Bicyclic Thiazolidine Lactam Peptidomimetics of the Dopamine Receptor Modulating Peptide Pro-Leu-Gly-NH_2

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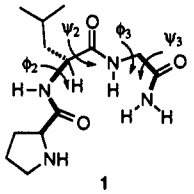
Bicyclic thiazolidine lactam peptidomimetics **3–5** have been synthesized as potential analogues of the dopamine receptor modulating peptide Pro-Leu-Gly-NH_2 (PLG). Peptidomimetics **3** and **4** were designed to constrain two, ψ_2 and ϕ_3, of the four torsion angles that define a β-turn to values approximating those found for a type-II β-turn, while **5** was designed as a compound that could not achieve a β-turn conformation. Peptidomimetics **3** and **4** were found to enhance the binding of the dopamine receptor agonist ADTN to the dopamine receptor, while **5** was found to be inactive. Like PLG the dose–response curves for **3** and **4** were bell-shaped in nature with the maximum effect occurring at a concentration of 1 μM. Both **3** and **4** were more effective than PLG in enhancing the binding of ADTN to dopamine receptors. The 5,5-bicyclic thiazolidine lactam peptidomimetic **3** enhanced the binding of ADTN by almost 200%, while the 6,5-bicyclic thiazolidine lactam peptidomimetic **4** enhanced the binding of ADTN by about 75%. These results provide further evidence in support of the hypothesis that the bioactive conformation of PLG is a type-II β-turn.

The tripeptide Pro-Leu-Gly-NH_2 (PLG, **1**) selectively enhances the binding of dopamine receptor agonists to dopamine receptors in the mammalian central nervous system.[1-3] PLG is also able to down-regulate supersensitized dopamine receptors produced by neuroleptic drugs.[4,5] In an attempt to elucidate the bioactive conformation of PLG, we previously synthesized a series of lactam analogues as in **2** where X was varied to give



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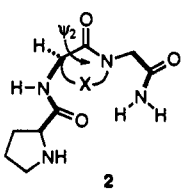

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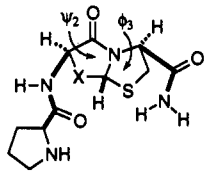
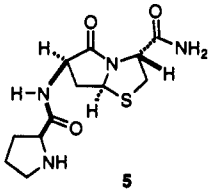


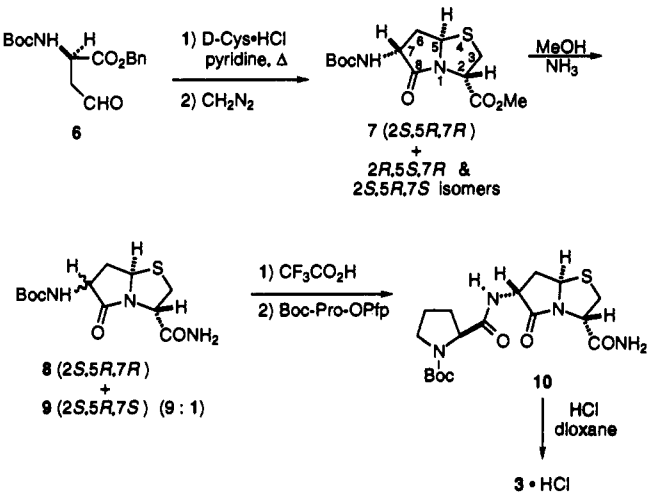
3: X = CH_2
4: X = CH_2CH_2



5

different sized or functionalized lactam rings.[6,7] The ability of these conformationally constrained analogues to enhance the binding of the agonist 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) to dopamine receptors led us to postulate that the bioactive conformation of PLG is a type-II β-turn. These conformationally constrained analogues are still flexible, however, and thus potentially can exist in a number of conformations, since only the ψ_2 torsional angle is constrained in this series. This is seen, for example, in the case of **2** where X = CH_2CH_2. NMR temperature and solvent composition studies suggest that this compound exists in a bend conformation,[8] while an extended conformation is found in the crystal structure of this compound.[9]

Scheme I



In order to further test our hypothesis that the bioactive conformation of PLG is a type-II β-turn, we have synthesized the bicyclic thiazolidine lactam peptidomimetics **3** and **4** in which two, ψ_2 and ϕ_3, of the four torsion angles that define a β-turn are now constrained to values approximating those found for a type-II β-turn. Analogue **5** was synthesized as a compound that would be incapable of achieving a β-turn conformation, since the carboxamide and (pyrrolidinylcarbonyl)amino groups are anti to one another.

Syntheses

The synthesis of peptidomimetic **3** is depicted in Scheme I. Construction of the 5,5-bicyclic thiazolidine lactam ring system was carried out in a manner similar to that previously reported by Baldwin et al.[10] Condensation of aldehyde **6** with D-cysteine gave predominately the desired (2*S*,5*R*,7*R*)-5,5-bicyclic amino acid which was directly converted to methyl ester **7** to facilitate its isolation and

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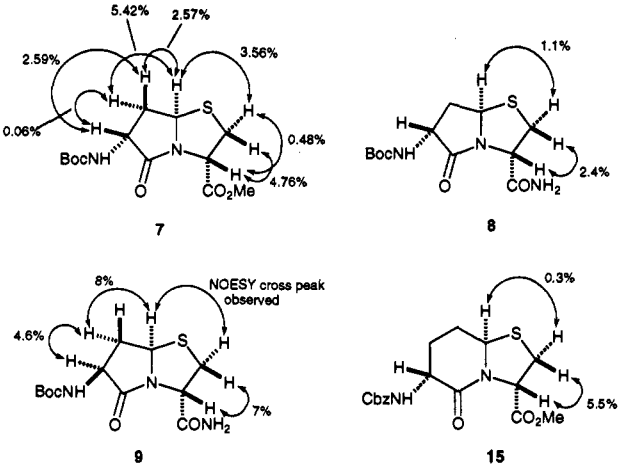
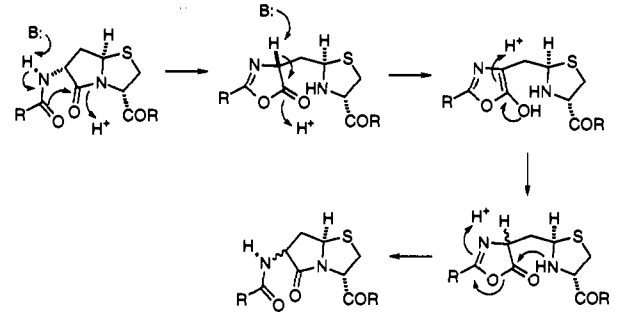


Figure 1. NOEs observed for the bicyclic thiazolidine lactam intermediates **7–9** and **15**.

