Expedited Articles

1-(((7,7-Dimethyl-2(S)-(2(S)-amino-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]-heptan-1(S)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (L-368,899): An Orally Bioavailable, Non-Peptide Oxytocin Antagonist with Potential Utility for Managing Preterm Labor

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Modifications to the previously reported spiroindenylpiperidine camphorsulfonamide oxytocin (OT) antagonist L-366,509 have produced a new series of *o*-tolylpiperazine (TP) camphorsulfonamides. A number of analogues in the TP series that incorporate a modified or unmodified L-methionine sulfone amide at the C2 *endo* position on the camphor ring exhibit high affinity for OT receptors (IC_{50} = 1.3–15 nM) and good selectivity for binding to OT versus arginine vasopressin V_{1a} and V_2 receptors. Several of these analogues were additionally characterized as potent antagonists of OT-stimulated contractions of the isolated and/or *in situ* rat uterus. Compound **7** (L-368,899) exhibited the best overall profile of OT receptor affinity (IC_{50} = 8.9 nM, rat uterus; 26 nM, human uterus), potency for inhibition of OT-stimulated contractions of the isolated rat uterus (pA_2 = 8.9) and *in situ* rat uterus (AD_{50} = 0.35 mg/kg after intravenous (iv) administration and 7.0 mg/kg after intraduodenal administration), aqueous solubility (3.7 mg/mL at pH 5.0), and oral bioavailability in several species (35% (rat), 25% (dog), and 21% (chimpanzee) as estimated from radioreceptor determination of drug levels in plasma after oral and iv dosing). On the basis of these favorable properties, **7** has begun clinical testing for use as an oral and iv tocolytic agent. Molecular modeling alignment studies have provided support for the hypothesis that the TP camphorsulfonamide portion of the non-peptide structures may serve as a mimetic of the important D-AA^2-Ile^3 dipeptide (AA = aromatic amino acid) found in many potent OT antagonists from the cyclic hexapeptide and OT analogue structural classes.

The neurohypophyseal nonapeptide hormone oxytocin (OT; Figure 1) plays a key role in the initiation and maintenance of uterine contractions of labor.[1-3] The potential clinical utility of an antagonist of OT at the uterine receptor has been demonstrated in recent studies in which intravenously administered atosiban (ORF 22164; Figure 1), an antagonist analogue of OT, was shown to be efficacious in inhibiting uterine contractions in women with threatened and established preterm labor.[4-7] Several distinct structural classes of peptidyl OT antagonists are known;[8-11] however, difficulties in obtaining useful levels of oral bioavailability places certain limitations on the utility of these antagonists as potential therapeutic agents. The design and discovery of non-peptide ligands for peptide hormone receptors is a rapidly growing area[12] in which examples of orally active, receptor selective antagonists for OT and the related neurohypophyseal hormone arginine vasopressin (AVP) have recently been reported.[13-15] For example, the spiroindenylpiperidine camphor-10-sulfonamide derivative L-366,509 reported by Evans[13] and Pettibone[16] is a prototypical member of a new class of selective, orally active OT antagonists. Herein we report a combination of modifications to the L-366,509 structure that has resulted in the identification of **7** (L-368,899), a potent OT antagonist with suitable properties for clinical testing as an intravenous and oral agent for managing preterm labor.

Chemical Methods[17]

Commercially available 1-phenylpiperazine and 1-(*o*-tolyl)piperazine were sulfonylated with (+)-10-camphorsulfonyl chloride to give sulfonamides **2a** and **2b**, respectively (Scheme 1). The *o*-tolyl ketone **2b** was heated with hydroxylamine hydrochloride in pyridine to give the oxime derivative **3**, which was hydrogenated over freshly prepared W-2 Raney nickel to give a ca. 1:3 mixture of *exo* and *endo* amines, **4a** and **4b**, respectively. The major *endo* isomer **4b** was acylated with *N*-Boc-L-methionine sulfone activated with EDC and HOBT. Removal of the Boc group with TFA gave **7**. The primary amino group in **7** was modified by reductive alkylation (**9–14**) and by alkylation with ethylene oxide (**15**). *N*-Methyl-*N*-Boc-L-methionine sulfone, obtained by the method of Benoiton,[18] was used to prepare **8**.

