US006172081B1

(12) **United States Patent**
Damon

(10) **Patent No.: US 6,172,081 B1**
(45) **Date of Patent: Jan. 9, 2001**

(54) **TETRAHYDROISOQUINOLINE 3-CARBOXAMIDE DERIVATIVES**

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(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/339,504**

(22) Filed: **Jun. 24, 1999**

(51) **Int. Cl.**[7] **A61K 31/47**
(52) **U.S. Cl.** **514/307**; 546/146
(58) **Field of Search** 514/307; 546/146

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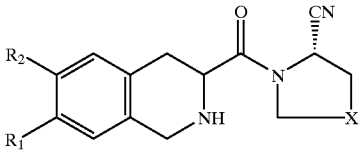
(57) **ABSTRACT**

Tetrahydroisoquinoline 3-carboxamide derivatives of formula



and pharmaceutically acceptable salts thereof wherein:

X is
(a) CH_2;
(b) S
(c) O; or
(d) $C(CH_3)_2$;

R_1 and R_2 are independently
(a) hydrogen;
(b) hydroxy;
(c) alkyl;
(d) alkoxy;
(e) aralkoxy; or
(f) halogen.

Compounds of formula I inhibit DPP-IV (dipeptidyl-peptidase-IV) activity. They are therefore useful in the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.

8 Claims, No Drawings

TETRAHYDROISOQUINOLINE 3-CARBOXAMIDE DERIVATIVES

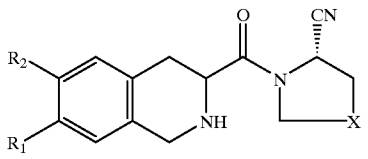
FIELD OF THE INVENTION

The present invention relates to the area of dipeptidyl peptidase-IV (DPP-IV) inhibition. DPP-IV is a serine protease which cleaves N-terminal dipeptides from a peptide chain containing, preferably, a proline residue in the penultimate position. Although the biological role of DPP-IV in mammalian systems has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, attachment of cancer cells to the endothelium and the entry of HIV into lymphoid cells.

More recently, it was discovered that DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1) More particularly, DPP-IV cleaves the amino-terminal His-Ala dipeptide of GLP-1. generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Since the half-life for DPP-IV cleavage is much shorter than the half-life for removal of GLP-l from circulation, a significant increase in GLP-1 bioactivity (5- to 10-fold) is anticipated from DPP-IV inhibition. Since GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition appears to represent an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM).

SUMMARY OF THE INVENTION

The instant invention relates to novel tetrahydroisoquinoline 3-carboxamide derivatives of formula I



and pharmaceutically acceptable salts thereof. As used in formula I, and throughout the specification, the symbols have the following meanings:

X is
- (a) CH_2;
- (b) S;
- (c) O; or
- (d) $C(CH_3)_2$;

R_1 and R_2 are independently
- (a) hydrogen;
- (b) hydroxy;
- (c) alkyl;
- (d) alkoxy;
- (e) aralkoxy; or
- (f) halogen.

Compounds of formula I are DPP-IV inhibitors which are effective in treating conditions mediated by DPP-IV.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. Listed below are

definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances either individually or as part of a larger group).

The term "alkyl" refers to optionally substituted straight or branched chain hydrocarbon groups having 1 to 8 carbon atoms, preferably 1 to 5 carbons. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, the various branched chain isomers thereof, such as isopropyl, t-butyl, isobutyl, isohexyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl and the like. Substituted alkyl groups include said alkyl groups substituted by one or more substituents selected from halogen, alkoxy, cycloalkyl, hydroxy, carboxy, $—CONR_3R_4$, $—NR_3R_4$ (where R_3 and R_4 are independently hydrogen or alkyl), nitro, cyano or thiol.

The term "alkoxy" refers to any of the above alkyl groups linked to an oxygen atom.

The term "cycloalkyl" refers to saturated cyclic hydrocarbon groups containing 3 to 7 ring carbons with cyclopropyl, cyclopentyl and cyclohexyl being preferred.

The term "halogen" or "halo" refers to chlorine, bromine and fluorine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl or biphenyl groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, amino, thiol, nitro, cyano, carboxy and the like.

The term "aralkoxy" refers to an aryl group bonded to an alkoxy group.

