetone/Et_2O to yield 9.8 g (94%) of the amide: mp 134–135 °C; MS m/e 261 (M^+); IR (CH_2Cl_2) ν 1630 cm^{-1} (C=O). This amide (8.5 g, 0.03 mol) was dissolved in THF (300 mL) and added dropwise during 10 min to a suspension of $LiAlH_4$ (5.0 g, 0.13 mol) in THF (200 mL). The reaction mixture was refluxed for 30 min and cooled to −20 °C, and saturated aqueous Na_2SO_4 was added to destroy the excessive hydride. The mixture was filtrated through a G 4 hyflo, and the solvent was evaporated. The residue was taken up in CH_2Cl_2 and extracted with water. The organic fraction was dried and evaporated to obtain a yellow oil, which was purified by column chromatography (CH_2Cl_2/2% MeOH) to yield 7.3 g (91%) of the N-ethylated oxazine as an oil, MS m/e 247 (M^+). This oxazine was iodinated according to the procedure described for **13**. The base was purified by column chromatography (CH_2Cl_2/0.5–1% MeOH), and recrystallized from acetone/Et_2O to yield 3.7 g (34%) of the iodo oxazine: mp 180–181 °C; MS m/e 373 (M^+). The corresponding HCl salt, mp 270 °C (recrystallized from MeOH/CH_2Cl_2/acetone). The free base was taken to introduce the SCH_3 group according to the procedure described for **14**. The product was purified by column chromatography (CH_2Cl_2/0.5–1% MeOH) and converted into the HCl salt (recrystallized from CH_2Cl_2/acetone/Et_2O) to obtain 2.2 g (68%) of **26**: mp 238–239 °C; MS m/e 293 (M^+); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.29 (t, 3 H, J = 8.0 Hz), 2.39 (s, 3 H), 2.52 (dd, 1 H, J = 12.0, 18.0 Hz), 2.98 (dd, 1 H, J = 10.5, 17.0 Hz), partly overlapped 3.03–3.16 (m, 2 H), 3.21 (dd, 1 H, J = 6.0, 18.0 Hz), 3.35 (dd, 1 H, J = 6.0, 17.0 Hz), partly overlapped 3.35–3.52 (m, 4 H), 3.80 (s, 3 H), 4.10 (m, 2 H), 6.92 (d, 1 H, J = 7.5 Hz), 7.21 (d, 1 H, J = 7.5 Hz), 12.20 (broad singlet, 1 H). Anal. ($C_{16}H_{23}NO_2S$·HCl) C, H, N, O, S, Cl.

(±)-*trans*-3,4,4a,5,10,10a-Hexahydro-6-methoxy-9-(methylthio)-4-*n*-propyl-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (27). The procedure described for **26** was followed, starting from propionyl chloride and **12**. The amide was purified by crystallization from Et_2O/petroleum ether to yield 10.2 g (93%): mp 108–110 °C; MS m/e 275 (M^+); IR (CH_2Cl_2) ν 1630 cm^{-1} (C=O). This amide was reduced and purified by column chromatography (CH_2Cl_2/2% MeOH) to obtain 8.6 g (89%) of the N-propylated oxazine, MS m/e 261 (M^+). This oxazine was iodinated and purified by column chromatography (CH_2Cl_2/2% MeOH), and recrystallized from acetone/Et_2O to yield 6.6 g (52%) of the iodo oxazine: mp >245 °C dec; MS m/e 387 (M^+). This product was taken to introduce the SCH_3 group. The crude brown, oily compound was converted into the HCl salt (recrystallization from MeOH/acetone/Et_2O) to obtain 4.2 g (72%) of **27**: mp 244–246 °C; MS m/e 307 (M^+); ^{1}H NMR (360 MHz, DMSO-d_6) δ 0.99 (t, 3 H, J = 7.0 Hz), 1.77 (sextet, 2 H, J = 7.0 Hz), 2.40 (s, 3 H), 2.52 (dd, 1 H, J = 12.0, 18.0 Hz), 2.99 (m, 2 H), 3.21 (dd, 1 H, J = 6.0, 18.0 Hz), partly overlapping 3.10–3.60 (m, 5 H), 3.80 (s, 3 H), 4.10 (m, 3 H), 6.92 (d, 1 H, J = 8.0 Hz), 7.21 (d, 1 H, J = 8.0 Hz), 11.90 (broad singlet, 1 H). Anal. ($C_{17}H_{25}NO_2S$·HCl) C, H, N, O, S, Cl.