Scheme II

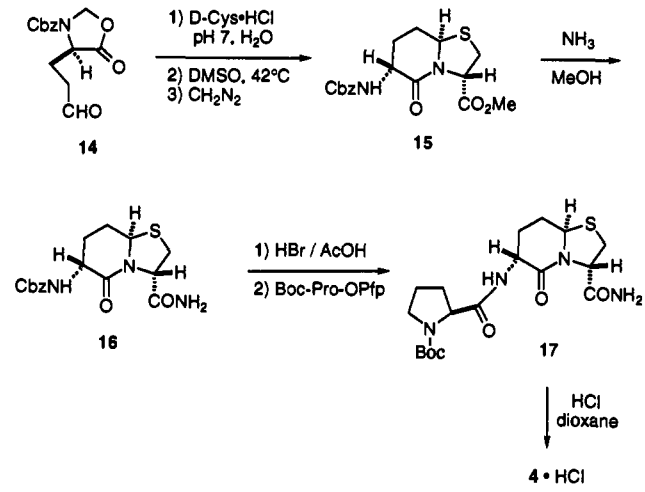


characterization. The configuration of the newly formed chiral bridgehead carbon in **7** was determined through the use of NOE experiments (Figure 1). Minor quantities of the diastereoisomeric (2*R*,5*S*,7*R*)- and (2*S*,5*R*,7*S*)-bicyclic thiazolidine lactams were also formed during the condensation reaction, a result also observed before by Baldwin et al.[10] with their derivatives of this system.

Treatment of **7** with NH_3 in MeOH yielded a mixture of two diastereoisomers in a ratio of 9:1 with the major component being the desired (2*S*,5*R*,7*R*)-isomer **8**. NOE (Figure 1) and NOESY (supplementary material) experiments carried out on both diastereoisomeric amides indicated that the minor diastereoisomer, **9**, arose through epimerization at the C-7 position. This conclusion was verified when the enantiomer of **9**, compound **12**, was made during the course of synthesizing the bicyclic thiazolidine lactam **5**. A similar result was seen when **7** was deprotected and then coupled to Boc-L-Pro-OH and the resulting ester amidated with NH_3 in MeOH. In the case of this N-acylated bicyclic lactam, however, greater epimerization at C-7 took place, since the ratio of the two diastereoisomers formed was 3:1. A possible mechanism for the epimerization observed during the above amidation reactions is depicted in Scheme II. It involves the formation of an oxazolone intermediate in a manner analogous to the racemization mechanism thought to occur during peptide synthesis[11] with the release of ring strain as the possible driving force for oxazolone formation in the present case.

The *tert*-butoxycarbonyl group of bicyclic amide **8** was removed, and the product which was obtained was coupled to Boc-Pro-OH to give **10**. Initially, the coupling reaction was carried out using the mixed anhydride method, but this method only provided **10** in a 30% yield. Other methods of coupling were investigated including dicyclohexylcarbodiimide/1-hydroxybenzotriazole, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), and the *p*-nitrophenyl ester of Boc-Pro-OH, but these methods also only gave **10** in yields of 30% or less. Ultimately, it was found that carrying out the coupling reaction with the pentafluorophenyl ester of Boc-Pro-OH provided **10** in yields greater than 70%. Deprotection of **10** provided peptidomimetic **3** as its hydrochloride salt.

Scheme III

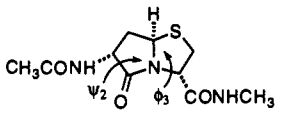


Diastereoisomeric 5,5-bicyclic thiazolidine lactam **5** was synthesized by initially condensing **6** with L-cysteine and then esterifying the resulting bicyclic acid to give methyl (2*R*,5*S*,7*R*)-1-aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (**11**). This material was converted to **5** via intermediates (2*R*,5*S*,7*R*)-1-aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (**12**), and (2*R*,5*S*,7*R*)-1-aza-7-[[[1-(*tert*-butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (**13**) employing the same set of reactions that were used in going from **7** to **3** in Scheme I.

The synthesis of pepidomimetic **4** is outlined in Scheme III. The starting material for this synthesis was the oxazolidinone aldehyde **14** which was synthesized by the route described by Lee and Miller.[12] This aldehyde was condensed with D-cysteine to give a thiazolidine adduct which was immediately cyclized by heating to form the 6,5-bicyclic thiazolidine lactam ring system. The resulting 6,5-bicyclic amino acid was directly converted to its methyl ester **15**. The relative stereochemistry of the bridgehead carbon of **15** was determined by NOE studies (Figure 1). A strong NOE was observed between the 2-H and one of the CH_2S hydrogens. No NOE was observed between the 2-H and the bridgehead hydrogen. The methyl ester was then converted to primary amide **16**. In contrast to the 5,5-bicyclic system described above, no epimerization was detected at the C-8 position of **16** during this amidation reaction. Removal of the *N*-(benzyloxycarbonyl) group from **16** followed by coupling of the resulting product with the pentafluorophenyl ester of Boc-Pro-OH gave **17**. Removal of the *tert*-butoxycarbonyl protecting group from **17** gave peptidomimetic **4** as its hydrochloride salt.

