Design, Synthesis and Evaluation of a PLG Tripeptidomimetic Based on a Pyridine Scaffold

Stina Saitton,[†,‡] Andria L. Del Tredici,[§] Nina Mohell,[§,||] Roeland C. Vollinga,[⊥] Dan Boström,[‡] Jan Kihlberg,[‡,#] and Kristina Luthman*[,†]

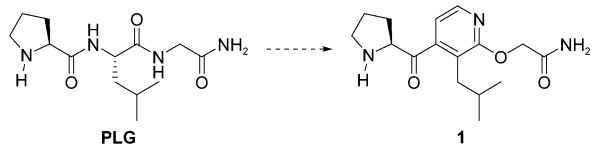
Department of Chemistry, Medicinal Chemistry, Göteborg University, SE-412 96 Göteborg, Sweden, Department of Chemistry, Organic Chemistry, Umeå University, SE−901 87 Umeå, Sweden, and ACADIA Pharmaceuticals Inc., 3911 Sorrento Valley Boulevard, San Diego, California 92121

Received June 29, 2004

A 2,3,4-substituted pyridine derivative has been identified as a potential tripeptidomimetic scaffold. The design of the scaffold was based on conformational and electrostatic comparisons with a natural tripeptide. The scaffold has been used in the synthesis of a Pro-Leu-Gly-NH_2 (PLG) mimetic. The different substituents in the 2-, 3-, and 4-positions of the pyridine ring were introduced via an aromatic nucleophilic substitution reaction, a "halogen-dancing" reaction, and a Grignard coupling of a Boc-protected amino aldehyde, respectively. The synthetic route involves eight steps and provides the mimetic in 20% overall yield. The pyridine based PLG-mimetic was evaluated for its ability to enhance the maximum response of the dopamine agonist *N*-propylapomorphine (NPA) at human D2 receptors using a cell based assay (the R-SAT assay). The dose−response curve of the mimetic was found to exhibit a down-turn phase, similar to that of PLG. In addition, the mimetic was more potent than PLG to enhance the NPA response; the maximum response was found to be 146% at 10 nM concentration, as compared to 115% for PLG at the same concentration. Interestingly, conformational analysis by molecular modeling showed that the pyridine mimetic cannot adopt a type II β-turn conformation that previously has been suggested to be the bioactive conformation of PLG.

Introduction

Several short peptides have been shown to be involved in vital physiological processes. Therefore, such peptides are interesting as lead compounds for drug development.[1] In general, the therapeutic potential of natural peptides is limited by their physicochemical properties. The instability of amide bonds toward enzymatic degradation prevents oral administration, peptides are usually poorly transported through cell membranes and they are rapidly excreted through liver and kidneys, and the conformational flexibility of short peptides often results in low receptor selectivity. To circumvent these limitations, nonpeptidic compounds that mimic the physiological effects of endogenous peptides are desired. These compounds are commonly referred to as peptidomimetics.[2,3] One approach toward the development of peptidomimetics is to use a molecular template or scaffold to which important pharmacophoric groups, supposedly amino acid side chains, can be attached.[4−7] Such compounds have the potential of being orally active, selective, and metabolically stable. Conformationally more rigid structures can also provide important information about the bioactive conformation of peptides. We have for some time been interested in the development of a general tripeptidomimetic scaffold useful for mimicry and for investigation of conformational properties of various tripeptides and tripeptide segments. In this study the design of a general tripeptidomimetic based on a 2,3,4-substituted pyridine scaffold and its application to the tripeptide L-Pro-L-Leu-Gly-NH_2 (PLG) by the synthesis and biological evaluation of mimetic **1** is presented.



PLG is an endogenous tripeptide found in the central nervous system. Pharmacological studies have shown that PLG exerts its biological effects by interaction with the dopaminergic pathways.[8] In particular, PLG enhances the effect of dopamine agonists. This modulation of the dopamine receptors emanates from an enhanced binding of agonists to the D2 receptor in the presence of PLG and a shift in the ratio between receptors in the low-affinity state versus the high-affinity state.[9] Numerous peptide analogues[10−17] and peptidomimetics[18−27] of PLG have been synthesized and evaluated in binding assays and in vivo models in the search for compounds with enhanced activity and stability in vivo. In addition, to provide structure−activity information of the interaction of PLG with the dopamine D2 receptors, such compounds have potential use in the treatment of dopamine-related disorders such as Parkinson's disease and tardive dyskinesia.

* To whom correspondence should be addressed. Telephone: +46-31-772 2894. Fax: +46-31-772 3840. E-mail: luthman@chem.gu.se.
† Göteborg University.
‡ Umeå University.
§ ACADIA Pharmaceuticals Inc.
|| Present address: R&D, Biovitrum AB, SE-112 76 Stockholm, Sweden.
⊥ Present address: DSM Anti-Infectives B.V., P.O. Box 425, 2600 AK Delft, The Netherlands.
Present address: AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden.

10.1021/jm049484q CCC: $27.50
Published on Web 11/18/2004

Scheme 1. Design Strategy

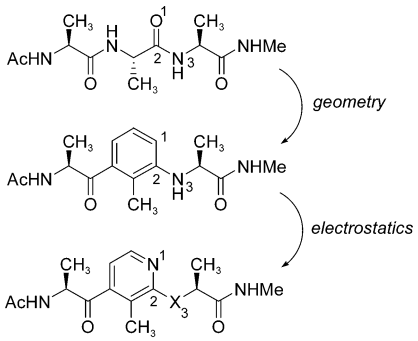


Table 1. Semiempirical Calculations of Atomic Charges for the Ac-Ala-Ala-Ala-NHMe Tripeptide and the Corresponding Tripeptidomimetics[a]

compound	atom 1	atom 2	atom 3
peptide	−0.56	0.75	−0.65
benzene mimetic	−0.23	0.31	−0.58
pyridine mimetic X = NH	−0.68	0.92	−0.74
pyridine mimetic X = O	−0.70	0.82	−0.42

[a] See Scheme 1 for structures and numbering of the atoms.

Results and Discussion

Design of a Tripeptidomimetic Scaffold. Initially a trisubstituted aromatic ring was investigated as a peptidomimetic scaffold (Scheme 1). Such system seemed attractive from a synthetic point of view due to the thoroughly explored chemistry of benzene derivatives and the lack of stereocenters in the ring. The idea was to replace the second amino acid of the tripeptide with the aromatic ring containing the amino acid side chain moiety and then let the peptide chain continue from the neighboring (ortho) positions.

To improve the mimicking ability of the six-membered, aromatic scaffold, different heterocyclic ring systems were examined by computer-based methods.[28] Molecular mechanics calculations[29] were used to examine conformational preferences, and AM1 semiempirical methods[30] were used to calculate electrostatic properties. An Ac-Ala-Ala-Ala-NHMe tripeptide was used as a model compound together with various suggestions of appropriate peptidomimetic structures. By comparing the predicted atomic charges with those of the model tripeptide, it was found that the pyridine ring system showed interesting properties. The nitrogen atom in the pyridine ring provides a good electrostatic mimic of the carbonyl oxygen in an amide bond (Table 1). The connecting atom (X) in the proposed tripeptidomimetic could be either a nitrogen or an oxygen atom. Figure 1 shows a geometrical comparison of the natural tripeptide and the proposed mimetic (X = NH). As can be seen, the geometric fit between the peptide and the mimetic is good overall, except for the direction of the second amino acid side chain, which is constrained by the aromatic ring.