(±)-*trans*-4-Ethyl-3,4,4a,5,10,10a-hexahydro-6-methoxy-2-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (28). The procedure described for **25** and **26** was followed. The crude product was converted into the HCl salt and recrystallized from MeOH/acetone/Et_2O to obtain 3.6 g (78%, last step) of **28**: mp 231–232 °C; MS m/e 307 (M^+); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.29 (t, 3 H, J = 7.5 Hz), 1.59 (d, 3 H, J = 6.5 Hz), 2.39 (s, 3 H), 2.50 (dd, 1 H, J = 10.5, 17.5 Hz), overlapping multiplets 3.07–3.52 (m, 8 H), 3.80 (s, 3 H), 4.15 (dt, 1 H, J = 4.0, 10.0 Hz), 4.36 (m, 1 H), 6.92 (d, 1 H, J = 9.0 Hz), 7.21 (d, 1 H, J = 9.0 Hz), 11.32 (broad singlet, 1 H). ($C_{17}H_{25}NO_2S$·HCl) C, H, N, O, S.

(±)-*trans*-2-Ethyl-3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine Hydrochloride (29). The procedure described for **25** was followed, using 2-bromobutyryl chloride. The cyclization reaction has to be carried out in dioxane under reflux. The amide [10.5 g; 98% yield; mp 172–174 °C; MS m/e 342 (M^+)] and the oxazinone [5.5 g; 69% yield; mp 176–178 °C; MS m/e 261 (M^+); IR (CH_2Cl_2) ν 1660 cm^{-1} (C=O)] were recrystallized from MeOH/acetone. The oxazine was purified by column chromatography (CH_2Cl_2/2–5% MeOH) to yield 2.5 g (48%); MS m/e 247 (M^+). The N-

methylated oxazine was purified by column chromatography (CH_2Cl_2/1% MeOH) and recrystallized from petroleum ether to yield 1.7 g (64%): mp 94–95 °C; MS *m/e* 261 (M^+). The tertiary amine was subsequently iodinated following the procedure described for **13**. The crude base was purified by column chromatography (CH_2Cl_2/0.5% MeOH) and characterized as the HCl salt. Recrystallization from MeOH/Et_2O; yield 1.3 g; 46%; mp 268–270 °C; MS *m/e* 387 (M^+). The iodinated oxazine was taken to introduce the SCH_3 group according to the procedure described for **14**. The crude product was converted into the HCl salt and recrystallized from MeOH/Et_2O to give rise to 0.5 g (45%) of **29**: mp 210–212 °C; MS *m/e* 307 (M^+); ^1H NMR (360 MHz, $CDCl_3$) δ 1.03 (t, 3 H, J = 7.5 Hz), 2.00 (septet, 1 H, J = 7.5 Hz), 2.39 (s, 3 H), 2.60 (dd, 1 H, J = 10.5, 17.0 Hz), overlapped multiplets 2.60 (m, 1 H), 2.95 (m, 1 H), 2.95 (s, 3 H), 3.20 (broad singlet, 1 H), overlapping double doublets 3.41 (dd, 1 H, J = 6.0, 17.0 Hz), 3.43 (dd, 1 H, J = 6.0, 17.5 Hz), overlapped multiplet (m, 2 H), 3.80 (s, 3 H), 3.99 (dt, 1 H, J = 6.0, 11.0 Hz), 4.30 (dt, 1 H, J = 6.0, 9.0 Hz), 6.72 (d, 1 H, J = 8.0 Hz), 7.17 (d, 1 H, J = 8.0 Hz), 12.90 (broad singlet, 1 H). Anal. ($C_{17}H_{25}NO_2S$·HCl) C, H, N, O, S, Cl.