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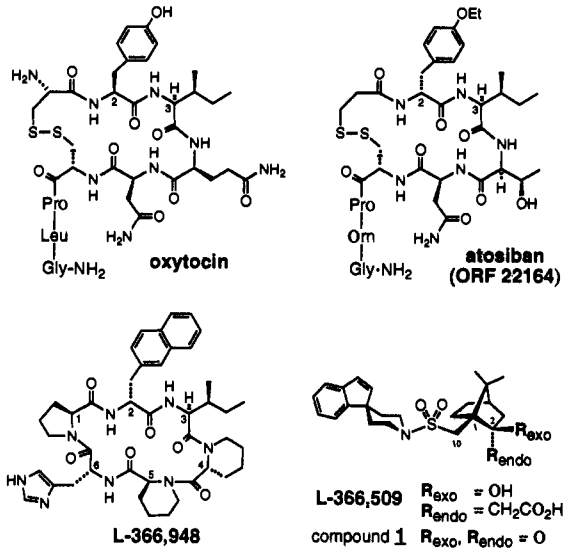
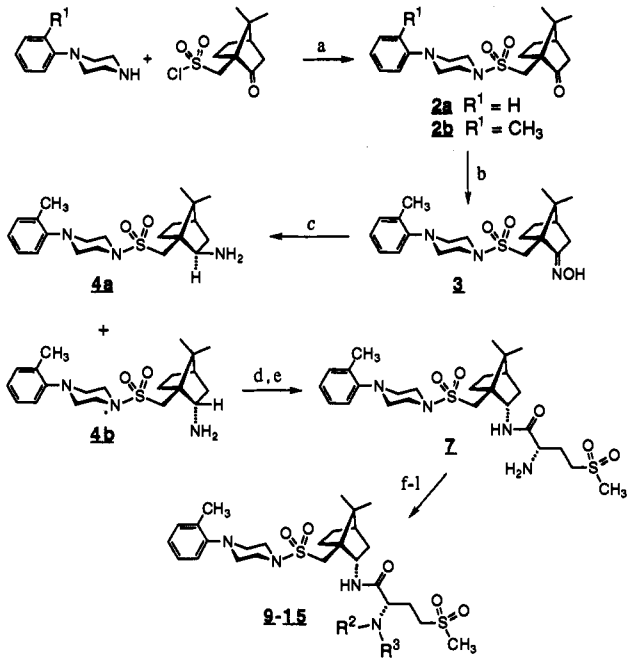


Figure 1. Structure of oxytocin and the oxytocin antagonists atosiban (ORF 22164), L-366,948, and L-366,509.

Scheme 1[a]



[a] Reagents: (a) DIEA, $CHCl_3$, 0 °C, 86%; (b) NH_2OH·HCl, pyridine, 80 °C, 88%; (c) H_2, Raney nickel, $CH_3OCH_2CH_2OH$; silica gel chromatographic separation of 1:3 *exo*:*endo* mixture, 61% (**4b**); (d) Boc-L-methionine sulfone, EDC, HOBT, DIEA, DMF, 98%; (e) 1:2 TFA–CH_2Cl_2, 98%; (f) cyclohexanone, $NaCNBH_3$, 100:1 MeOH–HOAc, 88% (**9**); (g) 4-tetrahydropyranone, $NaCNBH_3$, 100:1 MeOH–HOAc, 85% (**10**); (h) 4-tetrahydrothiopyranone, $NaCNBH_3$, 100:1 MeOH–HOAc; OsO_4, *N*-methylmorpholine *N*-oxide, THF, 55% (**11**); (i) *N*-Boc-4-piperidinone, $NaCNBH_3$, 100:1 MeOH–HOAc; 1:2 TFA–CH_2Cl_2, 75% (**12**); (j) 37% aqueous formaldehyde, $NaCNBH_3$, 100:1 MeOH–HOAc, 90% (**13**); (k) acetaldehyde, $NaCNBH_3$, 100:1 MeOH–HOAc, 89% (**14**); (l) ethylene oxide, EtOH, 50 °C, 69% (**15**).

Biological Methods[17]

Detailed procedures for the radioligand binding assays and the *in vitro* and *in vivo* functional assays measuring antagonism of OT-induced uterine contractions have been published.[19,20]

The high affinity binding of [^{3}H]OT to rat uterine tissue (OT site) and [^{3}H]AVP to rat liver (V_{1a} site) and rat kidney medulla (V_2 site) formed the basis for competition experiments to determine receptor affinities of the test compounds listed in Table 1. Uterine tissue was taken from pregnant rats (day 22–23 of gestation) or from DES-pretreated rats. Liver and kidney medulla were taken from male rats. The results are reported as IC_{50} values, the molar concentration of test compound that results in 50% displacement of the radioligand.

Results from an *in vitro* functional assay measuring antagonism of OT-stimulated contractions of the isolated rat uterus by compounds **7** and **13** are given in Table 1. Uteri were isolated from DES-pretreated rats. Potencies are expressed as pA_2 values, the negative logarithm of the molar concentration of antagonist that causes a 2-fold rightward shift in the dose–response curve (i.e., a dose ratio of 2).[21] The Schild plots for compounds **7** and **13** gave slopes that did not differ significantly from unity, consistent with competitive antagonism.

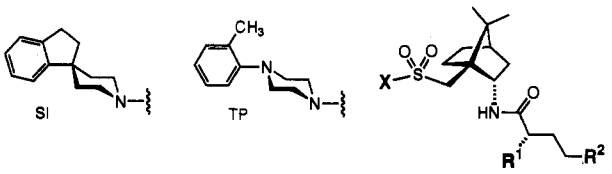
Results from an *in vivo* functional assay measuring antagonism of OT-stimulated contractions of the *in situ* rat uterus by selected compounds are given in Table 1. Anesthetized, DES-pretreated rats were prepared for recording of isometric contraction of the uterus *in situ*. OT was injected intravenously (1 μg/kg; approximately an ED_{50} dose) at 35-min intervals. The contractile response of the uterus to the third injection of OT was set as 100%, and then a solution of antagonist (in saline for soluble compounds, or in saline containing 2% DMSO or 15% DMSO and 15% emulphor for less soluble compounds) was infused intravenously over a 10-min period or injected intraduodenally as a suspension in saline containing 1% methocel. Potencies are expressed as AD_{50} values, the dose of compound that reduces the contractile response of the uterus to the fourth injection of OT by 50% compared to the vehicle-treated group.