To explore the synthetic feasibility of the designed scaffold, PLG was chosen as the first tripeptide target.

Synthesis. A strategy for the synthesis of the 2,3,4-trisubstituted pyridine system, where the introduction of the different substituents was investigated, has recently been reported.[31] A retrosynthetic analysis of

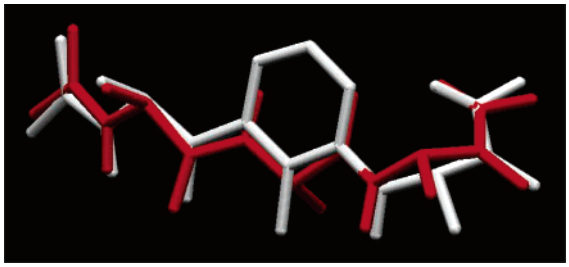
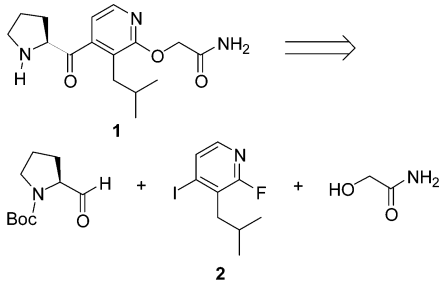


Figure 1. A geometrical comparison of two selected low-energy conformations of the model tripeptide and the corresponding mimetic (X = NH).

Scheme 2. Retrosynthetic Analysis of the PLG Mimetic

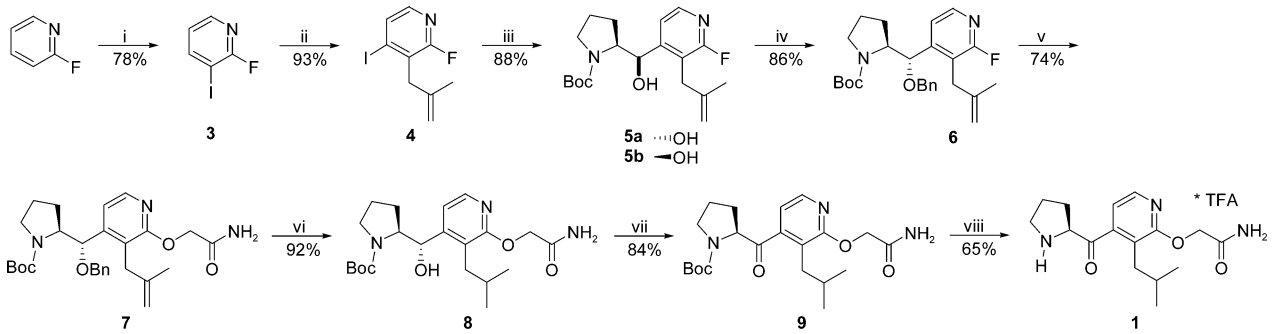


PLG mimetic **1** is shown in Scheme 2. The key intermediate is the functionalized scaffold **2**, in which the leucine side chain is attached to the 3-position of the pyridine ring and the neighboring positions are functionalized by fluorine and iodine, respectively. This substitution pattern allows for selective introduction of suitable groups in the 2- and 4-positions. The *N*-terminal amino acid (proline) could be attached to the scaffold via a metal-mediated coupling reaction, and the *C*-terminal amino acid equivalent (glycolamide) could be introduced via a nucleophilic aromatic substitution reaction. For synthetic reasons, the connecting atom X in the proposed tripeptidomimetic, was chosen to be an oxygen atom.[31]

The functionalized scaffold **4** was synthesized in two steps starting from 2-fluoropyridine as described earlier (Scheme 3).[31] In the first step, treatment of 2-fluoropyridine with LDA followed by addition of iodine afforded 2-fluoro-3-iodopyridine (**3**) in 78% yield.[32] To introduce the substituent in the 3-position, a phenomenon referred to as "halogen-dancing" was used.[33] Metalation of **3** with LDA initially forms an anion in the 4-position. This anion is rearranged to the 3-position while iodine migrates to the 4-position, presumably due to the additional stabilization of the anion by fluorine. Subsequent addition of an electrophile results in attachment of the desired side chain equivalent in the 3-position and provides a 3-alkyl-2-fluoro-4-iodopyridine. Attempts failed to introduce an isobutyl group directly by using isobutyl bromide or isobutyl iodide as electrophiles. Instead, an unsaturated side-chain equivalent was employed; reaction with metallyl bromide produced the isobutylene derivative **4** in 93% yield.

The metal-mediated coupling of the proline residue to the 4-position proved troublesome at first.[31] Several attempts to accomplish the coupling via a Stille reaction or a lithiated scaffold failed. Instead, the coupling was accomplished using a Grignard reaction. The Grignard reagent was formed by treatment of the pyridine scaffold with *i*PrMgCl in THF at room temperature.[34] Subse-

Scheme 3. Synthesis of the PLG Mimetic[a]



[a] Reaction conditions: (i) LDA, I_2, THF, −78 °C, 5 h; (ii) LDA, metallyl bromide, THF, −78 °C, 3.5 h; (iii) *i*PrMgCl, Boc-Pro-CHO, THF, rt, overnight; (iv) BnBr, NaH, cat. Bu_4NI, THF, rt, 28 h; (v) Glycolamide, KH, DMSO, 55 °C, 60 h; (vi) H_2, cat. Pd/C, MeOH, rt, 1.5 h; (vii) Dess−Martin periodinane, CH_2Cl_2, rt, overnight; (viii) TFA, CH_2Cl_2, rt, 5 min.

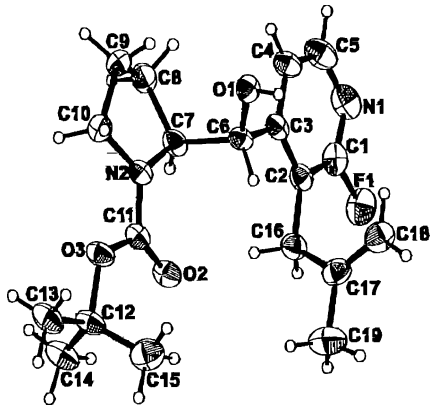
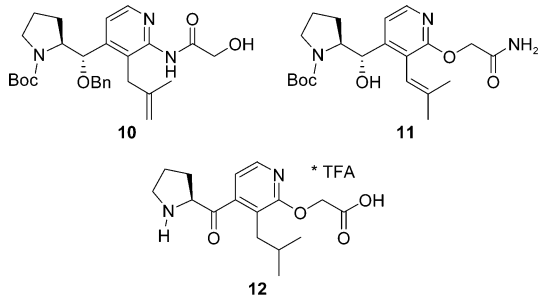