(±)-*trans*-6-(Ethylthio)-9-methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydromalonate (31). **19** was iodinated according to the procedure described for **13**. The iodo compound (4.2 g, 0.012 mol) was transposed with EtSLi (3.2 g, 0.05 mol) and Cu_2O (24.0 g, 0.16 mol) as described for **14**. The oily, crude product was converted into the hydrogen malonate salt and recrystallized from CH_2Cl_2/MeOH to obtain 3.8 g (81%) of **31**: mp 128–130 °C; MS *m/e* 291 (M^+); ^1H NMR (360 MHz, $CDCl_3$, of base) δ 1.14 (octet, 1 H, J = 5.0 Hz), 1.26 (t, 3 H, J = 7.0 Hz), overlapping multiplets 1.56–1.99 (m, 5 H), 2.18 (dt, 1 H, J = 4.0, 12.0 Hz), overlapping double doublets 2.27 (dd, 1 H, J = 12.0, 17.5 Hz), 2.32 (dd, 1 H, J = 11.0, 17.0 Hz), 2.40 (s, 3 H), 2.80 (q, 2 H, J = 7.0 Hz), 2.94 (broad doublet, 1 H, J = 11.0 Hz), 3.13 (dd, 1 H, J = 5.0, 17.0 Hz), 3.27 (dd, 1 H, J = 5.5, 17.5 Hz), 3.81 (s, 3 H), 6.67 (d, 1 H, J = 7.5 Hz), 7.20 (d, 1 H, J = 7.5 Hz). Anal. ($C_{17}H_{25}NOS$·$C_3H_4O_4$) C, H, N, O, S.

(±)-*cis*-6-(Ethylthio)-9-methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydromalonate (32). The procedure described for **31** was followed, using **20** as starting material, and **32** was recovered in 1.2 g, 72% yield: mp 78–80 °C (recrystallization from CH_2Cl_2/MeOH); MS *m/e* 291 (M^+); ^1H NMR (360 MHz, $CDCl_3$, of base) δ 1.26 (t, 3 H), J = 7.0 Hz), 1.37–1.54 (m, 2 H), 1.65 (10 line multiplet, 1 H, J = 4.5 Hz), 1.76–1.86 (m, 1 H), 2.20 (m, 1 H), 2.40 (s, 3 H), 2.44 (dt, 1 H, J = 4.0, 6.0 Hz), 2.64 (dd, 1 H, J = 7.0, 17.5 Hz), 2.71 (dd, 1 H, J = 5.0, 16.0), overlapped multiplet 2.71 (m, 1 H), 2.80 (q, 2 H, J = 7.0 Hz), 2.84–2.91 (m, 1 H), overlapping double-doublets 2.97 (dd, 1 H, J = 7.0, 17.5 Hz), 3.00 (dd, 1 H, J = 6.0, 17.5 Hz), 3.81 (s, 3 H), 6.66 (d, 1 H, J = 8.0 Hz), 7.20 (dd, 1 H, J = 8.0 Hz). Anal. ($C_{17}H_{25}NOS$·$C_3H_4O_4$) C, H, N, O, S.

(−)-*trans*-9-Methoxy-1-methyl-6-(methylthio)-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydromalonate (33). The racemate **19** (38.9 g, 0.17 mol) was resolved by (−)-ditoluyltartaric acid as described for **14** to yield 6.1 g (16%) of the (−) enantiomer: $[\alpha]_D$ −166° (c = 0.5, CH_2Cl_2); ee >99%. This (−)-antipode was converted according to the procedure described for **21** to obtain optically pure **33**, crystallized from acetone/EtOAc as the hydrogen malonate salt in colorless crystals: mp 133 °C; $[\alpha]_D$ −103° (c = 0.5, CH_2Cl_2); ee >99%. Anal. ($C_{16}H_{23}NOS$·$C_3H_4O_4$) C, H, N, O, S.

