Nanomolar-Affinity, Non-Peptide Oxytocin Receptor Antagonists†

Ben E. Evans,* George F. Lundell, Kevin F. Gilbert, Mark G. Bock, Kenneth E. Rittle, Leigh Anne Carroll, Peter D. Williams, Joseph M. Pawluczyk, James L. Leighton, Mary Beth Young, Jill M. Erb, Doug W. Hobbs, Norman P. Gould, Robert M. DiPardo, James B. Hoffman, Debra S. Perlow, Willie L. Whitter, Daniel F. Veber, Douglas J. Pettibone,‡ Bradley V. Clineschmidt,‡ Paul S. Anderson, and Roger M. Freidinger

Departments of Medicinal Chemistry and New Lead Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486

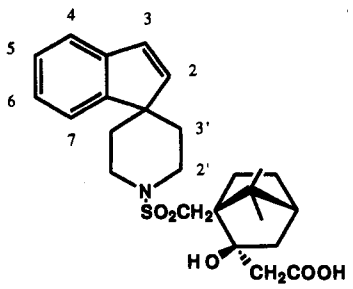
Received May 13, 1993•

Non-peptide antagonists of the peptide hormone oxytocin (OT) with nanomolar OT receptor affinities are described. These compounds incorporate novel amido- and amidoalkylcamphor variations to the lead structure L-366,509 (1) to achieve receptor affinity enhancements of 2-3 orders of magnitude over that compound. The new OT antagonist L-367,773 (35) is shown to be an orally bioavailable agent with good duration in vivo and to inhibit OT-stimulated uterine contractions effectively in several in vitro and in vivo models.

Introduction

Premature birth is a leading cause of morbidity and mortality in newborns.[1-4] Current therapy for preterm labor using β-adrenergic agonists is inadequate;[5,6] the peptide hormone oxytocin (OT) appears to play a major role in the induction and maintainance of labor,[1,7-9] and an oxytocin antagonist has been shown to block the uterine contractions of preterm labor.[10] Together, these recent observations suggest considerable therapeutic potential for an oxytocin antagonist. Such an agent might effectively interrupt preterm labor, allow gestation to proceed closer to term, and thereby minimize the health risks to the infant associated with preterm birth. For acute application, an iv drug would be suitable: for longer term, outpatient use, an orally effective agent with good duration in vivo would be preferred.

On the basis of these considerations, we developed L-366,509 (1), an orally effective, non-peptide antagonist for the peptide, oxytocin.[1,11] This compound showed



1

micromolar affinity for rat uterine OT receptors, was effective in blocking OT-induced contractions of uterine tissue in vitro and in vivo, and exhibited oral activity of good duration.[11] As a potential therapeutic agent, L-366,509 suffered from one key weakness: insufficient potency. Efforts to overcome this limitation have been successful, and new compounds with nanomolar affinities for oxytocin receptors have now been developed. In this paper, the structure–activity profile of these new compounds is presented, and the utility of a selected example as a pharmacologically useful oxytocin antagonist is described.

Chemistry

The compounds described in this paper are based on the spiroindenepiperidine–camphorsulfonamide nucleus present in L-366,509 (1), substituting amino- or aminoalkyl side chains for the carboxyalkyl group in that compound. Key intermediates for synthesis of the new compounds were prepared as shown in Scheme I. Here, the ketone precursor **2**[1] to L-366,509 (1) was subjected to (1) oximation/reduction, (2) cyanohydrin formation/reduction, or (3) acetonitrile addition/reduction to provide the amino (**4**), aminomethyl hydroxy (**6**), or aminoethyl hydroxy (**8**) compounds, respectively. As shown in Scheme I, the amino compound was obtained as a mixture of exo and endo isomers (**4a/b**; ca. 1/4) which were separated chromatographically. The exo/endo assignment was made based on chemical shift perturbation of one camphor methyl substituent by the exo, but not the endo amino group. This assignment was confirmed by NOE studies described in the Experimental Section.

The aminomethyl compound was obtained largely as the single isomer **6a**, although a small amount (<10%) of the isomer **6b** was isolable by preparative HPLC. The aminoethyl compound was obtained as the single, *exo*-hydroxy-*endo*-aminoalkyl isomer **8**. The acetonitrile addition product (**7**) leading to this compound and the stereoselectivity of its formation have been described previously.[1]

The amides of Tables I–IV were obtained by acylation of amines **4a,b**, **6a**, and **8** either directly with acid chlorides (method A) or anhydrides (method B) or with carboxylic acids in the presence of coupling reagents such as EDC (method C), BOP (method D), or carbonyldiimidazole (method E). Sulfonamides were prepared by substituting sulfonyl chlorides for acid chlorides in method A. Ureas

† Dedicated to the memory of our friend and colleague, Dr. Ta-Jyh Lee. Those who knew Ta-Jyh through his elegant work in the mevinolin series feel the loss of an outstanding medicinal chemist. Those of us who knew him personally bear the added loss of a true gentleman.

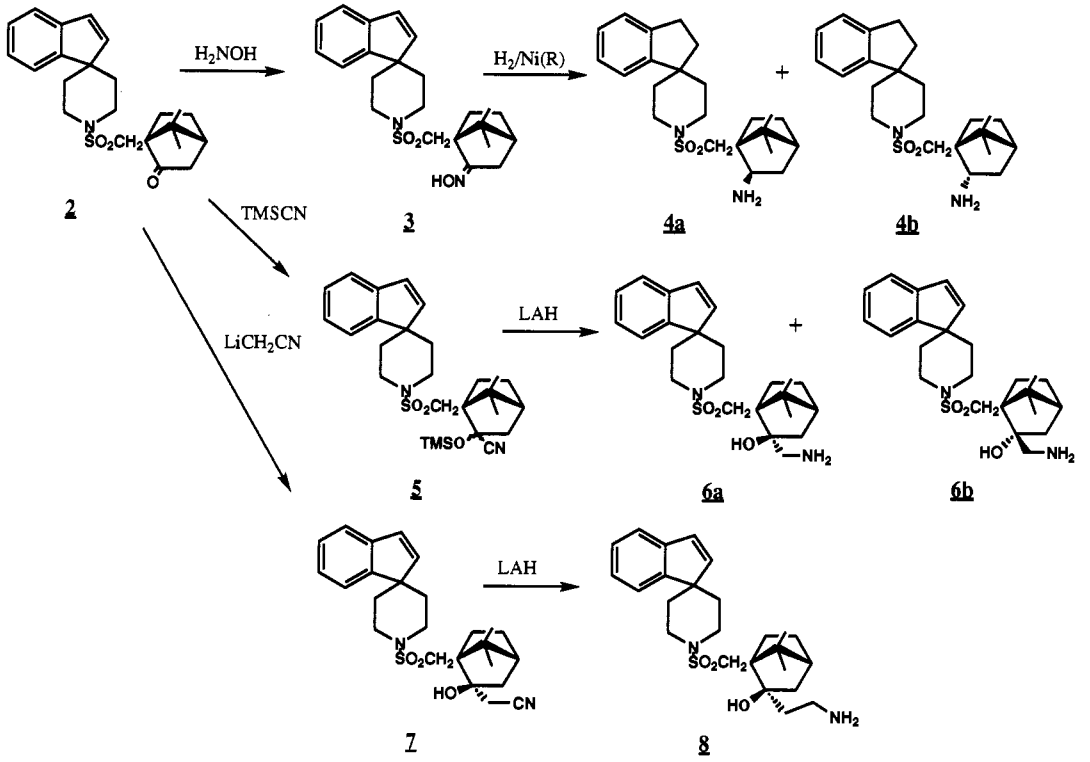
‡ Abbreviations: AUC, area under the curve (of plasma levels determined by radioreceptor bioassay vs time); BOM, (benzyloxy)methyl; BOP, (benzotriazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate; CDI, 1,1'-carbonyldiimidazole; EDC, 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride; MCPBA, 3-chloroperoxybenzoic acid; NBS, *N*-bromosuccinimide; OXONE, potassium peroxymonosulfate; TMS, trimethylsilyl; TMSCN, trimethylsilyl cyanide.

‡ Department of New Lead Pharmacology.

• Abstract published in *Advance ACS Abstracts*, November 1, 1993.

0022-2623/93/1836-3993$04.00/0

Scheme I



were synthesized by combining the parent amine with isocyanates (method F) or by treating the amine with 4-nitrophenyl chloroformate, then acylating the second amine component with the resulting 4-nitrophenyl carbamate (method G). N-Alkylations were carried out with sodium hydride/DMF and the appropriate alkyl halide for amide and imidazole nitrogen (method H), or by reductive alkylation with aldehydes and sodium cyanoborohydride for amine nitrogen (method J). Hydrolysis of esters to provide acids such as **151** was accomplished using LiOH or NaOH in aqueous methanol as described previously.[1] Deprotection of Boc-protected amines was carried out using HCl in ethyl acetate (method L) or TFA in dichloromethane (method L').

The bromoimidazole **41** was obtained by direct bromination of the parent compound **35** with NBS, and the bifunctional amides **49** and **89** were prepared by acylation of the appropriate *N*-alkylamines. The latter were products of Michael addition of amine **4b** to methyl acrylate or methyl vinyl sulfone, respectively (method P). Similar addition of histamine to methyl vinyl sulfone provided the second amine component for synthesis of urea **90** by method G, and DBU-mediated Michael addition of *N*-[(benzyloxy)methyl]imidazole-4-acetic acid methyl ester to methyl vinyl sulfone followed by ester hydrolysis gave the acid precursor to amide **91**. The BOM group was removed by hydrogenolysis over palladium black. The single isomer **92** was obtained by column chromatographic separation. Alkylation of the BOM methyl ester of imidazole-4-acetic acid with ethyl iodide or dialkylation with methyl iodide gave the acid precursors to amides **44** and **40**, respectively. The extended imidazolamide **48** was prepared from commercially available (Aldrich) urocanic acid and amine **4b** (method C). The 1-methyl-5-imidazoleacetic acid precursor to amide **39** was prepared according to the procedure of Pyman.[12]

Methionine sulfone derivatives (**80**, **81**) were prepared using method D with the commercially available (Bachem) N-protected free acid of L- or D-methionine sulfone, respectively. Other sulfoxide (**86**) and sulfone (**87**, **111**, **156**) compounds were prepared by coupling the amine with the appropriate N-protected divalent sulfur-based acid (method D), oxidizing sulfide sulfur to sulfoxide or sulfone with 1 or 2 equiv (respectively) of MCPBA or oxone (method Q), and removing the N-protecting group. Sulfonamides **77** and **78** were synthesized by EDC coupling (method C) of endo amine **4b** with the Cbz-protected acids (Sigma) followed by reductive deprotection over palladium hydroxide.

Alkylation of amine **6a** with ethyl 4-bromocrotonate, hydrogenation (10% Pd/C) of the double bond, and cyclization with sodium methoxide/methanol provided the lactam **114**. For synthesis of cycles **115** and **116**, ketone **2** was converted to the epoxide with dimethyl oxosulfonium methylide,[13] and the resulting intermediate was opened with the anion (sodium hydride/DMF) of succinimide or hydantoin, respectively. Cycle **117** was the result of spontaneous cyclization of the isocyanate produced by Curtius rearrangement of the acyl azide prepared from L-366,509 with diphenyl phosphorazidate (DPPA).

Hydantoins of Table IV were obtained by sodium hydride/DMF (method M) or sodium methoxide/methanol (method M') mediated ring closure of ureas prepared from the parent amine and an α-amino acid ethyl ester (method G). The ring-closure step epimerized the α-amino acyl unit in each case, and the hydantoins described are mixtures of diastereomers. In the case of compound **144**, these diastereomers were separated by preparative HPLC to afford the individual isomers, **142** and **143**. The requisite α-amino acid ethyl ester for synthesis of hydantoin **146** was prepared by alkylation of (3-aminopropyl)imidazole with ethyl bromoacetate in the presence of anhydrous potassium carbonate.

Imides **129**, **134**, and **135** of Table IV were prepared from the parent amine **4b** by reaction with variously substituted succinic anhydrides (method B), followed by closure by refluxing with TFA in toluene (method N).