Figure 2. X-ray crystal structure of **5b**, showing 50% probability displacement ellipsoids.[51]

quent addition of Boc-protected proline aldehyde afforded the expected alcohols (**5a** and **5b**) in a combined yield of 88% (approximately 85:15 diastereomeric ratio) and the deiodinated pyridine derivative corresponding to **4** (**5c**, 8% yield). The stereoisomers were separated in order to study the diastereoselectivity in this step and thereafter the reaction sequence was continued only with the major isomer. The minor isomer was crystallized and analyzed by X-ray crystallography.[35] It was found to be the *R*-isomer (Figure 2), which indicates that the reaction proceeds according to Cram's chelation model for carbonyl addition with preferential formation of the *S*-isomer.[36]

A first attempt to directly oxidize alcohol **5a** to the corresponding ketone (Dess−Martin periodinane), followed by nucleophilic substitution in the 2-position (glycolamide, KH), gave the desired product **9**. However, this product showed no optical activity, which indicated that a racemization occurred during the strongly basic conditions used in the substitution reaction. Analysis by chiral HPLC using a Pirkle Covalent (*S*,*S*)-Whelk-O 1 10/100 Krom Fec column confirmed the conclusion, as the chromatogram showed two peaks with a 1:1 ratio.

Attempts to introduce the 2-substituent on alcohol **5a** by a nucleophilic substitution reaction (KH, glycolamide) gave no desired product. The main product was instead identified by mass spectroscopy as a bicyclic oxazolidinone, resulting from attack by the hydroxy group on the carbonyl in the Boc group. Obviously, there was a need to protect the secondary alcohol of **5a**. First the use of various silyl protecting groups was explored. It was found that addition of a mixture of KH and glycolamide to silyl-protected[37] **5a** gave rapid deprotection and a mixture of **5a** and the oxazolidinone (see above) was observed. Instead, treatment of **5a** with benzyl bromide in the presence of NaH and tetrabutylammonium iodide afforded the benzyl ether **6** in 86% yield. The nucleophilic substitution reaction could then be accomplished by reaction of **6** with glycolamide and KH in DMSO at 55 °C to give amide **7** in 74% yield. Attempts to use mixtures of DMF and THF as solvents or NaH as base were considerably less successful. When the reaction was run at a higher temperature (80 °C), a byproduct (**10**) resulting from a nucleophilic attack of the amide functionality of glycolamide was detected in ∼10% yield.



Simultaneous cleavage of the benzyl ether and reduction of the double bond in the isobutylene group were achieved by catalytic hydrogenation using Pd/C to afford **8** in 92% yield. In some instances this reaction stopped before completion and the rearranged product **11** was formed. Fortunately, the conjugated double bond in **11** was easy to reduce by the same method using fresh catalyst. It should also be mentioned that in one instance methanolysis of the terminal amide was observed. Change of solvent to THF eliminated this side reaction. Oxidation of the secondary alcohol with Dess−Martin periodinane afforded ketone **9** in 84% yield. For similar substrates, this method was superior to the use of PDC or Jones' reagents. The optical purity of **9** was confirmed by chiral HPLC analysis. The chromatogram showed one single peak, as compared to the two peaks for the racemate (see above).

Finally, cleavage of the Boc group was achieved by TFA/CH_2Cl_2 (1:3). By shortening the reaction time from 30 to 5 min an unwanted amide hydrolysis[38] to acid **12** was avoided and the final product **1** was isolated as a TFA salt in 65% yield after purification by HPLC.

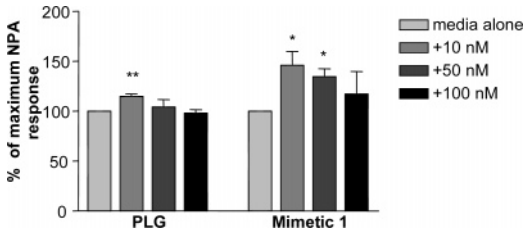


Figure 3. Stimulation of NPA response at the D2 receptor by PLG and **1**. Data represent the percentage of maximum NPA response over the media-alone control in the cell-based functional assay R-SAT. The indicated concentrations of PLG or **1** were added with NPA. Shown are the average and standard deviations of three to five separate experiments carried out in triplicate. Paired *t*-test indicates significant differences from media-alone values: *, $p < 0.05$; **, $p < 0.01$.

Pharmacological Testing. The PLG mimetic **1** was evaluated in the R-SAT assay, a pharmacologically predictive cell-based functional assay based on ligand-dependent transformation of NIH/3T3 cells as previously described.[39,40] Compound **1** and native PLG were tested for their ability to enhance the maximum response of the dopamine agonist *N*-propylapomorphine (NPA) at the human D2 receptor at three different concentrations (10, 50, and 100 nM). As described by Dolbeare et al.,[27] an enhancement in NPA maximum response was observed at 10 nM PLG (115 ± 6%, n=5) but not at higher concentrations (50 nM, 104 ± 13%, n=3; 100 nM, 98 ± 6%, n=3). However, for compound **1**, an enhancement in NPA response was observed at both 10 nM (146 ± 28%, n=4) and 50 nM (135 ± 14%, n=3) concentration of **1** (Figure 3). No enhancement of NPA response was however observed at 100 nM of **1** (117 ± 39%, n=3). In addition, no enhancement in NPA response was observed with the unrelated peptide, somatostatin-14 (10 or 50 nM). The down-turn phase exhibited by both PLG and mimetic **1** in this assay is in accordance with previous findings where PLG has shown a bell-shaped dose−response curve.[41] The mechanism of action for this behavior is however not presently known.

Druglike Properties. In the design of new drug candidates, it is of great importance to evaluate the physicochemical properties of the candidates in order to qualitatively estimate oral bioavailability and membrane permeability. The properties originally proposed by Lipinski et al.[42] (MW, H-bond donors, H-bond acceptors, log *P*) together with the properties more recently suggested by Veber et al.[43] [rotable bonds, sum of H-bond donors and acceptors, polar surface area (PSA)] have been calculated for mimetic **1** and PLG (Table 2). Both PLG and mimetic **1** satisfy all the parameters mentioned above and are hence expected to show acceptable absorption properties. However, the positive log *P* value and the lower number of H-bond donors and acceptors of mimetic **1** as compared to PLG are reflected in more favorable PSA predictions (99 vs 122 Å^2). In fact, it has been estimated that a polar surface area over 120 Å^2 only permits approximately 20% permeability in vivo.[44] Thus, even though both compounds can be considered to be within the "druglike limits", mimetic **1** is predicted to show more favorable membrane permeability properties than PLG.