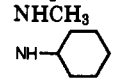
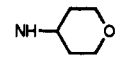
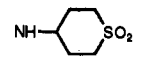
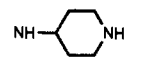
Results and Discussion

The presence of a phenylpiperidine substructure in L-366,509 suggested the investigation of a related series of phenylpiperazines. A number of phenylpiperazine camphor-10-sulfonamides substituted on the phenyl ring were examined in the OT receptor binding assay with the finding that the *o*-tolylpiperazine (TP) derivative **2b** provided optimal receptor affinity (IC_{50} = 770 nM), comparable to the spiroindenylpiperidine analogue **1** (Figure 1; IC_{50} = 1800 nM). The TP and spiroindenylpiperidine groups are topologically similar as evidenced by comparison of the X-ray crystal structure of **2b** and an energy-minimized conformation of **1**.[22] The phenyl and piperidine rings of the spiroindenylpiperidine group are orthogonal to one another due to the covalent constraint of the spiro linkage, and the *o*-methyl substituent of the TP group provides a noncovalent means of favoring a twisted orientation of the tolyl and piperazine rings. The out-of-plane orientation is preferred at the OT receptor as inferred from the low affinity of the unsubstituted phenylpiperazine analogue **2a** (IC_{50} > 30 000 nM), the X-ray crystal structure of which indicates that the phenyl and piperazine rings can adopt a nearly coplanar relationship.[22]

Evans and co-workers have recently described several modifications to the camphor C2 *endo* substituent in L-366,509 analogues that provide substantially improved OT receptor affinity.[23] An example is the camphor C2 *endo*-amine L-glutaminyl amide derivative **5** (Table 1). Structure–activity studies indicated that the glutamine side chain carboxamide group, its distance from the camphor ring, and the *S* configuration at the glutamine

Table 1



	X[a]	R[1]	R[2]	receptor affinities[b] IC50, nM OT	V_{1a}	V_2	antagonism of OT-induced uterine contractions[c] *in vitro* pA_2	*in vivo* AD_{50}, mg/kg iv	id	aq sol, mg/mL (at pH)[d]
5	SI	NH_2	$CONH_2$	12	2300	5100		ca. 2	>30	
6	SI	NH_2	SO_2CH_3	12	890	2400		0.84	ca. 20	1.5 (5.2)
7	TP	NH_2	SO_2CH_3	8.9	370	570	8.9	0.35	7.0	3.7 (5.0)
8	TP	$NHCH_3$	SO_2CH_3	9.2	320	350				1.5 (5.2)
9	TP		SO_2CH_3	15	600	230				
10	TP		SO_2CH_3	2.4	680	270		0.045	1.4	0.36 (5.2)
11	TP		SO_2CH_3	1.4	440	160		0.031	inactive at 1.0	<0.3 (5.2)
12	TP		SO_2CH_3	1.3	220	130		0.021	inactive at 1.0	3.0 (5.2)
13	TP	$N(CH_3)_2$	SO_2CH_3	4.9	360	290	9.0	0.13	2.6	3.1 (5.0)
14	TP	$N(CH_2CH_3)_2$	SO_2CH_3	18	1300	310				0.23 (5.2)
15	TP	$N(CH_2CH_2OH)_2$	SO_2CH_3	2.8	650	240		0.087	inactive at 3.0	0.19 (5.2)

[a] SI = spiroindanylpiperidine, TP = o-tolylpiperazine. [b] IC_{50} values refer to the concentration of test compound in nanomoles that displaces by 50% the binding of [^{3}H]OT to rat uterus (OT column), [^{3}H]AVP to rat liver (V_{1a} column), and [^{3}H]AVP to rat kidney (V_2 column). [c] pA_2 values refer to the negative logarithm of the molar concentration of test compound that produces a 2-fold rightward shift of the dose–response curve for contraction of the isolated rat uterus with OT. AD_{50} values refer to the dose of test compound given intravenously (iv) or intraduodenally (id) that reduces by 50% the contractile response of the *in situ* rat uterus to exogenous OT. [d] Aqueous solubilities were determined by dissolving an amorphous salt (trifluoroacetate: 6, 11, 12, 15; hydrochloride: 10) or free base (8, 14) in citrate buffer (pH 5.2). The solubilities of 7 and 13 were determined by dissolving the crystalline hemisulfate and dihydrochloride salts, respectively, in water, and adding acetate to pH 5.0. Concentrations are expressed in free base equivalents.

Cα-position are important determinants for obtaining optimal OT receptor affinity. The important carboxamide group in 5 could be replaced with a methylsulfonyl group (6) without loss in receptor affinity.[24] Similar structure–activity relationships were found in the TP series. For example, 7 exhibited similar OT receptor affinity to the spiroindanylpiperidine (SI) analogues 5 and 6, although selectivity versus the AVP receptor subtypes was somewhat diminished. Replacing the carboxamide group in 5 with the methylsulfonyl group (6) resulted in improved potency for antagonizing OT-induced uterine contractions *in vivo* by both intravenous (iv) and intraduodenal (id) routes of administration (Table 1). Further enhancement of *in vivo* potency was found with the TP analogue 7. Good aqueous solubility was also seen with 7, an important criterion for obtaining a compound that can be easily formulated for iv administration.