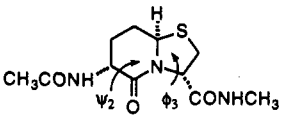
The three bicyclic thiazolidine lactams **3–5** were all obtained as extremely hygroscopic solids on which it was difficult to obtain suitable elemental analyses. They were thus analyzed by reversed-phase HPLC. Compound **3**

Table I. Torsion Angles and Relative Energies of Minimized Conformations of the Bicyclic Thiazolidine Lactams 18 and 19[a]



18

conformer	rel energy (kcal/mol)	torsion angle (deg) ψ_2	torsion angle (deg) ϕ_3
A	0.00	109.3	77.4
B	2.10	89.1	80.2
C	2.10	90.8	80.2
D	2.10	88.9	80.2
E	2.12	90.7	80.0
F	3.58	140.9	93.4



19

conformer	rel energy (kcal/mol)	torsion angle (deg) ψ_2	torsion angle (deg) ϕ_3
A	0.00	132.0	69.1
B	2.64	66.9	88.0
C	3.50	173.5	78.6
D	4.16	150.1	75.7
E	4.57	143.1	76.0
F	5.48	73.9	87.9

[a] Torsion angles and relative energies were determined from structures generated and minimized using the random incremental pulse search (RIPS) program developed by Ferguson and Raber (QCPE no. 588) combined with Allinger's MM2 program.[13,14] In the present study the torsion angle tolerance was set to 12°, thereby necessitating that torsion angles of unique structures differ by this amount. Conformers within 3 kcal/mol of the lowest energy conformer comprise 99% of the equilibrium population of conformers that are present at room temperature.

was found to be 98% pure, while compounds 4 and 5 were found to be homogenous by HPLC analysis.

Molecular Modeling

A molecular modeling study was carried out on the *N*-acetyl-*N'*-methylamide model compounds 18 and 19 using the random incremental pulse search (RIPS) program of Ferguson and Raber[13,14] in an effort to predict the manner in which the 5,5- and 6,5-bicyclic thiazolidine lactam ring systems would restrict the ψ_2 and ϕ_3 torsion angles. The ψ_2 and ϕ_3 torsion angles and relative energies of the six lowest energy conformations obtained for 18 and 19 with the RIPS program are listed in Table I. The lowest energy conformer of 18, conformer A, was found to possess ψ_2 and ϕ_3 torsion angles of 109.3° and 77.4°, respectively. The ψ_2 and ϕ_3 values that were obtained for the lowest energy conformer of the 6,5-bicyclic model compound 19, on the other hand, were 132.0° and 69.1°, respectively. Previously, the ψ_2 and ϕ_3 torsion angles for a compound containing the enantiomeric form of the 6,5-bicyclic thiazolidine lactam system used in this study were found through X-ray crystallography to be −161° and −69°, respectively.[15]

Pharmacology

The assay used to determine the ability of PLG and its analogues to modulate dopamine receptors involves measuring the ability of a compound to enhance the binding of the dopamine receptor agonist [^{3}H]ADTN to dopamine receptors. This in vitro assay uses a crude preparation of dopamine receptors isolated from freshly dissected bovine caudate and has been described in detail in previous papers.[1,6] In this binding assay, PLG typically enhances the binding of ADTN by 25–40% at a concentration of 1 μM.

In the present study, bicyclic thiazolidine lactam peptidomimetics 3 and 4 have been found to enhance the binding of ADTN to dopamine receptors. The dose response curves for 3 and 4 are shown in Figure 2. Like PLG, they both possess bell-shaped dose response curves. Although both of these analogues produce their maximum effect at the same concentration as does PLG (10^{-6} M), they appear to be much more effective than PLG. The 6,5-bicyclic thiazolidine lactam peptidomimetic 4 enhances the binding of ADTN by about 75%, whereas the 5,5-bicyclic thiazolidine lactam peptidomimetic 3 enhances the binding of ADTN by almost 200%. Thus, 3 and 4 are about 5 and 2 times as effective, respectively, as PLG in enhancing the binding of ADTN to dopamine receptors. The isomeric 5,5-bicyclic thiazolidine lactam 5 was found to be inactive.

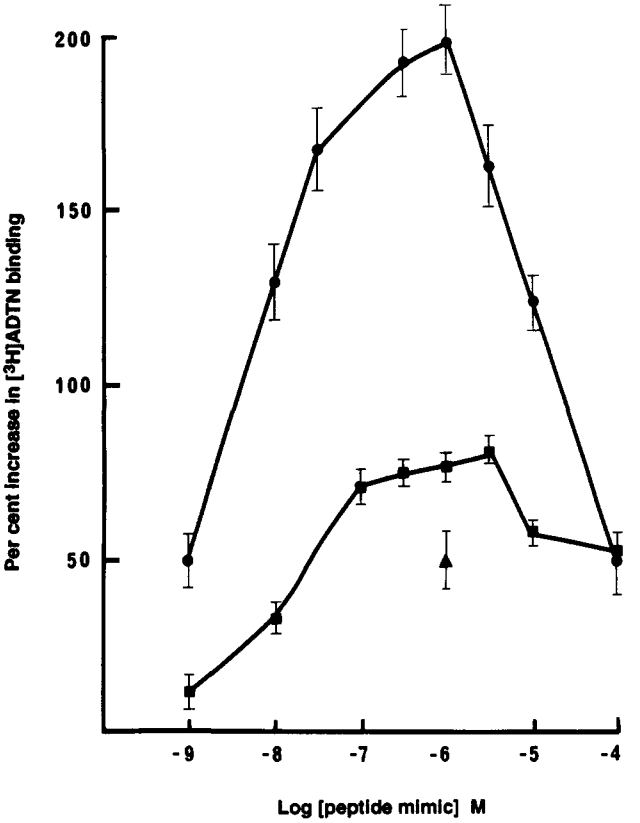


Figure 2. Percent enhancement over the control value of specific [^{3}H]ADTN binding to striatal membranes incubated with the indicated concentrations of peptidomimetics 3 (●) and 4 (■) and PLG (▲). In these experiments PLG was used for comparison purposes and was thus tested only at the concentration at which it produces ts maximum effect. A complete dose–response curve for PLG can be found in ref. 6. Results are the means ± SEM of three to four experiments each carried out in triplicate.