Table 2. Druglike Properties of Mimetic **1** and PLG

entry	property[a]	PLG	mimetic **1**
1	MW (g/mol)	284	305
2	H-bond donors	5	3
3[b]	H-bond acceptors	7	6
4[c]	*C* log *P*	−1.62	0.77
5	rotable bonds	7	7
6	H-bond total	10	7
7[d]	polar surface area (Å^2)	122	99

[a] Druglike properties are limited to MW ≤ 500 g/mol, H-bond donors ≤ 5, H-bond acceptors ≤ 10, *C* log *P* ≤ 5, rotable bonds ≤ 10, H-bond total ≤ 12, polar surface area ≤ 140 Å^2 (for definition of the parameters, see ref 42 for entries 1−4 and ref 43 for entries 5−7). [b] The pyrrolidine nitrogen was not counted as a hydrogen-bond acceptor since it is charged at physiological pH. [c] *C* log *P* was calculated using Spartan v. 5.1.3 ab initio calculation of log *P* (Ghose−Crippen). [d] Polar surface area was calculated using MARVEA version 2.4.[50]

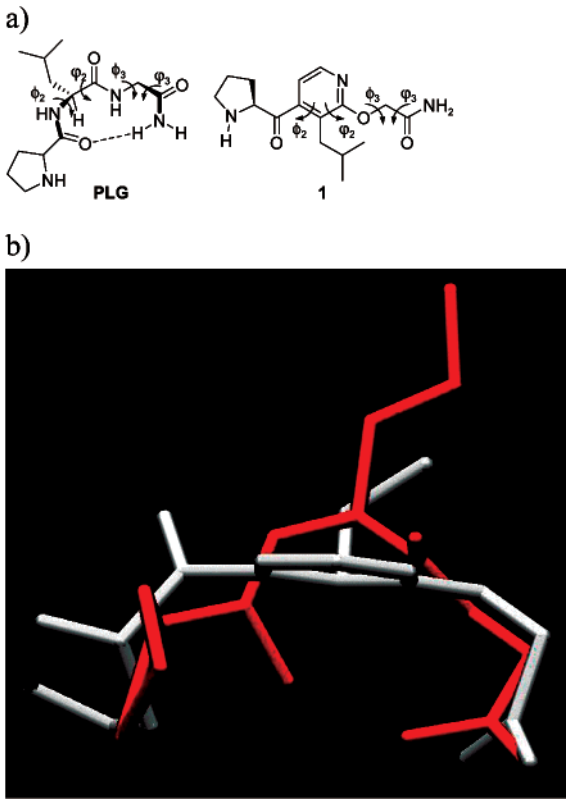


Figure 4. (a) PLG in a β-turn conformation and mimetic **1** with the φ and ψ dihedral angles shown. (b) Overlap picture between a selected turnlike low-energy conformation of mimetic **1** and PLG in a type II β-turn conformation.

Structure−Activity Relationships. On the basis of results from previous studies, a type II β-turn has been proposed as the bioactive conformation of PLG.[17,21,22,45] The conformational properties of peptidomimetic **1** have been examined by molecular modeling. In particular, the probability of **1** to adopt a type II β-turn was investigated. As expected, it was found that mimetic **1** cannot adopt a type II β-turn due to the aromaticity of the pyridine ring, which restricts the ϕ_2 and φ_2 torsion angles to approximately −180° and +180°, respectively (Figure 4a). In order for the mimetic to adopt any turnlike conformation, the pyrrolidine ring of the proline residue must be at the same face of the pyridine ring (which lies perpendicular to the plane of the turn) as the glycol amide tail. When doing so, the carbonyl group is forced to point in the direction out of

the turn, which makes a hydrogen bond between this functionality and the terminal amide impossible (Figure 4b). The H···O distance between the $(C{=}O)_i$ and $(HN)_{i+3}$ residues is approximately 6 Å, as compared to 2 Å for the peptide in the suggested bioactive conformation. Although a type II β-turn as a bioactive conformation is supported by test results of several highly constrained PLG mimetics,[20] the biological activity of **1** cannot emanate from its ability to adopt such a conformation. It has, however, been suggested that there might be two different ways in which mimetics can interact with the PLG modulatory site.[15] Our findings support this suggestion but today the properties of this second bioactive conformation are unknown.

Conclusion

A novel pyridine-based tripeptidomimetic scaffold has been designed, synthesized, and tested as a mimetic of PLG. The synthetic sequence, which involves eight steps, afforded the desired mimetic in 20% total yield. Compound **1** was found to efficiently mimic the dopamine agonist enhancing response of PLG. This effect makes **1** interesting as a modulator of dopaminergic activity, especially in dopamine dependent degenerative diseases such as Parkinson's disease and tardive dyskinesia. To investigate the structure−activity relationship for this type of compound, synthesis and evaluation of analogues of **1** as dopamine modulators are in progress.

Experimental Section

Chemistry. General Data. All chemical reagents were commercially available. THF was distilled from potassium/sodium. TLC analysis was performed on silica gel F_{254} (Merck) and detection was carried out by examination under UV light and staining with phosphomolybdic acid. After workup, all organic phases were dried with $MgSO_4$. Flash column chromatography was performed on silica gel with solvent of HPLC grade or analytical grade. Analytical reversed-phase HPLC was performed on a Beckman System Gold HPLC equipped with a Kromasil C-8 column (250 × 4.6 mm) using acetonitrile (0.1% TFA) in H_2O (0.1% TFA), 0−100% linear gradient over 60 min. A flow rate of 1.5 mL/min was used and detection was at 254 nm. Preparative reversed-phase HPLC was performed on a Kromasil C-8 column (250 × 20 mm) using the same eluent, a flow rate of 11 mL/min, and detection at 254 nm. Chiral HPLC chromatography was performed on a Pirkle Covalent (*S*,*S*)-Whelk-O 1 10/100 Krom Fec column using CH_2Cl_2/*i*PrOH/heptane (48:4:48) as eluent, a flow rate of 1.0 mL/min, and detection at 254 nm. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Specific rotations were measured with a Perking-Elmer model 343 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively, and calibrated using the residual peak of solvent as internal reference [$CDCl_3$ ($CHCl_3$ δ_H 7.26, $CDCl_3$ δ_C 77.0) or CD_3OD (CD_2HOD δ_H 3.34, CD_3OD δ_C 49.0)]. Infrared spectra were recorded using an ATI Mattson Infinity Series FTIR spectrometer. High-resolution mass spectral analysis was performed at Instrumentstationen, Lund University, Sweden. Elemental analyses were performed by MikroKemi AB, Uppsala, Sweden. Compounds **3**[32] and **4**[31] were synthesized as reported earlier.

(*S*)-[(2*S*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl)[2-fluoro-3-(2-methylallyl)pyridin-4-yl]methanol (5a), (*R*)-[(2*S*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl)[2-fluoro-3-(2-methylallyl)pyridin-4-yl]methanol (5b), and 2-Fluoro-3-(2-methylallyl)pyridine (5c). A 2.0 M solution of isopropylmagnesium chloride in THF (3.00 mL, 5.95 mmol) was added with syringe to a solution of the iodo derivative **4** (1.65 g, 5.95 mmol) in freshly distilled THF (8 mL), kept under nitrogen atmosphere at room temperature. The reaction was exothermic and became warm, cloudy, and somewhat discolored. After 1 h, Boc-Pro-CHO (1.19 g, 5.95 mmol) was added as a solution in THF (6 mL), whereby the reaction mixture again became warm but clear and kept the yellow-brown color. The reaction was stirred overnight before it was quenched by the addition of H_2O (20 mL) and extracted to diethyl ether. The combined organic phases were washed with brine, dried, and concentrated to yield 2.2 g of a crude oil (dr 85:15 according to crude NMR analysis). Purification by flash chromatography (EtOAc/heptane 1:6 then 1:2) afforded the diastereomers **5a** and **5b** (1.84 g, 88% combined yield) and the deiodinated byproduct **5c** (68 mg, 8%):