Imide **136** was obtained by coupling of compound **134** with 5-aminotetrazole using carbonyldiimidazole (method E).

Lactam **131** was obtained by cyclization with DPPA of the product of reductive amination (method J) of amine **4b** with levulinic acid. Lactam **161** was similarly prepared using α-ketoglutarate in place of levulinate. Imidazolidinone **132** was synthesized by alkylation of **4b** with iodoacetonitrile, hydrogenation of the resulting nitrile over Raney nickel, and cyclization of the resulting 1,2-diamine with carbonyldiimidazole (method E). Imidazolidinetrione **133** was prepared directly from urea **16** by treatment with oxalyl chloride.

The tetrazole ring in compound **147** was built up from nitrile **152** using sodium azide/ammonium chloride,[14] and the aminotriazole **149** was similarly constructed by elaboration of amine **148** with diphenyl cyanocarbonimidate/hydrazine.[15] The tetrazole-1-acetic acid utilized in the preparation of amide **33** was acquired commercially (Janssen), while the 5-isomer employed in synthesizing compound **32** was obtained by acid hydrolysis of the ester prepared according to the procedure of Finnegan, Henry, and Lofquist.[14]

The amino lactam **159** was obtained by sodium hydride mediated cyclization of the trimethylsulfonium derivative prepared by S-methylation of the Boc-L-methionine amide of amine **4b**, followed by Boc removal (method L). Repetition of the same sequence using Boc-D-methionine gave **160**, the unexpected product of an additional N-methylation.

The nitrile **76** was prepared by dehydration of the N^{α}-Boc derivative of amide **64** by the procedure of Claremon and Phillips[16] followed by N-deprotection (method L). Hydroxy compound **75** was synthesized by N^{α}-Boc protection of L-glutamic acid 5-methyl ester (Aldrich), coupling to amine **4b** (method C), saponification, borane reduction of the resulting acid, and N-deprotection (method L). For synthesis of nitro compound **79**, methyl 4-bromo-2-phthalimidobutyrate was prepared according to the procedure of Logusch.[17] Displacement of bromide with nitrite by the method of Crumbie, Nimitz, and Mosher[18] provided the corresponding nitrobutyrate which was saponified with aqueous potassium carbonate and coupled to amine **4b** (method D). Deprotection (hydrazine) provided **79**.

Biology

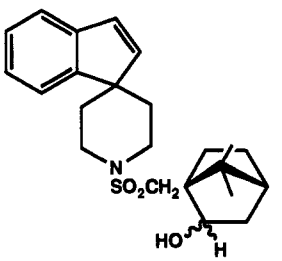
The methods for determination of oxytocin (OT) and vasopressin (AVP; rat liver = V_1, and rat kidney = V_2) receptor binding are as previously described.[11] The high-affinity binding of [^{3}H]OT ([*tyrosyl*-3,5-^{3}H]OT; 30–60 Ci/mmol; DuPont NEN, Boston, MA) to uterine OT receptors used a crude membrane preparation of uteri taken from diethylstilbesterol dipropionate (DES)-treated (0.3 mg/kg, ip; 18–24 h) rats.[11] Competitive studies were conducted at equilibrium (60 min; 22 °C) using 1 nM [^{3}H]-OT in the following assay buffer: 50 mM Tris-HCl, 5 mM $MgCl_2$, and 0.1% BSA, pH 7.4. Nonspecific binding (10% of the total binding) was determined using 1 mM unlabeled OT, and the binding reaction was terminated by filtration through glass fiber filters using a cell harvester (Model 7019, Skatron, Inc., Sterling, VA).

The measurement of [^{3}H]AVP ([*phenylalanyl*-3,4,5-^{3}H]AVP; 80–90 Ci/mmol; DuPont NEN) binding utilized crude membrane preparations of male rat liver (AVP-V_1 sites) or kidney medulla (AVP-V_2 sites).[11] Competition assays were conducted at equilibrium (30 min at 30 °C) using 1 nM [^{3}H]AVP (liver) or 2 nM [^{3}H]AVP (kidney) in the following assay buffer: 100 mM Tris-HCl, 5 mM $MgCl_2$, 0.1% BSA, 50 μM phenylmethylsulfonyl fluoride, and 50 μg/mL bacitracin, pH 8.0. Nonspecific binding (5–10% of the total binding) was determined using 10 μM unlabeled AVP, and the binding reaction was terminated by filtration as described above for the [^{3}H]OT binding assay.

IC_{50} values were determined by linear regression of percent inhibition of specific binding versus log concentration of antagonist (seven antagonist concentrations per IC_{50} determination).[11] The numbers of determinations per compound are listed in the tables (see footnote *a*, Table I).

Results

Structure–Activity: Aminocamphor Analogs. In the preceding paper,[1] we described a series of novel, nonpeptide oxytocin (OT) antagonists based on the spiroindenepiperidine ring system. The peak OT receptor affinities in this group were achieved with camphorsulfonamides and their reduction and metalalkyl addition products, represented by the key compounds **1**, **7**, and **9a/b** (Table I). These compounds are useful benchmarks



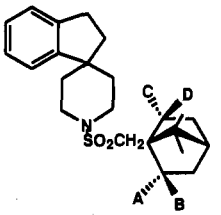
Exo OH **9a**
Endo OH **9b**

against which to assess the OT receptor affinity enhancements obtained in the present work. The new compounds described in this report utilize the spiroindenepiperidine–camphorsulfonamide ring system seen in the reference compounds but incorporate novel acylamino functionality in the camphor ring to achieve increases in OT receptor affinity of up to 3 orders of magnitude.

The base intermediate for preparation of the compounds described in this paper was the ketone **2**.[1] Conversion to the oxime **3** provided significant (ca. 3-fold) enhancement of OT receptor affinity compared with the parent ketone. As in the ketone series, saturation of the indene double bond had little effect on OT receptor affinity (**3** vs **10**).[1] In contrast to the potency enhancements seen upon reduction of the ketone **2** to the *exo*-carbinol[1] (**9a**), substantial potency losses resulted from reduction of the oxime **3**/**10** to the exo (**4a**) or endo (**4b**) amine. Despite this major loss in receptor affinity in amines vs carbinols, however, the apparent preference for the exo isomer seen in the carbinol series[1] was maintained in the amines.

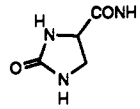
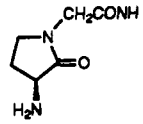
Acetylation restored OT receptor affinity in the (1*S*,2*S*) or "*S*-endo" amine series (**11a**) to the 10^{-7} M level seen in the best of the earlier compounds (e.g., **1**[1]). In those prior compounds, the exo positional preference for the hydroxy substituent (**9a** vs **9b**) is compatible with an apparent endo preference for an elaborated side chain. In acylamines such as **11a/b** and other compounds of Table I, this compatibility is not possible: the amine nitrogen and the extended side chain are part of one and the same group. The OT receptor affinities of exo/endo pairs such as **11a/11b** and **35/36** imply that it is the endo preference for the extended chain which prevails in these amides. Where

Table I. Oxytocin (OT) and Vasopressin (AVP-V_1, V_2) Receptor Binding Affinities for Spiroindanpiperidine Aminocamphorsulfonamides[a]



compd	structure: substituent	structure: position	IC_{50} (nM): OT	IC_{50} (nM): V_1	IC_{50} (nM): V_2
1	text		800 (10)	78000 (3)	70000 (4)
2	Scheme I		1800 (4)	>10000	>10000
3	Scheme I		650 (2)	ca. 10000	>10000
4a	Scheme I		6500	>10000	>10000
4b	Scheme I		30000	>10000	>10000
7	Scheme I		770	>10000	>10000
9a	text		470 (5)	8400	>10000
9b	text		2200	>10000	>10000
10	=NOH	A/B	450 (3)	3200 (2)	13000 (2)
11a	CH_3CONH	A	390 (2)	7600 (3)	26000 (3)
11b	CH_3CONH	B	1200	ca. 10000	>10000
12	cyclohexyl-CONH	A	650	ca. 10000	>10000
13	1-adamantyl-CH_2-CONH	A	12000 (2)	>10000	>10000
14	$EtOOC(CH_2)_2CONH$	A	240 (2)	16000	13000
15	$HOOC(CH_2)_2CONH$	A	410	>3000	>300
16	H_2NCONH	A	460	>3000	>3000
17	$CH_3OOCCH_2NHCONH$	A	160	>3000	>3000
18	$CH_3(CH_2)_2SO_2NH$	A	310	>1000	ca. 10000
19	C_6H_5CONH	A	ca. 1000	ca. 10000	>10000
20	$C_6H_5CH_2CONH$	A	250	2700	46000
21	$C_6H_5(CH_2)_2CONH$	A	530	ca. 10000	>10000
22	$C_6H_5(CH_2)_3CONH$	A	570	>1000	>10000
23	$C_6H_5CH_2CONH$	B	1000	>1000	ca. 10000
24	4-pyridyl-CONH	A	190	>1000	>10000
25	3-pyridyl-CONH	A	260	>1000	>10000
26	4-pyridyl-CH_2CONH	A	120	>1000	ca. 10000
27	3-pyridyl-CH_2CONH	A	170	>1000	ca. 10000
28	2-pyridyl-CH_2CONH	A	95	3900	6500
29	3-pyridyl-$(CH_2)_2CONH$	A	180	>3000	>3000
30	2-thienyl-CONH	A	620	>10000	>10000
31	4-(2-aminothiazolyl)-CH_2CONH	A	170	>3000	>3000
32	5-tetrazolyl-CH_2CONH	A	220	>3000	>3000
33	1-tetrazolyl-CH_2CONH	A	140	>1000	ca. 10000
34	4-(5-methylimidazolyl)-CONH	A	150	>3000	>3000
35	4-imidazolyl-CH_2CONH	A	52 (14)	5600 (3)	17000 (3)
36	4-imidazolyl-CH_2CONH	B	830	5100	13000
37	4-imidazolyl-CH_2CONH	C	1200	>3000	>3000
38[b]	4-imidazolyl-CH_2CONH	D	ca. 10000	>3000	>3000
39	5-(1-methylimidazolyl)-CH_2CONH	A	48	2900	7500
40	4-imidazolyl-$C(CH_3)_2CONH$	A	150	ca. 3000	>8000
41	4-(5-bromoimidazolyl)-CH_2CONH	A	110	8100	15000
42[c]	4-(1-methylimidazolyl)$CH(CH_3)CONH$	A	60	ca. 3000	>3000
43	4-(1-methylimidazolyl)CH_2CONH	A	65	4500 (2)	9400 (2)
44[c]	4-imidazolyl-CH(Et)CONH	A	170	4000	15000
45	1-imidazolyl-CH_2CONH	A	120	16000	10000
46	4-imidazolyl-$(CH_2)_2CONH$	A	94	5800	21000
47	1-imidazolyl-$(CH_2)_2CONH$	A	140	>3000	>3000
48	4-imidazolyl-t-CH=CHCONH	A	150	5200	20000
49	[4-(1-methylimidazolyl)-CH_2CO]N[$(CH_3OOC(CH_2)_2$]	A	32	2200	1700
50	4-imidazolyl-$(CH_2)_2NHCONH$	A	68 (3)	4700	14000
51	[4-imidazolyl-$(CH_2)_2$][$(HOOC(CH_2)_2$]NCONH	A	23 (3)	4000 (2)	8600 (2)
52	$H_2N(CH_2)_2CONH$	A	140	1000	9600
53	$(CH_3)_2NCH_2CONHCH_2CONH$	A	61	>300	ca. 3000
54[d]	3-piperidyl-CH_2CONH	A	130	1500	12000
55[e]	3-piperidyl-$(CH_2)_2CONH$	A	30	710	5200
56	3-quinuclidinyl-NHCONH isomer A	A	47	1700	8700
57	3-quinuclidinyl-NHCONH isomer B	A	37 (3)	2100 (2)	11000 (2)
58	3-quinuclidinyl-CONH	A	29 (2)	530	5500 (2)
59	L-histidinyl-NH	A	45	1500	5500
60	N^{α},N^{α}-dimethyl-L-histidyl-NH	A	49	1700	3400
61	N^{α}-($H_2NCO(CH_2)_2CO$)-L-histidyl-NH	A	32	ca. 3000	ca. 3000
62	L-leucyl-NH	A	580	>3000	>3000
63	L-valyl-NH	A	110	ca. 3000	>3000
64	L-glutaminyl-NH	A	12 (4)	2300 (3)	5100 (3)
65	D-glutaminyl-NH	A	55 (3)	2800	7900 (2)
66	L-asparaginyl	A	90	3900	16000
67	L-iso-glutaminyl	A	170	2200	13000