The compounds of formula I can exist in free form or in acid addition salt form. Salt forms may be recovered from the free form in known manner and vice-versa. Acid addition salts may e.g. be those of pharmaceutically acceptable organic or inorganic acids. Although the preferred acid addition salts are the trifluoroacetate, the hydrochloric, lactic or acetic acid may also be utilized.

The compounds of the invention may exist in the form of optically active isomers or diastereoisomers and can be separated and recovered by conventional techniques, such as chromatography.

A preferred group of compounds of the invention is the compounds of formula I wherein.

X is CH_2; and

R_1 and R_2 are independently hydrogen, hydroxy, or alkoxy.

More preferred compounds of the invention are those compounds of formula I wherein

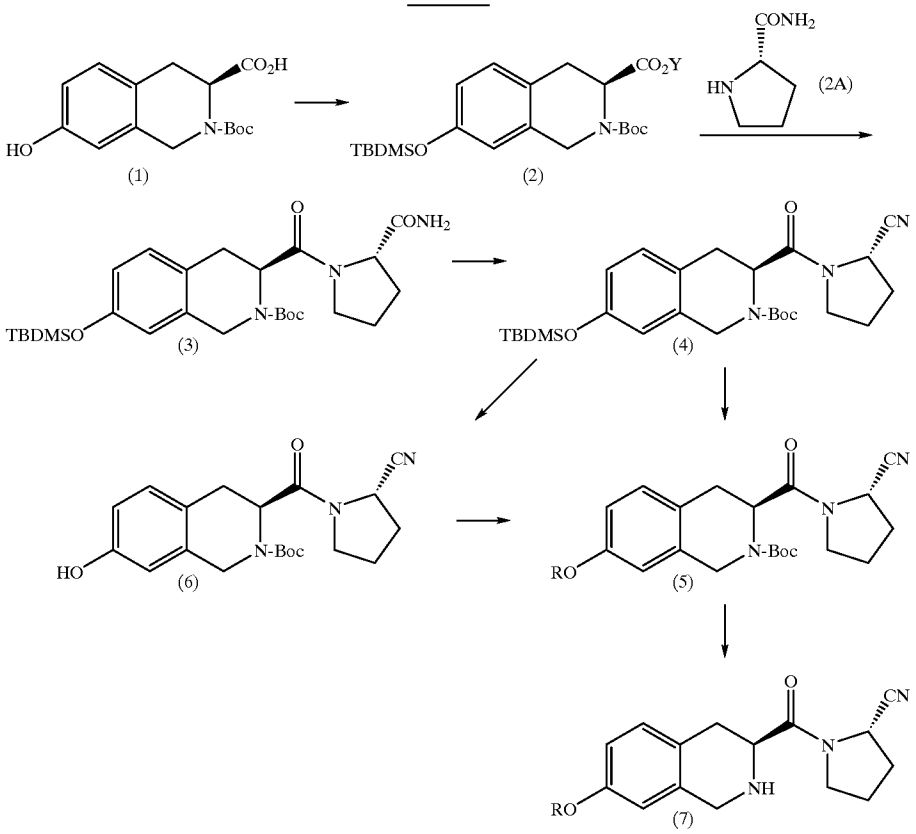
X is CH_2;

R_1 is alkoxy; and

R_2 is hydrogen.

The compounds of formula I may be prepared as illustrated for the compounds of formula I where X is CH_2 and one of R_1 or R_2 is hydroxy or alkoxy according to scheme 1 below:

Scheme 1



The Boc amino acid derivative (1) is silylated using a silating agent such as t-butyl dimethyl chlorosilane to form compounds of formula (2), where Y is H or a protecting group such as trialkylsilyl, arylalkylsilyl, arylsilyl or t-butyl ester, The silyl derivative (2) is condensed with prolineamide (2A; commercially available) mediated by an activating agent such as EDCI and HOAt in a solvent such as DMF. The resulting amide (3) is dehydrated to the nitrile (4) using a dehydrating agent such as phosphorus oxychloride. The nitrile (4) is then desilylated and alkylated using an alkylating agent such as an alkyl halide of the formula RaX (where Ra is an alkyl or arylalkyl group such as methyl or benzyl and X is a halogen such as iodine, bromine or chlorine) without isolation of the phenol, to form the ether (5). Alternatively, compound (5) can be prepared by alkylating the nitrile (4) with an alcohol subsequent to desilylation via a Mitsunobu-type reaction (via intermediates (6)).