5a: A colorless oil; $[\alpha]_D$ +9.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 1H, J = 5.3 Hz); 7.27 (d, 1H, J = 5.3 Hz), 6.08 (br s, 1H), 4.76 (s, 1H), 4.73 (d, 1H, J = 8.7 Hz), 4.37 (s, 1H), 4.13 (m, 1H), 3.44−3.30 (m, 4H), 1.75 (s, 3H), 1.72−1.59 (m, 3H), 1.44 (s, 9H), 1.34−1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.27 (d, J = 239 Hz), 158.22, 155.12 (d, J = 4 Hz), 145.24 (d, J = 15 Hz), 142.54, 120.20 (d, J = 3 Hz), 119.14 (d, J = 31 Hz), 111.69, 81.01, 73.57, 63.13, 47.54, 32.55, 28.22 (4 C:s), 23.96, 22.73; IR (neat) 3270, 2968, 1679, 1374 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{28}FN_2O_3$ $[M + H]^+$ 351.2084, found 351.2076. Anal. ($C_{19}H_{27}FN_2O_3$) C, H, N.

5b: A colorless oil; $[\alpha]_D$ −34.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H, J = 4.9 Hz), 7.40 (br s, 1H), 5.39 (s, 1H), 4.74 (s, 1H), 4.30 (br s, 1H), 4.00 (br s, 1H), 3.75−3.15 (m, 5H), 2.00−1.60 (m, 4H), 1.81 (s, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.38 (d, J = 239 Hz), 155.69, 154.73, 144.88 (d, J = 15 Hz), 143.15, 119.55, 118.42 (d, J = 31 Hz), 110.85, 79.95, 69.70, 61.67, 47.95, 32.43, 28.44 (3 C:s), 24.97, 24.33, 23.09; IR (neat) 3355, 2974, 1681, 1395 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{28}FN_2O_3$ $[M + H]^+$ 351.2084, found 351.2070. Anal. ($C_{19}H_{27}FN_2O_3$) C, H, N.

5c: A colorless oil; ^{1}H NMR ($CDCl_3$) δ 8.04 (m, 1H,), 7.57 (m, 1H), 7.10 (m, 1H), 4.83 (s, 1H), 4.65 (s, 1H), 3.29 (s, 2H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.06 (d, J = 239 Hz), 145.38 (d, J = 15 Hz), 142.39, 141.16 (d, J = 6 Hz), 121.44 (d, J = 32 Hz), 121.30 (d, J = 4 Hz), 112.80, 36.62, 22.05; IR (neat) 3077, 2971, 2917, 1604, 1577, 1436 cm^{-1}; HRMS (EI) calcd for $C_9H_{10}FN$ $[M]^+$ 151.0797, found 151.0786.

4-[(1*S*)-Benzyloxy-1-[(2*S*)-1-*tert*-butoxycarbonylpyrrolidin-2-yl]methyl]-2-fluoro-3-(2-methylallyl)pyridine (6). Alcohol **5a** (1.13 g, 3.22 mmol) was dissolved in freshly distilled THF and stirred while NaH (0.19 g, 4.84 mmol, 60%) was added carefully. Benzyl bromide (0.58 mL, 4.84 mmol) and tetrabutylammonium iodide (60 mg, 0.16 mmol) were added. The reaction was stirred at room temperature for 28 h before it was quenched by the addition of NH_4Cl (aq, sat.) and extracted into Et_2O. The combined organic phases were washed with brine, dried, and concentrated to a yellow oil. The crude product was purified by flash chromatography (EtOAc/heptane 1:10) to yield **6** (1.22 g, 86%) as a colorless oil: $[\alpha]_D$ −40.4 (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (rotamers) δ 8.07 (br s, 1H), 7.42 (br s, 1H), 7.36−7.23 (m, 5H), 5.03 (br s, 0.5H), 4.84−4.70 (m, 1.5H), 4.45−4.29 (m, 3H), 4.27−4.12 (m, 1H), 3.55−3.10 (m, 3.5H), 3.05−2.91 (m, 0.5H), 2.07−1.10 (m, 4H), 1.76 (s, 3H), 1.44 (s, 5H), 1.23 (s, 4H); ^{13}C NMR ($CDCl_3$) [δ for minor rotamer when observed and assigned (above 27 ppm)] δ 162.28 (d, J = 238 Hz), 154.92 [154.35], 152.88 (d, J = 4 Hz), 144.58 [144.93] (d, J = 16 Hz), 142.44 [142.10], 137.64 [137.37], 128.09 (2 C:s), 127.40, 127.30 (2 C:s), 120.16 [119.58] (d, J = 31 Hz), 120.05, 111.36 [111.55], 79.28, 76.68 [78.04], 71.31 [71.20], 60.46, 46.60 [46.47], 31.95 [32.10], 28.19 [27.89] (3 C:s), 25.80, 23.78, 23.11, 22.58; IR (neat) 3066, 2975, 2885, 1691, 1390 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{34}FN_2O_3$ $[M + H]^+$ 441.2553, found 441.2548.

2-{4-[(1*S*)-Benzyloxy-1-((2*S*)-1-*tert*-butoxycarbonylpyrrolidin-2-yl)methyl]-3-(2-methylallyl)pyridin-2-yloxy}-acetamide (7). Glycolamide (63 mg, 0.84 mmol) was dissolved in dry DMSO (1 mL) and KH was added carefully. After a few minutes, the gas evolution stopped and the pyridine derivative

6 (74 mg, 0.17 mmol) was added as a solution in DMSO (1 mL). The reaction was heated at 55 °C for 60 h or until no starting material could be detected by TLC. The reaction was quenched by the addition of H_2O, and aq HCl (5%) was added until neutral pH was achieved. The product was extracted to CH_2Cl_2, and the combined organic phases were washed with brine, dried, and concentrated to a crude yellow oil. Purification by flash chromatography (EtOAc/heptane 2:1) afforded **7** (62 mg, 74%) as a white foam: $[\alpha]_D$ −30.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (rotamers) δ 8.05 (br s, 1H), 7.36−7.15 (m, 6H), 6.48−6.33 (m, 1H), 6.27−5.97 (m, 1H), 5.92−5.78 (m, 0.5H), 5.15 (m, 0.5H), 5.03−4.10 (m, 7H), 3.54−2.90 (m, 3H), 2.09−1.06 (m, 17H); ^{13}C NMR ($CDCl_3$) (rotamers) [δ for minor rotamer when assigned (above 27 ppm)] δ 172.14 [171.91], 160.16 [159.10], 154.75 (br), 150.33 [150.00], 144.99 [144.24], 138.96 [138.38], 137.96 (br), 128.27 (2 C:s), 127.54 (3 C:s), 120.82 (br), 116.50 [116.96], 110.07 (br), 79.16 [79.48], 77.99 (br), 71.08 [71.47], 64.81 [64.13], 60.85 [60.35], 46.56 (br), 32.64 (br), 28.34 (br, 3 C:s), 26.62, 25.96, 25.41, 23.95, 23.32, 19.89; IR (neat) 1685, 1388 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{38}N_3O_5$ $[M + H]^+$ 496.2811, found 496.2814. Anal. ($C_{28}H_{37}N_3O_5$) C, H, N.