Table I (Continued)

compd	structure: substituent	position	IC_{50} (nM): OT	V_1	V_2
68		A	92	>3000	>3000
69		A	61 (7)	2700 (3)	8400 (3)
70	(*S*)-N^{α}-(3-aminopropanoyl)-L-glutaminyl-NH	A	6.3	490	1800
71	(*S*)-N^{α}-(4-imidazolylacetyl)-L-glutaminyl-NH	A	2.2 (4)	2300 (3)	810 (3)
72	(*S*)-N^{α}-((1-methyl-5-imidazolyl)acetyl)-L-glutaminyl-NH	A	2.3	>300	>300
73	(*S*)-N^{α}-((1-methyl-4-imidazolyl)acetyl)-L-glutaminyl-NH	A	1.7	1900	620
74[c]	4-imidazolyl-$CH_2CONHCH(CH_2CONH_2)CH_2CONH$	A	50	1300	5400
75	(*S*)-$HO(CH_2)_3CH(NH_2)CONH$	A	80	1700	6200
76	(*S*)-$NC(CH_2)_2CH(NH_2)CONH$	A	46	1400	6500
77	(*S*)-$H_2NSO_2(CH_2)_2CH(NH_2)CONH$	A	38	4000	6700
78	(*S*)-$H_2NSO_2(CH_2)CH(NH_2)CONH$	A	200	2900	14000
79	(*RS*)-$O_2N(CH_2)_2CH(NH_2)CONH$	A	330	>300	ca. 3000
80	(*S*)-$CH_3SO_2(CH_2)_2CH(NH_2)CONH$	A	12 (3)	890 (3)	2400 (3)
81	(*R*)-$CH_3SO_2(CH_2)_2CH(NH_2)CONH$	A	45 (2)	5200	12000
82	(*S*)-4-imidazolyl-$CH_2CONHCH((CH_2)_2SO_2CH_3)CONH$	A	1.2 (4)	440 (3)	280 (3)
83	(*S*)-4-(1-methylimidazolyl)-$CH_2CONHCH((CH_2)_2SO_2CH_3)CONH$	A	0.7	1200 (2)	490 (2)
84	(*S*)-$CH_3SO_2(CH_2)_2CH(NEt_2)CONH$	A	30	2100	1500
85	(*S*)-$CH_3SO_2(CH_2)_2CH(N(CH_3)_2)CONH$	A	4.9 (3)	530 (3)	1300 (3)
86	(*S*)-$CH_3SO(CH_2)_2CH(NH_2)CONH$	A	54 (3)	3600 (2)	7400 (2)
87	(2*S*,4*R*)-5-(3-CH_3SO_2-pyrrolidinyl)-CONH	A	100	4000	5500
88	(*S*)-$CH_3SO_2(CH_2)_2CH(NHCOCH_2NH_2)CONH$	A	4.1	440	1100
89	$[CH_3SO_2(CH_2)_2]$[4-(1-methylimidazolyl)-CH_2CO]N	A	6.0 (2)	320 (2)	650 (2)
90	$[CH_3SO_2(CH_2)_2]$[4-imidazolyl-$(CH_2)_2$]NCONH	A	16 (3)	700 (2)	1900 (2)
91	$[CH_3SO_2(CH_2)_2]$[4-imidazolyl]CHCONH isomer A	A	11 (2)	1500 (2)	2900 (2)
92	$[CH_3SO_2(CH_2)_2]$[4-imidazolyl]CHCONH isomer B	A	11 (2)	2200	3300

[a] Receptor binding is expressed as IC_{50}, the concentration (nM) of compound required for half-maximal inhibition of binding of [^{3}H]OT to rat uterine tissue (OT) or of [^{3}H]AVP to rat liver (V_1) or rat kidney (V_2) tissues as described by Pettibone et al.[11] All compounds were initially screened at one concentration. For some weakly bound compounds, IC_{50}'s have been estimated from this single determination at concentration "*C*", and the results appear as ">*C*" or "ca. *C*". For all other compounds, IC_{50}'s were determined from plots of inhibition vs log concentration at seven different concentrations selected on the basis of the initial screening result. Where repeat determinations of IC_{50} were carried out, the number of such determinations is given in parentheses following the IC_{50} entry. The IC_{50} value in these cases is the mean of all determinations. [b] **38** is a mixture of ca. 2:1 indene/indan. [c] These compounds are diastereomer mixtures, ca. 1:1. [d] This compound is a mixture of diastereomers, ca. 2.5:1. [e] This compound is derived from racemic piperidine propionic acid. HPLC and NMR do not indicate more than one diastereomer.

tested (see below), no exceptions to this general preference were found. The activity advantage of compounds derived from the (1*S*)- vs (1*R*)-camphor ketone was similarly retained in all cases studied, (e.g., **35** vs **37**) and the majority of amides examined in this work were therefore derived from the (1*S*,2*S*) or "*S*-endo" amine, **4b**.

Other simple amides, ureas, and sulfonamides (e.g., **12–18**) of amine **4b** proved comparable or inferior to the simple acetyl compound **11a** as OT receptor ligands. Phenyl substitution at the termini of simple alkanamide chains provided a series of compounds whose OT receptor affinities varied with substituent chain length (e.g., **19–22**). The maximum OT receptor affinity in this series, however, remained in the 10^{-7} M range of the benchmark compounds: the peak OT affinity achieved with a one-carbon link between the aryl and amido groups (**20**) was only marginally superior to that of the simple acetyl compound (**11a**). The endo orientation of the major camphor substituent in this group again proved more effective than the exo (**20** vs **23**), consistent with earlier observation (ref 1; see also above).

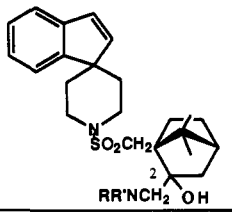
Heteroaryl-based substituents provided similarly potent OT receptor ligands such as **24–34** (Table I) with OT receptor affinities clustered in the 10^{-8} to 10^{-7} M range. The insensitivity of OT receptor affinity to a range of structure variations is perhaps surprising in a series of such relatively potent compounds. This insensitivity was not absolute, however, for the 2-pyridylacetyl (**28**), and especially the 4-imidazolylacetyl groups (**35**) enhanced OT receptor affinity into the 10^{-8} M IC_{50} range. The imidazolylacetyl compound L-367,773 (**35**) exhibits >10-fold improved OT receptor affinity over L-366,509 (**1**).

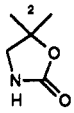
Among amide **35**, its exo isomer (**36**), and their enantiomers (**37** and **38**, respectively), the (1*S*,2*S*) or "*S*-endo" compound **35** proved most effective as an OT receptor ligand, consistent with the (1*S*) vs (1*R*) and endo vs exo preferences detailed above. Variations on the imidazole theme incorporating N-substitution (**39**, **42**, **43**), C-substitution (**41**), Cα-substitution (**40**, **42**, **44**), isomerization (**45**), homologation (**46–48**), amide N-substitution (**49**), and modification to a urea linkage (**50–51**) provided a number of compounds with comparable OT receptor affinities, and two (**49**, **51**) with significant improvement therein.

Major OT receptor affinity enhancements over benchmark compounds such as **1** and **11a** were also achieved with amides and ureas containing various alkyl-, cycloalkyl-, and bicycloalkylamine functions in the camphor 2-substituent (e.g., **52–58**). The quinuclidinyl amide **58**, for example is some 20-fold more tightly bound at OT receptors than is L-366,509 (**1**) and on a par with the best of the imidazole-containing group described above (i.e., **49**, **51**).

Endo amine amides and ureas with single-chain acyl groups, compounds such as **35**, **50**, and **58**, had provided

Table II. Oxytocin (OT) and Vasopressin (AVP-V_1, V_2) Receptor Binding Affinities for Spiroindenepiperidine (Aminomethyl)camphorsulfonamides[a]



compd	R[b,c]	IC_{50} (nM) OT	V_1	V_2
6a	H	1300	>1000	>10000
6b[b]	H	ca. 10000	100000	100000
93	$COCH_3$	130	>1000	ca. 10000
94	$COCH_2$-1-adamantyl	480	>3000	>3000
95	CO-2-pyridyl	180	1100	3600
96	CO-3-pyridyl	100	1500	6800
97	CO-4-pyridyl	180	1200	ca. 10000
98	CO-5-(3-amino-1,2,4-triazolyl)	50	680	4800
99	$COCH_2$-2-pyridyl	81 (2)	830	4700
100	$COCH_2$-3-pyridyl	53 (2)	890	4500
101	$COCH_2$-4-pyridyl	35 (2)	480	5100
102	$COCH_2$-4-imidazolyl	45	>300	>3000
103	CONH-cyclohexyl	170	950	18000
104[f]	CO-3-quinuclidinyl	57 (2)	470	6100
105[f]	CO-3-(1-(carboxymethyl)quinuclidinyl)	27	>300	>3000
106[f]	CO-3-piperidyl	110 (2)	>300	5100
107	L-leucyl	42	430	2200
108	L-valyl	43	290	4900
109	L-glutaminyl	90	>300	ca. 3000
110	(*S*)-$CH_3SO_2(CH_2)_2CH(NH_2)CO$	110	3700	9200
111[d]	(*S*)-$CH_3SO_2CH_2CH(NH_2)CO$	40	1100	3000
112	(*S*)-[$CH_3SO_2(CH_2)_2$][4-imidazolyl-CH_2CONH]CHCO	7.6 (2)	310	2500
113	N^{α}-(4-imidazolylacetyl)-L-valyl	8.3	67	540
114[c,d]	RR′ = $-(CH_2)_3CO-$	150	ca. 3000	>3000
115[c]	RR′ = $-CO(CH_2)_2CO-$	110	ca. 3000	>3000
116[c]	RR′ = $-CONHCH_2CO-$	50	2700	7400
117[e]		>1000	>10000	>10000

[a] Binding affinities defined as in Table I, footnote *a*. [b] Stereochemistry at position 2 of the camphor ring is *R* in all compounds except **6b**. [c] R′ = H in all compounds except **114**, **115**, and **116**. [d] The indene double bond in these compounds is saturated. [e] The 2-OH and $RNHCH_2$ groups in compound **117** are incorporated into an oxazolidinone ring as shown. [f] These compounds are diastereomer mixtures, ca. 1:1.

OT receptor ligands with IC_{50}'s in the 10^{-8} M range. A clue to methods for enhancing potency still further was provided by the high-affinity analogs **49** and **51** noted above. What distinguishes these compounds structurally from their confreres (e.g., **35–48**, **50**) is the presence of two major branches in the amide side chain, one bearing the imidazole unit, the other containing a three-carbon carboxylate chain. These features are keys to high OT receptor affinity. Addition of the second, or succinoyl chain to **50** to give **51**, for example, more than trebled OT receptor affinity.

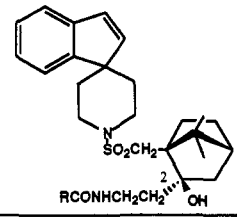
Another approach to such two-chain amide groups is through α-amino acid analogs. Appending simple α-amines onto the potent imidazole-based compound **46**, for example, provided 2–3-fold potency improvement as seen in the histidine derivatives **59** and **60**. Extension of the α-amine side chain with a glutaminyl group (**61**) gave a slight additional potency enhancement.