In all cases, the final step is the removal of the Boc group using an acid such as trifluoroacetic acid in an organic solvent such as acetonitrile, preferably in the presence of a scavenger such as 1,3-dimethoxybenzene to give compound (7) which are compounds of formula I where R_2 is hydrogen and R_1 is alkoxy.

For compounds of formula I where R_2 is other than hydroxy condensation with a prolineamide is carried out using the Boc amino acid derivative (1) directly.

The Boc amino acid derivative(1) is commercially available or can be derived using known methods.

Compounds of formula I where X is other than CH_2 can be prepared in a similar fashion using the appropriate analog of proline as a starting material. Proline analogs where X═S or O are commercially available and can be used with standard methods of converting the carboxylic acid functionality to a nitrile via the primary amide. In the case where X represents —$C(CH_3)_2$, the requisite proline analog may be prepared as described in either of two literature references: J. Ezquerra, C. Pedregal, A. Rubio, and J. B. Deeter, *Journal of Organic Chemistry* 1994, 59,4327 or F. Soucy, D. Wernic and P. Beaulieu, *JCS Perkin I,* 1991, 2885.

The compounds of the invention may be isolated from the reaction mixture and purified in conventional manner, e.g. by chromatography.

Insofar as its preparation is not particularly described herein, a compound used as starting material is known or may be prepared from known compounds in known manner or analogously to known methods or analogously to methods described in the Examples.

The instant invention also includes pharmaceutical compositions useful in inhibiting DPP-IV comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable acid addition salt thereof

In still another embodiment, the instant invention provides a method of inhibiting DPP-IV comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable acid addition salt thereof.

In a further embodiment, the instant invention provides a method of treating conditions mediated by DPP-IV inhibition comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I above, or a pharmaceutically acceptable acid addition salt thereof.

As indicated above, all of the compounds of formula I, and their corresponding pharmaceutically acceptable acid

addition salts, are useful in inhibiting DPP-IV. The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may be demonstrated employing the Caco-2 DPP-IV Assay which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression was accomplished as described by Reisher, et al. in an article entitled "Increased expression of . . . intestinal cell line Caco-2" in Proc. Natl. Acad. Sci., Vol. 90, pgs. 5757–5761 (1993). Cell extract is prepared from cells solubilized in 10 mM Tris-HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% nonidet-P40, pH 8.0, which is centrifuged at 35,000 g for 30 min. at 4° C. to remove cell debris. The assay is conducted by adding 20 mg solubilized Caco-2 protein, diluted to a final volume of 125 mL in assay buffer (25 mM Tris-HCl pH 7.4, 140 mM NaCl, 10 mM KCl, 1% bovine serum albumin) to microtiter plate wells. The reaction is initiated by adding 25 mL of 1 mM substrate (H-Alanine-Proline-pNA; pNA is p-nitroaniline). The reaction is run at room temperature for 10 minutes after which time a 19 mL volume of 25% glacial acetic acid is added to stop the reaction. Test compounds are typically added as 30 mL additions and the assay buffer volume is reduced to 95 mL. A standard curve of free p-nitroaniline is generated using 0–500 mM solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). The endpoint is determined by measuring absorbance at 405 nm in a Molecular Devices UV Max microtiter plate reader. The potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 8-point, dose-response curves using a 4-parameter logistic function.

The following IC_{50}s were obtained:

Compound	Caco-2 DPP-IV (μM)
Ex. 1	0.0076
Ex. 2	0.004
Ex. 3	0.014
Ex. 4	0.009
Ex. 5	0.008
Ex. 6	>10
Ex. 7	0.013
Ex. 8	0.01
Ex. 9	0.01
Ex. 10	0.016
Ex. 11	0.01

The ability of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to inhibit DPP-IV may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described by Kubota, et al. in an article entitled "Involvement of dipeptidylpeptidase IV in an in vivo immune response" in Clin. Exp. Immunol., Vol. 89, pgs. 192–197 (1992). Briefly, five mL of plasma are added to 96-well flat-bottom mictotiter plates (Falcon), followed by the addition of 5 mL of 80 mM $MgCl_2$ in incubation buffer (25 mM HEPES, 140 mM NaCl, 1% RIA-grade BSA, pH 7.8). After a 5 min. incubation at room temperature, the reaction is initiated by the addition of 10 mL of incubation buffer containing 0.1 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-4-methylcoumarin). The plates are covered with aluminum foil (or kept in the dark,) and incubated at room temperature for 20 min. After the 20 min. reaction, fluorescence is measured using a CytoFluor 2350 fluorimeter (Excitation 380 nm Emission 460 nm; sensitivity setting 4). Test compounds are typically added as 2 mL additions and the assay buffer volume is reduced to 13 mL. A fluorescence-concentration curve of free AMC is generated using 0–50 mM solutions of AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 8-point, dose-response curves using a 4 parameter logistic function.