Discussion

Previously, we postulated that the bioactive conformation of PLG is a type-II β-turn.[6,7] This hypothesis was put forth in light of computational calculations[16] and NMR[17] and X-ray[18] spectroscopic analyses that indicated that this was a preferred conformation for PLG. We

initially tested this hypothesis by designing and synthesizing a series of lactam analogues of PLG, **2**, in which the ψ_2 torsion angle was restricted to different values.[6,7] In this series of conformationally restricted PLG analogues, those lactams which possessed a ψ_2 value around the 120° value of an ideal type-II β-turn were, like PLG, able to enhance the binding of the agonist ADTN to the dopamine receptor.

In the present study, we have designed and synthesized the more conformationally restricted bicyclic thiazolidine lactams **3** and **4** as possible peptidomimetics of PLG. Although the enantioner of the 6,5-bicyclic thiazolidine lactam system of **4** has been reported previously by Nagai and Sato[19] as a β-turn mimic, the 5,5-bicyclic system of **3** has not, to our knowledge, been used before in this regard. Both of these bicyclic systems restrict two, ψ_2 and ϕ_3, of the four torsion angles that define a β-turn. Molecular modeling studies that were carried out on the model compounds **18** and **19** showed that both the 5,5- and 6,5-bicyclic thiazolidine lactam ring systems restrict the ψ_2 and ϕ_3 torsion angles to values which are quite close to those of an ideal type-II β-turn ($\psi_2 = 120°$, $\phi_3 = 80°$).[20] As might be expected, the most significant difference between the 5,5- and 6,5-bicyclic thiazolidine lactam constraints was found to lie in their different ψ_2 torsion angles (109° versus 132°).

The results of the present study show that the two compounds, **3** and **4**, which contain the bicyclic thiazolidine lactam constraints capable of mimicking a type-II β-turn are able to modulate dopamine receptors, while analogue **5** which possesses a bicyclic system that precludes formation of a type-II β-turn is inactive. Both peptidomimetics **3** and **4** were found to be more effective than PLG in enhancing the binding of the dopamine receptor agonist ADTN to dopamine receptors. Furthermore, **3** which possesses the 5,5-bicyclic system showed greater effectiveness than the peptidomimetic containing the 6,5-bicyclic system, compound **4**. Since a major difference between the 5,5- and 6,5-bicyclic thiazolidine lactam systems is the magnitude of the ψ_2 torsion angle, this may be a leading factor behind the difference in activity observed for **3** and **4**.

Several of the PLG analogues that have been made before have shown greater effectiveness than PLG in enhancing the binding of ADTN to dopamine receptors. These include several PLG analogues possessing cyclic amino acid residues in place of the glycinamide residue[1] and several of the compounds in the lactam series **2**.[7] In these previous cases the magnitude of enhancement was on the same order as that observed for peptidomimetic **4** in this study. The basis behind the greater enhancement in ADTN binding to dopamine receptors seen for such analogues is not known at present, although we speculate that these analogues differ in their ability to prevent the GTP-induced conversion of the high affinity state of the dopamine receptor to the low affinity state.[3,21]

In summary, the results of the present study show that the (2*S*,5*R*,7*R*)-5,5- and (2*S*,5*R*,8*R*)-6,5-bicyclic thiazolidine lactam constraints are potentially good mimics of a type-II β-turn. In addition, the results of the present study provide additional support for the hypothesis that the bioactive conformation of PLG is a type-II β-turn.

Experimental Section

General Aspects. Flash column chromatography was carried out on silica gel, Merck, grade 60 (240–400 mesh, 60 Å) from Aldrich Chemical Co., Inc. Thin-layer chromatography (TLC) was carried out on Analtech 250-μm silica gel HLF Uniplates. Visualization was achieved with either UV or I_2. HPLC was carried out on a Waters Associates Delta-Pak C18 column. Elution of the column was done with 1% aqueous HCl, and the eluant was monitored at $\lambda = 229$ nm. ^1H and ^{13}C NMR spectra were measured in either $CDCl_3$, D_2O, or DMOS-d_6 at 300 and 75.5 MHz, respectively. The following internal references were used: tetramethylsilane (δ 0.00) or HOD (δ 4.75) for ^1H and $CHCl_3$ (δ 77.06) or dioxane (δ 66.5) for ^{13}C. For those compounds where rotamers about the carbamate bond were observed both ^1H and ^{13}C resonances are listed.

Methyl (2*S*,5*R*,7*R*)-1-Aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (7). Aldehyde **6** (0.35 g, 1.1 mmol) and D-cysteine·HCl monohydrate (0.25 g, 1.4 mmol) in pyridine (30 mL) were stirred with molecular sieves (4 Å) for 3 h under Ar. The mixture was brought to reflux where it was stirred for 18 h. The reaction mixture was filtered to remove the molecular sieves, and the sieves were washed with a small amount of MeOH. The pyridine and MeOH were removed in vacuo and the residue partitioned between EtOAc and 5% citric acid. The organic phase was extracted with an additional portion of 5% citric acid, washed with saturated NaCl, dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in MeOH and treated with an Et_2O solution of CH_2N_2. The solvents and excess CH_2N_2 were removed in vacuo, and the residue which was obtained was subjected to flash chromatography (hexane/EtOAc (7:3)) to give 0.24 g (68%) of **7** as an oil. This material could not be separated from an unknown impurity and thus was used without further purification. ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H, $C(CH_3)_3$), 2.3–2.5 (m, 1 H, CH_2), 2.5–2.8 (m, 1 H, CH_2), 3.35 (dd, J = 4.8 and 15 Hz, 1 H, CH_2S), 3.45 (dd, J = 8.4 and 15 Hz, 1 H, CH_2S), 3.66 (s, 3 H, OCH_3), 4.25–4.42 (m, 1 H, 7-H), 5.0–5.05 (m, 1 H, 2-H), 5.14 (d, J = 7.2 Hz, 1 H, NCHS), 5.2 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 28.08 ($C(CH_3)_3$), 36.92 (CH_2), 42.98 (CH_2S), 51.94 (OCH_3), 52.83 (7-C), 59.19 (2-C), 64.65 (NCS), 81.0 ($C(CH_3)_3$), 155.26 (urethane C=O), 170.0 (C=O), 173.76 (C=O).