(±)-*cis*-9-Methoxy-1-methyl-6-(methylthio)-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydromalonate (34). The procedure described for **21** was followed, using **20** as starting material. **34** was obtained in 59% yield (1.5 g, overall from **20**) and recrystallized from acetone/MeOH/CH_2Cl_2/Et_2O: mp 147–148 °C; MS *m/e* 277 (M^+); ^1H NMR (360 MHz, $CDCl_3$, of base) δ 1.48 (m, 2 H), 1.62 (10 line multiplet, 1 H, J = 4.0 Hz), 1.82 (m, 1 H), 2.18 (m, 1 H), 2.36 (s, 3 H), overlapped double-doublet 2.37 (dd, 1 H, J = 7.0, 16.5 Hz), 2.38 (s, 3 H), 2.61 (dd, 1 H, J = 6.0, 18.0 Hz), 2.70 (m, 1 H), 2.77 (dd, 1 H, J = 7.0, 17.0 Hz), 2.80 (broad doublet, 1 H), 2.89 (dd, 1 H, J = 6.5, 17.0 Hz), 3.01 (dd, 1 H, J = 7.0, 18.0 Hz), 3.80 (s, 3 H), 6.69 (d, 1 H, J = 7.5 Hz), 7.07 (d, 1 H, J = 7.5 Hz). Anal. ($C_{16}H_{23}NOS$·$C_3H_4O_4$) C, H, N, O, S.

X-ray Crystal Structure of 14. The crystal of **14** suitable for X-ray analysis was obtained by recrystallization from Et_2O/CH_2Cl_2. Crystal data were measured on a CAD4-diffractometer equipped using graphite-monochromatized Cu Kα radiation (λ = 1.542 Å): space group $C2$; a = 15.66 (2), b = 14.57 (2), and c = 7.292 (7) Å; β = 112.13 (4)°, V = 1541.8 Å^3; d_c = 1.36 g/cm^3; Z = 4. Intensity data of 1519 unique reflexions were collected to $\theta \leq 70°$, using a $\omega/2\theta$ scan with a max. scan time of 120 s, of which 1465 reflexions had a significant intensity, $I > 3\sigma(I)$. Data correction for Lorentz and polarization effects (but not for absorption) and absolute scaling yielded an overall B factor of 3.47 Å^{-2} and the averages $\langle|E|\rangle$ = 0.871, $\langle|E^2-1|\rangle$ = 0.787, $\langle|E^2|\rangle$ = 1.007. The structure was solved by direct methods (MULTAN) and refined by block-diagonal least-squares method using anisotropic temperature factors for all heavy atoms, but keeping the H atoms in fixed theoretical positions. After convergence of all parameters at R = 0.042, anomalous scattering factors were used for sulfur and chlorine. The fractional coordinates of the heavy atoms of **14** are given in Table IV. The two enantiomeric structures yielded R factors of 0.037 and 0.040, respectively, clearly indicating the correct absolute configuration of the compound. In addition, 15 enantiosensitive Friedel pairs were carefully measured (Table V), and their intensity differences were used to experimentally determine the absolute configuration, which fully confirmed the computational result. The final R factor of the correct enantiomer was 0.036.