In comparison with the successful histidine modification (**59**), other simple α-aminoacyl groups such as Leu and Val (**62** and **63**, respectively) generally were less efficacious. Glutamine proved an exception, providing the 12 nM OT receptor ligand **64**. The D-Gln analog **65** was less effective at OT receptors than compound **64**, and modifications such as shortening the Gln chain (**66**) and translating the α-amine to the γ-position (**67**) were similarly detrimental to OT receptor affinity. The cyclized analogs **68** and **69** also exhibited reduced OT receptor affinity relative to compound **64**.

In keeping with the two-chain hypothesis, it was elaboration of the α-amine which opened the way to additional potency enhancements in glutamine derivative **64**. Thus, attachment of a β-alanyl side chain (**70**) enhanced potency some 2-fold, and acylation with the imidazolylacetyl unit seen in compound **35** gave entry into a series of still more potent, nanomolar level OT receptor antagonists, such as the prototype **71** and its *N*-methyl derivatives **72** and **73**. The β-amido analog **74** of compound **71** was substantially less effective at OT receptors.

The apparent effectiveness of the terminal amide group in compound **64** in enhancing OT receptor affinity prompted an examination of other potential hydrogen bond accepting groups in this position. Hydroxy (**75**) and cyano (**76**) were reasonably effective as alternate chain termini, though inferior to the prototype amide. Nitro (**79**) was considerably less effective. Sulfonamide was slightly inferior to carboxamide in both compounds **77** and **78** (cf. **64** and **66**, respectively), but methyl sulfone (**80**; cf. **64**) proved fully effective. The relationship between the glutamine (e.g., **64**) and methionine sulfone (e.g., **80**) series was maintained over several modifications, being reduced by ca. 4-fold upon inversion of the amino acid

Table III. Oxytocin (OT) and Vasopressin (AVP-V_1, V_2) Receptor Binding Affinities for Spiroindenepiperidine (Aminoethyl)camphorsulfonamides[a]



compd	R	IC50 (nM) OT	V_1	V_2
118	CH_3	150 (2)	2700 (2)	30000 (2)
119	$CH_3CH_2C(CH_3)_2$	45	2300	13000
120	phenyl	220	4600	23000
121	2-pyridyl	120	>1000	>1000
122	3-pyridyl	97	1900	6000
123	4-pyridyl	79	>1000	>1000
124	2-oxo-5-pyridyl	49	1000	2600
125	4-pyridylmethyl	110	ca. 3000	>3000
126	5-tetrazolylmethyl	300	>3000	>3000
127	4-imidazolylmethyl	90	>300	>3000
128[b]	3-quinuclidinylmethyl	100 (2)	640	6200

[a] Binding affinities defined as in Table I, footnote *a*. [b] Compound 128 was prepared from racemic quinuclidinylacetic acid. NMR and HPLC do not distinguish two diastereomers.

center (cf. 81 vs 65) and enhanced 5–10-fold by imidazoleacetate acylation (82, 83; cf. 71, 73). N-Alkylation (84, 85) produced only small changes, either for good (dimethylation: 85) or for ill (diethylation: 84) in the OT receptor affinity of Met sulfone 80, while reduction to sulfoxide (86) and cyclization (87) were decidedly detrimental. Other modifications to the Met sulfone unit (88–92) produced effective OT receptor ligands, but the imidazoleacetyl derivatives 82 and 83 remained the most potent in the series.

(Aminomethyl)camphor Analogs. With TMSCN, ketone 2 gave the aminomethyl derivatives **6a/b**, as described above (Scheme I). Like the amines **4a/b**, these compounds showed poor affinity for OT receptors (Table II). Even more so than with **4b**, however, acetylation enhanced the OT receptor affinity of the *endo*-aminomethyl compounds **6a** considerably, giving the 130 nM OT receptor ligand **93** (cf. **11a**). A series of amides and ureas of amine **6a** containing various carbocyclic and heterocyclic substituents (e.g., **94–103**; Table II) revealed numerous compounds with OT receptor affinities in the 10^{-8} M range, comparable, and in some cases superior, to analogous compounds in the aminocamphor series (cf. **13**, **24–28**, **35**). The imidazolylacetyl derivative **102**, though less outstanding in this series in the company of comparably potent analogs (i.e., **98**, **100**, and **101**), was nevertheless superior in OT receptor affinity to the aminocamphor analog **35** containing this same substituent.

Cycloalkyl- and bicycloalkylamine-based compounds such as **104–106** exhibited OT receptor affinities in line with those of similar derivatives in the aminocamphor series (e.g. **54–58**), and simple amino acid amides of amine **6a** (e.g., **107**, **108**) showed enhanced affinity compared with analogous amides in the aminocamphor **4b** (cf. **62**, **63**, respectively). Interestingly, cyclization of the aminocamphor α-amino acid amides such as **62** to hydantoins such as **140** (Table IV), a modification discussed in more detail below, also enhanced OT receptor affinity, though not to the level achieved in the aminomethyl derivative **107**.

The glutamine and Met sulfone amides **109** and **110** of the aminomethyl base proved inferior to the same compounds in the amino series (**64** and **80**, respectively), although such a result may not be unexpected, since the key spacing between the camphor and terminal units has been increased in the aminomethyl compounds relative to the amino derivatives. This implication, that the various amido chains serve merely as spacer units, is supported by the similarity in receptor affinity between various aminocamphor amides and the corresponding aminomethyl derivatives in which the camphor to end group spacing is the same, pairs such as **26/97**, **27/96**, **56 + 57/104**, and **54/106**. However, affinity differences in other such pairs as **28/95**, **29/100**, **46/102**, and **80/111** suggest this interpretation is less than completely rigorous.

Though less potent than its amine analog **80**, the aminomethyl Met sulfone derivative **110** enjoyed a similar (10–20-fold) enhancement in OT receptor affinity when acylated with imidazoleacetic acid (**112**). Similar imidazolacetylation of the valine amide **108** produced an analogous 5-fold OT affinity enhancement (**113**). Cyclizations to lactam (**114**), imide (**115**), and hydantoin (**116**) enhanced potency in the aminomethyl series, though not to the ultimate levels achieved in the amines (see below). Cyclization incorporating the exo hydroxy function (**117**) was decidedly counterproductive.

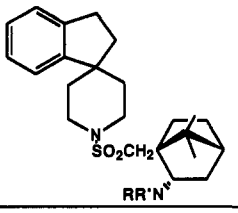
(Aminoethyl)camphor Analogs. Among the spiroindenecamphorsulfonamide derivatives prepared in conjunction with the investigation of L-366,509 (**1**) was the corresponding nitrile **7**, a compound with OT receptor affinity comparable to that of L-366,509 itself.[1] Reduction of this nitrile to the amine **8** and acetylation as above again gave a 100 nM level OT antagonist (**118**), and simple alkyl- (e.g., **119**), aryl- (e.g., **120**), heteroaryl- (e.g., **121–127**), and bicycloalkylamine- (e.g., **128**) based compounds again provided reasonably effective OT receptor ligands, although the peak affinities reached in this series, including the imidazolylacetyl and quinuclidinyl derivatives **127** and **128**, were inferior to those attained in the amino- and (aminomethyl)camphor groups.

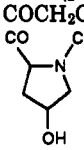
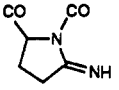
Hydantoin/Imide. As discussed above, simple aliphatic amides of the "endo amine" **4b** are relatively weak OT receptor ligands (IC_{50}, 10^{-7} M range). This generalization remained intact over a wide range of structure variants including the succinoyl class compounds **14**, **15**, and **17**. It was somewhat surprising, therefore, that simple cyclization of the latter compounds to imide **129** or hydantoin **130** enhanced receptor affinity by more than 1 order of magnitude, well down into the 10^{-8} M IC_{50} range. Interestingly, this effect of cyclization was not general, for closely related cycles, such as lactam (**131**, **159–161**), imidazolone (**132**), or imidazoletrione (**133**) did not engender this potency enhancement.

In the substituted imides (**134–136**), and particularly in the hydantoins (**137–158**), OT receptor affinity again remained relatively consistent over a broad range of substitutions, as in the acyclic amides cited above. In the cyclic cases, however, the receptor affinity plateau was significantly lower, with the hydantoins and imides hovering in the 10^{-8}–10^{-9} M OT receptor affinity range. The imidazolylmethyl compound **144**, for example, is a nanomolar level OT receptor ligand, some 5 times more tightly bound to OT receptor than is its acyclic precursor, the histidine amide **59**.

Biology. As the data in Tables I–IV indicate, numerous analogs with the requisite >10-fold potency enhancement over the L-366,509 lead have been uncovered. As is also shown, the majority of these exhibit good selectivity vs

Table IV. Oxytocin (OT) and Vasopressin (AVP-V_1, V_2) Receptor Binding Affinities for Spiroindanpiperidine Camphorsulfonamide Lactams, Imides, and Hydantoins[a]



compd	RR'	IC_{50} (nM) OT	V_1	V_2
129	$COCH_2CH_2CO$	11 (2)	910 (2)	1700 (2)
130	$COCH_2NHCO$	18 (2)	1100 (2)	2100 (2)
131[b]	$COCH_2CH_2CH(CH_3)$	180	3500	9300
132	$CONHCH_2CH_2$	100 (2)	>300	>3000
133	COCONHCO	180	9200	16000
134[b]	$COCH_2CH(CH_2COOH)CO$	30 (3)	1600 (3)	2500 (3)
135[b]	$COCH_2CH((CH_2)_2COOH)CO$	42 (2)	2100	6600
136[b]	$COCH_2CH(CH_2CONH\text{-}5\text{-}tetrazolyl)CO$	13 (2)	770	2400
137[b,c]		20	500	3200
138[b]	$COCH(CH_3)NHCO$	14	710	2100
139	$COCH_2N(CH_3)CO$	14	960	2700
140[b]	$COCH(CH_2CH(CH_3)_2)NHCO$	92	1200	4200
141[b]	$COCH(CH_2\text{-}3\text{-}pyridyl)NHCO$	36	>300	>300
142	$COCH(CH_2\text{-}4\text{-}imidazolyl)NHCO$ isomer A	16 (2)	600	2000
143	$COCH(CH_2\text{-}4\text{-}imidazolyl)NHCO$ isomer B	13 (2)	420	1400
144	$COCH(CH_2\text{-}4\text{-}imidazolyl)NHCO$ isomers A + B	15 (5)	580 (4)	1500 (4)
145	$COCH_2N(CH_2\text{-}4\text{-}imidazolyl)CO$	12 (3)	370 (2)	940 (2)
146	$COCH_2N((CH_2)_3\text{-}1\text{-}imidazolyl)CO$	19 (2)	500	1900
147	$COCH_2N(CH_2\text{-}5\text{-}tetrazolyl)CO$	49 (2)	2000	4400
148[b]	$COCH(CH_2NH_2)NHCO$	35	490	2100
149[b]	$COCH(CH_2NH\text{-}5\text{-}(3\text{-}amino\text{-}1,2,4\text{-}triazolyl)NHCO$	6.7 (3)	120	450
150[b]	$COCH(CH_2COOH)NHCO$	50	1900	4100
151	$COCH_2N(CH_2COOH)CO$	48 (2)	>300	>300
152	$COCH_2N(CH_2CN)CO$	4.2	530	1700
153[b]	$COCH(CH_2CONH\text{-}5\text{-}tetrazolyl)NHCO$	30	3700	6700
154	$COCH_2N(CH_2CONH\text{-}2\text{-}imidazolyl)CO$	5.9 (2)	500	740
155[b]	$COCH(CH_2CH_2CONH_2)NHCO$	3.2 (3)	160 (2)	570 (2)
156[b]	$COCH(CH_2CH_2SO_2CH_3)NHCO$	2.6	110	660
157[b]	$COCH(CH_2CH_2SO_2NH_2)NHCO$	13	410	1100
158[b]		21	1100	3800
159[c]	$CH_2CH_2CH(NH_2)CO$	60 (2)	1700	5500
160[c]	$CH_2CH_2CH(NHCH_3)CO$	210	4700	12000
161[b]	$COCH_2CH_2CH(COOH)$	270	>3000	>3000

[a] Binding affinities defined as in Table I, footnote *a*. [b] These compounds are diastereomer mixtures, ca. 1:1 (NMR). [c] Absolute stereochemistry at pyrrolidine ring 4-position undetermined. [c] HPLE does not distinguish diastereomers; NMR is equivocal.

vasopressin V_1 and V_2 receptors. The imidazoleacetate L-367,773 (**35**), for example, showed high affinity for both rat (K_i, 26 nM) and human (K_i, 61 nM) uterine OT receptors with good selectivity vs vasopressin V_1 and V_2 receptors. L-367,773 was effective in blocking OT-induced PI turnover in rat uterine slices and behaved as a competitive OT antagonist (pA_2, 7.93) in the isolated rat uterus, showing no agonist-like activity. In keeping with its hypothesized OT selectivity, L-367,773 did not affect uterine contractions induced by bradykinin or prostaglandin F2α.