(2*S*,5*R*,7*R*)- and (2*S*,5*R*,7*S*)-1-Aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (8 and 9). Bicyclic ester **7** (0.2 g, 0.63 mmol) was treated for 3 h with methanolic ammonia. The solvent was evaporated and the residue chromatographed on a silica gel column (EtOAc/hexane (5:2)) to give 0.13 g (70%) of **8** and 0.02 g (10%) of **9** as oils.

8: TLC R_f = 0.14 (EtOAc/hexane (5:2)); $[\alpha]_D$ +188.0° (*c* 5.03, MeOH); ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H, $C(CH_3)_3$), 2.4–2.6 (m, 2 H, CH_2), 3.48 (dd, J = 8.55 and 11.6 Hz, 1 H, CH_2S), 3.6 (dd, J = 5.5 and 11.6 Hz, 1 H, CH_2S), 4.1–4.2 (m, 1 H, 7-H), 4.8 (dd, J = 5.5 and 8.55 Hz, 1 H, 2-H), 5.16–5.2 (m, 1 H, NCHS), 5.7 (br s, 1 H, NH), 5.95 (s, 1 H, NH_2), 7.05 (s, 1 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 28.21 ($C(CH_3)_3$), 31.49 (CH_2), 36.23 (CH_2S), 53.71 (7-C), 58.18 (2-C), 64.11 (NCS), 80.78 ($C(CH_3)_3$), 155.46 (urethane C=O), 171.72 (C=O), 173.41 (C=O), FAB MS *m/z* 302 $(MH)^+$. Anal. ($C_{12}H_{19}N_3O_4S$) C, H, N. S.

9: TLC R_f = 0.1 (EtOAc/hexane (5:2)); $[\alpha]_D$ +175° (*c* 0.04, MeOH); ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H, $C(CH_3)_3$), 1.95–2.1 (m, 1 H, CH_2), 3.1–3.2 (m, 1 H, CH_2), 3.33 (dd, J = 7.2 and 11.7 Hz, 1 H, CH_2S), 3.78 (dd, J = 6.3 and 11.7 Hz, 1 H, CH_2S), 4.7–4.8 (m, 1 H, 7-H), 4.75–4.85 (m, 1 H, 2-H), 4.95–5.1 (m, 1 H, NCHS), 5.0–5.15 (m, 1 H, NH), 5.5 (s, 1 H, NH_2), 6.7 (s, 1 H, NH_2).

(2*S*,5*R*,7*R*)-1-Aza-7-[[[1-(*tert*-butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (10). Carboxamide **8** (0.17 g, 0.52 mmol) was treated with CF_3CO_2H under Ar for 45 min, after which time the CF_3CO_2H was removed under high vacuum. The CF_3CO_2H salt which was obtained was dissolved in 10 mL of dry THF. To this solution was added *N*-methylmorpholine (0.09 mL, 0.82 mmol). The mixture was stirred for 30 min under Ar, at which time (*tert*-butoxycarbonyl)-L-proline pentafluorophenol ester (0.31 g, 0.82 mmol) was added. This solution was stirred at room temperature for 22 h. The THF was removed under vacuum, and the residue which was obtained was dissolved in EtOAc. The EtOAc solution was washed with 10% citric acid and saturated NaCl and dried over $MgSO_4$. The EtOAc was removed under vacuum and the residue subjected to silica gel column chroma-

tography (2% MeOH in EtOAc) to give 0.16 g (77%) of **10** as an oil which turned to a glassy solid when dried under high vacuum: mp 114–116 °C (foam); $[\alpha]_D$ +87.2° (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H, $C(CH_3)_3$), 1.78–1.94 (m, 3 H, Pro γ-CH_2 and Pro β-CH), 2.18 (br s, 1 H, Pro β-CH), 2.35–2.5 (m, 1 H, 6-CH_2), 2.5–2.57 (m, 1 H, 6-CH_2), 3.2–3.5 (m, 2 H, Pro δ-CH_2), 3.46 (dd, *J* = 8.4 and 11.4 Hz, 1 H, CH_2S), 3.55 (dd, *J* = 5.4 and 11.4 Hz, 1 H, CH_2S), 4.0–4.4 (m, 2 H, Pro α-CH and 7-CH), 4.78 (dd, *J* = 5.5 and 8.4 Hz, 1 H, 2-CH), 5.17 (br s, 1 H, NCHS), 6.26 (s, 1 H, NH_2), 7.04 (br s, 1 H, NH_2), 7.52 and 7.96 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.97 (Pro γ-C), 23.6 and 24.3 (Pro β-C), 28.1 ($C(CH_3)_3$), 30.9 (6-C), 36.3 (CH_2S), 46.7 and 47.0 (Pro δ-C), 52.5 (Pro α-C), 58.19 and 58.24 (7-C), 59.4 and 60.6 (2-C), 64.1 and 64.2 (NCS), 80.4 ($C(CH_3)_3$), 154.4 and 155.3 (urethane C=O), 171, 171.9, 174 (C=O); FAB MS *m/z* 399 $(MH)^+$. Anal. ($C_{17}H_{26}N_4O_6S$) C, H, N, S.

(2*S*,5*R*,7*R*)-1-Aza-7-[(2(*S*)-pyrrolidinylcarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide Hydrochloride (3·HCl). Protected amide **10** (0.02 g, 0.05 mmol) was treated with 4 N HCl in dioxane (2 mL) under Ar for 20 min, after which time the dioxane solution was frozen and lyophilized to give 0.017 g (85%) and **3** as a highly hygroscopic white solid: $[\alpha]_D$ +110.8° (*c* 0.87, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.77–1.91 (m, 3 H, Pro β-CH and γ-CH_2), 2.26–2.35 (m, 2 H, Pro β-CH and 6-CH_2), 2.44–2.52 (m, 1 H, 6-CH_2), 3.1–3.2 (m, 3 H, Pro δ-CH_2 and CH_2S), 3.2 (dd, *J* = 4.88 and 11.29 Hz, 1 H, CH_2S), 4.18–4.2 (m, 1 H, Pro α-CH), 4.47 (m, 1 H, 7-CH), 4.66 (dd, *J* = 4.88 and 8.24 Hz, 1 H, 2-CH), 5.18 (dd, *J* = 2.45 and 7.02 Hz, 1 H, NCHS), 7.35 (s, 1 H, NH_2), 7.6 (s, 1 H, NH_2), 8.6 (br s, 1 H, $^+NH_2$), 9.43 (d, *J* = 8.24 Hz, 1 H, NH), 9.8 (br s, 1 H, $^+NH_2$); ^{13}C NMR (DMSO-d_6) δ 23.56 (Pro γ-C), 29.55 (Pro β-C), 30.13 (6-C), 30.13 (6-C), 36.88 (CH_2S), 45.61 (Pro δ-C), 50.84 (Pro α-C), 58.77 (7-C), 58.89 (2-C), 64.4 (NCS), 168.22 (C=O), 171.03 (C=O), 173.49 (C=O); FAB HRMS *m/z* 299.1172 ($C_{12}H_{19}N_4O_3S$ + H^+ requires 299.1178); HPLC analysis (C18, 1% aqueous HCl, 2 mL/min) indicated the product had a t_R = 36.6 min and a purity of 98%.