Acylation of the α-amino group in the glutamine or methionine sulfone portion of 5 or 6 has been reported to improve OT receptor affinity to the 1 nM range,[23,24] although this type of modification in general has not provided a corresponding increase in *in vivo* potency in the rat by the id route of administration. Similar results were obtained with such modifications of 7. A number of N^{α}-alkylated derivatives of 7 were therefore investigated to determine the effect on *in vitro* and *in vivo* potency (8–15). Monosubstitution with a small (8) or bulky group (9) reduced OT receptor affinity only slightly, whereas alkylation with heterocycles produced a significant improvement in receptor affinity (10–12). *In vivo* potency by the iv route of administration was also improved with the heterocycle-substituted analogues, although only compound 10 exhibited significant bioavailability from the gut as evidenced by its favorable id potency. The *N,N*-dimethyl analogue 13 exhibited improved OT receptor affinity, was characterized as a potent antagonist *in vitro*, and exhibited ca. 3-fold better potency *in vivo* by both the iv and id routes of administration versus 7. OT receptor affinity was reduced with the more bulky *N,N*-diethyl derivative 14. Incorporation of heteroatoms into the latter (15) improved both OT receptor affinity and *in vivo* potency by the iv route of administration, but poor id activity resulted with this modification.

Although measurable increases in OT receptor affinity and *in vivo* potency were seen with compounds 10 and 13, neither possessed the optimal combination of properties found with compound 7. For example, 10 is significantly less water soluble than 7 and exhibited poorer oral bioavailability in dogs. The *N,N*-dimethyl analogue 13 was substantially metabolized by N-demethylation to 7 and 8 after oral dosing in dogs and rats. Demethylation to 7 and 8 also was observed *in vitro* when 13 was incubated with hepatic microsomes from rats, dogs, rhesus, and humans.[25] These findings, in addition to the good affinity and selectivity of 7 for human OT versus AVP receptors (IC_{50} = 26 nM, human uterine OT site; 510 nM, human liver V_{1a} site; 960 nM, human kidney V_2 site)[26] and the favorable pharmacological and pharmacokinetic behavior of 7 in several species including primates (AD_{50} = 0.027 mg/kg iv for inhibition of OT-induced uterine contractions in the near term pregnant rhesus monkey; oral bioavailability = 35% (rat), 25% (dog), and 21% (chimpanzee) as estimated from radioreceptor determination of drug levels in plasma after oral and iv dosing)[26] have led to the selection

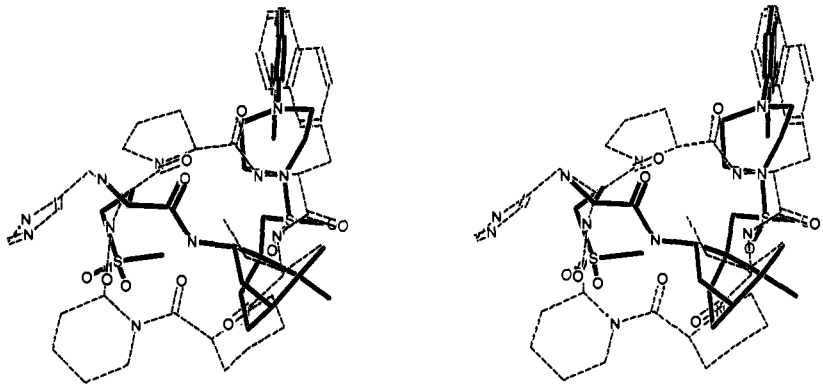


Figure 2. Stereoview showing the alignment of a low-energy conformer of 7 (solid) with an NMR-consistent, low-energy conformer of the cyclic hexapeptide L-366,948 (dashed).

of 7 (L-368,899) as a candidate for clinical testing as an iv and oral tocolytic agent.

Molecular modeling studies with 7 and its analogues have provided support for the hypothesis that the TP (or SI) camphorsulfonamide portion of the molecule functions as a mimetic of the D-Phe^2-Ile^3 or D-Nal^2-Ile^3 dipeptide found in potent cyclic hexapeptide OT antagonists such as L-366,219[27,28] and L-366,948,[10] respectively (see Figure 1 for the structure of L-366,948). Structure–activity studies in the cyclic hexapeptide OT antagonist class have demonstrated the importance of the 2,3-position dipeptide for obtaining good receptor affinity, and indeed, this dipeptide has been suggested to relate to the important D-AA^2-Ile^3 (AA = aromatic amino acid) dipeptide found in many potent antagonist analogues of OT.[10,29] An alignment of a low-energy conformer of 7 with an NMR-consistent, low-energy conformer of L-366,948 is given in Figure 2.[30] Good overlaps of important hydrophobic and hydrophilic elements from each molecule are seen, i.e., the D-Nal and Ile side chains align with the tolyl and camphor groups, respectively, and the 2,3-position amide bond oxo group aligns with one of the camphorsulfonamide oxo groups. Potency-enhancing camphor C2 *endo* substituents in this alignment are oriented toward other regions of the cyclic hexapeptide structure. For example, the flexible methionine sulfone portion of 7 has several available low-energy conformations in which it can occupy the space of the 5,6-dipeptide, a region of the cyclic hexapeptide structure that is known to tolerate numerous amino acid substitutions.[10] The specific conformation of the methionine sulfone group shown in Figure 2 provides a good alignment of important hydrophilic groups from each molecule while orienting the methionine sulfone α-amino group out toward the D-His^6 side chain. Additional modeling studies are underway to further develop our understanding of structural relationships between the non-peptide and other peptide OT antagonist classes (e.g., atosiban and rigid bicyclic OT analogues[11]) with the aim of developing a pharmacophore model that may be of utility in the design and discovery of new structural classes of OT antagonists.