As an important prerequisite for iv formulation, L-367,773 showed good aqueous solubility (HCl salt: 10.2 mg/mL in water, final pH 4.5; 5.4 mg/mL in physiological saline; 3.5 mg/mL in 0.1 M acetate buffer, pH 5.0). Administered iv, L-367,773 showed a long-lasting and dose-dependent (AD_{50}, 1.5 mg/kg) inhibition of OT-stimulated uterine activity in the rat. When administered intraduodenally (10 mg/kg), the compound showed substantial OT antagonist activity, indicative of significant absorption from the gut. The compound showed no appreciable AVP agonist or antagonist activity in the rat, consistent with the OT selectivity gleaned from receptor binding results.

In rat, dog, and rhesus macaque, L-367,773 (20 mg/kg) showed good oral bioavailability (50–100%; by AUC po/AUC iv) and good duration ($t_{1/2}$ ca. 60 min). Given orally or iv to near-term pregnant rhesus, L-367,773 was effective in blocking OT-stimulated uterine contractions.

Discussion

In the development of the non-peptide oxytocin receptor antagonist, L-366,509 (1), a large number of spiroindene-camphorsulfonamide compounds[1] were prepared based on an original screening lead, and an optimal compound (1) was selected from among them. Several criteria dictated this selection: L-366,509 was among the most potent OT antagonists uncovered in this study (IC_{50} 800

nM), it possessed reasonable selectivity vs vasopressin (AVP) receptors, it exhibited effectiveness in antagonizing OT-induced uterine contractions, it had aqueous solubility sufficient for iv formulation, and most importantly, it showed good oral bioavailability. While suitable as a prototype compound, L-366,509 was judged insufficiently potent by at least 1 order of magnitude for development as a potential drug candidate.

Investigation of a wider range of novel substitution patterns in the spiroindenecamphorsulfonamide series was the goal of the present effort. This investigation led to the amide-based compounds shown in Tables I–IV. Included in this group are compounds with IC_{50}'s for OT receptor binding in the 10^{-9} M range, potencies suitable for a potential drug. The development of these amides followed a series of stepwise progressions from the ca. 400 nM OT receptor affinity of a simple amide such as **11a** to the 1 nM level of compounds such as **71**, **82**, and **155**. Among the different major steps found to increase OT receptor affinity were two-chain amide formation (e.g., **51**, **61**), imidazole acetylation (e.g., **35**), bicycloalkylamino acid acylation (e.g., **58**) and imide/hydantoin cyclization (e.g., **129**, **130**). In some cases, the benefits of the individual modifications appeared to be synergistic in their combination (glutaminyl side chain, **64**, IC_{50}, 11.5 nM; imidazole acetylation, **35**, IC_{50}, 52 nM; combination, **71**, IC_{50}, 2.2 nM), while in others they did not (hydantoin, **130**, IC_{50}, 18 nM; imidazoleacetylation, **35**, IC_{50}, 52 nM; combination, **143**, IC_{50}, 12 nM).

In the course of the present investigation, numerous high affinity (IC_{50} 1–10 nM) OT receptor ligands have been uncovered (Tables I–IV). On the basis of OT receptor affinity alone, compound **35** would appear to be less than optimal as a candidate for further study. In practice, however, the cumulative profile of this compound—its good aqueous solubility, its bioavailability from the gut in several species, its duration in vivo, its oral effectiveness in rhesus—more than offset its apparent receptor affinity disadvantage. Though theoretically more potent in receptor binding assay, the 1–10 nM compounds proved uniformly less effective in vivo due to offsetting deficiencies in one or another of these properties. These results illustrate again how numerous factors, not only target receptor affinity, dictate the potential utility of new pharmacological agents.

In our previous report on L-366,509,[1] we described another example of how a single basic structural nucleus, in this case, the spiroindenepiperidine, can be targeted toward multiple receptors by appropriate structural modification. This approach, which we have recommended in the past,[19-21] provides a valuable route to new receptor ligand leads, but as noted in the previous report,[1] subsequent optimization remains a major undertaking. The present paper describes optimization of the L-366,509 (1) lead, and as is illustrated by the extent of the Tables I–IV, themselves by no means all-inclusive, the second, optimization stage of drug development was at least as labor intensive as the initial lead discovery process.

A key factor driving this labor requirement is the apparent high precision required to adjust receptor affinity in a base ligand such as **11a** using chemical structure variation. We have developed elsewhere a detailed model[19-21] which attempts to account for the levels of precision required in such an undertaking. Comparing ligand binding constants with free energies of binding, this model describes how seemingly small structure variations can (but might not) exert large effects on receptor binding affinity.[19-21] Such a high sensitivity to structure is illustrated by the OT receptor affinity data for the compounds of Tables I–IV, most of them closely related in structure but showing large differences of 10^3 M or more in OT receptor affinities. The model also predicts that the alternative result is possible: namely, that similar, or even more substantive structural changes, at or near the same locus, can have surprisingly little effect on affinity in the same base ligand, as in the subset **24–34** discussed above.[19-21] It is usually no surprise when structural change in a weakly bound receptor ligand produces a new ligand with similar (i.e., similarly poor) affinity. The series of compounds **24–34**, however, are relatively high affinity OT receptor ligands, so the insensitivity of receptor binding affinity to structure variation within this group is noteworthy.

Human oxytocin receptors have now been cloned and expressed,[22] but there is as yet no detailed structural information available for these receptors. Therefore, we have relied on the informed trial-and-error method of traditional medicinal chemistry to achieve oxytocin receptor ligand optimization. The success of this method in the present instance provides yet another affirmation of its continuing value in the practice of modern medicinal chemistry.

Conclusion

In the first paper in this series,[1] we described the development of a prototype for an orally bioavailable, nonpeptidal OT receptor ligand, the micromolar affinity compound, L-366,509 (1). That compound, and the many analogs prepared in its class, lacked adequate OT receptor affinity for further development as potential drugs. In this companion paper, we have detailed the structure–activity studies which have successfully refined the L-366,509 lead to yield a series of nanomolar affinity OT receptor antagonists. One of these, the amide L-367,773 (**35**), has been shown to be an effective OT antagonist in vitro and in vivo, orally bioavailable with good potency and duration in several animal models. It has demonstrated effectiveness in blocking OT stimulated uterine contractions in pregnant rhesus and represents a significant advance in the development of new tocolytic agents. Clinical evaluation is pending.

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) are uncorrected. Spectra were obtained as follows: FAB mass spectra on a VG MM/ZAB-HF spectrometer, ^{1}H NMR spectra on a Varian XL-300, Nicolet NT-360, or Varian VXR 400S spectrometer with Me_4Si as internal standard. HPLC was carried out on a Hewlett-Packard Model 1084B liquid chromatograph using a Waters C-18 column (30 × 0.39 cm). Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer. Analytical TLC was carried out on 250 μm, 5- × 20-cm silica gel plates (60 F-254, E. Merck) with ultraviolet light and/or phosphomolybdic acid for visualization.

Syntheses. The specific examples presented below illustrate the synthetic methods used in preparing the compounds of Tables I–IV. Methods used, HPLC purities, mass spectral molecular ion determinations, and C, H, N analytical data for new compounds are given in the supplementary material. All new compounds gave NMR spectra consistent with the reported structures. In general, samples prepared for physical and biological studies were dried in high vacuum (<5 Torr) over P_2O_5 for 18 h at temperatures ranging from ambient to 110 °C, depending on the sample melting point. Despite these measures, some compounds remained solvated. Where analytical data have

been acquired for such solvates, the presence and approximate stoichiometry of all indicated solvents have been verified by NMR.

Amines: (1*S*,2*R*)- and (1*S*,2*S*)-2,3-Dihydro-1′-(((2-amino-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl)sulfonyl))spiro-(1*H*-indene-1,4′-piperidine) (4a and 4b). (1*S*)-1′-(((7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine)[1] (30 g, 0.075 mol) in pyridine (500 mL) was heated in an oil bath to 70 °C (internal). Hydroxylamine hydrochloride (30 g) was added in three portions over ca. 20 min. After 2 h, an additional 10 g of hydroxylamine hydrochloride was added (over 10 min). At 30, 40, and 50 min additional elapsed time, further 3-g lots of hydroxylamine hydrochloride were added. After another 30 min, the mixture was poured into water (2 L) and extracted three times with ethyl acetate (300-mL portions). The organic layers were combined, washed with 1 N HCl (600 mL total), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. EtOH (absolute; ca. 250 mL) was added to the resulting thick syrup and the solution allowed to stand at ambient temperature overnight. The mixture was filtered and the filtrate boiled down to ca. 80 mL. After standing, the mixture was again filtered and boiled down to ca. 20 mL. After a third filtration, the filtered solids were combined to give oxime **3** (28 g, 90%): ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.1 (s, 3H), 1.3–1.4 (m, 1H), 1.43 (br d, J = 13 Hz, 2H), 1.6 (br s, 1H), 1.78 (dt, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 1.9–2.0 (br m, 2H), 2.1 (d, J = 18 Hz, 1H), 2.22 (2H, ddt, J_1 = 12 Hz, J_2 = 5 Hz, J_3 = 2 Hz, 2H), 2.55 (dd, J_1 = 6 Hz, J_2 = 2 Hz, 1H), 2.58 (dt, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 2.96 (d, J = 15 Hz, 1H), 3.3 (d,t,d J_1 = 18 Hz, J_2 = 12 Hz, J_3 = 2 Hz, 2H), 3.48 (d, J = 15 Hz, 1H), 3.96 (br m, 2H), 6.82 (d, J = 5 Hz, 1H), 6.86 (d, J = 5 Hz, 1H), 7.2–7.3 (m, 2H), 7.3–7.4 (m, 2H), 7.46 (br s, 1H).

Oxime **3** (20 g) in 2-methoxyethanol (200 mL) was hydrogenated at 60 psi overnight over freshly prepared Raney nickel catalyst (from 38 g of alloy).[23] TLC (180/10/1 CH_2Cl_2/MeOH/NH_4OH, silica gel) showed the reaction to be complete. The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was chromatographed on silica (5% v/v methanol in methylene chloride). The exo isomer **4a** (3.5 g, 20%) of the title amine was eluted first, followed by the endo isomer, **4b** (12.5 g, 72%), each obtained as a white solid upon evaporation of the respective fractions in vacuo. Also recovered were the starting oxime **3** (1.2 g) and its dihydro derivative, **10** (0.8 g). **4a**: ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.1 (s, 3H), 1.2 (m, 1H), 1.5–1.9 (m, 6H), 1.9–2.1 (m, 5H), 2.68 (d, J = 14 Hz, 1H), 2.9–3.1 (m, 4H), 3.34 (dd, J_1 = 9 Hz, J_2 = 5 Hz, 1H), 3.46 (d, J = 14 Hz, 1H), 3.82 (br m, 2H), 7.1–7.25 (m, 4H). **4b**: ^{1}H NMR ($CDCl_3$) δ 0.82 (dd, J_1 = 13 Hz, J_2 = 5 Hz, 1H), 0.94 (s, 3H), 1.1 (s, 3H), 0.97 (m, 1H), 1.3 (m, 1H) 1.55–1.7 (m, 4H), 1.75–1.9 (br s, ca. 4H), 1.97 (dt, J_1 = 13 Hz, J_2 = 5 Hz, 2H), 2.05 (t, J = 8 Hz, 2H), 2.27 (m, 1H), 2.36 (m, 1H), 2.8–3.0 (m, 6H), 3.46 (m, 1H), 3.82 (m, 2H), 7.1–7.25 (m, 4H).