Methyl (2*R*,5*S*,7*R*)-1-Aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (11). Aldehyde **6** (0.35 g, 1.1 mmol) and L-cysteine·HCl (0.25 g, 1.6 mmol) were reacted in the same manner as described above for compound **7** to give 0.16 g (46%) of **11** as a white solid: mp 143–144 °C; $[\alpha]_D$ −196.3 (*c* 0.59, $CHCl_3$); TLC R_f = 0.14 (hexane/EtOAc (3:2)); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, $C(CH_3)_3$), 1.9–2.05 (m, 1 H, CH_2), 3.1–3.25 (m, 1 H, CH_2), 3.3–3.4 (m, 2 H, CH_2S), 3.76 (s, 3 H, OCH_3), 4.55–4.7 (m, 1 H, 7-H), 5.05–5.2 (m, 3 H, 2-H, NH and NCHS); ^{13}C NMR ($CDCl_3$) δ 28.2 ($C(CH_3)_3$), 35.0 (CH_2), 38.8 (CH_2S), 52.91 (OCH_3), 54.17 (7-C), 57.55 (2-C), 61.67 (NCS), 80.12 ($C(CH_3)_3$), 155.29 (urethane C=O), 169.5 (C=O), 171.5 (C=O); FAB MS *m/z* 317 $(MH)^+$. Anal. ($C_{13}H_{20}N_2O_5S$) C, H, N, S.

(2*R*,5*S*,7*R*)-1-Aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (12). Bicyclic ester **11** (0.15 g, 0.47 mmol) was treated with methanolic ammonia and gave after workup 0.13 g (92%) of **12** as a white solid: mp 169–171 °C; $[\alpha]_D$ −177° (*c* 0.47, MeOH); TLC R_f = 0.1 (EtOAc/hexane (5:2)); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H, $C(CH_3)_3$), 1.96–2.12 (m, 1 H, CH_2), 3.04–3.2 (m, 1 H, CH_2), 3.34 (dd, *J* = 7.3 and 12 Hz, 1 H, CH_2S), 3.77 (dd, *J* = 6.4 and 12 Hz, 1 H, CH_2S), 4.7–4.8 (m, 1 H, 7-H), 4.8 (t, *J* = 7 Hz, 1 H, 2-H), 5.03 (dd, *J* = 6.41 and 7.3 Hz, 1 H, NCHS), 5.1 (br s, 1 H, NH), 5.56 (s, 1 H, NH_2), 6.74 (s, 1 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 28.26 ($C(CH_3)_3$, 34.48 (CH_2), 37.40 (CH_2S), 54.56 (7-C), 58.75 (2-C), 62.4 (NCS), 80.51 ($C(CH_3)_3$), 154.74 (urethane (C=O), 170.41 (C=O), 173.06; FAB MS *m/z* 302 $(MH)^+$. Anal. ($C_{12}H_{19}N_3O_4S$) C, H, N, S.

(2*R*,5*S*,7*R*)-1-Aza-7-[[[1-(*tert*-butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (13). Carboxamide **12** (0.05 g, 0.16 mmol) was deprotected with CF_3CO_2H and the amine salt which was obtained was reacted with (*tert*-butoxycarbonyl)-L-proline pentafluorophenol ester (0.09 g, 0.25 mmol) in a manner similar to that described above for **10** to give 0.03 g (47%) of **13** as a white solid: mp 127–132 °C; $[\alpha]_D$ −175.0° (*c* 0.4, MeOH); TLC R_f = 0.31 (EtOAc/MeOH (7:3)); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.8–2.1 (m, 3 H, Pro γ-CH_2 and 6-CH_2), 2.1–2.3 (m, 2 H, Pro β-CH_2), 3.0–3.2 (m, 1 H, 6-CH_2), 3.35 (dd, *J* = 7.3 and 11.7 Hz, 1 H, CH_2S), 3.44 (br s, 2 H, Pro δ-CH_2), 3.67 (dd, *J* = 5.9 and 12.2 Hz, 1 H, CH_2S), 4.15–4.35 (m, 1 H, Pro α-CH), 4.84 (dd, *J* = 5.9 and 6.8 Hz, 1 H, 2-H), 4.87–5 (m, 1 H, 7-H), 5.06 (t, *J* = 6.8 Hz, 1 H, NCHS), 5.96 (s, 1 H, NH_2), 6.85 and 7.6 (br s, 1 H, NH), 6.93 (s, 1 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 23.72 and 24.53 (Pro γ-C), 28.36 ($C(CH_3)_3$), 31.22 and 31.25 (Pro β-C), 34.63 (6-C), 36.98 (CH_2S), 47.16 (Pro δ-C), 53.28 (Pro α-C), 58.83 (2-C), 59.89 and 61.1 (7-C), 62.4 (NCS), 80.7 ($C(CH_3)_3$), 155.9 (urethane C=O), 170.67, 172.59, 173.29 (C=O); FAB MS *m/z* 399 $(MH)^+$.