The following IC_{50}s were obtained:

Compound	human plasma DPP-IV (μM)	rat plasma DPP-IV (μM)
Ex. 1	0.041	0.79
Ex. 3	0.004	0.016
Ex. 4	0.167	1.3
Ex. 5	0.049	0.315
Ex. 7	0.012	0.078
Ex. 10	0.005	0.012

In view of their ability to inhibit DPP-IV, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, are useful in treating conditions mediated by DPP-IV inhibition. Based on the above and findings in the literature, it is expected that the compounds disclosed herein are useful in the treatment of conditions such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, and calcitonin-osteoporosis. More specifically, for example, the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, improve early insulin response to an oral glucose challenge and, therefore, are useful in treating non-insulin-dependent diabetes mellitus.

The precise dosage of the compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, to be employed for treating conditions mediated by DPP-IV inhibition depends upon several factors, including the host, the nature and the severity of the condition being treated, the mode of administration and the particular compound employed. However, in general, conditions mediated by DPP-IV inhibition are effectively treated when a compound of formula I, or a corresponding pharmaceutically acceptable acid addition salt, is administered enterally, e.g., orally, or parenterally, e.g., intravenously, preferably orally, at a daily dosage of 0.002–5, preferably 0.02–2.5 mg/kg body weight or, for most larger primates, a daily dosage of 0.1–250, preferably 1–100 mg. A typical oral dosage unit is 0.01–0.75 mg/kg, one to three times a day.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The compounds of formula I, and their corresponding pharmaceutically acceptable acid addition salts, may be

formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating conditions mediated by DPP-IV inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The compounds of formula I (including those of each of the subscopes thereof and each of the examples) may be administered in enantiomerically pure form (e.g., ee 98%, preferably 99%) or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of the R enantiomer).

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be clearly understood that they are for purposes of illustration only.

Abbreviations:

EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HOAt: 1-Hydroxy-7-azabenzotriazole

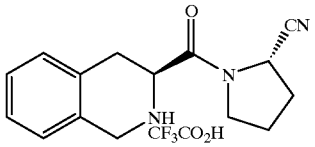
DMF: Dimethylformamide

THF: Tetrahydrofuran

TBAF: Tetrabutylammonium fluoride

EXAMPLE 1

[S-(R*,R*)]-1-(1,2,3,4-tetrahydro-3-isoquinolinyl) carbonyl-2-pyrrolidinecarbonitrile trifluoroacetate



A. [S-(R*,R*)]-3-(2-aminocarbonyl-1-pyrrolidinyl) carbonyl-3,4-dihydro-2(1H) isoquinolinecarboxylic acid 1,1-dimethylethyl ester

HOAt (450 mg, 3.6 mmol), EDCI (690 mg, 3.6 mmol) and L-prolinamide (411 mg, 3.6 mmol) were added sequentially to a solution of (S)-3,4-dihydro-2,3(1H)-isoquinolinedicarboxylic acid 2-(1,1-dimethylethyl) ester (1.0 g, 3.6 mmol) in 25 mL of dimethyl formamide. The resulting solution was stirred at room temperature for 20 h. The reaction mixture was diluted with 40 mL of water and extracted with methylene chloride. The organic solution was washed with 2N HCl, 10% aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated under vacuum to give 1.34 g of crude product as a white solid.

B. [S-(R*,R*)]-3-(2-cyano-1-pyrrolidinyl)carbonyl-3,4-dihydro-2(1H)-isoquinolinecarboxylic acid 1,1-dimethylethyl ester

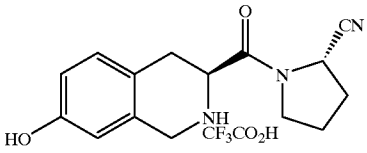
Phosphorus oxychloride (1.07 g, 0.65 mL, 6.97 mmol) was added to a solution of the amide (1.0 g, 2.68 mmol) and imidazole (237 mg, 3.48 mmol) in pyridine (22 mL) at room temperature. The reaction (which was exothermic) was stirred at room temperature for 1.25 h, then concentrated under vacuum to provide the crude product as a dark brown mushy solid. Flash chromatography on silica gel using ethyl acetate-hexane (60:40) gave 758 mg of product as a yellowish-white solid. This material was rechromatographed on silica gel using 1:1 ethyl acetate:hexane as the eluent to give 675 mg (71%) of the pure product.