The amine **4a** was assigned the 2*R*, or "exo" configuration based on the chemical shift perturbation of one of the two camphor methyl groups (δ = 0.88 and 1.1) by the adjacent exo amine. This perturbation was not observed in the 2*S* or "endo" compound, **4b** (δ = 0.94 and 0.97). This effect has been examined in detail by NOE in the analogous 2-hydroxy series where the methyl group chemical shift perturbation was found to be a reliable marker for the exo substituent.[1] In the present instance, the assignment was confirmed by 2D-NOE studies which revealed a correlation between the δ 0.97 methyl substituent and the 2-position hydrogen (α to the NH_2 group) in compound **4b**, supporting the exo assignment for this hydrogen and the corresponding endo assignment for the NH_2. The isomer **4a** revealed no correlation between either methyl substituent and this 2-hydrogen.

(1*S*,2*R*)- and (1*S*,2*S*)-1′-(((2-(Aminomethyl)-7,7-dimethyl-2-hydroxybicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro-(1*H*-indene-1,4′-piperidine). (6a and 6b). TMSCN (34 mg, 0.34 mmol) was added dropwise to a mixture of (1*S*)-1′-(((7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) (126 mg, 0.316 mmol) and zinc iodide (9 mg, 0.03 mmol) stirred in toluene (1 mL) under nitrogen. The mixture was heated to 100 °C for 2 h, at which time additional portions of TMSCN (34 mg) and zinc iodide (7 mg) were added. Heating was continued an additional 2 h. The mixture was then cooled and diluted with dry THF (4 mL). Lithium aluminum hydride (1 M in THF; 0.475 mL, 0.475 mmol) was added dropwise over 5 min, and the mixture was allowed to stir for 1 h at ambient temperature. The reaction mixture was then diluted with ether, and 10% sodium hydroxide solution was added dropwise until precipitate formation was complete. The mixture was filtered, and the ether layer was separated, washed with sodium bicarbonate and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and the residue chromatographed on silica gel eluted with 95/5/0.5 CH_2Cl_2/MeOH/NH_4OH. The product fractions were combined and concentrated to dryness, and the residue was crystallized from ether to give **6a** (77 mg, 57%): ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.13 (s, 3H), 1.3 (m, 1H), 1.45 (d, J = 14 Hz, 2H), 1.52 (d, J = 14 Hz, 1H), 1.7–1.9 (m, 4H), 2.05–2.25 (m, 5H), 2.7 (d, J = 15 Hz, 1H), 2.95 (d, J = 14 Hz, 1H), 3.1 (m, 3H), 3.43 (d, J = 14 Hz, 1H), 3.57 (d, J = 15 Hz, 1H), 3.96 (br d, J = 14 Hz, 2H), 6.8 (d, J = 6 Hz, 1H), 6.85 (d, J = 6 Hz, 1H), 7.2–7.4 (m, 4H). Preparative HPLC (0.1% TFA–acetonitrile/0.1% TFA–water) of a sample of crude **6** provided **6b** as the TFA salt: ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 6H), 1.37 (d, J = 13 Hz, 1H), 1.48 (br d, J = 13 Hz, 3H), 1.7–1.9 (m, 3H), 2.1–2.4 (m, 14H), 2.5 (br t, J = 11 Hz, 1H), 2.9 (d, J = 15 Hz, 1H), 3.05–3.2 (m, 3H), 3.35 (br s, 2H), 3.9 (br t, J = 15 Hz, 2H), 6.8 (s, 2H), 7.2–7.4 (m, 4H), 7.9 (br s, 2H).

(1*S*,2*S*)-1′-(((2-(Aminoethyl)-7,7-dimethyl-2-hydroxybicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) (8). Lithium aluminum hydride in THF (8.0 mL of a 1.0 M solution, 8.0 mmol) was cooled to 0 °C, treated dropwise with a solution of (1*S*,2*S*)-1′-(((2-(cyanomethyl)-7,7-dimethyl-2-hydroxybicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine)[1] (4.4 g, 10.0 mmol) in THF (37 mL), and the reaction mixture was stirred for 10 min in the cold. With rapid stirring, the reaction mixture was treated in succession with water (0.37 ml), 20% aqueous NaOH (0.4 mL), and water (1.46 mL) and then extracted with EtOAc (3 × 150 mL). The organic layers were combined, washed with water (25 ml) and brine (25 ml), dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. Chromatography on silica gel (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HOAc) provided product fractions which were pooled and concentrated to dryness. The residue was treated with saturated aqueous sodium carbonate and extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated to dryness to give amine **8** as a white foam (2.55 g, 57%): ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.17 (s, 3H), 1.3 (m, 1H), 1.45 (d, J = 14 Hz, 2H), 1.52 (d, J = 14 Hz, 2H), 1.7–2.2 (m, 8H), 2.7 (d, J = 14 Hz, 1H), 3.0 (dt, J_1 = 14 Hz, J_2 = 3 Hz, 1H), 3.05–3.3 (m, 3H), 3.69 (d, J = 14 Hz, 1H), 3.96 (br d, J = 14 Hz, 2H), 6.85 (m, 2H), 7.2–7.4 (m, 4H).

Method A. Acid Chloride Acylation: (1*S*,2*S*)-2,3-Dihydro-1′-(((7,7-dimethyl-2-(isonicotinylamino)bicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) (24). To (1*S*,2*S*)-2,3-dihydro-1′-(((2-amino-7,7-dimethylbicyclo[2.2.1]-hept-1-yl)methyl)sulfonyl))spiro(1*H*-indene-1,4′-piperidine) (**4b**; 50 mg, 0.125 mmol) stirred in methylene chloride (3 mL) under nitrogen at ambient temperature was added isonicotinoyl chloride dihydrochloride (22.4 mg, 0.125 mmol). The pH of the mixture was adjusted to ca. 9–9.5 with triethylamine (ca. 50 μL; E. Merck colorpHast sticks moistened with water). The mixture was stirred at ambient temperature until the reaction was complete (TLC: 10% MeOH/CH_2Cl_2). The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel (10% MeOH/CH_2Cl_2 elution). The product fractions were evaporated in vacuo, and the residue was dried in vacuo at ambient temperature to provide amide **24** (18 mg, 28%): ^{1}H NMR ($CDCl_3$) δ 1.0 (3H, s), 1.1 (3H, s), 1.15–2.3 (several m, 12H), 2.65 (m, 1H), 2.85–2.95 (m, 3H), 2.98 (d, J = 13 Hz, 1H), 3.08 (d, J = 13 Hz, 1H), 3.72 (br d, J = 11.3 Hz, 1H), 3.8 (br d, J = 11.3 Hz, 1H), 4.27 (br m, 1H), 7.1–7.25 (m, 3H), 7.7 (br d, J = 4.7 Hz, 1H), 7.76 (d, J = 6 Hz, 2H), 8.75 (d, J = 4.7 Hz, 2H).

Method B. Anhydride Acylation. Method N. TFAA Cyclization to Hydantoin: 1-[(1*S*,2*S*)-1-[[[2,3-Dihydrospiro-(1*H*-indene-1,4′-piperidin)-1′-yl]sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-3-(carboxymethyl)-2,5-dioxopyrrolidine (134). 2-(Carboxymethyl)succinic anhydride was prepared by dehydration of propane-1,2,3-tricarboxylic acid with acetic anhydride according to published procedures.[24] This anhydride (0.93 g, 5.88 mmol) and endo amine **4b** (2.4 g, 6.0

mmol) were stirred together in dry DMF (20 mL) at ambient temperature for 18 h. The solvent was removed under vacuum, and the residue was treated with water (80 mL) and 1 N HCl (3 mL) and extracted with ether (3×). The ether layer was dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give the succinic acid monoamide. This amide was combined with trifluoroacetic anhydride (5 mL) and toluene (100 mL) and then heated to reflux for 15 min while the excess trifluoroacetic anhydride was allowed to boil out. The mixture was then cooled and evaporated to dryness in vacuo. The residue was chromatographed on silica gel and eluted with 600/10/1/1 CH_2Cl_2/MeOH/HOAc/H_2O. The product fractions were combined and evaporated to dryness in vacuo, and the residue was evaporated three times from ether to give **134** as a white foam (1.39 g, 47%): ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.3 (m, 3H), 1.65 (br t, J = 13 Hz, 2H), 1.5–2.1 (m, 4H), 2.5 (m, 3H), 2.7–3.2 (m, 9H), 3.27 (dd, J_1 = 13 Hz, J_2 = 5 Hz), 3.6 (br d, J = 12 Hz, 1H), 3.76 (br d, J = 12 Hz, 1H), 4.63 (br m, 1H), 7.1–7.3 (m, 4H).

Method C. EDC Coupling: (1*S*,2*S*)-2,3-Dihydro-1′-(((7,7-dimethyl-2-((4-imidazolylacetyl)amino)bicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) Hydrochloride (35). (1*S*,2*S*)-1′-(((2-Amino-7,7-dimethylbicyclo[2.2.1.]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) (**4b**; 4.56 g, 11.3 mmol) was dissolved in 50 mL of DMF and the solution treated with 4-imidazoleacetic acid (2.30 g, 14.1 mmol), 1-hydroxybenzotriazole hydrate (HBT; 1.9 g, 14.1 mmol), and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC; 2.7 g, 14.1 mmol). The pH of the suspension was adjusted to 9.5 (moist colorpHast sticks) with triethylamine (ca. 4.65 mL, 33.4 mmol) and the reaction mixture stirred at 25 °C for 18 h. DMF was removed in vacuo, and the crude residue was quenched in water and extracted with EtOAc (3×). The combined organic layers were washed with water (1×) and brine (1×), dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. Column chromatography on silica gel (114/10/1 of CH_2Cl_2/MeOH/concentrated NH_4OH) gave **35** (5.29 g, 92%) as a white foam.

A 5.17-g (10.1-mmol) sample of this product was dissolved in 100 mL of EtOAc. While this mixture was stirred vigorously, a solution of HCl(g) in EtOAc was added dropwise until precipitation ceased. The slightly gummy mixture was stirred for 15 min at 25 °C and then evaporated to dryness in vacuo. The residue was three times treated with EtOAc and evaporated in vacuo, and the procedure was repeated with Et_2O. The white solid was triturated with Et_2O, giving 5.3 g (96%) of hydrochloride salt **35**: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.0 (s, 3H), 1.35 (br m, 1H), 1.45–1.55 (br t, J = 11 Hz, 2H), 1.63 (br t, J = 4 Hz, 1H), 1.7–1.8 (br m, 3H), 1.9–2.1 (m, 3H), 2.2 (br t, J = 12 Hz, 1H), 2.87 (t, J = 8 Hz, 3H), 2.92 (d, J = 15 Hz, 1H), 3.16 (d, J = 15 Hz, 1H), 3.2–3.4 (br, 4H), 3.55 (br d, J = 14z, 1H), 3.6 (d, 15 Hz, 1H), 3.66 (d, J = 15 Hz, 1H), 4.3–4.4 (br, 1H), 7.1–7.3 (4 H, m), 7.42 (s, 1H), 8.3 (d, J = 10 Hz, 1H), 9.0 (s, 1H).

Method D. BOP Coupling. Methods L/L′, HCl/TFA Boc Removal: (1*S*,2*S*)-2,3-Dihydro-1′-(((7,7-dimethyl-2-(*N*-L-histidinoylamino)bicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indene-1,4′-piperidine) (59). (1*S*,2*S*)-1′-(((2-Amino-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methyl)sulfonyl)spiro(1*H*-indan-1,4′-piperidine) (**4b**; 50 mg, 0.125 mmol), *N*-(*tert*-butoxycarbonyl)-L-histidine (29.9 mg, 0.125 mmol), and BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (Sequalog) (55 mg, 0.125 mmol) were combined in acetonitrile (3 mL). The pH of the mixture was adjusted to ca. 9–9.5 with diisopropylethylamine (ca. 50 μL; E. Merck colorpHast sticks moistened with water). The mixture was stirred at ambient temperature until the reaction was complete (TLC: 10% MeOH/CH_2Cl_2). The reaction was concentrated in vacuo to an oil which was dissolved in methylene chloride–ether (1:3) and washed with water, sodium bicarbonate (saturated, aqueous), water, 10% potassium bisulfate, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to an oil, which was purified by column chromatography on silica gel (10% methanol in methylene chloride elution). The combined product fractions were evaporated in vacuo, and the residue was triturated with ether–hexane to provide the Boc derivative (**59a**) of compound **59** as a white solid.