Pharmacology. Determination and Quantitation of Postjunctional α_1-Adrenergic Activity. After sacrifice of a rabbit, a 0.2-cm ring segment of the central ear artery was dissected free at the base of the ear, cleaned of connective tissue and fat, and mounted in an organ bath (50-mL capacity) containing oxygenated Krebs solution with cocaine (2×10^{-6} M) and rauwolscine (10^{-6} M). Cocaine was used to block neuronal uptake and rauwolscine to block α_2-receptors. The segment was suspended between two tungsten wires, one attached to the chamber and the other to a force-displacement transducer in a way that circular smooth muscle tension could be measured directly. Before administration of the test drug, noradrenaline (NA) was administered in increasing concentration (10^{-10}–10^{-5} M) to determine the maximum response of the artery. Each concentration was allowed to remain in contact with the tissue until a stable response was attained, at which time the next higher concentration was administered to produce a cumulative concentration–response curve. The pD_2 is the negative decadic logarithm of that molar concentration of the compound which produces 50% of the maximum response to NA. After the NA was washed out, a cumulative concentration–response curve was determined for the test drug, and the pD_2 values were evaluated. The efficacy was determined as the maximum response to the test drug related to NA.

Determination of Blood Pressure and α_1/α_2-Adrenergic Activity in Pithed Rats. Male Wistar normotensive rats (weight approximately 300 g) were anesthetized with ether. A tracheal cannula was inserted, and pithing was achieved by introducing a blunt steel rod into the vertebral canal via the orbit. Immediately thereafter the pithed animals were artificially ventilated with room air using a Braun Melsungen positive pressure pump. Catheters were inserted into the right jugular vein and common carotid artery for iv injection and measurement of arterial pressure respectively. Arterial pressure was monitored continuously by means of a Statham P23 pressure transducer and recorded with a W+W apparatus. The animals were allowed to equilibrate for approximately 15 min before the start of the experiment. The increase in diastolic blood pressure was determined and a dose-response curve from the test drug was obtained after iv administration of single increasing doses. In all cases 0.1 mL of fluid/100 g of body weight was injected. After an equilibration for about 30 min the test drug was administered to obtain a reference response and the full recovery was permitted. Fifteen minutes after iv pretreatment with the α_1-antagonist prazosin or the α_2-antagonist rauwolscine, respectively, the same dose was repeated. The increase in blood pressure before and in the presence of the antagonist was measured and the reduction of the effect (−%) evaluated, and the α_1/α_2-ratio determined. The potency (pD_2) was evaluated from the dose–response curve.

Stimulation of α_1-Receptor-Coupled Hydrolysis of Phos-

phatidylinositol (PI). PI hydrolysis in rat cerebral cortex slices was determined as described previously.[26]

Primary Observation Test with Rats. Male OFA rats were used. According to a checklist the induced behavioral changes in the rats after po administration of up to 30 mg/kg of 14 or the described agonists were recorded every 15 min during the first 2 h and every 30 min for a period of 6 h.[27]

Inhibition of Sedation Induced by DDC in Rats. The sedation was evaluated on a rating scale (overall activity 0–4 points) during 2 h after the administration of 300 mg/kg ip of diethyl dithiocarbamate sodium salt (DDC, E. Merck). The compound 14 or its solvent was administered po 1 h before DDC. Six male OFA rats were used for each experiment.

Shuttle Box Acquisition in Male Rats Pretreated with DSP_4. Thirty male OFA rats were pretreated for 20 days with 10 mg/kg po per day of 14. The control group C (10 rats) received vehicle only. At day 21 the 30 rats were subdivided into three groups (A, B, D; 10 rats each). Group A and B received 55 mg/kg ip of DSP_4. Groups A and D were then further treated for 11 days with 10 mg/kg po per day of 14, whereas the groups B and C remained untreated. At days 7, 8, 9, and 10 after DSP_4 administration, all rats were trained in the shuttle box.[28] One session in the shuttle box consisted in 30 trials. One trial lasted 30 s: 20 s without signal, 5 s with tone, and 5 s with tone and shock.

Determination of Cardiovascular Activity in Saimiri Monkeys. Blood pressure was measured by means of a cuff around the tail. Each value is the mean of at least five measurements of systolic blood pressure. The cardiovascular effects were determined immediately before and 1 h and 5 h after po administration of the drug.