2-{4-[1-[(2*S*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl]-(1*S*)-hydroxymethyl]-3-isobutylpyridin-2-yloxy}acetamide (8). Compound **7** (60 mg, 0.12 mmol) was dissolved in MeOH (1 mL), and Pd/C (10%, 22 mg) was added. The reaction was stirred vigorously under H_2 at room temperature for 1.5 h. The catalyst was filtered off using a plug of Celite and the filtrate was concentrated to afford **8** (45 mg, 92%) as a colorless oil/foam: $[\alpha]_D$ −35.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1H, *J* = 5.3 Hz), 7.14 (d, 1H, *J* = 4.7 Hz), 6.28 (br s, 1H), 6.06 (br s, 1H), 5.79 (br s, 1H), 4.91−4.75 (m, 3H), 4.19−4.10 (m, 1H), 3.53−3.38 (m, 2H), 2.70 (dd, 1H, *J* = 13.5, 6.8 Hz), 2.45 (dd, 1H, *J* = 13.5, 7.7 Hz), 1.99−1.86 (m, 1H), 1.85−1.75 (m, 2H), 1.72−1.61 (m, 1H), 1.51 (s, 9H), 1.37−1.27 (m, 1H), 0.96 (app t, 6H, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.00, 160.19, 158.42, 152.21, 144.30, 121.63, 116.66, 81.15, 73.33, 64.92, 63.79, 47.73, 34.22, 29.48, 28.38 (3 C:s), 28.26, 24.21, 22.79, 22.35; IR (neat) 3315, 2957, 1665, 1395 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{34}N_3O_5$ $[M + H]^+$ 408.2498, found 408.2484.

2-{4-[(2*S*)-1-*tert*-Butoxycarbonylpyrrolidine-2-carbonyl]-3-isobutylpyridin-2-yloxy}acetamide (9). Alcohol **8** (105 mg, 0.26 mmol) was dissolved in dry CH_2Cl_2 and Dess−Martin periodinane (15% in CH_2Cl_2, 0.71 mL) was added. After stirring at room temperature for 4 h, another 0.15 mL of the oxidizing agent was added and the reaction was stirred overnight. The reaction was quenched by the addition of $Na_2S_2O_5$ (350 mg, 1.8 mmol) in $NaHCO_3$ (aq, sat.) and extracted into CH_2Cl_2. The combined organic layers were washed with brine, dried, and concentrated to a crude oil. Purification by flash chromatography (EtOAc:heptane 2:1) afforded **9** (88 mg, 84%) as a white foam: $[\alpha]_D$ +9.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) major [minor] rotamer integral ratio 0.55 [0.45] δ 8.09 [8.13] (d, 1H, *J* = 5.2 Hz), 7.24 [7.10] (d, 1H, *J* = 5.2 Hz), 6.26 (br s, 1H), 5.91 (br s, 1H), 4.97−4.87 (m, 1H), 4.87−4.78 (m, 2H), 3.71−3.56 (m, 1H), 3.54−3.39 (m, 1H), 2.83−2.74 (m, 1H), 2.50−2.39 (m, 1H), 2.19−1.75 (m, 5H), 1.45 [1.39] (s, 9H), 0.95−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$) rotamers [δ for minor rotamer when assigned (above 30 ppm)] δ 203.03 [201.17], 171.46 [171.29], 161.21 [160.95], 154.41 [153.63], 147.48 [146.44], 144.36 [144.50], 122.42 [122.96], 116.32 [116.04], 79.95 [80.25], 65.03 [65.13], 64.06 [63.95], 46.84 [46.62], 35.03 [35.12], 29.50, 29.45, 29.29, 28.83, 28.37 [28.32] (3 C:s), 24.21, 23.07, 22.74, 22.60, 22.50; HRMS (FAB) calcd for $C_{21}H_{32}N_3O_5$ $[M + H]^+$ 406.2342, found 406.2346.

2-{3-Isobutyl-4-[(2*S*)-pyrrolidine-2-carbonyl]pyridin-2-yloxy}acetamide TFA Salt (1). Trifluoroacetic acid (0.5 mL) was added to a solution of **9** (20 mg, 0.049 mmol) in freshly distilled CH_2Cl_2 (1.5 mL) at room temperature. The reaction was allowed to stir for 5 min before it was concentrated under reduced pressure without heating to afford a yellowish solid. Purification by reversed-phase preparative HPLC afforded **1** (13 mg, 65%) as a yellow solid: $[\alpha]_D$ −25.4 (*c* 1.2, H_2O); ^{1}H NMR (CD_3OD) δ 8.23 (d, 1H, *J* = 5.3 Hz), 7.34 (d, 1H, *J* = 5.3 Hz), 5.34−5.30 (m, 1H), 4.94−4.84 (m, 2H), 3.50−3.43 (m, 2H), 2.97 (dd, 1H, *J* = 12.9 Hz, 7.4 Hz), 2.70 (dd, 1H, *J* = 12.9 Hz, 7.2 Hz), 2.47−2.40 (m, 1H), 2.19−2.01 (m, 3H), 1.97−1.88 (m, 1H), 0.97−0.93 (m, 6H); ^{13}C NMR (CD_3OD) δ 197.79, 173.94, 163.46, 146.07, 143.75, 125.98, 117.29, 66.66, 65.50, 47.25, 35.51, 30.48, 29.39, 24.89, 22.95, 22.85; IR (neat) 1665 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{24}N_3O_3$ $[M + H]^+$ 306.1818, found 306.1832. Anal. ($C_{18}H_{26}F_3N_3O_6$) $[M + TFA + H_2O]$: C, H, N.

X-ray Crystallography of 5b. The X-ray crystal structure of **5b** was determined at the Department of Inorganic Chemistry, Umeå University. Single colorless crystals of **5b** were obtained as prisms from heptane (dimensions: 0.45 mm × 0.15 mm × 0.10 mm) and are, at 150 K, orthorombic, space group $P2_12_12_1$ (No. 19) with a = 9.9070(4) Å, b = 10.0770(3) Å, c = 19.6780(4) Å, V = 1964.5 (1) Å^3, and Z = 4 {d_{calcd} = 1.185 g·cm^{-3}; μ_a(Mo K$_\alpha$) = 0.086 mm^{-1}}. A full hemisphere of diffracted intensities (φ and ω scans) was measured, using graphite-monochromated Mo Kα radiation on a Nonius KappaCCD single-crystal diffraction system. Lattice constants were determined with the HKL Scalepack software package using 10 590 reflections.[46] A total of 19 281 integrated reflection intensities having 2θ(Mo Kα) < 60.08° were produced using the Nonius program Collect.[47] Of these, 5726 (4101 > 2σ) reflections were unique and gave R_{int} = 0.079. Nonius SIR97[48] and SHELXL-97 software[49] were used to solve the structure using direct methods techniques. Weighted full-matrix least-squares refinements were conducted using F_o^2 data with the SHELXL-97 software package. Final agreement factors are R_1 = 0.0423 (unweighted, based on *F*, $I > 2\sigma$); R_1 = 0.0668 (unweighted, based on *F*, all reflections); wR_2 = 0.0862 (weighted, based on F^2, $I > 2\sigma$) and wR_2 = 0.0939 (weighted, based on F^2, all reflections)

The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The hydrogen atoms were located from difference Fourier synthesis and refined using a riding model.