The entire lot of compound **59a** was dissolved in ethyl acetate (5 mL) and the solution stirred in an ice bath. The solution was saturated with hydrogen chloride gas, then stirred in the cold for 30 min (in place of HCl/ethyl acetate, 50% trifluoroacetic acid/methylene chloride at room temperature for 2 h is comparably effective). The solvent was removed under reduced pressure. Ether was added and removed in vacuo to give **59** (29 mg, 53%) as a white solid: ^{1}H NMR (CD_3OD) δ 1.02 (s, 3H), 1.08 (s, 3H), 1.45 (br m, 1H), 1.62 (br d, J = 13 Hz, 2H), 1.75 (br, 1H), 1.82–1.96 (br m, 4H), 2.1 (t, J = 15 Hz, 2H), 2.2 (br, 1H), 2.45 (br t, J = 12 Hz, 1H), 2.63 (d, J = 10 Hz, 4.5H), 2.93 (t, J = 15 Hz, 2H), 3.05 (t, J = 12 Hz, 2H), 3.02 (d, J = 15 Hz, 1H), 3.2 (d, J = 15 Hz, 1H), 3.57 (dd, J_1 = 16 Hz, J_2 = 4.7 Hz, 1H), 3.7 (br d, J = 12 Hz, 2H), 4.4 (m, 1H), 4.53 (br d, J = 12 Hz, 1H), 7.15 (m, 4H), 7.55 (s, 1H), 8.95 (s, 1H).

Method E. CDI Coupling: *N*-(5-Tetrazolyl)-[1-[1-[[(2,3-dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]-methyl]-(1*S*,2*S*)-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-2,5-dioxopyrrolidin-3-yl]acetamide (136). Acid **134** (70 mg, 0.13 mmol) and carbonyldiimidazole (20 mg, 0.12 mmol) were combined in THF (2 mL) and heated at reflux for 1.5 h. 5-Aminotetrazole (11 mg, 0.13 mmol) was added and the mixture heated for another 2 h. Additional portions of carbonyldiimidazole (4 mg) and 5-aminotetrazole (2 mg) were added, and heating continued for another 1 h. The mixture was cooled and evaporated in vacuo, and the residue was treated with 1 N HCl (2 mL) and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel eluted with 160/10/1/1 CH_2Cl_2/MeOH/HOAc/H_2O and the combined product fractions were evaporated to dryness in vacuo. The residue was triturated with ether to provide **136** (14.3 mg, 18%) as a white solid: mp 188–192 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.3 (m, 3H), 1.5–2.1 (m), 2.5 (m, 2H), 2.7–3.1 (m), 3.15–3.4 (m), 3.62 (br d, J = 15 Hz, 1H), 3.76 (br d, J = 12 Hz, 1H), 4.63 (br m, 1H), 7.1–7.3 (m, 4H), 11.9 (s, 1H).

Method F. Urea Formation via Isocyanate: *N*-[[(1*S*,2*S*)-1-[[(Spiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl]methyl]-*N*′-cyclohexylurea (103). Amine **6a** (51 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was stirred under nitrogen and treated with cyclohexyl isocyanate (16.5 mg, 0.13 mmol). The mixture was made basic (pH 9–9.5, moistened colorpHast sticks) with triethylamine, stirred at ambient temperature for 1 h, and then concentrated in vacuo. The residue was chromatographed on silica gel eluted with 4% EtOAc in hexane. The combined product fractions were evaporated to dryness, and the residue was evaporated twice from ether to provide urea **103** as a white solid (42 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.15 (s, 3H), 1.2–2.0 (m, 11H), 2.05–2.4 (m, 4H), 2.75 (d, J = 14 Hz, 1H), 3.1 (dt, J_1 = 12.5 Hz, J_2 = 3 Hz, 2H), 3.18 (dd, J_1 = 16 Hz, J_2 = 5 Hz, 1H), 3.5 (m, 1H), 3.63 (d, J = 14 Hz, 1H), 3.72 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 3.88 (br d, J = 14 Hz, 1H), 3.96 (br d, J = 14 Hz, 1H), 4.3 (d, J = 9 Hz, 1H), 4.75 (s, 1H), 5.62 (br dd, 1H), 6.83 (s, 2H), 7.2–7.4 (m, 4H).

Method P. Michael Addition. Method G. Urea Formation via 4-Nitrophenyl Carbamate of Amine 4b: *N*-[(1*S*,2*S*)-1-[[(2,3-Dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-*N*′-[(methylsulfonyl)ethyl]-*N*′-(4-imidazolylethyl)urea (90). Histamine (1.53 g, 13.3 mmol), stirred under nitrogen in methanol (20 mL) was treated with methyl vinyl sulfone (0.49 g, 4.6 mmol), and the mixture was stirred at ambient temperature for 4 h. The mixture was concentrated in vacuo and the residue chromatographed on silica gel eluted with 93/7/0.7 CH_2Cl_2/MeOH/NH_4OH. The product fractions were combined and evaporated in vacuo to give *N*-[2-(4-imidazolyl)ethyl]-*N*-[2-(methylsulfonyl)-ethyl]amine (1.05 g, da. 100%).

4-Nitrophenyl Carbamate of Amine 4b. Compound **4b** (1.4 g, 3.47 mmol) and (4-nitrophenyl)carbonyl chloride (0.67 g, 3.64 mmol) were combined in THF, treated with triethylamine (0.46 g, 4.54 mmol), and stirred at ambient temperature for 3 h. The mixture was concentrated in vacuo and the residue chromatographed on silica gel eluted with 1% EtOAc in CH_2Cl_2. The combined product fractions were evaporated to dryness in vacuo, and the residue was triturated with ether to give the 4-nitrophenyl carbamate of amine **4b** as a white solid (1.75 g, 89%).

Urea Formation. *N*-[2-(4-Imidazolyl)ethyl]-*N*-[2-(methylsulfonyl)ethyl]amine (229 mg, 1.06 mmol) was combined with the 4-nitrophenyl carbamate of amine **4b** (300 mg, 0.53 mmol)

in DMF (10 mL) under nitrogen, treated with triethylamine (160 μL), and stirred at ambient temperature for 1.5 h. The mixture was concentrated in vacuo and the residue chromatographed on silica gel eluted with 5% MeOH in CH_2Cl_2 followed by 95/5/0.5 CH_2Cl_2/MeOH/NH_4OH. The product fractions were combined and evaporated in vacuo and triturated with ether to give **90** as a white foam (256 mg, 75%): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.0 (s, 3H), 1.4 (m, 1H), 1.63 (br d, J = 13 Hz, 2H), 1.72 (br t, J = 4 Hz, 1H), 1.8–2.0 (m, 4H), 2.06 (t, J = 8 Hz, 2H), 2.15 (m, 1H) 2.4 (br t, J = 12 Hz, 1H), 2.9–3.0 (m, 9H), 3.13 (d, J = 14 Hz, 1H), 3.33 (m, 2H), 3.45 (m, 2H), 3.6 (m, 1H), 3.8 (m, 4H), 4.2 (m, 1H), 6.05 (d + d, J = 6 Hz, 1H), 6.95 (s, 1H), 7.1–7.3 (m, 4H), 7.8 (s, 1H).

Method H: Base-Mediated N-Alkylation/Acylation: 1-[(1*S*,2*S*)-1-[[(2,3-Dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-1,3-dioxo-5-hydroxypyrrolo[1,2-*c*]imidazolidine (137). The 4-nitrophenyl carbamate of amine **4b** (see preparation of compound **90** above) was coupled to *trans*-4-hydroxy-L-proline methyl ester according to the procedure of method G. The resulting urea (95 mg, 0.17 mmol) was stirred under nitrogen in dry DMF (4 mL) and treated with sodium hydride (3.1 mg of a 60% suspension in mineral oil, 0.078 mmol). The mixture was stirred for 2.5 h at ambient temperature and then concentrated in vacuo. (For N-alkylations, the NH compound/NaH mixture was stirred 2.5 h at ambient temperature, then treated with 1 equiv of alkylating agent such as iodomethane, stirred another 1 h at ambient temperature, then concentrated in vacuo, and chromatographed as described.) The residue was chromatographed on silica gel eluted with 98/2/0.2 CH_2Cl_2/MeOH/NH_4OH. The combined product fractions were evaporated in vacuo, and the residue was concentrated from ether (3×) to give **137** as a white solid (26 mg, 29%): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.5–2.3 (m, 15H), 2.5 (dd, J_1 = 14 Hz, J_2 = 4 Hz, 1H), 2.75 (d, J = 16 Hz, 1H), 2.8–3.0 (m, 5H), 3.2 (d, J = 12 Hz, 1H), 3.45 (d, J = 16 Hz, 1H), 3.5 (m, 1H), 3.75 (br d, J = 15 Hz, 1H), 3.81 (br d, J = 12 Hz, 1H), 3.83 (m, 2H), 4.3–4.5 (m, 2H), 4.75 (br s, 1H), 7.1–7.3 (m, 4H).

Method J. Reductive Alkylation: 1-[(1*S*,2*S*)-1-[[(2,3-Dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-5-methyl-2-oxopyrrolidine (131). Amine **4b** (163 mg, 0.37 mmol) in methanol (5 mL) containing 3A molecular sieves and triethylamine (29 mg, 0.28 mmol) was combined with levulinic acid (26 mg, 0.22 mmol) and sodium cyanoborohydride (15 mg, 0.24 mmol). The mixture was treated with an additional portion (7.5 mg) of triethylamine to adjust the pH to ca. 7 and stirred overnight under nitrogen at ambient temperature. The mixture was filtered and the filtrate concentrated in vacuo to a clear oil. This oil was treated with 0.5 N HCl and extracted with EtOAc, and the EtOAc layers were combined, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel eluted with 5% followed by 10% MeOH in CH_2Cl_2. The combined product fractions were evaporated in vacuo, and the residue was concentrated from ether. The resulting amino acid (88 mg, 0.17 mmol) was dissolved in dry DMF (50 mL) and treated with powdered sodium bicarbonate (143 mg, 1.7 mmol). The mixture was stirred in an ice bath, and diphenyl phosphorazidate (100 mg, 0.36 mmol) was added. The mixture was stirred in the cold overnight and then concentrated in vacuo. Water was added and the resulting mixture extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel eluted with 1% followed by 5% Et_2O in CH_2Cl_2. The combined product fractions were evaporated in vacuo, and the residue was concentrated from Et_2O to give **131** as a white solid (38 mg, 46%): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.1–2.6 (m, 16 H), 2.75 (d, J = 14 Hz, 1H), 2.8–3.0 (m, 5H), 3.2 (d, J = 15 Hz, 1H), 3.8 (br d + d, J = 14 Hz, 2H), 3.81 (d, J = 15 Hz, 1H), 4.0 (m, 1H), 4.1 (dd, 1H), 4.7 (br d, 1H), 7.1–7.3 (m, 4H).