Experimental Section

Biological Methods. Procedures for the radioligand binding assays and *in vitro* and *in vivo* studies for antagonism of OT-induced contractions of the rat uterus have been reported in detail elsewhere.[19,20]

Chemical Methods.[17] All solvents were reagent grade. Dioxane was dried and freed of peroxides by passage through a column of activity I neutral alumina. TLC was performed on Uniplate silica gel GF TLC plates (250-μm thickness). Visualization was with UV light and phosphomolybdic acid staining. ^{1}H NMR spectra were measured at 300 MHz on a Varian XL-300 or at 400 MHz on a Varian XL-400 using $(CH_3)_4Si$ as an internal standard. Fast atom bombardment mass spectra (FAB MS) were obtained on a VG-ZAB-HF spectrometer using xenon as the reagent gas. Analytical HPLC were run on a Spectra Physics SP4270/8800 instrument using the following conditions: 0.2- × 15-cm Vydac "protein and peptide" C_{18} reverse-phase column; mobile phases, A = 0.1% TFA in H_2O, B = 0.1% TFA in CH_3CN; gradient, T = 0 min 95:5 A:B, T = 15 min 0:100 A:B; flow rate = 2.0 mL/min; UV detection at 215 nm. Purification methods: method A, pressurized column chromatography using 230–400-mesh silica gel;[31] method B, preparative reverse-phase HPLC using the following conditions: 2.5- × 25-cm Vydac "protein and peptide" C_{18} reverse-phase column; mobile phases, A = 0.1% TFA in H_2O, B = 0.1% TFA in CH_3CN: gradient, T = 0 min, 95:5 A:B, T = 45 min, 0:100 A:B; flow rate = 8.0 mL/min; UV detection at 215 nm. Melting points are uncorrected. All noncrystalline final products were dried under vacuum (ca. 0.5 Torr) for ca. 15 h. Combustion analyses for these amorphous materials indicated the presence of solvent(s). ^{1}H NMR analysis verified the presence and approximate stoichiometry of the indicated solvent(s).

X-ray Crystallography. Complete experimental details for determining the structures of compounds **2a** and **2b**, as well as figures with atomic numbering schemes, atomic coordinates, and selected bond distances and angles for the two structures are provided as supplementary material.

Molecular Modeling Methods.[30] Distance geometry calculations were employed to sample conformational space for compound 7. Conformers within this set were energy minimized using the Merck Molecular Force Field (MMFF),[32] and each conformer was overlaid with a low-energy, NOE-consistent conformer of the cyclic hexapeptide L-366,948 using SQUEAL,[33] an alignment algorithm developed at Merck that randomly rotates and translates two rigid structures and utilizes a scoring system based on molecular volume, hydrophobicity, and electrostatics to rank order the various alignments produced. The alignment shown in Figure 2 is one of several high-scoring alignments utilizing low-energy conformers of 7 which overlays the *o*-tolylpiperazine camphorsulfonamide moiety of the non-peptide with the D-Nal^2-Ile^3 dipeptide portion of L-366,948. The atomic coordinates for each of the two molecules in Figure 2 are provided as supplementary material.

1-(((7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (2b). To a stirred, 0 °C solution of 1-(2-methylphenyl)piperazine hydrochloride (50.0 g, 235 mmol) and (+)-10-camphorsulfonyl chloride (65.5 g, 260 mmol) in $CHCl_3$ (1000 mL) was added DIEA (103 mL, 590 mmol) dropwise over 30 min. The solution was stirred at 0 °C for 1 h and then at ambient temperature for 3 h. The solution was extracted with 5% aqueous HCl (2 × 500 mL), water (500 mL), and saturated aqueous $NaHCO_3$ (2 × 500 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The resulting solid was crystallized from MeOH to give the title compound: mp 112–114 °C (79 g; 86%); TLC R_f 0.49 (3:1 hexane–EtOAc); HPLC retention time 10.33 min; FAB MS m/z 391 (M^+ + H); ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.2 (m, 2H), 7.0 (m, 2H), 3.45 (m, 4H), 3.40 (d, J = 16 Hz, 1H), 3.0 (m, 4H), 2.57 (m, 1H), 2.40 (dt, J = 14 Hz, J_t = 3 Hz, 1H), 2.30 (s, 3H), 2.10 (m, 2H), 1.96 (d, J = 14 Hz, 1H), 1.67 (m, 1H), 1.44 (m, 1H), 1.18 (s, 3H), 0.91 (s, 3H). Anal. $C_{21}H_{30}N_2O_3S$ (C, H, N).