Biological Activity. Functional Assays. The R-SAT (receptor selection and amplification technology) assay was performed essentially as previously described.[39] Briefly, NIH/3T3 cells at 70−80% confluency were transfected using Polyfect (Qiagen, Los Angeles, CA) as described in the manufacturer's protocols with DNA encoding the human D2 receptor at 5 ng/well and DNA encoding β-galactosidase at 20 ng/well of a 96-well plate. After 24 h incubation, saturating amounts of *N*-propylapomorphine (0.75−1 μM) were added with or without PLG or **1** (NPA, pEC_{50} = 7.6 ± 0.4, n = 7). After a 5-day incubation, the β-galactosidase activity was measured by the addition of *o*-nitrophenyl β-D-galactopyranoside (in phosphate-buffered saline with 5% Nonidet P-40 detergent). The resulting colorimetric reaction was measured with a spectrophotometric plate reader (Titertek, Huntsville, AL) at 420 nM.

Statistical Analysis. Statistical analysis was performed using a paired two-tailed Student's *t*-test, to assess whether the NPA response in the presence of **1** or PLG was significantly different from the NPA response in the media alone as a control.

Acknowledgment. We thank the Knut and Alice Wallenberg Foundation, the Norwegian Research Council and the Swedish Research Council for providing financial support for this project. We also thank Umeå University for providing laboratory facilities. In addition, we thank Uli Hacksell for advice during the development of the functional assay.

Supporting Information Available: Experimental procedure and tables with structural information regarding the X-ray crystallographic analysis of **5b** in CIF format and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hokfelt, T.; Broberger, C.; Xu, Z. Q. D.; Sergeyev, V.; Ubink, R.; Diez, M. Neuropeptides—An overview. *Neuropharmacology* **2000**, *39*, 1337−1356.

(2) Giannis, A.; Rubsam, F. Peptidomimetics in Drug Design. *Advances in Drug Research*; Academic Press: London, 1997; pp 1−78.

(3) Ripka, A. S.; Rich, D. H. Peptidomimetic design. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441−452.

(4) Hanessian, S.; McNaughtonSmith, G.; Lombart, H. G.; Lubell, W. D. Design and synthesis of conformationally constrained amino acids as versatile scaffolds and peptide mimetics. *Tetrahedron* **1997**, *53*, 12789−12854.

(5) Souers, A. J.; Ellman, J. A. Beta-Turn mimetic library synthesis: Scaffolds and applications. *Tetrahedron* **2001**, *57*, 7431−7448.

(6) Eguchi, M.; Shen, R. Y. W.; Shea, J. P.; Lee, M. S.; Kahn, M. Design, synthesis, and evaluation of opioid analogues with nonpeptidic beta-turn scaffold: Enkephalin and endomorphin mimetics. *J. Med. Chem.* **2002**, *45*, 1395−1398.

(7) Le, G. T.; Abbenante, G.; Becker, B.; Grathwohl, M.; Halliday, J.; Tometzki, G.; Zuegg, J.; Meutermans, W. Molecular diversity through sugar scaffolds. *Drug Discovery Today* **2003**, *8*, 701−709.

(8) Mishra, R. K.; Chiu, P.; Mishra, C. P. Pharmacology of L-Prolyl-L-Leucyl-Glycinamide (PLG): A Review. *Methodol. Find. Exp. Clin.* **1983**, *5*, 203−233.

(9) Srivastava, L. K.; Bajwa, S. B.; Johnson, R. L.; Mishra, R. K. Interaction of L-Prolyl-L-Leucyl Glycinamide with Dopamine-D2 Receptor—Evidence for Modulation of Agonist Affinity States in Bovine Striatal Membranes. *J. Neurochem.* **1988**, *50*, 960−968.

(10) Rajakumar, G.; Naas, F.; Johnson, R. L.; Chiu, S.; Yu, K. L.; Mishra, R. K. Down-Regulation of Halperidol-Induced Striatal Dopamine Receptor Supersensitivity by Active Analogues of L-Prolyl-L-Leucyl-Glycinamide (Plg). *Peptides* **1987**, *8*, 855−861.

(11) Johnson, R. L.; Rajakumar, G.; Yu, K. L.; Mishra, R. K. Synthesis of Pro-Leu-Gly-NH2 Analogues Modified at the Prolyl Residue and Evaluation of Their Effects on the Receptor-Binding Activity of the Central Dopamine Receptor Agonist, ADTN. *J. Med. Chem.* **1986**, *29*, 2104−2107.

(12) Johnson, R. L.; Rajakumar, G.; Mishra, R. K. Dopamine Receptor Modulation by Pro-Leu-Gly-NH_2 Analogues Possessing Cyclic Amino-Acid-Residues at the C-Terminal Position. *J. Med. Chem.* **1986**, *29*, 2100−2104.

(13) Johnson, R. L.; Bontems, R. J.; Yang, K. E.; Mishra, R. K. Synthesis and Biological Evaluation of Analogues of Pro-Leu-Gly-NH_2 Modified at the Leucyl Residue. *J. Med. Chem.* **1990**, *33*, 1828−1832.

(14) Baures, P. W.; Pradhan, A.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Synthesis and dopamine receptor modulating activity of unsubstituted and substituted triproline analogues of L-prolyl-L-leucyl-glycinamide (PLG). *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2349−2352.

(15) Evans, M. C.; Pradhan, A.; Venkatraman, S.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Synthesis and dopamine receptor modulating activity of novel peptidomimetics of L-prolyl-L-leucyl-glycinamide featuring alpha,alpha-disubstituted amino acids. *J. Med. Chem.* **1999**, *42*, 1441−1447.

(16) Thomas, C.; Ohnmacht, U.; Niger, M.; Gmeiner, P. beta-analogues of PLG (L-prolyl-L-leucyl-glycinamide): Ex-chiral pool syntheses and dopamine D-2 receptor modulating effects. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2885−2890.

(17) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. Development of a new family of conformationally restricted peptides as potent nucleators of beta-turns. Design, synthesis, structure, and biological evaluation of beta-lactam peptide analogue of melanostatin. *J. Am. Chem. Soc.* **2003**, *125*, 16243−16260.

(18) Yu, K. L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. Dopamine Receptor Modulation by Conformationally Constrained Analogues of Pro-Leu-Gly-NH_2. *J. Med. Chem.* **1988**, *31*, 1430−1436.

(19) Baures, P. W.; Ojala, W. H.; Costain, W. J.; Ott, M. C.; Pradhan, A.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Design, synthesis, and dopamine receptor modulating activity of diketopiperazine peptidomimetics of L-prolyl-L-leucylglycinamide. *J. Med. Chem.* **1997**, *40*, 3594−3600.