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Registry No. **10a**, 138053-05-1; **10b**, 138053-06-2; **11**, 138053-07-3; **11** 2-chloroamide derivative, 138053-08-4; **11** 2-bromobutyryl derivative, 138053-09-5; **12**, 138053-10-8; **12** acetamide derivative, 138053-11-9; **12** *N*-ethylated derivative, 138053-12-0; **12** propanamide derivative, 138053-13-1; **12** *N*-propylated oxazine derivative, 138053-14-2; **13**, 138053-15-3; **13**·HCl, 138053-16-4; **14**, 104195-17-7; **14**·HCl, 103238-61-5; **15**, 103009-42-3; **15**·HCl, 103009-41-2; **16**, 5309-19-3; **17**, 138053-17-5; **17** nitrile derivative, 138059-71-9; **18**, 138053-18-6; **19**, 138053-19-7; (±)-**19**, 138312-49-9; (±)-**19** 6-iodo derivative, 138053-20-0; (±)-**19** 6-iodo derivative·malonate, 138053-21-1; **20**, 138053-22-2; **21**, 138053-23-3; **21**·malonate, 138053-24-4; **22**, 138053-25-5; **22**·HCl, 138053-26-6; **23**, 138128-12-8; **23**·HCl, 138230-48-5; **24**, 103009-21-8; **24**·HCl, 103009-20-7; **25**, 103009-44-5; **25**·HCl, 103009-43-4; **26**, 103009-48-9; **26**·HCl, 103009-47-8; **27**, 103009-46-7; **27**·HCl, 103009-45-6; **28**, 103009-56-9; **28**·HCl, 103009-55-8; **29**, 103009-52-5; **29**·HCl, 103009-51-4; **31**, 138053-27-7; **31**·malonate, 138053-28-8; **32**, 138053-29-9; **32**·malonate, 138053-30-2; **33**, 138059-61-7; **33**·malonate, 138053-24-4; **34**, 138053-31-3; **34**·malonate, 138053-32-4; 1,4-dihydro-5-methoxynaphthalene, 36230-47-4; 3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine, 103009-38-7; 2,4-dihydro-5-methoxy-3-oxo-1*H*-naphthalene-2-carboxylic acid, 138053-33-5; 2-chloropropionyl chloride, 7623-09-8; 3,4,4a,5,10,10a-hexahydro-6-methoxy-2-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-34-6; 3,4,4a,5,10,10a-hexahydro-6-methoxy-2,4-dimethyl-2*H*-naphth-[2,3-*b*]-1,4-oxazine, 138053-35-7; 3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-2,4-dimethyl-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-36-8; 4-ethyl-3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-37-9; 4-ethyl-3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazine hydrochloride, 138053-38-0; 3,4,4a,5,10,10a-hexahydro-9-iodo-6-methoxy-4-propyl-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-39-1; 2-bromobutyryl chloride, 22118-12-3; 3,4,4a,5,10,10a-hexahydro-2-ethyl-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazin-3-one, 138053-40-4; 3,4,4a,5,10,10a-hexahydro-2-ethyl-6-methoxy-4-methyl-2*H*-naphth[2,3-*h*]-1,4-oxazine, 138053-41-5; 3,4,4a,5,10,10a-hexahydro-2-ethyl-9-iodo-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine, 103009-29-6; 3,4,4a,5,10,10a-hexahydro-2-ethyl-9-iodo-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine hydrochloride, 103009-28-5; 3,4,4a,5,10,10a-hexahydro-6-methoxy-4-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-42-6; 3,4,4a,5,10,10a-hexahydro-6-methoxy-2-methyl-2*H*-naphth[2,3-*b*]-1,4-oxazine-3-one, 138053-43-7; 3,4,4a,5,10,10a-hexahydro-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazine-3-one, 138053-44-8; 3,4,4a,5,10,10a-hexahydro-2-ethyl-6-methoxy-2*H*-naphth[2,3-*b*]-1,4-oxazine, 138053-45-9.

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