1-(((7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-phenylpiperazine (2a). The title compound was prepared from 1-phenylpiperazine hydrochloride (5.0 g, 25 mmol) and (+)-10-camphorsulfonyl chloride (7.0 g, 28 mmol) using the procedure given for **2b**. The crude product crystallized from ether: mp 163–165 °C (6.7 g; 71%). TLC R_f 0.55 (7:3 hexane–EtOAc); HPLC retention time 8.76 min; FAB MS m/z 377 (M^+ + H). Anal. $C_{20}H_{28}N_2O_3S$ (C, H, N).

1-(((7,7-Dimethyl-2-oximinobicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (3). To a stirred solution of **2b** (65.0 g, 166 mmol) in pyridine (250 mL) was added hydroxylamine hydrochloride (35.0 g, 0.504 mol). The solution was heated to 70 °C for 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (500 mL) and washed with aqueous $NaHCO_3$ (2 × 200 mL), water (100 mL), and 5% aqueous HCL (2 × 200 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The title compound crystallized from EtOAc, giving off-white needles: mp 174–175 °C (59 g; 88%); TLC R_f 0.40 (3:1 hexane–EtOAc); HPLC retention time 9.98 min; FAB MS m/z 406 (M^+ + H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.18 (m, 2H), 7.02 (m, 2H), 3.47 (m, 4H), 4.43 (d, J = 14.4 Hz, 1H), 3.00 (m, 4H), 2.92 (d, J = 14.4 Hz, 1H), 2.4–2.6 (m, 2H), 2.31 (s, 3H), 2.09 (d, J = 16.9 Hz, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.32 (m, 1H), 1.08 (s, 3H), 0.87 (s, 3H). Anal. $C_{21}H_{31}N_3O_3S$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-aminobicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (4b). Compound **3** (5.0 g, 12 mmol) and freshly prepared W-2 Raney Nickel[34] (ca. 5 g) in 2-methoxyethanol (75 mL) were shaken on a Parr apparatus under 55 psig of hydrogen for 24 h. TLC (95:5:0.25 $CHCl_3$–MeOH–NH_4OH) indicated complete consumption of starting oxime and a ca. 1:3 mixture of *exo* (R_f = 0.55) and *endo* (R_f = 0.25) amines **4a** and **4b**, respectively. The mixture was cautiously filtered through Celite, and the filtercake was washed with EtOH and EtOAc. The solvents were removed under reduced pressure, and the resulting solid was suspended in water and filtered. The dried solid was purified (method A) using a 98:2 to 95:5 A:B gradient elution (A = $CHCl_3$, B = 95:5 MeOH–NH_4OH). The title compound was obtained as an amorphous solid by evaporation of a CH_2Cl_2 solution under reduced pressure (2.9 g; 61%): TLC R_f 0.25 (95:5:0.25 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 7.97 min; FAB MS m/z 392 (M^+ + H); ^{1}H NMR (300 MHz, CD_3OD) δ 7.15 (m, 2H), 7.04 (d, J = 6 Hz, 1H), 6.98 (t, J = 6 Hz, 1H), 3.42 (m, 4H), 3.40 (m, 1H), 3.06 (d, J = 15 Hz, 1H), 2.98 (d, J = 15 Hz, 1H), 2.95 (m, 4H), 2.38 (m, 1H), 2.31 (s, 3H), 2.15 (dt, J = 3.6, 9.5 Hz, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.60 (t, J = 4.5 Hz, 1H), 1.31 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.83 (dd, J = 4.1, 13 Hz, 1H). Anal. $C_{21}H_{33}N_3O_2S \cdot 0.5H_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-amino-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (7). To a stirred solution of **4b** (2.0 g, 5.1 mmol), *N*-Boc-L-methionine sulfone (1.5 g, 5.3 mmol), HOBT (0.81 g, 5.3 mmol), and EDC (1.1 g, 5.8 mmol) in DMF (25 mL) was added DIEA (1.77 mL, 10.2 mmol) dropwise over a period of 5 min. The reaction was stirred for 18 h, and the solvent was removed under reduced pressure. The residue was suspended in EtOAc (150 mL) and washed with 5% aqueous citric acid (2 × 50 mL), water (2 × 50 mL), and aqueous $NaHCO_3$ (2 × 75 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified (method A) using 4:1 EtOAc–hexanes as eluant. 1-(((7,7-Dimethyl-2-*endo*-(2(*S*)-((*tert*-butyloxycarbonyl)amino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine was obtained as an amorphous solid by evaporation from EtOAc under reduced pressure (3.3 g, 98%; TLC R_f 0.73 (95:5 $CHCl_3$–MeOH); HPLC retention time 11.02 min; FAB MS m/z 655). To a stirred solution of the coupling product (2.5 g, 3.8 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 mL). After 1 h, the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with aqueous $NaHCO_3$ (2 × 75 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid (2.1 g; 98%): TLC R_f 0.17 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 8.50 min; FAB MS m/z 455 (M^+ + H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1H), 7.20 (m, 2H), 7.02 (m, 2H), 4.43 (m, 1H), 2.94 (s, 3H), 2.31 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H). Anal. $C_{26}H_{42}N_4O_5S_2 \cdot 0.5H_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-2(*S*)-(methylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (8). To a solution of **4b** (1.80 g, 2.77 mmol), *N*-Boc-*N*-methyl-L-methionine sulfone (0.87 g, 3.1 mmol; prepared from *N*-Boc-L-methionine sulfone, NaH, and CH_3I in THF by the method of Benoiton[18]), and BOP (1.5 g, 3.4 mmol) was added DIEA (1.1 mL, 6.3 mmol) dropwise over a period of 5 min. The reaction mixture was stirred for 18 h, and the solvent was removed under reduced pressure. The residue was suspended in EtOAc (100 mL) and washed with 5% aqueous citric acid (2 × 50 mL), water (50 mL), and aqueous $NaHCO_3$ (2 × 75 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified (method A) using 3:2 EtOAc–hexanes as eluant. 1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(((*tert*-butyloxycarbonyl)methyl)amino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]-heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine was obtained as an amorphous solid by evaporation of an EtOAc solution under reduced pressure (1.66 g, 90%; TLC R_f 0.27 (3:2 EtOAc:hexanes); HPLC retention time 11.21 min; FAB MS m/z 669). The Boc group was removed with TFA in CH_2Cl_2 as described for compound **7**. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the title compound as an amorphous solid (1.38 g, 98%): TLC R_f 0.16 (97:3 CH_2Cl_2–MeOH); HPLC retention time 8.23 min; FAB MS m/z 569 (M + H^+). Anal. $C_{27}H_{44}N_4O_5S_2 \cdot 0.40EtOAc \cdot 0.45H_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(dimethylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (13). To a stirred solution of **7** (0.50 g, 0.90 mmol) in 1:100 HOAc–MeOH (15 mL) was added 37% aqueous formaldehyde (1 mL) and $NaBH_3CN$ (0.17 g, 2.7 mmol). The solution was stirred at ambient temperature for 18 h. Aqueous $NaHCO_3$ (5 mL) was added, and the solvents were removed under reduced pressure. The residue was suspended in EtOAc (100 mL) and washed with water (2 × 50 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified (method A) using 95:5:0.25 $CHCl_3$–MeOH–NH_4OH as eluant. The free base of the title compound was obtained as an amorphous solid by evaporation of an EtOAc solution under reduced pressure (0.47 g, 90%). The free base was lyophilized from H_2O–CH_3CN containing 1 N aqueous HCl (2 mL; 2.0 mmol). The dihydrochloride of the title compound crystallized from EtOH–EtOAc (0.45 g): TLC R_f 0.26 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 9.10 min; FAB MS m/z 583 (M^+ + H). Anal. $C_{28}H_{46}N_4O_5S_2 \cdot 2.0HCl \cdot 1.0H_2O$) (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(diethylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (14). Compound **7** (100 mg, 0.18 mmol) was reductively alkylated with acetaldehyde (0.033 mL; 0.6 mmol) and $NaBH_3CN$ (25 mg, 0.40 mmol) using the procedure given for compound **13**. The crude product was purified (method A) eluting with 95:5:0.25 $CHCl_3$–CH_3OH–NH_4-OH. The title compound was obtained as an amorphous solid by evaporation of an ether–$CHCl_3$ solution under reduced pressure (98 mg, 89%): TLC R_f 0.38 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 9.66 min; FAB MS m/z 611 (M + H^+). Anal. $C_{30}H_{50}N_4O_5S_2 \cdot 0.7CHCl_3 \cdot 0.15(CH_3CH_2)_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2*S*)-(cyclohexylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (9). Compound **7** (100 mg, 0.18 mmol) was reductively alkylated with cyclohex-