(20) Genin, M. J.; Mishra, R. K.; Johnson, R. L. Dopamine-Receptor Modulation by a Highly Rigid Spiro Bicyclic Peptidomimetic of Pro-Leu-Gly-NH_2. *J. Med. Chem.* **1993**, *36*, 3481−3483.

(21) Subasinghe, N. L.; Bontems, R. J.; McIntee, E.; Mishra, R. K.; Johnson, R. L. Bicyclic Thiazolidine Lactam Peptidomimetics of the Dopamine-Receptor Modulating Peptide Pro-Leu-Gly-NH_2. *J. Med. Chem.* **1993**, *36*, 2356−2361.

(22) Sreenivasan, U.; Mishra, R. K.; Johnson, R. L. Synthesis and Dopamine Receptor Modulating Activity of Lactam Conformationally Constrained Analogues of Pro-Leu-Gly-NH_2. *J. Med. Chem.* **1993**, *36*, 256−263.

(23) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Design, synthesis, and dopamine receptor modulating activity of spiro bicyclic peptidomimetics of L-prolyl-L-leucyl-glycinamide. *J. Med. Chem.* **1999**, *42*, 628−637.

(24) Khalil, E. M.; Pradhan, A.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Synthesis and dopamine receptor modulating activity of substituted bicyclic thiazolidine lactam peptidomimetics of L-prolyl-L-leucyl-glycinamide. *J. Med. Chem.* **1999**, *42*, 2977−2987.

(25) Weber, K.; Ohnmacht, U.; Gmeiner, P. Enantiopure 4-and 5-aminopiperidin-2-ones: Regiocontrolled synthesis and conformational characterization as bioactive beta-turn mimetics. *J. Org. Chem.* **2000**, *65*, 7406−7416.

(26) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. iso-lactam and reduced amide analogues of the peptidomimetic dopamine receptor modulator 3(*R*)-(2(*S*)pyrrolidinylcarbonyl)amino-2-oxo-1-pyrrolidineacetamide. *Bioorg. Med. Chem.* **2003**, *11*, 4103−4112.

(27) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. Synthesis and dopamine receptor modulating activity of 3-substituted gamma-lactam peptidomimetics of L-prolyl-L-leucyl-glycinamide. *J. Med. Chem.* **2003**, *46*, 727−733.

(28) Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. Design, synthesis, and evaluation of Phe-Gly mimetics: Heterocyclic building blocks for pseudopeptides. *J. Med. Chem.* **1999**, *42*, 4331−4342.

(29) The conformational analysis was performed in Macromodel (v. 5.5) using the AMBER force-field in vacuo. Conformations within a 3 kcal/mol range from the lowest conformation found were compared. See ref 28.

(30) The semiempirical calculations were performed in the Spartan program (v. 5.1.3) using AM1 as approximate Hamiltonian. The atomic charges were calculated by electrostatic fitting of the single point energies of the minimized structures.

(31) Saitton, S.; Kihlberg, J.; Luthman, K. A synthetic approach to 2,3,4-substituted pyridines useful as scaffolds for tripeptidomimetics. *Tetrahedron* **2004**, *60*, 6113−6120.

(32) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. Connection between metalation and cross-coupling strategies. A new convergent route to azacarbazoles. *Tetrahedron* **1993**, *49*, 49−64.

(33) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. 1st Metalation of Aryl Iodides—Directed Ortho-Lithiation of Iodopyridines, Halogen-Dance, and Application to Synthesis. *J. Org. Chem.* **1993**, *58*, 7832−7838.

(34) Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. Pyridylmagnesium chlorides from bromo and dibromopyridines by bromine−magnesium exchange: A convenient access to functionalized pyridines. *Tetrahedron Lett.* **1999**, *40*, 4339−4342.

(35) Depostition number CCDC 243122 at the Cambridge Crystallographic Data Centre; web site (http://www.ccdc.cam.ac.uk).

(36) Cram, D. J.; Elhafez, F. A. A. Studies in stereochemistry. X. The rule of "Steric control of asymmetric induction" in the synthesis of acyclic systems. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835.

(37) Silyl-protecting groups used were TES (triethylsilyl), TBDMS (tertbutyldimethylsilyl), and TIPS (triisopropylsilyl).

(38) Compare the ease of hydrolysis of the amide with the ease of forming the methyl ester in methanol. Presumably this is due to the intramolecular assistance of the pyridine nitrogen.

(39) Weiner, D. M.; Burstein, E. S.; Nash, N.; Croston, G. E.; Currier, E. A.; Vanover, K. E.; Harvey, S. C.; Donohue, E.; Hansen, H. C.; Andersson, C. M.; Spalding, T. A.; Gibson, D. F. C.; Krebs-Thomson, K.; Powell, S. B.; Geyer, M. A.; Hacksell, U.; Brann, M. R. 5-hydroxytryptamine(2A) receptor inverse agonists as antipsychotics. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 268−276.

(40) Burstein, E. S.; BraunerOsborne, H.; Spalding, T. A.; Conklin, B. R.; Brann, M. R. Interactions of muscarinic receptors with the heterotrimeric G proteins G(q) and G(12): Transduction of proliferative signals. *J. Neurochem.* **1997**, *68*, 525−533.

(41) Mishra, R. K.; Marcotte, E. R.; Chugh, A.; Barlas, C.; Whan, D.; Johnson, R. L. Modulation of dopamine receptor agonist-induced rotational behavior in 6-OHDA-lesioned rats by a peptidomimetic analogue of Pro-Leu-Gly-NH2 (PLG). *Peptides* **1997**, *18*, 1209−1215.

(42) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3−25.

(43) Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615−2623.
(44) Palm, K.; Stenberg, P.; Luthman, K.; Artursson, P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm. Res.* **1997**, *14*, 568−571.
(45) Baures, P. W.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. Design, Synthesis, X.-Ray-Analysis, and Dopamine Receptor-Modulating Activity of Mimics of the C5 Hydrogen-Bonded Conformation in the Peptidomimetic 2-Oxo-3(*R*)-(2(*S*)-pyrrolidinylcarbonyl)amino-1-pyrrolidineacetamide. *J. Med. Chem.* **1994**, *37*, 3677−3683.
(46) Otwinowski, Z.; Minor, W. Methods in Enzymology. In *Macromolecular Crystallography*; Carter, C. W., Jr., Sweet, R. M., Eds.; Academic Press: New York, 1997; Part A, pp 307−326.
(47) Nonius B. V., "Collect" data collection software, 1999.
(48) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. SIR97: A new tool for crystal structure determination and refinement. *J. Appl. Crystallogr.* **1999**, *32*, 115−119.
(49) Sheldrick, G. M. 1997. SHELXL-97. Program for the Refinement of Crystal Structures. University of Göttingen, Germany.
(50) The program MAREA is available from J. Gråsjö, Department of Pharmaceutics, Uppsala University, Uppsala, Sweden (e-mail: johan.grasjo@farmaci.uu.se).
(51) Dowty, E. 2000. ATOMS for Windows and Macintosh. Version 5.1. Shape Software, 521 Hidden Valley Road, Kingsport, TN 37663.

JM049484Q