Method M. Hydantoin Formation via Urea–Ester Cyclization. Method Q. Oxone Oxidation: 1-[(1*S*,2*S*)-1-[[(2,3-Dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-4-[(methylsulfonyl)ethyl]imidazolidine-2,5-dione (156). The 4-nitrophenyl carbamate of amine **4b** (see preparation of compound **90** above) was coupled with L-methionine methyl ester according to the procedure of method G. The resulting urea (96 mg, 0.16 mmol) in absolute ethanol (5 mL) was treated with sodium hydride (6 mg of a 60% suspension in mineral oil, 0.15 mmol) and the mixture stirred at ambient temperature for 4 h. The mixture was concentrated in vacuo and chromatographed on silica gel eluted with 1% MeOH in CH_2Cl_2. The combined product fractions were evaporated in vacuo, and the residue was concentrated from ether. The resulting hydantoin (80 mg, 0.143 mmol) was dissolved in methanol (50 mL). A solution of oxone (175 mg, 0.284 mmol) dissolved in the smallest volume of water possible was added slowly and the mixture stirred at ambient temperature for 4 h. The mixture was filtered and the filtrate concentrated in vacuo. The residue was treated with saturated aqueous sodium bicarbonate and extracted with EtOAc. The organic layers were combined, washed with sodium bicarbonate solution and then with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel eluted with 2% MeOH in CH_2Cl_2. The combined product fractions were evaporated in vacuo, and the residue was reconcentrated from ether to give **156** as a white solid (54 mg, 64%): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.55–1.7 (m, 2H), 1.7–2.2 (m, 10H), 2.25–2.6 (m, 3H), 2.75–3.0 (m, 8H), 3.1–3.2 (m, 1H), 3.25–3.6 (m, 3H), 3.7 (br d, 1H) 3.8 (d, J = 12 Hz, 1H), 4.15 + 4.2 (t + t, 1H), 4.5 (br t, 1H), 5.7 + 5.8 (s + s, 1H), 7.1–7.3 (m, 4 H).

1-[(1*S*,2*S*)-[[(2,3-Dihydrospiro-(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]hept-2-yl]-imidazolidine-2,4,5-trione (133). Amine **4b** was converted to the urea with ammonia by the procedure of method G. This urea (120 mg, 0.27 mmol) in CH_2Cl_2 (6 mL) was treated with oxalyl chloride (37.8 mg, 0.3 mmol) and the mixture heated at reflux for 3 h. An additional portion (10 mg) of oxalyl chloride was added and heating continued for another 2 h. The mixture was cooled and concentrated in vacuo. The residue was chromatographed on silica gel preparative plates eluted with 5% MeOH in CH_2Cl_2. The product band was sectioned and stirred with 6% MeOH in CH_2Cl_2 overnight. The slurry was filtered and the filtrate evaporated in vacuo. The residue was reconcentrated from ether to give **133** as a white solid (19 mg, 14%): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.55 (m, 2H), 1.75 (m, 6H), 2.0 (m, 4H), 2.2 (m, 1H), 2.75–3.1 (m, 5H), 3.1–3.4 (m, 2H), 3.5 (br d, 1H), 4.5 (br d, 1H), 7.1–7.3 (m, 4H).

(1*S*,2*S*)-2,3-Dihydro-1′-(((7,7-dimethyl-2-(((5-bromo-4-imidazolylacetyl)amino)bicyclo[2.2.1]hept-1-yl)methyl)-sulfonyl)spiro(1*H*-indene-1,4′-piperidine) Hydrochloride (41). Amide **35** (75 mg, 0.15 mmol) was dissolved in dry DMF (3 mL) and treated with *N*-bromosuccinimide (27.4 mg, 0.154 mmol), and the mixture was stirred for 2.5 h at ambient temperature. The solvent was removed in vacuo and the residue treated with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and evaporated in vacuo to dryness. The residue was chromatographed on silica gel eluted with 2% MeOH in CH_2Cl_2. The combined product fractions were evaporated in vacuo to give **41** as a white solid (80 mg, 85%: contains 26 mol % succinimide): ^1H NMR ($CDCl_3$) δ 0.97 (s, 3H), 1.02 (s, 3H), 1.3 (m, 1H), 1.5 (d, J = 13 Hz, 2H), 1.63 (m, 1H), 1.75 (br t, 3H), 1.97 (m, 4H), 2.2 (m, 1H), 2.55 (s, 1H), 2.7 (t, J = 12.5 Hz, 1H), 2.8–3.0 (m, 3H), 2.9 (d, J = 16 Hz, 1H), 3.1 (d, J = 16 Hz, 1H), 3.45 (s, 2H), 3.5 (br t, J = 14 Hz, 2H), 4.33 (m, 1H), 7.1–7.3 (m, 4H), 7.5 (s, 1H), 8.1 (d, J = 9 Hz, 1H), 12.2 (br s, 1H). Assignment of the bromo substituent to the 4-position was supported by the absence of an NOE enhancement of the amide methylene group upon irradiation of the imidazole ring proton.

3-Amino-1-[(1*S*,2*S*)-1-[[(2,3-dihydrospiro(1*H*-indene-1,4′-piperidin)-1′-yl)sulfonyl]methyl]-7,7-dimethylbicyclo[2.2.1]-hept-2-yl]pyrrolidin-2-one (159). Amine **4b** (1 g, 2.48 mmol) was coupled to N^{α}-Boc-L-methionine (0.62 g, 2.48 mmol) by the procedure of method C. The resulting amide was stirred in excess iodomethane overnight to provide the dimethyl sulfonium iodide which was obtained as a solid upon dilution of the reaction mixture with ether. This salt was stirred in a 1:1 mixture of DMF and CH_2Cl_2 (30 mL) under nitrogen, cooled in an ice bath, and treated with sodium hydride (200 mg of a 60% suspension in mineral oil, 5 mmol). The mixture was stirred in the cold for 3 h, quenched by addition of water, and extracted with EtOAc and CH_2Cl_2. The organic layers were combined, dried over sodium sulfate, filtered,

and evaporated in vacuo to dryness. The residue was chromatographed on silica gel eluted with 9/1 CH_2Cl_2/MeOH. The combined product fractions were evaporated to dryness in vacuo. The residue was deprotected by the procedure of method L, and the resulting free amine was purified by column chromatography on silica gel eluted with 9/1/1 CH_2Cl_2/MeOH/NH_4OH. Evaporation of the combined product fractions in vacuo gave **159** (0.3 g, 26% from **4b**): ^1H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.05 (s, 3H), 1.2–1.4 (m, 5H), 1.6–2.6 (m), 2.6–3.1 (m, 6H), 3.4–3.8 (m, 6H), 4.25 (m, 1H), 4.65 (br d, 1H), 7.1–7.3 (m, 4H), 8.5 (br s, 2H).

Acknowledgment. We gratefully acknowledge the efforts of Dr. Steven Pitzenberger, Ms. Joan Murphy, Ms. Susan Fitzpatrick, and Mr. Sandor Varga (NMR spectra), Mr. John Moreau (CHN analyses), Mr. Carl Homnick (HPLC), Dr. Haari Ramjit, and Mr. Arthur Coddington (mass spectra). We are also indebted to Dr. Michael Kaufman for solubility determinations on L-367,773, to Ms. Michelle Levy for the separation of isomer **6b**, and to Ms. Jean Kaysen for her efforts in the preparation of the manuscript.

Supplementary Material Available: A complete listing of molecular formula, method of preparation, HPLC purity, mass spectroscopic molecular ion, and combustion analytical data (CHN) for each new compound (10 pages). Ordering information is given on any current masthead page.

References

(1) Evans, B. E.; Leighton, J. L.; Rittle, K. E.; Gilbert, K. F.; Lundell, G. F.; Gould, N. P.; Hobbs, D. W.; DiPardo, R. M.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. Orally Active, Nonpeptide Oxytocin Antagonists. *J. Med. Chem.* **1992**, *35*, 3919–3927.
(2) Wilson, L., Jr.; Parsons, M. T.; Flouret, G. Inhibition of oxytocin-induced uterine contractions by an oxytocin antagonist in the pregnant baboon. *Am. J. Obstet. Gynecol.* **1991**, *165*, 456–460.
(3) Benson, R. T. Preterm Labor and the Low-Birth-Weight Infant. In *Obstetrics and Gynecology*, 4th ed.; Danforth, D. N., Ed.; Harper and Row: Philadelphia, 1982; pp 682–694.
(4) Olah, K. S.; Gee, H. The prevention of preterm delivery—can we afford to continue to ignore the cervix? *Br. J. Obstet. Gynaecol.* **1992**, *99*, 278–280.
(5) Leveno, K. J.; Cunningham, F. G. β-Adrenergic Agonists for Preterm Labor. *N. Engl. J. Med.* **1992**, *327*, 349–351.
(6) The Canadian Preterm Labor Investigators Group. Treatment of Preterm Labor with the Beta-Adrenergic Agonist Ritodrine. *N. Engl. J. Med.* **1992**, *327*, 308–312.
(7) Jenkins, J. S.; Nussey, S. S. The role of oxytocin: present concepts. *Clin. Endocrinol.* **1991**, *34*, 515–525.
(8) Lefebvre, D. L.; Giaid, A.; Bennett, H.; Lariviere, R.; Zingg, H. H. Oxytocin Gene Expression in Rat Uterus. *Science* **1992**, *256*, 1553–1555.
(9) Chibbar, R.; Miller, F. D.; Mitchell, B. F. Synthesis of Oxytocin in Amnion, Chorion, and Decidua May Influence the Timing of Human Parturition. *J. Clin. Invest.* **1993**, *91*, 185–192.
(10) Akerlund, M.; Stromberg, P.; Hauksson, A.; Andersen, L. F.; Lyndrup, J.; Trojnar, J.; Melin, P. Inhibition of uterine contractions of premature labour with an oxytocin analogue. *Br. J. Obstet. Gynaecol.* **1987**, *94*, 1040–1044.
(11) Pettibone, D. J.; Clineschmidt, B. V.; Kishel, M. T.; Lis, E. V.; Reiss, D. R.; Woyden, C. J.; Evans, B. E.; Freidinger, R. M.; Veber, D. F.; Cook, M. J.; Haluska, G. J.; Novy, M. J.; Lowensohn, R. I. Identification of an Orally Active, Nonpeptidyl Oxytocin Antagonist. *J. Pharmacol. Exp. Ther.* **1993**, *264*, 308–314.
(12) Pyman, F. L. *J. Chem. Soc.* **1911**, *99*, 2172–2183.
(13) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867–868.
(14) Finnegan, W. G.; Henry, R. A.; Lofquist, R. An Improved Synthesis of 5-Substituted Tetrazoles. *J. Am. Chem. Soc.* **1958**, *80*, 3908–3911.
(15) Webb, R. L.; Eggleston, D. L.; Labaw, C. S.; Lewis, J. J.; Wert, K. Diphenyl Cyancarbonimidate and Dichlorodiphenoxymethane as Synthons for the Construction of Heterocyclic Systems of Medicinal Interest. *J. Heterocyl. Chem.* **1987**, *24*, 275–278.
(16) Claremon, D. A.; Phillips, B. T. An Efficient Chemoselective Synthesis of Nitriles from Primary Amines. *Tetrahedron Lett.* **1988**, *29*, 2155–2158.
(17) Logusch, E. W. Facile Synthesis of D,L-Phosphinothricin from Methyl 4-Bromo-2-phthalimidobutyrate. *Tetrahedron Lett.* **1986**, *27*, 5935–5938.
(18) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. α-Nitro Ketones and Esters from Acylimidazoles. *J. Org. Chem.* **1982**, *47*, 4040–4045.
(19) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists. *J. Med. Chem.* **1988**, *31*, 2235–2246.
(20) Evans, B. E.; Bock, M. G. Promiscuity in Receptor Ligand Research. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; JAI Press, Inc.: Greenwich, CT, 1993; Vol. 2, pp 111–152.
(21) Evans, B. E. MK-329: A Non-peptide Cholecystokinin A Antagonist. *Drug Dev. Res.* **1993**, *29*, 255–261.
(22) Kimura, T.; Tanizawa, O.; Mori, K.; Brownstein, M. J.; Okayama, H. Structure and expression of a human oxytocin receptor. *Nature* **1992**, *356*, 526–529.
(23) Bergstahler, A. W. In *Reagents for Organic Synthesis*; Fieser, L. F., Fieser, M., Eds.; Wiley: New York, 1967; p 729.
(24) Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. Synthesis of Functional Chelating Diphosphines Containing the Bis[2-(diphenylphosphino)ethyl]amino Moiety and the Use of These Materials in the Preparation of Water-Soluble Diphosphine Complexes of Transition Metals. *J. Org. Chem.* **1981**, *46*, 2861–2867.