(2*R*,5*S*,7*R*)-1-Aza-7-[(2(*S*)-pyrrolidinylcarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide Hydrochloride (5·HCl). Protected amide **13** (0.02 g, 0.05 mmol) was deprotected with 4 N HCl in dioxane (2 mL) under Ar for 20 min, after which time the dioxane solution was frozen and lyophilized to give 0.018 g (90%) of **5**·HCl as a highly hygroscopic white solid: $[\alpha]_D$ = −127.4° (*c* 0.27, H_2O); ^{1}H NMR (DMSO-d_6) δ 1.7–2.02 (m, 4 H, Pro β and γ-CH_2), 2.2–2.34 (m, 1 H, 6-CH_2), 2.8–2.95 (m, 1 H, 6-CH_2), 3.1–3.4 (m, 4 H, Pro δ-CH_2 and CH_2S), 4.08–4.2 (m, 1 H, Pro α-CH), 4.7 (dd, *J* = 3.97 and 7.02 Hz, 1 H, 7-CH), 4.77–4.87 (m, 1 H, 2-CH), 4.99 (t, *J* = 7 Hz, 1 H, NCHS), 7.32 (s, 1 H, NH_2), 7.59 (s, 1 H, NH_2), 8.58 (br s, 1 H, $^+NH_2$), 9.02 (d, *J* = 7.94 Hz, 1 H, NH), 9.77 (br s, 1 H, $^+NH_2$); ^{13}C NMR (DMSO-d_6) δ 23.54 (Pro γ-C), 29.54 (Pro β-C), 34.93 (6-C), 36.11 (CH_2S), 45.56 (Pro δ-C), 52.85 (Pro α-C), 58.49 (7-C), 58.86 (2-C), 61.3 (NCS), 168.27 (C=O), 170.49 (C=O), 170.55 (C=O); FAB HRMS *m/z* 299.1192 ($C_{12}H_{19}N_4O_3S$ + H^+ requires 299.1178). HPLC analysis (C18, 1% aqueous HCl, 2 mL/min) indicated that the product was homogeneous with a t_R = 25.2 min.

Methyl (2*S*,5*R*,8*R*)-1-Aza-8-[(benzyloxycarbonyl)amino]-9-oxo-4-thiabicyclo[4.3.0]nonane-2-carboxylate (15). Oxazolidinone aldehyde **14**[12] (0.41 g, 1.5 mmol) was dissolved in EtOH (8 mL) and treated with a solution of D-cysteine·HCl (0.39 g, 2.2 mmol) in H_2O (5 mL). This mixture was neutralized with $NaHCO_3$ and then stirred overnight at room temperature under Ar. EtOH and H_2O were removed in vacuo and the resulting solid dispersed in dry DMF. This mixture was heated to 42 °C under an Ar atmosphere. The mixture was kept at this temperature for 24 h after which time the DMF solution was filtered and the solvent removed from the filtrate under high vacuum. The residue was dissolved in MeOH and treated with an Et_2O solution of CH_2N_2. The methyl ester which was obtained was chromatographed on a silica gel column (hexane/EtOAc (3:2)) to give 0.19 g (35%) of **15** as an oil: $[\alpha]_D$ +140.6° (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.78–2.00 (m, 2 H, 7-H), 2.3–2.4 (m, 1 H, 6-H), 2.5–2.6 (m, 1 H, 6-H), 3.16 (dd, *J* = 5.5 and 11.6 Hz, 1 H, CH_2S), 3.37 (dd, *J* = 8.55 and 11.6 Hz, 1 H, CH_2S), 3.77 (s, 3 H, OCH_3), 4.15–4.25 (m, 1 H, 8-H), 4.93 (dd, *J* = 4.27 and 10.68 Hz, 1 H, NCHS), 5.1–5.2 (m, 1 H, 2-H), 5.12 (s, 2 H, $PhCH_2$), 5.45 (br s, 1 H, NH), 7.2–7.4 (m, 5 H, Ph H's); ^{13}C NMR ($CDCl_3$) δ 27.61 (7-C), 28.02 (6-C), 31.93 (CH_2S), 52.1 (OCH_3), 52.65 (8-C), 60.6 (NCS), 62.87 (2-C), 66.94 ($PhCH_2$), 128.06, 128.11, 128.51, 136.34 (Ph C's), 156.49 (urethane C=O), 167.98, 170.42 (C=O); FAB MS *m/z* 365 $(MH)^+$. Anal. ($C_{17}H_{20}N_2O_5S$) C, H, N, S.

(2*S*,5*R*,8*R*)-1-Aza-8-[(benzyloxycarbonyl)amino]-9-oxo-4-thiabicyclo[4.3.0]nonane-2-carboxamide (16). Methyl ester **15** (0.14 g, 0.38 mmol) was dissolved in a solution of MeOH saturated with NH_3. This mixture was stirred for 3 h at room temperature, at which time the MeOH was removed under reduced pressure. The residue that was obtained was chromatographed on a silica gel column (EtOAc/hexane (5:2)) to give 0.1 g (76%) of **16** as a white solid: mp 162–163 °C; $[\alpha]_D$ +143.4° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.7–1.9 (m, 1 H, 6-H), 2.0–2.4 (m, 3 H, 6-H and 7-H), 3.1–3.3 (m, 1 H, CH_2S), 3.3–3.5 (m, 1 H, CH_2S), 3.75–3.9 (m, 1 H, 8-CH), 4.85 (br d, *J* = 9.9 Hz, 1 H, NCHS), 5.1 (s, 2 H, $PhCH_2$), 5.15–5.3 (m, 1 H, 2-CH), 5.75 (s, 1 H, NH_2), 6.22 (d, *J* = 7.2 Hz, 1 H, NH), 7.1 (s, 1 H, NH_2), 7.2–7.4 (m, 5 H, Ph H's); ^{13}C NMR ($CDCl_3$) δ 27.16 (7-C), 28.2 (6-C), 30.83 (CH_2S), 51.73 (8-C), 62.0 (NCS and 2-C), 67.15 ($PhCH_2$), 127.9, 128.2, 128.52, 135.92 (Ph C's), 156.63 (urethane C=O), 168.0, 171.68 (C=O); FAB MS *m/z* 350 $(MH)^+$. Anal. ($C_{16}H_{19}N_3O_4S$) C, H, N, S.