C. [S-(R*,R*)]-1-(1,2,3,4-tetrahydro-3-isoquinolinyl) carbonyl-2-pyrrolidinecarbonitrile trifluoroacetate

Trifluoroacetic acid (0.2 mL; 2.6 mmol) was added to a solution of 36 mg (0.1 mmol) of the nitrile in 3 mL of acetonitrile at room temperature. The reaction was stirred 21 h., diluted with toluene (1 mL) and concentrated under vacuum. Addition of toluene and concentration under vacuum was repeated three more times. The white solid residue was partitioned between ethyl acetate and water. The aqueous phase was concentrated under vacuum and toluene was again added and removed under vacuum three more times to give 26 mg (70%) of product as a white solid, m.p. 145–150° C. (dec).. MS: Base peak - 256 (MH^+ for free amine). ^1H NMR (CH_3OD; 300 MHz): 7.1–7.4 (m, 4H), 4.85 (m, 1H), 4.6 (dd, 1H), 3.7 (m, 2H), 3.5 (dd, 1H), 3.15 (dd, 1H), 2.1–2.4 (m, 4H). ^{13}C NMR (CH_3OD): 119.2 (CN).

EXAMPLE 2

[S-(R*,R*)]-1-(1,2,3,4-tetrahydro-7-hydroxy-3-isoquinolinyl)carbonyl-2-Pyrrolidinecarbonitrile trifluoroacetate



A. (S)-3-(dimethyl)(1,1-dimethylethyl)silyl-ester-7-[(dimethyl)(1,1-dimethylethyl)silyl]oxy-3,4-dihydro-2,3(1H)-Isoquinolinedicarboxylic acid 2-(1,1-dimethylethyl) ester

Imidazole (3.1 g; 45.54 mmol) and t-butyldimethylchlorosilane (6.86 g, 45.54 mmol) were added to a solution of (S)-3,4-dihydro-7-hydroxy-2,3(1H)-isoquinolinedicarboxylic acid 2-(1,1-dimethylethyl) ester (6 g, 18.2 mmol) in dimethyl formamide (50 mL) at room temperature. The mixture was stirred at room temperature overnight, then quenched with water and extracted with methyl t-butyl ether. The organic solution was washed with brine, dried (sodium sulfate) and concentrated to give 11.97 g of the title compound as a colorless oil.

B. [S-(R*,R*)]-3-(2-aminocarbonyl-1-pyrrolidinyl) carbonyl-3,4-dihydro-7-[(dimethyl)(1,1-dimethylethyl) silyl]oxy-2(1H)-Isoquinolinecarboxylic acid 1,1-dimethylethyl ester

To a solution of the crude title A compound, (S)-3-(dimethyl)(1,1-dimethylethyl)silyl-ester 7-[(dimethyl)(1,1-dimethylethyl)silyl]oxy-3,4-dihydro-2,3(1H)-isoquinolinedicarboxylic acid 2-(1,1-dimethylethyl) ester (9.49 g, 18.22 mmol) in 120 mL of DMF was added EDCI (4.1 g, 21.9 mmol) and HOAt (2.97 g, 21.0 mmol). After stirring for 10 minutes, triethyl amine (2.21 g, 3.05 mL, 21.9 mmol) was added, After an additional 10 minutes, L-prolinamide (2.5 g, 21.9 mmol) was added to the cloudy yellow mixture. The reaction was stirred overnight at room temperature, 1 hour at 50° C., and overnight again at room temperature, and then partitioned between ethyl acetate and water. The ethyl acetate solution was washed with 1N HCl, saturated aq. sodium bicarbonate, and brine, filtered, dried (sodium sulfate), and concentrated to give product as 9.2 g of a white foam. Purification of the crude product by flash chromatography on silica gel using 2% methanol in methylene chloride as the eluent gave 5.7 g of the title compound as a white foam, 91.3% pure by HPLC.

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