anone (19 mg, 0.20 mmol) and $NaBH_3CN$ (15 mg, 0.24 mmol) using the procedure given for compound 13. After 18 h, additional cyclohexanone (19 mg, 0.20 mmol) and $NaBH_3CN$ (15 mg, 0.24 mmol) were added to completely consume 7. The crude product was purified (method A) using 95:5 $CHCl_3$–MeOH as eluant. The title compound was obtained as an amorphous solid by evaporation of a MeOH solution under reduced pressure (100 mg, 88%): TLC R_f 0.41 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH). HPLC retention time 9.94 min; FAB MS m/z 637 ($M + H^+$). Anal. $C_{32}H_{52}N_4O_5S_2 \cdot 0.75MeOH$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(4-Tetrahydropyranylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1-(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (10). Compound 7 (0.50 g, 0.90 mmol) was reductively alkylated with 4-tetrahydropyranone (185 mg, 1.85 mmol) and $NaBH_3CN$ (125 mg, 2.0 mmol) using the procedure given for compound 13. The crude product was purified (method A) using 95:5:0.25 $CHCl_3$–MeOH–NH_4OH as eluant. The HCl salt of the title compound was obtained as an amorphous solid by lyophilization of dioxane solution of the free base containing 1 N HCl (2.0 mL; 2.0 mmol) (575 mg, 85%): TLC R_f 0.27 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 8.29 min; FAB MS m/z 639 ($M + H^+$). Anal. $C_{31}H_{50}N_4O_6S_2 \cdot 1.65HCl \cdot 0.6$dioxane (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-((1,1-dioxo-4-tetrahydrothiopyranyl)amino)-4-(methylsulfonyl)butyramido)bicyclo-[2.2.1]heptan-1(*S*)-yl)methylsulfonyl)-4-(2-methylphenyl)-piperazine (11). Compound 7 (150 mg, 0.27 mmol) was reductively alkylated with 4-tetrahydrothiopyranone (63 mg, 0.54 mmol) and $NaBH_3CN$ (34 mg, 0.54 mmol) using the procedure given for compound 13. The crude product was purified (method A) using 97:3:0.3 $CHCl_3$–CH_3OH–NH_4OH as eluant. 1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-((4-tetrahydrothiopyranyl)amino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)-sulfonyl)-4-(2-methylphenyl)piperazine was obtained as an amorphous solid by evaporation of a $CHCl_3$ solution under reduced pressure (132 mg, 75%; TLC R_f 0.44 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 9.91 min; FAB MS m/z 655). The sulfide was oxidized to the sulfone using the procedure of Caldor.[35] To a stirred solution of the sulfide (90 mg, 0.12 mmol) in 1:9 H_2O–acetone (3 mL) was added 4-methylmorpholine *N*-oxide (43 mg, 0.36 mmol) and OsO_4 (0.013 mL of 2.4 wt % solution). After 17 h the reaction was quenched with saturated aqueous $NaHSO_3$ (0.05 mL), and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and washed with 1 N $NaHSO_3$ (3 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was purified (method B). The TFA salt of the title compound was obtained as an amorphous powder by lyophilization from H_2O–CH_3CN (81 mg, 73%): TLC R_f 0.33 (95:5:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 9.02 min; FAB MS m/z 687 ($M + H^+$). Anal. $C_{31}H_{50}N_4O_7S_3 \cdot 2.05TFA \cdot 0.35H_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(4-piperidinylamino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (12). Compound 7 (150 mg, 0.27 mmol) was reductively alkylated with *N*-Boc-4-piperidinone (107 mg, 0.54 mmol) and $NaBH_3CN$ (32 mg, 0.51 mmol) using the procedure given for compound 13. The crude product was purified (method A) using 95:5 $CHCl_3$–MeOH as eluant. 1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-((4-(1-(*tert*-butyloxycarbonyl)piperidinyl))amino)-4-(methylsulfonyl)butyramido)bicyclo-[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine was obtained as an amorphous solid by evaporation of an EtOAc solution under reduced pressure (169 mg, 85%, TLC R_f 0.27 (95:5 $CHCl_3$–MeOH); HPLC retention time 10.72 min; FAB MS m/z 738). To a stirred solution of the reductive alkylation product (150 mg; 0.20 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 mL). After 45 min, the solvents were removed under reduced pressure, and the residue was dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure, and the residue was purified (method B). The TFA salt of the title compound was obtained as an amorphous solid by lyophilization from H_2O–CH_3CN (187 mg, 94%): TLC R_f 0.11 (90:10:1 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 8.13 min; FAB MS m/z 638 ($M + H^+$). Anal. $C_{31}H_{51}N_5O_5S_2 \cdot 3.15TFA \cdot 0.1H_2O$ (C, H, N).