(2*S*,5*R*,8*R*)-1-Aza-8-[[[1-(*tert*-butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-9-oxo-4-thiabicyclo[4.3.0]nonane-2-carboxamide (17). Protected amide **16** (90 mg, 0.26 mmol) was suspended in Et_2O (10 mL), and this suspension was treated with HBr/AcOH (4 mL). The reaction was stirred for 45 min at room temperature under Ar. Excess HBr and AcOH were removed under vacuum with the last traces of AcOH being

removed from the residue by azeotropic removal with toluene (3×). The resulting amine HBr salt was obtained as a buff colored solid after being dried under high vacuum overnight. This material was dissolved in dry DMF (10 mL). *N*-Methylmorpholine (33 μL, 0.3 mmol) was added to the solution, and the mixture which was obtained was stirred for 10 min under Ar. (*tert*-Butoxycarbonyl)-L-proline pentafluorophenol ester (100 mg, 0.26 mmol) was added to the reaction mixture, which then was stirred at room temperature for 22 h. The DMF was removed under vacuum, and the residue which was obtained was dissolved in EtOAc. The EtOAc solution was washed with 10% citric acid and saturated NaCl and dried over $MgSO_4$. The EtOAc was removed under reduced pressure, and the residue was chromatographed on a silica gel column (2% MeOH in EtOAc) to give 43 mg (40%) of 17 as an oil: $[\alpha]_D$ +35.5° (*c* 0.76, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H, $C(CH_3)_3$), 1.8–1.9 (m, 3 H, 6-CH_2 and Pro γ-CH_2), 2.1–2.4 (m, 5 H, 6-CH_2, 7-CH_2 and Pro β-CH_2), 3.25 (dd, *J* = 7.8 and 11.4 Hz, 1 H, CH_2S), 3.5 (dd, *J* = 4.2 and 11.4 Hz, 1 H, CH_2S), 3.6–3.65 (m, 1 H, Pro δ-CH_2), 3.75–3.8 (m, 1 H, Pro δ-CH_2), 3.8–3.9 (m, 1 H, 8-CH), 4.1–4.3 (m, 1 H, Pro α-CH), 4.9 (dd, *J* = 3.6 and 10.5 Hz, 1 H, NCHS), 5.3–5.35 (m, 1 H, 2-CH), 5.64 (br s, 1 H, NH), 7.45 (br s, 1 H, NH_2), 7.95 (br s, 1 H, NH_2). ^{13}C NMR ($CDCl_3$) δ 23.67, 24.51 (Pro γ-C), 26.7 (6-C), 28.26 and 28.57 ($C(CH_3)_3$), 30.72 (7-C), 31.0 (Pro β-C), 47.0 (CH_2S), 50.9 (Pro δ-C), 59.4 and 60.57 (8-C), 61.46 and 61.59 (Pro α-C), 62.02 (NCS), 72.33 (2-C), 80.46 ($C(CH_3)_3$), 154.4 and 155.5 (urethane C=O), 167.26, 171.88, 172.9, 174.19 (C=O); FAB MS *m/z* 413 $(MH)^+$. Anal. ($C_{18}H_{28}N_4O_5S$) C, H, N, S.

(2*S*,5*R*,8*R*)-1-Aza-8-[(2(*S*)-pyrrolidinylcarbonyl)amino]-9-oxo-4-thiabicyclo[4.3.0]nonane-2-carboxamide Hydrochloride (4·HCl). Amide 17 (20 mg, 0.05 mmol) was treated with 4 N HCl in dioxane under Ar for 20 min, at which time the dioxane solution was frozen and lyophilized to give 16 mg (92%) of the HCl salt of 4 as a highly hygroscopic white solid: $[\alpha]_D$ +118.9° (*c* 0.7, MeOH); ^{1}H NMR (D_2O) δ 1.8–2.0 (m, 1 H, 6-CH_2), 2.0–2.1 (m, 4 H, Pro β-CH_2, 7-CH_2 and Pro γ-CH_2), 2.1–2.3 (m, 1 H, Pro β-CH_2), 2.3–2.5 (m, 2 H, Pro γ-CH_2 and 6-CH_2), 3.15 (dd, *J* = 9 and 12 Hz, 1 H, CH_2S), 3.3–3.4 (m, 2 H, Pro δ-CH_2), 3.44 (dd, *J* = 7.8 and 12 Hz, 1 H, CH_2S), 4.36 (m, 2 H, Pro α-CH and 8-CH), 4.8–4.9 (m, 1 H, 2-H), 4.98 (dd, *J* = 4.2 and 10.8 Hz, 1 H, NCHS); ^{13}C NMR (D_2O) δ 23.59 (Pro γ-C), 26.44 (6-C), 29.39 (7-C), 31.88 (Pro β-C), 46.26 (CH_2S), 50.10 (Pro δ-C), 59.60 (8-C), 62.80 (Pro α-C), 63.83 (NCS), 71.43 (2-C), 168.9, 169.4, 174.2 (C=O); FAB HRMS *m/z* 313.1337 ($C_{13}H_{21}N_4O_3S$ + H^+ requires 313.1334); HPLC analysis (C18, 1% aqueous HCl, 3 mL/min) indicated that the product was homogeneous with a t_R = 42.4 min.

[^{3}H]ADTN Binding Assay. The detailed protocol for measuring the enhancement of binding of ADTN to dopamine receptors has been described earlier by us.[1,6] In short, striatal synaptosomal membranes from bovine caudate along with [^{3}H]-ADTN are incubated with or without (control) different concentrations (10^{-12}–10^{-4} M) of the peptidomimetics. Incubation is carried out in triplicate at 37 °C for 10 min. The mixtures are filtered and the filters counted on a liquid scintillation counter. In the present experiment the total binding was 2400 dpm's, and nonspecific binding was equal to 1100 dpm's. The nonspecific binding is defined as the amount of [^{3}H]ADTN remaining bound in the presence of 10 μM (+)-butaclamol. The statistical significance of the data at various doses was determined using the student *t*-test. The unpaired *t*-test was performed on the actual dpm's obtained at each dose level before converting them to percent enhancement. Values of *p* less than 0.05 are considered significantly different from the control.

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Supplementary Material Available: NOESY spectra of compounds 8 and 9 (2 pages). Ordering information is given on any current masthead page.

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