1-(((7,7-Dimethyl-2(*S*)-(2(*S*)-(bis(hydroxyethyl)amino)-4-(methylsulfonyl)butyramido)bicyclo[2.2.1]heptan-1(*S*)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperazine (15). A solution of compound 7 (310 mg, 0.56 mmol) in EtOH (10 mL) was cooled to 0 °C. Ethylene oxide was bubbled through the solution, the reaction vessel was sealed, and the mixture was warmed to 70 °C behind a blast shield. After 48 h, the reaction mixture was cooled to 0 °C and more ethylene oxide was bubbled through the solution. The reaction vessel was resealed and heated at 70 °C behind a blast shield for 24 h. The mixture was cooled, and the solvent was removed under reduced pressure. The residue was purified (method B). The TFA salt of the title compound was obtained as an amorphous powder by lyophilization from H_2O–CH_3CN (346 mg, 69%): TLC R_f 0.62 (90:10:0.5 $CHCl_3$–MeOH–NH_4OH); HPLC retention time 8.93 min; FAB MS m/z 643 ($M + H^+$). Anal. $C_{30}H_{50}N_4O_7S_2 \cdot 2.2TFA \cdot 0.35H_2O$ (C, H, N).

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Supplementary Material Available: Experimental details for determining the structures of **2a** and **2b** and atomic numbering schemes, atomic coordinates, and selected bond distances and angles for the two structures as well as atomic coordinates for compound 7 and L-366,948 shown in the alignment in Figure 2 (29 pages). Ordering information is given on any current masthead page.

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(17) Abbreviations: AVP = arginine vasopressin, Boc = *tert*-butyloxycarbonyl, BOP = benzotriazolyl-*N*-oxytris(dimethylamino)phosphonium hexafluorophosphate, DES = diethylstilbestrol dipropionate, DIEA = diisopropylethylamine, DMF = dimethylformamide, DMSO = dimethyl sulfoxide, EDC = 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide, EtOAc = ethyl acetate, EtOH = ethanol, FAB MS = fast-atom bombardment mass spectrum, HOAc = acetic acid, HOBT = 1-hydroxybenzotriazole, HPLC = high-pressure liquid chromatography, id = intraduodenal, iv = intravenous, MeOH = methanol, Nal = 2-naphthylalanine, NMR = nuclear magnetic resonance, OT = oxytocin, SI = spiroindanylpiperidine, TFA = trifluoroacetic acid, TLC = thin-layer chromatography, TP = o-tolylpiperazine.

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